Cross-Coupling

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Catalytic Synthesis of N-Unprotected Piperazines, Morpholines, and Thiomorpholines from Aldehydes and SnAP Reagents

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Abstract: *Commercially available SnAP (stannyl amine protocol) reagents allow the transformation of aldehydes and ketones into a variety of N-unprotected heterocycles. By identifying new ligands and reaction conditions, a robust catalytic variant that expands the substrate scope to previously inaccessible heteroaromatic substrates and new substitution patterns was realized. It also establishes the basis for a catalytic enantioselective process through the use of chiral ligands.*

Saturated N-heterocycles are privileged scaffolds for the preparation of bioactive small molecules as they offer several advantages, including improved solubility, bioavailability, and pharmacokinetics.[1,2] Their use is currently limited by poor commercial availability and the paucity of methods for their preparation, particularly for C-mono- and C-disubstituted variants. In seeking to provide a cross-coupling approach for the rapid synthesis of substituted saturated N-heterocycles, we recently disclosed a cross-coupling approach employing SnAP (stannyl amine protocol) reagents and aldehydes. This operationally simple process provides facile, one-step access to C-substituted thiomorpholines,[3] morpholines, piperazines,[4] diazepanes, and other medium-sized heterocycles[5] and spirocyclic structures (Figure 1).[6] Many of these SnAP reagents are now commercially available, and SnAP chemistry is finding widespread use in industry.

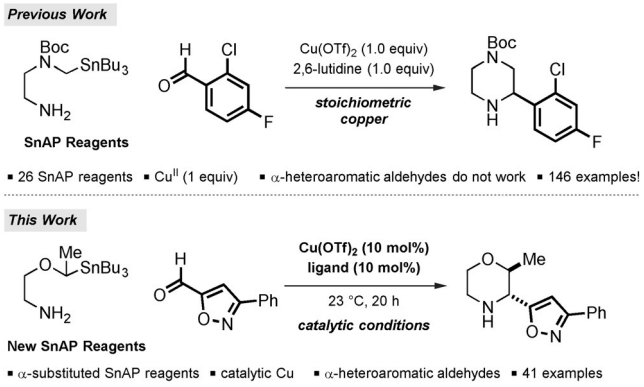

Figure 1. SnAP reagents for the synthesis of N-heterocycles from aldehydes and ketones. Boc = *tert*-butyloxycarbonyl, Tf = trifluoromethanesulfonyl.

Despite the outstanding substrate scope and operational simplicity of the SnAP method, we have identified two major limitations. First, SnAP processes have thus far required a stoichiometric amount of $Cu(OTf)_2$, which both decreases the efficiency and limits the possibilities of an enantioselective process. The need for a stoichiometric amount of copper is also at odds with our current mechanistic hypothesis, which postulates an overall redox-neutral reaction.[3,5] We attributed the need for stoichiometric copper to product inhibition—a common obstacle for metal-catalyzed reactions in which the products are more basic than the starting materials.[7] Second, aldehydes with proximal heteroatoms do not undergo cyclization. This is of special interest as the elusive 2-(pyridine-2-yl)piperazine moiety and related scaffolds are often found in bioactive small molecules.[8]

We herein report the identification of ligand-accelerated SnAP reactions that operate with catalytic amounts of copper and also further expand the substrate scope to include α-heteroaromatic aldehydes. We also introduce α-bis-substituted SnAP reagents for the synthesis of 2,3-disubstituted N-heterocycles, a new product class in SnAP chemistry (Figure 1), and demonstrate the viability of this system for the catalytic enantioselective synthesis of N-heterocycles.

We have postulated that product inhibition—rather than mechanistic considerations—has thus far precluded the use of catalytic amounts of copper, as experiments with 20 mol% of copper gave the desired product in only approximately 20% yield (Table 1, entries 1–3). Heating to 90 °C in the absence of any ligand increased conversion, but under these conditions, the reaction displayed a poor substrate scope (entry 4). As deactivation can often be reversed by additives or by changing the ligand, we initially focused on ligand screening. A survey of ligands commonly used in copper-catalyzed reactions, such as phenanthrolines, bipyridines, or phosphines, were shown to be of insufficient catalytic activity (entries 5–9).[9] Surprisingly, only a single ligand class, namely Box ligands, led to appreciable catalysis, and we established that 20 mol% of $Cu(OTf)_2$ in combination with 20 mol% of **L8** promoted full conversion (entry 10). Further optimization focusing on the reaction temperature and solvent revealed two crucial parameters: 1) the integrity of the catalyst[10] and 2) an increased amount of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP).[11] Heating the reaction to induce turnover was detrimental for catalytic activity (entry 11), a counterintuitive observation that we attribute to the enhancement of ligand exchange between bis(oxazoline) ligand **L8** and the unprotected product. With HFIP as the sole solvent, we were able to reduce the catalyst loading to 5 mol% (entry 13).[11] Based on

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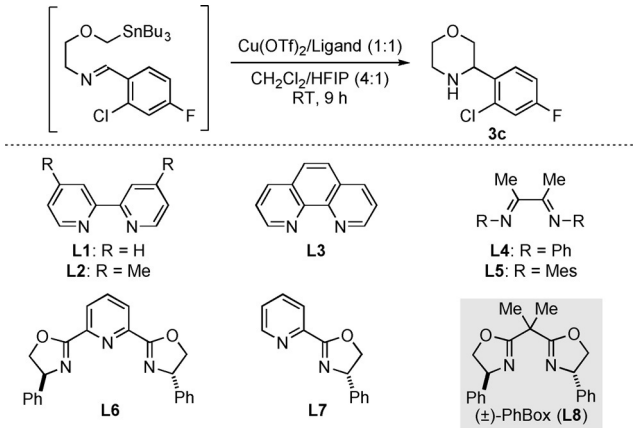
Table 1: Reaction optimization and ligand screening.[14]



Entry	$Cu(OTf)_2$ [mol%]	Ligand	Conv. [%]	Yield[a] [%]
1	100	2,6-lutidine	100	89
2	20	2,6-lutidine	33	25
3	20	–	24	15
4[b]	20	–	92	71
5	20	**L1** or **L2**	ca. 10	<5
6	20	**L3**	30	20
7	20	**L4** or **L5**	ca. 20	0
8	20	**L6 or L7**	<10	<10
9	20	PPh_3 or BINAP	0	–
10	20	**L8**	100	86
11[c]	5	**L8**	ca. 15	ca. 10
12	5	**L8**	25	19
13[d]	5	**L8**	88	76

[a] Yield of product **3c** determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b] At 90 °C. [c] At 45 °C. [d] HFIP as the solvent.

literature precedents,[3,11] we attribute the beneficial effect of HFIP, a solvent of broad utility owing to its strong hydrogen-bond-donor abilities,[12,13] to the complexation of the N-heterocycle product, thereby promoting turnover of the Lewis acidic copper catalyst (Figure 2).

Under the optimized conditions, morpholines and thiomorpholines were readily obtained from the corresponding SnAP reagents; aromatic, heteroaromatic, and branched aliphatic aldehydes generally gave the corresponding products in excellent yields. We were pleased to find that—unlike for the stoichiometric variant—all regioisomers of pyridine-

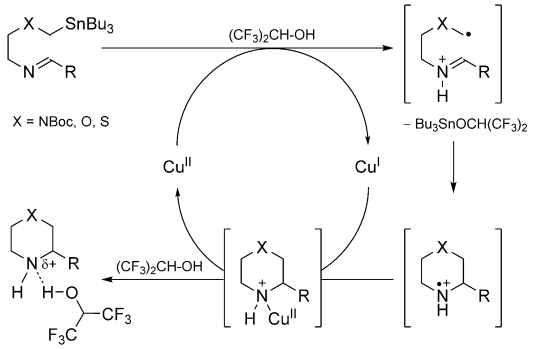


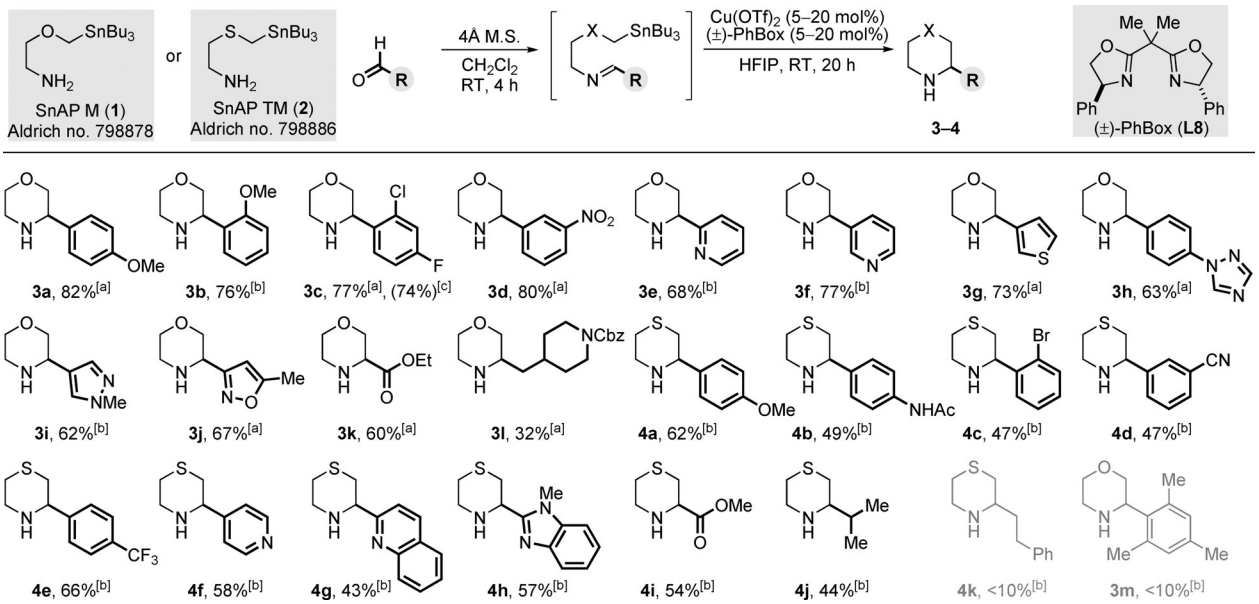
Figure 2. Proposed catalytic cycle for the copper-catalyzed cyclization.

carboxaldehyde and related heteroaromatic aldehydes were excellent substrates, an outcome that we attribute to the use of a superior ligand and the increased amount of HFIP. For some substrates, such as those containing additional coordinating heteroatoms, a higher catalyst loading (20 mol%) was beneficial. Substrate-specific optimization is also possible; for example, for the gram-scale synthesis of **3c**, 5.0 mmol of SnAP M (**1**) and a catalyst loading of 5 mol% were used. A few limitations remain, including the reactions of mesitylaldehyde (product **3m**) or aliphatic substrates that are prone to enamine formation (product **4k**), which gave mostly the protodestannylated side products (Scheme 1).

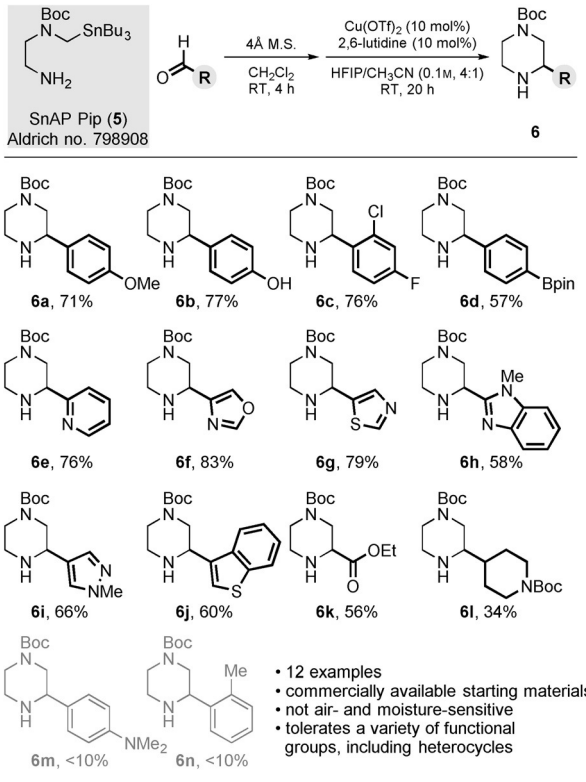
Interestingly, the same conditions did not prove as effective for piperazine synthesis using SnAP Pip (**5**) as increased amounts of the protodestannylated side products were observed. With these substrates, the use of $Cu(OTf)_2$ (10 mol%) and 2,6-lutidine (10 mol%) as the ligand was found to be optimal, provided that an increased amount of HFIP was employed to promote turnover. Acetonitrile was identified as a beneficial additive that improved the yields of the unprotected piperazines and also reduced the amounts of the protodestannylated side products (Scheme 2).[15] Other additives, such as $BF_3{\cdot}Et_2O$, TMSOTf, $Sc(OTf)_3$, or AgOTf did not have a significant effect, nor did the addition of fluoride sources (LiF, KF, CsF, TBAF, CuF_2) to facilitate transmetalation. Applying these conditions to reactions of SnAP M (**1**) or SnAP TM (**2**) resulted mostly in unreacted starting material, reinforcing the importance of the bis(oxazoline) ligand **L8** for these transformations.

These optimized conditions represent a general procedure for the synthesis of functionalized 1,4-diazacyclohexanes (**6a**–**6l**) in good yields using SnAP Pip (**5**; Scheme 2). No special precautions were necessary for the reaction setup as the reactions are not particularly air- or moisture sensitive. All experiments were performed using identical reaction conditions without substrate-specific optimization. Aldehydes containing various functional groups, such as ester (**6k**), aryl halide (**6c**), or pinacol boronate (**6d**) moieties, or diverse heterocycles (**6e**–**6j**) enabled the synthesis of scaffolds suitable for further elaboration. The tolerance of these conditions towards heterocyclic carboxaldehydes with heteroatoms in the *ortho* position (**6e**–**6h**) is noteworthy as no product was observed under the previously reported stoichiometric conditions with one equivalent of $Cu(OTf)_2$.[3-6] The catalytic conditions were unfortunately not applicable to the formation of larger rings, such as diazepanes, which were easily obtained under the stoichiometric conditions. Ketones also did not prove to be viable substrates under these conditions and afforded the desired spirocycles in low yields.

An advantage of SnAP chemistry is the ability to incorporate various substituents into the reagents themselves, facilitating the synthesis of substituted N-heterocycles, often as single diastereomers.[3,4,6b] To date, we have explored substitution at every position except for that adjacent to the tributyltin moiety. To complete the study on ring substitution, we investigated the use of α-bis-substituted SnAP reagents **7** and **9**, which would afford two adjacent stereocenters upon ring closure. Using the described standard conditions, these reagents were coupled with representative aldehydes to



Scheme 1. Catalytic synthesis of morpholines and thiomorpholines. Reactions were performed on a 0.5 mmol scale using the indicated SnAP reagent (1.0 equiv) and aldehyde (1.0 equiv). Yields of isolated, analytically pure compounds after chromatography are given. [a] $Cu(OTf)_2$ (10 mol%), (±)-PhBox (10 mol%), HFIP (0.1 M). [b] $Cu(OTf)_2$ (20 mol%), (±)-PhBox (20 mol%), HFIP (0.05 M). [c] Reaction on a 5.0 mmol scale: $Cu(OTf)_2$ (5 mol%), (±)-PhBox (5 mol%), HFIP (0.1 M), RT, 36 h. Cbz = benzyloxycarbonyl, M.S. = molecular sieves.



Scheme 2. Catalytic piperazine synthesis. Reactions were performed on a 0.5 mmol scale using SnAP Pip (**5**, 1.0 equiv) and an aldehyde (1.0 equiv). Yields of isolated, analytically pure compounds after chromatography are given.

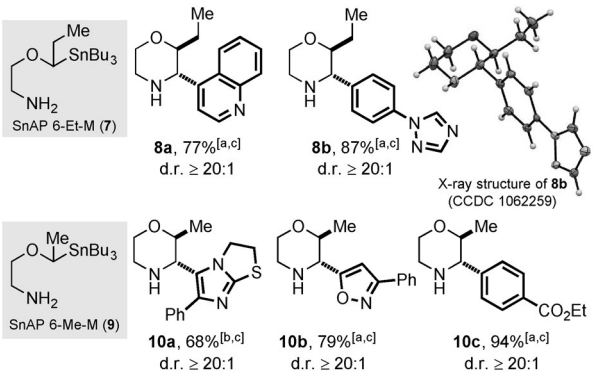
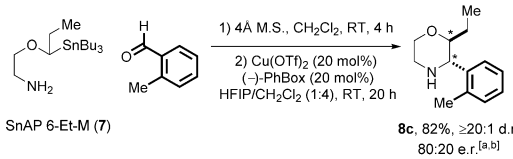


Figure 3. Synthesis of disubstituted morpholines. [a] $Cu(OTf)_2$ (10 mol%), (±)-PhBox (10 mol%), HFIP (0.1 M), 20 h, RT. [b] $Cu(OTf)_2$ (20 mol%), (±)-PhBox (20 mol%), HFIP (0.05 M), 20 h, RT. [c] The relative stereochemistry was confirmed by X-ray analysis of (±)-**8b**; all others were assigned by analogy.

provide the 2,3-disubstituted morpholines **8a** and **8b** or **10a**–**10c** in good to excellent yields and high diastereoselectivity (Figure 3). The *trans* relative configuration was confirmed by NMR spectroscopy and X-ray analysis. The facile formation of vicinally disubstituted heterocycles from these sterically more demanding SnAP reagents represents a promising approach to more congested structures that are difficult to access by other methods.[16]

The identification of substoichiometric reaction conditions presents the exciting opportunity to develop catalytic ligand-controlled enantioselective variants. Catalytic asymmetric methods to generate optically active saturated N-heterocycles remain quite rare and have various limitations, such as the need for complex linear precursors or protecting groups.[17] In preliminary experiments, we were pleased to find that using racemic SnAP 6-Et-M (**7**) in

combination with enantiopure (*S*)-PhBox as the ligand, enantioenriched 2,3-disubstituted morpholine **8c** was delivered in 82% yield and a promising enantiomeric ratio of 80:20 (Scheme 3). Furthermore, the observed stereoconvergence



Scheme 3. Catalytic enantioselective morpholine synthesis. For additional examples, see the Supporting Information. [a] The enantiomeric ratio (e.r.) was determined by HPLC analysis of the purified product on a chiral stationary phase. [b] Absolute stereochemistry not assigned.

supports our current mechanistic conjecture that the organostannane leads to a carbon radical upon oxidation by copper(II),[3,5] as also observed by Falck and co-workers.[18] In contrast, most cross-coupling methods of stereodefined nucleophiles with copper proceed by stereospecific transmetalation, and enantioenriched products are accessed only from non-racemic, configurationally stable precursors, which are often difficult to access.[19] Although improvements in the enantioselectivity are clearly needed, the observation of significant enantioinduction invites further studies on ligand optimization and investigations into the stereochemistry-determining step.

In summary, we have identified catalytic methods for the one-step synthesis of substituted N-unprotected piperazines, morpholines, and thiomorpholines. This robust and air- and moisture-tolerant procedure is a valuable addition to SnAP chemistry and expands the substrate scope to include 2-(pyridine-2-yl)piperazines and related substrates. This work also introduces a new class of SnAP reagents, with substitution adjacent to the heteroatom, resulting in the diastereoselective synthesis of 2,3-disubstituted N-heterocycles. Our preliminary findings on a catalytic enantioselective variant provide a promising start for the development of new routes to enantioenriched N-heterocycles.

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Keywords: aldehydes · cross-coupling · homogeneous catalysis · nitrogen heterocycles · SnAP reagents

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[14] A more detailed list can be found in the Supporting Information (Table S1).

[15] The reaction reaches full conversion using SnAP Pip (**5**) with protodestannylated side products as the main constituents when the standard conditions reported in Ref. [4] are applied in a catalytic manner: $Cu(OTf)_2$/2,6-lutidine (10 mol%) in HFIP/CH_2Cl_2 (1:4, 0.05 M) at room temperature. An increased amount of HFIP and CH_3CN as a co-solvent were vital to obtain piperazines in meaningful yields.

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