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

Journal Article

Author(s):

Jindakun, Chalupat; Hsieh, Sheng-Ying; Bode, Jeffrey W.

Publication date:

2018-04

Permanent link:

<https://doi.org/10.3929/ethz-b-000260450>

Rights / license:

In Copyright - Non-Commercial Use Permitted

Originally published in:

Organic Letters 20(7), <https://doi.org/10.1021/acs.orglett.8b00611>

Funding acknowledgement:

306793 - Catalytic asymmetric synthesis of amines and amides (EC)

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 Zurich, 8093 Zurich, Switzerland

Supporting Information Placeholder

ABSTRACT: Commercially available SnAP (tin amine protocol) 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) promotor and hexafluoroisopropanol can be replaced by photocatalytic conditions using Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ in CH₃CN. Continuous flow photochemical conditions provide a clean, scalable approach to valuable products including morpholines, piperazines, thiomorpholines, diazepanes, and oxazepanes from aldehyde starting materials.

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 conditions⁶ 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 CH₃CN/TFE rather than CH₂Cl₂/HFIP as the reaction solvent, and simplified workup. The reactions can be easily scaled up using a simple flow reactor without variation of the reaction conditions.

Scheme 1. Synthesis of saturated N-heterocycles with SnAP and SLAP reagents.

a. Copper Promoted N-Heterocycle Formation with SnAP Reagents

b. Lewis Acid Promoted Photoredox N-Heterocycle Formation with SLAP Reagents

c. This work: Photocatalytic N-Heterocycle Formation with SnAP Reagents

Selected examples

Figure 1. Proposed catalytic cycle for copper-promoted SnAP reactions⁷ 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.

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.

Based on the estimated potentials for oxidation of the carbon-tin bond¹² 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 condition (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 co-solvent 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 minutes 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 with no need for additives or changes to the reaction conditions, making this protocol more general and appealing than the Cu-based catalytic condition⁷ 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. For certain highly hydrophobic imines, a mixture of 1:1 CH_2Cl_2 /TFE was employed instead of CH_3CN .

Table 1. Optimization of Reaction Conditions for Photocatalytic SnAP reactions.

Im-6a

6a

$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**1**)
 $Ir(III)^+/Ir(II) = +1.21 \text{ V}$
 $Ir(III)/Ir(II) = -1.37 \text{ V}$

$Ir(ppy)_2(dtbbpy)PF_6$ (**2**)
 $Ir(III)^+/Ir(II) = +0.66 \text{ V}$
 $Ir(III)/Ir(II) = -1.51 \text{ V}$

2CzIPN (**3**)
 $(PC^+/PC^{\bullet-}) = +1.36 \text{ V}$
 $(PC/PC^{\bullet-}) = -1.51 \text{ V}$

Triphenylpyrylium (**4**)
 $(PC^+/PC^{\bullet-}) = +2.3 \text{ V (T1)}$
 $(PC/PC^{\bullet-}) = -0.35 \text{ V}$

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

^aConversion (conv) and yield were measured from 1H NMR using 1,3,5-trimethoxybenzene as an internal standard. ^bThe reaction

was performed in a glass vial under exposure to blue light (see Supporting Information). ^cUsed as a 1.0 M solution in DMF. TFE = 2,2,2-trifluoroethanol. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

Scheme 2. Substrate scope of N-heterocycles from aldehydes and SnAP reagents under continuous flow conditions.

^aFlow rate = 0.15 mL/min. ^bDiastereomeric ratio (d.r.) was determined from ¹H NMR spectroscopy of the unpurified reaction mixture. ^cCH₂Cl₂/TFE (1:1) was used as the solvent. ^dDiastereomeric ratio was not determined. Isolated yields were determined on 0.50 mmol reaction scale. MS = molecular sieves.

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 more sterically demanding aldehydes. The re-

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

Scheme 3. Gram scale synthesis of saturated N-heterocycles with continuous flow photochemistry.

Scheme 4. Unsuccessful cyclizations under photoredox conditions.

a) Unsuccessful reactions with naphthalene aldehydes

b) Over-oxidation of hindered SnAP reagent under photocatalytic 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.

Experimental procedures and characterization data (PDF)

AUTHOR INFORMATION

Corresponding Author

*Email: bode@chem.ethz.ch

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial support was provided by the Royal Thai Government Scholarship and the European Research Council (ERC Starting Grant 306793 – CASAA). We thank the LOC Mass Spectrometry Service and the LOC NMR Service of ETH Zurich. We also express our gratitude to Dr. Benedikt Wanner (ETH Zurich) and Dr. Anastasios Polyzos (University of Melbourne) for the construction of the photo-flow-reactor, and Dr. Michael Luescher, Dr. Tuo Jiang, Moritz Jackl, and Yayi Wang (ETH Zurich) for helpful discussions.

REFERENCES

- (1) (a) Luescher, M. U.; Geoghegan, K.; Nichols, P. L.; Bode, J. W. *Alldrichim. Acta* **2015**, *48*, 43–48. (b) Vo, C.-V.; Mikutis, G.; Bode, J. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 1705–1708. (c) Luescher, M. U.; Vo, C.-V.; Bode, J. W. *Org. Lett.* **2014**, *16*, 1236–1239. (d) Vo, C.-V.; Luescher, M. U.; Bode, J. W. *Nat. Chem.* **2014**, *6*, 310–314. (e) Luescher, M. U.; Bode, J. W. *Org. Lett.* **2016**, *18*, 2652–2655.
- (2) (a) Davies, A. G. *Organotin Chemistry*, 2nd Edition, Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004, pp. 387–388. (b) Kimbrough, R. D. *Environ. Health Perspect.* **1976**, *14*, 51–56. (c) Sunday, A. O.; Alafara, B. A.; Oladele, O. G. *Chem. Speciation Bioavailability* **2012**, *24*, 216–226.
- (3) (a) P. T. Anastas and M. M. Kirchhoff *Acc. Chem. Res.* **2002**, *35*, 686–694. (b) P. T. Anastas and R. Lankey. *Green Chemistry: Theory and Practice*, Oxford University Press: New York, 1998, pp. 30.
- (4) (a) Hsieh, S.-Y.; Bode, J. W. *Org. Lett.* **2016**, *18*, 2098–2101. (b) Hsieh, S.-Y.; Bode, J. W. *ACS Cent. Sci.* **2017**, *3*, 66–72. (c) Jackl, M. K.; Legnani, L.; Morandi, B.; Bode, J. W. *Org. Lett.* **2017**, *19*, 4696–4699.
- (5) Technology spotlight: SnAP reagent <https://www.sigmaaldrich.com/technical-documents/articles/technology-spotlights/snap-reagents.html>. (Accessed Dec 19, 2017).
- (6) (a) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, *117*, 11796–11893. (b) Cambià, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. *Chem. Rev.* **2016**, *116*, 10276–10341. (c) Neumann, M.; Zeitler, K. *Org. Lett.* **2012**, *14*, 2658–2661.
- (7) Luescher, M. U.; Bode, J. W. *Angew. Chem. Int. Ed.* **2015**, *54*, 10884–10888.
- (8) For recent reviews of photoredox catalysis: (a) Narayanan, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102–113. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363. (c) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166. (d) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898–6926. (e) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017**, *1*, 0052 (DOI: 10.1038/s41570-017-0052).
- (9) (a) Zhang, H.-H.; Yu, S. J. *Org. Chem.* **2017**, *82*, 9995–10006. (b) Patel, N. R.; Kelly, C. B.; Siegenfeld, A. P.; Molander, G. A. *ACS Catal.* **2017**, *7*, 1766–1770.
- (10) (a) Hager, D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 16986–16989. (b) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. *J. Am. Chem. Soc.* **2015**, *137*, 13768–13771. (c) Jeffrey, J. L.; Petronijević, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 8404–8407. (d) Fava, E.;

- Millet, A.; Nakajima, M.; Loescher, S.; Rueping, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6776–6779. (e) Kizu, T.; Uraguchi, D.; Ooi, T. *J. Org. Chem.* **2016**, *81*, 6953–6958.
- (11) Luescher, M. U. Ph.D. Dissertation, ETH Zurich (Zurich, Switzerland), 2017.
- (12) Yoshida, J.-i.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265–2299.
- (13) Wille, U.; Heuger, G.; Jargstorff, C. *J. Org. Chem.* **2008**, *73*, 1413–1421.
- (14) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712–5719.
- (15) Luo, J.; Zhang, J. *ACS Catal.* **2016**, *6*, 873–877.
- (16) (a) Akaba, R.; Sakuragi, H.; Tokumaru, K. *J. Chem. Soc., Perkin Trans. 2* **1991**, *3*, 291–297. (b) Wang, Y.; Haze, O.; Dinnocenzo, J. P.; Farid, S.; Farid, R. S.; Gould, I. R. *J. Org. Chem.* **2007**, *72*, 6970–6981.
- (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 0.20–0.25 mL/min.