Angewandte Chemie

DOI: 10.1002/ange.201208064

Saturated Heterocycles

SnAP Reagents for the Transformation of Aldehydes into Substituted Thiomorpholines—An Alternative to Cross-Coupling with Saturated Heterocycles[**]

*Cam-Van T. Vo, Gediminas Mikutis, and Jeffrey W. Bode**

Saturated N-heterocycles are increasingly common scaffolds for the discovery and development of biologically active small molecules.[1] Unlike their aromatic counterparts, they cannot be easily appended to a substrate by cross-coupling reactions. The most reliable method for constructing 2-aryl piperidines and pyrrolidines is an effective but laborious lithiation, transmetallation, and Pd-catalyzed cross-coupling.[2] Unfortunately, this method is not well-suited for cross-coupling morpholines, thiomorpholines, or piperazines. Researchers have therefore sought to identify new synthetic methods for the preparation of substituted, saturated N-heterocycles by C−H functionalization. For example, the groups of Nakamura,[3] Sames,[4] MacMillan,[5] Maulide,[6] and others[7] have reported α-arylation of N-heterocycles, but these reactions require *N*-aryl substituents that are difficult to remove or further elaborate.

Herein, we disclose SnAP reagents for the facile conversion of aldehydes into *N*-unprotected, 3-thiomorpholines (Figure 1). This strategy has the potential to be a general approach to installing saturated heterocycles using aldehydes as a synthetic handle. Its successful execution relies on the use of radical chemistry to overcome a long-standing challenge in organic synthesis: C−C bond-forming addition to unactivated primary imines.[8]

At the outset of our studies, we established two key design parameters for reaction development. First, we required that our approach deliver *N*-unprotected heterocycles directly from the reaction. Second, we wanted the N-heterocycle substituents to be derived from a stable, widely available functional group, ideally halide, aldehyde, or organoboronic acid. After several unsuccessful attempts, our studies led us to an unusual approach: intramolecular C−C bond-forming radical cyclization of an imine bearing a pendant nucleophilic carbon.

For our initial studies, we selected the preparation of 3-substituted thiomorpholines from aldehydes, as there are presently very few methods for their synthesis.[9] Amino tributylstannane **1** (SnAP-TM)[10] is readily obtained in one step by *S*-alkylation of 2-aminoethanethiol with commercially available tributyl(iodomethyl)-stannane.[11] Condensation with an aldehyde gives the corresponding imine, which we endeavored to cyclize to give *N*-unprotected 3-thiomorpholines. The poor electrophilicity of this imine, which lacks either the *N*-sulfonyl or *N*-aryl group typically found in imine electrophiles, presented numerous challenges. Initial attempts with stannane–lithium exchange or Lewis acid induced cyclization proved unsuccessful (Table 1, entry 1). Inspired by reports from the group of Kagoshima on the intermolecular addition of organostannanes to *N*-phenyl or *N*-*para*-methoxyphenyl imines using stoichiometric $Cu(OTf)_2$,[12] we

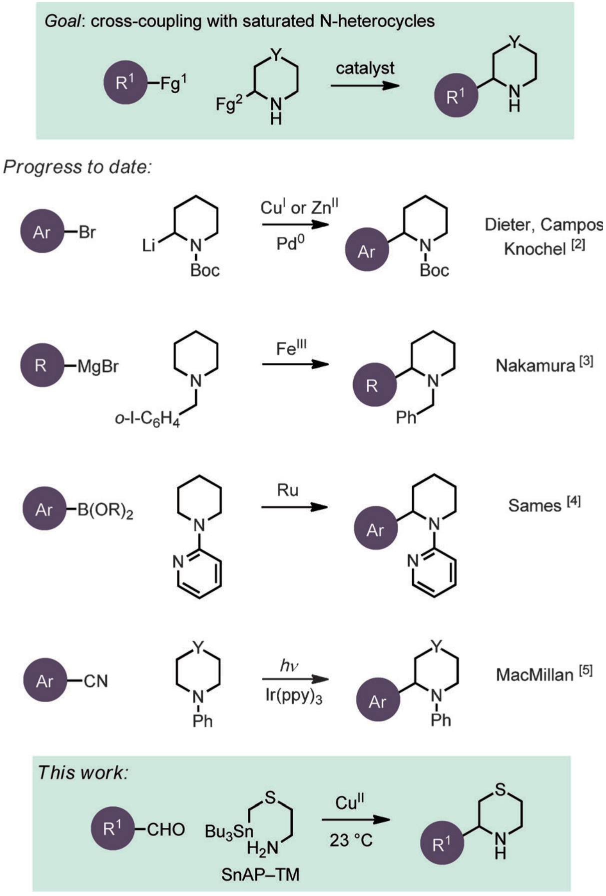


Figure 1. Approaches to cross-coupling with saturated heterocycles. Boc = *tert*-butoxycarbonyl, Fg = functional group.

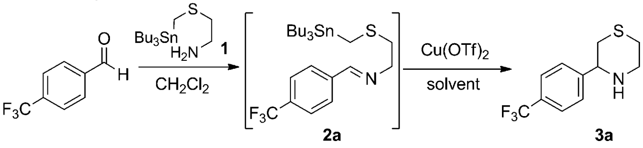
---

[*] C.-V. T. Vo, G. Mikutis, Prof. Dr. J. W. Bode
Laboratorium für Organische Chemie, Department of Chemistry and Applied Biosciences, ETH Zürich
Wolfgang Pauli Strasse 10, 8093 Zürich (Switzerland)
E-mail: bode@org.chem.ethz.ch
Homepage: http://www.bode.ethz.ch

[**] This work was supported by an ETH Research Grant (ETH-12 11-1). We are grateful to Drs. Xiangyang Zhang and Bernd Schweizer of ETH (Zürich) for mass spectrometry and for X-ray crystallographic structural determination. SnAP = tin (Sn) amine protocol.

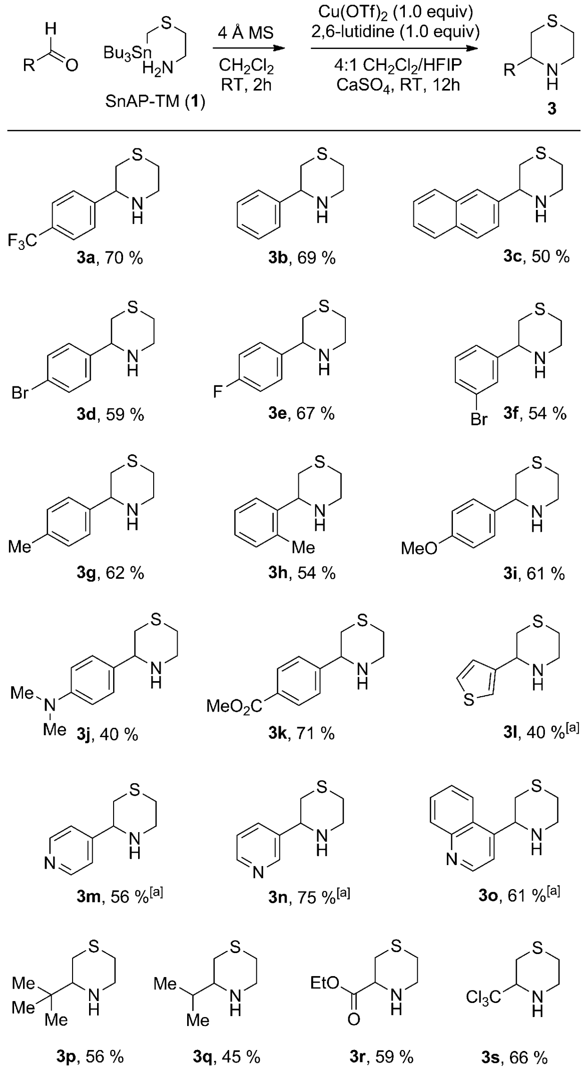
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201208064.

Table 1: Optimization of reaction conditions.[13]



Entry[a]	Solvent	Additive	*T* [°C]	Yield[b] [%]
1	THF	*n*BuLi	0→RT	0
2	ClC_2H_4Cl	–	RT	NR
3	ClC_2H_4Cl	–	60	35
4	toluene	–	95	44
5	HFIP	–	60	55
6	ClC_2H_4Cl	HCl	60	33
7	*t*BuOH	$KHCO_3$	60	15
8	1:1 ClC_2H_4Cl/HFIP	1,10-phenanthroline	60	trace
9	1:1 ClC_2H_4Cl/HFIP	2,6-di-*t*Bu-pyridine	60	65
10	1:1 ClC_2H_4Cl/HFIP	pyridine	60	38
11	1:1 ClC_2H_4Cl/HFIP	2,6-lutidine	60	75
12[c]	4:1 ClC_2H_4Cl/HFIP	2,6-lutidine	60	74
13	**4:1 CH_2Cl_2/HFIP**	**2,6-lutidine**	**RT**	**76**

[a] All reactions were performed on a 0.05 mmol scale by adding a solution of **2a** into a mixture of $Cu(OTf)_2$ (0.05 mmol), additive (0.05 mmol), and $CaSO_4$ in the solvent (0.05 M) and stirring for 12 h. [b] Yield determined by ^1H NMR spectroscopy with benzyl methyl ether as an internal standard. [c] Reaction performed at 60 °C for 2 h. HFIP = hexafluoroisopropyl alcohol, NR = no reaction.



Scheme 1. Conversion of aldehydes into thiomorpholines with SnAP-TM. All reactions were performed on a 0.50 mmol scale with $Cu(OTf)_2$ (0.50 mmol), 2,6-lutidine (0.50 mmol), and $CaSO_4$ at RT for 12 h. Yields shown are of isolated, analytically pure products following column chromatography. [a] reactions performed in 4:1 ClC_2H_4Cl/HFIP at 60 °C for 2 h. MS = molecular sieves.

examined the cyclization of imine **2a** under these conditions. At room temperature, no cyclization product was detected (Table 1, entry 2), but at 60 °C a small amount of the desired product was obtained (Table 1, entry 3). Further optimization of the conditions was unproductive until we found that hexafluoroisopropyl alcohol (HFIP) significantly improved the yield (55 % yield) and diminished the formation of side products (Table 1, entry 5). Other polar solvents (MeOH, *t*BuOH) failed to give similar improvement and we attributed the beneficial effects of HFIP to activation of the imine by protonation. Anhydrous conditions, which deterred imine hydrolysis, could be conveniently achieved by the addition of anhydrous $CaSO_4$ to the reaction mixture. To further improve the reactivity, monodentate and bidentate ligands for copper, including 1,10-phenanthroline, 2,6-di-*tert*-butylpyridine, 2,6-lutidine, and pyridine were tested, with 2,6-lutidine offering the best results (Table 1, entry 11). Using this ligand in a mixture of HFIP and CH_2Cl_2 or ClC_2H_4Cl as solvent, the cyclization was complete after 2 h at 60 °C or 12 h at room temperature (Table 1, entry 12–13).

With the optimized reaction conditions in hand, we explored the transformation of various aldehydes into *N*-unprotected 3-thiomorpholines with SnAP-TM **1** (Scheme 1). This occurred smoothly with a broad scope of aldehydes (aryl, heteroaryl, and alkyl aldehydes). Both electron-poor and electron-rich substituents on aryl rings gave good yields. Functional groups, including organohalides, protected alcohols, amines, and esters, were tolerated under the reaction conditions. The reactions succeeded with *meta*- or *para*-heteroaryl substrates, but failed with *ortho*-heteroaryl aldehydes. Imines prepared from pivalaldehyde, isobutyraldehyde, glyoxal, and chloral also afforded thiomorpholine products in good to moderate yields. Products from unbranched aliphatic aldehydes were observed, but in lower yields, presumably owing to facile enamine formation.

We also investigated the more substituted SnAP reagents **4** and **5**, prepared from *rac*-cysteine ethyl ester and *rac*-penicillinamine methyl ester, respectively. Under the standard conditions, these reagents coupled with representative aldehydes to give the more substituted thiomorpholines **6a–d** in good yields and high diastereoselectivity (Figure 2). The *cis* relative stereochemistry was confirmed by X-ray crystallographic analysis of **6a**. We presently ascribe the high diastereoselectivities observed in these cases to equilibration of an initially formed diastereomeric mixture to the thermodynamically favored *cis* product. Further studies of this process, including the use of enantiopure starting materials and efforts to modulate the diastereoselectivity are ongoing.

Kagoshima et al. proposed a role for the Cu^{II} as a Lewis acid in the the nucleophilic addition of α-thioalkyl stannanes

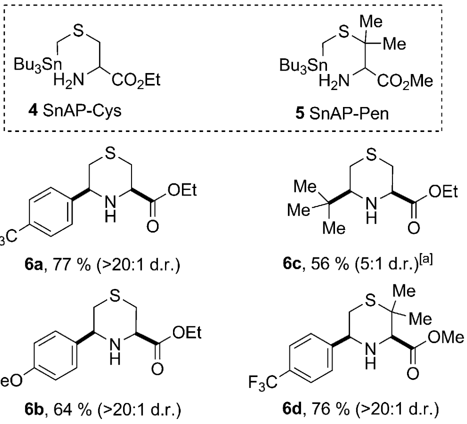
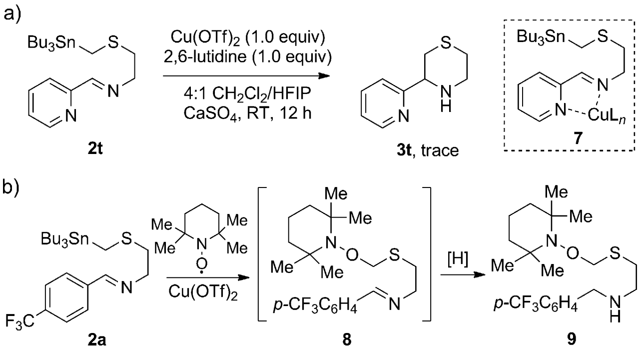


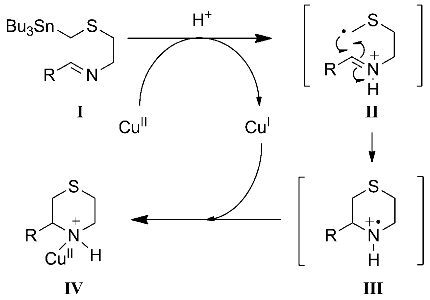
Figure 2. SnAP reagents for the synthesis of functionalized thiomorpholines. The d.r. was determined by ^{1}H NMR analysis of unpurified reaction mixtures. [a] The diastereomers could be separated by flash column chromatography.

to *N*-phenyl or *N*-*para*-methoxyphenyl imines.[12] We were therefore surprised that 2-pyridylaldehyde and related substrates, which should chelate Cu^{II}, showed poor reactivity (Scheme 2a). Likewise, other metal salts and Lewis acids, including $Zn(OTf)_2$ and $BF_3{\cdot}OEt_2$, failed to promote cyclization. These results led us to postulate an alternative mechanism. Organostannanes are well-known to form carbon-centered radicals under oxidative conditions,[14] thus suggesting a mechanism in which Cu^{II} acts as an oxidant. To test this hypothesis, TEMPO (1.5 equiv) was added into reaction. No cyclization product was obtained and trapped compound **8** was observed. The reduction of **8** to amine **9** allowed us to isolate and characterize this adduct (Scheme 2b).



Scheme 2. Experiments supporting a role for $Cu(OTf)_2$ as an oxidant rather than as a Lewis acid.

On the basis of these results, we proposed a mechanism for cyclization that features the generation and cyclization of a carbon radical (Scheme 3). Iminotributylstannane **I** undergoes protonation and one-electron oxidation with $Cu(OTf)_2$, leading to the formation of Cu^I and radical cation **II**. The α-thio radical **II** cyclizes with the intramolecular imine to form radical cation **III**, which is reduced by Cu^I to generate copper(II) complex **IV**. The observed 6-*endo* cyclization, rather than the competing 5-*exo* cyclization, is consistent with prior studies on ring closures of imines with pendant vinyl and aryl radicals.[15]



Scheme 3. Proposed mechanism for copper-mediated cyclization.

The reaction of carbon radicals with imines may be related to the recent work of Molander et al.[16] and Baran et al.[17] on oxidative C−C bond formation between aromatic N-heterocycles and radicals generated from organoboronic acids or their derivatives. In these transformations, a stoichiometric amount of oxidant is needed to reform the aromatic ring. In principle, our cyclization should be catalytic in Cu^{II}, but we believe that the coordination of the unprotected thiomorpholine product to the Cu^{II} leads to catalyst inhibition. The addition of sacrificial metal salts that can exchange the bound copper make possible the use of substoichiometric amounts of $Cu(OTf)_2$, but currently with poor turnover. Efforts to render this cyclization catalytic and to employ chiral ligands are ongoing. The similarities between this cyclization and the coupling of organoboronic acids with heteroaromatic compounds also suggest that organoboranes or organosilanes could serve as surrogates for the organostannanes in SnAP reagents.

In conclusion, we have developed SnAP reagents for the transformation of aldehydes into *N*-unprotected 3-thiomorpholines. The use of a radical cyclization overcomes the long-standing problem of the poor electrophilicity of unactivated imines. This method is effective on a wide range of aldehydes, including electron-rich and electron-poor aryl, heteroaryl, and alkyl aldehydes, as well as glyoxylates. We anticipate that this strategy will be rapidly extended to a family of SnAP reagents for generating other *N*-unprotected saturated heterocycles, including morpholines, piperazines, and diazepanes. The ease of execution, mild reaction conditions, and functional group tolerance mirror the convenience of metal-catalyzed cross-coupling reactions, and provides access to saturated N-heterocycles not currently accessible by traditional methods.

Experimental Section

To a solution of the SnAP-TM reagent **1** (0.50 mmol, 1.00 equiv) in CH_2Cl_2 (2.5 mL, 0.25 M) was added aldehyde (0.50 mmol, 1.00 equiv) and 4 Å molecular sieves. The reaction mixture was stirred at RT for 2 h, filtered through a layer of celite and concentrated under reduced pressure to provide imine **2**. Separately, $Cu(OTf)_2$ (0.50 mmol, 1.00 mmol) was added to a solution of 2,6-lutidine (0.50 mmol, 1.00 equiv) in HFIP (2 mL) and stirred at RT for 1 h. $CaSO_4$ (50 mg) was added to the reaction mixture, followed by imine **2** in CH_2Cl_2 (8 mL), and stirred at RT for 12 h. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), followed by 10% aq. NH_4OH (3 mL) and stirred vigorously for 15 min. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), washed with H_2O (3 × 30 mL) and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (0.1% NEt_3 was added to the mobile phase) delivered the *N*-unprotected 3-thiomorpholine **3**.

Received: October 7, 2012

Keywords: aldehydes · cross-coupling · nitrogen heterocycles · radical reactions · thiomorpholines

---

[1] a) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930; b) R. Wijtmans, M. K. S. Vink, H. E. Schoemaker, F. L. van Delft, R. H. Blaauw, F. P. J. T. Rutjes, *Synthesis* **2004**, 641–662; c) R. Dua, S. Shrivastava, S. K. Sonwane, S. K. Srivastava, *Adv. Bio Res.* **2011**, *5*, 120–144.

[2] a) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552–560; b) R. K. Dieter, C. M. Topping, K. R. Chandupatla, K. Lu, *J. Am. Chem. Soc.* **2001**, *123*, 5132–5133; c) R. K. Dieter, S. Li, *J. Org. Chem.* **1997**, *62*, 7726–7735; d) K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer, C.-Y. Chen, *J. Am. Chem. Soc.* **2006**, *128*, 3538–3539; e) G. Barker, P. O'Brien, K. R. Campos, *Org. Lett.* **2010**, *12*, 4176–4179; f) H. Prokopcová, S. D. Bergman, K. Aelvoet, V. Smout, W. Herrebout, B. Van der Veken, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2010**, *16*, 13063–13067; g) S. Seel, T. Thaler, K. Takatsu, C. Zhang, H. Zipse, B. F. Straub, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2011**, *133*, 4774–4777; h) P. O'Brien, J. L. Bilke, *Angew. Chem.* **2008**, *120*, 2774–2776; *Angew. Chem. Int. Ed.* **2008**, *47*, 2734–2736.

[3] N. Yoshikai, A. Mieczkowski, A. Matsumoto, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2010**, *132*, 5568–5569.

[4] S. J. Pastine, D. V. Gribkov, D. Sames, *J. Am. Chem. Soc.* **2006**, *128*, 14220–14221.

[5] C. K. P. A. McNally, D. W. C. MacMillan, *Science* **2011**, *334*, 1114–1117.

[6] I. D. Jurberg, B. Peng, E. Wöstefeld, M. Wasserloos, N. Maulide, *Angew. Chem.* **2012**, *124*, 1986–1989; *Angew. Chem. Int. Ed.* **2012**, *51*, 1950–1953.

[7] For reviews on α-functionalization of saturated *N*-heterocycles: a) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069–1084; b) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092–10142.

[8] R. Bloch, *Chem. Rev.* **1998**, *98*, 1407–1438; S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094.

[9] Most existing methods for thiomorpholine synthesis require the substituted 1,2-aminothiol as the starting material; for examples, see: a) G. N. Ziakas, E. A. Rekka, A. M. Gavalas, P. T. Eleftheriou, P. N. Kourounakis, *Bioorg. Med. Chem.* **2006**, *14*, 5616–5624; b) M. Yar, E. M. McGarrigle, V. K. Aggarwal, *Angew. Chem.* **2008**, *120*, 3844–3846; *Angew. Chem. Int. Ed.* **2008**, *47*, 3784–3786.

[10] We have adopted the abbreviation "SnAP" for tin (Sn) amine protocol, followed by a designation for the product formed (for example, TM refers to thiomorpholine).

[11] Tributyl(iodomethyl)-stannane can also be prepared easily from tributyltin hydride in two steps (68% yield). The synthesis is reported in the Supporting Information.

[12] a) H. Kagoshima, N. Takahashi, *Chem. Lett.* **2004**, *33*, 962–963; b) H. Kagoshima, K. Shimada, *Chem. Lett.* **2003**, *32*, 514–515; c) H. Kagoshima, K. Yonezawa, *Synth. Commun.* **2006**, *36*, 2427–2432.

[13] More detailed optimization of reaction conditions is reported in the Supporting Information.

[14] a) K. Narasaka, N. Arai, T. Okauchi, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2995–3003; b) T. Ikeno, M. Harada, N. Arai, K. Narasaka, *Chem. Lett.* **1997**, *26*, 169–170; c) G. K. Friestad, *Tetrahedron* **2001**, *57*, 5461–5496.

[15] a) M. L. J. Tomaszewski, J. Warkentin, *Tetrahedron Lett.* **1992**, *33*, 2123–2126; b) M. J. Tomaszewski, J. Warkentin, *J. Chem. Soc. Chem. Commun.* **1993**, 966–968; c) I. Ryu, S.-i. Ogura, S. Minakata, M. Komatsu, *Tetrahedron Lett.* **1999**, *40*, 1515–1518.

[16] G. A. Molander, V. Colombel, V. A. Braz, *Org. Lett.* **2011**, *13*, 1852–1855.

[17] I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196.