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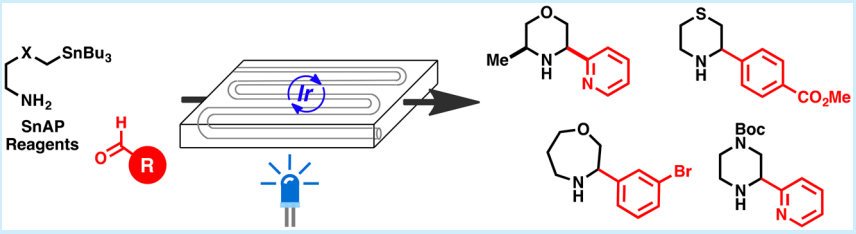
Iridium-catalyzed Synthesis of Saturated N-Heterocycles from Aldehydes and SnAP Reagents with Continuous Flow Photochemistry

Chalupat Jindakun, Sheng-Ying Hsieh, and Jeffrey W. Bode*

Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, 8093 Zürich, Switzerland

Supporting Information



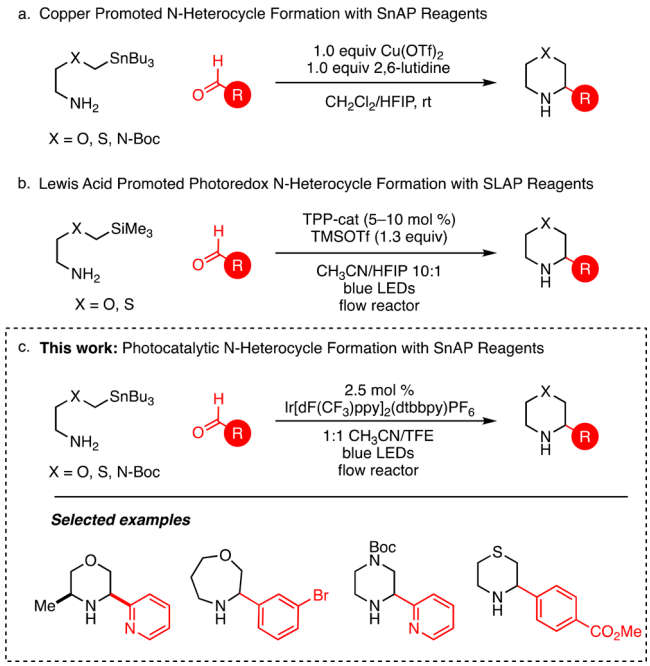
ABSTRACT: Commercially available tin amine protocol (SnAP) reagents provide a simple approach to the synthesis of a wide variety of saturated N-heterocycles from aldehydes. In this report, we disclose that the copper(II) promoter and hexafluoroisopropanol can be replaced by photocatalytic conditions using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ in CH_3CN. Continuous flow photochemical conditions provide a clean, scalable approach to valuable products including morpholines, piperazines, thiomorpholines, diazepanes, and oxazepanes from aldehyde starting materials.

Tin amine protocol (SnAP) reagents are widely used, commercially available starting materials for the one-step conversion of aldehydes to saturated N-heterocycles such as morpholines, piperazines, thiomorpholines, oxazepanes, diazepanes, substituted pyrrolidines, and piperidines (Scheme 1a).[1] The SnAP chemistry is distinguished by exceptionally broad substrate scope that tolerates aromatic heterocycles as well as unprotected functional groups including anilines, phenols, esters, nitriles, and halides under simple, consistent reaction conditions. These features make SnAP chemistry well suited to the preparation of small amounts of *N*-unprotected saturated N-heterocycles from readily available precursors.

The limitations of SnAP chemistry, particularly on larger scale, include the use of tin reagents,[2] the requirement for halogenated solvents,[3] and sometimes complicated aqueous workups to remove copper salts. To address these concerns, we have introduced the corresponding silicon (SLAP) reagents, which afford similar products under photocatalytic conditions (Scheme 1b).[4] While effective, most of the SLAP reagents require the addition of superstoichiometric amounts of Lewis acid additives and are therefore not compatible with all substrate combinations, particularly *N*-Boc protected amines.[4b,c] The SnAP reagents are also currently more readily available and provide access to many more types of saturated N-heterocycles.[5]

In this report, we document continuous flow, photocatalytic conditions[6] for the formation of saturated N-heterocycles from aldehydes and commercially available SnAP reagents (Scheme 1c). Although tin reagents are still employed, this approach offers the replacement of stoichiometric copper with catalytic amounts of an iridium photocatalyst, the use of CH_3CN/TFE rather than CH_2Cl_2/HFIP as the reaction solvent, and simplified workup.

Scheme 1. Synthesis of Saturated N-Heterocycles with SnAP and SLAP Reagents



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The reactions can be easily scaled up using a simple flow reactor without variation of the reaction conditions.

The shift from a stoichiometric, copper-mediated process to a catalytic, photoredox variant[8−10] began with the recognition that the SnAP chemistry proceeds by a series of single electron transfer steps initiated by copper(II) and mostly likely involves free radical intermediates (Figure 1).[11] We sought to mimic this sequence of events with a suitable photoredox catalyst.

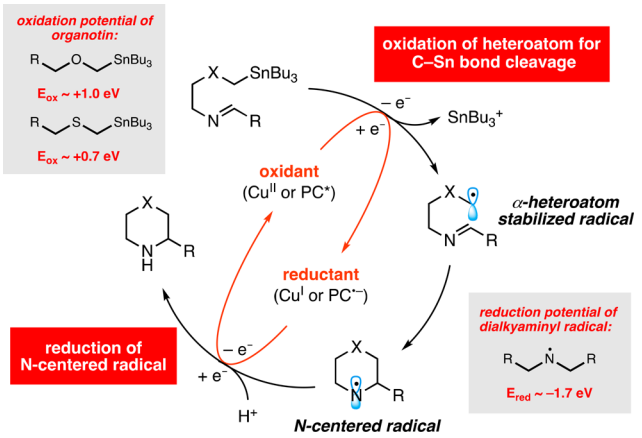
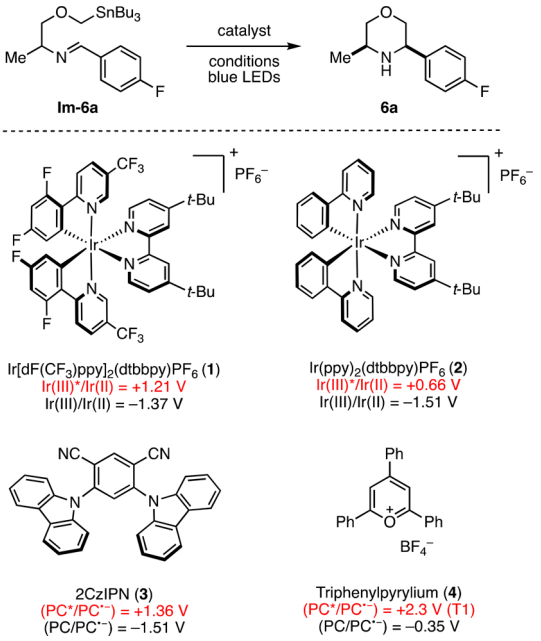


Figure 1. Proposed catalytic cycle for copper-promoted SnAP reactions[7] and the photoredox alternative. This catalytic cycle features a single electron transfer oxidation to generate the stabilized C-centered radical and reduction of the N-centered radical to form the N-heterocycle product upon protonation.

Based on the estimated potentials for oxidation of the carbon−tin bond[12] and subsequent reduction of the N-centered radical,[13] we evaluated and screened a number of potential photoredox catalysts[14−16] using imine **Im-6a** as the model substrate (Table 1, entry 1−5). As predicted from the compatible redox potentials of 2CzIPN (entry 3), it served as a competent photoredox catalyst for the reaction; however, it is nearly insoluble in CH_3CN, and no product was formed in DMF, rendering it unsuitable for flow chemistry.[15] We selected instead Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (**1**) as the catalyst for further optimization under continuous flow conditions. A preliminary result showed up to 50% of cyclized product **6a** was obtained under continuous flow conditions (entry 6), comparable with yields obtained under batch conditions (entry 1). The use of slightly increased amounts of the photoredox catalyst (entry 7) or more acidic alcohols (e.g., TFE or HFIP, entry 8−9) as the cosolvent facilitated the reaction and improved the yield. In the CH_3CN/TFE solvent system, the yield of the cyclized product was further increased by higher flow rate (entry 8 vs 10), while there was no such improvement in CH_3CN/MeOH (entry 7 vs 11). Presumably, the acidic alcohol enhanced the reactivity of the substrate, resulting in over-reaction (e.g., oxidation of α-radical or decomposition of the N-heterocycle product) when the reaction time was extended.

For the exploration of the substrate scope, we applied CH_3CN/TFE as the solvent system at 0.05 mM concentration and a flow rate of 0.20 or 0.25 mL/min (Table 1, entry 10), which gave a residence time of 7−9 min in our reactor.[17] Morpholines and oxazepanes were prepared from aromatic aldehydes with SnAP reagents under the standard conditions in moderate yields. Importantly, *N*-Boc protected piperazines and diazepanes, which cannot currently be prepared using SLAP chemistry, were also formed in good yields under the same reaction conditions. This condition is also applicable to the synthesis of thiomorpholines

Table 1. Optimization of Reaction Conditions for Photocatalytic SnAP Reactions



entry	catalyst	solvent	flow rate (mL/min)	conv (%)[a]	NMR yield (%)[a]
1	1 mol % **1**	4:1 CH_3CN/MeOH	batch[b]	100	47
2	2.5 mol % **2**	4:1 CH_3CN/MeOH	batch[b]	14	14
3	5 mol % **3**	4:1 CH_3CN/MeOH	batch[b]	100	51
4	5 mol % **3**[c]	15:4:1 CH_3CN/MeOH/DMF	batch[b]	0	0
5	5 mol % **4**	9:1 toluene/HFIP	batch[b]	0	0
6	1 mol % **1**	4:1 CH_3CN/MeOH	0.13	72	50
7	2.5 mol % **1**	4:1 CH_3CN/MeOH	0.13	82	69
8	2.5 mol % **1**	4:1 CH_3CN/TFE	0.13	92	58
9	2.5 mol % **1**	4:1 CH_3CN/HFIP	0.13	91	55
10	2.5 mol % **1**	1:1 CH_3CN/TFE	0.25	93	65
11	2.5 mol % **1**	1:1 CH_3CN/MeOH	0.25	89	58

[a]Conversion (conv) and yield were measured from ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]The reaction was performed in a glass vial under exposure to blue light (see Supporting Information). [c]Used as a 1.0 M solution in DMF. TFE = 2,2,2-trifluoroethanol. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

with no need for additives or changes to the reaction conditions, making this protocol more general and appealing than the Cu-based catalytic condition[7] or the SLAP chemistry.[4]

In the case of substrates such as **5f**, which contained an easily oxidizable thiophene, or highly hindered aldehydes (**7i** or **8e**), the flow rates were reduced to 0.15 mL/min for higher yields (Scheme 2). For certain highly hydrophobic imines, a mixture of 1:1 CH_2Cl_2/TFE was employed instead of CH_3CN.

In general, the yields of the N-heterocycle products from this flow protocol are slightly lower than those from the copper promoted SnAP chemistry. However, the iridium-catalyzed photoredox conditions offer certain advantages including the ability to employ 2-pyridyl aldehydes and related substrates without the need for additional ligands[7] and better results with

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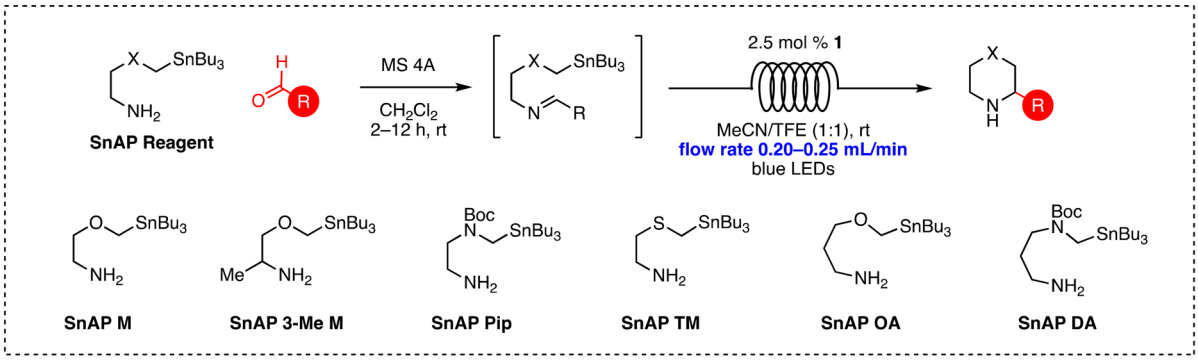
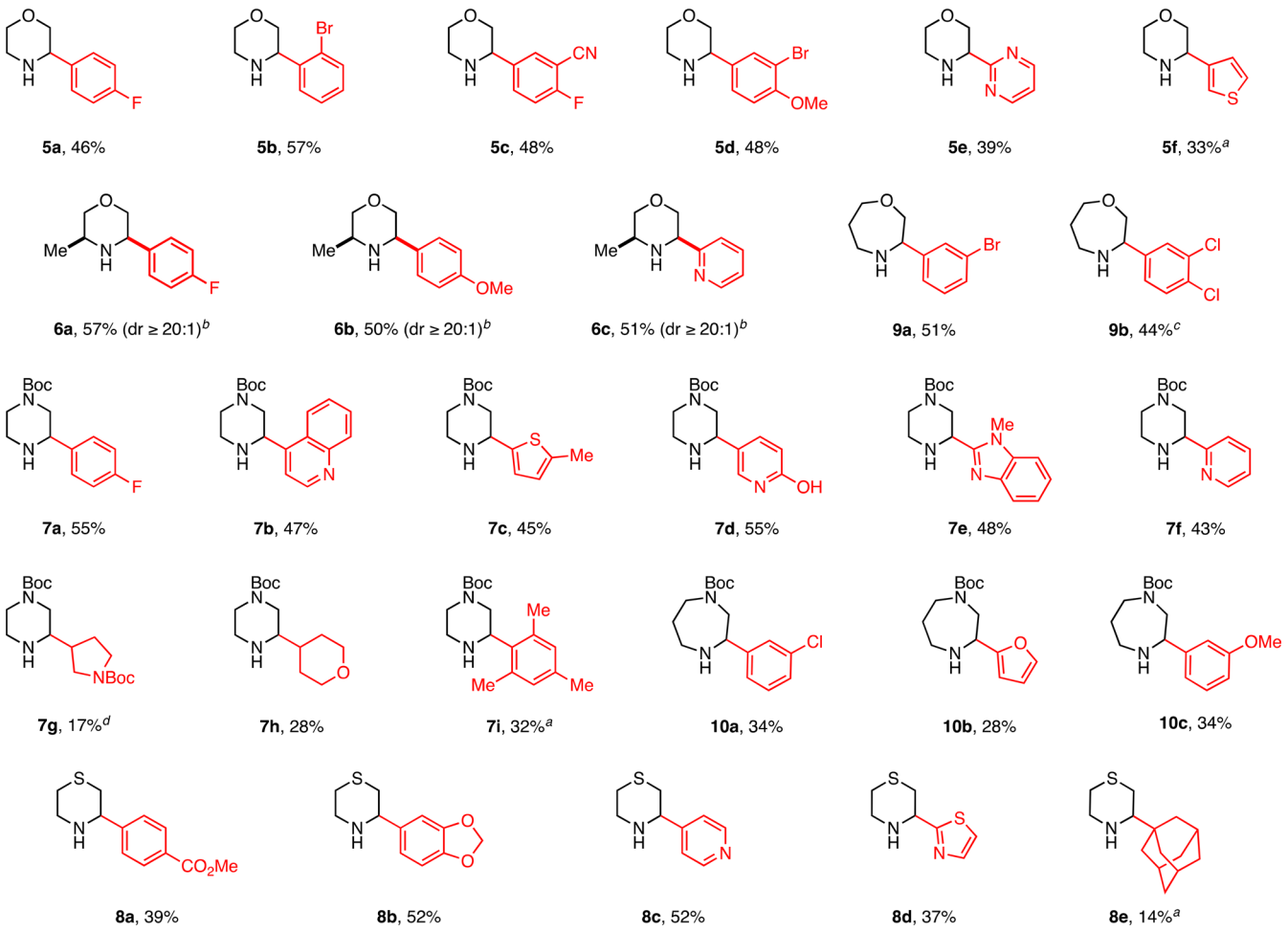
Scheme 2. Substrate Scope of N-Heterocycles from Aldehydes and SnAP Reagents under Continuous Flow Conditions





[a]Flow rate = 0.15 mL/min. [b]Diastereomeric ratio (d.r.) was determined from ^{1}H NMR spectroscopy of the unpurified reaction mixture. [c]CH_2Cl_2/TFE (1:1) was used as the solvent. [d]Diastereomeric ratio was not determined. Isolated yields were determined on 0.50 mmol reaction scale. MS = molecular sieves.

more sterically demanding aldehydes. The replacement of stoichiometric copper and amine ligands with a single photoredox catalyst resulted in easier reaction workup[1d,7] with particular significance for reaction scale-up. To demonstrate this, we performed a 10.0 mmol scale reaction under the identical continuous flow condition (Scheme 3). The desired product was obtained simply by acid–base extraction in 62% crude yield with only trace amounts of tin residue. Further purification by precipitation with 4 M HCl in dioxane gave the pure oxazepane salt **9a·HCl** in 41% yield.

Interestingly, a few substrates were reluctant to participate in cyclizations under these conditions for uncertain reasons. In particular, attempts to use naphthyl aldehydes failed to give any desired products, despite the fact that such aldehydes are excellent substrates for Cu-promoted SnAP chemistry. UV–vis spectroscopic experiments suggested that naphthylimine absorbs light in the region where photoredox catalyst **1** was excited under blue LEDs source, which could lead to the depletion of catalyst's quantum yield (see Supporting Information, Figure S3). Likewise, more elaborate SnAP reagents, such as SnAP-2-Spiro-(4-Pip) M, gave only trace amounts of the desired product; an

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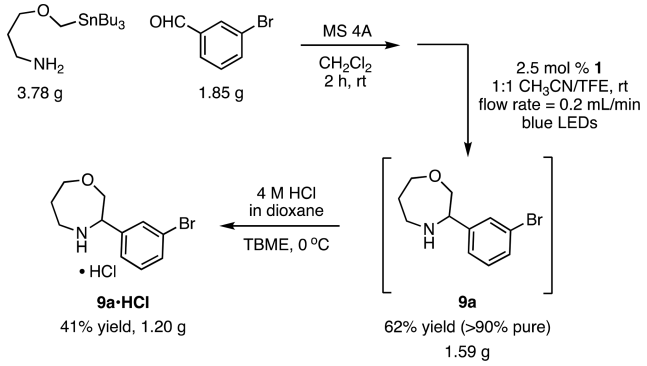
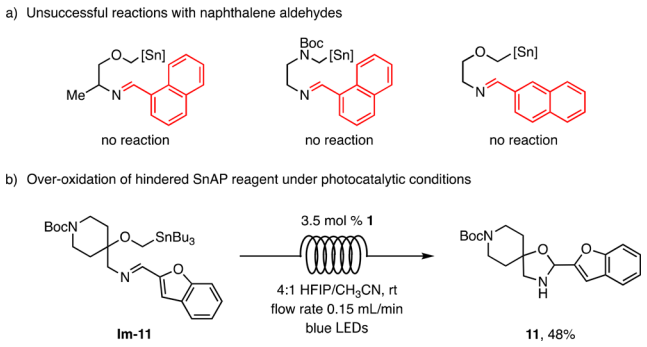
Scheme 3. Gram-Scale Synthesis of Saturated N-Heterocycles with Continuous Flow Photochemistry



oxazolidine, formed by two-electron oxidation of the C−Sn bond, was the major product (Scheme 4).

Scheme 4. Unsuccessful Cyclizations under Photoredox Conditions



In summary, we have identified catalytic, photoredox conditions for the formation of saturated N-heterocycles from commercially available SnAP reagents and aldehydes. Although the yields are somewhat lower than conditions with stoichiometric amounts of a copper complex, this continuous flow method facilitates reaction scale-up and offers simplified reaction workup. From a mechanistic point of view, it is noteworthy that a Cu^{II}/Cu^{I} couple can be effectively replaced by a photoredox catalyst that shows excellent functional group tolerance and no product inhibition.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00611.

Experimental procedures and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bode@chem.ethz.ch.

ORCID

Jeffrey W. Bode: 0000-0001-8394-8910

Notes

The authors declare no competing financial interest.

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(17) Residence time = reactor volume/flow rate; in this case, our reactor volume is 1.7 mL, which gives a residence time of 7−9 min for the flow rate of 0.20−0.25 mL/min.

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