



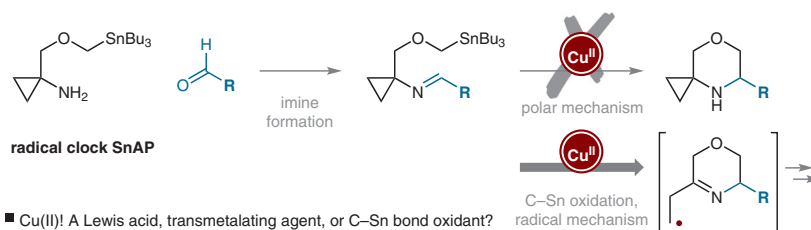
Evidence for a Radical Mechanism in Cu(II)-Promoted SnAP Reactions

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Dedicated to a great mentor and teacher – Rick L. Danheiser

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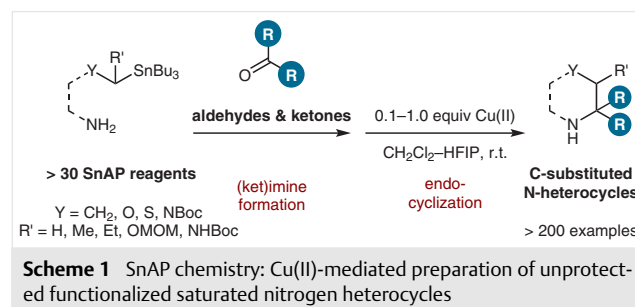
Abstract Saturated nitrogen heterocycles can be found with increasing abundance in bioactive molecules despite a limited number of methods to access these scaffolds. However, the coupling of recently introduced SnAP [tin (Sn) amine protocol] reagents with a wide range of aldehydes and ketones has proven to be a reliable, practical, and versatile one-step approach to saturated N-heterocycles. While effective, the lack of mechanistic understanding limits efforts to develop new catalytic and enantioselective variants. To distinguish between a polar or radical mechanism, we assessed Lewis and Brønsted acids, radical trapping experiments, and radical clock SnAP reagents reinforcing the current understanding of the SnAP protocol as a radical cyclization.

Key words SnAP reagents, N-heterocycles, morpholines, cyclization, radical clock, mechanism

Tin (Sn) amine protocol (SnAP) reagents are simple building blocks used for the direct transformation of aldehydes and ketones into saturated five- to nine-membered N-heterocycles such as substituted unprotected pyrrolidines, (thio)morpholines, piperazines, piperidines, oxazepanes, and diazepanes (Scheme 1).² The SnAP protocol is distinguished by a broad substrate scope tolerating aromatic, heteroaromatic, and aliphatic aldehydes, including substrates bearing various functional groups such as unprotected indoles, phenols, esters, nitriles, and halides under simple, robust, and consistent reaction conditions.

The key C–C bond forming reaction featured in SnAP chemistry relies on the addition of an organotin species to an imine, an underutilized transformation because of the poor electrophilicity of unfunctionalized and therefore unactivated imines. Circumventing the poor electrophilicity of imines through the use of an intramolecular reaction and avoiding the fundamental problems that are associated

with the addition of strong nucleophiles to C=N functionalities, e.g. aza-enolization or poor functional group tolerance,³ SnAP reagents with their α -heteroatom C(sp³)-Sn nucleophiles have emerged as valuable tools in the preparation of functionalized unprotected saturated heterocycles suitable for immediate further elaboration.²



Circumstantial evidence, including the reluctance of chelating imines as **3** to participate in the reaction (Scheme 2, a) and the ability to conduct the SnAP chemistry under photocatalytic conditions,⁴ strongly supports a radical mechanism. We have therefore favored a mechanistic scheme for the Cu-promoted reactions in which Cu^{II} acts as a one-electron oxidant.^{2a} While this radical-based mechanism for the SnAP reagents rationalizes most of the observations, further studies were required to strengthen our proposal.

We have previously shown that substoichiometric amounts of radical inhibitors such as BHT or TEMPO retarded the reaction and alkoxamines arising from possible intermediate radicals were obtained by using stoichiometric amounts of TEMPO.^{2a} With use of SnAP M for the preparation of morpholines rather than SnAP TM for the preparation of thiomorpholines as in our original publication, the

radical inhibitor experiments were repeated here by using SnAP reagents with lower oxidation potentials (Scheme 2, b) and similar results were obtained.

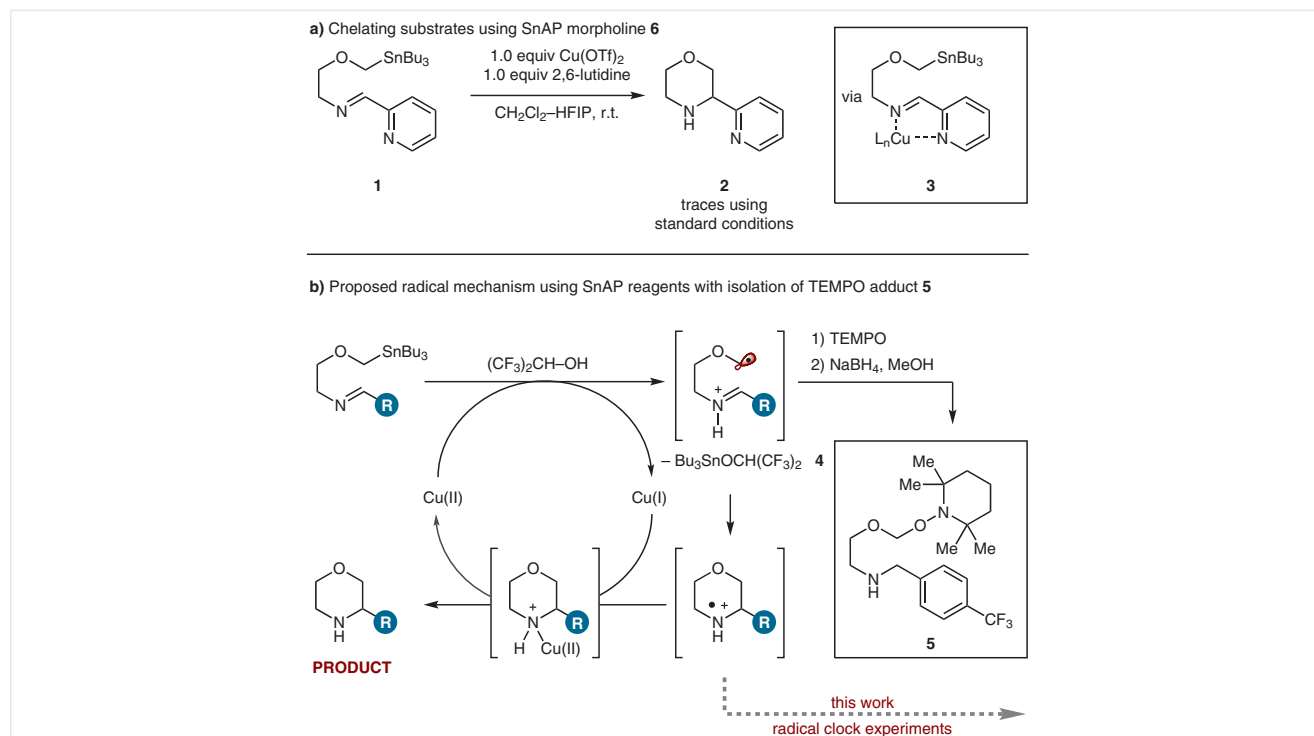
Although the observation of alkoxyamine adduct **5** from the addition of TEMPO is indicative of a radical process, it could also arise from an unproductive side reaction, such as the disproportionation of an organo-copper intermediate after transmetalation or trapping of an oxonium after further redox reactions.^{5,6} Bærendts, for example, has shown that CuX_2 -TEMPO can behave as an ionic electrophile by single-electron pairing of CuX_2 and TEMPO forming a reactive oxidant that releases Cu(I) and a nucleophile-TEMPO adduct after the reaction with a two-electron nucleophile.⁷ The isolation of such an adduct might therefore represent a side reaction that is not connected to the productive Cu(II) -mediated conversion, emphasizing the need for additional experiments aimed at elucidating the mechanism of the SnAP reaction.

Furthermore, a Lewis acid-mediated mechanism can be excluded on the basis of the aforementioned experiments and failure to afford the desired product in previous experiments. However, investigations aimed at separating Lewis and Brønsted acid mechanisms needed to be carried out to further exclude a polar mechanism because Cu(OTf)_2 with its weakly coordinating counterions is known to be a source of triflic acid (TfOH) acting as a Brønsted acid under conditions proposed to involve metal catalysis.⁸

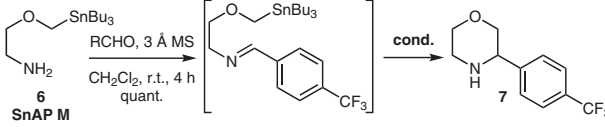
In this report, we describe our investigations into further separating H^+ - and Lewis acid-mediated mechanisms from a reaction pathway involving single-electron species with a radical clock SnAP reagent aimed to trap possible intermediate radicals further down the reaction after a successful cyclization.

As a Lewis acid-mediated mechanism was excluded in earlier experiments,^{2a,b} investigations aimed at elucidating the possibility of a Brønsted acid-mediated SnAP reaction mechanism were carried out (Table 1).

The standard SnAP reaction (Table 1, entry 1) involves the addition of stoichiometric quantities of a weak base, 2,6-lutidine, that is proposed to act as a ligand and form the active copper species. Leaving out 2,6-lutidine, which could interfere with a potential Brønsted acid-mediated mechanism, resulted in a decreased yield of the desired product **7** (entry 2). Furthermore, other Lewis acids known to be a source of triflic acid⁸ were unsuccessful in mediating the SnAP cyclization leaving Cu(OTf)_2 as the sole active mediator under these conditions (entries 2–5). To further dismiss a Brønsted acid-mediated mechanism, the addition of excess 2,6-di-*t*-butylpyridine, a weak base that binds protons but is unable to coordinate to metal centers because of the sterically demanding *t*-butyl groups,⁹ only retarded the reaction, affording the desired product in moderate amounts (entry 6). Experiments in which TfOH was used in place of



Scheme 2 Experiments supporting a role for Cu(OTf)_2 as an oxidant rather than as a Lewis acid; see Supporting Information for more detailed TEMPO and BHT studies

Table 1 Screening for Brønsted Acid-Mediated Cyclization


Entry	Conditions ^a	Results ^b
1 ^c	Cu(OTf) ₂ (1.0 equiv), 2,6-lutidine (1.0 equiv)	88% with 100% conv.
2	Cu(OTf) ₂ (1.0 equiv)	65% with 100% conv.
3	Bi(OTf) ₃ (1.0 equiv)	≤ 5% with ≤ 10% conv.
4	Yb(OTf) ₃ (1.0 equiv)	≤ 5% with ≤ 5% conv.
5	Sc(OTf) ₃ (1.0 equiv)	≤ 5% with ≤ 5% conv.
6	Cu(OTf) ₂ (1.0 equiv), 2,6-di- <i>t</i> -butylpyridine (2.5 equiv)	21% with 30% conv.
7	TfOH (1.0 equiv)	≤ 5% with 28% ^d
8	TfOH (2.5 equiv)	ca. 5% with 52% ^d
9	TfOH (2.5 equiv) ^e	6% with 48% ^d
10	TfOH (5.0 equiv)	ca. 6% with 93% ^d

^a Reactions were conducted on a 0.15 mmol scale at 23 °C for 8 h in CH₂Cl₂-HFIP (4:1, 0.05 M).

^b NMR yields and conversion (conv.) from ¹H NMR spectroscopic measurements of unpurified reaction mixtures with 1,3,5-trimethoxybenzene as an additional internal standard added after the reaction.

^c Standard SnAP conditions.

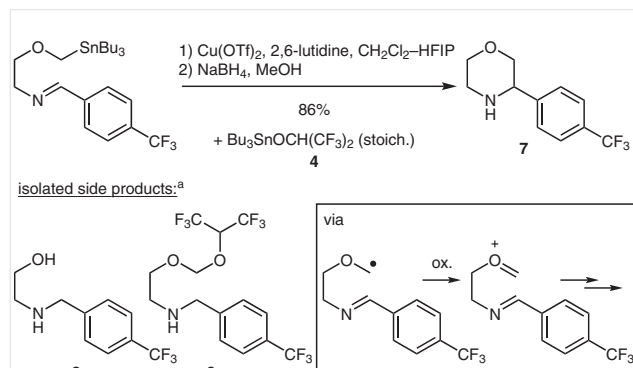
^d Imine hydrolysis as a side reaction.

^e Slow addition over 8 h.

Cu(OTf)₂ afforded some product (entries 7–10). Although Cu(OTf)₂ is known to be a source of slowly released TfOH in certain protic reaction media, there seems to be no correlation between the addition of TfOH at the beginning of the reaction or over the course of it (entries 8–10). This indicates that, although some product formation through a H⁺-mediated mechanism could occur, on the basis of our current understanding we exclude polar mechanisms as the principal source of product formation.

Excluding a Lewis or Brønsted acid-mediated mechanism, we started looking more closely into the idea of Cu(OTf)₂ acting as an oxidant, as proposed in the seminal SnAP publication.^{2a} The main side product isolated seems to arise from intermediates in which the C–Sn bond was oxidized to give an oxonium (Scheme 3). A free radical intermediate, which could arise through direct C–Sn bond oxidation or the disproportionation of in situ formed organo-copper intermediate after transmetalation (rather than the involvement of a polar two-electron species), was further supported through the loss of stereochemical information in reactions using α -bis substituted SnAP reagents. Racemic SnAP reagents bearing both a heteroatom and an alkyl substituent next to the organostannane group undergo stereoconvergent cyclizations in combination with enantiopure

PhBox ligands.^{2e} Likewise, enantiomerically enriched α -bis substituted SnAP-eX reagents afforded racemic 2,3-disubstituted piperidines by using the standard conditions.^{2f}

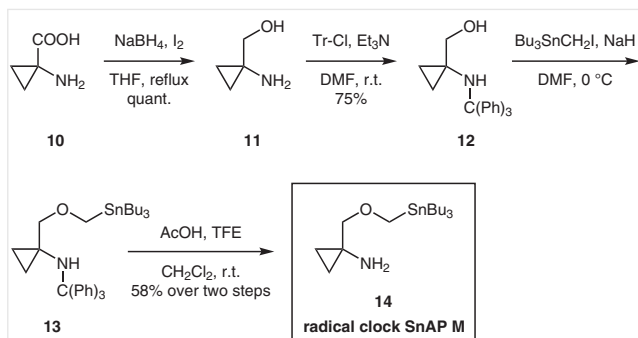
**Scheme 3** Side product formation through an oxidative mechanism.

^a Dimeric structures were not detected in the crude ¹H NMR spectrum as confirmed through independent synthesis (see Supporting Information).

Organostannanes are known to undergo bond fragmentation upon one-electron oxidation giving an organic radical and a stannylum cation fragment,^{10,11} a fragment that was previously isolated as the HFI-adduct **4**.^{2e} Not surprisingly, unsymmetrically substituted stannanes would lead to the formation of the most stable organic radical upon such oxidative fragmentations affording an α -heteroatom-stabilized alkyl radical by using SnAP reagents. Therefore, the postulated mechanistic picture (Scheme 2, b) in which the C–Sn bond is oxidized through a Cu(II) species is proposed to involve an α -heteroatom-stabilized carbon-centered radical. Such a radical is proposed to react in an intramolecular reaction with the imine LUMO being located on the azomethine carbon forming a nitrogen-centered radical.

Trapping of such an open-shell intermediate would provide strong support for a radical cyclization. On the basis of this assumption and to provide further evidence that a free radical intermediate is generated during the SnAP reaction, radical clock experiments aimed at trapping the proposed nitrogen-centered radical were conducted. With the knowledge that the addition of N-centered radicals onto alkenes in general is relatively slow, fragmentations that produce a relatively stable imine π -bond were investigated over the addition of N-centered radicals onto olefins.¹² To make sure that our radical indicator reactions are fast enough to compete with processes that intercept the proposed intermediates, an SnAP reagent for nitrogen radical fragmentation with known fast kinetics was designed.¹³

The unsubstituted cyclopropane analogue was synthesized in a short reaction sequence (Scheme 4). Starting from 1-amino-1-cyclopropane carboxylic acid, reduction, nitrogen protection, alkylation, and deprotection provided radical clock SnAP morpholine **14**. To examine our hypothesis, an imine formed from the radical clock SnAP reagent



Scheme 4 Preparation of radical clock SnAP reagent

was employed under standard SnAP cyclization conditions. As ring opening of the cyclopropane would afford unstable imine products, NaBH₄ reduction was performed on the crude material. Subsequent detection and isolation of ring-opened products arising from either reduction **15** or oxidation **16** of the intermediate ring-opened radical reinforce the proposal of an open-shell SnAP cyclization (Scheme 5).

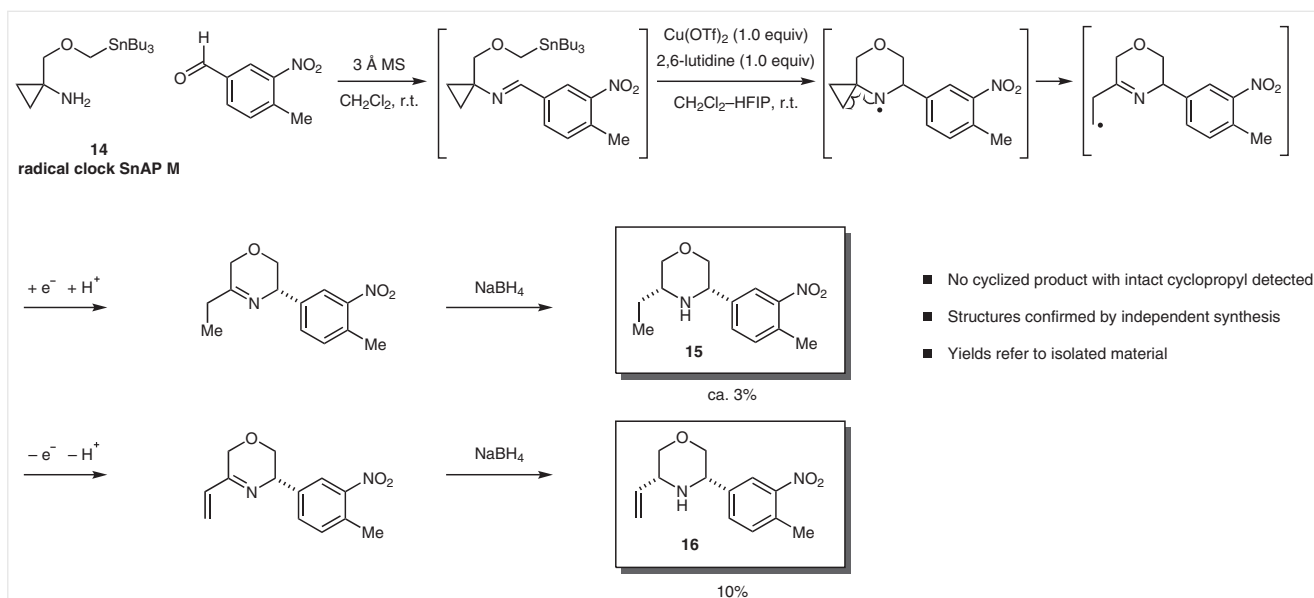
The structures of the isolated products were confirmed by their independent preparation (Scheme 6). The amino alcohol required for the synthesis of the vinyl SnAP reagent **23** was obtained through a diastereoselective addition of vinylmagnesium bromide to N-sulfinyl imine **18**¹⁴ followed by simultaneous amine and alcohol deprotection. Cyclization using SnAP morpholine reagent **23** under the same conditions as in the radical clock experiment afforded *cis*-2,6-disubstituted morpholine **16**, confirming the structure of the ring-opened product isolated from the radical clock experiment (Scheme 6, a). Furthermore, SnAP 3-Vinyl M **23**

demonstrates for the first time that the proposed nucleophilic α -heteroatom-stabilized radical preferentially reacts in a 6-endo-trig manner with a C=N double bond affording a stabilized nitrogen-centered radical which is preferred over the 5-exo-trig or 6-endo-trig addition onto an alkene. This is also observed for the preparation of medium-sized N-heterocycles with use of SnAP 3-Vinyl OA **24** by the 7-endo-trig addition onto an imine which is preferred over the 5-exo-trig or 6-endo-trig addition onto an internal alkene (Scheme 6, b).

The structure of *cis*-2,6-disubstituted morpholine **15** was confirmed in a short reaction sequence by using 2-aminobutanol **26** (Scheme 6, c). By using a reported O-stannylmethylation procedure of α -disubstituted aminoalcohols,^{15b} SnAP 3-Et M **27** reagent was prepared in one step (Scheme 6, c). With use of the same cyclization conditions as in the radical clock experiment, *cis*-2,6-disubstituted morpholine **15** was obtained in 82%, confirming the structure of the ring-opened product isolated from the radical clock experiment.

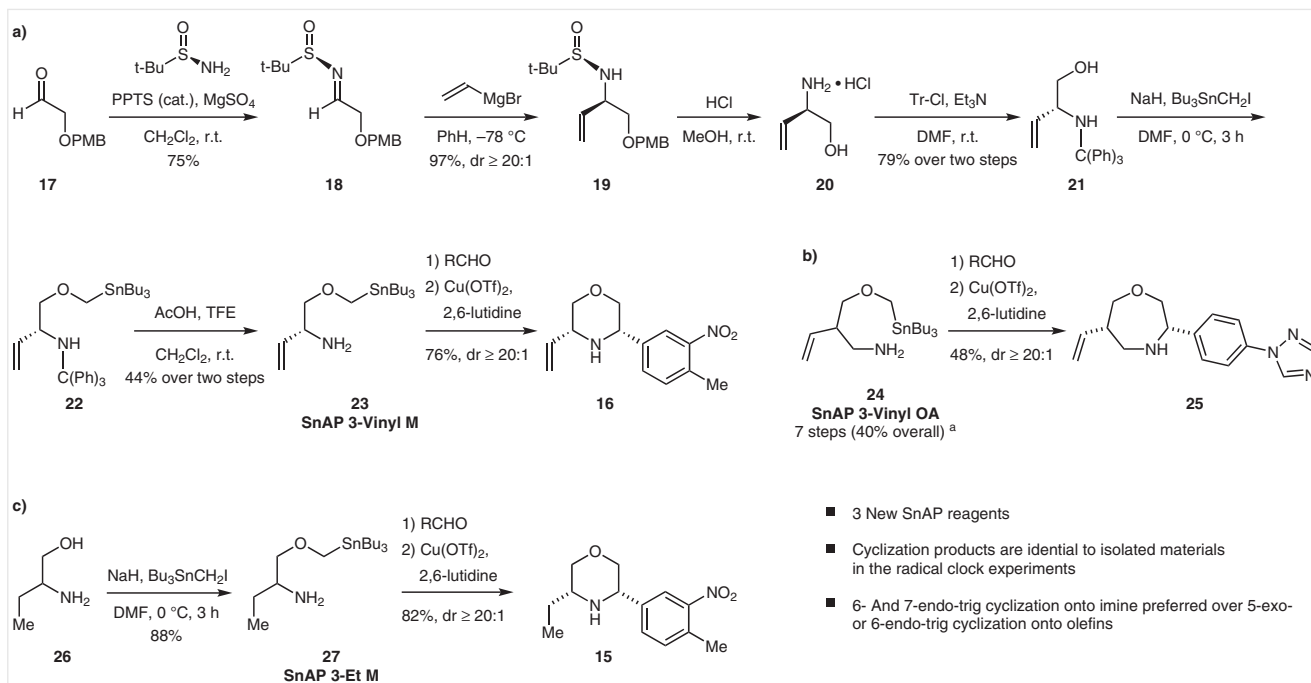
Finally, additional control experiments were performed to confirm that the ring-opened products are the direct results of a radical cyclization and subsequent cyclopropane fragmentation and test the stability of the cyclopropane scaffold under the reaction conditions applied (Scheme 7).

Destannylated starting material and side products arising from C–Sn bond oxidation were detected, but no ring-opened products were observed when the radical clock SnAP **14** was subjected to the standard cyclization conditions without prior imine formation (Scheme 7, a). Substituting the labile Bu₃Sn group in SnAP **14** to remove a potential source of unwanted side reactions and focus on the

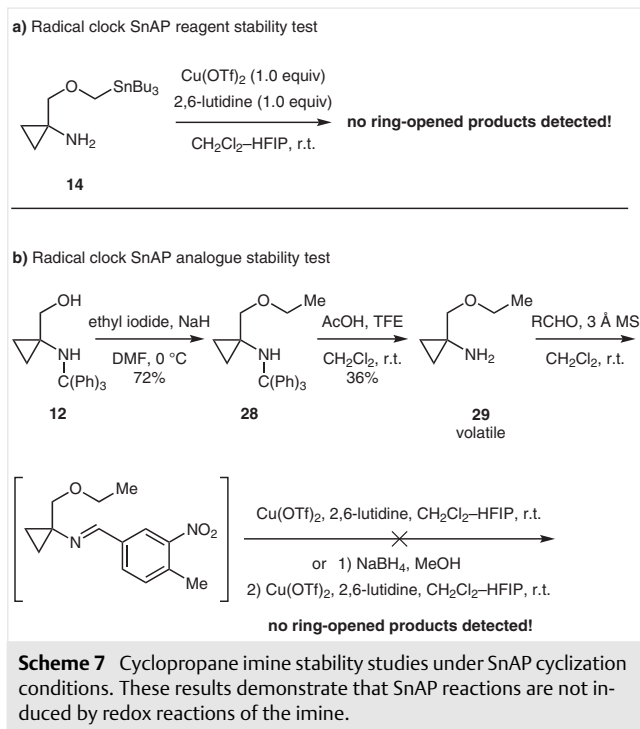


Scheme 5 Radical clock SnAP reaction to detect nitrogen-centered radicals upon successful cyclization

- No cyclized product with intact cyclopropyl detected
- Structures confirmed by independent synthesis
- Yields refer to isolated material



Scheme 6 Preparation of radical clock SnAP products by using alkyl- and alkenyl-SnAP reagents. ^a See Supporting Information for the preparation of SnAP 3-Vinyl OA **24**



stability of the imine and secondary amine of potential product, (ethoxymethyl)cyclopropanamine **29** was prepared (Scheme 7, b). No cyclopropane fragmentation

was observed by using **29** either as the imine or as the secondary amine after imine reduction, again supporting our proposal of a radical-based SnAP cyclization.

Considering the above results and the additional properties of HFIP to assist in intermolecular electron-transfer reactions through stabilization of radical cations, which extends their lifetime and facilitates subsequent fragmentations,¹⁶ through an HFIP nucleophile-assisted cleavage of a stannane radical cation,¹⁷ also seen in organosilane-cation radicals,¹⁸ strong support is found for the current proposal of a radical cyclization using SnAP reagents (Scheme 2, b). The fact that little conversion is observed without the addition of HFIP^{2a} and the finding that $\text{Bu}_3\text{Sn}-\text{OCH}(\text{CF}_3)_2$ **4** is formed in a 1:1 ratio to the desired N-heterocycle^{2e} further reinforce this mechanistic proposal, which might also be driven by the formation of the thermodynamically strong Sn–O bond (ca. 550 kJ mol⁻¹) vs. Sn–C (ca. 235 kJ mol⁻¹) that could facilitate fragmentation.¹⁹

In conclusion, several observations documented in these studies are consistent with the initial mechanistic proposal of the SnAP protocol as a radical-based method.²⁰ As $\text{Cu}(\text{OTf})_2$ is known to be a source of triflic acid, investigations on the role of a Brønsted acid-mediated mechanism allowed us to exclude this, as well as a Lewis acid-mediated process. Taken together, the further evidence of the radical-based nature of SnAP chemistry will guide ongoing efforts to develop new variants and selective catalysts.

Funding Information

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611670>.

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- General Procedure SnAP Protocol**
Imine formation: To a solution of the SnAP reagent (0.50 mmol, 1.00 equiv) in CH₂Cl₂ or acetonitrile (3.0 mL) at r.t. was added the corresponding aldehyde (0.50 mmol, 1.00 equiv) and 3 Å or 4 Å MS powder (ca. 50 mg). The reaction mixture was stirred at r.t. for 4 h and filtered through a short layer of Celite (CH₂Cl₂ rinse). The filtrate was concentrated under reduced pressure to afford the pure air-stable imine that was used in the next step without further purification.
SnAP cyclization: Separately, anhydrous Cu(OTf)₂ (0.50 mmol, 1.00 equiv) was suspended in CH₂Cl₂-HFIP (3:1; 8.0 mL). 2,6-Lutidine (0.50 mmol, 1.00 equiv) was added and the resulting bluish suspension was stirred at r.t. for 1 h to afford a dark green suspension. A solution of the imine (0.50 mmol, 1.00 equiv) in CH₂Cl₂ (2.0 mL) was added in one portion and the resulting mixture was stirred at r.t. for 12 h. The reaction mixture was diluted with CH₂Cl₂ (20 mL), treated with a solution of 12% aq NH₄OH and brine (1:1, 20 mL), and stirred vigorously for 20 min at r.t. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layers were washed with H₂O (2 x 5 mL) and brine (10 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography afforded the desired C-substituted unprotected morpholines.
Spectral Data for Selected Compounds
3-(4-(Trifluoromethyl)phenyl)morpholine (7): Yield: 98.5 mg (86%); clear colorless oil; IR (thin film): 3313, 3068, 2961, 2912, 2889, 2852, 1676, 1603, 1584, 1398, 1365, 1335, 1232, 1105 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.59 (d, J = 8.2 Hz, 2 H), 7.52 (d, J = 8.2 Hz, 2 H), 3.99 (dd, J = 10.0, 3.2 Hz, 1 H), 3.93–3.85 (m, 1 H), 3.81 (dd, J = 11.1, 3.2 Hz, 1 H), 3.65 (td, J = 11.1, 2.7 Hz, 1 H), 3.35 (dd, J = 11.1, 10.0 Hz, 1 H), 3.14 (td, J = 11.6, 3.3 Hz, 1 H), 3.01 (dt, J = 11.8, 2.0 Hz, 1 H), 1.90 (br s, NH); ¹³C NMR (100 MHz, CDCl₃): δ = 144.7 (q, J_{CF} = 1.40 Hz), 130.1 (q, J_{CF} = 32.4 Hz), 127.7, 125.6 (q, J_{CF} = 3.72 Hz), 124.2 (q, J_{CF} = 272.2 Hz), 73.6, 67.4, 60.3, 46.5; R_f = 0.18 (hexanes/EtOAc 1:1); ESI-HRMS: m/z [M + H] calcd for C₁₁H₁₃F₃N₁O₁: 232.0944; found: 232.0946.
(±)-cis-3-Ethyl-5-(4-methyl-3-nitrophenyl) morpholine (15): Yield: 102 mg (82%, d.r. > 20:1); colorless oil; IR (thin film): 2963, 2932, 2878, 2848, 1528, 1454, 1349, 1105 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 8.03 (d, J = 1.8 Hz, 1 H), 7.52 (dd, J = 7.9, 1.8 Hz, 1 H), 7.29 (d, J = 7.9 Hz, 1 H), 4.01 (dd, J = 10.2, 3.2 Hz, 1 H), 3.84 (dd, J = 10.9, 3.0 Hz, 1 H), 3.78 (dd, J = 11.0, 3.2 Hz, 1 H), 3.28–3.14 (m, 2 H), 2.96–2.85 (m, 1 H), 2.56 (s, 3 H), 1.89 (br s, NH), 1.50–1.27 (m, 2 H), 0.94 (t, J = 7.5 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ = 149.5, 147.4, 140.3, 132.9, 132.7, 132.0, 123.4, 73.2, 72.0, 59.7, 56.8, 25.5, 20.2, 10.1; R_f = 0.30 (hexanes/EtOAc 1:1); ESI-HRMS: m/z [M + H]⁺ calcd for C₁₃H₁₉N₂O₃: 251.1390; found: 251.1394.

(3S,5R)-3-(4-Methyl-3-nitrophenyl)-5-vinylmorpholine (16):

Yield: 94.4 mg (76%, d.r. > 20:1); colorless oil; IR (thin film): 2988, 2849, 1738, 1528, 1275, 1261, 1102 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 8.06 (d, J = 1.8 Hz, 1 H), 7.55 (dd, J = 7.9, 1.8 Hz, 1 H), 7.30 (d, J = 7.9 Hz, 1 H), 5.77 (ddd, J = 17.3, 10.4, 6.8 Hz, 1 H), 5.35 (dt, J = 17.3, 1.4 Hz, 1 H), 5.23–5.12 (m, 1 H), 4.07 (dd, J = 10.2, 3.2 Hz, 1 H), 3.81 (td, J = 10.4, 3.2 Hz, 2 H), 3.65–3.50 (m, 1 H), 3.33–3.19 (m, 2 H), 2.58 (s, 3H), 1.93 (br s, NH); ^{13}C NMR (100 MHz, CDCl_3): δ = 149.5, 140.1, 136.5, 133.1, 133.0, 132.0, 123.5, 117.6, 72.9, 71.3, 59.2, 58.6, 20.3; R_f = 0.68 (hexanes/EtOAc 1:1); ESI-HRMS: m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}_3$: 249.1234; found: 249.1231.

(±)-cis-3-[4-(1H-1,2,4-Triazol-1-yl)phenyl]-6-vinyl-1,4-oxaz-

epane (25): Yield: 64.5 mg (48%, d.r. > 20:1); colorless oil; IR (thin film): 3433, 2938, 2857, 1638, 1522, 1280, 1144, 983, 836 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 8.53 (s, 1 H), 8.09 (s, 1 H), 7.63 (d, J = 8.5 Hz, 2 H), 7.51 (d, J = 8.5 Hz, 2 H), 5.91 (ddd, J = 17.3, 10.5, 8.1 Hz, 1 H), 5.14–5.00 (m, 2 H), 4.13–3.97 (m, 3 H), 3.56 (dd, J = 12.4, 9.6 Hz, 1 H), 3.43 (dd, J = 13.0, 10.5 Hz, 1 H), 3.24 (dd, J = 13.9, 4.9 Hz, 1 H), 3.12 (dd, J = 13.9, 3.5 Hz, 1 H), 2.77–2.66 (m, 1 H), 2.09 (br s, NH); ^{13}C NMR (100 MHz, CDCl_3): δ = 152.7, 141.6, 141.0, 138.8, 136.4, 128.6, 120.3, 115.6, 80.6, 75.5, 66.3, 51.9, 47.2; R_f = 0.21 (hexanes/EtOAc 2:1); mp = 70–72 °C; ESI-HRMS: m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{N}_4\text{O}_1$: 271.1553; found: 271.1558.