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Copper Promoted Oxidative Coupling of SnAP Hydrazines and Aldehydes to Form Chiral 1,4,5-Oxadiazepanes and 1,2,5-Triazepanes

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Dedicated to Prof. Albert Padwa on the Occasion of his 80th Birthday

SnAP (Sn (tin) amine protocol) hydrazine reagents and aldehydes undergo oxidative, copper mediated coupling to form substituted 1,4,5-oxadiazepanes and 1,2,5-triazepanes. Unlike all prior reactions involving SnAP reagents, the SnAP hydrazine reagents undergo a molecular oxygen-assisted oxidative cyclization. The air- and moisture tolerant transformation accommodates a broad range of groups including electron-rich, electron-poor aromatic, heteroaromatic, and aliphatic aldehydes and is amenable to gram scale synthesis. These unusual, chiral heterocycles have unexpectedly large optical rotations, which may find use in optical materials.

Keywords: N-Heterocycles • Saturated N-Heterocycles • Aldehydes • SnAP Reagents • Cross-Coupling • Radicals

Introduction

Saturated nitrogen heterocycles have attracted considerable attention due to their wide range of pharmacological activities.[1][2][3][4][5] A number of modern methods are devoted to their construction and impressive progress in hydroamination,[6][7][8][9] C–H functionalization,[10][11][12][13] α-lithiation[14][15][16][17] or annulation[18][19][20][21][22][23][24] methologies have improved access to these structures. To this end, our group has introduced SnAP (Sn (tin) amine protocol) reagents,[25][26][27][28][29][30] and SLAP (silicon amine protocol) reagents[31][32] for the one-step transformation of aldehydes and ketones to saturated, substituted, N-unprotected aza-heterocycles as thiomorpholines, morpholines, piperazines, piperidines,[30] pyrrolidines,[30] medium-sized rings, and spirocycles. These processes tolerate a broad range of functional groups and are well suited to lead development and the preparation of libraries of saturated nitrogen heterocycles (Figure 1).

In an attempt to apply the same principles to the construction of more diverse N-heterocyclic structures, we now document SnAP hydrazine reagents **1** and **2** for the preparation of substituted, NH-unsubstituted 1,4,5-oxadiazepanes and 1,2,5-triazepanes (Figure 1).[i] This is the first use of hydrazones, rather than imines, in SnAP chemistry and leads to oxidative cyclization – in contrast to overall redox neutral processes observed for all other examples.[25–30]

The seven-membered oxadiazepanes and triazepanes can be considered as homologues of morpholines and piperazines and are found in various bioactive small molecules directed against disease such as Alzheimer's,[33] diabetes,[34] bacterial infections,[35][36] and others.[37][38] However, methods for their preparation lag behind those for saturated six-membered N-heterocycles. Current synthetic approaches include annulation[22] and alkylation strategies of hydrazines and hydroxylamines,[24] or Lewis acid mediated cyclizations of nitrones.[23] While such approaches are suitable for the preparation of single compounds, substituent groups are introduced at the beginning of the synthetic endeavors, making them less appealing in drug development limiting their usefulness in the preparation of compound libraries.

[i] Although perhaps not strictly correct, we have identified our products as the saturated „diazepanes", rather than „diazepines", as this term is typically associated with higher oxidation states.

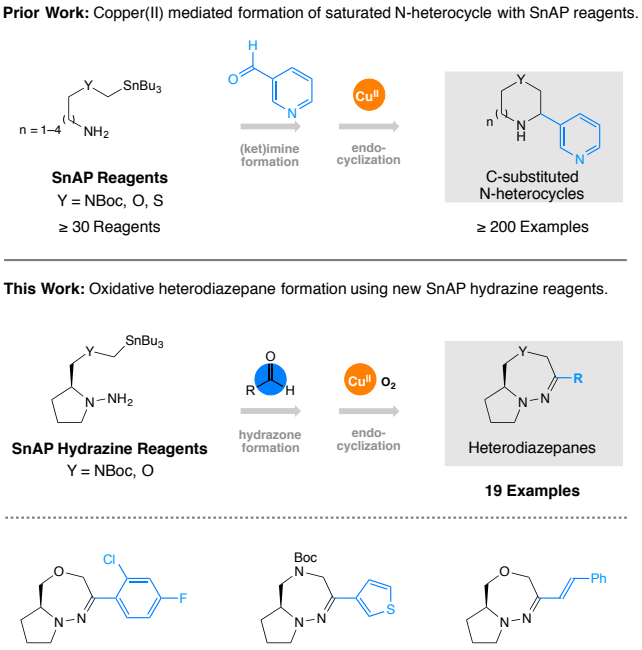
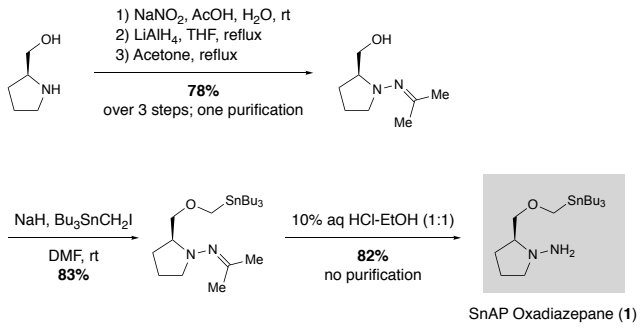


Figure 1: Preparation of saturated N-heterocycles using with SnAP reagents and oxidative synthesis of heterodiazepanes with hydrazine SnAP reagents.

Results and Discussion

Development of SnAP Hydrazine Reagents. As an initial attempt at developing SnAP hydrazine reagents, SnAP oxadiazepane reagent **1** was prepared from L-prolinol on a multigram scale using a straightforward, efficient route (Scheme 1), largely based on the pioneering work of Enders[39] and others on the synthesis of proline-derived hydrazines.[40] While stable at –10 °C for days, the unprotected ($R_2N–NH_2$) SnAP oxadiazepane (**1**) decomposes at room temperature within hours when stored neat.



Scheme 1. Preparation of SnAP oxadiazepane reagent **1**.

Instead, deprotection of the shelf stable hydrazone precursor and condensation with various aldehydes was carried out as a sequence with a single purification performed after the condensation. The freshly prepared oxadiazepane reagent **1** condensed with aromatic, heteroaromatic, and aliphatic aldehydes to give the corresponding hydrazones **3** (Scheme 2). Upon submitting these hydrazones to the standard stoichiometric SnAP conditions:[26–28] 1.0 equiv $Cu(OTf)_2$ and 1.0 equiv 2,6-lutidine in a mixture of 1,1,1,3,3,3-hexafluorisopropanol (HFIP) and CH_2Cl_2, moderate to good yields of oxadiazepanes were obtained. Interestingly, the resulting products were not the hydrazines, which would be expected from the analogous SnAP chemistry, but the oxadiazepane products arising from oxidative cyclization. The structure was confirmed by NMR studies, HRMS analysis, and X-ray diffraction of a single crystal of oxadiazepane **5a** (Figure 2).

No special precautions were taken for the reaction set-up, and all experiments were performed using identical conditions without substrate-specific optimization. HFIP, an additive used in SnAP protocols involving the amino tin SnAP reagents, believed to activate the imines for radical additions,[26,29] could be omitted out without a decrease in isolated yields. An observation that we attribute to the well-known characteristic of hydrazones as better radical acceptors than imines due to this additional stabilization of the intermediate nitrogen centered radical through the lone pair of the adjacent heteroatom.[41][42][43] However, the orbital overlap of the generated nitrogen-centered radical with adjacent heteroatom renders this intermediate hydrazine radical more nucleophilic, making it more susceptible to be oxidized through abundant Cu(II) than reduced through the Cu(I) formed in the first

step.[41–43][44] Furthermore, we believe that a possible protonation of the intermediate hydrazine radical through HFIP negatively affects the oxidation needed to afford the desired product.[31–32][44]

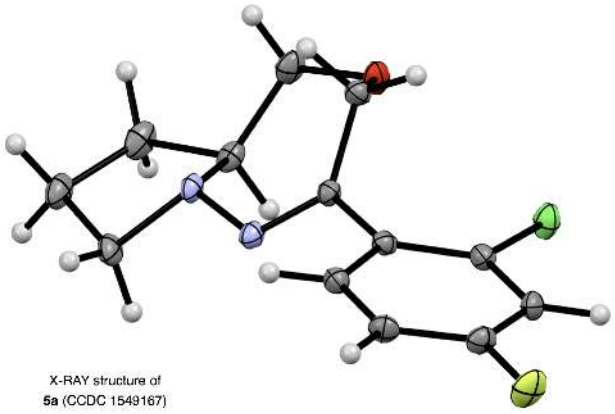
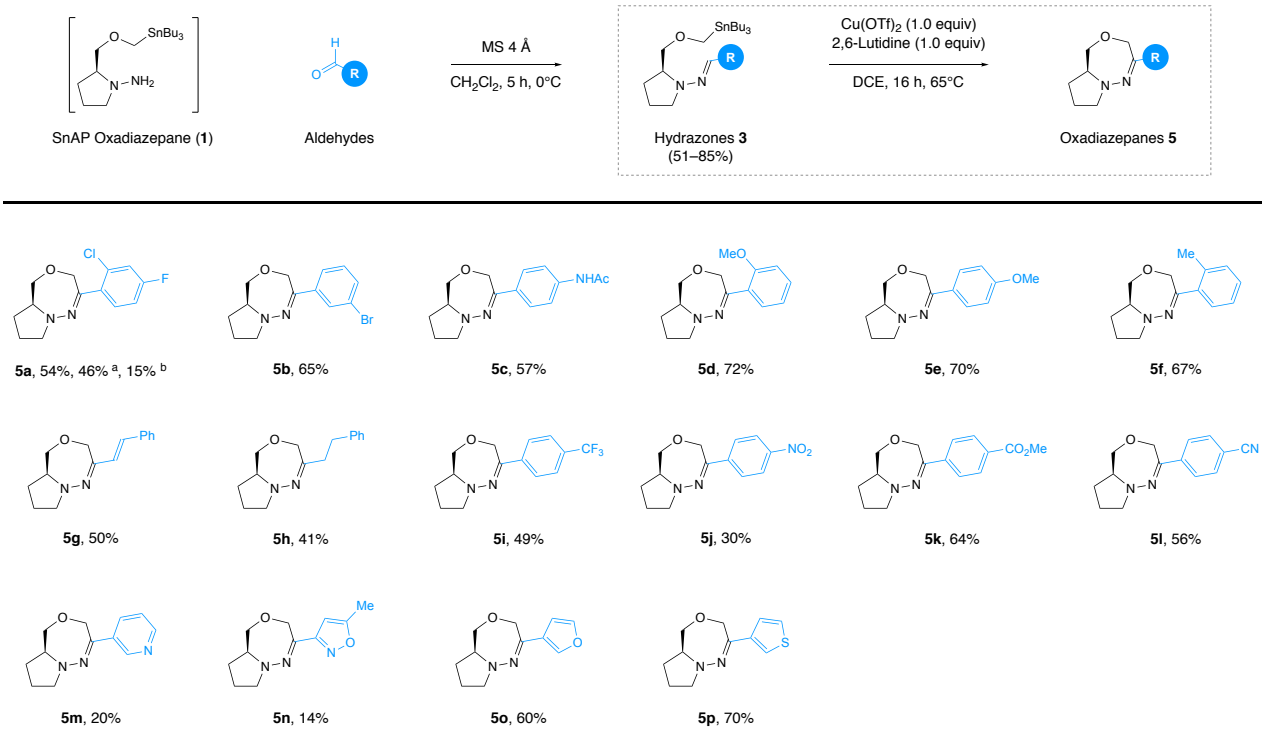


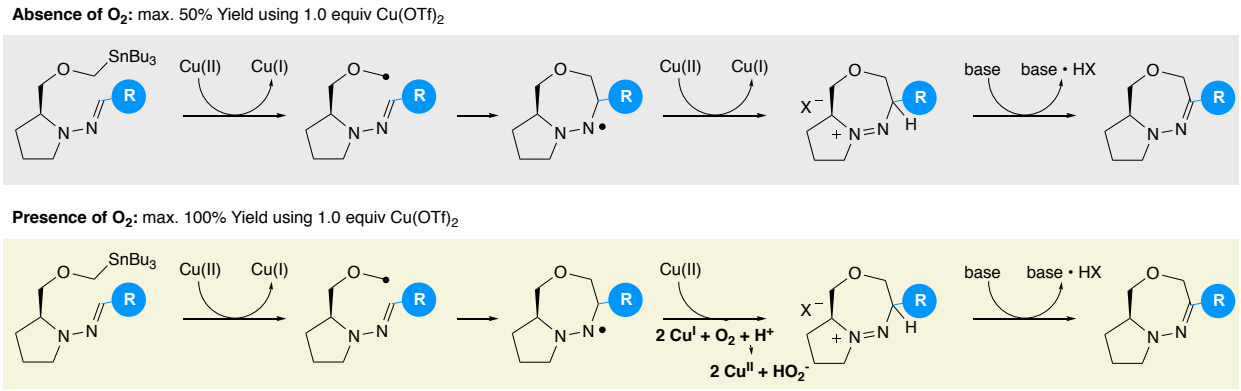
Figure 2: X-ray structure of (*S*)-2-(2-chloro-4-fluorophenyl)-5a,6,7,8-tetrahydro-3H,5H-pyrrolo[2,1-c][1,4,5]oxadiazepine (**5a**).



Scheme 2. Preparation of 1,4,5-oxadiazepanes from a SnAP hydrazine reagent **1** and aldehydes. Hydrazone formation conditions: SnAP Oxadiazepane (**1**) (1.0 equiv, 1.0 mmol), aldehyde (1.0 equiv, 1.0 mmol), MS 4 Å (100 mg), CH_2Cl_2 (0.2 M), 5 h, 0 °C. Cyclization conditions: $Cu(OTf)_2$ (1.0 equiv), 2,6-lutidine (1.0 equiv), DCE (0.05 M), 16 h, 65 °C; yields of isolated, chromatographically pure compounds are reported. [a]Reaction was performed in CH_2Cl_2:HFIP (4:1, 0.05 M). [b] Reaction was performed with rigorous exclusion of molecular O_2. DCE = 1,2-Dichloroethane. HFIP = 1,1,1,3,3,3-Hexafluoroisopropanol.

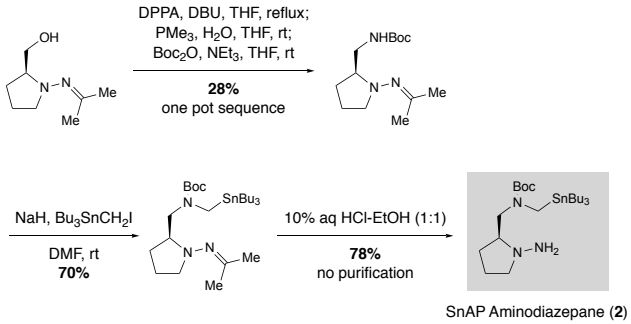
A salient feature of the general SnAP protocol is its high tolerance for functional groups;[26–30] the cyclization with oxadiazepane reagent **1** is no exception. Electron-rich, and electron-poor aromatic (**5a**, **5d**, **5e**, **5i**, **5j**), heteroaromatic (**5m**–**5p**), and aliphatic aldehydes (**5h**) containing halides (**5a**, **5b**), esters (**5k**), or nitriles (**5l**) at various positions of the aromatic rings, all were excellent substrates (Scheme 2). Unfortunately, using the current conditions, ketones proved to be inferior substrates, possibly due to their inability to participate in the oxidative cyclization. Attempts to use ketones as substrates afford only traces of desired the reduced hydrazines accompanied by destannylated side products. Using the same conditions, linear oxadiazepane SnAP reagents without elements in their backbone to favor cyclization turned out to be poor substrates, affording mostly destannylated side products. While this represents a limitation of this approach, the detection of small amounts of cyclized products using such linear reagents represents a good starting point for further ligand screening and reaction optimization to gain access to these scaffolds.

In light of the fact that the oxidized hydrazone products **5** are isolated as sole products and based on our current mechanistic picture of the SnAP protocols[26,29] as well as previous reports of copper mediated radical additions onto hydrazones,[45] we continue to favor a radical mechanism for the overall transformation (Scheme 3). Initial Cu(II) mediated oxidation of the organotin species generates Cu(I) and a heteroatom stabilized carbon-centered radical. This nucleophilic radical then adds to the hydrazone forming a stabilized nitrogen centered radical. Further oxidation – presumably by Cu(II) – leads to a cationic oxadiazepinium, which then undergoes proton abstraction restoring the hydrazone functional group. Endogenous molecular oxygen is presumed to re-oxidize the copper(I) species to copper(II) as reactions with rigorous exclusion of O_2 proceed sluggishly with poor yields (Scheme 2, **5a**), confirming the requirement of molecular oxygen for an effective cyclization. As proposed, this cyclization should be catalytic in Cu(II), however, we believe that coordination of the basic alkyl hydrazone products to Cu(II) leads to product inhibition. THe problem that was overcome for some of the SnAP amine reagents by the addition of excess HFIP.[29] This approach was not possible in the current casem as the addition of HFIP negatively affected the outcome of the reaction.



Scheme 3. Plausible SET based mechanistic picture.

Development of a SnAP Triazepane Reagent. A key feature of SnAP reagents is that the oxygen atom adjacent to the stannane group can be replaced with other heteroatoms lowering the oxidation potential of the C—Sn bond and stabilizing the resulting radical.[26–30] To test this in the present case, SnAP aminodiazepane reagent (**2**), for the synthesis of functionalized 1,2,5-triazepanes, was prepared by an analogous route (Scheme 4).



Scheme 4. Preparation of SnAP Aminodiazepane Reagent **2**.

To evaluate the formation of 1,2,5-triazepanes using SnAP aminodiazepane (**2**), we prepared the corresponding hydrazones **4a–c** from various (hetero)aromatic aldehydes (Figure 3a). Cyclization using identical conditions as for the preparation of the oxadiazepanes **5** afforded the desired 1,2,5-triazepanes **6a–c** in moderate isolated yields without further reaction optimization (Figure 3b).

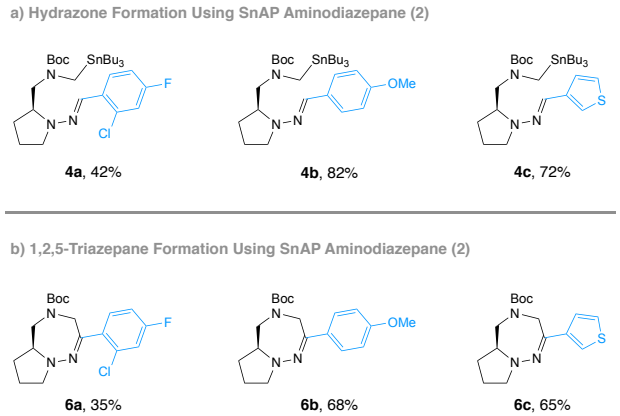


Figure 3. Synthesis of hydrazones and 1,2,5-triazepanes from aminodiazepane SnAP reagent **2**. Hydrazone formation reactions were performed using 1.0 equiv of SnAP **2** and 2.0 equiv of the aldehydes. Cyclization reactions were performed using 1.0 equiv $Cu(OTf)_2$, 1.0 equiv 2,6-lutidine in DCE (0.05 M) at 65 °C for 16 h.

Optical Properties of 1,4,5-Oxadiazepanes and 1,2,5-triazepanes. An unsual and unexpected property of the heterocycles prepared by this method is their high specific optical activity. The optical rotations of the chiral products measured under standard conditions were in between $[\alpha]_D$ = 300–1000, with some derivatives (e.g. **5g**) having rotation values of up to $[\alpha]_D$ = –2000. As anticipated, the compounds were also strongly active by CD spectrophotometries. Despite their high rotations, the compounds are colorless and may therefore find use in applications for transparent molecules with high specific optical rotation.

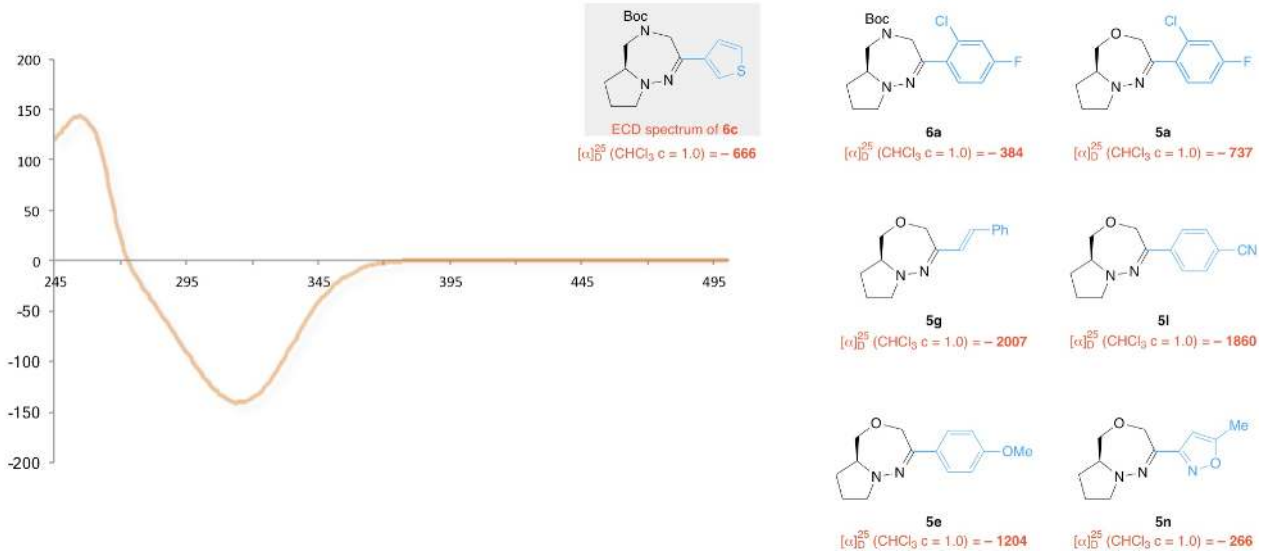


Figure 4. ECD spectrum of **6c** and optical rotation of selected N-heterocycles prepared using SnAP hydrazine reagents.

Conclusions

In conclusion, we have developed hydrazine-derived SnAP reagents and applied them to the conversion of aldehydes to seven-membered hetero diazepanes. Unlike all prior work in this area, these reagents gave products of oxidative cyclization, with preliminary studies implicating molecular oxygen as an oxidant. This approach to structurally attractive 1,4,5-oxadiazepanes and 1,2,4-triazepanes is characterized with a broad substrate scope with regard to the aldehydes starting materials; include electron-rich, electron-poor aromatic, heteroaromatic, and aliphatic aldehydes containing various functional groups. While, the limited stability of the NH-free hydrazine reagents likely precludes their storage and distribution in free form, they can be convenient stored in a hydrazone protected form. These reagents should find use in preparation of compound libraries for applications in medicinal chemistry or possibly the construction of new optical materials.

Experimental Section

General

Procedures: All reactions except the cyclization experiments were performed in dried glassware under an atmosphere of dry N_2, unless otherwise indicated. The generation of the N-heterocycles were performed under normal atmosphere. Reaction mixtures were stirred magnetically unless otherwise indicated and monitored by thin layer chromatography (TLC) on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates with visualization by fluorescence quenching at 254 nm. TLC plates were stained using potassium permanganate and ninhydrin solutions. Chromatographic purification of products (flash column chromatography) was performed on Silicycle Silica Flash F60 (230–400 Mesh) silica gel using a forced flow of eluent at 0.3–0.5 bar. Concentration of reaction product solutions and chromatography fractions under reduced pressure was performed by rotary evaporation at 35–40 °C at the appropriate pressure and then at rt, ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Yields given refer to chromatographically purified and spectroscopically pure compounds unless otherwise stated.

Materials: All chemicals were purchased from Acros, Aldrich, Fluka, Merck, ABCR, Maybridge, Fluorochem, TCI, Alfa Aesar or Strem and used as such unless stated otherwise. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane (CH_2Cl_2) was distilled from CaH_2 and stored over K_2CO_3 prior to use. N,N-Dimethylformamide (DMF) and tetrahydrofuran (THF) was purified by pressure filtration through activated alumina. 1,2-Dichloroethane (DCE) and 2,6-lutidine were used as purchased. Cu(OTf)2 was dried at 110 °C under high vacuum (ca. 0.1 mmHg) for 2 h and stored in desiccator for weeks. Yields given refer to chromatographically purified and spectroscopically pure compounds unless otherwise stated. Commercially available tributyl(iodomethyl)stannane was prepared according to a literature known procedure.

Instrumentation: Infrared (IR) spectra were recorded on a JASCO FT:IR-4100 spectrophotometer and reported as wavenumber (cm^{-1}) of the absorption maxima for the range between 4000 cm^{-1} and 750 cm^{-1} with only major peaks reported. Optical rotations were measured on a JASCO P-1010 operating at the sodium D line with a 100 mm path length cell. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz, 100 MHz spectrometer. ^1H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.26 ppm used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.16 ppm used as a standard) and $^{117, 119}Sn$–^{13}C couplings are not reported. All ^{13}C spectra were measured with complete proton decoupling. NMR coupling constants (J) are reported in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dddd, doublet of doublet of doublet of doublet; dt, doublet of triplet; dtd, doublet of triplet of doublet; t, triplet; td, triplet of doublet; tdd, triplet of doublet of doublet; tt, triplet of triplet; q, quartet; qd, quartet of doublet; m, multiplet. High-resolution mass spectrometric measurements (HRMS) were performed by the mass spectrometry service of the LOC at the ETHZ on Agilent 1200 (LC-MS), Bruker maXis for ESI-Q-TOF or Waters Micromass AutoSpec Ultima MassLynx 4.0 (GC-MS). Melting points were measured on an Electrothermal MeI-Temp melting point apparatus and are uncorrected.

General Hydrazone Formation

To an ice-cooled mixture of the SnAP diazepane reagent **1** or **2** (1.00 mmol, 1.00 equiv) and MS 4A. (100 mg / mmol) in CH_2Cl_2 (5.0 mL) was added the aldehyde (1.00–2.00 mmol, 1.00–2.00 equiv) in one portion. The reaction was stirred at 0 °C for 5 h, filtered to remove the molecular sieves (CH_2Cl_2 rinse), and concentrated under reduced pressure afforded the crude hydrazone. Purification by flash column chromatography on silica gel afforded the corresponding hydrazones **3**–**4** that was used in the cyclization step to access the hetero diazepanes **5**–**6**.

General Conditions for Cyclization

2,6-Lutidine (58 µL, 0.50 mmol, 1.00 equiv) was added dropwise to a suspension of anhydrous $Cu(OTf)_2$ (181 mg, 0.50 mmol, 1.00 equiv) and 1,2-dichloroethane (DCE, 5.0 mL). The suspension was stirred vigorously for 1 h at rt before the hydrazone (**3**–**4**; 0.50 mmol, 1.00 equiv) in DCE (5.0 mL) was added in one portion. The resulting mixture was stirred at 65 °C for 16 h. The reaction was allowed to cool to rt, 12% aq NH_4OH (10 mL) was added, and the resulting mixture was stirred vigorously for 15 min at rt. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O (2 x 10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography afforded the pure corresponding cyclized oxadiazepanes **5** or aminodiazepanes **6**.

(*S*)-2-(2-Chloro-4-fluorophenyl)-5a,6,7,8-tetrahydro-3*H*,5*H*-pyrrolo[2,1-*c*][1,4,5]-oxadiazepane (5a). Prepared according to the general cyclization reaction procedure from hydrazone **3a** (280 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:EtOAc 15:1) afforded

oxadiazepane **5a** (73 mg, 54% yield) as a white solid. **m.p.** = 83–85 °C; $[\alpha]_D^{26}$ (c = 1.0, $CHCl_3$) = –736.9; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 8.6, 6.1 Hz, 1 H), 7.12 (dd, *J* = 8.6, 2.6 Hz, 1 H), 6.97 (ddd, *J* = 8.6, 8.0, 2.6 Hz, 1 H), 4.60 (dd, *J* = 13.7, 0.9 Hz, 1 H), 4.18 (d, *J* = 13.7 Hz, 1 H), 4.04 (ddd, *J* = 11.5, 2.5, 0.9 Hz, 1 H), 3.66–3.53 (m, 2 H), 3.27 (dd, *J* = 11.5, 9.6 Hz, 1 H), 2.94 (apparent qd, *J* = 9.6, 2.5 Hz, 1 H), 2.11 (apparent dtd, *J* = 12.5, 8.2, 6.1 Hz, 1 H), 2.01–1.79 (m, 2 H), 1.59 (apparent dtd, *J* = 12.5, 9.1, 6.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.5 (d, J_{CF} = 250.8 Hz), 152.3, 135.0 (d, J_{CF} = 3.6 Hz), 133.5 (d, J_{CF} = 10.5 Hz), 132.0 (d, J_{CF} = 8.8 Hz), 117.1 (d, J_{CF} = 24.9 Hz), 114.3 (d, J_{CF} = 21.1 Hz), 74.8, 71.0, 65.8, 58.4, 27.6, 21.9; **HRMS** (ESI): calculated for $[C_{13}H_{15}ClFN_2O]^+$ = 269.0851, found 269.0852; **IR** (thin film): ν 2967, 2848, 1600, 1488, 1256, 1202, 1139, 1057, 897 cm^{-1}.

(*S*)-2-(3-Bromophenyl)-5a,6,7,8-tetrahydro-3*H*,5*H*-pyrrolo[2,1-*c*][1,4,5]oxadiazepane (5b). Prepared according to the general cyclization reaction procedure from hydrazone **3b** (293.0 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:EtOAc 20:1 – 10:1) afforded oxadiazepane **5b** (96 mg, 65% yield) as a white solid. **m.p.** = 46–48 °C; $[\alpha]_D^{25}$ (c = 1.0, $CHCl_3$) = –1107.5; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (t, *J* = 1.8 Hz, 1 H), 7.55 (ddd, *J* = 7.9, 1.8, 1.0 Hz, 1 H), 7.41 (ddd, *J* = 7.9, 1.8, 1.0 Hz, 1 H), 7.20 (t, *J* = 7.9 Hz, 1 H), 4.82 (dd, *J* = 13.7, 0.8 Hz, 1 H), 4.19 (d, *J* = 13.7 Hz, 1 H), 3.98 (ddd, *J* = 11.4, 2.6, 0.8 Hz, 1 H), 3.63 (dd, *J* = 7.7, 6.5 Hz, 2 H), 3.25 (dd, *J* = 11.4, 9.7 Hz, 1 H), 2.86 (apparent qd, *J* = 9.7, 2.6 Hz, 1 H), 2.08 (apparent dtd, *J* = 12.4, 8.2, 5.9 Hz, 1 H), 2.01–1.78 (m, 2 H), 1.56 (apparent dtd, *J* = 12.4, 9.0, 6.7 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 151.3, 140.4, 131.2, 129.9, 129.3, 124.7, 122.8, 74.6, 68.4, 65.5, 58.4, 27.7, 21.9; **HRMS** (ESI): calculated for $[C_{13}H_{16}BrN_2O]^+$ = 295.0441, found 295.0441; **IR** (thin film): ν 2965, 2846, 1575, 1551, 1473, 1447, 1343, 1314, 1134 cm^{-1}.

(*S*)-*N*-(4-(5a,6,7,8-Tetrahydro-3*H*,5*H*-pyrrolo[2,1-*c*][1,4,5]oxadiazepin-2-yl)phenyl) acetamide (5c). Prepared according to the general cyclization reaction procedure from hydrazone **3c** (282.0 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (CH_2Cl_2:EtOAc 1:1) afforded oxadiazepane **5c** (77 mg, 57% yield) as a white solid. **m.p.** = 128–130 °C; $[\alpha]_D^{26}$ (c = 1.0, $CHCl_3$) = –1033.0; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.7 Hz, 2 H), 7.57 (br s, 1 H), 7.49 (d, *J* = 8.7 Hz, 2 H), 4.84 (d, *J* = 13.6 Hz, 1 H), 4.23 (d, *J* = 13.6 Hz, 1 H), 3.99 (dd, *J* = 11.4, 2.6 Hz, 1 H), 3.64–3.55 (m, 2 H), 3.27 (dd, *J* = 11.4, 9.7 Hz, 1 H), 2.85 (apparent qd, *J* = 9.7, 2.6 Hz, 1 H), 2.14 (s, 3 H), 2.07 (apparent dtd, *J* = 12.5, 8.3, 6.3 Hz, 1 H), 1.99–1.78 (m, 2 H), 1.55 (apparent dtd, *J* = 12.5, 9.0, 6.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.5, 153.3, 138.3, 134.1, 127.1, 119.6, 74.9, 68.4, 65.2, 58.5, 27.6, 24.7, 21.9; **HRMS** (ESI): calculated for $[C_{15}H_{20}N_3O_2]^+$ = 274.1550, found 274.1552; **IR** (thin film): ν 3303, 2966, 2871, 2848, 1670, 1600, 1529, 1317, 1131 cm^{-1}.

(*S*)-2-(2-Methoxyphenyl)-5a,6,7,8-tetrahydro-3*H*,5*H*-pyrrolo[2,1-*c*][1,4,5]oxadiazepane (5d). Prepared according to the general cyclization reaction procedure from hydrazone **3d** (269 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:EtOAc 5:1 – 4:1) afforded oxadiazepane **5d** (88 mg, 72% yield) as a colorless solid. **m.p.** = 68–70 °C; $[\alpha]_D^{26}$ (c = 1.0, $CHCl_3$) = –796.9; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 7.5, 1.8 Hz, 1 H), 7.29 (ddd, *J* = 8.3, 7.5, 1.8 Hz, 1 H), 6.94 (td, *J* = 7.5, 1.1 Hz, 1 H), 6.88 (dd, *J* = 8.3, 1.1 Hz, 1 H), 4.68 (dd, *J* = 13.5, 0.9 Hz, 1 H), 4.20 (d, *J* = 13.5 Hz, 1 H), 4.02 (ddd, *J* = 11.5, 2.6, 0.9 Hz, 1 H), 3.84 (s, 3 H), 3.68–3.48 (m, 2 H), 3.29 (dd, *J* = 11.5, 9.7 Hz, 1 H), 2.93 (apparent qd, *J* = 9.7, 2.6 Hz, 1 H), 2.09 (apparent dtd, *J* = 12.5, 8.4, 6.5 Hz, 1 H), 2.02–1.76 (m, 2 H), 1.56 (apparent dtd, *J* = 12.5, 9.0, 6.2 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.4, 155.0, 130.2, 129.9, 128.9, 120.9, 111.0, 75.0, 70.9, 65.1, 58.5, 55.7, 27.4, 21.8; **HRMS** (ESI): calculated for $[C_{14}H_{19}N_2O_2]^+$ = 247.1441, found 247.1441; **IR** (thin film): ν 2945, 2836, 1598, 1488, 1460, 1435, 1345, 1265, 1245, 1127, 1055, 1024 cm^{-1}.

(*S*)-2-(4-Methoxyphenyl)-5a,6,7,8-tetrahydro-3*H*,5*H*-pyrrolo[2,1-*c*][1,4,5]oxadiazepane (5e). Prepared according to the general cyclization reaction procedure from hydrazone **3e** (269 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:EtOAc 6:1) afforded oxadiazepane **5e** (86 mg, 70% yield) as a colorless solid. **m.p.** = 70–71 °C; $[\alpha]_D^{26}$ (c = 1.0, $CHCl_3$) = –1203.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.9 Hz, 2 H), 6.87 (d, *J* = 8.9 Hz, 2 H), 4.84 (dd, *J* = 13.5, 0.9 Hz, 1 H), 4.26 (d, *J* = 13.5 Hz, 1 H), 3.99 (ddd, *J* = 11.4, 2.6, 0.9 Hz, 1 H), 3.81 (s, 3 H), 3.75–3.43 (m, 2 H), 3.29 (dd, *J* = 11.4, 9.8 Hz, 1 H), 2.84 (apparent qd, *J* = 9.8, 2.6 Hz, 1 H), 2.07 (apparent dtd, *J* = 12.5, 8.4, 6.3 Hz, 1 H), 1.98–1.78 (m, 2 H), 1.54 (apparent dtd, *J* = 12.5, 9.0, 6.2 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 160.1, 154.0, 131.0, 127.8, 113.9, 75.0, 68.4, 65.0, 58.5, 55.4, 27.5, 21.9; **HRMS** (ESI): calculated for $[C_{14}H_{19}N_2O_2]^+$ = 247.1441, found 247.1444; **IR** (thin film): ν 2953, 2836, 1607, 1511, 1302, 1249, 1178, 1129, 1028 cm^{-1}.

(*S*) - 2 - (*o*-Tolyl) - 5a,6,7,8 - tetrahydro - 3*H*,5*H* - pyrrolo [2,1-*c*] [1,4,5] oxadiazepane (5f). Prepared according to the general cyclization reaction procedure from hydrazone **3f** (261 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:EtOAc 10:1) afforded oxadiazepane **5f** (77 mg, 67% yield) as a colorless oil. $[\alpha]_D^{27}$ (c = 1.0, $CHCl_3$) = –809.9; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.31 (m, 1 H), 7.24–7.14 (m, 3 H), 4.47 (dd, *J* = 13.5, 0.9 Hz, 1 H), 4.23 (d, *J* = 13.5 Hz, 1 H), 4.04 (ddd, *J* = 11.4, 2.5, 0.9 Hz, 1 H), 3.77–3.50 (m, 2 H), 3.29 (dd, *J* = 11.4, 9.6 Hz, 1 H), 2.90 (apparent qd, *J* = 9.6, 2.5 Hz, 1 H), 2.42 (s, 3 H), 2.11 (apparent dtd, *J* = 12.6, 8.3, 6.3 Hz, 1 H), 2.00–1.80 (m, 2 H), 1.58 (apparent dtd, *J* = 12.6, 9.0, 6.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.2, 139.3, 135.8, 130.6, 128.5, 128.2, 125.9, 74.9, 71.2, 65.7, 58.4, 27.6, 21.8, 20.4; **HRMS** (ESI): calculated for $[C_{14}H_{19}N_2O]^+$ = 231.1492, found 231.1493; **IR** (thin film): ν 2954, 2845, 1448, 1344, 1313, 1132, 1030, 960 cm^{-1}.

(*S*,*E*)-2-Styryl-5a,6,7,8-tetrahydro-3*H*,5*H*-pyrrolo[2,1-*c*][1,4,5]oxadiazepane (5g). Prepared according to the general cyclization reaction procedure from hydrazone **3g** (267 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:EtOAc 6:1) afforded oxadiazepane **5g** (61 mg, 50% yield) as a pale yellow solid. **m.p.** = 77–78 °C; $[\alpha]_D^{25}$ (c = 1.0, $CHCl_3$) = –2007.4; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51–7.43 (m, 2 H), 7.39–7.30 (m, 2 H), 7.34–7.22 (m, 1 H), 6.88 (s, 2 H), 4.86 (dd, *J* = 13.6, 0.9 Hz, 1 H), 4.08 (d, *J* = 13.6 Hz, 1 H), 3.99 (ddd, *J* = 11.4, 2.7, 0.9 Hz, 1 H), 3.69–3.53 (m, 2H), 3.27 (dd, *J* = 11.4, 9.8 Hz, 1H), 2.86 (apparent qd, *J* = 9.8, 2.7 Hz, 2 H), 2.10 (apparent dtd, *J* = 12.4, 8.2, 6.3 Hz, 1 H), 2.02–1.81 (m, 2 H), 1.58 (apparent dtd, *J* = 12.4, 8.9, 6.5 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.6, 136.9, 131.1, 128.8, 128.2, 128.1, 126.8, 74.7, 65.8, 65.4, 58.2, 27.6, 22.0; **HRMS** (ESI): calculated for $[C_{15}H_{19}N_2O]^+$ = 243.1492, found 243.1493; **IR** (thin film): ν 2948, 2843, 1493, 1447, 1345, 1316, 1257, 1124, 1105, 963, 921 cm^{-1}.

(*S*)-2-Phenethyl-5a,6,7,8-tetrahydro-3*H*,5*H*-pyrrolo[2,1-*c*][1,4,5]oxadiazepane (5h). Prepared according to the general cyclization reaction procedure from hydrazone **3h** (268 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:EtOAc 8:1 – 5:1) afforded oxadiazepane **5h** (50 mg, 41% yield) as a colorless oil. $[\alpha]_D^{23}$ (c = 1.0, $CHCl_3$) = –484.6; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33–7.12 (m, 5 H), 4.20 (dd, *J* = 13.2, 0.8 Hz, 1 H), 4.06 (d, *J* = 13.2 Hz, 1 H), 3.94 (ddd, *J* = 11.5, 2.6, 0.8 Hz, 1 H), 3.50 (ddd, *J* = 9.5, 7.1, 3.7 Hz, 1 H), 3.38 (apparent td, *J* = 9.5, 7.9 Hz, 1 H), 3.21 (dd, *J* = 11.5, 9.7 Hz, 1 H), 2.99–2.74 (m, 2 H), 2.67 (apparent qd, *J* = 9.7, 2.6 Hz, 1 H), 2.61–2.50 (m, 2 H), 2.02 (apparent dtd, *J* = 12.5, 8.6, 6.8 Hz, 1 H), 1.97–1.73 (m, 2 H), 1.47 (apparent dtd, *J* = 12.5, 9.0, 5.7 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.2, 141.5, 128.6, 128.5, 126.1, 75.3, 69.8, 64.6, 58.2, 39.7, 33.7, 27.3, 21.7; **HRMS** (ESI): calculated for $[C_{15}H_{21}N_2O]^+$ = 245.1648, found 245.1648; **IR** (thin film): ν 2951, 2845, 1602, 1495, 1452, 1123, 1100 cm^{-1}.

(*S*)-2-(4-(Trifluoromethyl)phenyl)-5a,6,7,8-tetrahydro-3*H*,5*H*-pyrrolo[2,1-*c*][1,4,5]oxadiazepane (5i). Prepared according to the general cyclization reaction procedure from hydrazone **3i** (288 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (CH_2Cl_2) afforded oxadiazepane **5i** (70 mg, 49% yield) as a white solid. **m.p.** = 71–72 °C; $[\alpha]_D^{25}$ (c = 1.0, $CHCl_3$) = –1232.4; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.1 Hz, 2 H), 7.59 (d, *J* = 8.1 Hz, 2 H), 4.89 (dd, *J* = 13.7, 0.8 Hz, 1 H), 4.23 (d, *J* = 13.7 Hz, 1 H), 4.01 (ddd, *J* = 11.5, 2.7, 0.8 Hz, 1 H), 3.66 (dd, *J* = 7.6, 6.5 Hz, 2 H), 3.27 (dd, *J* = 11.5, 9.7 Hz, 1 H), 2.91 (apparent qd, *J* = 9.7, 2.7 Hz, 1 H), 2.11 (apparent dtd, *J* = 12.4, 8.1, 5.8 Hz, 1 H), 2.04–1.81 (m, 2 H), 1.60 (apparent dtd, *J* = 12.4, 9.0, 6.8 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 151.1, 141.8, 130.1 (q, J_{CF} = 32.4 Hz), 126.5, 125.5 (q, J_{CF} = 3.8 Hz), 124.3 (q, J_{CF} = 271.8 Hz), 74.6, 68.5, 65.7, 58.4, 27.8, 22.0; **HRMS** (ESI): calculated for $[C_{14}H_{16}F_3N_2O]^+$ = 285.1209, found 285.1209; **IR** (thin film): ν 2979, 2845, 1324, 1160, 1134, 1113, 1068, 848 cm^{-1}.

(*S*) - 2 - (4-Nitrophenyl)-5a,6,7,8-tetrahydro-3*H*,5*H*-pyrrolo [2,1-*c*] [1,4,5] oxadiazepane (5j). Prepared according to the general cyclization reaction procedure from hydrazone **3j** (276 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (CH_2Cl_2:EtOAc 100:0 – 50:1) afforded oxadiazepane **5j** (38 mg, 30% yield) as a yellow solid. **m.p.** = 126–128 °C; $[\alpha]_D^{28}$ (c = 0.2, $CHCl_3$) = –2069.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 9.0 Hz, 2 H), 7.81 (d, *J* = 9.0 Hz, 2 H), 4.92 (dd, *J* = 13.8, 0.8 Hz, 1 H), 4.19 (d, *J* = 13.8 Hz, 1 H), 4.01 (ddd, *J* = 11.5, 2.6, 0.8 Hz, 1 H), 3.79–3.62 (m, 2 H), 3.26 (dd, *J* = 11.5, 9.8 Hz, 1 H), 2.95 (apparent tdd, *J* = 9.8, 7.7, 2.6 Hz, 1 H), 2.12 (apparent dtd, *J* = 12.4, 7.9, 5.5 Hz, 1 H), 2.03–1.84 (m, 2 H), 1.62 (apparent dtd, *J* = 12.4, 9.0, 6.8 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 149.0, 147.3, 144.5, 126.7, 123.9, 74.3, 68.3, 66.1, 58.4, 27.9, 22.1; **HRMS** (ESI): calculated for $[C_{13}H_{16}N_3O_3]^+$ = 262.1186, found 262.1189; **IR** (thin film): ν 2979, 2954, 2853, 1515, 1347, 1312, 1140 cm^{-1}.

Methyl (*S*)-4-(5a,6,7,8-tetrahydro-3*H*,5*H*-pyrrolo[2,1-*c*][1,4,5]oxadiazepin-2-yl)benzoate (5k). Prepared according to the general cyclization reaction procedure from hydrazone **3k** (283 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (CH_2Cl_2:EtOAc 10:1) afforded oxadiazepane **5k** (88 mg, 64% yield) as a pale yellow oil. $[\alpha]_D^{26}$ (c = 1.0, $CHCl_3$) = –1430.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.8 Hz, 2 H), 7.71 (d, *J* = 8.8 Hz, 2 H), 4.89 (dd, *J* = 13.6, 0.9 Hz, 1 H), 4.20 (d, *J* = 13.6 Hz, 1 H), 3.98 (ddd, *J* = 11.4, 2.6, 0.9 Hz, 1 H), 3.89 (s, 3 H), 3.69–3.57 (m, 2 H), 3.24 (dd, *J* = 11.4, 9.7 Hz, 1 H), 2.89 (apparent qd, *J* = 9.7, 2.6 Hz, 1 H), 2.08 (apparent dtd, *J* = 12.4, 8.1, 5.8 Hz, 1 H), 1.99–1.77 (m, 2 H), 1.57 (apparent dtd, *J* = 12.4, 9.0, 6.8 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.9, 151.4, 142.6, 129.8, 129.5, 126.0, 74.5, 68.4, 65.6, 58.4, 52.2, 27.7, 22.0; **HRMS** (ESI): calculated for $[C_{15}H_{19}N_2O_3]^+$ = 275.1390, found 275.1392; **IR** (thin film): ν 2950, 2845, 1719, 1434, 1276, 1109 cm^{-1}.

(*S*) - 4 - (5a,6,7,8-Tetrahydro-3*H*,5*H*-pyrrolo[2,1-*c*][1,4,5]oxadiazepin-2-yl) benzonitrile (5l). Prepared according to the general cyclization reaction procedure from hydrazone **3l** (266 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:EtOAc 6:1) afforded oxadiazepane **5l** (68 mg, 56% yield) as a pale yellow solid. **m.p.** = 91–93 °C; $[\alpha]_D^{27}$ (c = 1.0, $CHCl_3$) = –1859.9; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.7 Hz, 2 H), 7.61 (d, *J* = 8.7 Hz, 2 H), 4.87 (dd, *J* = 13.8, 0.8 Hz, 1 H), 4.18 (d, *J* = 13.8 Hz, 1 H), 4.00 (ddd, *J* = 11.5, 2.6, 0.8 H z, 1 H), 3.76–3.57 (m, 2 H), 3.25 (dd, *J* = 11.5, 9.7 Hz, 1 H), 2.91 (apparent tdd, *J* = 9.7, 7.8, 2.6 Hz, 1 H), 2.10 (apparent dtd, *J* = 12.4, 8.0, 5.6 Hz, 1 H), 2.00–1.82 (m, 2 H), 1.61 (apparent dtd, *J* = 12.4, 9.0, 7.1 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 149.7, 142.6, 132.3, 126.6, 119.0, 111.4, 74.4, 68.2, 65.9, 58.4, 27.8, 22.0; **HRMS** (ESI): calculated for $[C_{14}H_{16}N_3O]^+$ = 242.1288, found 242.1289; **IR** (thin film): ν 2963, 2871, 2839, 2224, 1446, 1435, 1406, 965, 916 cm^{-1}.

(*S*) - 2 - (Pyridin-3-yl) - 5a,6,7,8 - tetrahydro -3*H*,5*H*- pyrrolo [2,1-*c*] [1,4,5] oxadiazepane (5m). Prepared according to the general cyclization reaction procedure from hydrazone **3m** (254 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (EtOAc:CH_2Cl_2 1:1 – 2:1) afforded

oxadiazepane **5m** (22 mg, 20% yield) as a colorless oil. $[\alpha]_D^{28}$ (c = 1.0, $CHCl_3$) = –957.6; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.88 (dd, *J* = 2.3, 0.8 Hz, 1 H), 8.53 (dd, *J* = 4.8, 1.7 Hz, 1 H), 7.95 (ddd, *J* = 8.0, 2.3, 1.7 Hz, 1 H), 7.30–7.20 (m, 1 H), 4.87 (dd, *J* = 13.8, 0.8 Hz, 1 H), 4.23 (d, *J* = 13.8 Hz, 1 H), 4.01 (ddd, *J* = 11.5, 2.6, 0.8 Hz, 1 H), 3.65 (dd, *J* = 7.6, 6.5 Hz, 2 H), 3.27 (dd, *J* = 11.5, 9.7 Hz, 1 H), 2.90 (apparent qd, *J* = 9.7, 2.6 Hz, 1 H), 2.10 (apparent dtd, *J* = 12.4, 8.2, 5.8 Hz, 1 H), 2.00–1.82 (m, 2 H), 1.59 (apparent dtd, *J* = 12.4, 9.0, 6.8 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 149.9, 149.3, 147.7, 134.1, 133.5, 123.3, 74.7, 68.4, 65.7, 58.4, 27.7, 22.0; **HRMS** (ESI): calculated for $[C_{12}H_{16}N_3O]^+$ = 218.1288, found 218.1289; **IR** (thin film): ν 2952, 2848, 1344, 1314, 1137, 1019, 962 cm^{-1}.

(*S*) - 2 - (5-Methylisoxazol-3-yl)-5a,6,7,8-tetrahydro-3*H*,5*H*-pyrrolo [2,1-*c*] [1,4,5] oxadiazepane (5n). Prepared according to the general cyclization reaction procedure from hydrazone **3n** (256 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:EtOAc 6:1) afforded oxadiazepane **5n** (16 mg, 14% yield) as a pale yellow solid. **m.p.** = 75–77 °C; $[\alpha]_D^{26}$ (c = 0.2, $CHCl_3$) = –265.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.27 (q, *J* = 0.9 Hz, 1 H), 5.26 (dd, *J* = 14.1, 0.9 Hz, 1 H), 4.09 (d, *J* = 14.1 Hz, 1 H), 4.00 (ddd, *J* = 11.6, 2.6, 0.9 Hz, 1 H), 3.76–3.51 (m, 2 H), 3.21 (dd, *J* = 11.6, 9.7 Hz, 1 H), 2.97 (apparent tdd, *J* = 9.7, 7.6, 2.6 Hz, 1 H), 2.39 (d, *J* = 0.9 Hz, 3 H), 2.09 (apparent dtd, *J* = 12.4, 7.8, 5.5 Hz, 1 H), 2.01–1.80 (m, 2 H), 1.62 (apparent dtd, *J* = 12.4, 9.0, 7.5 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.1, 162.6, 142.0, 99.6, 74.4, 67.6, 66.3, 58.1, 27.8, 21.9, 12.3; **HRMS** (ESI): calculated for $[C_{11}H_{16}N_3O_2]^+$ = 222.1237, found 222.1238; **IR** (thin film): ν 2954, 2927, 2850, 1608, 1445, 1343, 1142, 1124, 908 cm^{-1}.

(*S*)-2-(Furan-3-yl)-5a,6,7,8-tetrahydro-3*H*,5*H*-pyrrolo[2,1-*c*][1,4,5]oxadiazepane (5o). Prepared according to the general cyclization reaction procedure from hydrazone **3o** (249 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:EtOAc 6:1) afforded oxadiazepane **5o** (62 mg, 60% yield) as a pale yellow oil. $[\alpha]_D^{27}$ (c = 1.0, $CHCl_3$) = –938.3; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 1.7, 0.9 Hz, 1 H), 7.37 (t, *J* = 1.7 Hz, 1 H), 6.72 (dd, *J* = 1.7, 0.9 Hz, 1 H), 4.56 (dd, *J* = 13.5, 0.9 Hz, 1 H), 4.21 (d, *J* = 13.5 Hz, 1 H), 3.97 (ddd, *J* = 11.5, 2.6, 0.9 Hz, 1 H), 3.67–3.47 (m, 2 H), 3.24 (dd, *J* = 11.5, 9.7 Hz, 1 H), 2.82 (apparent qd, *J* = 9.7, 2.6 Hz, 1 H), 2.06 (apparent dtd, *J* = 12.4, 8.3, 6.1 Hz, 1 H), 1.97–1.77 (m, 2 H), 1.54 (apparent dtd, *J* = 12.4, 9.0, 6.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 147.5, 143.9, 140.6, 126.1, 108.4, 75.0, 68.8, 65.2, 58.4, 27.5, 21.9; **HRMS** (ESI): calculated for $[C_{11}H_{15}N_2O_2]^+$ = 207.1128, found 207.1128; **IR** (thin film): ν 2968, 2845, 1513, 1344, 1160, 1133, 1054, 927, 872 cm^{-1}.

(*S*)-2-(Thiophen-3-yl)-5a,6,7,8-tetrahydro-3*H*,5*H*-pyrrolo [2,1-*c*] [1,4,5] oxadiazepane (5p). Prepared according to the general cyclization reaction procedure from hydrazone **3p** (257 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:EtOAc 15:1) afforded oxadiazepane **5p** (77 mg, 70% yield) as a pale yellow oil. $[\alpha]_D^{27}$ (c = 1.0, $CHCl_3$) = –1307.4; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 (dd, *J* = 5.1, 1.3 Hz, 1 H), 7.40 (dd, *J* = 2.9, 1.3 Hz, 1 H), 7.26 (dd, *J* = 5.1, 2.9 Hz, 1 H), 4.83 (dd, *J* = 13.5, 1.0 Hz, 1 H), 4.24 (d, *J* = 13.5 Hz, 1 H), 3.98 (ddd, *J* = 11.5, 2.7, 1.0 Hz, 1 H), 3.77–3.50 (m, 2 H), 3.25 (dd, *J* = 11.5, 9.7 Hz, 1 H), 2.84 (apparent qd, *J* = 9.7, 2.7 Hz, 1 H), 2.06 (apparent dtd, *J* = 12.4, 8.3, 6.1 Hz, 1 H), 1.99–1.77 (m, 2 H), 1.54 (apparent dtd, *J* = 12.4, 9.0, 6.5 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 149.7, 140.8, 126.2, 126.0, 122.4, 74.8, 68.7, 65.2, 58.4, 27.5, 21.9; **HRMS** (ESI): calculated for $[C_{11}H_{15}N_2OS]^+$ = 223.0900, found 223.0897; **IR** (thin film): ν 2965, 2948, 2868, 2845, 1447, 1342, 1311, 1203, 1129 cm^{-1}.

***tert*-Butyl (*S*) - 2 - (2-chloro-4-fluorophenyl) -5a,6,7,8- tetrahydro -3*H*- pyrrolo [1,2-*b*] [1,2,5] triazepine-4(5*H*)-carboxylate (6a).** Prepared according to the general cyclization reaction procedure from hydrazone **4a** (329 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:Et_2O 10:1) afforded aminodiazepane **6a** (64 mg, 35% yield as rotamers 3:7) as a pale yellow oil. $[\alpha]_D^{25}$ (c = 1.0, $CHCl_3$) = –384.1; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47–7.26 (m, 1 H), 7.13 (d, *J* = 7.7 Hz, 1 H), 7.04–6.93 (m, 1 H), 4.69 (d, *J* = 14.8 Hz, 1 H), 4.15 (d, *J* = 11.0 Hz, 1 H), 4.00 (d, *J* = 14.8 Hz, 1 H), 3.64–3.52 (m, 1 H), 3.45 (q, *J* = 8.8 Hz, 1 H), 3.09–2.77 (m, 2 H), 2.21–2.10 (m, 1 H), 1.96–1.80 (m, 2 H), 1.68–1.57 (m, 1 H), 1.44 (s, 9 H × 0.3), 1.19 (s, 9 H × 0.7); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.5 (d, J_{CF} = 250.3 Hz), 154.6, 154.3, 135.9 (d, J_{CF} = 3.0 Hz), 133.0 (d, J_{CF} = 10.4 Hz), 132.1 (d, J_{CF} = 9.0 Hz), 117.0 (d, J_{CF} = 24.8 Hz), 114.1 (d, J_{CF} = 20.9 Hz), 80.2, 63.8, 58.4, 53.2, 51.9, 48.9, 29.0, 28.4, 28.1, 22.0; **HRMS** (ESI): calculated for $[C_{18}H_{24}ClFN_3O_2]^+$ = 368.1536, found 368.1536; **IR** (thin film): ν 2972, 2928, 2873, 1698, 1600, 1490, 1448, 1246, 1167 cm^{-1}; R_f = 0.26 (hexanes:Et_2O 4:1).

***tert*-Butyl (*S*)-2-(4-methoxyphenyl) -5a,6,7,8- tetrahydro-3*H*-pyrrolo [1,2-*b*] [1,2,5] triazepine-4(5*H*)-carboxylate (6b).** Prepared according to the general cyclization reaction procedure from hydrazone **4b** (318 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:Et_2O 5:1) afforded aminodiazepane **6b** (117 mg, 68% yield as rotamers 2:3) as a pale yellow oil. $[\alpha]_D^{25}$ (c = 1.0, $CHCl_3$) = –734.9; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.4 Hz, 1 H), 7.76 (d, *J* = 8.4 Hz, 1 H), 6.95–6.81 (m, 2 H), 5.02 (d, *J* = 14.7 Hz, 1 H × 0.4), 4.91 (d, *J* = 14.7 Hz, 1 H × 0.6), 4.26 (d, *J* = 9.2 Hz, 1 H × 0.6), 4.12 (d, *J* = 9.2 Hz, 1 H × 0.4), 3.90–3.71 (m, 1 H), 3.82 (s, 3 H), 3.62–3.48 (m, 2 H), 2.87–2.62 (m, 2 H), 2.21–2.07 (m, 1 H), 1.95–1.78 (m, 2 H), 1.65–1.56 (m, 1 H), 1.45 (s, 9 H × 0.4), 1.40 (s, 9 H × 0.6); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 160.3, 155.3, 154.6, 154.4, 154.0, 130.9, 128.6, 128.0, 113.9, 113.7, 80.7, 80.2, 64.2, 58.9, 55.5, 53.2, 52.2, 46.2, 29.3, 29.3, 28.5, 22.0; **HRMS** (ESI): calculated for $[C_{19}H_{28}N_3O_3]^+$ = 346.2125, found 346.2127; **IR** (thin film): ν 2972, 2933, 2875, 2838, 1693, 1608, 1514, 1453, 1248, 1175 cm^{-1}; R_f = 0.16 (hexanes:Et_2O 4:1).

***tert*-Butyl (*S*)-2-(thiophen-3-yl)-5a,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-*b*][1,2,5]triazepine-4(5*H*)-carboxylate (6c).** Prepared according to the general cyclization reaction procedure from hydrazone **4c** (306 mg, 0.50 mmol, 1.00 equiv). Purification by flash column chromatography (hexanes:Et_2O 10:1)

afforded aminodiazepane **6c** (104 mg, 65% yield as rotamers 2:3) as a pale yellow oil. $[\alpha]_D^{25}$ (c = 1.0, $CHCl_3$) = –666.2; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94 (s, 1 H), 7.64–7.44 (m, 2 H), 7.24 (s, 1 H), 4.99 (d, *J* = 14.7 Hz, 1 H × 0.4), 4.86 (d, *J* = 14.7 Hz, 1 H × 0.6), 4.23 (m, 1 H × 0.6), 4.08 (d, *J* = 13.0 Hz, 1 H × 0.4), 3.85 (d, *J* = 14.6 Hz, 1 H × 0.6), 3.77 (d, *J* = 14.6 Hz, 1 H × 0.4), 3.62–3.40 (m, 2 H), 2.89–2.58 (m, 2 H), 2.20–2.06 (m, 1 H), 1.96–1.75 (m, 2 H), 1.67–1.54 (m, 1 H), 1.42 (s, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.6, 154.4, 151.6, 149.8, 140.9, 126.3, 126.2, 125.7, 125.2, 123.2, 80.7, 80.2, 64.2, 58.6, 53.0, 52.2, 46.8, 46.5, 29.3, 29.3, 28.5, 22.0; **HRMS** (ESI): calculated for $[C_{16}H_{24}N_3O_2S]^+$ = 322.1584, found 322.1582; **IR** (thin film): ν 2973, 2929, 2873, 1692, 1452, 1246, 1167 cm^{-1}; R_f = 0.30 (hexanes:Et_2O 4:1).

Supplementary

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

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Author Contribution Statement

T. S., M. U. L., S.-Y. H. and J. W. B. designed the studies. T. S. and M. U. L. performed the experiments. M. U. L. and J. W. B. wrote the manuscript. [†] These authors contributed equally.

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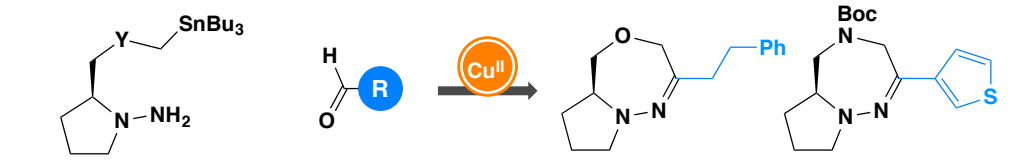

SnAP Hydrazine Reagents **Aldehydes**

Y = O, NBoc

Oxadiazepanes & Triazepanes (19 Examples)