SnAP REAGENTS FOR THE PREPARATION OF
FUNCTIONALIZED, SATURATED N-HETEROCYCLES

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Abstract

Saturated N-heterocycles, for example, piperidines, piperazines, or morpholines can be found with increasing frequency in small bioactive molecules, despite their limited commercial availability and challenging synthesis. Enormous efforts have been made on the synthesis of cyclic amines, but a direct extension of cross-coupling methods to include saturated N-heterocycles remains elusive. Strategies are often specific to a single target, effective for narrow classes of N-heterocycles or substitution patterns, and require multiple protection-deprotection steps.

In 2013, our group disclosed SnAP (tin (Sn) amine protocol) reagents for the one-step transformation of aldehydes into unprotected thiomorpholines. This copper mediated cyclization takes place under mild conditions, affords unprotected, saturated N-heterocycles in one-step and tolerates a wide range of functional groups. To evaluate whether SnAP reagents are a practical, versatile approach to saturated functionalized N-heterocycles, we designed new reagents to access 5–9 membered unprotected secondary amines. SnAP reagents are combined with aldehydes or ketones in the presence of molecular sieves to afford the corresponding imine which is cyclized subsequently with stoichiometric Cu(OTf)$_2$ (Scheme 1).

Scheme 1. Substrate scope SnAP, SnAP-eX reagents.

More than 20 SnAP reagents were prepared, which proved to be general to access functionalized, unprotected, sat. N-heterocycles. In collaboration with Sigma-Aldrich, routes viable to large-scale preparation of the air- and moisture-stable SnAP reagents were designed and reagents were brought to market.
Mechanistic investigations involving radical clocks and stereoconvergent cyclization of an enantiopure SnAP reagent suggest a radical-based process initiated by a copper-mediated oxidation of the C–Sn bond to form a stabilized nucleophilic carbon radical driven by formation of the thermodynamically strong Sn–O bond (Scheme 2). Coordination of the unprotected N-heterocycles to Cu(II) may lead to catalyst inhibition rendering this process stoichiometric in Cu(II).

Scheme 2. Proposed reaction mechanism including experimental evidence.

Screening of solvents, ligand classes (phosphines, bisoxazolines, etc.) and additives allowed for the identification of ligand-accelerated conditions that operate with catalytic amounts of copper (Scheme 2 and 3). An excess of HFIP was found to be crucial for catalyst turnover. We attribute this to its strong hydrogen bond-donor character, complexing the N-heterocyclic products, thereby promoting turnover of the Lewis acidic copper catalyst.

Scheme 3. Substrate scope catalytic procedure.

The observation of significant enantioinduction solicited further studies on ligand optimization. Therefore, a chemoinformatic approach in collaboration with the Denmark group (University of Illinois, Urbana-Champaign, USA) involving rounds of calculation, ligand synthesis, and screening, is currently ongoing. Looking at 15’936 bisoxazoline ligands, a subset of 30 candidates, which represent the greatest chemical diversity, was selected and synthesized. Empirical data (TON, enantiomeric ratio) were recorded and computational analysis to suggest ligands that are predicted to be superior for the given transformation are ongoing. Nevertheless, initial results indicate that bisoxazoline ligands are valuable to minimize side reactions as protodestannylation, improve catalyst turn-over, and the enantiomeric ratio.
Zusammenfassung


**Schema 1.** Anwendungsbereich von SnAP, SnAP-eX Reagenzien.

Mehr als 20 SnAP Reagenzien wurden hergestellt, wobei festgestellt wurde, dass diese Methodologie tatsächlich einer gerellen Lösung zur Herstellung von funktionalisierten, ungeschützten N-Heterozyklen nahe kommt. In Zusammenarbeit mit Sigma-Aldrich wurden die
Herstellungsprozesse zur Produktion grösserer Mengen optimiert, wonach die luft- und feuchtigkeitsunempfindlichen SnAP Reagenzien kommerziell erhältlich gemacht wurden.


Untersuchungen des Lösemittels, der Ligandenklassen (Phosphine, Bisoxazoline, usw.) und anderen Zusatzstoffen ermöglichte die Identifizierung katalytischer Bedingungen, wobei grössere Mengen HFIP nötig waren um den Katalysator zu regenerieren, was wir darauf schliessen, dass das Produkt durch Wasserstoffbrückenbindungen komplexiert wird und die aktive Spezies so frei gesetzt wird (Schema 2 und 3).


Aufgrund der Beobachtung signifikanter Enantioselektivität wurden weitere Untersuchung der Liganden unternommen. In Kollaboration mit der Forschungsgruppe von Prof. Denmark (Universität von Illinois, Urbana-Champaign, USA) wurden Berechnungen zu den Liganden unternommen, wonach einige Kandidaten hergestellt und in der Reaktion getestet wurden. Aus 15’936 analysierten Bisoxazolin Liganden wurden diese 30 hergestellt, welche die grösste chemische Vielfalt abdecken. Anwendung dieser Liganden in der SnAP Reaktion ermöglichte es, Messung einiger empirischer Daten (katalytische Produktivität - TON,
Enantiomerenverhältnis) anzustellen, wonach zurzeit stattfindende Berechnungen Liganden mit optimierten Eigenschaften vorhersagen sollten. Erste Daten aus den Untersuchungen deuten jedoch bereits darauf hin, das Bisoxazolin Liganden in der Lage sind Nebenreaktionen zu unterbinden, die katalytische Produktivität zu steigern vermögen und das Enantiomerenverhältnis zu verbessern wissen.
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Michael Umberto Luescher

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List of Abbreviations, Chemical Structures and Symbols

δ chemical shift
ν wave number
$^1$H NMR hydrogen-1 nuclear magnetic resonance
$^{13}$C NMR carbon-13 nuclear magnetic resonance
Å Angstrom ($10^{-10}$m)
Ac acetyl
aq aqueous
Ar aryl
BDE bond dissociation energy
Bn benzyl
Boc tert-butoxycarbonyl
BOX or Box bisoxazoline
bpy 2,2'-bipyridine
Bu butyl
BQ benzoquinone
br broad
°C degree Celcius
cat. catalyst
cf. confer
chp. chapter
cm$^{-1}$ reciprocal centimeter (kayser for wavenumber)
conv. Conversion
d doublet
dd doublet of doublet
DCE 1,2-dichloroethane
DIAD diisopropyl azodicarboxylate
DMAP 4-dimethylaminopyridine
DMF $N,N$-dimethylformamide
DMSO dimethyl sulfoxide
dr diastereomeric ratio
ee enantiomeric excess
EI electron impact ionization
equiv equivalent(s)
ESI electrospray ionization
e.r. enantiomeric ratio
Et ethyl
EtOAc ethyl acetate
et al. et alia, and others
rac.  racemic
rt  room temperature
s  singlet
SAR  structure-activity relationship
sat.  saturated
SLAP  silicon light amine protocol, silicon amine protocol
SnAP  tin (Sn) amino protocol
SOMO  singly occupied molecular orbital
sp  sparteine
stoich.  stoichiometric
t  triplet
TBAF  tetra-n-butylammonium fluoride
TBDPS  tert-butyldiphenylsilyl
TBS  tert-butyldimethylsilyl
TC  thiophene-2-carboxylate
THP  tetrahydropyran
TEMPO  (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
TFA  trifluoroacetic acid
TFE  2,2,2-trifluoroethanol
TFOH  trifluoromethanesulfonic acid, triflic acid
THF  tetrahydrofuran
TIPS  triisopropylsilyl
TMEDA  N,N,N',N'-tetramethylenediamine
Trityl / Trtl  triphenylmethylamine
Ts  4-toluenesulfonyl
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“Your assumptions are your windows on the world. Scrub them off every once in a while, or the light won’t come in.”
– Isaac Asimov

DEDICATED TO MY FAMILY AND MY FIANCEÉ ANA LAURA DOMINGUEZ FERNANDEZ FOR THEIR CONSTANT SOURCE OF SUPPORT AND ENCOURAGEMENT DURING THE CHALLENGES OF GRADUATE SCHOOL AND LIFE. I AM TRULY THANKFUL FOR HAVING ALL OF YOU IN MY LIFE.
1

INTRODUCTION
1. Introduction

1.1 Saturated N-Heterocycles - A Perspective

Bioactive small molecules continue to dominate humankind’s ability to treat disease;\(^1\) of the 152 pharmaceuticals approved by the US Food and Drug Administration (FDA) in the years 2012–2015, 107 were small molecules.\(^2\) Nevertheless, the high attrition rate of small molecule drug candidates in clinical trials due to unforeseen complications, such as poor bioavailability, poor pharmacokinetic properties or unwanted toxicological effects is a major obstacle in the delivery of new treatments.

In recent years, advances in chemoinformatics have exposed an intrinsic link between the success of drug candidates in clinical trials and the molecular properties of the leads from which these candidates are derived.\(^3\) In preparing leads with more appropriate properties, it could be possible to reduce the failure rate, increase the likelihood of more new molecular entities reaching the market, and at the same time reduce costs.

Drug discovery approaches, however, depend heavily on the availability of appropriate synthetic methods producing drug-like molecules. Despite this, most reactions have limited success rates using building blocks containing polar functionalities important in such endeavors. As a result, a routine set of reactions is used,\(^4\) resulting in a limited area of chemical space being covered.\(^4a,5\) For example, the advent of efficient and reliable C(sp\(^2\))–C(sp\(^2\)) transition metal-mediated coupling reactions has had a profound influence on the design of synthesis elements of medicinal chemistry approaches that it has been implicated as one of the factors leading to an industry-wide trend towards the synthesis of clinical candidates low in C(sp\(^3\)), a characteristic that results in planar, rod and disk-like conformations.\(^4a\) Attributes like this are associated with an increased attrition risk in development, illustrating a need for the preparation of novel drug-like scaffolds with improved properties.\(^6,7\) Furthermore, increasing investments over recent decades into these areas of chemical space have not led to an increase of new drugs brought onto the market.

There are certainly many factors playing a significant role in the output of new drugs (e.g. rules and regulations or the differentiation from therapies on the market) and synthetic organic chemistry is just one piece of this puzzle. However, it is fair to ask if coverage of a more diverse chemical space could provide different and new opportunities to meet the emerging targets of the industry at present. The introduction of robust new methodologies that are broad in substrate scope, enabling access to more diverse screening collections, for example, could enhance such drug discovery approaches. Central to the goals of such new methods should be
the deliverance of protocols exhibiting improved or complementary characteristics to state-of-the-art transformations and if possible utilize pre-existing molecular building blocks facilitating their implementation.

### 1.2 Saturated N-Heterocycles

Recent studies on pharmaceutical small molecule collections confirmed that a high aromatic ring count has an overall negative impact on several important physiochemical properties of drug candidates, including aqueous solubility, lipophilicity, plasma protein binding, cytochrome P450 inhibition, and hERG channel binding.\(^7\) In light of these limitations, increasing attention was turned to the replacement of carboaromatics with heteroaromatic and heteroaliphatic rings, among which saturated heterocycles present advantages in preparing architecturally more complex molecules. This allows for the exploration of more diverse chemical space without a significant increasing in molecular weight (Figure 1.1).

![Figure 1.1. Isomers of dimethyl substituted pyridine and its saturated counterpart, piperidine.](image)

As recent reviews on frameworks in FDA approved drugs revealed, Nitrogen heterocycles are amongst the most significant structural elements of pharmaceuticals, with 59% of small-molecule drugs approved containing such a N-heterocycle (Figure 1.2).\(^8\) On top of this list are, saturated piperidines (1\(^{st}\)), piperazines (3\(^{rd}\)), and pyrrolidines (5\(^{th}\)).
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Figure 1.2. Selected FDA approved drugs containing substituted saturated nitrogen heterocycles.

The constraint in using saturated heterocyclic scaffolds is that chemistry to introduce structural diversity via substituents on their carbon backbones is often rather tedious, compared to derivatizing their aromatic counterparts. Most piperazine drugs, for example, are limited to a 1,4-substitution pattern with substituents solely on the nitrogen atoms (Figure 1.3). Limited commercial availability of saturated, substituted building blocks further limits their potential for application in novel drug-like scaffolds, placing strategies to access such molecules in high demand.

Figure 1.3. Substitution pattern of FDA approved pharmaceuticals containing piperidine and piperazine scaffolds.

1.3 Synthesis of Mono- / Disubstituted Saturated N-Heterocycles

Saturated aza-heterocycles are common components defining pharmaceuticals,\textsuperscript{8,9,c} natural products,\textsuperscript{9} chiral auxiliaries,\textsuperscript{9c} ligands\textsuperscript{10} and more, due to their high density of structural information. However, the direct synthesis of such compounds remains challenging and facile methods with complete chemo-, regio-, diastereo-, and enantioselectivity are in high demand. Furthermore, in light that more than 20% of reactions carried out in drug discovery approaches are non-productive protecting group manipulations,\textsuperscript{4b} one-step methods are an alluring goal.
Even though the direct functionalization of C–H bonds adjacent to the nitrogen atom is predominant in the field,\(^\text{11}\) and several approaches to access individual multi-substituted scaffolds exist, general strategies to obtain the most common frameworks, mono- and disubstituted saturated nitrogen heterocycles, will be discussed in the following sections.

### 1.3.1 C–H Functionalization

**Organolithium-mediated α-deprotonation and functionalization.** Since the pioneering work of Beak on the direct α-lithiation of Boc-protected N-heterocycles to form dipole-stabilized carbanions, followed by electrophilic substitution to access racemic α-substituted derivatives,\(^\text{12}\) research efforts focused on the expansion of this approach (Scheme 1.1). Reactivity series for alkyllithium-diamine mediated deprotonations at different temperatures,\(^\text{13}\) and in different solvents were established,\(^\text{14}\) and investigations on the steric course of the \(\text{S}_\text{E}2\) reactions of such α-aminoorganolithiums were carried out.\(^\text{15}\) Asymmetric α-functionalization was achieved using natural product (−)-sparteine (denoted (−)-sp) as chiral diamine ligand,\(^\text{16}\) and synthetic (+)-sparteine surrogate (denoted (+)-sp), developed in 2002 by O’Brien et al.,\(^\text{17}\) to access enantiomeric products as natural (+)-sp is difficult to obtain. Furthermore, due to the low configurational stability of α-aminoorganolithiums at temperatures above −30°C,\(^\text{13}\) transmetallation to Cu(I)\(^\text{18}\) or Zn(II)\(^\text{19}\) salts is needed for reactions involving less reactive electrophiles such as vinyl halides, α,β-unsaturated esters, or aryl halides using a Negishi coupling protocol.

![Scheme 1.1. Organolithium-mediated α-deprotonation and α-functionalization.](image-url)
Recent developments involving α-aminoorganolithiums include an enantioconvergent nickel catalyzed cross-coupling approach of racemic alkylzinc reagents and alkyl halides to access enantioenriched α-alkylated pyrrolidines, reported from Prof. Fu et al., and work from Prof. Baudoin’s group using a phosphinopyrrole ligand to access β-arylated Boc-protected piperidines, thereby partly overcoming the restriction to functionalize saturated aza-heterocycles exclusively in α-position using an organolithium α-deprotonation approach.

While α-lithiation and functionalization is an effective approach to access α- or β-substituted, as well as α,α-disubstituted pyrrolidines, piperidines, and azepanes, eliminative ring fission often excludes morpholines, thiomorpholines, or piperazines (Scheme 1.2a), with the first direct α-lithiation of Boc-protected piperazines reported by van den Hoogenband and van Maarseveen in 2005, sixteen years after Beak’s seminal discovery. Extensive studies on piperazines, however, revealed an unexpected role of the electrophiles and distal nitrogen substituents, expanding the α-functionalization protocol to include piperazines (Scheme 1.2b,c).

Scheme 1.2. a) Eliminative ring fission of saturated 1,4-diheteroatom heterocycles upon α-lithiation. b) Mechanistic proposal for ring-fragmentation in lithiation-trapping of Boc-protected piperazines, c) and its prevention through the use of a more bulky protecting group on the distal nitrogen.

Metal-catalyzed C−H functionalization. Following the pioneering work of Murai et al. in 2001 on the Ru3(CO)12-catalyzed addition of C(sp3)−H bonds across unactivated alkenes to access α-alkylated, saturated cyclic amines (Scheme 1.3a), Sames and Maes disclosed direct ruthenium-catalyzed C(sp3)−H α-arylation of pyrrolidines and piperidines using (hetero)aromatic boronic esters as coupling partners based on the same concept (Scheme 1.3b,c). While the commercial availability of organoboron spieces and the catalytic protocol of these ruthenium-catalyzed methods offer distinct advantages, the presence of undesired α,α'-diarylation and difficult to remove pyrroline or pyridine directing groups limits the synthetic utility.
saturated, cyclic amines at sites remote to nitrogen. Substrates, recent developments offer new approaches to selectively manipulate C–H bonds of functionalized N-aryl amination with high regioselectivity using thioamide directed, palladium-catalyzed mono- and difunctionalization approaches afford α'-difunctionalized 38% prod. (R=H) and 38% α,α-difunctionalized prod. (R=Ph), trans/cis ≈ 3:1. Despite the difficult to remove protecting group, the possibility to access enantiomerically enriched substrates using chiral phosphoric acid ligands renders this thioamide directed, palladium-catalyzed cross-coupling valuable for the synthesis of α-aryl N-heterocycles.

Using enecarbamates, Beng and co-workers made important progress towards direct α-arylation of 5-, 6-, and 7-membered saturated cyclic amines (Scheme 1.4a).

\[
\text{Method A: } 1:1 \text{ MeOTf, CH}_2\text{CN, 0°C; 1:2 NaBH}_4 \text{ MeOH, 0°C}
\]
\[
\text{Method B: } 1:1 \text{ PdCl}_2, \text{H}_2 (1 \text{ atm), EtOH, rt; 1:2 NaBH}_4 \text{ MeOH, 0°C}
\]

This functional group tolerant C(sp^2)–H functionalization approach affords simple Boc-protected, mono-functionalized N-heterocycles after follow-up hydrogenation. Direct α-(sp^3)–H transition metal-catalyzed mono-functionalization of pyrrolidines, piperidines, and azepanes, however, was reported only recently (Scheme 1.4b). Despite the difficult to remove protecting group, the possibility to access enantiomerically enriched substrates using chiral phosphoric acid ligands renders this thioamide directed, palladium-catalyzed cross-coupling valuable for the synthesis of α-aryl N-heterocycles.

While most transition-metal-catalyzed C(sp^3)–H functionalization methods of alicyclic amines depend on hard to remove directing groups requiring multiple steps to access NH-free substrates, recent developments offer new approaches to selectively manipulate C–H bonds in saturated, cyclic amines at sites remote to nitrogen. Despite the limited substrate scope and
harsh reaction conditions of these methods, the fact that such C–H bonds are present in a vast number of bioactive small molecules makes this a valuable addition into the toolbox of medicinal chemists.

**Radical-based C–H activation.** The pioneering work of Snieckus and Curran on the C(sp³)–H functionalization of pyrrolidines and piperidines via the formation of carbon-centered α-amino radicals through 1,5-hydrogen atom transfer set a mild new precedent for the α-functionalization of alicyclic amines (Scheme 1.5a). Nakamura further developed this concept into an iron-catalyzed α-C(sp³)–C(sp²) bond formation of organomagnesium and organozinc reagents with benzyl protected pyrrolidines, piperidines, and azepanes (Scheme 1.5b).

![Scheme 1.5. Radical translocation C–H functionalization.](image)

Using a photoredox approach, MacMillan et al. reported on the α-arylation of various saturated N-heterocycles, including pyrrolidines, piperidines, morpholines, piperazines, and azepanes (Scheme 1.5c). This iridium-catalyzed C–H arylation displays an unprecedented strategy to form α-amino radicals for the construction of substituted cyclic amines with high functional group compatibility. Furthermore, despite the need for an excess amine, an unremovable phenyl protecting group to facilitate amine oxidation, as well as being limited to electron poor (hetero)aromatic nitriles, the operationally trivial reaction protocol, and availability of starting materials makes this carbon–carbon bond-forming concept valuable for the synthesis of benzylic amines.

Through the combination of photoredox-mediated hydrogen atom transfer and nickel catalysis, an improvement was made to the aforementioned protocol. α-Heteroatom C(sp³)–H arylation of various cyclic and acyclic systems was achieved using electronically diverse (hetero)aromatic halides (Scheme 1.6). While the broad substrate scope, including a variety of cyclic saturated amines, is a clear advantage, the complex reaction set-up should be addressed for this method to find broader utility in the future.
**Redox-neutral C–H functionalization.** Different strategies are available to functionalize cyclic amine α-C–H bonds with a focus on tertiary or protected amines. Redox-neutral methods operating via a hydride transfer mechanism can avoid external oxidants or reductants and often do not generate unwanted byproducts.\(^{36}\) Seidel et al. recently introduced such a concept for α-C(sp\(^3\))–H functionalizations on secondary, alicyclic amines providing products regioisomeric to classic Strecker or Mannich reactions (Scheme 1.7a).\(^{37}\) Acid-catalyzed iminium isomerization led to direct α-alkynylation\(^{38}\) or alkylation\(^{39}\) of pyrrolidines and piperidines (Scheme 1.7b). Bulky 2,6-dichlorobenzaldehyde as protecting group was identified to be crucial in order to prevent formation of the undesired regioisomer; however, other classes of saturated N-heterocycles such as morpholines and azepanes suffered a significant decrease of regioselectivity regardless of the choice of aldehyde.

**Scheme 1.6.** Triple catalytic photoredox, HAT, nickel-catalyzed C(sp\(^3\))–H arylation.

**Scheme 1.7.** Redox-neutral C–H functionalization.
1.3.2 Addition to Imines

Inter- and intramolecular carbon-carbon bond forming reactions utilizing imines have been extensively reviewed, in particular those involving addition of organometallic reagents and radicals onto imine derivatives. Furthermore, the addition of nucleophilic reagents to imines represents one of the most versatile and useful methodologies to construct α-substituted amines, which are commonly found in bioactive small molecules such as pharmaceutical agents, amino acids, and others. While the direct addition of reactive organometallic reagents to imines can provide useful routes, such harsh reagents often limit the scope and functional group compatibility of those reactions. As such, milder methods of functionalizing imine electrophiles are of significant interest. The use of Lewis acids, electron-withdrawing groups on the imine nitrogen, and oxidation strategies to give iminium salts or nitrones, for example, can increase the imine electrophilicity, such that weaker organometallic reagents become compatible in the addition reaction. The basicity and strong nucleophilicity of reactive organometallics can also be moderated using ligands, making these reagents more compatible with reactive functional groups, as illustrated by Denmark with the asymmetric \( \text{tBu-BOX} \)-mediated addition of alkyllithiums to aza-enolizable aliphatic imines (Scheme 1.8). Additionally, less basic reagents such as allylic organometallic reagents (e.g. allylstannanes, allylboronates), alkyl cuprates, or organocerium reagents have been used.

\[ \text{RLi (2.0 equiv), (R)\text{-tBu-BOX} (1.0 equiv)} \]

Scheme 1.8. Ligand-mediated addition of reactive organolithiums to enolizable imines.

In the following section, the addition of organometallic nucleophilic reagents and the radical addition to imines for the synthesis of functionalized saturated N-heterocycles will be discussed.
Addition of organometallic nucleophilic reagents to imine derivatives for the synthesis of substituted, saturated N-heterocycles. A contribution to the functionalization of saturated N-heterocycles was reported from Caprio et al. (Scheme 1.9a).44 A variety of Grignard reagents and organolithium species were employed in the addition to a nitrone, providing unprotected trans-α,β-disubstituted piperidines after reduction. Using a different approach for the synthesis of such 3-hydroxy-2-substituted piperidine scaffolds, Wei et al. presented a highly diastereoselective cascade process involving a linear N-tert-butanesulfonyl iminoacetate precursor (Scheme 1.9b).45 Using alkynyl organometallics, the configuration of the sulfinyl imine determined the stereochemical outcome at C-2 position allowing to access both, the cis- or trans-diastereomeric products, in switching enantiomers of Ellman’s auxiliary. Using alkyl-, vinyl-, or (hetero)aryl Grignard reagents, the R–OTBS group controlled the stereochemistry in the α-position to the secondary amine, affording only the trans-diastereomer. While these procedures are versatile in organometallic nucleophiles, the sensitivity to the nature of cyclic amines, working well solely for piperidines, limits their synthetic utility.

![Scheme 1.9. Addition or organometallic nucleophiles onto C–N double bonds.](attachment:scheme.png)

Radical cyclization onto C–N double bonds. Radical cyclizations onto C–C or C–N multiple bonds involving heteroatomic tethers are common strategies for the synthesis of saturated heterocycles (Scheme 1.10a).46 In contrast, less focus has been placed on radical cyclizations in which the imine nitrogen ends up the within the ring core (Scheme 1.10b). Studies addressing regiochemistry, reaction rates, effect of imine substituents, and the nature of radicals in such intramolecular radical addition reactions onto imines have been conducted by Takano, Warkentin, Johnston, and Bowman et al.42
Unfortunately, this type of alkyl radical cyclization is often plagued by poor selectivities giving mixtures of nitrogen-containing heterocycles via exo and endo cyclizations, limiting the synthetic utility (Scheme 1.10c). Increasing the electrophilic character of the radical through introduction of a polar component was shown to increase the selectivity correlating to the $\delta^+$, $\delta^-$ character of the C–N double bond (Scheme 1.11). Selective cyclization onto the imine nitrogen atom was achieved affording $N$-alkyl pyrrolidinones in good yield. More nucleophilic methoxymethyl radicals, on the other hand, were proven to add more selectively and with a higher reaction rate onto azomethine imine carbons when compared with simple alkyl radicals.

![Scheme 1.10](image)

Scheme 1.10. Radical cyclizations for the synthesis of nitrogen heterocycles.

In light of this, and the drawback that most current methods dealing with the preparation of substituted alicyclic amines remain multi-step procedures requiring protection-deprotection steps, Bode and co-workers developed SnAP ($\text{Sn} \ (\text{Sn}) \text{Amine Protocol}$) reagents. Using stoichiometric amounts of a Cu(II) complex, aldehydes were readily cross-coupled with these reagents to form $\alpha$-substituted, unprotected thiomorpholines in one step, after intermolecular imine formation (Scheme 1.12). Conceptually, it was envisioned that this process may be initiated via single-electron oxidation and demetalative fragmentation of the organometallic reagent to generate a nucleophilic, $\alpha$-heteroatom stabilized radical, followed by endo-trig cyclization and reduction affording functionalized thiomorpholines. This radical reaction has several advantages over conventional organometallic protocols, which require rigorous

![Scheme 1.11](image)

Scheme 1.11. “Nitrogen-philic” cyclization of electron deficient acyl radicals.
reactions conditions such as dried reagents and apparatus. Furthermore, in agreement with the general advantages of radical over polar reactions, the present method shows exceptional functional group tolerance including (hetero)aromatic, ester, halide, or amide moieties.

Scheme 1.12. Radical cyclization onto imines using SnAP reagents.

Organostannanes are essential and versatile organometallic reagents in organic synthesis, characterized by their bench stability and ease of handling arising from their inertness towards oxygen and moisture. However, their utilization has often been hampered by their possible hazards. While toxicity is sometimes exaggerated from a strict chemical point of view (LD_{50} of Bu_{3}Sn–R derivatives is in the range of 100–300 mg kg^{-1}; cf. caffeine 192 mg kg^{-1}) and methods to remove traces of tin byproducts have been developed, concerns cannot be ignored due to unknown long-term toxicities.

Therefore, a silicon derived alternative, so called SLAP (SiLicon Amine Protocol) reagents, was developed by Bode et al. (Scheme 1.13). Using iridium photocatalysts, functionalized 1,4-diazacyclohexanes and recently thiomorpholines and thiazepanes were obtained displaying a similar substrate scope and functional group tolerance as the previously reported method with SnAP reagents. Stable reagents, application of commercially available aldehydes as coupling partners, and unprotected final products are the core strengths of this methodology, while its application to include scaffolds like morpholines requires further research as no general protocol as in the SnAP method was identified so far.

Scheme 1.13. Photocatalytic radical cyclization onto imines using SLAP reagents.
1.3.3 Cross-Coupling Approaches

As opposed to C–H activation strategies, cross-coupling approaches involve functionalization of pre-functionalized alicyclic amines with coupling partners such as (hetero)aryl halides, boronic acids, and others.

**Boronic acid functionalized saturated N-heterocycles as coupling partners.** As an alternative approach to α-C–H deprotonative functionalization of piperidines, Hesp et al. reported a two-step procedure consisting of an initial Pd-catalyzed Suzuki cross-coupling followed by subsequent tetrahydropyridine reduction (Scheme 1.14). While such a Suzuki coupling of a valerolactam-derived vinyl boronate was initially developed by Occhiato, the inclusion of heteroaromatic electrophiles was met with poor yields and incomplete conversions. Optimization of the catalyst system allowed Hesp to couple heteroaryl bromides with a boronate ester derived from N-Boc-piperidinone, affording α-heteroaromatic Boc-protected tetrahydropyridines. Attempts to expand this methodology to include other scaffolds such as piperazines have not met with success so far.

![Scheme 1.14. α-Heteroaryl piperidines using a Suzuki cross-coupling, reduction sequence.](image)

**Alkyl halide derived coupling partners.** Cossy and co-workers recently described iron- and cobalt-catalyzed coupling of (hetero)aromatic Grignard reagents and saturated halogenated N-heterocycles as part of efforts towards the development of powerful, cheap, and sustainable methods (Scheme 1.15). Although Grignard reagents prohibit usage of reactive functional groups such as esters, aldehydes, or alcohols, the simple, cheap, and scalable protocol gives this transformation some advantages, especially since applicability on several N-heterocyclic scaffolds was demonstrated.

![Scheme 1.15. Fe-, and Co-catalyzed cross-coupling of halogenated alicyclic amines.](image)
Using more functional group tolerant organometallic species, Molander and Buchwald developed nickel- and palladium-catalyzed reductive cross-coupling approaches. The in-situ generation of aliphatic organometallic intermediates using a variety of shelf-stable alicyclic amine halides or tosylates for construction of C(sp^3)–C(sp^3) bonds, makes those methods amenable to parallel synthesis. A surfactant system in Buchwald’s aqueous palladium-catalyzed Lipshutz-Negishi protocol of halogenated saturated N-heterocycles prevented competitive, unproductive reduction pathways, instead affording functionalized, Boc-protected aza-heterocycles in good yields (Scheme 1.16). While this method presents a large substrate scope in terms of aryl halides and N-heterocycles, the cost of the catalyst-ligand system and aliphatic halide precursors is a clear downside of this approach.

**Scheme 1.16.** Aqueous Lipshutz-Negishi cross-coupling of halogenated sat. N-heterocycles with aryl electrophiles.

**Carboxylic acid derived coupling partners.** In 2014, MacMillan et al. were able to circumvent application of a difficult to remove phenyl protecting group and the complex reaction set-up described in the aforementioned iridium-catalyzed photoredox - hydrogen atom transfer C(sp^3)–H functionalization approach for the α-functionalization of alicyclic amines. Carboxylic acids and oxalates act as traceless activation groups for the generation of α-heteroatom stabilized or secondary alkyl radicals, allowing for alkylation of alicyclic amines via conjugate addition. Using halide electrophiles and merging photoredox with nickel catalysis, α-carboxyl C(sp^3) arylation, vinylation, and alkylation was achieved (Scheme 1.17).
In 2016, nickel-catalyzed decarboxylative cross-coupling reactions of redox-active aliphatic N-hydroxyphthalimide esters with aryl boronic acids and alkyl and aryl zinc compounds were reported by Baran and co-workers (Scheme 1.18). Avoiding difficult to scale up photo redox conditions, single-electron-transfer cycle was achieved using a monometallic nickel catalyst. Despite the need for excess nucleophile and a multi-step procedure to afford unprotected, functionalized N-heterocycles, the commercial availability of all reagents as well as robust reaction conditions offers an advantage over previous methods.

**Scheme 1.18.** Ni-catalyzed alkyl-alkyl/aryl coupling of aliphatic redox-active esters.

### 1.3.4 Dearomatization

In addition to functionalization of the saturated core of N-heterocycles, another strategy involves dearomatization of their unsaturated counterparts via hydrogenation. The high stability of such heteroaromatic compounds usually requires elevated temperatures and pressures, adversely affecting the development of enantioselective methods. Furthermore,
catalyst deactivation or poisoning from the more nucleophilic hydrogenation products often limits the substrate scope. A recent report on the asymmetric hydrogenation of quinolines affording tetrahydroquinolines using an iridium catalyst noted, for example, that the natural extension of their work to include isoquinoline failed due to product inhibition. Accordingly, substrate modification via onium formation avoids strong binding to the metal center. Racemic catalytic hydrogenation of pyridines, for example, is usually performed with heterogeneous catalysts in acidic media. Protonation not only activates the pyridines for hydrogenation, it also suppresses catalyst poisoning by the resulting piperidines. Activating and protecting pyridine derivatives via N-benzylation, Zhou et al. reported in 2012 on an Ir-catalyzed asymmetric hydrogenation affording protected, 2-substituted piperidines with good to excellent yields and enantioselectivities. Using the same concept, enantioenriched piperazines were obtained via iridium-catalyzed, asymmetric hydrogenation of substituted pyrazines (Scheme 1.19). One nitrogen atom of the product was blocked through alkylation and in-situ generated acid is proposed to protonate the secondary amine thereby inhibiting catalyst poisoning.

![Scheme 1.19. Catalytic asymmetric hydrogenation.](image)

Unfortunately, the lack of corresponding aromatic starting materials precludes this dearomatization strategy from the synthesis of saturated N-heterocycles as morpholines, thiomorpholines, azetidines or azepanes. With good access to functionalized heteroaromatic compounds, however, this hydrogenation process remains appealing as a powerful tool for a rapid and simple preparation of cyclic amines in a large scale commonly used in chemical industry.
1.3.5 Cyclizations and Annulations Strategies as Alternatives to Access Functionalized Saturated N-Heterocycles

Functionalization of the saturated core fragments as well as dearomatization are common strategies to prepare cyclic amines such as pyrrolidines, piperidines, or piperazines, while methods to include saturated N-heterocycles, such as morpholines, thiomorpholines, or diazepanes are rare. Alkylation followed by lactamization and reduction, or ring-closing metathesis followed by reduction are multistep approaches in which substituents are introduced at the beginning. Such cyclization and annulation processes to access saturated N-heterocycles can feature atom-economic and/or short synthetic sequences, which will be discussed in the following section.

**Nucleophilic substitution using sulfonium salts.** In 2006, Aggarwal and co-workers introduced an annulation reaction for the synthesis of epoxide-fused pyrrolidines and piperidines using tosyl-protected β-keto amines and a diphenyl vinyl sulfonium salt. Expansion of this strategy to include the synthesis of functionalized morpholines, thiomorpholines, and piperazines as well as their medium-sized ring homologues (diazepanes and oxazepanes), was achieved using readily available β-, or δ-heteroatom amines as nucleophiles (Scheme 1.20a,b). While the use of functionalized vinyl sulfonium salts further expanded the substrate scope (Scheme 1.20c,d), the reliance on difficult-to-remove protecting groups on nitrogen (tosyl, nosyl) represents a major limitation of this approach.

![Scheme 1.20](image-url)

_Scheme 1.20. Vinyl sulfonium salts for functionalized, saturated N-heterocycles._
Intramolecular hydroamination. The catalytic addition of an N−H bond across an unsaturated C−C bond, known as hydroamination, is an often-targeted 100% atom economical C−N bond forming reaction. Difficulties originate from inefficient competition between strongly binding amines and weakly binding alkenes for vacant coordination sites at the catalytically active metal center and a high activation barrier due to the electrostatic repulsion between the nitrogen lone pair and the π-electrons of unsaturated C−C bonds. Over recent decades, catalysts to activate amines or unsaturated carbon−carbon bonds have been developed. Rare-earth metals (Y, La, Sm, and Lu) and group 4 metals (Ti, Zr, and Ta), for example, have been proven to be effective in producing pyrrolidines and piperidines in enantiomerically enriched fashion. The extension of this concept to include heterocycles with more than one heteroatom, such as morpholines and piperazines, has only recently been achieved using late transition metal intramolecular hydroaminations. In 2012, Schaefer et al. reported a one-pot process to enantioenriched 3-substituted morpholines and piperazines (Scheme 1.21). An approach involving asymmetric imine reduction after alkyne hydroamination, and isomerization was developed to circumvent the long-standing challenge of intramolecular enantioselective alkene hydroamination.

Unfortunately, application to piperidine and piperazine substrates didn’t reach the enantioselectivities seen in the preparation of substituted morpholines. Nevertheless, this regioselective hydroamination affords unprotected N-heterocycles in high yields.

Metal-mediated carboamination. Palladium-catalyzed alkene aminoarylation has emerged as a useful method for the synthesis of 2-(arylmethyl)pyrrolidines and other saturated N-heterocycles from aminoalkenes and aryl halides. Since the first report in 2004, the Wolfe group has developed a series of Pd-catalyzed stereoselective syntheses of alicyclic amines, including pyrrolidines, morpholines, piperazines, and 1,4-benzodiazepines (Scheme 1.22). This cross-coupling reaction proceeds via a chemoselective intramolecular syn-insertion of an unactivated alkene into the Pd−N bond of an intermediate [Pd^{II}(Ar)(NRR')] complex, followed by reductive elimination resulting in simultaneous C−N and C−C bond formation. While heteroaryl halides were not tolerated, electron-rich and electron-poor aryl halides were suitable coupling
partners affording $N$-Boc-, and $N$-phenyl protected alicyclic amines in good yields. In using substituted aminoalkenes, excellent diastereoselectivities were observed. To access enantioenriched alicyclic 2-(arylmethyl) amines, monodentate phosphoramidite ligand SIPHOS-PE was reported to be of value affording pyrrolidine derivatives in 72–93\% ee.\textsuperscript{71b}

Scheme 1.22. Palladium catalyzed carboamination.

An alternative strategy involving a Cu-catalyzed intermolecular carboamination of vinylarenes with potassium $N$-carbamoyl-$\beta$-aminoethyltrifluoroborates was recently developed by Chemler et al. (Scheme 1.23).\textsuperscript{72} The reaction occurs with terminal, 1,2- and 1,1-disubstituted styrene derivatives affording 2-arylpyrrolidines in moderate to good yields. Alkyl radicals generated in-situ via Cu(II) mediated oxidation of an alkylboron reagent, add to vinylarenes affording a stabilized benzylic radical intermediate. Pairing with a Cu(II) species gives alkylcopper(III) intermediates undergoing C–N bond formation via reductive elimination. Alternatively, oxidation of the benzylic radical followed by trapping with the pendant amine was proposed as a possible reaction mechanism. Using simple to access starting materials, affording Cbz-protected $\alpha$-substituted pyrrolidines, and tolerating reactive functional groups such as esters, this strategy offers itself as a serious alternative to commonly used $\alpha$-lithiation approaches.

Scheme 1.23. Vinylarene carboamination with $\beta$-aminoalkyltrifluoroborate.
1.4 Conclusions

With increasing interest in functionalized saturated N-heterocycles, the need for reliable, robust, and simple methods is growing. Current synthetic strategies require multiple steps to incorporate functionalities on the substrates, and most often furnish protected alicyclic amines, not applicable to further modifications without the additional removal of protecting groups.

In spite of the success of photoredox decarboxylation methods, procedures for direct α-functionalization of available alicyclic amine precursors are seemingly ideal but remain confined to a relatively narrow substrate scope. They often do not offer solutions to more complex N-heterocycles as thiomorpholines, piperazines, medium-sized homologues or new substitution patterns. Annulation, cyclization or dearomatization approaches suffer from the same drawbacks. Additionally, complexity is introduced early in these synthetic endeavors, limiting their application for library synthesis.

While SnAP (tin (Sn) amino protocol) chemistry fulfills our criteria on generality, diversity, simplicity, and access of starting materials, the use of toxic tin reagents is sometimes regarded as a disadvantage, which further encouraged the development of SLAP (silicon amine protocol) reagents in the Bode group. With a low catalyst loading, generation of little non-toxic waste, and a similar substrate scope as SnAP reagents, this photoredox concept has several distinct advantages. However, limitations in the oxidation potentials of such iridium photocatalysts prompts questions as to whether this concept can be applied to other α-heteroatom organosilicon reagents bearing higher oxidation potentials (e.g. α-alkyloxymethyl, or α-alkylthiomethyl trimethylsilane).

Possessing low oxidation potentials, new organotin reagents might enable expansion of the SnAP concept, making it a potential solution for accessing other classes of functionalized saturated N-heterocycles. Furthermore, with numerous ligands reported for copper mediated asymmetric transformations, a catalytic asymmetric one-step approach to access substituted unprotected alicyclic amines seems an unsolved, yet possible problem.

As a consequence, new SnAP reagents were synthesized, characterized and studied, and protocols were developed accessing unprotected N-heterocycles using substoichiometric amounts of copper(II) complexes.
1.5 References


SYNTHESIS OF SATURATED N-
HETEROCYCLES USING SnAP
REAGENTS
2. Synthesis of Saturated N-Heterocycles Using SnAP Reagents*,**

Functionalized saturated N-heterocycles are important scaffolds in the construction of small bioactive molecules. Used as ionizable solubilizing appendages, a tactic often deployed for molecules, which have already been optimized for potency but suffer from poor solubility, cyclic amines such as piperidines, morpholines, or piperazines have gained popularity among medicinal chemists. Recent awareness of the fact that aromatic rings and sp²-hybridized carbon atoms generally have a negative effect on lipophilicity and other important physiochemical parameters, further prompted the usage of saturated N-heterocycles as scaffolds of pharmaceuticals. However, despite the importance of these building blocks and the many methods described in the previous section dealing with their preparation, their application in pharmaceutical set-ups are still rare. There appears to be no general method to introduce diversified substituents late in a synthetic sequence and the requirement of additional manipulations per analogue like protection- deprotection steps, as well as the limited commercial availability of diverse structures further retards their implementation. In this context, identification of robust methods for the coupling of versatile, bench-stable building blocks with a large feedstock of reagents would be ideal for rapid exploring of the chemical space. As a possible solution, our group developed SnAP (tin (Sn) amine protocol) reagents for cross-coupling reactions with aldehydes affording α-substituted, NH-free thiomorpholines (Scheme 2.1).

*Bode group SnAP chemistry 2013: Cu(II) mediated thiomorpholine synthesis using amino tin reagents.

Combination of the SnAP thiomorpholine reagent with various (hetero)aromatic and aliphatic aldehydes afforded imines, which were cyclized under mild conditions at room temperature, giving access to unprotected α-functionalized thiomorpholines in a short sequence. Featured with a broad substrate scope, accepting electronically and sterically diverse aldehydes, under a standard set of reaction conditions, this SnAP protocol could be suited for the preparation of libraries of saturated N-heterocycles, applicable to further manipulations without additional deprotection steps.

As tentative mechanistic studies suggest the oxidative generation of a sulfur-stabilized carbon-centered radical followed of a 6-endo-trig ring closure with an unactivated intramolecular imine (cf. chp. 1.3.2), we thought to explore the development of new SnAP reagents for the preparation of other classes of saturated N-heterocycles containing different radical stabilizing heteroatoms, such as nitrogen for example (Figure 2.1a). While the replacement of the sulfur atom in the SnAP thiomorpholine reagent through a Boc-protected nitrogen should lead to reagents with similar reactivities, replacement with an O-atom would lead to reagents that stabilize an intermediate radical less and possess higher oxidation potentials, questioning the synthesis of morpholines using SnAP reagents (Figure 2.1b).6,7,9a

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**Figure 2.1.** New SnAP reagents design plan.
2.1 SnAP Reagents for the Synthesis of Morpholines and Piperazines

Organostannanes are known to undergo bond fragmentation upon one-electron oxidation giving an organic radical and a stannylium cation fragment.\textsuperscript{8,9} Not surprisingly, unsymmetrically substituted stannanes, such as the SnAP thiomorpholine reagent, lead to the formation of the most stable organic radical upon such oxidative fragmentations. Based on the assumption that, in a neutral molecule, the overlap between a C–Sn σ-bond with the 2p orbital of other heteroatoms such as oxygen or nitrogen might also rise the HOMO level to promote electron transfer, as in β-heteroatom silicon compounds,\textsuperscript{9} reagents for the synthesis of morpholines and piperazines were designed. It should also be noted that the decrease in oxidation potentials can also be explained in terms of stabilization of a possible heteroatom radical cation produced by the electron transfer. The filled σ-C–Sn orbital interacts with the half-filled 2p orbital of the heteroatom producing two new orbitals. Formation of nucleophilic α-heteroatom stabilized carbon-centered radicals, postulated reactive intermediates in SnAP chemistry, is proposed to take place via the generation of such a β-cation radical of the heteroatom, fragmentation of the C–Sn bond, and radical translocation.\textsuperscript{9} The radicals are then proposed to react in an intramolecular reaction with the imine LUMO being located on the azomethine carbon. To this end, and the fact that the preparation of α-alkoxymethyl and α-aminomethyl radicals from α-stannyl ethers and carbamates is known,\textsuperscript{9a,c,10} SnAP reagents for further studies were designed. However, model substrate studies for the preparation of the new α-heteroatom substituted alkylstannane reagents revealed several stability issues of the stannane moieties, including the intolerance towards strong acids. This led to the identification of two protecting groups, the triphenylmethyl (Trtl) and the phthalimide protecting group that could be removed in the presence of the stannane moieties, out of which the Trtl group was selected, for the SnAP reagent preparation, due to higher yields in the alkylation step (Scheme 2.2).

\begin{center}
\textbf{Scheme 2.2.} Preparation of SnAP M and SnAP Pip.
\end{center}
Prepared on multigram scale using inexpensive, straightforward synthetic sequences, reagents 2.2, 2.4 were selected in an effort to expand the SnAP reagent concept (Scheme 2.3). Condensation of SnAP M 2.2 and SnAP Pip 2.4 with (hetero)aromatic and aliphatic aldehydes afforded the corresponding imines. Using a single reaction protocol for the purpose of evaluation, as established for the synthesis of thiomorpholines, copper(II) mediated cyclization afforded α-functionalized NH-free morpholines 2.5a–2.5i and piperazines 2.6a–2.6j in good yields. The salient feature of the SnAP concept, a remarkable tolerance towards functional groups, was maintained tolerating electron-rich, electron-poor, and heteroaromatic aldehydes, as well as substituents in all positions of the aromatic ring. While substrates prone for aza-enolization didn’t afford the imine for cyclization, non-aza-enolizable and cyclic aliphatic aldehydes provided access to morpholine 2.5h and piperazines 2.6h, 2.6i.

Scheme 2.3. Substrate scope with SnAP Morpholine and SnAP Piperazine.
However, despite the exceptional substrate scope and operational simplicity of the SnAP method, we identified some limitations. First, aldehydes with proximal heteroatoms do not undergo reaction, a fact, which we attribute to possible chelation of the copper complex as seen for the preparation of 2.5j. Second, the steric hindrance in combination with the electropositive nature of mesitaldehyde promoted formation of destannylated side products 2.7–2.9 affording almost none of the desired, cyclized product (Scheme 2.4). At this point, it should be mentioned that the detection of trace amounts of reduction product 2.9 and oxidation products 2.7 and 2.8, arising out of an iminium cation intermediated, was noted to form via free α-heteroatom radicals, which supports the aforementioned mechanistic proposal of a radical cyclization using SnAP reagents.

![Scheme 2.4](image)

**Scheme 2.4.** Characterized reaction products in cyclization using SnAP M and mesitaldehyde; NuH = HO-CH(CF3)2. a Reference compound prepared. b Product isolated after NaBH₄ reduction.

Having established that both, morpholines and piperazines are accessible using SnAP reagents, in combination with the remarkable chemical robustness of the stannane group, the preparation of substituted SnAP reagents 2.11–2.14 to access 2,5- and 3,5-disubstituted scaffolds was investigated. All reagents proved to be suitable partners in the copper mediated synthesis, regardless of the stereochemical features of either the SnAP reagents or aldehydes used (Scheme 2.5). The diastereomeric ratio varied depending on the SnAP reagents used. 3,5-Disubstituted morpholines 2.16a–b and piperazines 2.18a–b with substituents in a 1,3-
relationship showed a high diastereomeric ratio towards the thermodynamically favored cis-diastereomers, which are formed via a transition state that minimizes 1,3-diaxial interactions.

Scheme 2.5. Synthesis of disubstituted morpholines and piperazines using SnAP reagents.

SnAP 2-Me-M 2.11 predominantly afforded trans-configured 3,6-disubstituted morpholines 2.15a–b, and SnAP 2-Me-Pip 2.11 afforded the 1,4-diazacyclohexanes 2.17a–b as mixtures of separable diastereomers, favoring the cis-isomers. We attribute the reduced diastereoselectivity with SnAP 2-Me-Pip to the presence of the nitrogen protecting group (Boc) next to the methyl, which is forced into the axial position to reduce steric interactions (Scheme 2.6). Furthermore, racemization during the synthesis of disubstituted morpholines 2.16a–b was not observed using enantiomerically pure SnAP 3-Me-M, permitting fast access to enantiomerically enriched building blocks.

Scheme 2.6. Rationalization of the stereochemical outcome of 2,5-disubstituted piperazines.
The expansion of the SnAP reagents concept for the cross-coupling with aldehydes to afford unprotected mono- and disubstituted morpholines and piperazines demonstrated that a sulfur-stabilized radical is no necessity for the success of the reaction. The fact that all saturated N-heterocycles can be accessed using a single reaction protocol, and the lack of observed 5-exo-trig cyclization, as expected for radical cyclizations onto olefins, encouraged us to explore the preparation of more challenging medium-sized substrates.

2.2 SnAP Reagents for the Synthesis of Medium-Sized Rings

Saturated N-heterocycles can be useful for organizing the overall presentation of functional groups to biological targets and the conformational constraint provided through such scaffolds can afford enhanced binding affinity compared to corresponding linear structures. Conformational restriction has also been correlated with, for example, improved bioavailability. However, the extent to which such frameworks can be utilized in medicinal chemistry endeavors depends on the selective and efficient synthetic methods for their preparation from simple, and abundant starting materials. Saturated medium-ring (7- to 11-membered) heterocycles, in particular, are a class of challenging synthetic targets. Natural products containing medium-ring N-heterocycles, for example, exhibit a broad range of chemical activities, which makes the rarity of such scaffolds among approved pharmaceuticals surprising. For example, medium-sized rings are absent among the current top 200 brand name and top 200 generic drugs. As this could be indicative of the acknowledged difficulties associated with their preparation, air- and moisture-stable SnAP reagents addressing this challenge were designed for the exploration of this less-charted area of chemical space (Scheme 2.7). Reagents were prepared in short and efficient reaction sequences using phthalimide to insert the primary amine of the final SnAP reagents. All reactions were performed on scales of more than 5.0 g and the final unprotected SnAP reagents were stored neat at 0°C for more than 12 months without detectable formation of decomposed material.
Advantages of the SnAP reagents allow easy access to various saturated NH heterocycles using simple methods. Functional groups such as phenols, organohalides, or esters were elaborated onto the desired products, including unprotected phenols, organohalides, or esters giving aldehydes using the corresponding SnAP reagents. Preparation of these reagents is performed in the reaction solvent, isolation is not needed.

Scheme 2.7. Preparation of selected SnAP reagents for the synthesis of medium-sized rings.

2.2.1 Preparation of 7-Membered Saturated N-Heterocycles

Direct closures to medium-sized saturated heterocycles are often slow and hampered by unfavorable entropies and enthalpies of reactions. With stereochemical features resisting medium-ring formation, namely, bond angle deformation, forced adoption of eclipsed conformations, and transannular interactions, reliable methods for their preparation are scare.

Formation of α-substituted, unprotected oxazepanes and diazepanes using SnAP reagents 2.23, 2.29, 2.33–2.35, however, provided the desired products in moderate to good yields (Scheme 2.8). Using the same mild standard conditions as before, the reaction proceeded well with both electron-rich and electron-poor (hetero)aromatic, as well as sterically hindered aldehydes giving the corresponding 7-endo products. Functional groups suitable for further elaboration of the products, including unprotected phenols, organohalides, or esters were tolerated. Imines prepared from cyclic or non-aza-enolizable aliphatic aldehydes all afforded the desired products and similar results were obtained with either nitrogen- or oxygen-based SnAP reagents.

As the imine formation is performed in the reaction solvent, isolation is not needed. Reactions in which imine formations were diluted with additional solvent, then transferred to a pre-mixed copper-complex, afforded products in almost identical amounts. The fact that these SnAP reagents allow simple access to various saturated NH-free N-heterocycles is a major advantage of this approach over other macrocyclization strategies, which most often operate on...
a limited set of scaffolds, require protection-deprotection steps, and high dilutions to prevent intermolecular reactions from happening (cf. chp. 1).

Scheme 2.8. Preparation of 7-membered saturated N-heterocycles using SnAP reagents. a The imine-formation step was diluted with CH₂Cl₂ to 0.0625 M and transferred to the cyclization reaction by a syringe equipped with a filter. b Gram-scale synthesis of substituted 1,4-oxazepane.
Preparing libraries of multi-substituted oxazepanes, for example, is best exemplified looking at SnAP PhOA 2.34. This reagent was prepared in one-step from commercial available starting materials and allows the one-step access of unprotected 3,5-disubstituted oxazepanes. Using commercially available aldehydes as coupling partners, vast numbers of frameworks and substitution patterns are conceivable using SnAP reagents. Furthermore, a gram-scale preparation of 3-(4-trifluoromethyl)phenyl)-1,4-oxazepane (2.36a) was performed using 13.2 mmol (5.0 g) of SnAP OA 2.23. Demonstrating the ease of our approach, precipitation via HCl salt formation from the crude product as the sole method of purification gave the desired product in good yield and purity.

The successful preparation of more-challenging 7-membered alicyclic amines, the tolerance towards substituents in the tethers of the reagents and the generality of the SnAP reaction conditions, prompted us to further explore the limitations of this approach.

2.2.2 Preparation of 8- and 9-Membered Saturated N-Heterocycles

Encouraged by the successful preparation of functionalized 7-membered nitrogen heterocycles, we explored the use of SnAP reagents for the synthesis of 8-, and 9-membered saturated scaffolds. Substituted oxazocanes 24, 41, diazocanes 42, and oxazonanes 30 were obtained in moderate yields (Scheme 2.9).
Featured with a broad substrate scope under a standard set of reaction conditions, aldehydes similar to the syntheses of the saturated 7-membered N-heterocycles, including (hetero)aromatic and aliphatic aldehydes all afforded cyclized NH-free products. As anticipated, cyclization yields were somewhat lower, with the corresponding destannylated imines as primary side products (cf. Scheme 2.4). Screening of reaction conditions did not help to improve the ratio of product and side products, however, including an aromatic ring into the tether as in SnAP BOAC 2.41, facilitated the cyclization affording the corresponding 8-membered products in good yields.

As opposed to the synthesis of 6-membered rings using SnAP reagents, the electronic properties of the aldehydes had a strong influence on the cyclization of the medium-sized frameworks. Less product and more destannylated side products were obtained using electron-rich aldehydes. It is remarkable, however, that this process affords access to 8-, and 9-memberes N-heterocycles, even in cases with SnAP reagents without elements in the backbone to favor cyclization, creating simple access to these challenging to make structures in useful amounts.

2.3 The SnAP Protocol: A Tool to Access Chemical Space?

Genetics is increasingly revealing the root causes of various diseases. However, numerous targets and processes are considered difficult to modulate with small molecules, which is at least in part due to candidate small molecules populating screening collections. Although the criteria that define the part of chemical space of drugs are more or less clear, the synthetic methodologies, which would allow navigating this chemical space, are not easily accessible. Suitable chemical starting points are essential. Drug discovery approaches (i.e. lead optimization) almost inevitably produce heavier and more lipophilic molecules as medicinal chemists add complexity and functionality. Most approaches, however, focus on obtaining individual drug-like molecules so there is little room for optimization (i.e. target-oriented synthesis). This led to the concept of lead-oriented synthesis (LOS) – an approach to prepare libraries of more polar, sp³-enriched compounds with low molecular weight. Sites for further decoration on the scaffolds could give access to diverse screening collections, increasing the methodologies potential, which is where the SnAP protocol comes in. A broad range of functionalized NH-free alicyclic amines for immediate further elaboration can be obtained in one-step using commercially available aldehydes or ketones, facilitating library synthesis and covering a large area of chemical space. The evaluation of the SnAP protocol to drive molecular diversity and ability to help in the coverage of the chemical space was accomplished using LLAMA, an open-access computational tool for decoration of scaffolds with common
medicinal chemistry capping reagents (Figure 2.2).\textsuperscript{22a} A morpholine scaffold prepared using our SnAP protocol was selected and added to this database. In silico decoration with predetermined capping reagents and principal moment of inertia (PMI) analysis of the derived products revealed a good coverage of the chemical space indicating that the SnAP protocol is indeed able to assist significant chemical space to be explored. Furthermore, the tolerance of our approach towards basic functionalities also needs to be mentioned as such groups are an inherent part of most screening libraries and transition metal mediated reactions often do not proceed in the presence of these functionalities due to catalyst deactivation.\textsuperscript{23}

Figure 2.2. Chemical space evaluation of a morpholine scaffold prepared using the Bode group SnAP protocol.

2.4 Conclusions

The generality of the SnAP protocol for the preparation of NH-free 6–9 membered saturated alicyclic amines is commendable since it is known knowledge to the synthetic community that extrapolating reactivity trends from one N-heterocycle to another can sometimes be quite daunting. And although the yields of these substituted medium-sized ring N-heterocycles are modest and variations of the ligand, oxidant, solvent, or temperature did not improve isolated yields, the facile synthesis of the starting materials and the lack of convenient entry into these structures with other methods makes the use of SnAP reagents an attractive approach.
2.5 References


PYRROLIDINES AND PIPERIDINES

USING SnAP-eX REAGENTS
3. Pyrrolidines and Piperidines Using SnAP-eX Reagents*

Functionalized, saturated N-heterocycles often cannot be made using methods applicable on various scaffolds, as it is the case of their heteroaromatic counterparts. Therefore, with the goal to develop a predictable cross-coupling approach for these scaffolds, our group introduced SnAP (tin (Sn) amine protocol) reagents for the simple conversion of aldehydes and ketones into functionalized, unprotected N-heterocycles including thiomorpholines, morpholines, piperazines, and medium-sized homologues, as described in the previous chapters.\textsuperscript{1,2} Bespoke SnAP reagents afforded multi-substituted scaffolds,\textsuperscript{2a} while the application of ketones gave access to spirocyclic structures.\textsuperscript{2b} However, two of the most common saturated N-heterocycles used in pharmaceuticals, substituted pyrrolidines and piperidines,\textsuperscript{3} were not accessible using SnAP reagents. The need for a proximal heteroatom in the SnAP reagents, to lower the oxidation potential of the reagents and differentiate the groups on tin for predictable generation of the most stable radicals, as described in chapter 2, excluded these scaffolds so far (Figure 3.1).\textsuperscript{4,5}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.1.png}
\caption{SnAP-eX concept for the preparation of functionalized pyrrolidines and piperidines.}
\end{figure}

As such, it was proposed that a limited, but important class of frameworks could be accessed using SnAP reagents bearing a radical-stabilizing group ending up exocyclic, rather than endocyclic, ensuring productive radical generation. Reagents for the preparation of pyrrolidines and piperidines with exocyclic NH-Boc or O-MOM groups, so-called SnAP-eX reagents, were subsequently prepared and studied.

3.1 Preparation of Disubstituted Piperidines

Pyrrolidines and piperidines, having exocyclic heteroatoms are found in various pharmaceuticals and make up the basic skeleton of several alkaloids (Figure 3.2). Current approaches for their preparation include C–H functionalizations, cycloadditions, nucleophilic additions to nitrones, or cyclizations. While such approaches are suitable once a lead structure has been identified, substituents are introduced at an early stage of the synthesis, making them less appealing for library synthesis and compound screening approaches.

![Figure 3.2. Heteroatom substituted bioactive piperidines and pyrrolidines.](image)

3.1.1 SnAP-eX Reagent Preparation

To investigate the use of secondary α-heteroatom substituted alkylstannanes, we designed and prepared shelf-stable SnAP-eX 3-O-Ac P 3.3, SnAP-eX 3-O-MOM P 3.6, and SnAP-eX 3-NH-Boc P 3.9 on multigram scale (Scheme 3.1). The eminent chemical robustness of the SnBu3 group allowed for simple functional group modifications allowing access to SnAP-eX reagents in short reaction sequences. While no special precautions are needed, it is important to know that the first product in the reaction sequence towards SnAP-eX reagents 3.3 and 3.6, the tributylstannyl alcohol, is unstable. Containing an unprotected alcohol, this class of compounds is known to undergo the reverse reaction giving back the aldehyde and tributyltin hydride. Therefore, it is important to continue the reaction sequence as fast as possible, protecting the free alcohol.
3.1.2 Preparation of Piperidines using SnAP-eX Reagents

Having the shelf-stable reagents in hand, evaluation of the substrate scope was performed next. Heating of SnAP-eX 3-O-Ac P 3.3, solid supported triphenylphosphine (PPh₃), and 4-( trifluoromethyl)benzaldehyde in THF at 45°C provided the desired imine for further copper(II) mediated cyclization. However, using the standard SnAP conditions – Cu(OTf)₂ (1.0 equiv), 2,6-lutidine (1.0 equiv) in CH₂Cl₂-HFIP (4:1) at room temperature – no reaction took place. Screening of reaction conditions including temperature, solvent, copper sources, and ligands did not improve conversion, with the imine recovered in most instances.

As opposed to previous SnAP reagents, e.g. for the synthesis of morpholines, the heteroatom adjacent to the stannane group of SnAP-eX 3-O-Ac P contains an electron-withdrawing substituent. This could lead to an increase in the oxidation potential, making the first electron transfer step more difficult. Furthermore, as O–Ac groups stabilize a possible carbon intermediate radical less than an O–alkyl groups do (ca. 17.7 kJ mol⁻¹ vs ca. 31.1 kJ mol⁻¹); follow-up fragmentation of the C–Sn group generating the proposed radical might not be
favored. Additional steric factors of the secondary tin nucleophile could be responsible for a higher oxidation potential, as it was shown that the overlap of the C–Sn σ-bond and lone pair of the heteroatom is important to achieve a reduction in the oxidation potential.

Using SnAP-eX 3-O-MOM P 3.6 and SnAP-eX 3-NH-Boc P 3.9, reagents electronically more similar to previous α-heteroatom stannyl SnAP reagents, NH-free 2,3-disubstituted piperidines were obtained in moderate yields under standard SnAP conditions (Scheme 3.2). This also proofs that sterics using SnAP-ex 3.3 was not the main reason that no product was observed, but electronics.

Scheme 3.2. Synthesis of 3-NHBoc and 3-OMOM piperidines from SnAP-eX reagents.
No special precautions were needed for reaction setup, and all reactions were performed using identical conditions without substrate-specific optimization. It was found that using an increased amount of HFIP as reaction solvent, reduced side product formation was observed and shorter reaction times were required. The preparation of NH-free products and broad substrate scope, tolerating various functional groups, the signature features of the SnAP protocol, was also true for SnAP-eX reagents. Electron-rich and electron-poor aldehydes containing unprotected phenols 3.11b, heterocycles 3.10a, 3.10b, 3.11c, 3.11d, or alkyl moieties 3.10d, 3.11e were excellent substrates, providing 3-alkoxy- and 3-aminopiperidines suitable for further elaboration. Furthermore, ketones were also successfully employed, allowing the preparation of polyfunctionalized spirocycles 3.10e, 3.11f, which possess rigid, metabolically robust frameworks, on demand in medicinal chemistry approaches.\textsuperscript{13}

In all cases, only modest diastereoselectivity was observed. A slight preference for \textit{trans}-products was observed in the NH-Boc series, which is presumably due to 1,3-diaxial interactions of the sterically demanding Boc-group on nitrogen (Figure 3.3). The preference for \textit{cis}-products using SnAP-eX 3-O-MOM P 3.6 containing a smaller O-MOM group can be tentatively explained by postulating the formation of a 6-membered chair-like transition state, assuming that the imine is in \textit{E}-configuration.\textsuperscript{14} Chelation of a copper species via the imine nitrogen and O–MOM group might stabilize the \textit{cis}-transition state, leading to a preference for the 2,3-\textit{cis} piperidine products.

\textbf{Figure 3.3.} Proposed pathway for \textit{trans}-, and \textit{cis}-diastereoselectivity in the piperidine synthesis using SnAP-eX reagents.
3.1.3 Enantioenriched SnAP-eX P Reagents

The proposed mechanism of the SnAP protocol involves generation of a heteroatom-stabilized radical via Cu(II) mediated one-electron oxidation, C–Sn bond fragmentation and radical translocation (cf. chap. 1.3.2).\textsuperscript{2e} However, despite the fact that all experiments to date are consistent with this mechanistic picture, tin to copper transmetallation and nucleophilic addition to the imine cannot be rule out in full. Examples of such transmetalations are known and have been reported to occur with stereoretention.\textsuperscript{15} Therefore, using the fact that the tin group is attached to a stereogenic center in the SnAP-eX reagents, enantioenriched SnAP-eX\textsuperscript{3.9} was prepared as test substrate to see if enantioenriched scaffolds are accessible using enantioenriched SnAP reagents (Scheme 3.3).

Scheme 3.3. Preparation of enantioenriched SnAP-eX 3-NH-Boc P.

Addition of Bu\textsubscript{3}SnLi to enantiopure 4-butenesulfinimine derivative 3.12 and a protecting group switch gave access to enantioenriched α-aminoorganostannane 3.9 after further functional group manipulations.\textsuperscript{16}

Using this reagent under standard conditions, piperidine product 3.11a was formed as racemate (Scheme 3.4). While not conclusive, this experiment further supports a free-radical mechanism for the Cu-promoted SnAP protocol, indicating that enantioenriched SnAP reagents are unsuitable tools to access enantioenriched saturated N-heterocycles.

Scheme 3.4. Racemization studies using enantiomerically enriched SnAP-eX 3.9.
3.2 Preparation of Disubstituted Pyrrolidines

Substituted pyrrolidines are important architectures central to life, biology, medicine, and are also privileged catalysts for stereoselective transformations. Further substitution of these templates would give rise to more structural complexity, generating attractive scaffolds important in exploring chemical space as in the preparation of pharmaceuticals. The facile 6-endo-trig cyclization of SnAP-eX reagents for the synthesis of piperidines, encouraged us to explore the preparation of the 2,3-disubstituted 5-membered analogues via a disfavored radical 5-endo-trig cyclization.

3.2.1 SnAP-eX Pyr Reagent Preparation

SnAP-eX 3-O-MOM Pyr and SnAP-eX 3-NH-Boc Pyr reagents, for the synthesis of disubstituted NH-free pyrrolidines, were prepared using analogous routes of their homologues (Scheme 3.5). As before, no special precautions are needed in the reaction sequence accessing these reagents. However, containing an unprotected alcohol in α-position, tributylstannyl alcohols undergo the reverse reaction giving back the aldehyde and tributyltin hydride. Therefore, manipulations of such intermediates are difficult and a low yielding sequence via the preparation of a stable α-amido sulfone was adapted for accessing NH-Boc reagent. In the presence of TMSSnBu3 and CsF, stannylation of in-situ generated Boc-protected imine afforded the corresponding α-NH-Boc stannane in acceptable and reproducible amounts.

Scheme 3.5. Preparation of SnAP-eX reagents for the synthesis of 3-heteroatom substituted pyrrolidines.
3.2.2 Preparation of Pyrrolidines using SnAP-eX Reagents

Using the standard SnAP conditions – Cu(OTf)$_2$ - 2,6-lutidine (1.0 equiv) in CH$_2$Cl$_2$-HFIP at rt – the good functional group tolerance and large substrate scope, as know from previous SnAP procedures, was retained using SnAP-eX reagents 3.19 and 3.22 for the synthesis of unprotected disubstituted pyrrolidines (Figure 3.4).$^6$

![Figure 3.4. Synthesis of 3-amino-/3-alkoxypyrrrolidines using SnAP-eX reagents. $^a$ (CF$_3$SO$_3$Cu)$_2$ • C$_8$H$_8$CH$_3$ (0.5 equiv) used instead of Cu(OTf)$_2$ - 2,6-lutidine (1.0 equiv). $^b$ Relative configuration was established spectroscopically as the coupling constants of the diastereomers are significantly different and in agreement with reported data of related structures.\textsuperscript{14,21}

Aldehydes bearing nitriles 3.23a, esters 3.24a, nitro groups 3.24c, halides 3.24d, and various heterocyclic substrates 3.23c, 3.23d, 3.24c, 3.24d, all are viable substrates. Electron-rich (hetero)aromatic or sterically more demanding aldehydes and ketones gave the corresponding pyrrolidines (3.23b, 3.23e, 3.24d, 3.24e) in low isolated yields at the expense of formation of destannylated side products. However, in some cases (e.g. 3.23c, 3.24d) it was found that the use of an alternative Cu(II) source can provide a small improvement in isolated yields. While not a general solution (cf. 3.23b, 3.24c), it suggests that substrate-specific optimization is possible.

As in the synthesis of piperidines using SnAP-eX reagents, trans-2,3-disubstituted pyrrolidines were isolated using the NH-Boc reagent 3.22. While sterics seem to be more important in the formation of 5-membered scaffolds as opposed to the preparation of piperidines, and is the dominant factor in the formation of the NH-Boc series, chelation of a copper species in the O-MOM series seems to override this preference (Figure 3.5).
The generation of mixtures of separable 3-alkoxypyrrrolidines using SnAP-eX 3.19, with a preference for cis-products, can therefore be explained by postulating the formation of a similar 5-membered envelope-like transition state involving chelation of a copper species.\textsuperscript{14}

\[ \text{Pyrrolidine synthesis: With SnAP-eX 3-NH-Boc Pyr} \]

\[ \text{With SnAP-eX 3-O-MOM Pyr} \]

**Figure 3.5.** Proposed pathway for trans-, and cis-diastereoselectivity in the pyrrolidine synthesis using SnAP-eX reagents.

### 3.2.3 SnAP-eX Reagents for Disfavored 5-endo-trig Radical Cyclizations – A Reflection

The generation of cyclic structures from acyclic scaffolds is indispensable for the construction of complex organic molecules. Radical cyclizations forming 5- and 6-membered rings, in particular, are well documented. However, some cyclization patterns, as for example 5-endo-trig cyclizations, still remain underrepresented. One important factor is certainly the size of the ring being formed. Strain effects, for example, disfavor the formation of 3- and 4-membered rings, whereas entropic factors disfavor cyclization to medium-sized rings. An additional factor is stereoelectronics, describing the efficient overlap of the bond-forming orbitals.

In the case of the SnAP-eX reaction for the preparation of 5-membered saturated N-heterocycles, a disfavored 5-endo-trig radical cyclization onto the azomethine carbon takes place in favor of a 4-exo-trig cyclization onto the imine nitrogen. While strain is no longer an issue in the formation of 5-membered rings, favoring the 5-endo-products, 4-exo-trig cyclizations are commonly favored stereoelectronically, as the orbital overlap for endocyclic closures of less than six atoms is not easily achieved. Computational calculations and follow-up
experiments, however, have shown that 5-endo-trig radical closures are possible to be the kinetically and thermodynamically favored product as the strain of a four-membered ring in the transition state can induce a much higher activation energy.\textsuperscript{19c}

Therefore, we attribute the reliable formation of 5-endo-trig products using SnAP-eX reagents to the thermodynamic preference of forming a more stable C–C bond over a C–N bond also providing a less strained ring system. Also kinetic factors, such as less ring strain in the transition state, the orbital overlap of the SOMO with the lowest occupied molecular orbital (\(\pi^*\)) of the imine, which has the higher orbital coefficient on the carbon, polarization effects (nucleophilic radical adds to electrophilic imine carbon), or angle tightening that improves orbital alignment (C–C=N angle equals ca. 119° vs C–C=C angle of ca. 125°), might all contribute to the observed regioselectivity.\textsuperscript{22}

### 3.3 Conclusions

In conclusion, we have successfully applied the principle of the SnAP chemistry to the development of SnAP-eX reagents for the one-step conversion of aldehydes and ketones into NH-free, saturated, 2,3-disubstituted piperidines and pyrrolidines. The process is distinguished with mild and simple reaction conditions, a remarkable broad substrate scope and functional group tolerance, with simple access to the shelf-stable reagents employed. While this approach might not yet be suitable on large scale, it provides an attractive and reliable approach to library synthesis.

### 3.4 References


Mechanistic Considerations of SnAP Reactions
4. Mechanistic Considerations of SnAP Reactions

Radical reactions have emerged as valuable tool for the preparation of small molecules. However, despite increasing interest in radical reactions, the carbon radical addition to the C=N functionality of imine derivatives has received little attention. As the addition of a neutral species, such as an uncharged free radical, could provide solutions to 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, more general methods should be possible.\(^1\) In light of this fact and inspired by reports from Kagoshima et al. on Cu(II)-mediated intermolecular additions of \(\alpha\)-heteroatom alkylstannanes to PMP-activated imines (Scheme 4.1a),\(^2\) Bode et al. developed SnAP reagents for the synthesis of functionalized saturated N-heterocycles (Scheme 4.1b).\(^3\),\(^4\) Combination of these reagents with commercial available ketones or aldehydes affords stable (ket)imines. Circumventing the poor electrophilicity of imines through the use of intramolecular reactions, subsequent cyclization with the same conditions for all SnAP reagents allows for a simple, mild, and direct synthesis of functionalized NH-free saturated N-heterocycles, which are suitable for immediate further elaboration.

In this chapter, the proposed radical mechanism of the SnAP protocol for the preparation of saturated N-heterocycles will be further elucidated and supported with additional experiments.

**Scheme 4.1.** Cu(II)-mediated addition reactions of \(\alpha\)-heteroatom alkylstannanes to imines.
4.1 Initial Mechanistic Investigations - Radical vs. Polar Mechanism

The addition of organotin species to imines is an underutilized transformation, due to the poor electrophilicity of unmodified imines. A key example from Kagoshima et al. uses stoichiometric amounts of \( \text{Cu(OTf)}_2 \) in the intermolecular addition of \( \alpha \)-heteroatom alkylstannanes to PMP-activated/protected imines, proposed to proceed via a polar mechanism in which a copper(II) species acts as a Lewis acid activating the imine and the stannane acts as the nucleophile.\(^2\) Therefore, mechanistic studies were performed to elucidate if the SnAP chemistry also proceeds via such a polar mechanism. However, when the SnAP cyclization was performed using Lewis acids other than \( \text{Cu(OTf)}_2 \) (e.g. \( \text{BF}_3 \cdot \text{Et}_2\text{O} \), \( \text{Yb(OTf)}_3 \), \( \text{Sc(OTf)}_3 \), \( \text{Zn(OTf)}_2 \), \( \text{AgOTf} \), \( \text{MgCl}_2 \), etc.) no reaction was observed. Also, substrates with proximal heteroatoms possible to chelate a copper complex enhancing the positive charge on the azomethine carbon afforded no desired product, which was seen as evidence that the reaction using SnAP reagents does not follow a polar mechanism (Scheme 4.2a).

Considering a mechanism in which Cu(II) acts as one-electron oxidant as substoichiometric amounts of radical inhibitors like BHT or TEMPO retarded the reaction and alkoxamines arising from possible intermediate radicals were obtained using stoichiometric amounts of TEMPO, a radical cyclization pathway was proposed (Scheme 4.2b).\(^3\) However, despite a possible catalytic cycle, stoichiometric amounts of \( \text{Cu(OTf)}_2 \) are needed, which was assumed to be due to the enhanced basicity of the products over the starting materials, leading to problems of product inhibition and catalyst turnover.

\begin{align*}
\text{a) Exclusion of Kagoshima's polar mechanism} \\
\text{b) Proposed radical mechanism using SnAP reagents}
\end{align*}

\[ \text{Scheme 4.2. Previous mechanistic studies of thiomorpholine synthesis using SnAP reagents.} \]
While the proposal of a radical based mechanism for the SnAP reagents makes sense looking at the experiments performed, further studies were required to strengthen our proposal as the isolated alkoxamine adduct from the addition of TEMPO could also arise from an unproductive side reaction, such as the disproportionation of an organocopper intermediate after transmetalation.\textsuperscript{5} For example, while Lewis acid-mediated mechanism can be excluded based on the aforementioned experiments, investigations aimed at separating Lewis and Brønsted acid mechanisms needed to be carried out to further exclude a polar mechanism as Cu(OTf)\textsubscript{2} is known to be a source of triflic acid (TfOH).\textsuperscript{6} All the more as strong Lewis acids known for a slower generation of H\textsuperscript{+} than Cu(OTf)\textsubscript{2} (e.g. lanthanide triflates) were unsuccessful in mediating the SnAP cyclization.

### 4.1.1 \textbf{Cu(OTf)}\textsubscript{2} as a Source of Triflic Acid – H\textsuperscript{+} Catalysis?

Recent examples have shown that Cu(OTf)\textsubscript{2} can act as a source for triflic acid, acting as a Brønsted acid under conditions proposed to involve metal catalysis.\textsuperscript{6} Therefore, investigations aimed at elucidating the possibility of a Brønsted acid mediated SnAP reaction mechanism were carried out (Table 4.1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions\textsuperscript{a}</th>
<th>Results\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{c}</td>
<td>Cu(OTf)\textsubscript{2} (1.0 equiv), 2,6-lutidine (1.0 equiv), CH\textsubscript{2}Cl\textsubscript{2}-HFIP (4:1, 0.05 M), rt</td>
<td>4.2, 89% with 100% conversion</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)\textsubscript{2} (1.0 equiv), CH\textsubscript{2}Cl\textsubscript{2}-HFIP (4:1, 0.05 M), rt</td>
<td>4.2, 65% with 100% conversion</td>
</tr>
<tr>
<td>3</td>
<td>Bi(OTf)\textsubscript{3} (1.0 equiv), CH\textsubscript{2}Cl\textsubscript{2}-HFIP (4:1, 0.05 M), rt</td>
<td>4.2, ≤ 5% with ≤ 10% conversion</td>
</tr>
<tr>
<td>4</td>
<td>Yb(OTf)\textsubscript{3} (1.0 equiv), CH\textsubscript{2}Cl\textsubscript{2}-HFIP (4:1, 0.05 M), rt</td>
<td>4.2, ≤ 5% with ≤ 5% conversion</td>
</tr>
<tr>
<td>5</td>
<td>Sc(OTf)\textsubscript{3} (1.0 equiv), CH\textsubscript{2}Cl\textsubscript{2}-HFIP (4:1, 0.05 M), rt</td>
<td>4.2, ≤ 5% with ≤ 5% conversion</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OTf)\textsubscript{2} (1.0 equiv), 2,6-di-tert-butylpyridine (2.5 equiv), CH\textsubscript{2}Cl\textsubscript{2}-HFIP (4:1, 0.05 M), rt</td>
<td>4.2, 21% with 30% conversion</td>
</tr>
<tr>
<td>7</td>
<td>TfOH (2.5 equiv), CH\textsubscript{2}Cl\textsubscript{2}-HFIP (4:1, 0.05 M), rt</td>
<td>4.2, 8% with 50% conversion\textsuperscript{d}</td>
</tr>
<tr>
<td>8</td>
<td>TfOH (2.5 equiv), toluene (0.05 M), rt</td>
<td>4.2, 12% with 31% conversion</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reactions were conducted on a 0.15 mmol scale at 23°C for 16 h. \textsuperscript{b} NMR yields from \textsuperscript{1}H measurements of unpurified reaction mixtures with 1,3,5-trimethoxybenzene as an additional internal standard added after the reaction. \textsuperscript{c} Standard SnAP conditions. \textsuperscript{d} Imine hydrolysis as side product.
The standard SnAP reaction involves the addition of stoichiometric quantities of the weak base, 2,6-lutidine, that is proposed to act as a ligand, forming the active copper species giving access to NH-free products. Leaving out 2,6-lutidine, which could interfere with a potential Brønsted acid mediated mechanism, resulted in a decreased yield of the desired product (entry 2). Furthermore, other Lewis acids that are known to be a source of triflic acid did not afford the desired product 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-tert-butylpyridine, a weak base that binds protons but is unable to coordinate to metal centers due to the bulky butyl groups, only retarded the reaction, affording the desired product in moderate amounts (entry 6). Experiments where excess amounts of TfOH was used in place of Cu(OTf)₂ afforded some product (entries 7 and 8), indicating that, although not the main source of product formation, it is possible for product to arise via a H⁺-mediated mechanism.

Furthermore, given that the capture of radicals using TEMPO has been known for more than a decade, the proposal of a radical cyclization for the SnAP process appears to be more than reasonable. However, a wealth of mechanistic studies have demonstrated that carbon-centered radicals in reactions of an organometallic species can be generated as a result of the addition of TEMPO and that it is possible for TEMPO to undergo metal complexation to form a reactive oxidant. It was shown, for example, that CuX₂ • TEMPO can act as an ionic electrophile via single-electron pairing of CuX₂ and TEMPO. The isolation of such an adduct might therefore represent a side reaction that is not connected to the productive Cu(II)-mediated conversion of the SnAP reagent to the thiomorpholine products (Scheme 4.3), emphasizing the need for additional experiments aimed at elucidating the mechanism of the SnAP reaction.

![Scheme 4.3.](image-url)
4.2 Radical Clock Experiments

Mechanistic probes are often applied to study organic reactions that may proceed via radical intermediates. The probe substrate bears a reactive moiety that will undergo a characteristic unimolecular reaction if a radical intermediate is formed, providing evidence that such intermediates are involved in the mechanism. In our mechanistic hypothesis an α-heteroatom stabilized carbon-centered radical is proposed to cyclize with an imine forming a nitrogen-centered radical. Trapping of this open-shell intermediate would provide strong support for a radical cyclization. Therefore, 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. Two common radical clock technologies were employed: The intramolecular addition onto an alkene to generate a more stable radical and an irreversible fragmentation reaction of a strained substrate.

4.2.1 Intramolecular Double Bonds to Trap a Potential N-Centered Radical

Using existing SnAP reagents, aldehydes containing olefins to trap potential aminyl radicals, thereby generating bicyclic structures, were investigated (Scheme 4.4a). Most importantly, the formation of such structures will exclusively indicate the presence of nitrogen-centered radicals, most likely appearing through a radical cyclization. However, the formation of bicyclic structures was not detected examining various aldehydes containing olefin radical clocks (Scheme 4.4b). It was concluded that steric might be the problem as only little product formation next to destannylated side products, but no trapping of a nitrogen-centered radical, was observed. Furthermore, knowing that the addition reaction of N-centered radicals onto alkenes in general is rather slow,9,10 fragmentation reactions that produce a relatively stable imine π-bond were investigated next.

Scheme 4.4. Cascade cyclization reactions for mechanistic investigations.
4.2.2 Cyclopropane Radical Clock Experiments

To make sure that our radical indicator reaction is fast enough to compete with processes that intercept the proposed intermediates, SnAP reagents for nitrogen radical fragmentation with known fast kinetics were designed. As such, the unsubstituted cyclopropane analogue 4.6 was synthesized in a short reaction sequence (Scheme 4.5). Starting from naturally occurring 1-amino-1-cyclopropane carboxylic acid, reduction, nitrogen protection, alkylation, and deprotection provided radical clock SnAP morpholine.

![Scheme 4.5. Preparation of radical clock SnAP reagent.](image)

To examine our hypothesis, an imine formed from the radical clock SnAP reagent 4.6 was employed under standard SnAP cyclization conditions. As ring opening of the cyclopropane affords an unstable imine product, NaBH₄ reduction was performed on the crude material. Subsequent detection and isolation of ring opened products 4.7, 4.8 confirmed the proposal of a free radical SnAP cyclization (Scheme 4.6).

![Scheme 4.6. Radical clock SnAP reaction to detect nitrogen-centered radicals.](image)
The structure of the isolated product was confirmed via independent preparation (Scheme 4.7). The amino alcohol required for the synthesis of the vinyl SnAP reagent 4.14 was obtained through a diastereoselective addition of vinylmagnesium bromide to N-sulfinyl imine 4.9 followed by simultaneous amine and alcohol deprotection. Cyclization using 4.14 under the same conditions as in the radical clock experiment afforded cis-2,6-disubstituted morpholine 4.8, confirming the structure of the ring opened product isolated from the radical clock experiment.

Additional control experiments were performed to confirm that the ring-opened products are the direct result of the SnAP cyclization and subsequent cyclopropane fragmentation (Scheme 4.8). Only destannylated and no ring-opened products were observed when the radical clock SnAP reagent 4.6 was subjected to the standard SnAP conditions without prior imine formation (Scheme 4.8a). Additionally, no cyclopropane fragmentation was observed when a reagent similar to the radical clock SnAP reagent, but without the labile stannane group, was used (Scheme 4.8b), supporting our proposal of a radical-based SnAP cyclization.
4.3 Solvent Effects

Having established that the SnAP process involves free radicals and knowing that solvents often execute a prominent role in the behavior of a reaction due to specific solute-solvent interactions at various stages of a chemical transformation, we were interested to elucidate the role of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) in the reaction. Among protic solvents, HFIP exhibits unique properties being at the top of Reichardt's polarity scale, and H-bond donation scale.

H-bond donation from HFIP was proposed to activate the imine towards the nucleophilic radical addition in making the imine more electrophilic, circumventing the need for an activating protecting group. Therefore, formation of possible HFIP complexes with the starting imine 4.1 and the NH-free product N-heterocycle 4.2 were studied. The stoichiometries of the imine-HFIP and morpholine-HFIP complexes were determined using $^1$H NMR experiments, recording the change in chemical shift of the HFIP C–H proton at changing molar ratios while keeping the total concentration of the two binding partners constant. Both resulting Job plots show a maximum at ca. 0.53, suggesting that the stoichiometries of binding for both imine and morpholine with HFIP are 1:1, demonstrating the formation of the proposed HFIP complex with the imine (Figure 4.1.a, b). However, as the complexation shift ($\Delta \delta$) of the HFIP C–H resonance is more significant for the NH-free morpholine-HFIP complex than for the imine-HFIP complex, morpholine complexation seems of more relevance despite similar stoichiometries.
In the seminal SnAP publication,\textsuperscript{3d} it was proposed that association of the active copper species with the more basic amine products prevented the use of substoichiometric amounts of Cu(OTf)\textsubscript{2}, termed product inhibition. As the NMR studies described above indicated that HFIP complexes to the basic amine products, the ability of this complexation to break up unproductive product-copper complexes was investigated.

Table 4.2 depicts the results of a short solvent screening to overcome product inhibition. When the standard reaction conditions were employed, full conversion was observed (entry 2). However, when the Cu(OTf)\textsubscript{2} loading was reduced to 20 mol \%, only small amounts of N-heterocycle formation was observed, indicating product inhibition or catalyst decomposition (entry 3). Using an increased amount of HFIP, some catalyst turn-over was observed and full conversion was achieved using 50 mol \% of Cu(OTf)\textsubscript{2} (entry 4–6). This observation was consistent with other research groups in which product inhibition was proposed, sequestering the catalyst from the catalytic cycle.\textsuperscript{14} This suggests that the proposed product inhibition and the formation of a HFIP-N-heterocycle complex to overcome this phenomena are valid assumptions, although we cannot rule out coordination of HFIP to Cu(OTf)\textsubscript{2} to produce a more active species.
Table 4.2. Optimization of reaction conditions to overcome proposed product inhibition.\textsuperscript{a}

\begin{tabular}{|c|c|c|c|c|c|}
\hline
Entry & Cu(OTf)\textsubscript{2} [mol %] & Ligand (Cu\textsuperscript{II}-Ligand 1:1) & Solvent & Conv. [%]\textsuperscript{b} & Yield 4.2 [%]\textsuperscript{b} \\
\hline
1 & 100 & - & CH\textsubscript{2}Cl\textsubscript{2}-HFIP (4:1, 0.05 M) & 100 & 65 \\
2 & 100 & 2,6-lutidine & CH\textsubscript{2}Cl\textsubscript{2}-HFIP (4:1, 0.05 M) & 100 & 89 \\
3 & 20 & 2,6-lutidine & CH\textsubscript{2}Cl\textsubscript{2}-HFIP (4:1, 0.05 M) & 33 & 25 \\
4 & 20 & 2,6-lutidine & CH\textsubscript{2}Cl\textsubscript{2}-HFIP (1:1, 0.05 M) & 41 & 35 \\
5 & 20 & 2,6-lutidine & HFIP (0.05 M) & 64 & 56 \\
6 & 50 & 2,6-lutidine & HFIP (0.05 M) & 100 & 88 \\
\hline
\end{tabular}

\textsuperscript{a} Reactions were conducted on a 0.15 mmol scale at 23°C for 16 h. \textsuperscript{b} NMR yields from \textsuperscript{1}H measurements of unpurified reaction mixtures with 1,3,5-trimethoxybenzene as an additional internal standard added after the reaction.

4.4 Extended Mechanistic Picture

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,\textsuperscript{15} an updated mechanistic picture is proposed (Scheme 4.9). Including the fact that no reaction takes place in the absence of HFIP, the precedents of HFIP to take part in a nucleophile-assisted cleavage of stannane radical cations,\textsuperscript{16} often seen in organosilane cation radicals,\textsuperscript{17} and the isolation of stoichiometric amounts of Bu\textsubscript{3}Sn-OCH(CF\textsubscript{3})\textsubscript{2}, a HFIP nucleophile-assisted cleavage is included in the updated mechanistic picture. The formation of Bu\textsubscript{3}Sn-OCH(CF\textsubscript{3})\textsubscript{2} in a ca. 1:1 ratio to the desired N-heterocycle furthermore supports the proposal that the reaction is driven by the formation of the thermodynamically strong Sn–O bond (548 kJ mol\textsuperscript{-1}) vs. Sn–C (ca. 238 kJ mol\textsuperscript{-1}), which facilitates fragmentation.\textsuperscript{18} Imparting the required electrophilic character for radical reduction through protonation of the nitrogen HFIP plays an important part in the SnAP radical cyclization.\textsuperscript{19}
4.5 Conclusions

Although a thorough mechanistic investigation has not been pursued, several observations are consistent with the mechanism. As Cu(OTf)$_2$ is known to be a source of triflic acid, investigations in this direction were undertaken and a Brønsted acid mediated mechanism could be excluded. Trapping of the initial radical with TEMPO provided some evidence of a radical cyclization, where subsequent radical clock experiments reinforced this initial proposal, in which HFIP seems to be important at various stages of the process.

4.6 References


Catalytic Asymmetric Synthesis of 6-Membered N-Heterocycles
Organic compounds containing nitrogen atoms at a stereogenic center are ubiquitous in nature and are of unparalleled importance in pharmaceutical substances. As a result, significant attention has been devoted to the study of methods for the stereoselective generation of chiral centers containing nitrogen atoms. Addition reactions to C=N functionalities or α-lithiation - trapping sequences using chiral diamine ligands (e.g. (−)-sp or (+)-sp surrogates) for protected saturated mono-nitrogen heterocycles are the most studied approaches. However, progress for the enantioselective α-functionalization of Boc-protected piperazines, for example, has been rather slow since the first report of a (−)-sp-mediated chiral deprotonation from McDermott et al. in 2008. Furthermore, as most of the aforementioned C=N addition reactions make use of diastereoselective processes involving chiral C=N electrophiles or the addition of chiral nucleophiles, obvious drawbacks as the need for stoichiometric quantities of the chiral source or the removal and recovery of the chiral auxiliary.

Bye permitting the generation of large amounts of enantioenriched materials for the investment of small quantities of a chiral source, catalytic enantioselective addition reactions offer an attractive solution. However, photo-, or thermo-activated imine isomerization, or isomerization via reversible N,O-acetal formation and the resulting conformational freedom of the metal-coordinated form of these imines make progress in this area rather slow (Figure 5.1). In addition, most chiral additives get trapped by the basic nitrogen atoms of the final products, making catalytic reactions using imines as electrophiles and metal as catalysts difficult to perform.

Figure 5.1. Imine coordination modes, isomerization, and selectivity.

Circumventing these imine functionalizing challenges through the addition of a second coordination side for catalyst binding and withdrawing electron density from the nitrogen atom preventing product inhibition, a multitude of imine derivatives have been studied (Figure 5.2). While successful, difficulties associated with the removal of these groups makes such an approach unappealing for the development of a catalytic SnAP protocol. Therefore, and with the idea in mind not to lose the signature feature of the SnAP protocol, the direct access of NH-free saturated N-heterocycles, a screening of ligands and metal salts was performed. Reduction in the amount of Cu(OTf)₂ in the overall redox-neutral reaction would aid the development of an enantioselective process as smaller quantities of a chiral source could be applied.

**Figure 5.2. Selected imine activating groups.**

### 5.1 Catalytic Synthesis of 6-Membered N-Heterocycles

Despite the exceptional functional group tolerance, scope of N-heterocycles, and operational ease of the SnAP protocol, we have identified the need for a stoichiometric amount of Cu(OTf)₂ as a major limitation. It complicates the purification, creates additional waste, limits possibilities for enantioselective processes, and is at odds with the current mechanistic picture, which we attributed to product inhibition – a common obstacle for metal-catalyzed reactions in which the products are more basic than the starting materials.

As the preparation of more reactive azastannatrane SnAP reagents failed due to stability issues (Figure 5.3), and encouraged by the fact that the SnAP reaction conditions for all reported saturated N-heterocycles are rather similar, we wondered if a general catalytic protocol, applicable to various scaffolds, could be identified (Scheme 5.1).

**Figure 5.3. Azastannatrane SnAP reagents.**
5.1.1 Screening and Optimization of Reaction Conditions

Investigation into the development of catalytic conditions for the SnAP reaction began by screening various ligands. The imine formed from SnAP M reagent 5.1 and the sterically demanding, reactive electron deficient 2-chloro-4-fluorobenzaldehyde was chosen for a ligand screening, with 1,3,5-trimethoxybenzene added at the end of the reaction as an internal standard (Table 5.1). Product inhibition had thus far precluded the use of substoichiometric amounts of Cu(OTf)$_2$, as shown by experiments with 20 mol % Cu(OTf)$_2$ (entries 1–2). While heating to 90 °C increased conversion, poor substrate scope was observed for these conditions (entries 3–5). Examination of ligands often used in copper-catalyzed reactions, such as phenanthrolines, bipyridines, salen derivatives, diamines or phosphines were not successful, and full conversion was not achieved (entries 6–14).

Fortunately, a single ligand class, bisoxazoline ligands, led to appreciable conversion, and we established that 20 mol % of Cu(OTf)$_2$, in combination with 20 mol % L12, promoted full conversion for using electron-deficient and electron-rich benzaldehydes (entries 15–24). Further optimization focusing on the reaction temperature and solvent revealed two crucial parameters: 1) the integrity of the catalyst and 2) the use of HFIP as the sole solvent to overcome product inhibition (cf. chp. 4.3). Heating the reaction to induce catalyst turnover was detrimental (entry 25), an observation that we attribute to the instability of the active species in the presence of NH-free products at increased temperatures. With HFIP as solvent, we were able to reduce the loading of the catalyst to 5 mol % achieving almost full conversion within 9 hours (entries 26–27). We attribute this success to the beneficial effect of HFIP, a solvent with strong H-bond donor abilities, in forming H-bond complexes with the NH-free alicyclic amine products promoting turnover of the Lewis acidic copper species (cf. chp. 4.4).
With optimal reaction conditions in hand, a screening of metal salts was carried out. We observed that Cu(II) salts with coordinating anions (e.g. chloride, bromide, acetate) obstructed the catalytic reaction while Cu(II) salts containing non-coordinating anions (e.g. trifluoroacetate, triflate, tetrafluoroborate, hexafluorophosphonate, or perchlorate) enhanced the reaction rate and exhibited good catalytic activity. Copper(I) salts (e.g. CuI, Cu(OTf) • C₆H₅CH₃, CuPF₆(CH₃CN)₄, CuCN, CuTC) all followed the same trend. However, an increased catalyst loading was necessary to achieve similar results as in reactions performed with copper(II) salts. Lewis acidic metals salts derived from scandium, magnesium, manganese, silver, zinc, titanium, and others, did not prove to be catalytically active and Cu(OTf)₂ was selected for further studies.⁹
Table 5.1. Reaction optimization and ligand screening.

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<th>Conv. [%]</th>
<th>Yield [%]</th>
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L4: R = Me  
L5: R = Ph  
L6: R = Mes  
L7: R = H & C₆H₄ Backbone  
L8: R = tBu & C₆H₄ Backbone  
L9  
(+)-sp  
(R)-TRIP  
L10: R = H  
L11: R = Me  
L12: R = Ph; L13: R = iPr  
L14: R = tBu; L15: R = Bn

\(^a\) Reactions were performed on a 0.15 mmol scale. \(^b\) Yield were calculated from \(^1\)H NMR of unpurified reaction mixtures with 1,3,5-trimethoxybenzene as an additional internal standard. \(^c\) Reaction was performed at 90°C. \(^d\) Reaction was performed with 4-methoxybenzaldehyde instead of 2-chloro-4-fluorobenzaldehyde. \(^e\) Reaction was performed at 45°C. \(^f\) Reaction was performed in HFIP as the sole solvent.
5.1.2 Synthesis of Substituted Morpholines, Thiomorpholines, and Piperazines

With the optimized conditions, morpholines 5.4 and thiomorpholines 5.5 were prepared using substoichiometric amounts of Cu(OTf)$_2$ using the corresponding SnAP reagents (Scheme 5.2). Aromatic, heteroaromatic, and branched aliphatic aldehydes gave the NH-free alicyclic amines in moderate to good yields. Furthermore, we were pleased to find that – unlike for the stoichiometric variants$^{10}$ – all regioisomers of pyridine-derived carboxaldehydes and related heteroaromatic aldehydes with proximal heteroatoms were excellent substrates, an outcome that we attribute to the use of the increased amount of HFIP. For some substrates, such as those containing additional coordinating groups, a higher catalyst loading was needed to achieve full conversion (e.g. 5.4d). Substrate specific optimization was also possible; for example, for the gram-scale preparation of 5.2 and 5.5.c, a catalyst loading of 5 mol % could be used. However, a few limitations remain, including the fact that aliphatic substrates prone to enamine formation (product 5.5k) mostly afford destannylated side products.$^9$

**Scheme 5.2.** Catalytic synthesis of morpholines and thiomorpholines. $^a$ Cu(OTf)$_2$ (10 mol %), (±)-PhBox (10 mol %), HFIP (0.1 M). $^b$ Cu(OTf)$_2$ (20 mol %), (±)-PhBox (20 mol %), HFIP (0.05 M). $^c$ Reaction on a 5.0 mmol scale: Cu(OTf)$_2$ (5 mol %), (±)-PhBox (5 mol %), HFIP (0.1 M), rt, 36 h.
Interestingly, the same conditions did not prove as effective for piperazine synthesis using SnAP Pip reagent 5.6, with increased amounts of destannyalted side products observed. For this substrate, the use of 2,2,2-trifluoroethanol (TFE) instead of HFIP or a combination of Cu(OTf)$_2$ (10 mol %) and 2,6-lutidine (10 mol %) as the ligand was found to be optimal, provided that an increased amount of a protic solvent was employed to promote turnover. In this case acetonitrile was identified as a beneficial additive, reducing the amount of destannyalted side products (Scheme 5.3). Aldehydes containing various functional groups, such as unprotected phenols (5.7b), aryl halides (5.7c), or diverse heterocycles (5.7e–5.7j) enabled the preparation of NH-free scaffolds suitable for immediate further elaboration.

\[ \text{Conditions A: Cu(OTf)$_2$ - (±)-PhBox (10 mol %), TFE (0.1 M), rt, 20 h; Conditions B: Cu(OTf)$_2$ - 2,6-Lutidine (10 mol %), HFIP-CH$_3$CN (4:1, 0.1 M), rt, 20 h.} \]

Scheme 5.3. Catalytic synthesis of piperazines.

As with the synthesis or morpholines 5.4 and thiomorpholines 5.5, these conditions also tolerate carboxaldehydes with proximal heteroatoms (5.7e–5.7h), which is worth mentioning as such piperazines could not be prepared using the stoichiometric SnAP protocols reported.

5.1.3 Synthesis of α-bis-substituted Morpholines

The ability to incorporate heterocyclic aldehydes with proximal heteroatoms into the α-position of saturated N-heterocycles further expands the accessible substrate scope using the SnAP protocol. Various substituents can be placed into the backbone of the SnAP reagents themselves, or in the α-position via (ket)imine formation, cyclization.$^9,^{10}$ We had previously studied substitution at all positions of the saturated N-heterocyclic scaffolds except for that.
adjacent of the tributyltin moiety. Therefore, to complete our studies on ring substitution, we investigated the use of α-bis-substituted SnAP reagents, which would afford two adjacent stereocenters upon ring closure.

Using a short reaction sequence, shelf-stable α-bis-substituted SnAP reagents 5.10 and 5.11 were readily accessed, with only a single purification needed throughout the entire sequence (Scheme 5.4). Stannylation of aldehydes generated tributystannyl alcohols, which decompose in neat form within minutes at room temperature. Immediate mesylation afforded tributylstannyl mesylates, which then gave the stable phthalimide protected SnAP 6-Me-M and SnAP 6-Et-M reagents after nucleophilic substitution. The incorporation of substituents other than alkyl groups was unsuccessful as the tributylstannyl alcohols derived from benzaldehydes, for example, are not stable enough to be isolated and in-situ mesylation did not afford the protected α-alkoxytin compounds.

![Scheme 5.4](image)

**Scheme 5.4.** Preparation of α-bis-substituted SnAP reagents for the synthesis of unprotected 2,3-disubstituted morpholines.

With the reagents 5.10 and 5.11 in hand, the aforementioned conditions for the catalytic synthesis of morpholines were applied and 2,3-disubstituted morpholines 5.12a–c and 5.13a–c were afforded in good to excellent yields and high diastereoselectivity after condensation with representative aldehydes (Scheme 5.5). The facile formation of such vicinal disubstituted scaffolds from sterically more demanding SnAP reagents represents a promising approach towards more congested structures, which are difficult to make by other methods or often require harsh conditions.

Currently, these catalytic protocols are limited to the formation of α-, and α, β-substituted morpholines, thiomoropholines, and piperazines. The formation of spirotcycles using ketone substrates, the cyclization with SnAP-eX reagents, or the formation of larger rings, such as diazepanes, which were easily obtained under the stoichiometric conditions, was unsuccessful. With further modification of the ligand and reaction conditions, we expect to address some of these issues and identify more general catalytic conditions.
5.2 Catalytic Asymmetric Synthesis of 6-Membered N-Heterocycles

The identification of substoichiometric reaction conditions comprising a bisoxazoline ligand presented us with the exciting opportunity for the development of ligand-controlled enantioselective variants. Catalytic asymmetric methods for the generation of enantioenriched saturated N-heterocycles remain quite rare and have various limitations, such as the need for complex linear precursors, protecting groups, or a narrow substrate scope.\(^{12}\)

In a preliminary experiment we were pleased to find that when using SnAP M 5.1 was used in combination with (S)-PhBox as the ligand, enantioenriched morpholine 5.14 was obtained in 86% yield and a promising enantiomeric ratio of 71:29 (Table 5.2, entry 1). However, an extended screening of bisoxazoline ligands\(^{13}\) did not lead to a major improvement of the enantiomeric ratio. The results also did not provide a clear picture in which direction to change the ligand structure to improve enantioinduction (entries 2–12). Therefore, several reaction parameters were screened in an effort to improve the reaction conditions for a catalytic asymmetric transformation (entries 13–20).\(^{9}\)
Table 5.2. Bisoxazoline ligand screening for enantioinduction.

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<th>Entry</th>
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<td>100</td>
<td>88</td>
<td>70:30</td>
</tr>
<tr>
<td>15$^f$</td>
<td>20</td>
<td>L12</td>
<td>N.D.</td>
<td>N.D.</td>
<td>70:30</td>
</tr>
<tr>
<td>16$^g$</td>
<td>20</td>
<td>L12</td>
<td>N.D.</td>
<td>N.D.</td>
<td>71:29</td>
</tr>
<tr>
<td>17$^h$</td>
<td>20</td>
<td>L12</td>
<td>N.D.</td>
<td>N.D.</td>
<td>70:30</td>
</tr>
<tr>
<td>18$^i$</td>
<td>20</td>
<td>L12</td>
<td>100</td>
<td>85</td>
<td>72:28</td>
</tr>
<tr>
<td>19$^i$</td>
<td>20</td>
<td>L12</td>
<td>100</td>
<td>78</td>
<td>62:38</td>
</tr>
<tr>
<td>20$^{i,k}$</td>
<td>20</td>
<td>L12</td>
<td>36</td>
<td>30</td>
<td>70:30</td>
</tr>
</tbody>
</table>

Ligands:

- L12: R = iPr
- L13: R = nPr
- L14: R = tBu
- L15: R = Bn
- L19: R = Mes
- L20: R = p-OMePh
- L21: R = p-CF$_3$Ph
- L22: R = 2-Naphthyl
- L23
- L24
- L25
- L26

a Reactions were performed on a 0.10 mmol scale. b Yields were calculated from $^1$H NMR of unpurified reaction mixtures with 1,3,5-trimethoxybenzene as an additional internal standard. c Daicel Chiralpak ADH (4.6 x 250 mm), eluent: 4% iPrOH in hexane + 0.1% Et$_3$N, flow: 0.80 mL min$^{-1}$, detection: 254nm. d Reaction was performed at 0°C. e Cu(OTf)$_2$-Ligand (2:1). f Reaction was stopped after 1 h. g Reaction was stopped after 2 h. h Reaction was stopped after 4 h. i Reaction was performed in CH$_2$Cl$_2$-HFIP (4:1). j Reaction was performed in CH$_2$Cl$_2$-TFE (1:1). k Reaction performed at −30°C.
Reducing the temperature to just above the freezing point of HFIP resulted in a slight increase of the enantiomeric ratio, while switching to 2,2,2-trifluoroethanol and reducing the temperature even further had no beneficial effect (entries 13, 19–20). Furthermore, it was found that when the reaction is conducted with excess Cu(OTf)₂ (40 mol %) relative to the ligand (20 mol %) the reaction proceeded to completion without a significant decrease in enantioselectivity. This highlighted the importance of ligand acceleration in this reaction, and excluded the presence of a background reaction responsible for the rather low enantiomeric ratio (entry 14). Catalyst poisoning by the NH-free product heterocycles leading to a decreasing of the enantiomeric ratio was also excluded as samples taken over the course of the reaction all afforded a similar result (entries 16–18).

Although a useful enantiomeric ratio was not achieved, we were keen to examine a preliminary substrate scope of this catalytic asymmetric SnAP protocol (Scheme 5.6). Unprotected morpholines and piperazines were isolated in low to moderate enantiomeric excess, whereas a racemic product was obtained in the preparation of thiomorpholines 5.5e, which contain a nucleophilic sulfur able to coordinate to the active species. It was observed that electron-rich 5.4a, 5.13c, and 5.15 or sterically demanding 5.13c, 5.15 aldehydes afforded NH-free products in slightly higher enantiomeric excess than electron-neutral 5.14. Furthermore, we were pleased to find that when racemic SnAP 6-Et-M 5.11, a stereoconvergent reaction took place affording enantioenriched 2,3-disubstituted morpholines 5.13a–c, supporting the current mechanistic conjecture that the organostannanes generates a carbon centered radical upon oxidation, also reported by Falck et al. (cf. chp. 4).

![Scheme 5.6. Substrate scope of the catalytic asymmetric preparation of 6-membered saturated N-heterocycles using SnAP reagents.](image-url)
In contrast, most cross-coupling methods of stereodefined nucleophiles relying on a copper catalyst proceed via a stereospecific transmetalation step, and enantioenriched products are accessed only from non-racemic, configurationally stable precursors, which are often difficult to access,\textsuperscript{15} giving our radical based SnAP approach a distinct advantage.

### 5.3 Chemoinformatic Bisoxazoline Ligand Screening

An important application of computational calculations are its implementations in the design of ligands for active species, in which such calculations are done generating optimized structures and energies of reactive intermediates as well as transition states. However, the lack of a detailed mechanistic understanding of the rate and stereodetermining events in a process can hinder its success and it might not feasible to use this technique for catalyst design. Given this limitation, a chemoinformatic approach aimed to find ligands with improved properties for the catalytic asymmetric SnAP transformation was explored. As this approach provides an attractive alternative to common ab initio calculations because no mechanistic information of the transformation is needed, as the substrates are not included in the analysis, a collaboration with the research group of Prof. Dr. Scott Denmark (University of Illinois at Urbana-Champaign, USA) was started.

The implementation of this chemoinformatic optimization approach involves a series of interdependent computational and experimental phases. First, the Denmark group constructed a combinatorial library of 15'936 bisoxazoline ligand structures in silico (Figure 5.4), in which the database of substituents at the R\textsubscript{1} position contains 166 (hetero)aromatic and aliphatic members, the R\textsubscript{2} and R\textsubscript{3} position share a database, which can be either hydrogen, methyl, \textsuperscript{1}Bu, phenyl, 4-methoxyphenyl, or 4-(trifluoromethyl)phenyl, and the R\textsubscript{4} position is either hydrogen, methyl, or a 3-, 4-, 5-, or 6-membered carbocyclic ring. Next, geometries of the ligands were minimized as Cu-bisoxazoline complexes with chlorine atoms occupying the open coordination sites. However, before calculation of the 3D-descriptors of their steric and electronic properties, the copper and chlorine atoms were deleted and the geometries fixed so that the only part going into the descriptor calculation is the bisoxazoline ligand itself. Then, a small subset of the candidates representing the greatest chemical diversity in the library was selected. The candidates of this test set were synthesized in a joint effort (Scheme 5.7), and we evaluated the resulting bisoxazoline ligands in our SnAP transformation measuring the enantiomeric ratio and turnover number (Figure 5.4).

Figure 5.4. Generalized bisoxazoline structure.
Phase-transfer catalysis with a glycine imino ester, using a dimeric cinchona alkaloid phase-transfer catalyst, afforded the desired amino acids for bisoxazoline ligand synthesis upon amine deprotection.

Scheme 5.7. Preparation of selected bisoxazoline ligands.
Reduction and condensation with dimethylmalononitrile,\textsuperscript{18} or preparation of the Weinreb amide 5.24, ketone synthesis 5.25, diastereoselective α-amino ketone reduction followed by deprotection, acylation and cyclization afforded the desired bisoxazoline ligands 5.20 and 5.29 in more than 100 mg each.

The test set of ligands was prepared in a joint effort and the cyclization using SnAP Pip 5.6 in combination with 4-fluorobenzaldehyde was selected as a model reaction (Scheme 5.8). All screening reactions were performed twice on a 0.15 mmol scale with 1,3,5-trimethoxybenzene added as an internal standard at the end of the reaction.

\[ \text{Scheme 5.8. Screening of chemoinformatics bisoxazoline ligand test set.} \]
Scheme 5.8. Screening of chemoinformatics bisoxazoline ligand test set.
As anticipated, a range of results were observed including, ligands forming unreactive species, ligands forming reactive species that generate racemic product, and ligands forming active species that increased the enantiomeric ratio. Next, using a number of different regression algorithms, a correlation of some combination of molecular descriptors and the empirical data is sought and should then be validated for statistical significance. Finally, the mathematical correlation will then be applied to the remainder of the in silico library of bisoxazoline ligands to identify candidates that are predicted to be superior for this given transformation.

5.4 Conclusions

In summary, we have identified catalytic methods for the preparation of substituted, NH-free piperazines, morpholines and thiomorpholines overcoming the aforementioned product inhibition of the stoichiometric SnAP protocols. This robust air- and moisture-tolerant procedure is a valuable addition to the SnAP chemistry and expands the substrate scope to include 2-(pyridine-2-yl) Piperazines and related substrates. A new class of SnAP reagents with additional substituents adjacent to the tin group was introduced, resulting in the diastereoselective preparation of 2,3-disubstituted morpholines. Preliminary findings on the catalytic enantioselective variant provided a promising start for the development of new routes to enantioenriched N-heterocycles and an expanded ligand screening is in progress.

5.5 References


[8] For selected examples on the use of HFIP or TFE to overcome product inhibition, see:


CONCLUSIONS AND OUTLOOK
## 6. Conclusions and Outlook

In our efforts, we have developed new SnAP reagents for the direct transformation of aldehydes and ketones into functionalized, unprotected saturated N-heterocycles (Figure 6.1).\(^1,2\)

**Bode group SnAP protocol:** Cu(II)-mediated preparation of NH-free functionalized sat. N-heterocycles

\[
\begin{align*}
\text{aldehydes; ketones} & \quad \text{3Å MS} \\
& \quad \text{CH}_2\text{Cl}_2, \text{rt} \\
& \quad (k)\text{et}imine \text{ formation} \\
& \quad \text{Cu(II)} \\
& \quad \text{SnAP reagents for the preparation of 6-membered sat. N-heterocycles} \\
& \quad \text{SnAP reagents for the preparation of medium-sized sat. N-heterocycles} \\
& \quad \text{SnAP-eX reagents for the preparation of functionalized piperidines; pyrrolidines}
\end{align*}
\]

**SnAP reagents for the preparation of 6-membered sat. N-heterocycles**

- **SnAP TM**
  - SnAP Thiomorpholine
  - Aldrich no. 798886
- **SnAP M**
  - SnAP Morpholine
  - Aldrich no. 798878
- **SnAP 2-Me-M**
  - SnAP 2-Methylmorpholine
  - Aldrich no. 798951
- **SnAP 3-Me-M**
  - SnAP 3-Methylmorpholine
  - Aldrich no. 798953
- **SnAP 6-Me-M**
  - SnAP 6-Methylmorpholine
- **SnAP 6-Et-M**
  - SnAP 6-Ethylmorpholine
- **SnAP Pip**
  - SnAP Piperazine
  - Aldrich no. 798908
- **SnAP 2-Me-Pip**
  - SnAP 3-Methylpiperazine
- **SnAP 3-Me-Pip**
  - SnAP 3-Methylpiperazine

**SnAP reagents for the preparation of medium-sized sat. N-heterocycles**

- **SnAP OA**
  - SnAP 1,4-Oxazepane
  - Aldrich no. 798916
- **SnAP BOA**
  - SnAP Tetrahydrobenzo-1,4-oxazepine
- **SnAP PhOA**
  - SnAP 3-Phenyl-1,4-oxazepane
- **SnAP DA**
  - SnAP 1,4-Diazepane
  - Aldrich no. 798954
- **SnAP BDA**
  - SnAP Tetrahydrobenzo-1,4-diazepine
- **SnAP OAC**
  - SnAP 1,4-Oxazocane
- **SnAP BOAC**
  - SnAP Tetrahydrobenzo-1,4-oxazocine
- **SnAP DAC**
  - SnAP 1,4-Diazocane
- **SnAP BOAN**
  - SnAP Hexahydrobenzo-1,4-oxazonine

**SnAP-eX reagents for the preparation of functionalized piperidines; pyrrolidines**

- **SnAP-eX 3-O-MOM P**
  - SnAP 3-(Methoxymethoxy)piperidine
- **SnAP-eX 3-NH-Boc P**
  - SnAP 3-(NHBoc)piperidine
- **SnAP-eX 3-O-MOM Pyr**
  - SnAP 3-(Methoxymethoxy)pyrrolidine
- **SnAP-eX 3-NH-Boc Pyr**
  - SnAP 3-(NHBoc)pyrrolidine

**Figure 6.1. SnAP reagent concept and SnAP reagents.**
Air- and moisture stable liquid SnAP reagents with different substitution patterns were prepared and brought to market in collaboration with Sigma-Aldrich. Their usefulness in cross-coupling reactions using aldehydes or ketones to access different scaffolds of functionalized, saturated N-heterocycles, including morpholines, piperazines, and their homologues, has been proven in extensive studies (Figure 6.2). The reaction accepts (hetero)aromatic, glyoxylic, and aliphatic aldehydes not prone to aza-enolization, tolerates various functional groups, and proceeds under mild and simple conditions. Experiments carried out further support the occurrence of proposed radical intermediates\(^3\) in the SnAP protocol and a procedure using substoichiometric amounts of Cu(OTf)\(_2\) in combination with bisoxazoline ligands was developed.

**Figure 6.2.** SnAP reagent substrate overview.

Given the importance of functionalized alicyclic amines in drug discovery approaches and the lack of alternative reliable synthetic methods for their preparation, we believe that the SnAP reagents and their transformation will enhance the toolbox of synthetic chemists. A statement supported by Sigma-Aldrich’s interest in bringing the SnAP reagents to market and requests from pharmaceutical companies directed at this research program.
6.1 Outlook and Future Directions

This dissertation has demonstrated that SnAP reagents are indeed a general tool to access functionalized, saturated N-heterocycles. The expansion of the substrate scope accessible using SnAP reagents, the experiments carried out further supporting a radical mechanism, and the studies on a catalytic asymmetric protocol could guide the direction for additional studies on SnAP reagents.

While the search for surrogates of the possible toxic organostannane group as a radical precursor in the SnAP reagents has been fruitful and silicon based SLAP (SiLicon Amine Protocol) reagents were developed, further improvements on the catalytic asymmetric protocol are indispensable for accessing the product heterocycles in a useful enantiomeric ratio.

Furthermore, the fact that aliphatic aldehydes prone to aza-enolization are not good substrates for the SnAP protocol resulting in poor to moderate yields at best is a major limitation (Table 6.1, entries 1–2). However, inspired by a report on an acid catalyzed intramolecular Mannich reaction in which such imines from aliphatic aldehydes were stabilized as benzotriazole adduct, stoichiometric amounts of benzotriazole were added to the imine formation step of the SnAP reaction (entries 3–5). The resulting benzotriazole intermediates were separated from the molecular sieves as usual and immediately subjected to the cyclization conditions. The reaction with 2,6-lutidine as a ligand for the Cu(II) species gave the desired product in moderate amounts and a reaction with (±)-PhBox afforded the desired product in a clean reaction in almost quantitative yield. While further optimization of the reaction for the application of aliphatic aldehydes to the SnAP protocol is needed, it was shown that benzotriazole can indeed be beneficial to prevent unproductive aza-enolization and that the desired α-aliphatic substituted, saturated N-heterocycles can be obtained in useful amounts using the SnAP reagents developed.

Table 6.1. SnAP protocol for the incorporation of aliphatic aldehydes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu(OTf)₂ (mol %)</th>
<th>Ligand</th>
<th>Conv. [%]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>100</td>
<td>2,6-Lutidine (100 mol%)</td>
<td>100</td>
<td>28</td>
</tr>
<tr>
<td>2a</td>
<td>100</td>
<td>(±)-PhBox (100 mol%)</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>2,6-Lutidine (100 mol%)</td>
<td>100</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>(±)-PhBox (100 mol%)</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>(±)-PhBox (20 mol%)</td>
<td>100</td>
<td>32</td>
</tr>
</tbody>
</table>

a Reactions were performed on a 0.10 mmol scale. b Yields were calculated from ¹H NMR of unpurified reaction mixtures with 1,3,5-trimethoxybenzene as an additional internal standard. c Reactions were performed without the addition of benzotriazole in the imine formation step.
6.2 References


7

EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA
7. Experimental Procedures and Characterization Data

7.1 General Information

7.1.1 General Procedures

All reactions were performed in dried glassware under an atmosphere of N₂. 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 or 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 35–45°C at the appropriate pressure and then at rt, ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Compounds not described in this experimental part were prepared according to literature known procedures.

7.1.2 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. N,N-Dimethylformamide (DMF), acetonitrile (CH₃CN), toluene, tetrahydrofuran (THF) and dichloromethane (CH₂Cl₂) were purified by pressure filtration through activated alumina. 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP), 2,2,2-trifluoroethanol (TFE) and ethanol (EtOH) 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. Commercially available SnAP TM 5.3 (2-(((Tributylstannyl)methyl)thio)ethanamine)¹ for the synthesis of the thiomorpholines was synthesized according to a literature known procedure. Yields given refer to chromatographically purified and spectroscopically pure compounds unless otherwise stated.

7.1.3 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. \(^1\)H NMR and \(^{13}\)C NMR spectra were recorded on a Bruker Avance 400 MHz, 100 MHz spectrometer. \(^1\)H NMR chemical shifts are expressed in parts per million (\(\delta\)) 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 (\(\delta\)) 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, double of doublet of doublet; dt, doublet of triplet; t, triplet; q, quartet; quint, quintet; sext, sextet; hept, heptet; 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 Mel-Temp melting point apparatus and are uncorrected. Chiral HPLC (High-Performance Liquid Chromatography) was performed on Jasco liquid chromatography unit. An ADH and ODH column (0.46 × 25 cm) was used. Details of chromatographic conditions are indicated under each compound. Melting points were measured on an Electrothermal Mel-Temp melting point apparatus and are uncorrected.
7.2 Experimental Section for Chapter 2

7.2.1 Preparation of Tributyl(iodomethyl)stannane

\[
\text{Tributyl(chloromethyl)stannane.} \quad 2 \text{ To a stirred solution of } N,N\text{-diisopropylamine (32.1 mL, 227 mmol, 1.20 equiv) in THF (420 mL) at 0°C was added } n\text{-BuLi (1.6 M in hexanes, 136 mL, 218 mmol, 1.15 equiv) over 30 min. The light yellow solution was stirred for 30 min at 0°C and tributyltin hydride (51.0 mL, 190 mmol, 1.00 equiv) was added dropwise over 10 min. The resulting yellow solution was stirred for 30 min at 0°C and paraformaldehyde (5.98 g, 199 mmol, 1.05 equiv) was added in one portion. The reaction mixture was allowed to warm to rt and stirred at this temperature for 3 h before being cooled to –78°C. Methanesulfonyl chloride (18.4 mL, 237 mmol, 1.25 equiv) was added dropwise over 15 min. The resulting yellow suspension was allowed to warm to rt and stirred for an additional 14 h. H_2O (250 mL) was added in one portion at rt. The layers were separated and the aqueous layer was extracted with hexanes (2 x 200 mL). The combined organic layers were washed with H_2O (2 x 100 mL) and brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes) afforded chloride (57.1 g, 89% yield) as a clear, colorless liquid. \text{^1H NMR (400 MHz, CDCl}_3): \delta 3.06 (s, J^{117/119\text{Sn}-^1\text{H}} = 16.2 Hz, 2H), 1.59–1.44 (m, 6H), 1.32 (sext, J = 7.3 Hz, 6H), 1.08–0.95 (m, 6H), 0.90 (t, J = 7.3 Hz, 9H); \text{^13C NMR (100 MHz, CDCl}_3): \delta 29.0, 27.4, 24.6, 13.8, 9.7. These spectral characteristics were identical to those previously reported.} \quad 3 \text{ Note: The chloride is less UV active as tributyltin hydride but can easily be detected with a KMnO}_4 \text{ stain on TLC as the spot just below tributyltin hydride.}
\]

\[
\text{Tributyl(iodomethyl)stannane.} \quad 4 \text{ A procedure from the literature was modified as follows:} \quad 2 \text{ To a stirred solution of the chloride (54.9 g, 162 mmol, 1.00 equiv) in acetone}
\]

4. Decomposes at room temperature over time. Can be stored neat at –10°C for weeks.
(800 mL) at rt was added sodium iodide (49.7 g, 332 mmol, 2.05 equiv) in one portion. The resulting suspension was stirred at rt for 16 h. The reaction mixture was concentrated to give a colorless suspension that was filtered through a short plug of silica (hexanes rinse). The filtrate was concentrated to afford pure tributyl(iodomethyl)stannane (68.6 g, 98% yield) as a clear, colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.95 (s, $J^{117/119}$Sn-$^1$H) = 17.8 Hz, 2H) 1.62–1.44 (m, 6H), 1.33 (sext, $J = 7.2$ Hz, 6H), 1.08–0.95 (m, 6H), 0.91 (t, $J = 7.2$ Hz, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 29.0, 27.4, 13.8, 10.8. These spectral characteristics were identical to those previously reported. $^5$

7.2.2 Preparation of SnAP Reagents for the Synthesis of Morpholines and Piperazines

$$\text{OH} \quad \text{NH}_2 \quad \xrightarrow{1.0 \text{ equiv Trityl-Cl, 1.1 equiv Et}_3\text{N}} \quad \text{CH}_2\text{Cl}_2-\text{TFE}-\text{AcOH (7:2:1, 0.05 M), 6 h, rt} \quad \text{85\%}$$

- $^{1}$OH-\text{SnBu}_3
- $^{1}$NH-\text{C(Ph)}_3

2-((Tributylstannyl)methoxy)-N-tritylethan-1-amine (2.1). Trityl chloride (1.46 g, 5.25 mmol, 1.05 equiv) in DMF (13 mL) was added dropwise to a solution of 2-aminoethanol (300 µL, 5.00 mmol, 1.00 equiv) and triethylamine (765 µL, 5.50 mmol, 1.10 equiv) in DMF (20 mL) at 0°C. The resulting pale yellow suspension was warmed to 40°C and stirred for 24 h before re-cooled to 0°C. Sodium hydride (440 mg of a 60% suspension in mineral oil, 11.0 mmol, 2.20 equiv) was slowly added and the resulting suspension was allowed to warm to rt. The pale brown suspension was re-cooled to 0°C after 6 h and tributyl(iodomethyl)stannane (2.80 g, 6.50 mmol, 1.30 equiv) was added dropwise over 10 min. The reaction mixture was allowed to warm to rt and stirred for 24 h. The reaction was slowly quenched with H$_2$O (50 mL) at rt. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with H$_2$O (5 x 10 mL), brine (2 x 20 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by flash

---

column chromatography (hexanes:EtOAc 100:0 to 95:5) afforded 2.1 (2.55 g, 84% yield) as a clear, colorless liquid. IR (thin film): ν 3084, 3059, 3030, 2955, 2925, 2870, 2852, 1489, 1449, 1083 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.51–7.44 (m, 6H), 7.30–7.22 (m, 6H), 7.21–7.13 (m, 3H), 3.65 (s, J¹¹⁷/¹¹⁹Sn-¹H) = 14.2 Hz, 2H), 3.45 (dd, J = 5.3, 4.5 Hz, 2H), 2.31 (br t, J = 5.3 Hz, 2H), 2.14 (br s, 1H), 1.57–1.43 (m, 6H), 1.35–1.22 (m, 6H), 1.01–0.78 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 146.3, 128.9, 127.9, 126.3, 75.4, 70.7, 62.1, 43.3, 29.3, 27.4, 13.9, 9.2; Rᵣ = 0.63 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C₃₄H₅₀N₁O₁Sn₁ [M + H]⁺ 608.2916, found 608.2917.

2-((Tributylstannyl)methoxy)ethan-1-amine (2.2). Trityl protected SnAP M 2.1 (8.00 g, 13.2 mmol, 1.0 equiv) was dissolved in CH₂Cl₂:2,2,2-trifluoroethanol:AcOH (7:2:1 v/v, 265 mL) and stirred at rt for 6 h. The clear colorless solution was diluted with CH₂Cl₂ (200 mL) and slowly set to pH ~ 8 with sat aq NaHCO₃ (450 mL) at 0°C. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with H₂O (2 x 30 mL), brine (2 x 50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc:MeOH 100:0 to 90:10 + 0.1% Et₃N v/v) afforded SnAP M 2.2 (4.81 g, 85% yield) as a pale yellow oil. IR (thin film): ν 3372, 2955, 2924, 2870, 1581, 1463, 1375, 1091, 873 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.73 (s, J¹¹⁷/¹¹⁹Sn-¹H) = 7.2 Hz, 2H), 3.35 (t, J = 5.1 Hz, 2H), 2.81 (t, J = 5.1 Hz, 2H), 1.62–1.45 (m, 6H), 1.41 (br s, NH₂), 1.36–1.22 (m, 6H), 1.00–0.79 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 77.8, 62.3, 42.1, 29.3, 27.4, 13.9, 9.2; Rᵣ = 0.12 (EtOAc); ESI-HRMS calcd for C₁₅H₃₆N₁O₁Sn₁ [M + H]⁺ 366.1816, found 366.1813.

tert-Butyl (2-(tritylamino)ethyl)carbamate (S2.1). Trityl chloride (3.35 g, 12.0 mmol, 1.05 equiv) in DMF (10 mL) was added dropwise to a solution of commercially available tert-
butyl (2-aminoethyl)carbamate (1.83 g, 11.4 mmol, 1.00 equiv) and NEt₃ (1.75 mL, 12.5 mmol, 1.10 equiv) in DMF (65 mL) at 0°C. The resulting pale yellow suspension was warmed to 40°C and stirred for 18 h followed by the addition of H₂O (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H₂O (5 x 20 mL), brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to yield S2.1 (4.42 g, 96% yield) as colorless solid that is usually used without further purification in the next step. Purification by preparative TLC (hexane:s:EtOAc 1:9) was performed to afford analytically pure material for characterization. IR (thin film): ν 3315, 3058, 2976, 2926, 2858, 1696, 1490, 1170 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.50–7.43 (m, 6H), 7.30–7.25 (m, 6H), 7.22–7.15 (m, 3H), 4.83 (br s, NH), 3.30–3.16 (m, 2H), 2.25 (t, J = 5.9 Hz, 2H), 1.60 (br s, NH), 1.46 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 156.3, 146.0, 128.7, 128.0, 79.4, 70.8, 44.0, 41.4, 28.6; Rf = 0.28 (hexanes:EtOAc 9:1); ESI-HRMS calcd for C₂₆H₃₀N₂NaO₂[M + Na]⁺ 425.2199, found 425.2208.

**tert-Butyl ((tributylstannyl)methyl)(2-(tritylamino)ethyl)carbamate (2.3).** Sodium hydride (285 mg of a 60% suspension in mineral oil, 7.14 mmol, 1.30 equiv) was washed with pentane (3 x 3 mL) and suspended in DMF (27 mL). The suspension was cooled to 0°C and carbamate S2.1 (2.21 g, 5.49 mmol, 1.00 equiv) in DMF (10 mL) was added dropwise over 10 min. The resulting suspension was allowed to warm to rt. After 60 min, the reaction mixture was re-cooled to 0°C and tributyl(iodomethyl)stannane (2.84 g, 6.59 mmol, 1.20 equiv) was added dropwise over 10 min. The resulting suspension was allowed to warm to rt over 3 h and stirred at rt for 24 h. The reaction mixture was cooled to 0°C and slowly quenched with sat aq NH₄Cl (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with H₂O (5 x 30 mL), brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexanes:EtOAc 100:0 to 97:3) recovered unreacted tributyl(iodomethyl)stannane and afforded trityl protected SnAP Pip 2.3 (2.60 g, 67% yield, rotamers 5:2) as a pale yellow liquid. IR (thin film): ν 3315, 3058, 2955, 2921, 2870, 2851, 1676, 1487, 1455, 1364, 1161 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.53–7.41 (m, 6H), 7.30–7.24 (m, 6H), 7.23–7.13 (m, 3H), 3.36–3.23 (m, 2H), 3.01 (s, J(¹¹⁷/¹¹⁹Sn⁻¹H) = 16.4 Hz, 2H × 0.28), 2.78 (s, J(¹¹⁷/¹¹⁹Sn⁻¹H) = 25.4 Hz, 2H × 0.72), 2.37–2.24 (m, 2H), 1.51–1.40 (m, 6H + 9H × 0.28), 1.38 (s, 9H × 0.72), 1.27 (sext, J = 7.1 Hz, 6H), 0.92–0.75 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 155.7, 146.2, 128.7, 128.0, 126.4, 79.1, 70.9, 51.0, 42.0, 34.1, 29.3, 28.7, 28.6, 27.6, 27.6,
13.9, 10.8, 10.5, 9.7; \( R_f = 0.23 \) (hexanes:EtOAc 10:1); ESI-HRMS calcd for \( C_{39}H_{59}N_2O_2Sn_1 [M + H]^+ \) 707.3601, found 707.3589.

**tert-Butyl (2-aminoethyl)((tributylstannyl)methyl)carbamate (2.4).** Trityl protected SnAP Pip 2.3 (1.00 g, 1.42 mmol, 1.0 equiv) was dissolved in \( CH_2Cl_2:2,2,2\)-trifluoroethanol:AcOH (7:2:1 v/v, 28 mL) and stirred at rt for 6 h. The clear colorless solution was diluted with \( CH_2Cl_2 \) (50 mL) and slowly set to pH ~ 8 with sat aq NaHCO\(_3\) (45 mL) at 0°C. The layers were separated and the aqueous layer was extracted with \( CH_2Cl_2 \) (3 x 20 mL). The combined organic layers were washed with \( H_2O \) (2 x 20 mL), brine (2 x 20 mL), dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc + 0.1% Et\(_3\)N v/v) afforded SnAP Pip 2.4 (572 mg, 87% yield, rotamers 7:3) as a pale yellow oil. IR (thin film): \( \nu \) 3370, 2956, 2924, 2871, 2853, 1678, 1463, 1404, 1365, 1154; \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 3.29–3.13 (m, 2H), 3.04 (s, \( J^{\(117/119\)Sn-1}H \) = 17.2 Hz, 2H × 0.3), 2.88–2.76 (m, 2H and 2H × 0.7), 1.56–1.37 (m, 15H), 1.35–1.19 (m, 8H), 0.96–0.75 (m, 15H); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 170.9, 155.8, 79.6, 79.2, 53.5, 52.1, 40.6, 40.2, 34.1, 33.4, 29.2, 28.6, 27.6, 13.8, 10.5, 9.7; \( R_f = 0.18 \) (EtOAc); ESI-HRMS calcd for \( C_{20}H_{45}N_2O_2Sn_1 [M + H]^+ \) 465.2501, found 465.2487.

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**2-((Tributylstannyl) methoxy)-N-tritylpropan-1-amine (S2.2).** Trityl chloride (3.75 g, 13.4 mmol, 1.05 equiv) in DMF (15 mL) was added dropwise to a solution of 1-amino-2-propanol (1.00 mL, 12.8 mmol, 1.00 equiv) and triethylamine (1.96 mL, 14.1 mmol, 1.10 equiv) in DMF (70 mL) at 0°C. The resulting pale yellow suspension was warmed to 40°C and stirred for 24 h before re-cooled to 0°C. Sodium hydride (1.13 g of a 60% suspension in mineral oil, 28.2 mmol, 2.20 equiv) was slowly added and the resulting suspension was allowed to warm to room temperature. The pale brown suspension was re-cooled to 0°C after 5 h and
tributyl(iodomethyl)stannane (7.17 g, 16.6 mmol, 1.30 equiv) was added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction was slowly quenched with H₂O (80 mL) at rt. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O (5 x 20 mL), brine (2 x 30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexanes:EtOAc 100:0 to 97:3) afforded trityl protected SnAP 2Me-M S2.2 (6.60 g, 83% yield) as a pale yellow liquid. IR (thin film): ν 3331, 3084, 3059, 3031, 2956, 2925, 2870, 2852, 1597, 1490, 1449, 1375, 1046; ¹H NMR (400 MHz, CDCl₃): δ 7.51–7.46 (m, 6H), 7.29–7.24 (m, 7H), 7.21–7.15 (m, 3H), 3.75–3.67 (m, 1H), 3.51–3.42 (m, 1H), 3.41–3.30 (m, 1H), 2.29–2.20 (m, 1H), 2.17–2.06 (m, 2H), 1.55–1.40 (m, 1H), 1.27 (dq, J = 14.4, 7.3 Hz, 6H), 1.11 (d, J = 6.2 Hz, 3H), 0.93–0.81 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 146.5, 128.9, 127.8, 126.2, 79.3, 70.5, 58.6, 48.5, 29.3, 27.4, 17.2, 13.8, 9.1; Rᵣ = 0.83 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C₃₅H₅₅N₉O₁Sn₁ [M + Na]^⁺ 644.2892, found 644.2893.

2-((Tributylstannyl)methoxy)propan-1-amine (2.11). Trityl protected SnAP 2Me-M S2.2 (650 mg, 1.05 mmol, 1.0 equiv) was dissolved in CH₂Cl₂:2,2,2-trifluoroethanol:AcOH (7:2:1, 35 mL) and stirred at rt for 5 h. The clear colorless solution was diluted with CH₂Cl₂ (100 mL) and slowly set to pH ~ 8 with sat aq NaHCO₃ (70 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with H₂O (2 x 20 mL), brine (2 x 10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (CH₂Cl₂:MeOH 95:5 + 0.1% Et₃N v/v) afforded SnAP 2Me-M 2.11 (358 mg, 90% yield) as a pale yellow oil. IR (thin film): ν 3370, 2956, 2925, 2871, 2853, 1576, 1464, 1376, 1068; ¹H NMR (400 MHz, CDCl₃): δ 3.83–3.78 (m, 1H), 3.58–3.49 (m, 1H), 3.27–3.17 (m, 1H), 2.77 (dd, J = 13.0, 3.6 Hz, 1H), 2.69 (br s, 2H), 2.61 (dd, J = 13.0, 7.4 Hz, 1H), 1.59–1.41 (m, 6H), 1.35–1.25 (m, 6H), 1.09 (d, J = 6.2 Hz, 3H), 0.94–0.84 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 80.2, 59.0, 47.1, 29.3, 27.4, 16.4, 13.9, 9.1; Rᵣ = 0.29 (CH₂Cl₂:MeOH 9:1); ESI-HRMS calcd for C₁₆H₃₈N₁O₁Sn₁ [M + Na]^⁺ 380.1970, found 380.1974.
1-(((Tributylstannyl)methoxy)propan-2-amine (2.12).} Sodium hydride (188 mg of a 60% suspension in mineral oil, 4.70 mmol, 1.10 equiv) was washed with pentane (3 x 3 mL) and suspended in DMF (23 mL). The suspension was cooled to 0°C and commercially available 2-amino-1-propanol (321 mg, 333 µL, 4.27 mmol, 1.00 equiv) was added dropwise over 5 min. The resulting suspension was allowed to warm to rt. After 1 h, the reaction mixture was cooled to 0°C and tributyl(iodomethyl)stannane (1.84 g, 4.27 mmol, 1.00 equiv) in DMF (20 mL) was added dropwise over 10 min. The suspension was allowed to warm to rt and stirred for 3 h. The reaction mixture was cooled to 0°C and slowly quenched with sat aq NH₄Cl (5 mL) before being poured onto a mixture of EtOAc:H₂O (4:1, 50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H₂O (2 x 15 mL), brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc:MeOH 10:1 + 0.1% Et₃N v/v) afforded SnAP 3-Me-M 2.12 (1.40 g, 87% yield) as a clear, pale brown liquid. IR (thin film): ν 2957, 2925, 2871, 2853, 1457, 1088 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.81–3.64 (m, 2H), 3.28–3.19 (m, 1H), 3.13–3.02 (m, 2H), 1.67 (br s, NH₂), 1.59–1.41 (m, 6H), 1.35–1.25 (m, 6H), 1.02 (d, J = 6.2 Hz, 3H), 0.98–0.81 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 82.6, 62.5, 46.7, 29.3, 27.4, 19.8, 13.9, 9.2; Rᵣ = 0.17 (EtOAc:MeOH 10:1); ESI-HRMS calcd for C₁₆H₃₈N₇O₇Sn₁ [M + H⁺]⁺ 380.1973, found 380.1973.
**Chapter 7: Experimental Procedures and Characterization Data**

**tert-Butyl (1-((triisopropylsilyl)oxy)propan-2-yl)carbamate (S2.3).** Imidazole (1.46 g, 21.4 mmol, 1.50 equiv) was added in one portion to a solution of the Boc-protected amino alcohol (2.50 g, 14.3 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (72 mL) at rt. The resulting solution was cooled to 0°C and treated with TIPSCl (3.20 mL, 15.0 mmol, 1.05 equiv) over 10 min before stirred at rt for 18 h. The reaction mixture was diluted with CH$_2$Cl$_2$ (50 mL), washed with sat aq NH$_4$Cl (2 x 20 mL), H$_2$O (20 mL), brine (30 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure by rotary evaporation at 40°C, 375 mmHg and then at 100°C, ca. 0.1 mmHg (vacuum pump) for 2 h to remove most of the triisopropylsilanol. Purification by flash column chromatography (hexanes:EtOAc 25:1) afforded the desired product S2.3 (4.11 g, 87% yield) as a clear, pale yellow liquid. IR (thin film): ν 3451, 3354, 2963, 2943, 2894, 2867, 1719, 1706, 1497, 1462, 1365, 1174, 1114, 1060 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 4.69 (br s, 1H), 3.80–3.64 (m, 2H), 3.61 (dd, $J = 9.5$, 3.4 Hz, 1H), 1.44 (s, 9H), 1.16 (d, $J = 6.6$ Hz, 3H), 1.12–1.02 (m, 21H); $^{13}$C NMR (100 MHz, CDC$_3$): δ 155.6, 79.2, 66.7, 48.0, 28.6, 18.1, 17.8, 12.1; R$_f$ = 0.35 (hexanes:EtOAc 20:1); ESI-HRMS calcd for C$_{17}$H$_{37}$N$_1$Na$_1$O$_3$Si$_1$ [M + Na]$^+$ 354.2435, found 354.2436.

**tert-Butyl (tributylstannyl)methyl(1-((triisopropylsilyl)oxy)propan-2-yl)carbamate (S2.4).** Sodium hydride (242 mg of a 60% suspension in mineral oil, 6.03 mmol, 2.00 equiv) was washed with pentane (3 x 2 mL) and suspended in DMF (20 mL). The suspension was cooled to 0°C and carbamate S2.3 (1.00 g, 3.02 mmol, 1.00 equiv) in DMF (10 mL) was added dropwise over 15 min. The resulting suspension was stirred 1.5 h at 0°C and tributyl(iodomethyl)stannane (2.60 g, 6.03 mmol, 2.00 equiv) was added dropwise over 10 min. The suspension was allowed to warm to rt over 1 h and stirred for 5 h. The reaction mixture
was cooled to 0°C and slowly quenched with sat aq NH₄Cl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with H₂O (3 x 10 mL), brine (2 x 10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 100:0 to 96:4) afforded the alkylated product S2.4 (1.65 g, 86% yield, rotamers 3:1) as a clear, pale brown liquid. IR (thin film): ν 2956, 2924, 2867, 1672, 1464, 1365, 1162 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.28–4.15 (m, 1H × 0.25), 4.16–4.07 (m, 1H × 0.75), 3.75–3.67 (m, 1H), 3.66–3.49 (m, 1H), 2.93 (q, J = 13.7 Hz, 2H × 0.25), 2.60 (s, J_{¹¹⁷/¹¹⁹Sn–¹H} = 29.6 Hz, 2H × 0.75), 1.54–1.40 (m, 15H), 1.34–1.23 (m, 6H), 1.12 (d, J = 6.8 Hz, 3H), 1.10–1.02 (m, 21H), 0.93–0.78 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 155.9, 155.3, 79.4, 79.0, 65.7, 65.5, 54.2, 53.1, 29.3, 28.8, 28.7, 27.7, 27.6, 18.2, 15.0, 14.6, 13.9, 12.1, 10.9, 9.8; Rᵣ = 0.51 (hexanes:EtOAc 20:1); ESI-HRMS calcd for C₃₀H₆₅N₁Na₁O₃Si₁Sn₁ [M + Na]⁺ 658.3653, found 658.3651.

**tert-Butyl (1-(1,3-dioxoisindolin-2-yl)propan-2-yl)((tributylstannyl)methyl) carbamate (S2.5).** TBAF (2.84 mL of a 1.0 M solution in THF, 2.84 mmol, 1.20 equiv) was added dropwise over 10 min to a solution of the TIPS protected alcohol S2.4 (1.50 g, 2.36 mmol, 1.00 equiv) in THF (12 mL) at 0°C. The resulting solution was allowed to warm to rt and was stirred for 2 h before being poured into a mixture of EtOAc:H₂O (2:1, 100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with H₂O (2 x 10 mL), brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure by rotary evaporation at 40°C, 375 mmHg and then at 80°C, ca. 0.1 mmHg (vacuum pump) for 2 h to remove most of the triisopropylsilanol and to afford the desired alcohol that was used in the next step without further purification.

Diisopropyl azodicarboxylate (535 μL, 2.72 mmol, 1.15 equiv) was added dropwise over 15 min to a clear, pale yellow solution of the alcohol, triphenyolphosphine (713 mg, 2.72 mmol, 1.15 equiv), and phthalimide (0.400 g, 2.72 mmol, 1.15 equiv) in THF (16 mL) at 0°C. The clear, yellow solution was allowed to warm to rt and stirred for 16 h. The resulting reaction mixture was concentrated and purification by flash column chromatography (hexanes:EtOAc 25:1) afforded the phthalimide protected SnAP 2-Me-Pip S2.5 (1.15 g, 80% yield, 2 steps, rotamers 4:1) as a colorless solid. IR (thin film): ν 2955, 2924, 2871, 2853, 1719, 1673, 1392, 1358, 1156 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.87–7.80 (m, 2H), 7.72–7.68 (m, 2H × 0.80), 7.67–7.63 (m, 2H × 0.20), 4.75–4.67 (m, 1H × 0.20), 4.67–4.56 (m, 1H × 0.80), 3.90 (dd, J = 13.7, 10.6, 1H), 3.49 (dd, J = 13.7, 3.3, 1H × 0.20), 3.43 (dd, J = 13.7, 4.1, 1H × 0.80), 3.04–
2.40 (m, 2H), 1.54–1.40 (m, 6H), 1.35–1.23 (m, 6H), 1.20 (d, J = 6.9 Hz, 3H), 1.13 (s, 9H × 0.20), 1.11 (s, 9H × 0.80), 0.91–0.76 (m, 15H); 13C NMR (100 MHz, CDCl₃): δ 168.2, 168.0, 155.7, 134.0, 133.7, 132.5, 132.3, 123.4, 123.3, 79.5, 79.3, 50.1, 48.9, 40.2, 40.0, 29.3, 28.3, 28.1, 27.7, 27.7, 26.2, 17.9, 16.4, 16.1, 13.9, 13.8, 11.0, 9.8; Rᵣ = 0.40 (hexanes:EtOAc 10:1); m.p. = 68–70°C; ESI-HRMS calcd for C₂₉H₄₈N₂Na₁O₄Sn₁ [M + Na]⁺ 631.2534, found 631.2531.

**tert-Butyl (1-aminopropan-2-yl)((tributylstannylmethyl)carbamate (2.13).** The phthalimide protected SnAP 2-Me-Pip S2.5 (600 mg, 0.988 mmol, 1.00 equiv) in EtOH (10 mL) was heated to reflux. Hydrazine monohydrate (480 μL, 9.88 mmol, 10.0 equiv) was added dropwise at reflux over 3 min. The resulting reaction mixture was stirred for further 45 min at reflux while colorless solid crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (50 mL) and H₂O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford pure SnAP 2-Me-Pip 2.13 (448 mg, 95% yield, rotamers 7:3) as a colorless oil. IR (thin film): ν 2956, 2924, 2871, 1675, 1463, 1365, 1158 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.28–4.14 (m, 1H × 0.30), 4.12–3.98 (m, 1H × 0.70), 2.97–2.54 (m, 2H + 2H × 0.30), 2.50 (s, J(¹¹⁷/¹¹⁹Sn-¹H) = 29.9 Hz, 2H × 0.70), 1.52–1.41 (m, 15H), 1.34–1.24 (m, 8H), 1.05 (d, J = 5.9 Hz, 3H), 0.93–0.80 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 156.5, 156.1, 79.8, 79.3, 55.4, 53.9, 45.5, 45.4, 29.3, 28.7, 27.6, 26.9, 26.1, 17.9, 16.1, 15.8, 13.9, 10.9, 10.0; Rᵣ = 0.20 (EtOAc); ESI-HRMS calcd for C₂₁H₄₇N₂O₂Sn₁ [M + H]⁺ 479.2658, found 479.2656.

**tert-Butyl (2-((triisopropylsilyl)oxy)propyl)carbamate (S2.6).** Imidazole (1.94 g, 28.5 mmol, 2.00 equiv) was added in one portion to a solution of the Boc-protected amino alcohol
(2.50 g, 14.3 mmol, 1.00 equiv) in CH₂Cl₂ (72 mL) at rt. The resulting solution was cooled to 0°C and treated with TIPSCl (4.58 mL, 21.4 mmol, 1.50 equiv) over 10 min before stirred at reflux for 18 h. The reaction mixture was cooled to rt, diluted with CH₂Cl₂ (50 mL), washed with sat aq NH₄Cl (2 x 20 mL), H₂O (20 mL), brine (30 mL), dried over Na₂SO₄, and concentrated under reduced pressure by rotary evaporation at 40°C, 375 mmHg and then at 100°C, ca. 0.1 mmHg (vacuum pump) for 2 h to remove most of the triisopropylsilanol. Purification by flash column chromatography (hexanes:EtOAc 25:1) afforded the desired product S2.6 (4.03 g, 85% yield) as a clear, pale yellow liquid. IR (thin film): ν 3461, 3368, 2965, 2943, 2893, 2868, 1721, 1709, 1506, 1464, 1366, 1174, 1124, 1070 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.96–4.47 (m, 1H), 4.13–3.92 (m, 1H), 3.31–3.09 (m, 1H), 3.09–2.93 (m, 1H), 1.44 (s, 9H), 1.15 (d, J = 6.1 Hz, 3H), 1.08–1.03 (m, 21H); ¹³C NMR (100 MHz, CDCl₃): δ 156.3, 79.2, 67.9, 48.2, 28.6, 21.4, 18.3, 18.2, 12.6; Rₜ = 0.35 (hexanes:EtOAc 20:1); ESI-HRMS calcd for C₁₇H₃₇N₁Na₁O₃Si₁ [M + Na]⁺ 354.2435, found 354.2435.

tert-Butyl ((tributylstannyl)methyl)(2-((triisopropylsilyl)oxy)propyl)carbamate (S2.7). Sodium hydride (242 mg of a 60% suspension in mineral oil, 6.03 mmol, 2.00 equiv) was washed with pentane (3 x 3 mL) and suspended in DMF (20 mL). The suspension was cooled to 0°C and carbamate S2.6 (1.00 g, 3.02 mmol, 1.00 equiv) in DMF (10 mL) was added dropwise over 15 min. The resulting suspension was stirred 1.5 h at 0°C and tributyl(iodomethyl)stannane (2.60 g, 6.03 mmol, 2.00 equiv) was added dropwise over 10 min. The suspension was allowed to warm to rt over 1 h, and then stirred for 5 h. The reaction mixture was cooled to 0°C and slowly quenched with sat aq NH₄Cl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with H₂O (2 x 10 mL), brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 100:0 to 96:4) afforded the alkylated product S2.7 (1.85 g, 97% yield, rotamers 7:3) as a clear, colorless liquid. IR (thin film): ν 2956, 2925, 2868, 1678, 1464, 1365, 1164, 1136 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.26–4.17 (m, 1H × 0.30), 4.15–4.06 (m, 1H × 0.70), 3.34–3.02 (m, 2H + 1H × 0.30), 3.02–2.78 (m, 1H + 1H × 0.70), 1.52–1.39 (m, 15H), 1.33–1.24 (m, 6H), 1.18–1.13 (m, 3H), 1.07 (s, 21H), 0.94–0.80 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 155.7, 155.6, 79.3, 79.1, 68.0, 67.5, 57.9, 56.9, 35.6, 35.4, 29.3, 28.7, 28.7, 27.6, 27.6, 21.9, 18.3, 18.2, 13.9, 13.8, 12.7, 12.6, 10.6, 9.7; Rₜ = 0.49 (hexanes:EtOAc 20:1); ESI-HRMS calcd for C₃₀H₆₈N₁Na₁O₃Si₁Sn₁ [M + Na]⁺ 658.3653, found 658.3652.
**tert-Butyl (2-(1,3-dioxoisoinolin-2-yl)propyl)((tributylstannyl)methyl)carbamate (S2.8)**. TBAF (2.84 mL of a 1.0 M solution in THF, 2.84 mmol, 1.20 equiv) was added dropwise over 10 min to a solution of the TIPS protected alcohol S2.7 (1.50 g, 2.36 mmol, 1.00 equiv) in THF (12 mL) at 0°C. The resulting solution was allowed to warm to rt and was stirred for 2 h before being poured into a mixture of EtOAc:H₂O (2:1, 100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with H₂O (2 x 10 mL), brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure by rotary evaporation at 40°C, 375 mmHg and then at 80°C, ca. 0.1 mmHg (vacuum pump) for 2 h to remove most of the triisopropylsilanol and to afford the desired alcohol that was used in the next step without further purification.

Diisopropyl azodicarboxylate (535 μL, 2.72 mmol, 1.15 equiv) was added dropwise over 15 min to a clear, pale yellow solution of the alcohol, triphenylphosphine (713 mg, 2.72 mmol, 1.15 equiv), and phthalimide (0.400 g, 2.72 mmol, 1.15 equiv) in THF (16 mL) at 0°C. The clear, yellow solution was allowed to warm to rt and stirred for 16 h. The resulting reaction mixture was concentrated and purification by flash column chromatography (hexanes:EtOAc 25:1) afforded the phthalimide protected SnAP 3-Me-Pip S2.8 (1.19 g, 83% yield, 2 steps, rotamers 3:1) as a pale yellow oil. IR (thin film): ν 2955, 2923, 2871, 2853, 1712, 1678, 1394, 1380, 1365, 1161 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.84–7.78 (m, 2H), 7.72–7.68 (m, 2H × 0.75), 7.70–7.63 (m, 2H × 0.25), 4.72–4.62 (m, 1H), 4.06–3.86 (m, 1H), 3.19 (dd, J = 14.2, 4.8 Hz, 1H × 0.75), 3.09 (d, J = 13.5 Hz, 1H × 0.25), 3.04–2.44 (m, 2H), 1.55–1.39 (m, 9H), 1.31–1.18 (m, 15H), 0.90–0.75 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 168.7, 168.3, 155.5, 155.3, 134.0, 133.7, 132.4, 132.2, 123.3, 123.2, 79.5, 53.0, 51.4, 45.2, 34.0, 33.5, 29.2, 28.3, 27.6, 17.8, 16.0, 13.8, 10.6, 9.7; Rₚ = 0.43 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C₂₉H₄₆N₂Na₁O₄Sn₁ [M + Na]⁺ 631.2534, found 631.2531.

**tert-Butyl (2-aminopropyl)((tributylstannyl)methyl)carbamate (2.14)**. The phthalimide protected SnAP 3-Me-Pip S2.8 (600 mg, 0.988 mmol, 1.00 equiv) in EtOH (10 mL) was heated to reflux. Hydrazine monohydrate (480 μL, 9.88 mmol, 10.0 equiv) was added dropwise at reflux over 3 min. The resulting reaction mixture was stirred for further 45 min at reflux while colorless solid crashed out. The colorless suspension was allowed to cool to rt and
poured into a mixture of EtOAc (50 mL) and H₂O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford pure SnAP 3-Me-Pip 2.14 (471 mg, 98% yield, rotamers 2:1) as a colorless oil. IR (thin film): ν 2956, 2924, 2871, 1676, 1457, 1365, 1163 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.24–2.76 (m, 5H), 1.52–1.40 (m, 15H), 1.35–1.22 (m, 8H), 1.07–1.04 (m, 3H), 0.94–0.81 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 156.1, 155.9, 79.6, 79.3, 59.0, 57.6, 46.1, 45.8, 34.8, 34.1, 29.3, 28.6, 27.6, 21.5, 17.9, 13.8, 10.6, 9.8; Rᵣ = 0.26 (EtOAc); ESI-HRMS calcd for C₂₁H₄₁N₂O₂Sn₁ [M + H]⁺ 479.2658, found 479.2655.

7.2.3 Preparation Morpholines and Piperazines using SnAP Reagents

GENERAL PROCEDURE FOR THE IMINE FORMATION: To a solution of the amino tributylstannane – SnAP reagent (0.50 mmol, 1.00 equiv) in CH₂Cl₂ (2.5 mL) at rt was added the aldehyde (0.50 mmol, 1.00 equiv) and molecular sieves 4Å (ca. 100 mg/mmol). The reaction mixture was stirred at rt for 2–6 h and filtered through a short layer of Celite (CH₂Cl₂ rinse). The filtrate was concentrated under reduced pressure to afford the pure imine.

GENERAL PROCEDURE FOR THE CYCLIZATION: Separately, 2,6-lutidine (0.50 mmol, 1.00 equiv) was added in one portion to a suspension of HFIP (2.0 mL) and anhydrous Cu(OTf)₂ (0.50 mmol, 1.00 equiv) and stirred at rt for 1 h, during which time a homogeneous suspension was formed. A solution of the imine (0.50 mmol, 1.00 equiv) in CH₂Cl₂ (8.0 mL) was added in one portion and the resulting mixture was stirred at rt for 12 h. The reaction was quenched at rt with 10% aq NH₄OH (5 mL), and stirred vigorously for 15 min. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 3 mL). The combined organic layers were washed with H₂O (3 x 5 mL) and brine (10 mL), dried over Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography afforded the corresponding N-heterocycle.

Notes on the purification of substituted heterocycles (0.50 mmol scale)
- Column for flash Column chromatography: 20 mm column with ca. 8–9 cm silica gel.
- Sample loading: Dry loading on silica gel.
- Solvent: Appropriate solvent mixture with 0.1% Et₃N v/v.
- If desired, most of the tin byproducts can be removed before the flash column chromatography to simplify the purification by column chromatography and afford more pure heterocycles: the crude product was dissolved in acetonitrile and washed several times with a small amount of hexanes. The combined hexanes layers were extracted
with a small amount of acetonitrile. The combined acetonitrile layers concentrated under reduced pressure to afford the crude product with much less tin residues compared to the original one.\(^6\)

- If desired, further purification could be carried out by salt formation of the N-heterocycle to remove any trace of tin impurities.

Additional information

- \(\text{Cu(OTf)}_2\) from Strem used for the cyclization afforded the best results with various results and lower yields using \(\text{Cu(OTf)}_2\) from other suppliers.

- Product heterocycles are detected by TLC in the unpurified reaction mixture using both, potassium permanganate and ninhydrin\(^7\) stains. The product is visible with both developing agents. Using the ninhydrin stain, the products show up as pink/purple spots on TLC.

- Some of the aldehydes and imines are not soluble in CH\(_2\)Cl\(_2\) (0.15 M) at rt, which is the standard condition for imine formation. In these cases, acetonitrile (0.15 M) was used as solvent.

- The reaction is not very sensitive to oxygen or H\(_2\)O and can be conducted in standard glassware without degassed, extra dry solvents or without pre-dried \(\text{Cu(OTf)}_2\) with only slightly diminished yields.

- The imines were isolated by filtering over a glass sintered funnel followed by evaporation to ensure clean and full conversion before subjection to the cyclization. Alternatively, the imine formation can be diluted with additional CH\(_2\)Cl\(_2\) and transferred to the heterogeneous copper-ligand suspension by a syringe equipped with an HPLC filter. All imine formations were completed after 4 h at rt.

- 2,6-Lutidine is sometimes hard to separate from the desired heterocyclic products using

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\(^7\) 0.300 g Ninhydrin, 1.0 mL AcOH, 100 mL EtOH
flash column purification. Therefore, the unpurified reaction mixture can be adsorbed onto silica gel and put onto the high vacuum for a prolonged time to remove most of the 2,6-lutidine before the flash column chromatographic purification.

3-Phenylmorpholine (2.5a). Purification by flash column chromatography (hexanes:EtOAc:MeOH 20:20:1) afforded 2.5a (56 mg, 68% yield) as a colorless solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42–7.36 (m, 2H), 7.36–7.30 (m, 2H), 7.30–7.24 (m, 1H), 3.92 (dd, $J$ = 10.1, 3.2 Hz, 1H), 3.91–3.85 (m, 1H), 3.82 (dd, $J$ = 11.1, 3.2 Hz, 1H), 3.66 (td, $J$ = 11.1, 2.7 Hz, 1H), 3.40 (dd, $J$ = 11.1, 10.1 Hz, 1H), 3.13 (td, $J$ = 11.7, 3.2 Hz, 1H), 3.03–2.97 (m, 1H), 1.83 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 140.7, 128.6, 127.9, 127.3, 73.8, 67.4, 60.7, 46.8. These spectral characteristics were identical to those previously reported.8

Methyl 4-(morpholin-3-yl)benzoate (2.5b). Purification by flash column chromatography (hexanes:EtOAc 1:2) afforded 2.5b (87 mg, 79% yield) as a colorless solid. IR (thin film): $\nu$ 3327, 2952, 2850, 1720, 1610, 1435, 1280, 1105, 1018, 931, 857 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.03–7.90 (m, 2H), 7.51–7.38 (m, 2H), 3.97 (dd, $J$ = 10.0, 3.2 Hz, 1H), 3.90–3.84 (m, 4H), 3.80 (dd, $J$ = 11.2, 3.2 Hz, 1H), 3.63 (td, $J$ = 11.2, 2.6 Hz, 1H), 3.34 (dd, $J$ = 11.0, 10.0 Hz, 1H), 3.11 (td, $J$ = 11.6, 3.2 Hz, 1H), 2.99 (dt, $J$ = 11.6, 2.6 Hz, 1H), 1.94 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.9, 145.7, 129.9, 129.7, 127.2, 73.5, 67.3, 60.4, 52.2, 46.4; $R_f$ = 0.17 (hexanes:EtOAc 1:2); m.p. = 69–70°C; ESI-HRMS calcd for C$_{12}$H$_{16}$N$_2$O$_3$ [M + H]$^+$ 222.1125, found 222.1128.

3-(3-Bromophenyl)morpholine (2.5c). Purification by flash column chromatography (CH$_2$Cl$_2$:EtOAc 1:1) afforded 2.5c (79 mg, 66% yield) as a colorless liquid. IR (thin film): $\nu$ 3316,

3-(4-Methoxyphenyl)morpholine (2.5d). Purification by flash column chromatography (hexanes:EtOAc:MeOH 10:10:1) afforded 2.5d (94 mg, 94% yield) as a colorless solid. IR (thin film): \( \nu \) 3319, 2957, 2847, 1611, 1512, 1248, 1102, 1033, 829 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.34–7.28 (m, 2H), 6.90–6.84 (m, 2H), 3.87 (dd, \( J = 10.5, 3.3 \) Hz, 1H), 3.90–3.32 (m, 1H), 3.85–3.81 (m, 1H), 3.68 (td, \( J = 11.3, 2.6 \) Hz, 1H), 3.63 (dd, \( J = 11.3, 3.3 \) Hz, 1H), 3.10 (td, \( J = 11.6, 3.2 \) Hz, 1H), 2.99 (dt, \( J = 11.6, 2.0 \) Hz 1H), 1.69 (br s, NH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 159.3, 132.9, 128.4, 114.0, 73.9, 67.3, 60.1, 55.4, 46.8; \( R_f = 0.33 \) (hexanes:EtOAc:MeOH 10:10:1); m.p. = 54–55°C; ESI-HRMS calcd for C\(_{11}\)H\(_{16}\)N\(_2\)O\(_2\) [M + H]\(^+\) 194.1176, found 194.1179.

3-Mesitylmorpholine (2.5e). Purification by flash column chromatography (hexanes:EtOAc 3:2) afforded 2.5e (4 mg, 4% yield) as a pale yellow oil. IR (thin film): \( \nu \) 3328, 2918, 2851, 1732, 1456, 1260, 1104 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 6.82 (d, \( J = 0.6 \) Hz, 2H), 4.38 (dd, \( J = 10.5, 3.3 \) Hz, 1H), 3.90–3.32 (m, 1H), 3.85–3.81 (m, 1H), 3.68 (td, \( J = 11.3, 2.6 \) Hz, 1H), 3.63 (dd, \( J = 11.3, 3.3 \) Hz, 1H), 3.10 (td, \( J = 11.6, 3.2 \) Hz, 1H), 3.01 (dt, \( J = 11.6, 2.1 \) Hz, 1H), 2.52 (s, 6H), 2.23 (s, 3H), 1.64 (br s, NH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 137.7, 136.9, 132.7, 130.4, 69.0, 67.3, 58.3, 47.8, 21.7, 20.8; \( R_f = 0.26 \) (hexanes:EtOAc 1:1); ESI-HRMS calcd for C\(_{13}\)H\(_{20}\)N\(_2\)O\(_1\) [M + H]\(^+\) 206.1539, found 206.1544.

3-(Pyridin-4-yl)morpholine (2.5f). Purification by flash column chromatography (CH\(_2\)Cl\(_2\):MeOH 15:1) afforded 2.5f (65 mg, 79% yield) as a colorless liquid. \(^1\)H NMR (400 MHz,
CDCl$_3$): $\delta$ 8.65–8.50 (m, 2H), 7.37–7.29 (m, 2H), 3.94 (dd, $J = 10.0, 3.2$ Hz, 1H), 3.91–3.85 (m, 1H), 3.83 (dd, $J = 11.1, 3.2$ Hz, 1H), 3.64 (td, $J = 11.1, 2.7$ Hz, 1H), 3.34 (dd, $J = 11.1, 10.0$ Hz, 1H), 3.11 (td, $J = 11.5, 3.2$ Hz, 1H), 3.04–2.97 (br d, $J = 11.5, 1.0$ Hz, 1H), 2.05 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 150.2, 149.2, 122.3, 73.0, 67.3, 59.5, 46.1. These spectral characteristics were identical to those previously reported.\(^9\)

3-(Benzo[b]thiophen-3-yl)morpholine (2.5g). Purification by flash column chromatography (hexanes:EtOAc 1:2) afforded 2.5g (92 mg, 85% yield) as a colorless liquid. IR (thin film): $\nu$ 3317, 2957, 2850, 1427, 1311, 1104, 930, 760 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.94–7.83 (m, 2H), 7.47 (s, 1H), 7.42–7.31 (m, 2H), 4.39 (dd, $J = 9.7, 3.0$ Hz, 1H), 4.05 (dd, $J = 11.2, 3.0$ Hz, 1H), 3.92 (br d, $J = 11.2$ Hz, 1H), 3.70 (td, $J = 11.1, 2.7$ Hz, 1H), 3.50 (dd, $J = 11.1, 9.7$ Hz, 1H), 3.17 (td, $J = 11.7, 3.3$ Hz, 1H), 3.04 (br d, $J = 11.7$ Hz, 1H), 1.97 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 140.7, 137.7, 135.8, 124.6, 124.2, 123.1, 123.0, 121.8, 72.7, 67.6, 55.2, 46.8; R$_f$ = 0.35 (hexanes:EtOAc 1:2); ESI-HRMS calcd for C$_{12}$H$_{13}$Na$_1$N$_1$O$_1$S$_1$ [M + Na]$^+$ 242.0610, found 242.0613.

 tert-Butyl 4-(morpholin-3-yl)piperidine-1-carboxylate (2.5h). Purification by flash column chromatography (CH$_2$Cl$_2$:MeOH 10:1) afforded 2.5h (81 mg, 60% yield) as a colorless liquid. IR (thin film): $\nu$ 3433, 2972, 2933, 2855, 1681, 1428, 1171, 1107, 868, 769 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.10 (br s, 2H), 3.84 (dd, $J = 11.0, 2.6$ Hz, 1H), 3.76 (br d, $J = 11.0$ Hz, 1H), 3.48–3.41 (m, 1H), 3.27–3.16 (m, 1H), 2.97–2.83 (m, 2H), 2.71–2.50 (m, 3H), 1.82 (br s, NH), 1.70 (br d, $J = 12.6$ Hz, 1H), 1.56 (br d, $J = 11.4$ Hz, 1H), 1.48–1.39 (m, 9H), 1.40–1.30 (m, 1H), 1.24–1.10 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.8, 79.5, 70.9, 67.7, 59.0, 46.3, 43.9, 38.6, 28.5, 28.3, 28.2; R$_f$ = 0.46 (CH$_2$Cl$_2$:MeOH 10:1); ESI-HRMS calcd for C$_{14}$H$_{27}$N$_2$O$_3$ [M + H]$^+$ 217.2016, found 217.2020.

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Ethyl morpholine-3-carboxylate (2.5i). Purification by flash column chromatography (hexanes:EtOAc:MeOH 10:10:1) afforded 2.5i (69 mg, 84% yield) as a colorless liquid. IR (thin film): ν 3418, 2982, 2863, 1732, 1457, 1373, 1208, 1102, 856 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.20 (q, J = 7.1 Hz, 2H), 3.99 (dd, J = 11.2, 3.2 Hz, 1H), 3.80–3.68 (m, 2H), 3.59 (ddd, J = 11.1, 7.9, 2.9 Hz, 1H), 3.53 (dd, J = 7.2, 3.5 Hz, 1H), 3.02 (ddd, J = 12.2, 4.9, 2.9 Hz, 1H), 2.86 (ddd, J = 12.2, 8.0, 3.2 Hz, 1H), 1.95 (s, 1H), 1.27 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 171.4, 68.6, 63.8, 61.3, 57.0, 44.4, 14.3; Rᵥ = 0.30 (hexanes:EtOAc:MeOH 10:10:1); ESI-HRMS calcd for C₇H₁₄N₁O₃ [M + H]⁺ 160.0968, found 160.0970.

**tert-Butyl 3-(2-chloro-4-fluorophenyl)piperazine-1-carboxylate (2.6a).** Purification by flash column chromatography (hexanes:TBME 1:1) afforded 2.6a (129 mg, 82% yield) as a colorless oil. IR (thin film): ν 3315, 2976, 2928, 2858, 1693, 1490, 1419, 1168, 1127 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.70–7.54 (m, 1H), 7.11 (dd, J = 8.5, 2.6 Hz, 1H), 6.99 (td, J = 8.5, 2.6 Hz, 1H), 4.32–3.92 (m, 3H), 3.13–3.02 (m, 1H), 2.99–2.82 (m, 2H), 2.58 (dd, J = 12.7, 10.2 Hz, 1H), 1.73 (br s, NH), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 161.8 (d, J_CF = 249.7 Hz), 154.8, 134.9 (d, J_CF = 3.5 Hz), 133.7 (d, J_CF = 11.7 Hz), 129.2 (d, J_CF = 8.7 Hz), 117.0 (d, J_CF = 24.6 Hz), 114.4 (d, J_CF = 20.7 Hz), 80.0, 56.0, 50.2, 46.2, 43.5, 28.6; Rᵥ = 0.18 (hexanes:TBME 1:1); ESI-HRMS calcd for C₁₅H₁₄Cl₁F₁N₂O₂ [M + H]⁺ 315.1270, found 315.1271.

**tert-Butyl 3-(4-(trifluoromethyl)phenyl)piperazine-1-carboxylate (2.6b).** Purification by flash column chromatography (hexanes:TBME 1:1) afforded 2.6b (128 mg, 78% yield) as a colorless solid. IR (thin film): ν 3317, 2978, 2939, 2857, 2812, 1685, 1620, 1418, 1327, 1167, 1125, 1067 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.60 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 4.05 (br s, 2H), 3.77 (br d, J = 10.1 Hz, 1H), 3.08 (br d, J = 7.7 Hz, 1H), 2.99–2.80 (m, 2H), 2.80–2.61 (m, 1H), 1.77 (br s, NH), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 154.8, 145.7,
130.2 (q, $J_{CF} = 32.6$ Hz), 127.5, 125.6 (q, $J_{CF} = 3.7$ Hz), 124.2 (q, $J_{CF} = 272.1$ Hz), 80.1, 60.0, 51.1, 46.1, 43.8, 28.6; $R_f = 0.23$ (hexanes:EtOAc 4:1); m.p. = 115–116°C; ESI-HRMS calcd for $C_{16}H_{22}F_3N_2O_2 [M + H]^+ 331.1628$, found 331.1632.

**tert-Butyl 3-(4-methoxyphenyl)piperazine-1-carboxylate (2.6c).** Purification by flash column chromatography (hexanes:EtOAc 1:1) afforded 2.6c (111 mg, 76% yield) as a colorless solid. IR (thin film): $\nu$ 3321, 2974, 2931, 2834, 1692, 1514, 1417, 1248, 1171 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.35–7.29 (m, 2H), 6.90–6.58 (m, 2H), 4.03 (br s, 2H), 3.80 (s, 3H), 3.64 (dd, $J = 10.5, 2.5$ Hz, 1H), 3.09–3.00 (m, 1H), 2.95–2.80 (m, 2H), 2.71 (br s, 1H), 1.76 (br s, NH), 1.46 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 159.3, 154.9, 133.9, 128.2, 114.0, 79.8, 59.8, 55.4, 51.3, 46.3, 28.6; $R_f = 0.17$ (hexanes:EtOAc 1:1); m.p. = 121–123°C; ESI-HRMS calcd for $C_{16}H_{25}N_2O_3 [M + H]^+ 293.1860$, found 293.1863.

**tert-Butyl 3-(benzo[d][1,3]dioxol-5-yl)piperazine-1-carboxylate (2.6d).** Purification by flash column chromatography (hexanes:EtOAc 1:1) afforded 2.6d (104 mg, 68% yield) as a colorless solid. IR (thin film): $\nu$ 3324, 2975, 2897, 2817, 1691, 1489, 1419, 1251, 1171, 1126, 1038 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.92 (d, $J = 1.6$ Hz, 1H), 6.85 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 5.94 (m, 2H), 4.03 (br s, 2H), 3.68–3.54 (m, 1H), 3.05 (d, $J = 8.4$ Hz, 1H), 2.97–2.80 (m, 2H), 2.68 (br s, 1H), 1.77 (br s, NH), 1.46 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.9, 147.8, 147.2, 135.8, 120.4, 108.3, 107.6, 101.1, 79.9, 60.2, 51.1, 46.2, 43.9, 28.6; $R_f = 0.23$ (hexanes:EtOAc 1:1); m.p. = 121–123°C; ESI-HRMS calcd for $C_{16}H_{23}N_2O_4 [M + H]^+ 307.1652$, found 307.1656.

**tert-Butyl 3-(1H-indol-3-yl)piperazine-1-carboxylate (2.6e).** Purification by flash column chromatography (CH$_2$Cl$_2$:MeOH 95:5) afforded 2.6e (88 mg, 58% yield) as a colorless
oil. IR (thin film): ν 3298, 2977, 2928, 2860, 1671, 1456, 1424, 1248, 1170, 1127 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 8.18 (s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.25–7.17 (m, 2H), 7.13 (t, J = 7.4 Hz, 1H), 4.24 (br s, 1H), 4.09 (dd, J = 10.3, 2.9 Hz, 1H), 4.08 (br s, 1H), 3.18–2.86 (m, 4H), 1.81 (br s, NH), 1.49 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 155.0, 136.4, 126.2, 122.5, 121.3, 119.8, 119.2, 117.0, 111.4, 79.8, 53.1, 50.5, 46.3, 44.7, 28.6; Rᵣ = 0.19 (CH₂Cl₂:MeOH 95:5); ESI-HRMS calcd for C₁₇H₂₄N₃O₂ [M + H]⁺ 302.1863, found 302.1864.

**tert-Butyl 3-(furan-3-yl)piperazine-1-carboxylate (2.6f).** Purification by flash column chromatography (hexanes:EtOAc 1:1) afforded 2.6f (81 mg, 64% yield) as an orange solid. IR (thin film): ν 3320, 2976, 2929, 2859, 1690, 1420, 1250, 1167 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.40 (s, 1H), 7.38–7.35 (m, 1H), 6.40 (dd, J = 1.7, 0.7 Hz, 1H), 4.23–3.80 (m, 2H), 3.69 (dd, J = 10.1, 2.9 Hz, 1H), 3.06–2.97 (m, 1H), 2.92 (t, J = 12.3 Hz, 1H), 2.82 (tt, J = 13.8, 6.7 Hz, 1H), 2.77 (br s, 1H), 1.91 (br s, NH), 1.46 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 154.8, 143.3, 139.3, 126.0, 109.1, 80.0, 51.9, 50.2, 45.7, 44.1, 28.6; Rᵣ = 0.16 (hexanes:EtOAc 1:1); m.p. = 97–98°C; ESI-HRMS calcd for C₁₃H₂₁N₂O₃ [M + H]⁺ 253.1547, found 253.1553.

**tert-Butyl 3-(1-methyl-1H-pyrazol-4-yl)piperazine-1-carboxylate (2.6g).** Purification by flash column chromatography (CH₂Cl₂:MeOH 95:5) afforded 2.6g (95 mg, 71% yield) as a colorless oil. IR (thin film): ν 3421, 3299, 2976, 2932, 2860, 1686, 1419, 1250, 1167 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.43 (s, 1H), 7.32 (s, 1H), 4.16–3.80 (m, 2H), 3.85 (s, 3H), 3.71 (dd, J = 10.1, 2.9 Hz, 1H), 2.99 (br d, J = 11.2 Hz, 1H), 2.95–2.85 (m, 1H), 2.81 (td, J = 11.1, 2.5 Hz, 1H), 2.76 (br s, 1H), 1.99 (br s, NH), 1.45 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 154.8, 137.5, 128.0, 122.5, 79.9, 51.5, 50.8, 45.7, 44.0, 39.1, 28.5; Rᵣ = 0.15 (CH₂Cl₂:MeOH 95:5); ESI-HRMS calcd for C₁₃H₂₃N₄O₂ [M + H]⁺ 267.1816, found 267.1820.

**tert-Butyl 3-(tert-butyl)piperazine-1-carboxylate (2.6h).** Purification by flash column...
chromatography (hexanes:TBME 1:4) afforded 2.6h (79 mg, 65% yield) as a colorless oil. IR (thin film): ν 2964, 2869, 1696, 1419, 1365, 1246, 1173 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.00 (br d, J = 56.5 Hz, 2H), 3.05–2.94 (m, 1H), 2.81–2.62 (m, 2H), 2.57–2.38 (m, 1H), 2.24 (br d, J = 10.2 Hz, 1H), 1.60 (br s, NH), 1.45 (s, 9H), 0.93 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 155.2, 79.6, 64.3, 46.5, 44.9, 44.2, 32.8, 28.6, 26.6; Rᵣ = 0.21 (hexanes:TBME 4:1); ESI-HRMS calcd for C₁₃H₂₇N₂O₂ [M + H]⁺ 243.2067, found 243.2072.

**tert-Butyl 3-cyclopropylpiperazine-1-carboxylate (2.6i).** Purification by flash column chromatography (CH₂Cl₂:MeOH 95:5) afforded 2.6i (85 mg, 75% yield) as a colorless oil. IR (thin film): ν 3448, 3297, 3081, 2978, 2931, 1696, 1421, 1267, 1177 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.16–3.80 (m, 2H), 2.96 (br d, J = 11.3 Hz, 1H), 2.91–2.78 (m, 1H), 2.67 (td, J = 11.4, 3.1 Hz, 2H), 1.74 (td, J = 10.2, 2.8 Hz, 1H), 1.66 (br s, NH), 1.46 (s, 9H), 0.77–0.67 (m, 1H), 0.58–0.41 (m, 2H), 0.29–0.11 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 155.0, 79.7, 60.8, 45.9, 28.6, 14.5, 2.8, 2.2; Rᵣ = 0.19 (CH₂Cl₂:MeOH 95:5); ESI-HRMS calcd for C₁₂H₂₂N₂NaO₂ [M + Na]⁺ 249.1573, found 249.1579.

**1-(tert-Butyl) 3-ethyl piperazine-1,3-dicarboxylate (2.6j).** Purification by flash column chromatography (hexanes:EtOAc 1:1) afforded 2.6j (97 mg, 75% yield) as a colorless oil. IR (thin film): ν 3553, 3341, 2978, 2931, 2865, 1738, 1698, 1421, 1366, 1250, 1168 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.16 (q, J = 7.1 Hz, 3H), 3.66 (br d, J = 12.4 Hz, 1H), 3.30–2.83 (m, 3H), 2.75–2.64 (m, 1H), 2.23 (br s, NH), 1.42 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 171.2, 154.6, 80.0, 61.2, 56.9, 45.8, 44.3, 43.5, 28.4, 14.2; Rᵣ = 0.17 (hexanes:EtOAc 1:1); ESI-HRMS calcd for C₁₂H₂₂N₂NaO₄ [M + Na]⁺ 281.1472, found 281.1476.

**trans-Ethyl 6-methylmorpholine-3-carboxylate (2.15a).** Purification by flash column chromatography (hexanes:EtOAc 1:2) afforded 2.15a in a diastereomeric ratio of > 10:1 (68
mg, 79% yield) as a colorless oil. IR (thin film): ν 3565, 3460, 3329, 2977, 2936, 2858, 1739, 1448, 1372, 1285, 1105, 1042 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl₃): 4.16 (q, \(J = 7.1\) Hz, 2H), 4.09 (dd, \(J = 10.6, 3.2\) Hz, 1H), 3.54 (dd, \(J = 10.6, 3.2\) Hz, 1H), 3.51–3.41 (m, 2H), 2.94 (dd, \(J = 12.3, 2.4\) Hz, 1H), 2.54 (dd, \(J = 12.3, 10.2\) Hz, 1H), 2.21 (br s, NH), 1.24 (t, \(J = 7.1\) Hz, 3H), 1.10 (d, \(J = 6.3\) Hz, 3H); \(^1\)C NMR (100 MHz, CDCl₃): δ 170.6, 72.6, 69.1, 61.2, 57.0, 51.7, 18.7, 14.2; R\(_f\) = 0.20 (hexanes:EtOAc 1:2); ESI-HRMS calcd for C₈H₁₆N₁O₃ [M + H]\(^+\) 174.1125, found 174.1133.

**trans-N,N-Dimethyl-4-(6-methylmorpholin-3-yl)aniline (2.15b).** Purification by flash column chromatography (CH₂Cl₂:MeOH 100:0 to 97:3) afforded 2.15b in a diastereomeric ratio of ≥ 5:1 (47 mg, 43% yield) as a colorless solid. IR (thin film): ν 2967, 2929, 2889, 2849, 2802, 1615, 1523, 1336, 1098 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl₃): 7.24 (d, \(J = 8.7\) Hz, 2H), 6.70 (d, \(J = 8.7\) Hz, 2H), 3.86–3.74 (m, 2H), 3.73–3.63 (m, 1H), 3.46 (dd, \(J = 10.3, 9.9\) Hz, 1H), 3.03 (dd, \(J = 11.6, 2.3\) Hz, 1H), 2.93 (s, 6H), 2.72 (dd, \(J = 11.6, 10.3\) Hz, 1H), 1.73 (br s, NH), 1.18 (d, \(J = 6.3\) Hz, 3H); \(^1\)C NMR (100 MHz, CDCl₃): δ 150.4, 128.2, 128.1, 112.7, 74.0, 72.3, 59.5, 53.5, 40.8, 19.1; R\(_f\) = 0.31 (CH₂Cl₂:MeOH 95:5); m.p. = 79–81°C; ESI-HRMS calcd for C₁₃H₂₁N₂O₁ [M + H]\(^+\) 221.1648, found 221.1654.

**cis-Ethyl 5-methylmorpholine-3-carboxylate (2.16a).** Purification by flash column chromatography (hexanes:EtOAc 4:1) afforded 2.16a in a diastereomeric ratio of ≥ 5:1 (44 mg, 51% yield) as a colorless oil. IR (thin film): ν 3586, 3460, 3327, 2966, 2851, 1738, 1458, 1379, 1284, 1209, 1103, 1027 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl₃): 4.22–4.11 (m, 2H), 4.07 (dd, \(J = 11.0, 3.4\) Hz, 1H), 3.70 (dd, \(J = 10.1, 2.0\) Hz, 1H), 3.65 (dd, \(J = 10.1, 3.4\) Hz, 1H), 3.31 (t, \(J = 10.7\) Hz, 1H), 3.04–2.88 (m, 2H), 1.98 (br s, NH), 1.25 (t, \(J = 7.1\) Hz, 3H), 1.00 (d, \(J = 6.1\) Hz, 3H); \(^1\)C NMR (100 MHz, CDCl₃): δ 170.4, 73.2, 68.2, 61.2, 57.7, 50.0, 17.5, 14.2; R\(_f\) = 0.25 (hexanes:EtOAc 1:2); EI-HRMS calcd for C₈H₁₅N₂O₃ [M]\(^\circ\) 173.1052, found 173.1051.
(3R,5S)-3-Methyl-5-(quinolin-4-yl)morpholine (2.16b). Purification by flash column chromatography (hexanes:EtOAc 1:2) afforded 2.16b in a diastereomeric ratio of > 10:1 (96 mg, 84% yield) as a colorless oil. IR (thin film): ν 3388, 3299, 3063, 2963, 2847, 1590, 1509, 1328, 1101 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 8.79 (d, J = 4.5 Hz, 1H), 8.11–8.02 (m, 2H), 7.66–7.59 (m, 2H), 7.52–7.45 (m, 1H), 4.69 (dd, J = 9.9, 3.0 Hz, 1H), 3.97 (dd, J = 11.1, 3.0 Hz, 1H), 3.79 (d, J = 7.8 Hz, 1H), 3.25–3.09 (m, 3H), 2.29 (br s, NH), 1.07–0.99 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 150.4, 148.1, 145.9, 130.3, 129.1, 126.6, 126.2, 122.5, 118.6, 73.3, 72.2, 55.7, 51.0, 17.8; Rᵣ = 0.17 (hexanes:EtOAc 1:2); ESI-HRMS calcd for C₁₄H₁₇N₂O₁ [M⁺] 229.1335, found 229.1334; Chiral HPLC: column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: 10% iPrOH in hexane + 0.1 % Et₃N, flow: 1.0 mL/min; detection: 254 nm. Retention time: tᵣ = 10.6 min ((3R,5S)-3-methyl-5-(quinolin-4-yl)morpholine) and 13.9 min ((3S,5R)-3-methyl-5-(quinolin-4-yl)morpholine).

1-〈tert-Butyl〉 3-ethyl 6-methylpiperazine-1,3-dicarboxylate (2.17a). Purification by flash column chromatography (hexanes:EtOAc 2:3) afforded 2.17a in a diastereomeric ratio of 3:2 (50 mg, 37% yield, major diastereomer) as a pale yellow oil and (33 mg, 24% yield, minor diastereomer) as a pale yellow oil. Major diastereomer: IR (thin film): ν 3353, 2976, 2931, 1733, 1692, 1415, 1167, 1094 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 4.37 (d, J = 13.6 Hz, 1H), 4.26–4.12 (m, 3H), 3.53–3.46 (m, 1H), 3.28 (dd, J = 13.6, 4.4 Hz, 1H), 3.09 (dd, J = 12.1, 4.4
Hz, 1H), 2.57 (dd, J = 12.1, 2.1 Hz, 1H), 2.06 (br s, NH), 1.44 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 172.9, 154.7, 79.7, 61.2, 55.6, 46.5, 46.2, 39.3, 28.5, 15.1, 14.4; R$_f$ = 0.15 (hexanes:EtOAc 1:2); ESI-HRMS calcd for C$_{13}$H$_{25}$N$_2$O$_4$ [M + H]$^+$ 273.1809, found 273.1815. **Minor diastereomer:** IR (thin film): v 3343, 2976, 2932, 1740, 1693, 1409, 1168 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 4.29 – 4.05 (m, 4H), 3.36 (dd, J = 11.3, 3.8 Hz, 1H), 2.92 (dd, J = 12.3, 3.8 Hz, 1H), 2.85 (t, J = 9.9 Hz, 2H), 1.89 (br s, NH), 1.46 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 171.1, 154.9, 80.0, 61.3, 57.8, 49.6, 46.2, 41.1, 28.5, 14.9, 14.3; R$_f$ = 0.30 (hexanes:EtOAc 1:2); ESI-HRMS calcd for C$_{13}$H$_{25}$N$_2$O$_4$ [M + H]$^+$ 273.1809, found 273.1817.

**tert-Butyl 2-methyl-5-(o-tolyl)piperazine-1-carboxylate (2.17b).** Purification by flash column chromatography (hexanes:EtOAc 4:1) afforded 2.17b in a diastereomeric ratio of 5:1 (5:4 rotamers by $^1$H NMR integration, 77 mg, 53% yield, cis diastereomer) as a colorless solid and (15 mg, 10% yield, trans diastereomer) as a colorless oil. **cis diastereomer:** IR (thin film): v 3502, 2974, 2932, 2868, 2822, 1691, 1412, 1171 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 7.61 (t, J = 7.8 Hz, 1H), 7.26–7.10 (m, 3H), 4.37 (br s, 1H × 0.57), 4.20 (br s, 1H × 0.43), 3.95 (d, J = 13.1 Hz, 1H × 0.43), 3.90–3.77 (m, 1H and 1H × 0.57), 3.09 (dd, J = 13.1 Hz, 1H × 0.43), 2.98–2.74 (m, 2H), 2.39 (s, 3H), 1.53 (br s, NH), 1.48 (s, 9H × 0.43), 1.46 (s, 9H × 0.57), 1.37–1.31 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 155.0, 154.6, 140.0, 135.6, 135.4, 130.5, 127.4, 126.5, 126.3, 79.6, 79.5, 57.4, 57.1, 51.0, 45.9, 45.7, 44.4, 28.6, 19.3, 19.2, 15.5, 15.2; R$_f$ = 0.59 (hexanes:EtOAc 1:1); m.p. = 78–80°C; ESI-HRMS calcd for C$_{17}$H$_{27}$N$_2$O$_2$ [M + H]$^+$ 291.2067, found 291.2074. **trans diastereomer:** IR (thin film): v 2971, 2927, 2868, 1685, 1411, 1456, 1162 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$): 7.52–7.48 (m, 1H), 7.17–7.14 (m, 3H), 4.24 (t, J = 4.4 Hz, 1H), 4.07–4.00 (m, 1H), 3.84 (dd, J = 13.8, 3.8 Hz, 1H), 3.60 (dd, J = 13.8, 4.9 Hz, 1H), 3.05 (dd, J = 12.7, 4.4 Hz, 1H), 2.60 (dd, J = 12.7, 4.9 Hz, 1H), 2.38 (s, 3H), 1.61 (s, 3H), 1.45 (s, 9H), 1.31 (d, J = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 155.4, 140.6, 135.9, 130.9, 127.3, 127.1, 126.0, 79.8, 52.4, 48.9, 46.7, 44.0, 28.7, 19.5, 16.6; R$_f$ = 0.35 (hexanes:EtOAc 1:1); ESI-HRMS calcd for C$_{17}$H$_{27}$N$_2$O$_2$ [M + H]$^+$ 291.2067, found 291.2074.
cis-1-(tert-Butyl) 3-ethyl 5-methylpiperazine-1,3-dicarboxylate (2.18a). Purification by flash column chromatography (hexanes:EtOAc 1:1) afforded 2.18a in a diastereomeric ratio of > 10:1 (77 mg, 57% yield) as a colorless oil. IR (thin film): ν 3446, 2977, 2932, 2872, 1739, 1697, 1420, 1267, 1165, 1136 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): 4.34 (br s, 1H), 4.23–4.13 (m, 2H), 3.93 (br s, 1H), 3.43 (dd, \(J = 10.9, 3.3\) Hz, 1H), 2.79–2.69 (m, 1H), 2.68 (br s, 1H), 2.31 (br s, 1H), 2.00 (br s, 1H), 1.45 (s, 9H), 1.26 (t, \(J = 7.1\) Hz, 3H), 1.08 (d, \(J = 6.3\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 170.7, 154.6, 80.2, 61.3, 57.6, 50.4, 50.2, 45.6, 28.5, 19.2, 14.3; R\(_f\) = 0.36 (hexanes:EtOAc 1:1); ESI-HRMS calcd for C\(_{13}\)H\(_{25}\)N\(_2\)O\(_4\) [M + H]\(^+\) 273.1809, found 273.1816.

 cis-tert-Butyl 3-methyl-5-(pyridin-3-yl)piperazine-1-carboxylate (2.18b). Purification by flash column chromatography (EtOAc:MeOH 97:3) afforded 2.18b in a diastereomeric ratio of > 10:1 (119 mg, 86% yield) as a colorless oil. IR (thin film): ν 3420, 2975, 2931, 2868, 1652, 1522, 1408, 1169, 1049 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): 8.64 (d, \(J = 1.5\) Hz, 1H), 8.54 (dd, \(J = 4.8, 1.5\) Hz, 1H), 7.76 (d, \(J = 7.8\) Hz, 1H), 7.28 (d, \(J = 4.8\) Hz, 1H), 4.02 (br s, 2H), 3.82 (dd, \(J = 10.7, 2.8\) Hz, 1H), 2.97–2.85 (m, 1H), 2.65 (br s, 1H), 2.46 (br s, 1H), 1.63 (br s, NH), 1.47 (s, 9H), 1.11 (d, \(J = 6.2\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 154.7, 149.5, 149.2, 137.1, 134.8, 123.7, 80.1, 58.3, 51.1, 49.9, 28.6, 19.5; R\(_f\) = 0.23 (EtOAc:MeOH 20:1); ESI-HRMS calcd for C\(_{15}\)H\(_{28}\)N\(_3\)O\(_2\) [M + H]\(^+\) 278.1863, found 278.1867.
7.2.4 Preparation of SnAP Reagents for the Synthesis of Medium-Sized Rings

3-((Tributylstannyl)methoxy)propan-1-ol (2.19). Sodium hydride (250 mg of a 60% suspension in mineral oil, 6.25 mmol, 1.25 equiv) was washed with pentane (3 x 3 mL) and suspended in DMSO/THF (1:10, 33 mL). The suspension was cooled to 0°C, followed by the dropwise addition of 1,3-propanediol (1.10 mL, 15.0 mmol, 3.00 equiv). The resulting suspension was allowed to warm to rt. After 1 h, the reaction was cooled to 0°C, followed by the dropwise addition of tributyl(iodomethyl)stannane (2.16 g, 5.00 mmol, 1.00 equiv) in THF (20 mL) over 10 min. The reaction mixture was allowed to warm to rt and heated to 55°C for 15 h. The reaction was slowly quenched with H₂O (20 mL) at rt and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (pentane:EtOAc 10:1) afforded 2.19 (1.79 g, 94% yield) as clear, colorless liquid. IR (thin film): ν 3356, 2955, 2924, 2870, 2853, 1463, 1375, 1078, 873 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.81-3.67 (m, 4H), 3.54 (d, J = 5.5 Hz, 2H), 2.50 (t, J = 5.5 Hz, 1H), 1.80 (quint, J = 5.5 Hz, 2H), 1.60-1.40 (m, 6H), 1.38-1.22 (m, 6H), 1.01-0.80 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 76.0, 63.0, 62.8, 32.1, 29.2, 27.4, 13.8, 9.1; Rᵣ = 0.28 (pentane:EtOAc 10:1); ESI-HRMS calcd for C₁₆H₃₆O₂Na₁Sn₁ [M + Na]^⁺ 403.1632, found 403.1635.

10. SnAP OA & OAC: A different route starting from the amino alcohol instead of the diol affords these SnAP reagents in slightly lower overall yields via trityl protection of the amine, O-alkylation and trityl deprotection (CH₂Cl₂:2,2,2-trifluoroethanol:AcOH 7:2:1). The advantage of this method is, however, that the position of potential substituents in the backbone of these SnAP reagents can be directed.
2-(3-((Tributylstannyl)methoxy)propyl)isoindoline-1,3-dione (2.21). To a solution of 2.19 (1.78 g, 4.68 mmol, 1.00 equiv) in Et₂O (25 mL) at rt was added Et₃N (1.30 mL, 9.36 mmol, 2.00 equiv) in one portion followed by the dropwise addition of methanesulfonyl chloride (405 µL, 5.15 mmol, 1.10 equiv) over 5 min. The reaction mixture was stirred at rt and monitored by TLC. After 2 h, the reaction was quenched with H₂O (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude mesylate which was used in the next step without any further purification.

To a solution of the mesylated product in DMF (50 mL) was added potassium phthalimide (1.28 g, 6.90 mmol, 1.50 equiv) at rt in one portion. The suspension was stirred vigorously at 100°C for 3 h. After the disappearance of the mesylated product by TLC, the reaction was quenched with H₂O (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H₂O (2 x 20 mL), brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (pentane:EtOAc 40:1 to 30:1) afforded 2.21 (2.09 g, 88% yield, 2 steps) as clear, colorless liquid. IR (thin film): ν 2954, 2925, 2869, 2852, 1774, 1715, 1465, 1395, 1089, 1043 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.84 (dd, J = 5.4, 3.0 Hz, 2H), 7.70 (dd, J = 5.4, 3.0 Hz, 2H), 3.75 (t, J = 7.2 Hz, 2H), 3.68 (s, J(¹¹⁷/¹¹⁹Sn-¹H) = 7.2 Hz, 2H), 3.38 (t, J = 6.2 Hz, 2H), 1.92 (tt, J = 7.2, 6.2 Hz, 2H), 1.53-1.39 (m, 6H), 1.36-1.20 (m, 6H), 0.96-0.75 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 168.5, 133.9, 132.4, 123.3, 73.2, 62.2, 35.8, 29.3, 28.9, 27.4, 13.9, 9.1; Rf = 0.40 (pentane:EtOAc 10:1); ESI-HRMS calcd for C₂₄H₃₉N₁Na₁O₃Sn₁[M + Na]⁺ 532.1848, found 532.1854.

3-((Tributylstannyl)methoxy)propan-1-amine (2.23). To a solution of 2.21 (1.27 g, 2.50 mmol, 1.00 equiv) in EtOH (10 mL) was added hydrazine monohydrate (1.21 mL, 25.0 mmol, 10.0 equiv). The reaction mixture was refluxed for 20 min while colorless solid crashed out. The solvent was removed under reduced pressure. The resulting residue was suspended in CH₂Cl₂ and filtered over Celite. The organic filtrate was concentrated under reduced pressure to afford pure SnAP-OA 2.23 in quantitative yield (860 mg) as clear, colorless liquid. IR (thin film): ν 2955, 2924, 2870, 2853, 1576, 1463, 1375, 1338, 1089 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.70 (s, J(¹¹⁷/¹¹⁹Sn-¹H) = 7.2 Hz, 2H), 3.39 (t, J = 6.0 Hz, 2H), 2.76 (t, J = 6.8...
Hz, 2H), 1.69 (quint, J = 6.4 Hz 2H), 1.63-1.40 (m, 6H), 1.39-1.15 (m, 8H), 1.02-0.77 (m, 15H); 13C NMR (100 MHz, CDCl3): δ 73.9, 62.2, 40.1, 33.8, 29.3, 27.4, 13.9, 9.2; ESI-HRMS calcd for C16H38N1O1Sn1 [M + H]+ 380.1972, found 380.1975.

4-((Tributylstannyl)methoxy)butan-1-ol (2.20). Sodium hydride (960 mg of a 60% suspension in mineral oil, 24.0 mmol, 1.20 equiv) was washed with pentane (3 x 4 mL) and suspended in DMSO:THF (1:4, 50 mL). The suspension was cooled to 0°C, followed by the dropwise addition of commercially available 1,4-butandiol (5.32 mL, 60.0 mmol, 3.00 equiv) over 5 min. The reaction was allowed to warm to rt. After 1 h, the reaction was re-cooled to 0°C, followed by the dropwise addition of tributyl(iodomethyl)stannane (8.65 g, 20.0 mmol, 1.00 equiv) in THF (40 mL) over 15 min. The reaction mixture was allowed to warm to rt and heated to 55°C for 15 h. The reaction was slowly quenched with H2O (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H2O (20 mL), brine (20 mL), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (pentane:EtOAc 10:1 to 5:1) afforded 2.20 (7.64 g, 97% yield) as clear, colorless liquid. IR (thin film): ν 3357, 2954, 2924, 1462, 1375, 1085, 1069, 958, 873 cm−1; 1H NMR (400 MHz, CDCl3): δ 3.72 (s, J117/119Sn-H) = 7.2 Hz, 2H), 3.66-3.57 (m, 2H), 3.37 (t, J = 5.0 Hz, 2H), 2.47 (t, J = 5.8 Hz, 1H), 1.65 (d, J = 5.0 Hz, 4H), 1.59-1.40 (m, 6H), 1.39-1.22 (m, 6H), 1.02-0.70 (m, 15H); 13C NMR (100 MHz, CDCl3): δ 75.9, 62.9, 62.3, 30.7, 29.3, 27.4, 27.2, 13.9, 9.1; Rf = 0.18 (pentane:EtOAc 10:1); ESI-HRMS calcd for C17H38Na1O4Sn1 [M + Na]+ 417.1789, found 417.1776.

2-(4-((Tributylstannyl)methoxy)butyl)isoindoline-1,3-dione (2.22). To a solution of 2.20 (7.64 g, 19.4 mmol, 1.00 equiv) in Et2O (100 mL) was added Et3N (5.40 mL, 38.8 mmol, 2.00 equiv) in one portion, and methanesulfonyl chloride (1.68 mL, 21.3 mmol, 1.10 equiv) dropwise over 5 min. The reaction mixture was stirred at rt and monitored by TLC. After 2 h, the reaction was quenched with H2O (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H2O (2 x 20 mL), brine (20 mL), dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure to afford the crude mesylated product which was used in the next step without any further purification.

To a solution of the mesylated product in DMF (200 mL) was added potassium phthalimide
(5.38 g, 29.1 mmol, 1.50 equiv) at rt in one portion. The suspension was stirred vigorously at 100°C for 3 h. After the disappearance of mesylated product on TLC, reaction was quenched with H₂O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O (3 x 50 mL), brine (2 x 50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (pentane:EtOAc 20:1) afforded 2.22 (6.49 g, 64% yield, 2 steps) as clear, colorless liquid. IR (thin film): ν 2954, 2925, 2853, 1773, 1715, 1465, 1395, 1371, 1086, 1051, 866 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.83 (dd, J = 5.1, 3.2 Hz, 2H), 7.70 (dd, J = 5.3, 3.1 Hz, 2H), 3.78-3.63 (m, 4H), 3.33 (t, J = 6.2 Hz, 2H), 1.84-1.65 (m, 2H), 1.65-1.39 (m, 8H), 1.36-1.16 (m, 6H), 0.97-0.76 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 168.6, 133.9, 132.3, 123.3, 74.9, 62.1, 38.0, 29.3, 27.4, 27.2, 25.7, 13.8, 9.2; Rᵥ = 0.22 (pentane:EtOAc 10:1); ESI-HRMS calcd for C₂₅H₄₁N₁O₃Sn₁ [M + Na]⁺ 546.2005, found 546.2008.

4-((Tributylstannyl)methoxy)butan-1-amine (2.24). To a solution of 2.22 (1.50 g, 2.86 mmol, 1.00 equiv) in EtOH (12 mL) was added hydrazine monohydrate (1.40 mL, 28.6 mmol, 10.0 equiv). The reaction mixture was refluxed for 20 min while colorless solid cracked out. The solvent was removed under reduced pressure. The resulting residue was suspended in CH₂Cl₂ and filtered over Celite. The organic filtrate was concentrated under reduced pressure to obtain pure SnAP-OAC 2.24 in quantitative yield (1.10 g) as clear, colorless liquid. IR (thin film): ν 3330, 2955, 2924, 2869, 2853, 1574, 1463, 1376, 1317, 1087, 873 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.71 (s, J¹¹⁷/¹¹⁹Sn-¹H) = 6.8 Hz, 2H), 3.32 (t, J = 6.2 Hz, 2H), 2.70 (t, J = 6.9 Hz, 2H), 1.64-1.43 (m, 8H), 1.39-1.22 (m, 9H), 0.95-0.81 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 75.4, 62.0, 42.3, 30.8, 29.3, 27.5, 27.2, 13.9, 9.2; ESI-HRMS calcd for C¹₇H₄ₒN₁O₁Sn₁ [M + H]⁺ 394.2129, found 394.2130.

(2-((Tributylstannyl)methoxy)phenyl)methanol (2.25). A solution of commercially available 2-hydroxymethylphenol (1.50 g, 12.1 mmol, 1.00 equiv) in acetone (60 mL) was
treated with K$_2$CO$_3$ (2.00 g, 14.5 mmol, 1.20 equiv) and tributyl(iodomethyl)stannane (5.73 g, 13.3 mmol, 1.10 equiv) at rt. The resulting suspension was refluxed for 12 h. The reaction mixture was allowed to cool to rt and was diluted with EtOAc (100 mL). The acetone was removed under reduced pressure and the resulting organic layer was washed with H$_2$O (3 × 10 mL), brine (20 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated to yield a yellow oil. Purification by flash column chromatography (hexanes:EtOAc 30:1) afforded benzyl alcohol 2.25 (3.56 g, 69% yield) as clear, colorless liquid. IR (thin film): ν 3366, 2955, 2925, 2871, 2852, 1603, 1588, 1487, 1455, 1254, 1204, 1043, 1002 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.32-7.23 (m, 2H), 7.05 (d, $J$ = 8.1 Hz, 1H), 6.95-6.89 (m, 1H), 4.66 (d, $J$ = 6.6 Hz, 2H), 4.19 (s, $J_{(117/119)Sn}^{-1}H$) = 14.8 Hz, 2H), 2.23 (t, $J$ = 6.6 Hz, 1H), 1.58-1.48 (m, 6H), 1.32 (sext, $J$ = 7.3 Hz, 6H), 1.07-0.96 (m, 6H), 0.90 (t, $J$ = 7.3 Hz, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 159.6, 129.2, 129.0, 128.4, 120.4, 110.4, 62.5, 58.5, 29.2, 27.5, 13.8, 9.3; ESI-HRMS calcd for C$_{20}$H$_{36}$Na$_1$O$_2$Sn$_1$ [M + Na]$^+$ 451.1633, found 451.1630.

2-(2-((Tributylstannyl)methoxy)benzyl)isoindoline-1,3-dione (2.27). Diisopropyl azodicarboxylate (1.14 mL, 5.81 mmol, 1.00 equiv) was added dropwise over 10 min to a solution of benzyl alcohol 2.25 (2.48 g, 5.81 mmol, 1.00 equiv), triphenylphosphine (1.67 g, 6.39 mmol, 1.10 equiv), and phthalimide (897 mg, 6.10 mmol, 1.05 equiv) in THF (60 mL) at 0°C. The resulting solution was allowed to warm to rt and stirred for 16 h before diluted with EtOAc (100 mL). The organic layer was washed with sat aq NaHCO$_3$ (2 × 20 mL), brine (30 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 20:1) afforded the phthalimide protected SnAP-BOA 2.27 (2.13 g, 66% yield) as clear, colorless liquid. IR (thin film): ν 2955, 2925, 2871, 2851, 1773, 1719, 1391 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.89-7.84 (m, 2H), 7.74-7.70 (m, 2H), 7.26-7.22 (m, 1H), 7.05-7.01 (m, 2H), 6.85-6.80 (m, 1H), 4.88 (s, 2H), 4.19 (s, $J_{(117/119)Sn}^{-1}H$) = 14.9 Hz, 2H), 1.60-1.48 (m, 6H), 1.31 (sext, $J$ = 7.3 Hz, 6H), 1.08-0.96 (m, 6H), 0.89 (t, $J$ = 7.3 Hz, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 168.2, 159.0, 134.0, 132.4, 128.6, 127.3, 124.1, 123.4, 112.0, 110.4, 58.5, 36.9, 29.2, 27.5, 13.8, 9.4; ESI-HRMS calcd for C$_{26}$H$_{36}$Na$_1$O$_3$Sn$_1$ [M + Na]$^+$ 580.1849, found 580.1836.
(2-((Tributylstannyl)methoxy)phenyl)methanamine (2.29). Phthalimide protected SnAP-BOA 2.27 (1.50 g, 2.70 mmol, 1.00 equiv) in EtOH (27 mL) was heated to reflux. Hydrazine monohydrate (1.30 mL, 27.0 mmol, 10.0 equiv) was added dropwise at reflux over 10 min. The resulting reaction mixture was stirred for further 15 min at reflux while colorless solid crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (100 mL) and H₂O (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford pure SnAP-BOA 2.29 (1.13 g, 99% yield) as colorless oil. IR (thin film): ν 2955, 2925, 2871, 2852, 1601, 1487, 1454, 1001 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.27-7.21 (m, 1H), 7.19 (dd, J = 7.3, 1.6 Hz, 1H), 7.04 (d, J = 7.7 Hz, 1H), 6.91-6.86 (m, 1H), 4.16 (s, J¹¹⁷/¹¹⁹Sn-¹H) = 15.1 Hz, 2H), 3.79 (s, 2H), 1.59-1.44 (m, 6H), 1.32 (sext, J = 7.3 Hz, 6H), 1.09-0.95 (m, 6H), 0.89 (t, J = 7.3 Hz, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 159.6, 132.0, 128.2, 128.1, 120.2, 110.3, 58.1, 42.9, 29.2, 27.5, 13.8, 9.3; ESI-HRMS calcd for C₂₀H₃₈N₁O₁Sn₁ [M + H]⁺ 428.1973, found 428.1961.

3-(2-((Tributylstannyl)methoxy)phenyl)propan-1-ol (2.26). Tributyl(iodomethyl) stannane (1.38 g, 3.21 mmol, 1.05 equiv) in acetone (3 mL) was added dropwise over 5 min to a suspension of the diol (465 mg, 3.06 mmol, 1.00 equiv) and K₂CO₃ (550 mg, 3.97 mmol, 1.30 equiv) in acetone (12 mL) at rt and stirred at reflux for 12 h. The resulting suspension was allowed to cool to rt and was diluted with EtOAc (50 mL). The acetone was removed under reduced pressure and the resulting organic layer was washed with H₂O (3 x 5 mL), brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to yield a colorless oil. Purification by flash column chromatography (hexanes:EtOAc 15:1) afforded alcohol 2.26 (1.24 g, 89% yield) as clear, colorless liquid. IR (thin film): ν 3334, 2955, 2925, 2871, 2852, 1600, 1489, 1455, 1208, 1003 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.23-7.17 (m, 1H), 7.12 (dd, J = 7.4, 1.7 Hz, 1H), 7.02 (dd, J = 7.6, 1.1 Hz, 1H), 6.89-6.84 (m, 1H), 4.15 (s, J¹¹⁷/¹¹⁹Sn-¹H) = 14.8 Hz, 2H), 3.62 (t, J = 5.8 Hz, 2H), 2.70 (t, J = 7.4 Hz, 2H), 1.89-1.80 (m, 2H), 1.60-1.46 (m, 7H), 1.32 (sext, J = 7.3 Hz, 6H), 1.07-0.92 (m, 6H), 0.90 (t, J = 7.3 Hz, 9H); ¹³C NMR (100
MHz, CDCl$_3$): δ 159.6, 130.0, 129.9, 127.2, 120.2, 110.5, 62.5, 33.0, 29.2, 27.5, 26.4, 13.8, 9.3; ESI-HRMS calcd for C$_{22}$H$_{40}$Na$_1$O$_2$Sn$_1$ [M + Na]$^+$ 479.1946, found 479.1946.

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\begin{align*}
\text{2-(3-(2-((Tributylstannyl)methoxy)phenyl)propyl)isoindoline-1,3-dione (2.28).} \\
\text{Diisopropyl azodicarboxylate (450 μL, 2.22 mmol, 1.05 equiv) was added dropwise over 15 min to a clear, colorless solution of alcohol 2.26 (964 mg, 2.12 mmol, 1.00 equiv), triphenylphosphine (612 mg, 2.33 mmol, 1.10 equiv), and phthalimide (338 mg, 2.29 mmol, 1.08 equiv) in THF (22 mL) at 0°C. The clear, colorless solution was allowed to warm to rt and stirred for 16 h. EtOAc (50 mL) was added in one portion and the resulting organic solution was washed with H$_2$O (2 x 10 mL) and brine (15 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated to yield colorless oil. Purification by flash column chromatography (hexanes:EtOAc 25:1) afforded the phthalimide protected SnAP-BOAN 2.28 (1.13 g, 95% yield) as clear, colorless liquid. IR (thin film): ν 2954, 2925, 2871, 2851, 1772, 1715, 1489, 1394, 1001 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.21-8.15 (m, 2H), 8.07-8.02 (m, 2H), 7.54-7.45 (m, 2H), 7.32 (dd, J = 8.2, 1.0 Hz, 1H), 7.20-7.14 (m, 1H), 4.45 (s, J($^{117/119}$Sn-1H) = 15.2 Hz, 2H), 4.07 (t, J = 7.3 Hz, 2H), 2.99 (t, J = 7.7 Hz, 2H), 2.37-2.28 (m, 2H), 1.91-1.80 (m, 6H), 1.63 (sext, J = 7.3 Hz, 6H), 1.39-1.24 (m, 6H), 1.21 (t, J = 7.3 Hz, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 168.5, 159.7, 133.9, 132.4, 129.6, 129.5, 127.3, 123.3, 120.0, 110.2, 58.1, 38.2, 29.2, 28.5, 28.0, 27.5, 13.8, 9.3; ESI-HRMS calcd for C$_{30}$H$_{43}$N$_1$Na$_1$O$_3$Sn$_1$ [M + Na]$^+$ 608.2163, found 608.2169.
\end{align*}
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\begin{align*}
\text{3-(2-((Tributylstannyl)methoxy)phenyl)propan-1-amine (2.30). Phthalimide protected SnAP-BOAN 2.28 (1.10 g, 1.88 mmol, 1.00 equiv) in EtOH (19 mL) was heated to reflux. Hydrazine monohydrate (915 μL, 18.8 mmol, 10.0 equiv) was added dropwise at reflux over 5 min. The resulting reaction mixture was stirred for further 15 min at reflux while colorless solid crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (100 mL) and H$_2$O (10 mL). The layers were separated and the aqueous layer was}
\end{align*}
\]
extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford pure SnAP-BOAN 2.30 (855 mg, 100% yield) as colorless oil. IR (thin film): ν 3372, 3297, 2955, 2925, 2871, 2852, 1600, 1715, 1489, 1455, 1207, 1002 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.21-7.15 (m, 1H), 7.10 (dd, J = 7.4, 1.6 Hz, 1H), 7.00 (dd, J = 7.6, 1.0 Hz, 1H), 6.87-6.82 (m, 1H), 4.12 (s, J₁¹¹¹¹¹Sn-¹H) = 15.1 Hz, 2H), 2.71 (t, J = 7.1 Hz, 2H), 2.63 (t, J = 7.4 Hz, 2H), 1.77-1.18 (m, 2H), 1.61-1.43 (m, 8H), 1.31 (sext, J = 7.3 Hz, 6H), 1.08-0.92 (m, 6H), 0.89 (t, J = 7.3 Hz, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 159.6, 130.5, 129.7, 127.1, 120.0, 110.3, 58.1, 42.3, 34.2, 29.2, 27.8, 27.5, 13.8, 9.3; ESI-HRMS calcd for C₂₂H₄₂N₁O₁Sn₁ [M + H]⁺ 456.2287, found 456.2287.

Rotamers 1:2 (¹H NMR integration)

**tert-Butyl (3-chloropropyl)((tributylstannyl)methyl)carbamate (2.31).** Sodium hydride (124 mg of a 60% suspension in mineral oil, 3.10 mmol, 1.50 equiv) was washed with pentane (3 x 2 mL) and suspended in THF/DMF (1:1, 8 mL). The suspension was cooled to 0°C and tert-butyl (3-chloropropyl)carbamate (400 mg, 2.07 mmol, 1.00 equiv) in THF:DMF (1:1, 10 mL) was added dropwise over 10 min. The resulting suspension was allowed to warm to rt. After 15 min, the reaction mixture was cooled to 0°C and tributyl(iodomethyl)stannane (1.33 g, 3.10 mmol, 1.50 equiv) in THF:DMF (1:1, 3 mL) was added dropwise over 10 min. The suspension was allowed to warm to rt over 1 h, and then stirred at rt for 1 h. The reaction mixture was cooled to 0°C and slowly quenched with sat aq NH₄Cl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with H₂O (2 x 10 mL), brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 100:0 to 98:2) afforded the alkylated product 2.31 (554 mg, 54% yield) as clear, colorless liquid. IR (thin film): v 2956, 2923, 2871, 2853, 1679, 1365, 1162 cm⁻¹; ¹H NMR
(400 MHz, CDCl$_3$): $\delta$ 3.61-3.46 (m, 2H), 3.46-3.15 (m, 2H), 3.12-3.00 (s, 2H $\times$ 0.33), 2.82 (s, J($^{117/119}$Sn-$^1$H) = 25.8 Hz, 2H $\times$ 0.66), 2.05-1.94 (m, 2H), 1.57-1.41 (m, 15H), 1.34-1.22 (m, 6H), 0.94-0.82 (m, 15H);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.6, 79.6, 79.3, 47.7, 46.8, 42.8, 42.6, 33.8, 33.6, 31.5, 31.1, 29.3, 28.6, 27.6, 13.9, 10.6, 9.8; R$_f$ = 0.59 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C$_{21}$H$_{44}$Cl$_1$N$_1$O$_2$Sn$_1$ [M + Na]$^+$ 520.1972, found 520.1976.

Rotamers 3:7 ($^1$H NMR integration)

**tert-Butyl (3-(1,3-dioxoisindolin-2-yl)propyl)((tributylstannyl)methyl)carbamate (2.32).** Chloride 2.31 (400 mg, 0.81 mmol, 1.00 equiv) in DMF (8 mL) was treated with potassium phthalimide (154 mg, 0.85 mmol, 1.05 equiv) in one portion at rt. The resulting suspension was heated to 100°C for 45 min, allowed to cool to rt and diluted with EtOAc (50 mL). This organic layer was washed with H$_2$O (2 x 10 mL), brine (2 x 10 mL), dried over Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (hexanes:EtOAc 15:1) afforded the phthalimide protected SnAP-DA 2.32 (397 mg, 81% yield) as clear, colorless liquid. IR (thin film): $\nu$ 2955, 2924, 2871, 2853, 1773, 1716, 1679, 1395, 1161 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.89-7.78 (m, 2H), 7.74-7.67 (m, 2H), 3.74-3.65 (m, 2H), 3.26-3.19 (m, 2H), 3.06 (s, 2H $\times$ 0.30), 2.81 (s, J($^{117/119}$Sn-$^1$H) = 26.2 Hz, 2H $\times$ 0.70), 1.97-1.87 (m, 2H), 1.56-1.41 (m, 9H), 1.38 (br s, 6H), 1.32-1.22 (m, 6H), 0.92-0.78 (m, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.4, 155.4, 134.1, 132.3, 123.4, 79.5, 79.2, 48.3, 46.5, 36.0, 33.6, 32.7, 29.3, 28.7, 28.5, 27.6, 27.4, 26.8, 13.9, 10.6, 9.7; ESI-HRMS calcd for C$_{29}$H$_{49}$N$_2$O$_4$Sn$_1$ [M + H]$^+$ 609.2714, found 609.2699.

Rotamers 3:5 ($^1$H NMR integration)

**tert-Butyl (3-aminopropyl)((tributylstannyl)methyl)carbamate (2.33).** Phthalimide protected SnAP-DA 2.32 (1.37 g, 2.26 mmol, 1.00 equiv) in EtOH (23 mL) was heated to reflux. Hydrazine monohydrate (1.13 mL, 22.6 mmol, 10.0 equiv) was added dropwise at reflux over 10 min. The resulting reaction mixture was stirred for further 15 min at reflux while colorless solid crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (100 mL) and H$_2$O (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10
mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford pure SnAP-DA 2.32 (1.02 g, 95% yield) as colorless oil. IR (thin film): $\nu$ 3370, 2956, 2924, 2871, 1677, 1578, 1481, 1467, 1163 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.28-3.20 (m, 2H), 3.01 (s, 2H), 2.78 (s, $J^{(117/119}\text{Sn}^1\text{H}) = 26.2$ Hz, 2H), 2.68 (t, $J = 6.7$ Hz, 2H), 1.69-1.62 (m, 2H), 1.52-1.39 (m, 17H), 1.34-1.23 (m, 6H), 0.91-0.82 (m, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.6, 79.5, 79.1, 47.5, 45.7, 39.5, 39.2, 33.3, 32.6, 32.1, 31.2, 29.3, 28.6, 27.6, 13.9, 10.6, 9.8; ESI-HRMS calcd for C$_{21}$H$_{47}$N$_2$O$_2$Sn$_1$ [M + H]$^+$ 479.2658, found 479.2662.

1-Phenyl-3-((tributylstannyl)methoxy)propan-1-amine (2.34). Sodium hydride (160 mg of a 60% suspension in mineral oil, 4.00 mmol, 1.10 equiv) was washed with pentane (3 x 2 mL) and suspended in DMF (20 mL). The suspension was cooled to 0°C and commercially available amino alcohol (550 mg, 3.64 mmol, 1.00 equiv) in DMF (8 mL) was added dropwise over 5 min. The resulting suspension was allowed to warm to rt. After 1 h, the reaction mixture was cooled to 0°C and tributyl(iodomethyl)stannane (1.57 g, 3.64 mmol, 1.00 equiv) in DMF (8 mL) was added dropwise over 10 min. The suspension was allowed to warm to rt over 1 h, and then stirred at rt for 2 h. The reaction mixture was cooled to 0°C and slowly quenched with sat aq NH$_4$Cl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H$_2$O (2 x 10 mL), brine (10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 4:1 + 0.1% Et$_3$N v/v) afforded the pure SnAP PhOA 2.34 (1.26 g, 76% yield) as clear, pale yellow liquid. IR (thin film): $\nu$ 3384, 2955, 2925, 2870, 1455, 1376, 1087 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36-7.28 (m, 4H), 7.26-7.20 (m, 1H), 4.07 (dd, $J = 7.3$, 6.3 Hz, 1H), 3.68 (s, $J^{(117/119}\text{Sn}^1\text{H}) = 14.2$ Hz, 2H), 3.41-3.34 (m, 1H), 3.32-3.24 (m, 1H), 1.95-1.82 (m, 2H), 1.76 (br s, NH$_2$), 1.60-1.42 (m, 6H), 1.35-1.26 (m, 6H), 0.96-0.81 (m, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 146.6, 128.6, 127.0, 126.5, 73.3, 62.2, 53.9, 39.5, 29.3, 27.5, 13.9, 9.1; ESI-HRMS calcd for C$_{21}$H$_{45}$N$_2$O$_2$Sn$_1$ [M + H]$^+$ 455.2210, found 456.2300.
tert-Butyl (2-(((triisopropylsilyl)oxy)methyl)phenyl)carbamate (S2.9). To a solution of Boc-protected amino alcohol (2.27 g, 9.56 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (48 mL) at 0°C was added imidazole (976 mg, 14.34 mmol, 1.50 equiv), followed by the slow addition of TIPSCl (2.31 mL, 10.52 mmol, 1.10 equiv). The reaction mixture was stirred at 40°C for 15 h before slowly quenched with H$_2$O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H$_2$O (30 mL), brine (30 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (pentane:EtOAc 30:1) afforded S2.9 (3.35 g, 92% yield) as clear, colorless liquid. IR (thin film): $\nu$ 3363, 2942, 2866, 1732, 1592, 1529, 1452, 1233, 1161, 1056, 881, 790 cm$^{-1}$; $^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.36 (s, 1H), 8.04 (d, $J$ = 8.0 Hz, 1H), 7.35 - 7.22 (m, 1H), 7.04 (d, $J$ = 7.4 Hz, 1H), 6.94 (t, $J$ = 7.4 Hz, 1H), 4.80 (s, 2H), 1.50 (s, 9H), 1.23 - 1.12 (m, 3H), 1.08 (d, $J$ = 6.7 Hz, 18H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 153.2, 138.9, 128.0, 127.9, 122.2, 119.7, 79.9, 66.0, 28.5, 18.1, 11.9; ESI-HRMS calcd for C$_{21}$H$_{37}$N$_1$Na$_1$O$_3$Si$_1$ [M + Na]$^+$ 402.2435, found 402.2426.

**tert-Butyl ((tributylstannyl)methyl)(2-(((triisopropylsilyl)oxy)methyl)phenyl)carbamate (S2.10).** Sodium hydride (158 mg of a 60% suspension in mineral oil, 3.95 mmol, 1.50 equiv), was washed with pentane (3 x 2 mL) and suspended in DMF (8 mL). The suspension was cooled to 0°C, followed by the dropwise addition of S2.9 (1.00 g, 2.63 mmol, 1.00 equiv) in THF (6 mL) over 5 min. The resulting suspension was allowed to warm to rt and stirred for 1 h. The suspension was re-cooled to 0°C, followed by the dropwise addition of
tributyl(iodomethyl)stannane (1.70 g, 3.95 mmol, 1.50 equiv) in THF (6 mL) over 5 min. The reaction mixture was stirred at 0°C for 1 h and at rt for 1 h. The reaction was quenched with H2O (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (pentane:EtOAc 30:1) afforded S2.10 (1.63 g, 91% yield) as clear, colorless liquid. IR (thin film): ν 2956, 2923, 2867, 1682, 1461, 1365, 1162, 1118, 1085, 995, 881 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.65 (d, J = 7.5 Hz, 1H), 7.31-7.24 (m, 2H), 7.21 (t, J = 6.9 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 4.79 (s, 2H), 2.95 (dd, J = 80.2, 12.7 Hz, 2H), 1.53-1.37 (m, 7H), 1.38-1.24 (m, 14H), 1.23-1.14 (m, 3H), 1.10 (d, J = 6.4 Hz, 18H), 0.88 (t, J = 7.5 Hz, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 155.3, 141.7, 138.3, 127.3, 126.9, 126.5, 79.5, 126.9, 79.5, 61.3, 36.7, 29.3, 28.4, 27.6, 18.3, 13.8, 12.2, 11.0; ESI-HRMS calcd for C₃₄H₆₅N₁O₃Si₁Sn₁ [M + Na]⁺ 706.3654, found 706.3650.

**tert-Butyl (2-(hydroxymethyl)phenyl)((tributylstannyl)methyl)carbamate (S2.11).**

To a solution of S2.10 (1.62 g, 2.38 mmol, 1.00 equiv) in THF (10 mL) was added TBAF (2.85 mL of a 1.0 M solution in THF, 2.85 mmol, 1.20 equiv) at 0°C over 5 min. The reaction mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure. Purification by flash column chromatography (pentane:EtOAc 30:1 to 15:1) afforded S2.11 (1.20 g, 96% yield) as clear, colorless liquid. IR (thin film): ν 3418, 2956, 2922, 2870, 1681, 1455, 1378, 1376, 1162, 1044, 995, 872, 761 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.55-7.47 (m, 1H), 7.36-7.27 (m, 2H), 7.22-6.98 (m, 1H), 4.74-4.24 (m, 2H), 3.78-3.26 (m, 1H), 3.21-2.86 (m, 1H), 1.85 (s, 1H), 1.56-1.19 (m, 21H), 0.87 (s, 15H); ¹³C NMR (126 MHz, CDCl₃): δ 156.6, 155.3, 143.3, 142.7, 137.9, 137.6, 131.4, 129.3, 128.9, 128.8, 127.9, 127.5, 127.2, 126.8, 81.3, 80.2, 62.2, 61.8, 37.6, 29.2, 28.4, 27.6, 13.8, 10.9, 9.9; ESI-HRMS calcd for C₂₅H₄₅N₁O₃Sn₁ [M + Na]⁺ 550.2318, found 550.2321.

**tert-Butyl (2-((1,3-dioxoisindolin-2-yl)methyl)phenyl)((tributylstannyl)methyl)carbamate (S2.12).**

To a solution of S2.11 (1.20 g, 2.27 mmol, 1.00 equiv) in THF (8 mL) was
added phthalimide (355 mg, 2.38 mmol, 1.05 equiv) and triphenylphosphine (624 mg, 2.38 mmol, 1.05 equiv) in one portion, followed by a dropwise addition of diisopropyl azodicarboxylate (515 µL, 2.38 mmol, 1.05 mmol) at 0°C over 10 min. The clear mixture was allowed to warm to rt and stirred at rt for 24 h. The solvent was removed under reduced pressure. Purification by flash column chromatography (pentane:EtOAc 30:1) afforded S2.12 (1.32 g, 88% yield) as clear, colorless liquid. IR (thin film): ν 2955, 2922, 2870, 1774, 1720, 1680, 1390, 1366, 1159 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 7.95-7.80 (m, 2H), 7.79-7.64 (m, 2H), 7.30-7.21 (m, 1H), 7.20-7.01 (m, 3H), 4.91 (d, J = 15.7 Hz, 1H), 4.74 (d, J = 15.7 Hz, 1H), 3.36 (d, J = 12.7 Hz, 1H), 2.95 (d, J = 12.7 Hz, 1H), 1.70-1.41 (m, 8H), 1.39-1.15 (m, 14H), 1.02-0.71 (m, 15H); 13C NMR (100 MHz, CDCl₃): δ 168.1, 155.2, 143.5, 134.2, 133.2, 132.3, 128.4, 127.3, 127.2, 127.1, 123.5, 79.9, 37.7, 36.9, 29.3, 28.3, 27.6, 13.9, 11.1; ESI-HRMS calcd for C₃₃H₄₈N₂Na₄O₄Sn₁ [M + Na]⁺ 679.2535, found 679.2524.

**tert-Butyl (2-(aminomethyl)phenyl)((tributylstannyl)methyl)carbamate (2.35).** To a solution of phthalimide protected SnAP BDA S2.12 (394 mg, 0.60 mmol, 1.00 equiv) in EtOH (3 mL) was added hydrazine monohydrate (0.30 mL, 6.0 mmol, 10.0 equiv). The reaction was refluxed for 20 min while colorless solid crashed out. The solvent was removed under reduced pressure. The resulting residue was suspended in CH₂Cl₂ and filtered over Celite. The organic filtrate was concentrated under reduce pressure to obtain pure SnAP BDA 2.35 in quantitative yield (315 mg) as clear, colorless liquid. IR (thin film): ν 2955, 2921, 2870, 2853, 1681, 1455, 1417, 1161, 995, 872, 760 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 7.49-7.35 (m, 1H), 7.33-7.17 (m, 2H), 7.14-6.94 (m, 1H), 3.90-3.52 (m, 2H), 3.15 (d, J = 12.7 Hz, 1H), 2.86 (d, J = 12.7 Hz, 1H), 1.65-1.37 (m, 9H), 1.36-1.16 (m, 14H), 1.01-0.70 (m, 15H); 13C NMR (100 MHz, CDCl₃): δ 155.4, 143.4, 140.0, 128.4, 127.7, 127.5, 127.4, 79.7, 42.4, 37.4, 29.3, 28.4, 27.6, 13.9, 11.0; ESI-HRMS calcd for C₃₃H₄₆N₂Na₁O₄Sn₁ [M + H]⁺ 527.2658, found 527.2659.
(2-(((Tributylstannyl)methoxy)methyl)phenyl)methanol (S2.13). 1,2-Benzenedimethanol (3.19 g, 23.1 mmol, 3.00 equiv) in THF-DMF (5:1, 32 mL) was added dropwise over 15 min to a solution of sodium hydride (308 mg of a 60% suspension in mineral oil, 7.70 mmol, 1.00 equiv) in THF-DMF (5:1, 64 mL) at 0°C. The reaction mixture was allowed to warm to rt and stirred for further 1.5 h. Tributyl(iodomethyl)stannane (3.65 g, 8.47 mmol, 1.10 equiv) was added dropwise over 15 min at 0°C. The resulting mixture was allowed to warm to rt and stirred for 16 h before sat aq NH₄Cl (20 mL) and H₂O (50 mL) was added slowly. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with H₂O (2 x 10 mL), brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford orange oil. Purification by flash column chromatography (hexanes:EtOAc 10:1 to 1:1) afforded the recovered diol (2.02 g, 89%) as colorless solid and the alkylated benzyl alcohol S2.13 (2.90 g, 85% yield) as colorless liquid.

IR (thin film): ν 3419, 2954, 2923, 2870, 2852, 1456, 1039 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.40-7.27 (m, 4H), 4.64 (d, J = 6.4 Hz, 2H), 4.52 (s, 2H), 3.77 (s, J₁₁₁.Sn⁻¹H = 15.8 Hz, 2H), 3.30 (t, J = 6.4 Hz, 1H), 1.54-1.40 (m, 6H), 1.28 (sext, J = 7.2 Hz, 6H), 0.93-0.84 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 140.9, 136.5, 130.4, 129.8, 128.9, 127.9, 77.3, 64.3, 62.0, 29.2, 27.4, 13.8, 9.1; ESI-HRMS calcd for C₂₁H₃₈Na₂O₂Sn₁ [M + Na]⁺ 465.1789, found 465.1792.
Methanesulfonyl chloride (147 µL, 1.89 mmol, 1.10 equiv) was added dropwise over 5 min to a solution of benzyl alcohol S2.13 (760 mg, 1.72 mmol, 1.00 equiv) and triethylamine (290 µL, 2.07 mmol, 1.20 equiv) in Et₂O (9 mL) at 0°C. The resulting mixture was allowed to warm to rt and stirred for further 2 h before poured into H₂O (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 10 mL). The combined organic layers were washed with H₂O (2 x 5 mL), brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford pure mesylate that was used immediately in the next step without further purification.

Potassium phthalimide (351 mg, 1.89 mmol, 1.10 equiv) was added in one portion to a solution of the mesylate in DMF (17 mL) at rt followed by vigorous stirring at 100°C for 3 h. The reaction mixture was allowed to cool to rt and poured into H₂O (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with H₂O (3 x 20 mL), brine (2 x 20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford yellow oil. Purification by flash column chromatography (hexanes:TBME 10:1) afforded the phthalimide protected SnAP BOAC S2.14 (883 mg, 90% yield, 2 steps) as clear, colorless liquid. IR (thin film): ν 2954, 2923, 2870, 2851, 1771, 1716, 1392 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.89-7.83 (m, 2H), 7.74-7.69 (m, 2H), 7.34-7.29 (m, 2H), 7.25-7.20 (m, 2H), 4.93 (s, 2H), 4.67 (s, 2H), 3.79 (s, J(¹¹⁷/¹¹⁹Sn-¹H) = 15.8 Hz, 2H), 1.55-1.43 (m, 6H), 1.29 (s, J = 7.3 Hz, 6H), 0.94-0.85 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 168.3, 136.7, 135.2, 134.1, 132.3, 129.4, 128.6, 128.1, 127.6, 123.5, 76.0, 61.8, 38.3, 29.3, 27.5, 13.9, 9.1; ESI-HRMS calcd for C₂₉H₄₅N₁Na₁O₃Sn₁ [M + Na]⁺ 594.2006, found 594.2008.

(2-(((Tributylstannyl)methoxy)methyl)phenyl)methanamine (2.41). The phthalimide protected SnAP BOAC S2.14 (2.30 g, 4.03 mmol, 1.00 equiv) in EtOH (40 mL) was heated to reflux. Hydrazine monohydrate (1.95 mL, 40.3 mmol, 10.0 equiv) was added dropwise at reflux over 5 min. The resulting reaction mixture was stirred for further 15 min at reflux while colorless
solid crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (200 mL) and H₂O (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford pure SnAP BOAC 2.41 (1.72 g, 97% yield) as colorless oil. IR (thin film): ν 2955, 2925, 2870, 2852, 1456, 1059 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.35-7.20 (m, 4H), 4.46 (s, 2H), 3.86 (s, 2H), 3.76 (s, J (¹¹⁷/¹¹⁹Sn-H) = 15.5 Hz, 2H), 1.56-1.43 (m, 6H), 1.29 (sext, J = 7.3 Hz, 6H), 0.99-0.84 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 142.6, 136.1, 129.8, 128.4, 128.2, 126.8, 76.1, 61.8, 44.2, 29.3, 27.4, 13.8, 9.1; ESI-HRMS calcd for C₂₁H₄₀N₁O₁Sn¹ [M + H]+ 442.2130, found 442.2133.

tert-Butyl (4-((triisopropylsilyl)oxy)butyl)carbamate (S2.15). Imidazole (1.35 g, 19.8 mmol, 1.50 equiv) was added in one portion to a solution of the Boc-protected amino alcohol (2.50 g, 13.2 mmol, 1.00 equiv) in CH₂Cl₂ (66 mL) at rt. The resulting solution was cooled to 0°C and treated with TIPSCl (3.11 mL, 14.5 mmol, 1.10 equiv) over 10 min before stirred at rt for 20 h. The reaction mixture was diluted with CH₂Cl₂ (50 mL), washed with sat aq NH₄Cl (2 x 15 mL), H₂O (15 mL), brine (20 mL), dried over Na₂SO₄, filtered over a short plug of silica gel (CH₂Cl₂ rinse) and concentrated to yield the desired product S2.15 next to triisopropylsilanol as impurity. 100°C under high vacuum (ca. 0.1 mmHg) for 2 h afforded the pure tert-butyl (4-((triisopropylsilyl)oxy)butyl)carbamate (S2.15; 3.88 g, 85% yield) as colorless oil. IR (thin film): ν 3461, 2942, 2867, 1698, 1522, 1175, 1106 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.71 (br s, 1H), 3.73-3.65 (m, 2H), 3.19-3.08 (m, 2H), 1.59-1.52 (m, 4H), 1.43 (s, 9H), 1.13-1.01 (m, 21H); ¹³C NMR (100 MHz, CDCl₃): δ 156.1, 79.0, 63.1, 40.6, 30.4, 28.6, 26.7, 18.2, 12.1; ESI-HRMS calcd for C₁₈H₃₉N₁Na₁O₃Si₁ [M + Na]+ 368.2591, found 368.2597.
Rotamers 1:2 ($^1$H NMR integration)

**tert-Butyl (((tributylstannyl)methyl) (4-((trisopropylsilyl)oxy)butyl) carbamate**  \(\text{S2.16}\). Sodium hydride (512 mg of a 60% suspension in mineral oil, 12.8 mmol, 1.50 equiv) was washed with pentane (3 x 3 mL) and suspended in THF/DMF (1:1, 20 mL). The suspension was cooled to 0°C and **tert-butyl** (4-((trisopropylsilyl)oxy)butyl) carbamate  \(\text{S2.15}\) (2.95 g, 8.54 mmol, 1.00 equiv) in THF-DMF (1:1, 20 mL) was added dropwise over 15 min. The resulting suspension was allowed to warm to rt. After 30 min, the reaction mixture was cooled to 0°C and tributyl(iodomethyl)stannane (5.52 g, 12.8 mmol, 1.50 equiv) in THF-DMF (1:1, 17 mL) was added dropwise over 15 min. The suspension was allowed to warm to rt over 1 h, and then stirred at rt for 8 h. The reaction mixture was cooled to 0°C and slowly quenched with sat aq NH$_4$Cl (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H$_2$O (2 x 10 mL), brine (10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 50:1) afforded the alkylated product \(\text{S2.16}\) (5.37 g, 97% yield) as clear, colorless liquid. IR (thin film): ν 2955, 2925, 2867, 1676, 1464, 1162, 1110 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 3.70 (t, \(J = 6.2\) Hz, 2H), 3.24-3.12 (m, 2H), 3.04 (s, 2H $\times 0.33$), 2.82 (s, \(J^{(117/119}\text{Sn}-^1\text{H}) = 25.9\) Hz, 2H $\times 0.66$), 1.63-1.42 (m, 19H), 1.29 (sext, \(J = 7.3\) Hz, 6H), 1.11-1.03 (m, 21H), 0.93-0.79 (m, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 155.7, 79.2, 78.8, 63.1, 63.3, 50.2, 48.9, 33.4, 30.5, 30.5, 29.3, 28.7, 28.6, 27.6, 24.8, 24.2, 18.2, 13.9, 12.2, 10.6, 9.8; ESI-HRMS calcd for C$_{31}$H$_{67}$N$_1$Na$_1$O$_3$Si$_1$Sn$_1$ [M + Na]$^+$ 672.3809, found 672.3801.

Rotamers 12:19 ($^1$H NMR integration)

**tert-Butyl (((tributylstannyl)methyl) (4-((trisopropylsilyl)oxy)butyl) carbamate**  \(\text{S2.17}\). TBAF (2.59 mL of a 1.0 M solution in THF, 2.59 mmol, 1.20 equiv) was added dropwise over 10 min to a solution of the TIPS protected alcohol \(\text{S2.16}\) (1.40 g, 2.16 mmol, 1.00 equiv) in THF (11 mL) at 0°C. The resulting solution was allowed to warm to rt and was stirred for 2 h before poured into a mixture of EtOAc:H$_2$O (2:1, 100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with H$_2$O (2 x 10 mL), brine (20 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography
(hexanes:EtOAc 9:1) afforded the alcohol S2.17 (987 mg, 93% yield) as clear, colorless liquid. IR (thin film): ν 3420, 2955, 2925, 2871, 2855, 1673, 1457, 1365, 1164 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.72-3.62 (m, 2H), 3.23-3.15 (m, 2H), 3.03 (s, 2H), 2.81 (s, J(¹²⁷/¹⁹Sn-¹H) = 25.7 Hz, 2H), 1.87 (br s, 1H), 1.63-1.41 (m, 19H), 1.29 (sext, J = 7.3 Hz, 6H), 0.93-0.76 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 155.6, 79.5, 79.0, 62.9, 62.7, 49.9, 48.5, 33.4, 32.8, 30.0, 29.6, 29.3, 28.7, 27.6, 24.5, 24.4, 13.9, 10.6, 9.8; ESI-HRMS calcd for C₂₂H₄₂N₁NaO₃Sn₁ [M + Na]⁺ 516.2474, found 516.2475.

Rotamers (1:2 by ¹H NMR integration)

**tert-Butyl (4-(1,3-dioxoisoindolin-2-yl)butyl) ((tributylstannyl)methyl) carbamate (S2.18).** Methanesulfonyl chloride (156 µL, 2.01 mmol, 1.10 equiv) was added dropwise over 5 min to a solution of the alcohol S2.17 (900 mg, 1.83 mmol, 1.00 equiv) and Et₃N (510 µL, 3.66 mmol, 2.00 equiv) in Et₂O (9 mL) at 0°C. The resulting mixture was allowed to warm to rt and stirred for further 2 h before poured into H₂O (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (2 x 10 mL). The combined organic layers were washed with H₂O (2 x 5 mL), brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford pure mesylate that was used immediately in the next step without further purification.

Potassium phthalimide (508 mg, 2.74 mmol, 1.50 equiv) was added in one portion to a solution of the mesylate in DMF (20 mL) at rt followed by vigorous stirring at 100°C for 3 h. The reaction mixture was allowed to cool to rt before poured into H₂O (50 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organic layers were washed with H₂O (3 x 20 mL), brine (2 x 20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford yellow oil. Purification by flash column chromatography (hexanes:EtOAc 15:1) afforded the phthalimide protected SnAP DAC S2.18 (1.10 g, 97% yield, 2 steps) as clear, colorless liquid. IR (thin film): ν 2954, 2925, 2871, 2853, 1716, 1676, 1395, 1162 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.87-7.70 (m, 2H), 7.74-7.66 (m, 2H), 3.71 (t, J = 7.0 Hz, 2H), 3.25-3.13 (m, 2H), 3.01 (s, 2H), 2.78 (s, J(¹²⁷/¹⁹Sn-¹H) = 25.9 Hz, 2H), 1.72-1.63 (m, 2H), 1.60-1.53 (m, 2H), 1.52-1.36 (m, 15H), 1.27 (sext, J = 7.3 Hz, 6H), 0.95-0.78 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 168.5, 155.6, 155.3, 134.1, 134.0, 132.3, 123.3, 79.4, 79.0, 49.6, 48.4, 37.9, 37.8, 33.5, 32.9, 29.3, 28.7, 28.6, 27.6, 26.2, 26.0, 25.5, 25.2, 13.9, 10.6, 9.8; ESI-HRMS calcd for C₃₀H₅₀N₂Na₁O₃Sn₁ [M + Na]⁺ 645.2690, found 645.2689.
Rotamers (ca. 1:2 by $^1$H NMR integration)

**tert-Butyl (4-aminobutyl) ([tributylstannyl)methyl] carbamate (2.42).** Phthalimide protected SnAP DAC S2.18 (230 mg, 0.37 mmol, 1.00 equiv) in EtOH (4 mL) was heated to reflux. Hydrazine monohydrate (180 µL, 3.70 mmol, 10.0 equiv) was added dropwise at reflux over 5 min. The resulting reaction mixture was stirred for further 15 min at reflux while colorless solid crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (50 mL) and H$_2$O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford pure SnAP DAC 2.42 (180 mg, 99% yield) as colorless oil. IR (thin film): ν 3308, 2955, 2924, 2871, 2854, 1676, 1481, 1464, 1162 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 3.21-3.09 (m, 2H), 3.02 (s, 2H × 0.33), 2.79 (s, J($^{117/119}$Sn-$^1$H) = 26.0 Hz, 2H × 0.66), 2.70 (t, J = 7.0 Hz, 2H), 1.67-1.32 (m, 19H), 1.34-1.14 (m, 8H), 0.92-0.78 (m, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 155.6, 155.3, 79.3, 78.8, 50.0, 48.8, 42.1, 33.4, 31.1, 29.3, 28.7, 28.6, 27.6, 25.5, 25.1, 13.84, 10.6, 9.7; ESI-HRMS calcd for C$_{22}$H$_{48}$N$_2$Na$_1$O$_2$Sn$_1$ [M + Na]$^+$ 515.2634, found 515.2625.

### 7.2.5 Preparation Medium-Sized Rings

All medium-sized saturated N-heterocycles were prepared according to the general procedure described in chp. 7.2.3

**3-(4-(Trifluoromethyl)phenyl)-1,4-oxazepane (2.36a).** Purification by flash column chromatography (pentane:EtOAc 2:1 to 1:2) afforded 2.36a (105 mg, 86% yield) as colorless solid. IR (thin film): v 3316, 2946, 1455, 1417, 1333, 1162, 1112, 1070, 763 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.58 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 4.08-3.88 (m, 3H), 3.87-3.75 (m, 1H), 3.48 (dd, J = 12.4, 9.4 Hz, 1H), 3.22 (dt, J = 13.5, 4.9 Hz, 1H), 3.02 (dt, J = 13.5, 6.6 Hz, 1H), 1.93 (dt, J = 11.6, 6.6 Hz, 2H), 1.78 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 145.6, 129.8 (q, J$_{CF}$ = 32.4 Hz), 127.6, 125.6 (q, J$_{CF}$ = 3.7 Hz), 124.2 (q, J$_{CF}$ = 273.6 Hz), 78.31, 70.2, 66.1, 46.3, 32.9; m.p. = 41-42°C; ESI-HRMS calcd for C$_{12}$H$_{15}$F$_3$N$_1$O$_1$ [M + H]$^+$ 246.1106, found 246.1105.
Ethyl 1,4-oxazepane-3-carboxylate (2.36b). Purification by flash column chromatography (CH$_2$Cl$_2$:MeOH 30:1) afforded 2.36b (45 mg, 52% yield) as clear, colorless liquid. IR (thin film): $\nu$ 3348, 2937, 2858, 1735, 1466, 1370, 1207, 1163, 1025 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.19 (q, $J$ = 7.1 Hz, 2H), 4.03 (dd, $J$ = 12.6, 3.6 Hz, 1H), 3.92-3.59 (m, 4H), 3.28-3.12 (m, 1H), 2.94-2.80 (m, 1H), 2.26 (br s, NH), 1.93-1.78 (m, 2H), 1.27 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.5, 72.8, 70.8, 62.7, 61.3, 45.0, 33.4, 14.3; ESI-HRMS calcd for C$_8$H$_{16}$N$_1$O$_3$ [M + H]$^+$ 174.1125, found 174.1127.

3-(3-Bromophenyl)-1,4-oxazepane (2.36c). Purification by flash column chromatography (CH$_2$Cl$_2$:EtOAc 2:1 to 1:2) afforded 2.26c (101 mg, 78% yield) as clear, colorless liquid. IR (thin film): $\nu$ 3321, 2938, 2855, 1592, 1566, 1473, 1424, 1336, 1137, 1105, 1076, 997, 782 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.54 (s, 1H), 7.38 (d, $J$ = 7.5 Hz, 1H), 7.27 (d, $J$ = 7.5 Hz, 1H), 7.18 (d, $J$ = 7.5 Hz, 1H), 4.03-3.87 (m, 3H), 3.82 (dt, $J$ = 12.6, 6.4 Hz, 1H), 3.46 (dd, $J$ = 12.6, 10.2 Hz, 1H), 3.20 (dt, $J$ = 13.4, 4.9 Hz, 1H), 3.00 (dt, $J$ = 13.4, 6.4 Hz, 1H), 1.98 (dd, $J$ = 11.6, 6.4 Hz, 2H), 1.74 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 143.9, 130.7, 130.3, 130.2, 125.9, 122.8, 78.4, 70.2, 66.0, 46.3, 32.8; ESI-HRMS calcd for C$_{11}$H$_{15}$Br$_1$N$_1$O$_1$ [M + H]$^+$ 256.0332, found 256.0334.

tert-Butyl 4-(1,4-oxazepan-3-yl)piperidine-1-carboxylate (2.36d). Purification by flash column chromatography (CH$_2$Cl$_2$:MeOH 10:1) afforded 2.36d (60 mg, 43% yield) as clear, colorless liquid. IR (thin film): $\nu$ 3442, 2933, 2857, 1690, 1426, 1365,1280, 1246, 1169, 867, 769 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.11 (s, 2H), 3.84 (dd, $J$ = 12.5, 3.5 Hz, 1H), 3.78 (dd, $J$ = 12.5, 6.0 Hz, 1H), 3.72 (dt, $J$ = 12.5, 6.0 Hz, 1H), 3.50 (dd, $J$ = 12.7, 8.3 Hz, 1H), 3.33 (s, 1H), 3.15 (dt, $J$ = 13.5, 4.9 Hz, 1H), 2.87 (dt, $J$ = 13.5, 6.4 Hz, 1H), 2.76-2.68 (m, 1H), 2.62 (t, $J$ = 11.9 Hz, 2H), 1.89 (quint, $J$ = 5.8 Hz, 2H), 1.73 (dt, $J$ = 12.8, 2.4 Hz, 1H), 1.63 (dt, $J$ = 12.9, 2.4 Hz, 1H), 1.61-1.49 (m, 1H), 1.42 (s, 9H), 1.32-1.13 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.8, 79.5, 73.0, 69.9, 64.0, 45.7, 43.9, 38.9, 32.2, 28.7, 28.5; ESI-HRMS calcd for C$_{15}$H$_{28}$N$_2$O$_3$ [M + H]$^+$ 285.2173, found 285.2169.
3-(4-(Trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzo[\f][1,4]oxazepine (2.37a). Purification by flash column chromatography (hexanes:EtOAc 15:1) afforded 2.37a (80 mg, 55% yield) as colorless solid. IR (thin film): ν 3316, 2954, 2915, 2814, 1619, 1582, 1490, 1325, 1165, 1124, 1108, 1067 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.60 (d, \(J = 8.2\) Hz, 2H), 7.50 (d, \(J = 8.2\) Hz, 2H), 7.26-7.19 (m, 2H), 7.10-7.02 (m, 2H), 4.41-4.32 (m, 2H), 4.20 (d, \(J = 14.3\) Hz, 1H), 4.00 (d, \(J = 14.3\) Hz, 1H), 3.80-3.72 (m, 1H), 1.92 (br s, NH); \(^1\)C NMR (100 MHz, CDCl\(_3\)): δ 159.7, 144.4, 134.5, 130.2 (q, \(J_{CF} = 32.3\) Hz), 129.5, 128.7, 127.8, 125.8 (q, \(J_{CF} = 3.8\) Hz), 124.2 (q, \(J_{CF} = 272.0\) Hz), 123.9, 121.1, 78.6, 66.1, 52.1; m.p. = 114-115°C; ESI-HRMS calcd for C\(_{16}\)H\(_{15}\)F\(_3\)N\(_1\)O\(_1\) [M + H]\(^+\) 294.1100, found 294.1099.

Ethyl 2,3,4,5-tetrahydrobenzo[\f][1,4]oxazepine-3-carboxylate (2.37b). Purification by flash column chromatography (hexanes:EtOAc 10:1) afforded 2.37b (45 mg, 41% yield) as pale orange oil. IR (thin film): ν 3340, 2979, 2933, 1735, 1489, 1454, 1301, 1188, 1021 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.20-7.10 (m, 2H), 7.03-6.97 (m, 2H), 4.54 (dd, \(J = 12.0, 2.7\) Hz, 1H), 4.28-4.19 (m, 2H), 4.10-4.03 (m, 2H), 4.02-3.98 (m, 1H), 3.95 (dd, \(J = 7.6, 2.7\) Hz, 1H), 2.08 (br s, NH), 1.30 (t, \(J = 7.1\) Hz, 3H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): δ 171.0, 159.5, 134.0, 129.4, 128.5, 123.7, 120.9, 74.9, 63.4, 61.5, 50.1, 14.3; ESI-HRMS calcd for C\(_{12}\)H\(_{16}\)N\(_1\)O\(_3\) [M + H]\(^+\) 222.1125, found 222.1126.

Methyl 4-(2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-3-yl)benzoate (2.37c). Purification by flash column chromatography (hexanes:EtOAc 5:1) afforded 2.37c (92 mg, 65% yield) as colorless oil. IR (thin film): ν 3323, 2952, 2909, 2812, 1721, 1281 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.01 (d, \(J = 8.3\) Hz, 2H), 7.44 (d, \(J = 8.3\) Hz, 2H), 7.24-7.17 (m, 2H), 7.07-7.01 (m, 2H), 4.41-3.31 (m, 2H), 4.20 (d, \(J = 14.3\) Hz, 1H), 4.00 (d, \(J = 14.3\) Hz, 1H), 3.91 (s, 3H), 3.74 (dd, \(J = 12.0, 9.1\) Hz, 1H), 1.93 (br s, NH); \(^1\)C NMR (100 MHz, CDCl\(_3\)): δ 166.9, 159.7, 145.4, 134.6, 130.1, 129.8, 129.5, 128.7, 127.4, 123.9, 121.1, 78.7, 66.3, 52.3, 52.1; ESI-HRMS calcd for C\(_{17}\)H\(_{18}\)N\(_1\)O\(_3\) [M + H]\(^+\) 284.1281, found 284.1276.
3-(Pyridin-3-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (2.37d). Purification by flash column chromatography (CH$_2$Cl$_2$:MeOH 95:5) afforded 2.37d (67 mg, 59% yield) as colorless oil. IR (thin film): ν 3263, 3034, 2954, 2919, 2852, 2816, 1489, 1227 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.73-8.45 (m, 2H), 7.74-7.67 (m, 1H), 7.30-7.24 (m, 1H), 7.24-7.18 (m, 2H), 7.10-6.99 (m, 2H), 4.42-4.30 (m, 2H), 4.20 (d, $J$ = 14.4 Hz, 1H), 4.00 (d, $J$ = 14.4 Hz, 1H), 3.79 (dd, $J$ = 12.0, 9.0 Hz, 1H), 1.85 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 159.6, 149.5, 149.1, 135.9, 134.9, 134.5, 129.5, 128.7, 123.9, 123.7, 121.1, 78.4, 64.0, 52.1; ESI-HRMS calcd for C$_{14}$H$_{15}$N$_2$O$^+$ [M + H$^+$] 227.1179, found 227.1179.

**cis 4-(5-Phenyl-1,4-oxazepan-3-yl)phenol (2.38a).** Purification by flash column chromatography (hexanes:EtOAc 4:1) afforded 2.38a (101 mg, 75% yield, d.r. ≥ 10:1) as clear, colorless solid. IR (thin film): ν 3247, 3059, 3025, 2940, 2855, 1613, 1515, 1454, 1233, 1131 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.47-7.41 (m, 2H), 7.37-7.30 (m, 2H), 7.30-7.24 (m, 3H), 6.81-6.74 (m, 2H), 4.17 (dd, $J$ = 8.7, 5.4 Hz, 1H), 4.14-4.06 (m, 2H), 4.02 (dd, $J$ = 12.4, 6.1 Hz, 1H), 3.98 (dd, $J$ = 12.1, 3.4 Hz, 1H), 3.72-3.65 (m, 1H), 2.28-2.15 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 155.5, 146.0, 133.0, 128.8, 128.7, 127.4, 126.7, 115.6, 78.8, 68.8, 65.9, 63.0, 40.6; m.p. = 122–125°C; ESI-HRMS calcd for C$_{17}$H$_{20}$N$_1$O$_2$ [M + H$^+$] 270.1489, found 270.1494.

**cis 4-(5-Phenyl-1,4-oxazepan-3-yl)benzonitrile (2.38b).** Purification by flash column chromatography (hexanes:EtOAc 7:1) afforded 2.38b (103 mg, 74% yield, d.r. = 9:1) as clear, colorless solid. IR (thin film): ν 2940, 2857, 2227, 1607, 1131 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.65-7.57 (m, 2H), 7.56-7.52 (m, 2H), 7.44-7.39 (m, 2H), 7.36-7.30 (m, 2H), 7.28-7.23 (m, 1H), 4.21 (dd, $J$ = 9.5, 3.2 Hz, 1H), 4.17 (dd, $J$ = 9.5, 3.9 Hz, 1H), 4.07-3.90 (m, 3H), 3.60 (dd, $J$ = 12.3, 9.5 Hz, 1H), 2.31-2.11 (m, 2H), 1.77 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 146.7, 145.9, 132.5, 128.9, 128.2, 127.5, 126.6, 118.9, 111.6, 78.2, 69.1, 65.7, 62.2, 40.9; m.p. = 114–117°C; ESI-HRMS calcd for C$_{18}$H$_{19}$N$_2$O$_1$ [M + H$^+$] 279.1492, found 279.1494.
cis 5-Phenyl-3-(o-toly)-1,4-oxazepane (2.38c). Purification by flash column chromatography (hexanes:EtOAc 20:1) afforded 2.38c (95 mg, 71% yield, d.r. ≥ 9:1) as clear, colorless oil. IR (thin film): ν 2939, 2858, 1459, 1130 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.58 (d, J = 7.2 Hz, 1H), 7.47-7.41 (m, 2H), 7.35-7.28 (m, 2H), 7.27-7.11 (m, 4H), 4.37 (dd, J = 9.8, 3.1 Hz, 1H), 4.17 (dd, J = 8.2, 5.8 Hz, 1H), 4.13-3.98 (m, 2H), 3.95 (dd, J = 12.1, 3.2 Hz, 1H), 3.63 (dd, J = 12.1, 9.9 Hz, 1H), 2.41 (s, 3H), 2.26-2.15 (m, 2H), 1.75 (br s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 146.3, 139.4, 135.2, 130.5, 128.7, 127.3, 127.3, 126.8, 126.6, 126.5, 77.7, 68.8, 63.2, 62.2, 41.0, 19.6; ESI-HRMS calcd for C₁₈H₂₂N₁O₁ [M + H]⁺ 268.1696, found 268.1707.

 cis 3-(Furan-3-yl)-5-phenyl-1,4-oxazepane (2.38d). Purification by flash column chromatography (hexanes:EtOAc 10:1) afforded 2.38d (81 mg, 67% yield, d.r. > 10:1) as clear, colorless solid. IR (thin film): ν 2938, 2854, 1457, 1134, 1021 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.44-7.38 (m, 3H), 7.36-7.29 (m, 3H), 7.27-7.22 (m, 1H), 6.41 (dd, J = 1.8, 10.0 Hz, 1H), 4.16-4.09 (m, 2H), 4.08-3.92 (m, 3H), 3.62 (dd, J = 12.0, 9.9 Hz, 1H), 2.23-2.07 (m, 2H), 1.83 (br s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 146.3, 139.4, 135.2, 128.7, 127.3, 127.3, 126.8, 126.6, 125.2, 109.4, 78.2, 68.8, 62.8, 57.9, 40.8; m.p. = 70–73°C; ESI-HRMS calcd for C₁₅H₁₈N₁O₂ [M + H]⁺ 244.1332, found 244.1331.

tert-Butyl 3-(4-(trifluoromethyl)phenyl)-1,4-diazepane-1-carboxylate (2.39a). Purification by flash column chromatography (hexanes:EtOAc 4:1) afforded 2.39a (1:1 rotamers by ¹H NMR integration, 113 mg, 66% yield) as colorless solid. IR (thin film): ν 3327, 2976, 2933, 2939, 1691, 1414, 1325, 1165, 1124, 1067 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.62-7.55 (m, 2H), 7.55-7.44 (m, 2H), 4.08 (dd, J = 13.8, 3.0 Hz, 1H × 0.5), 3.99-3.81 (m, 2H and 1H × 0.5), 3.28-3.14 (m, 2H), 2.92 (dd, J = 13.8, 9.7 Hz, 1H × 0.5), 2.84-2.69 (m, 1H and 1H × 0.5), 2.11-1.79 (m, 2H), 1.69 (br s, NH), 1.50 (s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 155.8, 155.5, 146.7, 146.4, 129.8 (q, J_CF = 31.7 Hz), 127.4, 127.2, 125.6, 124.3 (q, J_CF = 272.2 Hz), 79.8,
79.7, 64.7, 64.5, 56.8, 56.6, 47.1, 46.8, 46.4, 45.7, 45.1, 43.7; m.p. = 92–93°C; ESI-HRMS calcd for C\textsubscript{17}H\textsubscript{24}F\textsubscript{3}N\textsubscript{2}O\textsubscript{2} [M + H\textsuperscript{+}] 345.1784, found 345.1788.

**1-tert-Butyl 3-ethyl 1,4-diazepane-1,3-dicarboxylate (2.39b).** Purification by flash column chromatography (hexanes:EtOAc 3:1) afforded 2.39b (1:1 rotamers by \textsuperscript{1}H NMR integration, 84 mg, 62% yield) as colorless oil. IR (thin film): ν 3352, 2977, 2933, 1736, 1695, 1471, 1415, 1365, 1165 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 4.26-4.11 (m, 2H and 1H × 0.5), 4.04 (dd, J = 14.3, 4.2 Hz, 1H × 0.5), 3.80-3.53 (m, 2H), 3.28-3.04 (m, 3H), 2.71-2.56 (m, 1H), 1.93-1.67 (m, 3H), 1.46 (s, 9H), 1.27 (m, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 172.4, 172.3, 155.6, 155.3, 79.9, 79.8, 61.4, 61.3, 61.2, 51.8, 46.9, 46.6, 45.9, 45.6, 30.7, 28.6, 14.3; ESI-HRMS calcd for C\textsubscript{13}H\textsubscript{25}N\textsubscript{2}O\textsubscript{4} [M + H\textsuperscript{+}] 273.1809, found 273.1809.

**tert-Butyl 3-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1,4-diazepane-1-carboxylate (2.39c).** Purification by flash column chromatography (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 95:5) afforded 2.39c (1:1 rotamers by \textsuperscript{1}H NMR integration, 142 mg, 83% yield) as colorless oil. IR (thin film): ν 3326, 3114, 2974, 2928, 2852, 1684, 1523, 1168 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 8.53 (s, 1H), 8.12-8.07 (m, 1H), 7.67-7.60 (m, 2H), 7.58-7.49 (m, 2H), 4.10 (dd, J = 13.8, 3.0 Hz, 1H × 0.5), 4.00-3.80 (m, 2H and 1H × 0.5), 3.29-3.14 (m, 2H), 2.94 (dd, J = 14.6, 10.6 Hz, 1H × 0.5), 2.83 (dd, J = 13.8, 10.6 Hz, 1H × 0.5), 2.80-2.70 (m, 1H), 2.10-1.82 (m, 2H), 1.68 (br s, NH), 1.53-1.48 (m, 9H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 155.8, 155.5, 152.8, 152.7, 143.0, 142.8, 141.0, 136.3, 136.3, 128.4, 128.2, 120.4, 120.0, 79.8, 79.7, 64.6, 64.4, 56.8, 56.7, 47.2, 46.9, 46.3, 45.6, 30.1, 30.1, 28.7, 28.7; ESI-HRMS calcd for C\textsubscript{18}H\textsubscript{26}N\textsubscript{5}O\textsubscript{2} [M + H\textsuperscript{+}] 344.2081, found 344.2080.

**tert-Butyl 3-(4-methoxyphenyl)-1,4-diazepane-1-carboxylate (2.39d).** Purification by flash column chromatography (hexanes:EtOAc 1:1) afforded 2.39d (1:1 rotamers by \textsuperscript{1}H NMR integration, 109 mg, 72% yield) as colorless oil. IR (thin film): ν 3526, 3330, 2973, 2933, 2835, 1691, 1247, 1173 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.33-7.26 (m, 2H), 6.89-6.80 (m, 2H), 7.33-7.26 (m, 2H), 6.89-6.80 (m, 2H).
4.03 (dd, J = 13.7, 3.0 Hz, 1H × 0.5), 3.97-3.88 (m, 1H × 0.5), 3.88-3.75 (m, 2H), 3.80-3.76 (m, 3H), 3.28-3.14 (m, 2H), 2.90 (dd, J = 13.8, 10.2 Hz, 1H × 0.5), 2.80 (dd, J = 13.8, 10.7 Hz, 1H × 0.5), 1.99-1.86 (m, 1H × 0.5), 1.88-1.75 (m, 1H), 1.77 (br s, NH), 1.50-1.45 (m, 9H); 13C NMR (100 MHz, CDCl3): δ 159.0, 159.0, 155.7, 155.6, 134.8, 134.6, 128.1, 127.9, 114.1, 114.0, 79.5, 79.4, 64.9, 64.8, 57.1, 55.4, 55.4, 47.3, 47.1, 46.2, 45.6, 29.9, 29.9, 28.7, 28.7; ESI-HRMS calcd for C17H27N2O3 [M + H]+ 307.2016, found 307.2019.

**tert-Butyl 3-(4-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-1-carboxylate (2.40a).** Purification by flash column chromatography (CH2Cl2:EtOAc 15:1) afforded 2.40a (4:6 rotamers by 1H NMR integration, 168 mg, 86% yield) as clear, colorless liquid. IR (thin film): ν 3318, 2978, 2933, 1695, 1390, 1322, 1166, 1126, 910, 839, 768 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 7.74-7.44 (m, 4H), 7.44-7.15 (m, 4H), 4.51 (d, J = 13.7 Hz, 1H × 0.6), 4.41-4.17 (m, 1H and 1H × 0.4), 4.01 (s, 2H), 3.02-2.71 (m, 1H), 1.94 (br s, NH), 1.57 (s, 3H), 1.44 (s, 6H); 13C NMR (100 MHz, CDCl3): δ 154.2, 145.8, 142.4, 138.3, 129.7 (q, JCF = 34.0 Hz), 129.1, 128.3, 127.7, 127.3, 126.9, 125.6 (q, JCF = 3.7 Hz), 124.2 (q, JCF = 273.2 Hz), 80.6, 65.1, 64.2, 57.1, 55.8, 52.9, 28.6, 28.4; ESI-HRMS calcd for C21H24F3N2O2 [M + H]+ 393.1784, found 393.1785.

**1-tert-Butyl 3-ethyl 2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-1,3-dicarboxylate (2.40b).** Purification by flash column chromatography (CH2Cl2:EtOAc 10:1 to 4:1) afforded 2.40b (rotamers, 105 mg, 66% yield) as clear, colorless liquid. IR (thin film): ν 3342, 2977, 2932, 1737, 1698, 1494, 1455, 1388, 1317, 1163, 1041, 861, 760 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 7.41-7.07 (m, 4H), 4.60 (br d, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.08-3.69 (m, 3H), 2.85 (br d, 1H), 1.98 (br s, NH), 1.56-1.37 (m, 9H), 1.27 (t, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 171.4, 154.1, 142.1, 138.3, 128.9, 128.3, 127.6, 126.9, 80.7, 61.3, 51.8, 51.2, 29.8, 28.3, 14.3; ESI-HRMS calcd for C17H25N2O4 [M + H]+ 321.1809, found 321.1814.
**Chapter 7: Experimental Procedures and Characterization Data**

**tert-Butyl 3-(tert-butyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-1-carboxylate (2.40c).** Purification by flash column chromatography (pentane:EtOAc 10:1 to 4:1) afforded **2.40c** (4:6 rotamers by 1H NMR integration, 118 mg, 78% yield) as clear, colorless liquid. IR (thin film): ν 3425, 2963, 1697, 1494, 1391, 1366, 1170, 758 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 7.42-7.05 (m, 4H), 4.60 (d, J = 12.3 Hz, 1H × 0.6), 4.44 (d, J = 12.3 Hz, 1H × 0.4), 3.97-3.94 (m, 1H × 0.4), 3.94-3.89 (m, 1H × 0.6), 3.83 (t, J = 11.6 Hz, 1H), 2.75-2.39 (m, 2H), 1.49-1.26 (m, 9H), 0.98 (s, 9H); 13C NMR (100 MHz, CDCl₃): δ 154.4, 154.2, 142.9, 139.3, 139.1, 129.2, 128.7, 128.1, 127.8, 127.3, 126.9, 126.5, 80.5, 80.1, 69.7, 68.6, 53.4, 53.2, 52.7, 51.4, 33.6, 28.6, 28.4, 27.0; ESI-HRMS calcd for C₁₈H₂₉N₂O₂ [M + H]⁺ 305.2224, found 305.2223.

**tert-Butyl 3-cyclopropyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-1-carboxylate (2.40d).** Purification by flash column chromatography (hexanes:EtOAc 2:1 to 1:2) afforded **2.40d** (rotamers, 120 mg, 84% yield) as clear, colorless liquid. IR (thin film): ν 3420, 2976, 2930, 1697, 1494, 1389, 1325, 1234, 1165, 1103, 1034, 856, 759 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 7.40-7.09 (m, 4H), 4.59-4.21 (m, 1H), 3.92-3.69 (m, 2H), 2.91-2.49 (m, 1H), 2.30-2.00 (m, 1H), 1.61-1.31 (m, 9H), 0.76-0.19 (m, 5H); 13C NMR (100 MHz, CDCl₃): δ 154.2, 142.7, 138.4, 129.4, 129.0, 128.3, 127.9, 127.5, 127.1, 126.7, 80.2, 66.3, 65.1, 55.6, 54.3, 52.6, 28.5, 15.0, 3.9, 3.6, 2.8; ESI-HRMS calcd for C₁₇H₂₅N₂O₂ [M + H]⁺ 289.1911, found 289.1915.

**3-(4-(Trifluoromethyl)phenyl)-1,4-oxazocane (2.43a).** Purification by flash column chromatography (CH₂Cl₂:EtOAc 10:1 to 4:1) afforded **2.43a** (60 mg, 46% yield) as colorless solid. IR (thin film): ν 3340, 2922, 2859, 1618, 1417, 1325, 1164, 1121, 1068, 1018, 834 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 7.57 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 3.95 (dd, J = 10.0, 3.4 Hz, 1H), 3.91-3.72 (m, 3H), 3.47 (dd, J = 12.2, 10.0 Hz, 1H), 3.25 (dt, J = 14.0, 5.3 Hz, 1H), 2.96 (ddd, J = 14.0, 8.7, 5.3 Hz, 1H), 2.13 (ddd, J = 18.2, 8.7, 4.5 Hz, 1H), 1.82-1.68 (m, 2H), 1.60 (s, 2H); 13C NMR (100 MHz, CDCl₃): δ 146.4, 129.7 (q, JCF = 32.3 Hz), 127.6, 125.5 (q, JCF = 3.8 Hz), 124.2 (q, JCF = 272.0 Hz), 76.1, 72.4, 64.2, 48.3, 29.2, 26.3; m.p. = 45-47°C; ESI-HRMS calcd for C₁₃H₁₆F₃N₁Na₁O₁ [M + Na]⁺ 282.1076, found 282.1082.
Methyl 4-(1,4-oxazocan-3-yl)benzoate (2.43b). Purification by flash column chromatography (hexanes:EtOAc 2:1 to 1:2) afforded 2.43b (46 mg, 38% yield) as clear, colorless liquid. IR (thin film): ν 3422, 2920, 2856, 1723, 1611, 1435, 1279, 1113, 1020, 769 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.97 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 3.93 (dd, J = 9.9, 3.5 Hz, 1H), 3.89 (s, 3H), 3.87-3.73 (m, 3H), 3.46 (dd, J = 12.2, 10.0 Hz, 1H), 3.24 (dt, J = 14.0, 5.2 Hz, 1H), 2.95 (ddd, J = 14.0, 8.7, 5.2 Hz, 1H), 2.22-2.04 (m, 1H), 1.83-1.65 (m, 3H), 1.65-1.52 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 167.0, 147.5, 129.9, 129.3, 127.3, 76.2, 72.4, 64.4, 52.2, 48.4, 29.2, 26.3; ESI-HRMS calcd for C₁₄H₂₀N₁O₃ [M + H]⁺ 250.1438, found 250.1442.

3-(Benzo[d][1,3]dioxol-5-yl)-1,4-oxazocane (2.43c). Purification by flash column chromatography (CH₂Cl₂:MeOH 10:1) afforded 2.43c (24 mg, 20% yield) as clear, colorless liquid. IR (thin film): ν 3342, 2918, 2859, 1720, 1504, 1486, 1438, 1247, 1116, 1039, 929, 809 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.86 (d, J = 1.6 Hz, 1H), 6.83-6.77 (m, 1H), 6.76-6.71 (m, 1H), 5.92 (s, 2H), 3.93-3.67 (m, 4H), 3.44 (dd, J = 12.1, 10.0 Hz, 1H), 3.21 (dt, J = 14.0, 5.1 Hz, 1H), 2.94 (ddd, J = 14.0, 9.1, 5.1 Hz, 1H), 2.22-1.99 (m, 1H), 1.83-1.63 (m, 3H), 1.63-1.47 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 147.8, 146.8, 136.3, 120.4, 108.3, 107.8, 101.0, 76.6, 72.4, 64.5, 48.4, 29.2, 26.3; ESI-HRMS calcd for C₁₃H₁₈N₁O₃ [M + H]⁺ 236.1281, found 236.1284.

4-(4-(Trifluoromethyl)phenyl)-3,4,5,6-tetrahydro-1H-benzo[f][1,4]oxazocine (2.44a). Purification by flash column chromatography (hexanes:EtOAc 9:1) afforded 2.44a (111 mg, 72% yield) as pale yellow solid. IR (thin film): ν 3312, 3062, 3018, 2923, 2854, 1619, 1326, 1165, 1123, 1067 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.54 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.32-7.27 (m, 2H), 7.23-7.18 (m, 1H), 7.18-7.13 (m, 1H), 5.07 (d, J = 14.9 Hz, 1H), 4.94 (d, J = 14.9 Hz, 1H), 4.63 (d, J = 14.0 Hz, 1H), 4.16-4.11 (m, 1H), 4.14 (d, J = 14.0 Hz, 1H), 3.92-3.85 (m, 2H), 1.69 (br s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 145.9, 138.3, 138.1, 131.2, 129.9 (q, J_CF = 32.4 Hz), 128.2, 127.8, 127.6, 127.5, 125.6 (q, J_CF = 3.8 Hz), 124.3 (q, J_CF = 272.3 Hz), 77.5, 73.4, 60.6, 50.8; m.p. = 62-63°C; ESI-HRMS calcd for C₁₇H₁₇F₃N₁O₁ [M + H]⁺ 308.1257, found 308.1254.
4-(4-Methoxyphenyl)-3,4,5,6-tetrahydro-1H-benzo[f][1,4]oxazocine (2.44b). Purification by flash column chromatography (hexanes:EtOAc 2:1) afforded 2.44b (57 mg, 42% yield) as pale yellow oil. IR (thin film): ν 3315, 3010, 2930, 2835, 1611, 1512, 1247 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.29-7.24 (m, 2H), 7.24-7.20 (m, 2H), 7.20-7.16 (m, 1H), 7.13 (dd, J = 5.3, 3.7 Hz, 1H), 6.86-6.78 (m, 2H), 5.09 (d, J = 15.0 Hz, 1H), 4.94 (d, J = 15.0 Hz, 1H), 4.65 (d, J = 14.0 Hz, 1H), 4.12 (d, J = 14.0 Hz, 1H), 4.04 (dd, J = 7.9, 4.2 Hz, 1H), 3.91-3.83 (m, 2H), 3.77 (s, 3H), 1.71 (br s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 159.1, 138.4, 138.4, 133.9, 131.2, 128.5, 128.0, 127.4, 127.1, 114.0, 78.3, 73.5, 60.1, 55.4, 51.2; ESI-HRMS calcd for C_{17}H_{20}N_{1}O_{2} [M + H]⁺ 270.1489, found 270.1493.

4-(tert-Butyl)-3,4,5,6-tetrahydro-1H-benzo[f][1,4]oxazocine (2.44c). Purification by flash column chromatography (CH₂Cl₂:MeOH 98:2) afforded 2.44c (86 mg, 79% yield) as pale yellow oil. IR (thin film): ν 3344, 2954, 2868, 1681, 1475, 1365, 1110 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.29-7.21 (m, 2H), 7.20-7.11 (m, 2H), 4.86 (d, J = 13.9 Hz, 1H), 4.80 (d, J = 13.9 Hz, 1H), 4.35 (d, J = 14.3 Hz, 1H), 4.05 (d, J = 14.3 Hz, 1H), 4.00 (dd, J = 12.4, 2.2 Hz, 1H), 3.52 (dd, J = 12.4, 8.0 Hz, 1H), 2.54 (d, J = 7.0 Hz, 1H), 1.54 (br s, NH), 0.87 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 139.8, 137.9, 130.4, 128.7, 128.4, 127.4, 127.0, 73.0, 72.6, 65.8, 51.5, 33.7, 26.8; ESI-HRMS calcd for C_{14}H_{22}N_{1}O_{1} [M + H]⁺ 220.1696, found 220.1693.

Ethyl 3,4,5,6-tetrahydro-1H-benzo[f][1,4]oxazocine-4-carboxylate (2.44d). Purification by flash column chromatography (hexanes:EtOAc 4:1) afforded 2.44d (79 mg, 68% yield) as pale yellow oil. IR (thin film): ν 3345, 2979, 2930, 2871, 1733, 1447, 1369, 1293, 1201, 1151, 1111 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.31-7.19 (m, 3H), 7.16-7.08 (m, 1H), 5.01 (d, J = 14.2 Hz, 1H), 4.83 (d, J = 14.2 Hz, 1H), 4.43 (d, J = 14.1 Hz, 1H), 4.22-4.13 (m, 2H), 4.08 (dd, J = 12.2, 2.6 Hz, 1H), 4.04 (d, J = 14.1 Hz, 1H), 3.91 (dd, J = 12.2, 7.1 Hz, 1H), 3.67 (dd, J = 7.1, 2.6 Hz, 1H), 2.05 (br s, NH), 1.26 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 172.3, 139.1, 136.9, 131.1, 128.7, 128.6, 127.7, 73.0, 72.0, 61.3, 60.3, 49.6, 14.3; ESI-HRMS calcd for C_{13}H_{17}N_{1}NaO_{3} [M + Na]⁺ 258.1101, found 258.1102.
**tert-Butyl 3-(4-(trifluoromethyl)phenyl)-1,4-diazocane-1-carboxylate (2.45a).**

Purification by flash column chromatography (hexanes:EtOAc 10:1 to 4:1) afforded 2.45a (1:1 rotamers by $^1$H NMR integration, 61 mg, 34% yield) as clear, colorless liquid. IR (thin film): ν 3343, 2929, 2858, 1689, 1406, 1423, 1165, 1125, 1107, 1067, 831 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.62-7.53 (m, 2H), 7.53-7.43 (m, 2H), 4.09-3.94 (m, 1H and 1H × 0.5), 3.92-3.78 (m, 1H), 3.70 (d, $J$ = 14.3 Hz, 1H × 0.5), 3.28-3.12 (m, 1H and 1H × 0.5), 3.09-2.99 (m, 1H × 0.5), 2.97-2.62 (m, 2H), 2.07-1.93 (m, 1H × 0.5), 1.90-1.75 (m, 1H and 1H × 0.5), 1.73-1.57 (m, 3H), 1.56-1.46 (m, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 155.7, 155.3, 147.6, 129.6 (dd, $J_{CF}$ = 34.2, 19.2 Hz), 127.2, 127.1, 125.7, 125.5, 124.5 (q, $J_{CF}$ = 277 Hz, 19.2 Hz), 79.8, 79.6, 63.2, 62.0, 56.7, 56.3, 48.9, 48.7, 48.4, 48.2, 29.6, 28.8, 28.7, 28.6, 26.0, 24.4; ESI-HRMS calcd for C$_{18}$H$_{26}$F$_3$N$_2$O$_2$ [M + H]$^+$ 359.1941, found 359.1938.

**tert-Butyl 3-(2-chloro-4-fluorophenyl)-1,4-diazocane-1-carboxylate (2.45b).**

Purification by flash column chromatography (hexanes:EtOAc 4:1) afforded 2.45b (4:6 rotamers by $^1$H NMR integration, 77 mg, 45% yield) as colorless oil. IR (thin film): ν 3343, 2976, 2930, 2863, 1690, 1489, 1167 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.50-7.40 (m, 1H), 7.13-7.07 (m, 1H), 7.01-6.93 (m, 1H), 4.40-4.28 (m, 1H), 3.96-3.87 (m, 1H × 0.6), 3.79-3.69 (m, 1H), 3.67-3.58 (m, 1H × 0.4), 3.45-3.36 (m, 1H × 0.4), 3.22-3.07 (m, 1H and 1H × 0.6), 3.04 (dd, $J$ = 14.0, 10.6 Hz, 1H × 0.4), 2.95 (dd, $J$ = 14.0, 10.0 Hz, 1H × 0.6), 2.86-2.72 (m, 1H), 1.99-1.76 (m, 2H), 1.74-1.55 (m, 2H), 1.53 (br s, NH), 1.50-1.45 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 161.5 (d, $J_{CF}$ = 249.5 Hz), 161.4 (d, $J_{CF}$ = 249.5 Hz), 155.9, 155.5, 137.4 (d, $J_{CF}$ = 3.7 Hz), 137.2 (d, $J_{CF}$ = 3.6 Hz), 133.6 (d, $J_{CF}$ = 9.5 Hz), 133.40 (d, $J_{CF}$ = 10.0 Hz), 129.3 (d, $J_{CF}$ = 8.7 Hz), 129.1 (d, $J_{CF}$ = 8.8 Hz), 116.9 (d, $J_{CF}$ = 24.5 Hz), 116.9 (d, $J_{CF}$ = 24.5 Hz), 114.6 (d, $J_{CF}$ = 20.7 Hz), 114.4 (d, $J_{CF}$ = 20.9 Hz), 79.9, 79.6, 58.1, 57.3, 54.5, 54.1, 49.2, 48.6, 48.4, 48.4, 29.0, 28.8, 28.7, 28.1, 26.5, 24.8; ESI-HRMS calcd for C$_{17}$H$_{25}$ClF$_3$N$_2$O$_2$ [M + H]$^+$ 343.1583, found 343.1578.
tert-Butyl 3-(quinolin-4-yl)-1,4-diazocane-1-carboxylate (2.45c). Purification by flash column chromatography (hexanes:EtOAc 1:2) afforded 2.45c (1:1 rotamers by ¹H NMR integration, 66 mg, 39% yield) as colorless oil. IR (thin film): ν 3340, 2975, 2929, 2862, 1686, 1408, 1165, 1144 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.87 (dd, J = 12.4, 4.5 Hz, 1H), 8.52 (d, J = 7.7 Hz, 1H × 0.5), 8.32 (d, J = 8.5 Hz, 1H × 0.5), 8.17-8.08 (m, 1H), 7.75-7.63 (m, 1H and 1H × 0.5), 7.58-7.51 (m, 1H and 1H × 0.5), 4.75 (ddd, J = 25.2, 10.2, 2.4 Hz, 1H), 4.11-4.02 (m, 1H), 3.99-3.86 (m, 1H), 3.31-3.10 (m, 2H), 3.04-2.77 (m, 2H), 2.10-1.75 (m, 2H), 1.75-1.65 (m, 3H), 1.57-1.49 (m, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 155.8, 155.4, 150.7, 150.4, 149.4, 149.2, 148.5, 130.6, 130.2, 129.3, 127.1, 126.5, 126.4, 126.1, 124.1, 123.5, 118.6, 118.2, 80.3, 79.6, 58.4, 57.6, 56.1, 55.6, 49.2, 49.0, 48.9, 48.5, 29.2, 29.0, 28.9, 28.7, 25.8, 24.6; ESI-HRMS calcd for C₂₀H₂₈N₃O₂ [M + H]⁺ 342.2176, found 342.2180.

1-tert-Butyl 3-ethyl 1,4-diazocane-1,3-dicarboxylate (2.45d). Purification by flash column chromatography (hexanes:EtOAc 6:1 to 2:1) afforded 2.45d (4:6 rotamers by ¹H NMR integration, 75 mg, 52% yield) as clear, colorless liquid. IR (thin film): ν 3352, 2975, 2932, 1732, 1695, 1466, 1413, 1365, 1168, 1048, 873, 772 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.32 (dd, J = 13.6, 2.9 Hz, 1H × 0.6), 4.26-4.11 (m, 2H), 4.04 (dd, J = 14.1, 3.2 Hz, 1H × 0.4), 3.88-3.76 (m, 1H × 0.4), 3.76-3.65 (m, 1H × 0.6), 3.64-3.49 (m, 1H), 3.41-3.25 (m, 1H × 0.6), 3.22-3.05 (m, 1H), 3.00 (dt, J = 13.4, 6.8 Hz, 1H × 0.6), 2.92 (dd, J = 14.1, 9.8 Hz, 1H × 0.4), 2.78-2.56 (m, 1H and 1H × 0.6), 2.17 (s, 1H), 1.95-1.77 (m, 1H), 1.76-1.51 (m, 4H), 1.47 (s, 9H), 1.27 (q, J = 6.9 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 173.2, 172.9, 155.9, 155.2, 79.7, 79.6, 61.5, 61.3, 60.9, 60.1, 53.1, 52.9, 48.8, 48.7, 48.4, 48.1, 28.6, 28.6, 28.4, 26.4, 25.4, 14.4, 14.3; ESI-HRMS calcd for C₁₄H₂₇N₂O₄ [M + H]⁺ 287.1965, found 287.1962.

3-(4-(Trifluoromethyl)phenyl)-2,3,4,5,6,7-hexahydrobenzo[hh][1,4]oxazonine (2.46a). Purification by flash column chromatography (hexanes:EtOAc 7:1) afforded 2.46a (47 mg, 29% yield) as pale yellow oil. IR (thin film): ν 3373, 3065, 3020, 2926, 2868, 1618, 1581, 1491, 1453,
1326, 1164, 1122, 1067 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.57 (d, $J$ = 8.2 Hz, 2H), 7.47 (d, $J$ = 8.2 Hz, 2H), 7.26-7.22 (m, 1H), 7.21-7.16 (m, 1H), 7.10-7.03 (m, 2H), 4.35 (dd, $J$ = 11.5, 4.4 Hz, 1H), 4.05 (dd, $J$ = 11.5, 9.3 Hz, 1H), 3.95 (dd, $J$ = 9.3, 4.4 Hz, 1H), 3.13-3.04 (m, 1H), 2.92 (m, 1H), 2.83-2.76 (m, 1H), 2.61-2.54 (m, 1H), 1.98-1.79 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.1, 146.7, 135.2, 131.0, 129.6 (q, $J_{CF}$ = 32.3 Hz), 128.0, 127.5, 125.5 (q, $J_{CF}$ = 3.8 Hz), 124.3 (q, $J_{CF}$ = 272.3 Hz), 124.3, 120.6, 76.9, 61.1, 45.7, 30.4, 26.3; ESI-HRMS calcd for C$_{18}$H$_{19}$F$_3$N$_1$O$_1$ [M + H]$^+$ 322.1413, found 322.1409.

3-[(3-Bromophenyl)-2,3,4,5,6,7-hexahydrobenzo[h][1,4]oxazonine (2.46b). Purification by flash column chromatography (hexanes:EtOAc 6:1) afforded 2.46b (58 mg, 41% yield) as colorless oil. IR (thin film): $\nu$ 3368, 3060, 3016, 2924, 2865, 1490, 1220, 1012 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.55-7.51 (m, 1H), 7.43-7.38 (m, 1H), 7.29-7.24 (m, 2H), 7.22-7.18 (m, 2H), 7.12-7.05 (m, 2H), 4.34 (dd, $J$ = 11.6, 4.6 Hz, 1H), 4.06 (dd, $J$ = 11.6, 9.4 Hz, 1H), 3.88 (dd, $J$ = 9.4, 4.6 Hz, 1H), 3.14-3.05 (m, 1H), 3.02-2.94 (m, 1H), 2.85-2.77 (m, 1H), 2.62-2.53 (m, 1H), 1.98-1.80 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.1, 145.0, 135.2, 130.9, 130.4, 130.3, 130.2, 128.0, 125.8, 124.2, 122.8, 120.6, 77.0, 61.0, 45.73, 30.3, 26.3; ESI-HRMS calcd for C$_{17}$H$_{19}$Br$_1$N$_1$O$_1$ [M + H]$^+$ 332.0645, found 332.0639.

3-[(Pyridin-3-yl)-2,3,4,5,6,7-hexahydrobenzo[h][1,4]oxazonine (2.46c). Purification by flash column chromatography (CH$_2$Cl$_2$:MeOH 95:5) afforded 2.46c (28 mg, 22% yield) as colorless oil. IR (thin film): $\nu$ 3364, 3029, 2923, 2855, 1578, 1490, 1222, 1016 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.51 (d, $J$ = 2.1 Hz, 1H), 8.46 (dd, $J$ = 4.8, 1.6 Hz, 1H), 7.71-7.65 (m, 1H), 7.22-7.18 (m, 2H), 7.14 (dd, $J$ = 7.5, 1.6 Hz, 1H), 7.06-6.99 (m, 2H), 4.31 (dd, $J$ = 11.6, 4.6 Hz, 1H), 4.05 (dd, $J$ = 11.6, 9.1 Hz, 1H), 3.91 (dd, $J$ = 9.1, 4.6 Hz, 1H), 3.10-3.00 (m, 1H), 2.95-2.87 (m, 1H), 2.79-2.72 (m, 1H), 2.57-2.48 (m, 1H), 1.91-1.76 (m, 2H), 1.68 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.3, 149.0, 148.9, 137.9, 135.1, 134.8, 131.0, 128.1, 124.3, 123.6, 120.6, 76.7, 59.2, 45.4, 30.3, 26.3; ESI-HRMS calcd for C$_{16}$H$_{19}$N$_2$O$_1$ [M + H]$^+$ 255.1492, found 255.1490.
Ethyl 2,3,4,5,6,7-hexahydrobenzo[h][1,4]oxazonine-3-carboxylate (2.46d).

Purification by flash column chromatography (hexanes:EtOAc 5:1) afforded 2.46d (51 mg, 41% yield) as colorless oil. IR (thin film): ν 3370, 2979, 2925, 2856, 1733, 1491, 1449, 1219, 1186, 1023 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.22-7.16 (m, 1H), 7.15-7.10 (m, 1H), 7.05-7.00 (m, 2H), 4.50 (dd, J = 11.5, 5.2 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.13 (dd, J = 11.5, 8.8 Hz, 1H), 3.64 (dd, J = 8.8, 5.2 Hz, 1H), 3.05-2.97 (m, 1H), 2.92-2.86 (m, 1H), 2.82-2.74 (m, 1H), 2.44-2.37 (m, 1H), 1.86-1.67 (m, 3H), 1.27 (t, J = 7.1 Hz, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 172.8, 158.8, 134.6, 130.7, 127.8, 124.1, 120.2, 73.2, 61.5, 61.3, 45.1, 30.6, 26.1, 14.4; ESI-HRMS calcd for C\(_{14}\)H\(_{20}\)N\(_2\)O\(_3\) [M + H]\(^+\) 250.1438, found 250.1436.

### 7.2.6 Side Product Characterization of SnAP Reactions

To a solution of the amino tributylstannane – SnAP M 2.2 reagent (0.50 mmol, 1.00 equiv) in CH\(_2\)Cl\(_2\) (2.5 mL) at rt was added mesitaldehyde (0.50 mmol, 1.00 equiv) and molecular sieves 4Å (ca. 50 mg). The reaction mixture was stirred at rt for 6 h and filtered through a short layer of Celite (CH\(_2\)Cl\(_2\) rinse). The filtrate was concentrated under reduced pressure to afford the pure imine.

Separately, 2,6-lutidine (0.50 mmol, 1.00 equiv) was added in one portion to a suspension of HFIP (2.0 mL) and anhydrous Cu(OTf)\(_2\) (0.50 mmol, 1.00 equiv) and stirred at rt for 1 h, during which time a homogeneous suspension was formed. A solution of the imine (0.50 mmol, 1.00 equiv) in CH\(_2\)Cl\(_2\) (8.0 mL) was added in one portion and the resulting mixture was stirred at rt for 12 h. The reaction was quenched at rt with 10% aq NH\(_4\)OH (5 mL), and stirred vigorously for 15 min. The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 3 mL). The combined organic layers were washed with H\(_2\)O (3 x 5 mL) and brine (10 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated affording the crude material, in which the side products 2.8 and 2.9 were detected using \(^1\)H and \(^13\)C NMR. 2.10 was not detected in the crude product.

The crude material was dissolved in MeOH (2.0 mL) and cooled to 0°C after which NaBH\(_4\) (2.5 mmol, 5.0 equiv) was added in portions. The reaction mixture was stirred at rt for 6 h before quenched at rt with H\(_2\)O (5 mL). EtOAc (10mL) was added and the layers were separated after which the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with H\(_2\)O (3 x 5 mL) and brine (10 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated. Purification using flash column chromatography (hexanes:EtOAc 2:1) afforded the reduced HFIP adduct 2.7 as colorless oil.
2-(((1,1,3,3,3-Hexafluoropropan-2-yl)oxy) methoxy)-N-(2,4,6-trimethylbenzyl) ethan-1-amine (2.7). IR (thin film): ν 2951, 2921, 2863, 1455, 1383, 1362, 1290, 1220, 1200, 1103, 1065, 962 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 6.84 (s, 2H), 4.89 (s, 2H), 4.44 (hept, \(J = 6.1\) Hz, 1H), 3.85–3.65 (m, 4H), 2.88 (t, \(J = 5.2\) Hz, 2H), 2.35 (s, 6H), 2.25 (s, 3H), 1.47 (br s, NH); \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 137.0, 136.7, 133.6, 129.2, 121.7 (q, \(J_{CF} = 281.4\) Hz), 96.5, 71.5 (hept, \(J_{CF} = 32.6\) Hz), 69.3, 49.1, 47.5, 21.0, 19.6; \(R_f = 0.32\) (hexanes:EtOAc 1:1); ESI-HRMS calcd for C\(_{16}\)H\(_{22}\)F\(_6\)N\(_1\)O\(_2\) [M + H]\(^+\) 374.1549, found 374.1549.

General procedure for the preparation of possible side products of the SnAP reaction:

To a solution of mesitaldehyde (0.15 mmol, 1.00 equiv) in CH\(_2\)Cl\(_2\) (1.0 mL) at rt was added the corresponding amine (0.15 mmol, 1.00 equiv) or bisamine (0.075 mmol, 0.50 equiv) and molecular sieves 4Å (ca. 100 mg/mmol). The reaction mixture was stirred at rt for 6 h and filtered through a short layer of Celite (CH\(_2\)Cl\(_2\) rinse). The filtrate was concentrated under reduced pressure to afford the pure imine in quantitative yield.

(E)-2-((2,4,6-Trimethylbenzylidene)amino)ethan-1-ol (2.8). IR (thin film): ν 3284, 2929, 2873, 1647, 1611, 1439, 1376, 1124, 1062, 851 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.66 (s, 1H), 6.87 (s, 2H), 3.93–3.88 (m, 2H), 3.79–3.75 (m, 2H), 2.49 (br s, OH), 2.40 (s, 6H), 2.28 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 163.2, 139.1, 137.6, 131.0, 129.6, 64.2, 62.8, 21.3, 20.8; ESI-HRMS calcd for C\(_{12}\)H\(_{18}\)N\(_1\)O\(_1\) [M + H]\(^+\) 192.1383, found 192.1382.

(E)-1-Mesityl-N-(2-methoxyethyl)methanimine (2.9). IR (thin film): ν 2970, 2929, 2877, 1646, 1611, 1449, 1376, 1124, 851 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.56 (s, 1H), 6.85
(s, 2H), 3.83–3.78 (m, 2H), 3.47–3.66 (m, 2H), 3.39 (s, 3H), 2.38 (s, 6H), 2.27 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.0, 138.7, 137.4, 131.6, 129.3, 72.3, 62.0, 58.9, 21.2, 20.5; ESI-HRMS calcd for C$_{13}$H$_{20}$N$_1$O$_1$ [M + H]+ 206.1539, found 206.1537.

(1E,1′E)-N,N’-((Ethane-1,2-diylbis(oxy)) bis(ethane-2,1-diyl))bis(1-mesitylmethanimine) (2.10). IR (thin film): ν 2917, 2861, 1685, 1647, 1610, 1436, 1375, 1126 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.54 (s, 2H), 6.84 (s, 5H), 3.84–3.74 (m, 8H), 3.64 (s, 4H), 2.36 (s, 12H), 2.27 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.0, 138.7, 137.4, 131.6, 129.3, 71.0, 70.6, 62.1, 21.3, 20.5; ESI-HRMS calcd for C$_{26}$H$_{37}$N$_2$O$_2$ [M + H]$^+$ 409.2850, found 409.2848.

7.3 Experimental Section for Chapter 3

7.3.1 Preparation of SnAP-eX Reagents for the Synthesis of Piperidines

1-(Tributylstannyl)-4-((triisopropylsilyl)oxy)butyl acetate (3.1). To a stirred solution of N,N-diisopropylamine (1.34 mL, 9.48 mmol, 1.15 equiv) in THF (15 mL) at 0°C was added n-BuLi (1.6 M in hexanes, 5.80 mL, 9.24 mmol, 1.12 equiv) over 5 min. The light yellow solution was stirred for 30 min at 0°C before tributyltin hydride (2.22 mL, 8.27 mmol, 1.00 equiv) was added dropwise over 5–10 min. The resulting yellow solution was stirred for 30 min at 0°C before cooled to $-78^\circ$C. 4-((tert-Butyldimethylsilyl)oxy)butanal (1.84 g, 9.07 mmol, 1.10 equiv)
in THF (4 mL) was slowly added and the resulting reaction mixture was stirred at −78°C for 0.5 h before being poured cold onto sat aq NH₄Cl (20 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organic layers were washed with H₂O (1 x 20 mL) and brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure at 0–20°C to afford the tributylstannyl alcohol as a colorless oil that was used in the next step immediately.

The resulting tributylstannyl alcohol was dissolved in CH₂Cl₂ (5 mL) and added to a pre-formed solution of DMAP (550 mg, 4.54 mmol, 0.55 equiv), Ac₂O (4.4 mL, 24.7 mmol, 3.00 equiv), and Et₃N (1.5 mL, 10.5 mmol, 1.30 equiv) in CH₂Cl₂ (15 mL). The resulting mixture was stirred at rt for 12 h before being poured cold H₂O (50 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (1 x 20 mL). The combined organic layers were washed with H₂O (2 x 40 mL) and brine (2 x 40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 40:1) afforded 3.1 (3.06 g, 64% yield) as a colorless oil. IR (thin film): ν 2956, 2926, 2867, 1723, 1464, 1371, 1245, 1106 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.85–4.71 (m, 1H), 3.75–3.65 (m, 2H), 2.02 (s, 3H), 1.97–1.80 (m, 2H), 1.70–1.58 (m, 2H), 1.54–1.42 (m, 6H), 1.35–1.28 (m, 6H), 1.08–1.03 (m, 21H), 0.92–0.82 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 171.4, 71.8, 63.0, 31.3, 30.7, 29.2, 27.6, 21.1, 18.2, 13.8, 12.2, 9.7; Rᵣ = 0.35 (hexanes:EtOAc 20:1); ESI-HRMS calcld for C₂₇H₅₈Na₅O₃Si₁Sn₁ [M + Na]⁺ 601.3074, found 601.3069.

![Image of molecular structure](attachment:image.png)

**4-Hydroxy-1-(tributylstannyl)butyl acetate (3.2).** TBAF (6.30 mL of a 1.0 M solution in THF, 6.30 mmol, 1.10 equiv) was added dropwise over 10 min to a solution of the TIPS protected alcohol 3.1 (3.30 g, 5.71 mmol, 1.00 equiv) in THF (38 mL) at 0°C. The resulting solution was allowed to warm to rt and was stirred for 4 h before being poured into a mixture of EtOAc:H₂O (2:1, 100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with H₂O (2 x 10 mL), brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 7:1) afforded 3.2 (1.70 g, 71% yield) as a colorless oil. IR (thin film): ν 3419, 2955, 2926, 2871, 2853, 1720, 1463, 1373, 1185 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.82–4.74 (m, 1H), 3.67 (t, J = 6.5 Hz, 2H), 2.02 (s, 3H), 2.00–1.78 (m, 2H), 1.69–1.53 (m, 3H), 1.50–1.44 (m, 6H), 1.35–1.24 (m, 6H), 0.95–0.80 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 171.5, 71.5, 62.7, 31.1, 30.5, 29.2, 27.6, 21.1, 13.8, 9.7; Rᵣ = 0.22 (hexanes:EtOAc 4:1); ESI-HRMS calcld for C₁₅H₃₈Na₁O₃Sn₁ [M + Na]⁺ 445.1738, found 445.1744.
4-Azido-1-(tributylstannyl)butyl acetate (3.3). To a solution of 3.2 (1.70 g, 4.04 mmol, 1.00 equiv) in Et₂O (20 mL) at rt was added Et₃N (1.11 mL, 8.07 mmol, 2.00 equiv) in one portion followed by the dropwise addition of methanesulfonfyl chloride (375 µL, 4.84 mmol, 1.20 equiv) over 5 min. The reaction mixture was stirred at rt and monitored by TLC. After 0.5 h, the reaction was quenched with H₂O (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude mesylate which was used in the next step without any further purification.

To a solution of the mesylated product in DMF (30 mL) was added sodium azide (393 mg, 4.84 mmol, 1.50 equiv) at rt in one portion. The suspension was stirred vigorously at 65°C for 12 h. After the disappearance of the mesylated product by TLC, the reaction was quenched with H₂O (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H₂O (2 x 20 mL), brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude SnAP-eX 3-OAc P 3.3 (1.52 g, 84% yield, 2 steps) as clear, colorless liquid. IR (thin film): ν 2956, 2925, 2095, 1723, 1463, 1372, 1247 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.80–4.70 (m, 1H), 3.30 (t, J = 6.8 Hz, 2H), 2.03 (s, 3H), 2.01–1.90 (m, 1H), 1.86–1.78 (m, 1H), 1.75–1.55 (m, 2H), 1.53–1.43 (m, 6H), 1.34–1.25 (m, 6H), 0.95–0.75 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 171.4, 70.9, 51.2, 31.4, 29.2, 27.6, 27.4, 21.1, 13.8, 9.7; Rᵣ = 0.85 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C₁₈H₃₇N₃Na₁O₂Sn₁ [M + Na]⁺ 470.1803, found 470.1803.
**IMPORTANT:** The first product in this reaction sequence (tributylstannyl alcohol) is unstable. This compound decomposes within hours at rt. It is important to follow the procedure, including the reaction times, the solvents for the extractions and the temperature of the water bath. The reaction sequence up to the stable MOM protected SnAP reagent precursor should be done as fast as possible in one go!

10,10,11,11-Tetramethyl-5-(tributylstannyl)-2,4,9-trioxa-10-siladodecane (3.4). To a stirred solution of N,N-diisopropylamine (1.34 mL, 9.48 mmol, 1.15 equiv) in THF (15 mL) at 0°C was added n-BuLi (1.6 M in hexanes, 5.80 mL, 9.24 mmol, 1.12 equiv) over 5 min. The light yellow solution was stirred for 30 min at 0°C before tributyltin hydride (2.22 mL, 8.27 mmol, 1.00 equiv) was added dropwise over 5–10 min. The resulting yellow solution was stirred for 30 min at 0°C before cooled to –78°C. 4-((tert-Butyldimethylsilyl)oxy)butanal (1.84 g, 9.07 mmol, 1.10 equiv) in THF (4 mL) was slowly added and the resulting reaction mixture was stirred at –78°C for 0.5 h before being poured cold onto sat aq NH₄Cl (20 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organic layers were washed with H₂O (1 x 20 mL) and brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure at 0–20°C to afford the tributylstannyl alcohol as a colorless oil that was used in the next step immediately.

The resulting tributylstannyl alcohol was dissolved in CH₂Cl₂ (5 mL) and added to a pre-formed solution of N,N-dimethylaniline (1.88 mL, 14.8 mmol, 1.80 equiv) and MOM–Cl (1.88 mL, 24.7 mmol, 3.00 equiv) in CH₂Cl₂ (15 mL). The resulting mixture was stirred at rt for 12 h before being poured onto cold H₂O (50 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (1 x 20 mL). The combined organic layers were washed with H₂O (2 x 40 mL) and brine (2 x 40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 100:0 to 40:1) afforded 3.4 (3.48 g, 79% yield) as a colorless oil. IR (thin film): ν 2956, 2926, 2856, 1464, 1255, 1147, 1096, 1038, 889, 835 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.60 (d, J = 6.6 Hz, 1H), 4.54 (d, J = 6.6 Hz, 1H), 4.06 (dd, J = 7.3, 6.0 Hz, 1H), 3.63 (td, J = 6.3, 1.6 Hz, 2H), 3.34 (s,
3H), 1.93–1.76 (m, 2H), 1.62–1.57 (m, 2H), 1.53–1.43 (m, 6H), 1.36–1.25 (m, 6H), 0.92–0.85 (m, 24H), 0.04 (s, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 96.5, 73.9, 63.2, 55.6, 31.7, 31.5, 29.4, 27.7, 26.1, 18.5, 13.8, 9.3, -5.1, -5.1; \(R_f = 0.48\) (hexanes:EtOAc 10:1); ESI-HRMS calcd for C\(_{24}\)H\(_{54}\)Na\(_1\)O\(_3\)Si\(_1\)Sn\(_1\) [M + Na\(^+\)] 561.2760, found 561.2763.

4-(Methoxymethoxy)-4-(tributylstannyl)butan-1-ol (S3.1). TBAF (9.00 mL of a 1.0 M solution in THF, 9.00 mmol, 1.40 equiv) was added dropwise over 10 min to a solution of the TBS protected alcohol 3.4 (3.48 g, 6.48 mmol, 1.00 equiv) in THF (45 mL) at 0°C. The resulting solution was allowed to warm to rt and was stirred for 5 h before being poured into a mixture of EtOAc:H\(_2\)O (2:1, 100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with H\(_2\)O (2 x 10 mL), brine (20 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 4:1) afforded S3.1 (2.21 g, 81% yield) as a colorless oil. IR (thin film): \(\nu\) 2957, 2925, 1464, 1276, 1261, 1033, 907, 750 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 4.61 (d, \(J = 6.6\) Hz, 1H), 4.56 (d, \(J = 6.6\) Hz, 1H), 4.08 (dd, \(J = 7.4, 5.2\) Hz, 1H), 3.66 (q, \(J = 6.0\) Hz, 2H), 3.35 (s, 3H), 1.94–1.82 (m, 2H), 1.74–1.60 (m, 2H), 1.55–1.42 (m, 6H), 1.36–1.25 (m, 6H), 0.96–0.82 (m, 15H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 96.6, 74.1, 63.1, 55.8, 31.9, 29.3, 27.6, 13.8, 9.4; \(R_f = 0.29\) (hexanes:EtOAc 4:1); ESI-HRMS calcd for C\(_{18}\)H\(_{40}\)Na\(_1\)O\(_3\)Sn\(_1\) [M + Na\(^+\)] 447.1895, found 447.1896.

2-(4-(Methoxymethoxy)-4-(tributylstannyl)butyl)isoindoline-1,3-dione (3.5). Diisopropyl azodicarboxylate (956 μL, 4.85 mmol, 1.08 equiv) was added dropwise over 15 min to a clear, pale yellow solution of the alcohol S3.1 (1.90 g, 4.49 mmol, 1.00 equiv), triphenylphosphine (1.32 g, 5.03 mmol, 1.12 equiv), and phthalimide (727 mg, 4.94 mmol, 1.10 equiv) in THF (30 mL) at 0°C. The clear, yellow solution was allowed to warm to rt and stirred for 5 h. The resulting reaction mixture was concentrated and purification by flash column chromatography (hexanes:EtOAc 10:1) afforded the phthalimide protected SnAP-eX 3-O-MOM P 3.5 (2.15 g, 87% yield) as a colorless oil. IR (thin film): \(\nu\) 2954, 2925, 2871, 2853, 1772, 1713, 1394, 1369, 1275, 1261, 1032, 750 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.83 (dd, \(J = 5.5, 3.0\) Hz, 2H), 7.70 (dd, \(J = 5.5, 3.0\) Hz, 2H), 4.56 (d, \(J = 6.6\) Hz, 1H), 4.52 (d, \(J = 6.6\) Hz, 1H),
4.10–4.00 (m, 1H), 3.72 (t, $J = 6.7$ Hz, 2H), 3.32 (s, 3H), 1.92–1.71 (m, 4H), 1.54–1.36 (m, 6H), 1.32–1.19 (m, 6H), 0.95–0.76 (m, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 168.5, 134.0, 132.3, 123.3, 96.7, 73.3, 55.7, 38.1, 29.3, 27.6, 27.4, 13.8, 9.3; $R_f = 0.81$ (hexanes:EtOAc 4:1); ESI-HRMS calcd for C$_{26}$H$_{43}$N$_1$Na$_1$O$_4$Sn$_1$ [M + Na]$^+$ 576.2111, found 576.2109.

4-(Methoxymethoxy)-4-(tributylstannyl)butan-1-amine (3.6). The phthalimide protected SnAP-eX 3-O-MOM P 3.5 (2.40 g, 4.35 mmol, 1.00 equiv) in EtOH (44 mL) was heated to reflux. Hydrazine monohydrate (2.11 mL, 43.5 mmol, 10.0 equiv) was added dropwise at reflux over 3 min. The resulting reaction mixture was stirred for further 45 min at reflux while colorless solid crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (50 mL) and H$_2$O (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford pure SnAP-eX 3-O-MOM P 3.6 (1.70 g, 93% yield) as a colorless oil. IR (thin film): $\nu$ 2954, 2923, 2872, 2852, 1464, 1276, 1261, 1145, 1034, 918, 750 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.59 (d, $J = 6.6$ Hz, 1H), 4.54 (d, $J = 6.6$ Hz, 1H), 4.08–4.01 (m, 1H), 3.34 (s, 3H), 2.83–2.66 (m, 2H), 2.19 (br s, NH$_2$), 1.97–1.71 (m, 2H), 1.62–1.39 (m, 8H), 1.37–1.23 (m, 6H), 0.89 (t, $J = 7.4$ Hz, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 96.6, 73.8, 55.7, 42.2, 32.5, 31.9, 29.3, 27.6, 13.8, 9.4; $R_f = 0.81$ (hexanes:EtOAc 4:1); ESI-HRMS calcd for C$_{18}$H$_{42}$N$_1$O$_2$Sn$_1$ [M + H]$^+$ 424.2235, found 424.2235.
**tert-Butyl (4-(1,3-dioxoisooindolin-2-yl)-1-tosylbutyl)carbamate (3.7).** A solution of commercially available 4-(1,3-dioxoisooindolin-2-yl)butanal (2.00 g, 9.21 mmol, 1.00 equiv), tert-butyl carbamate (1.08 g, 9.21 mmol, 1.00 equiv), and sodium \( p\)-toluenesulfinate (1.64 g, 9.21 mmol, 1.00 equiv) in \( \text{H}_2\text{O}:\text{MeOH}:\text{HCOOH} \) (8:4:1, 48.75 mL) was stirred at rt for 48 h while colorless solids crashed out. The suspension was cooled to 0 °C, filtered, washed with \( \text{H}_2\text{O} \) (3 x 5 mL), and dried at high vacuum to afford pure 3.7 (3.94 g, 91% yield) as a colorless solid.

IR (thin film): \( \nu \) 3002, 2935, 2879, 1661, 1497, 1440, 1415, 1391, 1255, 1103 cm\(^{-1}\); \(^1\)H NMR (400 MHz, \( \text{CDCl}_3 \)): \( \delta \) 7.87–7.82 (m, 2H), 7.78 (d, \( J = 8.3 \) Hz, 2H), 7.74–7.70 (m, 2H), 7.40–7.27 (m, 2H), 5.08 (d, \( J = 10.9 \) Hz, NHBoc), 4.94–4.82 (m, 1H), 3.74 (t, \( J = 6.8 \) Hz, 2H), 2.40 (s, 3H), 2.33–2.19 (m, 1H), 1.98–1.86 (m, 1H), 1.87–1.67 (m, 2H), 1.21 (s, 9H); \(^{13}\)C NMR (100 MHz, \( \text{CDCl}_3 \)): \( \delta \) 168.4, 153.9, 145.1, 134.2, 133.9, 132.2, 129.9, 129.5, 123.5, 81.0, 70.4, 37.2, 28.1, 24.9, 23.9, 21.8; m.p. = 155 °C; ESI-HRMS calcd for \( \text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_6\text{S}_1 \) [M + \( \text{NH}_4^+ \)]\(^{+} \) 490.2006, found 490.1997.

**tert-Butyl (4-(1,3-dioxoisooindolin-2-yl)-1-(tributylstannyl)butyl)carbamate (3.8).** CsF (482 mg, 3.17 mmol, 3.00 equiv) was placed in a round-bottomed flask and heated under vacuum (<5 mmHg at ca. 400 °C by a heat gun) for 10–15 min, cooled to rt, and suspended in DMF (13 mL). \( \alpha\)-Amino sulfone 3.7 (500 mg, 1.06 mmol, 1.00 equiv) in DMF (3 mL) was added dropwise. After 5 min, commercially available TMSSnBu\(_3\) (769 mg, 739 \( \text{fL}, 2.12 \) mmol, 2.00 equiv) was slowly added followed by vigorous stirring at rt for 4h. MeOH (10 mL) was added to
quench the reaction followed by the addition of H₂O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H₂O (3 x 10 mL), brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 10:1) afforded the phthalimide protected SnAP-eX 3-NH-Boc P 3.8 (299 mg, 47% yield) as a colorless oil. IR (thin film): ν 3380, 2955, 2925, 2871, 2852, 1772, 1714, 1505, 1395, 1365, 1172 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.86–7.82 (m, 2H), 7.73–7.69 (m, 2H), 4.78–4.62 (m, 1H), 3.69 (t, J = 6.6 Hz, 2H), 3.31–3.08 (m, 1H), 1.81–1.59 (m, 4H), 1.51–1.35 (m, 6H), 1.43 (s, 9H), 1.27 (sext, J = 7.2 Hz, 6H), 0.86 (t, J = 7.2 Hz, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 168.5, 156.1, 134.0, 132.3, 123.3, 78.9, 40.1, 37.8, 32.2, 29.3, 28.6, 27.7, 27.4, 13.8, 9.9; Rᵣ = 0.20 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C₂₉H₄₉N₂O₄Sn₁ [M + H]+ 609.2715, found 609.2711.

**tert-Butyl (4-amino-1-(tributylstannyl)butyl)carbamate (3.9).** The phthalimide protected SnAP-eX 3-NH-Boc P 3.8 (2.10 g, 3.46 mmol, 1.00 equiv) in EtOH (35 mL) was heated to reflux. Hydrazine monohydrate (1.68 mL, 34.6 mmol, 10.0 equiv) was added dropwise at reflux. The resulting reaction mixture was stirred for further 45 min at reflux while colorless solids crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (100 mL) and H₂O (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 x 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford pure SnAP-eX 3-NH-Boc P 3.9 (1.61 g, 98% yield) as a colorless oil. IR (thin film): ν 3421, 2955, 2923, 2870, 2853, 1690, 1499, 1251, 1172 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.84–4.72 (m, 1H), 3.28–3.10 (mz, 1H), 2.83–2.70 (m, 2H), 2.49 (br s, NH₂), 1.79–1.52 (m, 4H), 1.50–1.40 (m, 6H), 1.42 (s, 9H), 1.30 (sext, J = 7.2 Hz, 6H), 0.89 (t, J = 7.2 Hz, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 156.2, 79.0, 41.7, 40.4, 32.4, 31.4, 29.3, 28.6, 27.7, 13.9, 9.9; ESI-HRMS calcd for C₂₁H₄₉N₂O₂Sn₁ [M + H]+ 479.2658, found 479.2655.
**CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA**

(R,E) - 2 - Methyl - N - (4-((triisopropylsilyl)oxy)butylidene) propane - 2-sulfinamide (3.12). Pyridinium p-toluenesulfonate (103 mg, 0.409 mmol, 0.05 equiv) and (R)-tert-butanesulfonamide (1.19 g, 9.82 mmol, 1.20 equiv) were added to a suspension of MgSO₄ (10.0 g, 40.9 mmol, 5.00 equiv) in CH₂Cl₂ (40 mL). 4-((Triisopropylsilyl)oxy)butanal (2.00 g, 8.18 mmol, 1.00 equiv) was added dropwise followed by stirring for 16 h at rt. The suspension was filtered (EtOAc rinse) and concentrated under reduced pressure to afford pale yellow oil. Purification by flash column chromatography (hexanes:EtOAc 20:1) afforded 3.12 (2.45 g, 86% yield) as a colorless oil. IR (thin film): ν 3444, 2944, 2893, 2866, 1624, 1463, 1363, 1088, 882 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.11 (t, J = 4.5 Hz, 1H), 3.76 (t, J = 6.2 Hz, 2H), 2.69–2.56 (m, 2H), 1.93–1.81 (m, 2H), 1.19 (s, 9H), 1.11–1.02 (m, 21H); ¹³C NMR (100 MHz, CDCl₃): δ 169.7, 62.5, 56.7, 32.9, 28.9, 22.5, 18.2, 12.1; Rᵣ = 0.54 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C₁₇H₃₇N₁O₁S₁Na₁O₂Si₁ [M + Na]⁺ 370.2206, found 370.2205.

(R) - 2 - Methyl - N - ((R)-1-(tributylstannyl)-4-((triisopropylsilyl)oxy)butyl)propane-2-sulfinamide (3.13). To a stirred solution of N,N-diisopropylamine (1.12 mL, 7.90 mmol, 1.28 equiv) in THF (15 mL) at 0°C was added n-BuLi (1.6 M in hexanes, 4.80 mL, 7.70 mmol, 1.24 equiv) over 5 min. The light yellow solution was stirred for 30 min at 0°C before tributyltin hydride (1.85 mL, 6.87 mmol, 1.11 equiv) was added dropwise over 5–10 min. The resulting yellow solution was stirred for 30 min at 0°C before cooled to –78°C. 3.12 (1.83 g, 5.26 mmol,
1.00 equiv) was slowly added neat and the resulting reaction mixture was stirred at –78°C for 3 h. MeOH (5 mL) was added at –78°C to the reaction mixture before being poured cold onto sat aq NH₄Cl (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with H₂O (2 x 10 mL) and brine (1 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 4:1) afforded sulfinamide 3.13 (2.45 g, 86% yield) as a colorless oil. IR (thin film): ν 3194, 2955, 2925, 2867, 1463, 1104, 1060, 882 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.70 (t, J = 6.2 Hz, 2H), 3.48–3.32 (m, 1H), 3.27–3.13 (m, 1H), 2.02–1.80 (m, 2H), 1.68–1.54 (m, 2H), 1.54–1.40 (m, 6H), 1.30 (h, J = 7.3 Hz, 6H), 1.18 (s, 9H), 1.12–0.98 (m, 21H), 0.96–0.83 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 63.3, 56.0, 48.1, 33.4, 31.8, 29.3, 27.6, 22.9, 18.2, 13.8, 12.1, 9.8; Rᵣ = 0.18 (hexanes:EtOAc 3:1); ESI-HRMS calcd for C₂₉H₆₅N₁Na₁O₂S₁Si₁Sn₁ [M + Na]⁺ 662.3423, found 662.3416.

**tert-Butyl (((R)-tert-butylsulfinyl) ((R)-1-(tributylstannyl)-4-(triisopropylsilyl)oxy) butyl)carbamate (3.14).** N,N-Dimethylaniline (1.43 g, 11.7 mmol, 3.00 equiv) was added to a solution of (Boc)₂O (2.56 g, 11.7 mmol, 3.00 equiv) in THF (18 mL) at 0°C. The resulting mixture was allowed to warm to rt and stirred for 1 h. In a separate flask, n-BuLi (1.6 M in hexanes, 7.40 mL, 11.7 mmol, 3.00 equiv) was slowly added to a solution of sulfinamide 3.13 (2.50 g, 3.91 mmol, 1.00 equiv) in THF (22 mL) at –78°C followed by stirring for 20 min. The pre-mixed DMAP-(Boc)₂O solution was added in one portion at –78°C before the cooling bath was removed and stirring was continued for 2 h. The reaction mixture was poured onto sat aq NH₄Cl (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with H₂O (2 x 20 mL) and brine (1 x 40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 95:5 to 80:20) afforded mixed imide 3.14 (1.99 g, 69% yield) as a colorless oil. IR (thin film): v 2956, 2927, 2867, 1697, 1464, 1368, 1307, 1283, 1161, 1093 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.78–3.60 (m, 2H), 3.48–3.29 (m, 1H), 2.33–2.12 (m, 1H), 1.83–1.63 (m, 1H), 1.55–1.41 (m, 8H), 1.46 (s, 9H), 1.31 (h, J = 7.3 Hz, 6H), 1.21 (s, 9H), 1.09–1.01 (m, 21H), 0.93–0.78 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 154.6, 82.0, 63.4, 59.3, 38.3, 31.9, 29.7, 29.2, 28.4, 27.7, 22.9, 18.2, 13.8, 12.2, 10.4; Rᵣ = 0.52 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C₃₄H₇₅N₁Na₁O₄S₁Si₁Sn₁ [M + Na]⁺ 762.3949, found 762.3944.
**t*ert-Butyl (R)-(1-(tributylstannyl))-4-((triisopropylsilyl)oxy)butyl)carbamate (3.15).**

The mixed imide 3.14 (1.90 g, 2.57 mmol, 1.00 equiv) in THF (45 mL) at −78°C was treated with MeLi (1.6 M in Et₂O, 3.20 mL, 5.14 mmol, 2.00 equiv) followed by stirring for 45 min at −78°C. The reaction mixture was poured onto sat aq NH₄Cl (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with H₂O (2 x 20 mL) and brine (1 x 40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford pure α-amino sulfone 3.15 (1.52 g, 93% yield) as a colorless oil that was used in the next step without further purification. Purification by flash column chromatography (hexanes:EtOAc 99:1) was performed to afford analytically pure material for characterization.

IR (thin film): ν 3358, 2956, 2943, 2867, 1699, 1498, 1464, 1365, 1249, 1173, 1105 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.85–4.70 (m, NHBoc), 3.75–3.64 (m, 2H), 3.32–3.14 (m, 1H), 1.88–1.70 (m, 2H), 1.56–1.44 (m, 8H), 1.41 (s, 9H), 1.34–1.25 (m, 6H), 0.92–0.83 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 156.1, 78.7, 63.3, 40.8, 31.8, 31.4, 29.4, 28.6, 27.7, 18.2, 13.9, 12.2, 9.9; Rᵣ = 0.53 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C₃₀H₆₅N₁Na₁O₃Si₁Sn₁ [M + Na]⁺ 658.3653, found 658.3650.

**t*ert-Butyl (R)-(4-hydroxy-1-(tributylstannyl))butyl)carbamate (3.16).**

TBAF (3.12 mL of a 1.0 M solution in THF, 3.12 mmol, 1.20 equiv) was added dropwise over 10 min to a solution of the TIPS protected alcohol 3.15 (1.80 g, 2.84 mmol, 1.00 equiv) in THF (20 mL) at 0°C. The resulting solution was stirred at 0°C for 3 h before being poured into a mixture of EtOAc:H₂O (2:1, 50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H₂O (2 x 10 mL), brine (1 x 20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 9:1) afforded alcohol 3.16 (1.17 g, 86% yield) as a colorless oil. IR (thin film): ν 3344, 2955, 2925, 2871, 2853, 1692, 1501, 1463, 1365, 1250, 1173, 1056 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.97–4.60 (m, NHBoc), 3.41–3.09 (m, 1H), 1.76–1.56 (m, 4H), 1.55–1.44 (m, 6H), 1.41 (s, 9H), 1.35–1.24 (m, 6H), 0.96–0.77 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 156.3, 79.0, 62.8, 40.2, 31.6, 31.2, 29.3, 28.6, 27.7, 13.8, 9.7; Rᵣ = 0.13 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C₂₁H₄₅N₁Na₁O₃Sn₁ [M + Na]⁺ 502.2317, found 502.2311.
*tert-Butyl (R)-(4-(1,3-dioxoisoindolin-2-yl)-1-(tributylstannyl)butyl)carbamate (R)-3.8.* Diisopropyl azodicarboxylate (593 μL, 3.01 mmol, 1.50 equiv) was added dropwise over 10 min to a clear, pale yellow solution of the alcohol **3.16** (960 mg, 2.01 mmol, 1.50 equiv), triphenylphosphine (790 mg, 3.01 mmol, 1.50 equiv), and phthalimide (443 mg, 3.01 mmol, 1.50 equiv) in THF (15 mL) at 0°C. The clear, yellow solution was allowed to warm to rt and stirred for 5 h. The resulting reaction mixture was concentrated and purified by flash column chromatography (hexanes:EtOAc 10:1) to afford the phthalimide protected **SnAP-eX (R)-3-NHBoc** **P 3.8** (1.19 mg, 98% yield) as a colorless oil with an enantiomeric ratio of 0.5:99.5.

**1H NMR (400 MHz, CDCl₃):** δ 7.86–7.82 (m, 2H), 7.73–7.69 (m, 2H), 4.78–4.62 (m, 1H), 3.69 (t, J = 6.6 Hz, 2H), 3.31–3.08 (m, 1H), 1.81–1.59 (m, 4H), 1.51–1.35 (m, 6H), 1.43 (s, 9H), 1.27 (sext, J = 7.2 Hz, 6H), 0.86 (t, J = 7.2 Hz, 15H); **13C NMR (100 MHz, CDCl₃):** δ 168.5, 156.1, 134.0, 132.3, 123.3, 78.9, 40.1, 37.8, 32.2, 29.3, 28.6, 27.7, 27.4, 13.8, 9.9. These spectral characteristics are identical to those previously reported in the racemic synthesis.

**Chiral HPLC:** column: Daicel Chiralpak IA (4.6 × 250 mm); eluent: 1% iPrOH in hexane, flow: 0.30 mL/min; detection: 254 nm. Retention time: tᵣ = 46.0 min (*tert*-butyl (S)-(4-(1,3-dioxoisoindolin-2-yl)-1-(tributylstannyl)butyl)carbamate) and 51.0 min (*tert*-butyl (R)-(4-(1,3-dioxoisoindolin-2-yl)-1-(tributylstannyl)butyl)carbamate).
tert-Butyl (R)-(4-amino-1-(tributylstannyl)butyl)carbamate ((R)-3.9). The enantiomerically enriched phthalimide protected SnAP-eX (R)-3-NH-Boc P 3.8 (300 mg, 0.494 mmol, 1.00 equiv) in EtOH (5 mL) was heated to reflux. Hydrazine monohydrate (240 \text{ mL}, 4.94 mmol, 10.0 equiv) was added dropwise at reflux. The resulting reaction mixture was stirred for further 45 min at reflux while colorless solid crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (20 mL) and H$_2$O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 x 10 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford pure enantiomerically enriched SnAP-eX (R)-3-NH-Boc P 3.9 (231 mg, 98% yield) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.84–4.72 (m, 1H), 3.28–3.10 (mz, 1H), 2.83–2.70 (m, 2H), 2.49 (br s, NH$_2$), 1.79–1.52 (m, 4H), 1.50–1.40 (m, 6H), 1.42 (s, 9H), 1.30 (sext, J = 7.2 Hz, 6H), 0.89 (t, J = 7.2 Hz, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.2, 79.0, 41.7, 40.4, 32.4, 31.4, 29.3, 28.6, 27.7, 13.9, 9.9. These spectral characteristics are identical to those previously reported in the racemic synthesis.
7.3.2 Preparation Piperidines using SnAP-eX Reagents

**GENERAL PROCEDURE FOR THE IMINE FORMATION:** To a solution of the amino tributylstannane – SnAP-eX reagent (0.50 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (2.5 mL) at rt was added the corresponding aldehyde (0.50 mmol, 1.00 equiv) and molecular sieves 4Å (ca. 100 mg/mmol). The reaction mixture was stirred at rt for 2–6 h and filtered through a short layer of Celite (CH$_2$Cl$_2$ rinse). The filtrate was concentrated under reduced pressure to afford the pure imine.

**GENERAL PROCEDURE FOR THE KETIMINE FORMATION:** To a solution of the SnAP-eX reagent (0.50 mmol, 1.00 equiv) in toluene (2.0 mL) at rt was added the ketone (0.50 mmol, 1.00 equiv) and molecular sieves 4Å (ca. 200 mg/mmol). The reaction mixture was stirred at 100°C for 12 h and filtered through a short layer of Celite (CH$_2$Cl$_2$ rinse). The filtrate was concentrated under reduced pressure to afford the pure ketimine.

**GENERAL PROCEDURE FOR THE CYCLIZATION:** Separately, 2,6-lutidine (0.50 mmol, 1.00 equiv) was added in one portion to a suspension of HFIP (2.5 mL) and anhydrous Cu(OTf)$_2$ (0.50 mmol, 1.00 equiv) and stirred at rt for 1 h, during which time a homogeneous suspension was formed. A solution of the (ket)imine (0.50 mmol, 1.00 equiv) in CH$_2$Cl$_2$-HFIP (1:1, 7.5 mL) was added in one portion and the resulting mixture was stirred at rt for 12 h. The reaction was quenched at rt with 10% aq NH$_4$OH (5 mL), and stirred vigorously for 15 min. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 3 mL). The combined organic layers were washed with H$_2$O (3 x 5 mL) and brine (10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated. Purification by flash column chromatography afforded the corresponding N-heterocycle.

**Notes on the purification of substituted heterocycles (0.50 mmol scale)**

- Column for flash Column chromatography: 20 mm column with ca. 8–9 cm silica gel.
- Sample loading: Dry loading on silica gel.
- Solvent: Appropriate solvent mixture with 0.1% Et$_3$N v/v.
- If desired, most of the tin byproducts can be removed before the flash column chromatography to simplify the purification by column chromatography and afford more pure heterocycles: the crude product was dissolved in acetonitrile and washed several times with a small amount of hexanes. The combined hexanes layers were extracted with a small amount of acetonitrile. The combined acetonitrile layers concentrated under reduced pressure to afford the crude product with much less tin residues compared to the original one.$^{11}$

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- If desired, further purification could be carried out by salt formation of the N-heterocycle to remove any trace of tin impurities.

**Additional information**

- **Cu(OTf)$_2$** from Strem used for the cyclization afforded the best results with various results and lower yields using Cu(OTf)$_2$ from other suppliers.
- Product heterocycles are detected by TLC in the unpurified reaction mixture using both, potassium permanganate and ninhydrin\(^\text{12}\) stains. The product is visible with both developing agents. Using the ninhydrin stain, the products show up as pink/purple spots on TLC.

![TLC images](image)

- Some of the aldehydes and imines are not soluble in CH$_2$Cl$_2$ (0.15 M) at rt, which is the standard condition for imine formation. In these cases, acetonitrile (0.15 M) was used as solvent.
- The reaction is not very sensitive to oxygen or H$_2$O and can be conducted in standard glassware without degassed, extra dry solvents or without pre-dried Cu(OTf)$_2$ with only slightly diminished yields.
- The imines were isolated by filtering over a glass sintered funnel followed by evaporation to ensure clean and full conversion before subjection to the cyclization. Alternatively, the imine formation can be diluted with additional CH$_2$Cl$_2$ and transferred to the heterogeneous copper-ligand suspension by a syringe equipped with an HPLC filter. All imine formations were completed after 4 h at rt.
- 2,6-Lutidine is sometimes hard to separate from the desired heterocyclic products using flash column purification. Therefore, the unpurified reaction mixture can be adsorbed onto silica gel and put onto the high vacuum for a prolonged time to remove most of the 2,6-lutidine before the flash column chromatographic purification.

12. 0.300 g Ninhydrin, 1.0 mL AcOH, 100 mL EtOH
2-(4-(1H,1,2,4-Triazol-1-yl)phenyl)-3-(methoxymethoxy) piperidine (3.10a).

Purification by flash column chromatography (CH$_2$Cl$_2$:MeOH 95:5) afforded 3.10a in a diastereomeric ratio of 2:3 (36 mg, 25%, trans diastereomer) as a colorless oil and (54 mg, 38%, cis diastereomer) as a colorless oil. **trans diastereomer:** IR (thin film): $\nu$ 3314, 2933, 2858, 2824, 1608, 1524, 1280, 1149, 1105, 1037, 834 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.54 (s, 1H), 8.09 (s, 1H), 7.64 (d, $J$ = 8.6 Hz, 2H), 7.59 (d, $J$ = 8.6 Hz, 2H), 4.45 (d, $J$ = 6.9 Hz, 1H), 4.11 (d, $J$ = 6.9 Hz, 1H), 3.56 (ddd, $J$ = 9.1, 4.0, 4.0 Hz, 1H), 3.54 (d, $J$ = 9.1 Hz, 1H), 3.14–3.05 (m, 1H), 2.93 (s, 3H), 2.77–2.69 (m, 1H), 2.32–2.18 (m, 1H), 1.80 (d, $J$ = 13.4 Hz, 1H), 1.76–1.64 (m, 1H + NH), 1.51–1.39 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 152.7, 143.1, 140.9, 136.4, 129.7, 119.8, 95.0, 78.0, 67.1, 55.2, 46.8, 32.1, 25.3; $R_f$ = 0.22 (CH$_2$Cl$_2$:MeOH 95:5); ESI-HRMS calc'd for C$_{15}$H$_{21}$N$_4$O$_2$ [M + H]$^+$ 289.1659, found 289.1662. **cis diastereomer:** IR (thin film): $\nu$ 3329, 2935, 2857, 2819, 1609, 1518, 1283, 1150, 1109, 1037, 834 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.54 (s, 1H), 8.09 (s, 1H), 7.64 (d, $J$ = 8.6 Hz, 2H), 7.54 (d, $J$ = 8.6 Hz, 2H), 4.54 (d, $J$ = 7.0 Hz, 1H), 4.20 (d, $J$ = 7.0 Hz, 1H), 3.93 (br s, 1H), 3.92–3.88 (m, 1H), 3.31 (d, $J$ = 12.3 Hz, 1H), 2.91 (s, 3H), 2.86 (t, $J$ = 12.0 Hz, 1H), 2.22–1.95 (m, 1H + NH), 1.95–1.84 (m, 1H), 1.75–1.63 (m, 1H), 1.58–1.48 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 152.7, 143.1, 140.9, 136.4, 129.7, 119.8, 95.0, 78.0, 67.1, 55.2, 46.8, 32.1, 25.3; $R_f$ = 0.22 (CH$_2$Cl$_2$:MeOH 95:5); ESI-HRMS calc'd for C$_{15}$H$_{21}$N$_4$O$_2$ [M + H]$^+$ 289.1659, found 289.1662.

5-(3-(Methoxymethoxy)piperidin-2-yl)-3-phenylisoxazole (3.10b). Purification by flash column chromatography (hexanes:EtOAc 1:2) afforded 3.10b in a diastereomeric ratio of 2:3 (31 mg, 22%, trans diastereomer) as a colorless oil and (47 mg, 33%, cis diastereomer) as a colorless oil. **trans diastereomer:** IR (thin film): v 3319, 2935, 2857, 2819, 1609, 1518, 1283, 1150, 1109, 1037, 834 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.85–7.73 (m, 2H), 7.51–7.39 (m, 3H), 6.59 (s, 1H), 4.63 (d, $J$ = 7.0 Hz, 1H), 4.42 (d, $J$ = 7.0 Hz, 1H), 3.88 (d, $J$ = 8.8 Hz, 1H), 3.80–3.69 (m, 1H), 3.17 (s, 3H), 3.13–3.05 (m, 1H), 2.76–2.67 (m, 1H), 2.31–2.20 (m, 1H), 1.87–1.77 (m, 1H), 1.65 (br s, NH), 1.62–1.46 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 173.5, 162.4, 130.1, 129.3, 129.1, 126.9, 100.1, 95.2, 76.0, 59.0, 55.5, 45.9, 31.2, 25.0; $R_f$ = 0.31.
(hexanes:EtOAc 1:2); ESI-HRMS calcd for $\text{C}_{16}\text{H}_{21}\text{N}_{2}\text{O}_{3}$ [M + H]$^+$ 289.1547, found 289.1547. **cis diastereomer:** IR (thin film): $\nu$ 3005, 2935, 2853, 1604, 1580, 1442, 1408, 1276, 1261, 1037, 764, 750 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.83–7.75 (m, 2H), 7.51–7.36 (m, 3H), 6.59 (d, $J = 1.0$ Hz, 1H), 4.65 (d, $J = 6.9$ Hz, 1H), 4.50 (d, $J = 6.9$ Hz, 1H), 4.18–4.13 (m, 1H), 4.13–4.10 (m, 1H), 3.21–3.14 (m, 1H), 3.18 (s, 3H), 2.82 (ddd, $J = 12.8$, 11.4, 3.2 Hz, 1H), 2.16–2.08 (m, 1H), 1.93–1.80 (m, 1H), 1.77–1.70 (m, 1H), 1.67 (br s, NH), 1.57–1.50 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 173.4, 162.3, 130.1, 129.3, 129.0, 126.9, 99.9, 95.4, 71.5, 57.9, 55.6, 46.1, 28.3, 21.3; $R_f$ = 0.24 (hexanes:EtOAc 1:2); ESI-HRMS calcd for $\text{C}_{16}\text{H}_{21}\text{N}_{2}\text{O}_{3}$ [M + H]$^+$ 289.1547, found 289.1549.

Ethyl 3-(methoxymethoxy)piperidine-2-carboxylate (3.10c). Purification by flash column chromatography (EtOAc:MeOH 100:0 to 95:5) afforded 3.10c in a diastereomeric ratio of 1:3 (17 mg, 19%, trans diastereomer) as a colorless oil and (51 mg, 47%, cis diastereomer) as pale yellow oil. **trans diastereomer:** IR (thin film): $\nu$ 2988, 2937, 2860, 1733, 1276, 1261, 1193, 1035, 750 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.69 (d, $J = 6.9$ Hz, 1H), 4.63 (d, $J = 6.9$ Hz, 1H), 4.25–4.16 (m, 2H), 3.76–3.68 (m, 1H), 3.34 (s, 3H), 3.31 (d, $J = 8.2$ Hz, 1H), 3.02–2.94 (m, 1H), 2.65–2.55 (m, 1H), 2.14–2.06 (m, 1H), 1.79–1.68 (m, 1H + NH), 1.55–1.42 (m, 2H), 1.29 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.5, 95.5, 74.7, 64.0, 61.1, 55.6, 44.9, 30.2, 25.0, 14.3; $R_f$ = 0.20 (EtOAc:MeOH 95:5); ESI-HRMS calcd for $\text{C}_{10}\text{H}_{20}\text{N}_{1}\text{O}_{4}$ [M + H]$^+$ 218.1387, found 218.1388. **cis diastereomer:** IR (thin film): $\nu$ 2989, 2949, 2860, 1739, 1276, 1261, 1203, 1039, 750 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.69 (d, $J = 6.9$ Hz, 1H), 4.63 (d, $J = 6.9$ Hz, 1H), 4.24–4.16 (m, 2H), 4.11–4.07 (m, 1H), 3.46 (d, $J = 2.1$ Hz, 1H), 3.32 (s, 3H), 3.18–3.11 (m, 1H), 2.68–2.57 (m, 1H), 2.15–2.04 (m, 2H), 1.81–1.67 (m, 1H), 1.60–1.48 (m, 1H), 1.45–1.35 (m, 1H), 1.27 (t, $J = 7.1$ Hz, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.4, 95.5, 71.7, 62.5, 61.0, 55.7, 45.5, 28.7, 20.7, 14.3; $R_f$ = 0.15 (EtOAc:MeOH 95:5); ESI-HRMS calcd for $\text{C}_{10}\text{H}_{20}\text{N}_{1}\text{O}_{4}$ [M + H]$^+$ 218.1387, found 218.1391.

**tert-Butyl 3-(methoxymethoxy)-[2,4'-bipiperidine]-1'-carboxylate (3.10d).** Purification by flash column chromatography (CH$_2$Cl$_2$:MeOH 95:5 to 90:10) afforded 3.10d in a diastereomeric ratio of 1:3 (11 mg, 10%, trans diastereomer) as a colorless oil and (33 mg, 29%, cis
diastereomer) as a colorless oil. **trans diastereomer:** IR (thin film): ν 2930, 2858, 1685, 1423, 1369, 1265, 1171, 1034, 830 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.76 (d, J = 6.9 Hz, 1H), 4.58 (d, J = 6.9 Hz, 1H), 4.18 (br s, 2H), 3.54–3.43 (m, 1H), 3.37 (s, 3H), 3.07 (d, J = 11.5 Hz, 1H), 2.75–2.54 (m, 3H), 2.54–2.46 (m, 1H), 2.25–2.13 (m, 1H), 2.10–1.97 (m, 1H), 1.75–1.51 (m, 4H + NH), 1.44 (s, 9H), 1.37–1.27 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 154.9, 95.0, 79.5, 73.3, 65.0, 56.0, 45.9, 44.4, 36.0, 30.5, 29.5, 28.6, 27.0, 26.3, 17.7; Rᵣ = 0.31 (CH₂Cl₂:MeOH 9:1); ESI-HRMS calcd for C₁₇H₃₃N₂O₄ [M + H]⁺ 329.2435, found 329.2438.

**cis diastereomer:** IR (thin film): ν 2928, 2858, 1686, 1426, 1366, 1265, 1170, 1035, 829 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.76 (d, J = 7.1 Hz, 1H), 4.60 (d, J = 7.1 Hz, 1H), 4.25–4.03 (m, 2H), 3.83 (br s, 1H), 3.39 (s, 3H), 3.22 (d, J = 10.6 Hz, 1H), 2.74–2.57 (m, 3H), 2.38–2.29 (m, 1H), 2.11 (d, J = 14.1 Hz, 1H), 1.98 (d, J = 12.8 Hz, 1H), 1.88–1.69 (m, 3H), 1.49–1.35 (m, 2H), 1.44 (s, 9H), 1.18–1.05 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 154.9, 94.9, 79.5, 76.8, 69.3, 64.2, 56.3, 46.8, 43.9, 36.8, 29.8, 29.4, 28.6, 28.3, 28.1, 20.2; Rᵣ = 0.22 (CH₂Cl₂:MeOH 9:1); ESI-HRMS calcd for C₁₇H₃₃N₂O₄ [M + H]⁺ 329.2435, found 329.2435.

**tert-Butyl 9-(methoxymethoxy)-2,5-diazaspiro[3.5]nonane-2-carboxylate (3.10e).** Purification by flash column chromatography (EtOAc:MeOH 95:5) afforded 3.10e as a colorless oil (42 mg, 37%). IR (thin film): ν 2935, 2888, 1696, 1449, 1405, 1371, 1153, 1106, 1039 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.76 (d, J = 6.9 Hz, 1H), 4.65 (d, J = 6.9 Hz, 1H), 3.96 (d, J = 8.8 Hz, 1H), 3.87 (d, J = 8.8 Hz, 1H), 3.58 (d, J = 8.8 Hz, 1H), 3.56 (d, J = 8.8 Hz, 1H), 3.58–3.49 (m, 1H), 3.39 (s, 3H), 2.71 (t, J = 5.4 Hz, 2H), 2.18–1.93 (m, 1H), 1.81–1.70 (m, 1H), 1.72–1.60 (m, 1H), 1.63–1.48 (m, 1H), 1.43 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 156.6, 95.6, 79.5, 76.8, 69.3, 64.2, 56.3, 46.8, 43.9, 36.8, 29.8, 29.4, 28.6, 28.3, 28.1, 20.2; Rᵣ = 0.22 (EtOAc); ESI-HRMS calcd for C₁₄H₂₇N₂O₄ [M + H]⁺ 287.1965, found 287.1963.

**trans-3-(Methoxymethoxy)-2-methyl-2-phenylpiperidine (3.10f).** Purification by flash column chromatography (hexanes:EtOAc 1:2) afforded 3.10f as a colorless oil (21 mg, 18%). IR (thin film): ν 3333, 2924, 2850, 1670, 1447, 1243, 1148, 1103, 1039 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.59–7.54 (m, 2H), 7.36–7.31 (m, 2H), 7.24–7.20 (m, 1H), 4.66 (d, J = 6.9 Hz, 1H), 4.43 (d, J = 6.9 Hz, 1H), 3.98 (t, J = 5.0 Hz, 1H), 3.23 (s, 3H), 2.90 (ddd, J = 12.9, 6.2, 3.9
HZ, 1H), 2.78 (ddd, J = 12.9, 8.2, 4.1 Hz, 1H), 1.81–1.75 (m, 1H), 1.75–1.71 (m, 2H), 1.66 (br s, NH), 1.43–1.38 (m, 1H), 1.40 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 146.1, 128.4, 126.6, 126.4, 95.6, 77.2, 59.6, 55.6, 51.1, 25.9, 24.7, 22.6; Rf = 0.27 (hexanes:EtOAc 1:2); ESI-HRMS calcd for C14H22N1O2 [M + H]+ 236.1645, found 236.1647.

TerBu (2-(o-tolyl)piperidin-3-yl)carbamate (3.11a). Purification by flash column chromatography (CH2Cl2:MeOH 95:5) afforded 3.11a in a diastereomeric ratio of 3:1 (51 mg, 37%, trans diastereomer) as a colorless solid and (17 mg, 12%, cis diastereomer) as a colorless solid. Trans diastereomer: IR (thin film): ν 3325, 2975, 2931, 2855, 2818, 1699, 1505, 1390, 1365, 1248, 1173, 1023, 753, 735 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.59–7.47 (m, 1H), 7.23–7.16 (m, 1H), 7.16–7.08 (m, 2H), 4.19 (br s, NHBoc), 3.91–3.53 (m, 2H), 3.08 (d, J = 12.2 Hz, 1H), 2.76–2.60 (m, 1H), 2.39 (s, 3H), 2.21 (d, J = 13.0 Hz, 1H), 1.80–1.68 (m, 2H), 1.49–1.32 (m, 1H), 1.22 (s, 9H); 13C NMR (100 MHz, CDCl3): δ 154.9, 138.5, 136.4, 130.4, 128.9, 127.5, 126.5, 79.3, 62.5, 52.7, 47.0, 33.0, 28.3, 25.7, 19.8; Rf = 0.19 (CH2Cl2:MeOH 95:5); m.p. = 86–89°C; ESI-HRMS calcd for C17H27N2O2 [M + H]+ 291.2067, found 291.2063. These spectral characteristics are identical to those previously reported.13 cis diastereomer: IR (thin film): ν 3430, 2974, 2933, 2858, 2816, 1712, 1490, 1364, 1171, 744 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.49–7.36 (m, 1H), 7.22–7.06 (m, 3H), 5.44 (d, J = 8.1 Hz, NHBoc), 3.99 (d, J = 0.9 Hz, 1H), 3.92 (dd, J = 9.0, 0.9 Hz, 1H), 3.24–3.13 (m, 1H), 2.88–2.74 (m, 1H), 2.36 (s, 3H), 1.97 (d, J = 9.2 Hz, 1H), 1.73–1.67 (m, 2H), 1.60–1.51 (m, 1H + NH), 1.23 (s, 9H); 13C NMR (100 MHz, CDCl3): δ 155.7, 139.9, 135.0, 130.4, 126.8, 126.1, 125.9, 78.7, 60.8, 48.1, 47.5, 30.9, 28.4, 20.9, 19.3; Rf = 0.24 (CH2Cl2:MeOH 95:5); m.p. = 65–66°C; ESI-HRMS calcd for C17H27N2O2 [M + H]+ 291.2067, found 291.2065.

trans-tert-Butyl (2-(o-tolyl)piperidin-3-yl)carbamate

Chiral HPLC: column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: 2% iPrOH in hexane, flow: 1.0 mL/min; detection: 254 nm. Retention time: $t_R = 19.0$ min and 20.3 min.

NHBoc
\[
\begin{array}{c}
\text{NH}_2 \\
\text{SnBu}_3
\end{array}
\]

racemic

≥ 98% ee

NHBoc
\[
\begin{array}{c}
\text{NH}_2 \\
\text{SnBu}_3
\end{array}
\]

racemic


cis-tert-Butyl (2-(o-tolyl)piperidin-3-yl)carbamate

Chiral HPLC: column: Daicel Chiralpak ASH (4.6 × 250 mm); eluent: 2% iPrOH in hexane, flow: 0.8 mL/min; detection: 254 nm. Retention time: $t_R = 7.18$ min and 8.02 min.

NHBoc
\[
\begin{array}{c}
\text{NH}_2 \\
\text{SnBu}_3
\end{array}
\]

racemic

≥ 98% ee

NHBoc
\[
\begin{array}{c}
\text{NH}_2 \\
\text{SnBu}_3
\end{array}
\]

racemic
tert-Butyl (2-(3-bromo-4-hydroxyphenyl)piperidin-3-yl)carbamate (3.11b). Purification by flash column chromatography (hexanes:EtOAc 1:2) afforded 3.11b in a diastereomeric ratio of 2:1 (52 mg, 29%, trans diastereomer) as a colorless solid and (26 mg, 15%, cis diastereomer) as a colorless solid. trans diastereomer: IR (thin film): ν 3427, 2980, 2940, 2914, 2864, 1646, 1446, 1291, 1165, 1043 cm⁻¹; ¹H NMR (400 MHz, CD₃OD): δ 7.59–7.41 (m, 1H), 7.25–7.08 (m, 1H), 6.82 (d, J = 8.4 Hz, 1H), 3.57–3.42 (m, 1H), 3.30–3.19 (m, 1H), 3.09–2.98 (m, 1H), 2.71–2.56 (m, 1H), 2.07–1.98 (m, 1H), 1.72–1.62 (m, 1H), 1.51–1.40 (m, 1H), 1.24 (s, 9H); ¹³C NMR (100 MHz, CD₃OD): δ 157.3, 155.3, 134.2, 133.2, 129.3, 117.0, 110.5, 79.8, 66.7, 53.0, 47.1, 33.1, 28.6, 26.0; Rᵥ = 0.15 (hexanes:EtOAc 1:2); m.p. = 159–161°C; ESI-HRMS calcd for C₁₆H₂₄Br₁N₂O₃ [M + H]⁺ 371.0965, found 371.0962. cis diastereomer: IR (thin film): ν 3419, 2979, 2940, 2861, 1646, 1508, 1365, 1288, 1168 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.46 (s, 1H), 7.18–7.10 (m, 1H), 6.89 (d, J = 8.4 Hz, 1H), 5.39 (d, J = 9.4 Hz, 1H), 3.84 (d, J = 8.3 Hz, 1H), 3.75 (br s, 1H), 3.21–3.11 (m, 1H), 2.84–2.72 (m, 1H), 1.98–1.90 (m, 1H), 1.71–1.62 (m, 2H), 1.57–1.51 (m, 1H), 1.29 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 155.6, 151.6, 135.8, 130.2, 127.9, 116.0, 110.0, 79.0, 63.4, 50.0, 47.6, 30.7, 28.4, 20.6; Rᵥ = 0.20 (hexanes:EtOAc 1:2); m.p. = 127–130°C; ESI-HRMS calcd for C₁₆H₂₄Br₁N₂O₃ [M + H]⁺ 371.0965, found 371.0957.

tert-Butyl (2-(2-phenylpyrimidin-5-yl)piperidin-3-yl)carbamate (3.11c). Purification by flash column chromatography (hexanes:EtOAc 1:2) afforded 3.11c in a diastereomeric ratio of 3:2 (41 mg, 29%, trans diastereomer) as a colorless solid and (13 mg, 9%, cis diastereomer) as a colorless solid. trans diastereomer: IR (thin film): ν 3304, 2979, 2940, 2861, 1646, 1508, 1365, 1288, 1168 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.82 (s, 2H), 8.47–8.32 (m, 2H), 7.58–7.36 (m, 3H), 4.45–4.02 (m, NHBOc), 3.74–3.48 (m, 1H), 3.35 (d, J = 9.6 Hz, 1H), 3.22–3.10 (m, 1H), 2.77–2.63 (m, 1H), 2.21–2.07 (m, 2H), 1.83–1.70 (m, 2H), 1.66 (br s, NH), 1.41–1.31 (m, 1H), 1.18 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 164.4, 157.2, 154.8, 137.8, 132.3, 130.6, 128.6, 128.3, 79.6, 64.7, 53.0, 46.9, 32.7, 28.2, 25.7; Rᵥ = 0.16 (hexanes:EtOAc 1:2); m.p. = 159–160°C; ESI-HRMS calcd for C₂₀H₂₂N₂O₂ [M + H]⁺ 355.2129, found 355.2124. cis diastereomer: IR (thin film): ν 3433, 2981, 2944, 2859, 2814, 1644, 1430, 1364, 1167, 747 cm⁻¹.
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

1H NMR (400 MHz, CDCl₃): δ 8.76 (s, 2H), 8.45–8.35 (m, 2H), 7.56–7.40 (m, 3H), 5.43 (d, J = 10.1 Hz, NHBoc), 4.00–3.85 (m, 1H), 3.93 (br s, 1H), 3.28–3.16 (m, 1H), 2.88–2.74 (m, 1H), 2.06–1.93 (m, 1H), 1.82–1.63 (m, 2H), 1.63–1.59 (m, 1H), 1.57 (br s, NH), 1.25 (s, 9H); 13C NMR (100 MHz, CDCl₃): δ 164.1, 156.1, 155.4, 137.7, 132.5, 130.6, 128.7, 128.2, 79.4, 60.8, 49.5, 47.5, 30.4, 28.4, 20.4; Rf = 0.20 (hexanes:EtOAc 1:2); m.p. = 130–133°C; ESI-HRMS calcd for C₂₀H₂₇N₄O₂ [M + H]+ 355.2129, found 355.2125.

tert-Butyl (2-(thiazol-4-yl)piperidin-3-yl)carbamate (3.11d). Purification by flash column chromatography (CH₂Cl₂:MeOH 95:5) afforded 3.11d in a diastereomeric ratio of 3:1 (41 mg, 29%, trans diastereomer) as a colorless oil and (13 mg, 9%, cis diastereomer) as a colorless oil. trans diastereomer: IR (thin film): ν 3313, 2974, 2930, 2856, 1703, 1497, 1275, 1260, 1167, 750 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 8.73 (d, J = 2.0 Hz, 1H), 7.35 (s, 1H), 4.61 (s, NHBoc), 3.85–3.51 (m, 2H), 3.15–3.04 (m, 1H), 2.77–2.61 (m, 1H), 2.25–2.12 (m, 1H + NH), 1.80–1.71 (m, 1H), 1.71–1.58 (m, 1H), 1.47–1.35 (m, 1H), 1.30 (s, 9H); 13C NMR (100 MHz, CDCl₃): δ 157.7, 155.1, 152.4, 114.8, 79.2, 62.9, 52.4, 46.2, 32.5, 28.4, 25.8; Rf = 0.13 (CH₂Cl₂:MeOH 95:5); ESI-HRMS calcd for C₁₃H₂₂N₃O₂S₁ [M + H]+ 284.1427, found 284.1422.

cis diastereomer: IR (thin film): ν 3352, 2977, 2935, 2860, 1681, 1520, 1260, 1167, 750 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 8.75 (d, J = 2.0 Hz, 1H), 7.21 (s, 1H), 5.50 (d, J = 9.4 Hz, NHBoc), 4.26–4.13 (m, 1H), 4.09 (br s, 1H), 3.20–3.10 (m, 1H), 2.92–2.75 (m, 1H), 2.02–1.93 (m, 1H), 1.79–1.68 (m, 2H + NH), 1.61–1.52 (m, 1H), 1.33 (s, 9H); 13C NMR (100 MHz, CDCl₃): δ 157.6, 155.7, 152.4, 114.8, 79.0, 60.8, 47.9, 47.2, 30.3, 28.5, 21.0; Rf = 0.13 (CH₂Cl₂:MeOH 95:5); ESI-HRMS calcd for C₁₃H₂₁N₃O₂S₁ [M + H]+ 284.1427, found 284.1422.

trans-tert-Butyl (2-(pentan-3-yl)piperidin-3-yl)carbamate (3.11e). Purification by flash column chromatography (EtOAc:MeOH 9:1) afforded 3.11e as single diastereomer (42 mg, 31%) as a colorless solid. IR (thin film): ν 3433, 2962, 2932, 2874, 2812, 1687, 1646, 1525, 1365, 1245, 1173 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 4.42–3.94 (m, NHBoc), 3.65–3.23 (m, 1H), 3.12–2.92 (m, 1H), 2.53–2.40 (m, 1H), 2.29 (dd, J = 9.4, 2.6 Hz, 1H), 2.11–2.00 (m, 1H), 1.70–1.57 (m, 2H), 1.53–1.48 (m, 2H + NH), 1.44 (s, 9H), 1.38–1.30 (m, 1H), 1.25–1.13 (m, 2H), 1.11–0.97 (m, 1H), 0.90 (t, 6H); 13C NMR (100 MHz, CDCl₃): δ 155.3, 79.1, 63.2, 49.0,
46.4, 41.4, 33.1, 28.6, 26.4, 23.1, 22.0, 13.0, 12.5; Rf = 0.22 (EtOAc:MeOH 9:1); m.p. = 55–59°C; ESI-HRMS calcd for C_{15}H_{31}N_{2}O_{2} [M + H]^+ 271.2380, found 271.2379.

*tert*-Butyl (9-oxa-1-azaspiro[5.5]undecan-5-yl)carbamate (3.11f). Purification by flash column chromatography (EtOAc:MeOH 95:5) afforded 3.11f (56 mg, 41%) as a colorless oil. IR (thin film): ν 3318, 2943, 2864, 1695, 1522, 1365, 1245, 1165, 1097, 1019 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.12–4.75 (m, NHBoc), 3.79–3.59 (m, 4H), 3.58–3.47 (m, 1H), 2.89–2.75 (m, 1H), 2.74–2.61 (m, 1H), 1.92–1.80 (m, 1H), 1.80–1.72 (m, 1H), 1.67–1.30 (m, 7H), 1.42 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 155.8, 79.2, 63.2, 63.1, 52.9, 52.5, 39.5, 33.6, 31.2, 28.5, 26.0, 23.8; Rf = 0.23 (EtOAc:MeOH 95:5); ESI-HRMS calcd for C_{14}H_{27}N_{2}O_{3} [M + H]^+ 271.2016, found 271.2019.

7.3.3 Preparation of SnAP-eX Reagents for the Synthesis of Pyrrolidines

**IMPORTANT:** The first product in this reaction sequence (tributylstannyl alcohol) is unstable. This compound decomposes within hours at rt. It is important to follow the procedure, including the reaction times, the solvents for the extractions and the temperature of the water bath. The reaction sequence up to the stable MOM protected SnAP reagent precursor should be done as fast as possible in one go!
9,9,10,10-Tetramethyl-5-(tributylstannyl)-2,4,8-trioxa-9-silaundecane (3.17). To a stirred solution of N,N-diisopropylamine (3.62 mL, 25.7 mmol, 1.15 equiv) in THF (45 mL) at 0°C was added n-BuLi (1.6 M in hexanes, 16.0 mL, 25.0 mmol, 1.12 equiv) over 10 min. The light yellow solution was stirred for 30 min at 0°C before tributyltin hydride (6.00 mL, 22.3 mmol, 1.00 equiv) was added dropwise over 5–10 min. The resulting yellow solution was stirred for 30 min at 0°C before cooled to −78°C. 3-((tert-Butyldimethylsilyl)oxy)propanal (4.63 g, 24.6 mmol, 1.10 equiv) in THF (5 mL) was slowly added and the resulting reaction mixture was stirred at −78°C for 0.5 h before being poured cold onto sat aq NH₄Cl (50 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organic layers were washed with H₂O (1 x 20 mL) and brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure at 0–20°C to afford the tributylstannyl alcohol as a colorless oil that was used in the next step immediately.

The resulting tributylstannyl alcohol was dissolved in CH₂Cl₂ (5 mL) and added to a pre-made solution of N,N-dimethylaniline (5.10 mL, 40.2 mmol, 1.80 equiv) and MOM–Cl (5.10 mL, 70.0 mmol, 3.00 equiv) in CH₂Cl₂ (45 mL). The resulting mixture was stirred at rt for 12 h before being poured cold H₂O (50 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (1 x 20 mL). The combined organic layers were washed with H₂O (2 x 40 mL) and brine (2 x 40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 100:0 to 50:1) afforded 3.17 (8.60 g, 74% yield) as a colorless oil. IR (thin film): ν 2956, 2930, 2864, 1464, 1253, 1078, 1039 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.58 (d, J = 6.5 Hz, 1H), 4.54 (d, J = 6.5 Hz, 1H), 4.16 (dd, J = 9.1, 4.3 Hz, 1H), 3.75–3.63 (m, 2H), 3.34 (s, 3H), 2.12–1.89 (m, 2H), 1.59–1.43 (m, 6H), 1.35–1.28 (m, 6H), 0.92–0.83 (m, 25H), 0.09–0.02 (m, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 96.9, 70.1, 61.5, 55.6, 38.6, 29.3, 27.7, 26.1, 18.5, 13.8, 9.3, -5.1, -5.1; Rf = 0.46 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C₂₃H₅₂Na₁O₃Si₁Sn₁ [M + Na]⁺ 547.2604, found 547.2598.

3-(Methoxymethoxy)-3-(tributylstannylo)propan-1-ol (S3.2). TBAF (9.00 mL of a 1.0 M solution in THF, 9.06 mmol, 1.40 equiv) was added dropwise over 10 min to a solution of the TBS protected alcohol 3.17 (3.39 g, 6.48 mmol, 1.00 equiv) in THF (45 mL) at 0°C. The resulting solution was allowed to warm to rt and was stirred for 5 h before being poured into a
mixture of EtOAc:H₂O (2:1, 100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with H₂O (2 x 10 mL), brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 6:1) afforded S3.2 (1.86 g, 70% yield) as a colorless oil.

IR (thin film): ν 3426, 2956, 2926, 2872, 2854, 1464, 1146, 1028, 908, 874 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.59 (d, J = 6.6 Hz, 1H), 4.54 (d, J = 6.6 Hz, 1H), 4.30–4.21 (m, 1H), 3.90–3.67 (m, 2H), 3.37 (s, 3H), 2.50 (t, J = 5.8 Hz, 1H), 2.12–1.93 (m, 2H), 1.58–1.41 (m, 6H), 1.37–1.20 (m, 6H), 0.93–0.84 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 96.9, 72.9, 62.9, 55.9, 37.3, 29.3, 27.6, 13.8, 9.4; Rᵥ = 0.52 (hexanes:EtOAc 4:1); ESI-HRMS calcd for C₁₇H₃₈NaO₃Sn [M + Na]⁺ 433.1738, found 433.1736.

2-(3-(Methoxymethoxy)-3-(tributylstannyl)propyl)isoindoline-1,3-dione (3.18).

Diisopropyl azodicarboxylate (2.73 mL, 13.9 mmol, 1.08 equiv) was added dropwise over 15 min to a clear, pale yellow solution of the alcohol S3.2 (5.25 g, 12.8 mmol, 1.00 equiv), triphenylphosphine (3.77 g, 14.4 mmol, 1.12 equiv), and phthalimide (2.08 g, 14.1 mmol, 1.10 equiv) in THF (85 mL) at 0°C. The clear, yellow solution was allowed to warm to rt and stirred for 5 h. The resulting reaction mixture was concentrated and purification by flash column chromatography (hexanes:EtOAc 10:1) afforded the phthalimide protected SnAP-eX 3-O-MOM Pyr 3.18 (6.42 g, 93% yield) as a colorless oil. IR (thin film): ν 2956, 2927, 2872, 2858, 1772, 1712, 1396, 1035, 980 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.84 (dd, J = 5.4, 3.0 Hz, 2H), 7.70 (dd, J = 5.4, 3.0 Hz, 2H), 4.62 (d, J = 6.7 Hz, 1H), 4.58 (d, J = 6.7 Hz, 1H), 4.06 (t, J = 6.5 Hz, 1H), 3.85–3.74 (m, 2H), 3.38 (s, 3H), 2.21–2.05 (m, 2H), 1.60–1.41 (m, 6H), 1.37–1.24 (m, 6H), 0.98–0.84 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 168.5, 133.9, 132.4, 123.3, 96.9, 72.9, 62.9, 55.9, 37.3, 29.3, 27.6, 13.8, 9.4; Rᵥ = 0.81 (hexanes:EtOAc 4:1); ESI-HRMS calcd for C₂₅H₄₃Na₂O₄Sn [M + Na]⁺ 562.1955, found 562.1949.

3-(Methoxymethoxy)-3-(tributylstannyl)propan-1-amine (3.19). The phthalimide protected SnAP-eX 3-O-MOM Pyr 3.18 (4.00 g, 7.43 mmol, 1.00 equiv) in EtOH (75 mL) was heated to reflux. Hydrazine monohydrate (3.60 mL, 74.3 mmol, 10.0 equiv) was added dropwise at reflux over 5 min. The resulting reaction mixture was stirred for further 45 min at
reflux while colorless solid crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (80 mL) and H2O (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure to afford pure SnAP-eX 3-O-MOM Pyr 3.19 (2.91 g, 96% yield) as a colorless oil. IR (thin film): ν 2958, 2927, 2853, 1464, 1150, 1093, 1032, 907, 843 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ 4.58 (d, J = 6.6 Hz, 1H), 4.54 (d, J = 6.6 Hz, 1H), 4.15 (dd, J = 9.0, 4.3 Hz, 1H), 3.35 (s, 3H), 2.81 (t, J = 6.9 Hz, 2H), 2.04–1.93 (m, 1H), 1.93–1.82 (m, 1H), 1.57–1.45 (m, 6H), 1.43 (br s, NH₂), 1.36–1.25 (m, 6H), 0.89 (t, J = 7.4 Hz, 15H); ¹³C NMR (100 MHz, CDCl3): δ 96.7, 71.7, 55.7, 41.1, 39.2, 29.3, 27.7, 13.8, 9.4; ESI-HRMS calcd for C₁₇H₄₀N₁O₂Sn₁ [M + H]+ 410.2078, found 410.2076.

 tert-Butyl (3-(1,3-dioxoisoindolin-2-yl)-1-tosylpropyl)carbamate (3.20). A solution of commercially available 3-(1,3-dioxoisoindolin-2-yl)propanal (3.00 g, 14.8 mmol, 1.00 equiv), tert-butyl carbamate (1.73 g, 14.8 mmol, 1.00 equiv), and sodium p-toluenesulfinate (2.63 g, 14.8 mmol, 1.00 equiv) in H₂O:MeOH:HCOOH (8:4:1, 78.0 mL) was stirred at rt for 48 h while colorless solids crashed out. The suspension was cooled to 0°C, filtered, washed with H₂O (3 x 5 mL), and dried at high vacuum to afford pure 3.20 (5.02 g, 74% yield) as a colorless solid. IR (thin film): ν 3345, 2979, 2874, 1773, 1713, 1517, 1398, 1368, 1317, 1142, 721 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ 7.83 (dd, J = 5.4, 3.1 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 7.70 (dd, J = 5.4, 3.1 Hz, 2H), 7.39–7.26 (m, 2H), 5.22 (d, J = 10.9 Hz, 1H), 4.96–4.84 (m, NHBoc), 3.95–3.80 (m, 2H), 2.74–2.63 (m, 1H), 2.39 (s, 3H), 2.25–2.01 (m, 1H), 1.19 (s, 9H); ¹³C NMR (100 MHz, CDCl3): δ 168.1, 153.7, 145.2, 134.2, 133.6, 132.1, 129.9, 129.5, 123.5, 81.0, 68.9, 34.4, 28.0, 25.4, 21.7; m.p. = 146–149°C; ESI-HRMS calcd for C₂₃H₂₆N₂O₆S₁ [M + Na]+ 481.1404, found 481.1397.
tert-Butyl (3-(1,3-dioxoisoodolin-2-yl)-1-(tributylstannyl)propyl)carbamate (3.21). CsF (2.98 g, 19.6 mmol, 3.00 equiv) was placed in a round-bottomed flask and heated under vacuum (<5 mmHg at ca. 400°C by a heat gun) for 10–15 min and suspended in DMF (120 mL). α-Amino sulfone 3.20 (3.00 g, 6.54 mmol, 1.00 equiv) in DMF (10 mL) was added dropwise. After 5 min, commercially available TMSSnBu3 (4.75 g, 4.57 mL, 13.1 mmol, 2.00 equiv) was slowly added followed by vigorous stirring at rt for 4 h. MeOH (30 mL) was added to quench the reaction followed by the addition of H2O (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (5 x 50 mL). The combined organic layers were washed with H2O (5 x 20), brine (5 x 20 mL), dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 20:1) afforded the phthalimide protected SnAP-eX3-NH-Boc Pyr 3.21 (1.44 mg, 37% yield) as a colorless oil. IR (thin film): ν 3395, 2955, 2923, 2871, 2853, 1772, 1714, 1501, 1393, 1171, 720 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.84 (dd, J = 5.4, 3.1 Hz, 2H), 7.71 (dd, J = 5.4, 3.1 Hz, 2H), 5.58–5.13 (m, NHBoc), 3.80 (ddd, J = 15.2, 9.7, 5.5 Hz, 1H), 3.70 (ddd, J = 13.7, 6.4, 3.8 Hz, 1H), 2.76 (ddd, J = 12.3, 6.4, 2.9 Hz, 1H), 2.09–1.93 (m, 1H), 1.90–1.76 (m, 1H), 1.46–1.33 (m, 6H), 1.41 (s, 9H), 1.29–1.19 (m, 6H), 0.81 (t, J = 7.3 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 168.9, 156.6, 134.1, 132.2, 123.4, 78.9, 36.3, 36.2, 33.1, 29.3, 28.6, 27.6, 13.8, 10.3; Rf = 0.33 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C29H49N2O4Sn [M + H]+ 609.2715, found 609.2711.

tert-Butyl (3-amino-1-(tributylstannyl)propyl)carbamate (3.22). The phthalimide protected SnAP-eX 3-NH-Boc Pyr 3.21 (2.00 g, 3.37 mmol, 1.00 equiv) in EtOH (35 mL) was heated to reflux. Hydrazine monohydrate (1.63 mL, 3.37 mmol, 10.0 equiv) was added dropwise at reflux. The resulting reaction mixture was stirred for further 45 min at reflux while colorless solid crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (100 mL) and H2O (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 x 10 mL), dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure to afford pure SnAP-eX 3-NH-Boc Pyr 3.22 (1.51 g, 97% yield) as a colorless oil. IR (thin film): ν 3275, 2955, 2923, 2871, 2853, 1693, 1499, 1457, 1275, 1251, 1173 cm−1; 1H NMR
(400 MHz, CDCl$_3$): δ 5.00–4.72 (m, NHBoc), 3.40 (ddd, $J = 10.4, 8.2, 4.6$ Hz, 1H), 2.84–2.65 (m, 2H), 1.82–1.66 (m, 2H + NH$_2$), 1.55–1.44 (m, 6H), 1.42 (s, 9H), 1.35–1.23 (m, 6H), 0.89 (t, $J = 7.3$ Hz, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 156.4, 79.0, 40.5, 38.3, 37.5, 29.3, 28.6, 27.7, 13.8, 9.7; ESI-HRMS calcd for C$_{21}$H$_{47}$N$_2$O$_2$Sn$_1$ [M + H]$^+ 479.2658$, found 479.2655.

7.3.4 Preparation Pyrrolidines using SnAP-eX Reagents

All pyrrolidines were prepared according to the general procedure described in chp. 7.3.2

3-(3-(Methoxymethoxy)pyrrolidin-2-yl)benzonitrile (3.23a). Purification by flash column chromatography (CH$_2$Cl$_2$:MeOH 97:3) afforded 3.23a in a diastereomeric ratio of 1:3 (11 mg, 9%, trans diastereomer) as a colorless oil and (35 mg, 31%, cis diastereomer) as a colorless oil. 

**trans diastereomer:** IR (thin film): ν 3327, 3070, 2949, 2927, 2897, 2852, 2231, 1703, 1665, 1437, 1150, 1105, 1031 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.76 (s, 1H), 7.66 (d, $J = 7.8$ Hz, 1H), 7.56–7.50 (m, 1H), 7.45–7.40 (m, 1H), 4.68 (d, $J = 6.8$ Hz, 1H), 4.62 (d, $J = 6.8$ Hz, 1H), 4.28–4.14 (d, $J = 2.5$ Hz, 1H), 4.08–4.01 (m, 1H), 3.32 (s, 3H), 3.28–3.14 (m, 2H), 2.07–1.96 (m, 1H), 1.93–1.82 (m, 1H), 1.83 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 144.6, 131.4, 130.9, 130.6, 129.2, 119.1, 112.6, 95.7, 84.1, 67.2, 55.6, 45.3, 31.7; $R_f$ = 0.28 (CH$_2$Cl$_2$:MeOH 95:5); ESI-HRMS calcd for C$_{13}$H$_{17}$N$_2$O$_2$ [M + H]$^+ 233.1285$, found 233.1287.

**cis diastereomer:** IR (thin film): ν 3328, 3071, 2943, 2929, 2898, 2852, 2231, 1700, 1666, 1151, 1039 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.75 (s, 1H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.57–7.50 (m, 1H), 7.45–7.39 (m, 1H), 4.45 (d, $J = 6.9$ Hz, 1H), 4.35–4.30 (m, 1H), 4.22 (d, $J = 6.9$ Hz, 1H), 4.17 (d, $J = 3.9$ Hz, 1H), 3.41–3.28 (m, 1H), 3.14–3.04 (m, 1H), 2.98 (s, 3H), 2.20–2.10 (m, 1H), 2.09–2.01 (m, 1H), 1.96 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 141.1, 132.7, 131.9, 130.8, 128.8, 119.2, 112.2, 95.0, 78.2, 66.3, 55.4, 44.6, 32.9; $R_f$ = 0.19 (CH$_2$Cl$_2$:MeOH 95:5); ESI-HRMS calcd for C$_{13}$H$_{17}$N$_2$O$_2$ [M + H]$^+ 233.1285$, found 233.1288.

2-(2-Methoxy-5-(trifluoromethoxy)phenyl)-3-(methoxymethoxy)pyrrolidine (3.23b). Purification by flash column chromatography (CH$_2$Cl$_2$:MeOH 95:5) afforded 3.23b in a
diastereomeric ratio of 2:5 (14 mg, 9%, trans diastereomer) as a colorless oil and (35 mg, 22%, cis diastereomer) as a colorless oil. **trans diastereomer:** IR (thin film): ν 2947, 2897, 2840, 2785, 1496, 1247, 1173, 1105, 1034, 907, 833 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.37–7.30 (m, 1H), 7.06 (dd, J = 8.8, 2.4 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 4.78 (d, J = 6.6 Hz, 1H), 4.68 (d, J = 6.6 Hz, 1H), 4.46 (d, J = 1.7 Hz, 1H), 4.24–4.14 (m, 1H), 3.85 (s, 3H), 3.36 (s, 3H), 3.31–3.16 (m, 2H), 1.89–1.79 (m, 2H), 1.76 (br s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 155.1, 143.0, 133.0, 121.2, 120.7 (q, ¹JCF = 256.0 Hz), 120.5, 110.7, 95.0, 81.9, 63.4, 55.7, 55.4, 45.7, 31.1; Rᵣ = 0.19 (CH₂Cl₂:MeOH 95:5); ESI-HRMS calcd for C₁₄H₁₉F₃N₁O₄ [M + H]+ 322.1261, found 322.1260.

**cis diastereomer:** IR (thin film): ν 2934, 2892, 2849, 2793, 1523, 1498, 1246, 1222, 1150, 1039, 833 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.42 (d, J = 3.0 Hz, 1H), 7.07 (dd, J = 8.8, 2.4 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 4.46 (ddd, J = 5.6, 4.1, 1.5 Hz, 1H), 4.33 (d, J = 6.8 Hz, 1H), 4.28 (d, J = 4.1 Hz, 1H), 4.16 (d, J = 6.8 Hz, 1H), 3.84 (s, 3H), 3.31 (ddd, J = 10.5, 8.3, 5.6 Hz, 1H), 3.04–2.94 (m, 1H), 2.97 (s, 3H), 2.24–2.10 (m, 1H), 2.03–1.93 (m, 1H), 1.66 (br s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 155.3, 142.8, 129.7, 121.9, 120.8 (q, JCF = 255.2 Hz), 120.3, 110.1, 95.1, 61.4, 55.8, 55.0, 44.2, 33.5; Rᵣ = 0.16 (CH₂Cl₂:MeOH 95:5); ESI-HRMS calcd for C₁₄H₁₉F₃N₁O₄ [M + H]+ 322.1261, found 322.1263.

Purification by flash column chromatography (CH₂Cl₂:MeOH 95:5 to 90:10) afforded 3.23 in a diastereomeric ratio of 5:9 (16 mg, 14%, trans diastereomer) as a colorless oil and (30 mg, 26%, cis diastereomer) as a colorless oil. **trans diastereomer:** IR (thin film): ν 2926, 2906, 2850, 1714, 1599, 1504, 1454, 1394, 1149, 1104, 1041 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.57 (s, 1H), 7.50–7.35 (m, 5H), 4.69 (d, J = 6.8 Hz, 1H), 4.65 (d, J = 6.8 Hz, 1H), 4.30–4.21 (m, 1H), 4.10 (d, J = 4.5 Hz, 1H), 3.34 (s, 3H), 3.26–3.14 (m, 2H), 2.35 (s, 3H), 2.25–2.13 (m, 1H), 1.99–1.90 (m, 1H), 1.83 (br s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 140.0, 138.0, 136.6, 129.2, 127.8, 125.2, 120.6, 95.8, 82.9, 60.2, 55.6, 45.2, 32.5, 11.1; Rᵣ = 0.21 (CH₂Cl₂:MeOH 9:1); ESI-HRMS calcd for C₁₆H₂₂N₃O₂ [M + H]+ 288.1707, found 288.1705. **cis diastereomer:** IR (thin film): ν 2925, 2901, 2851, 1714, 1599, 1504, 1454, 1394, 1150, 1038 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.85 (s, 1H), 7.52–7.35 (m, 5H), 4.66 (d, J = 6.9 Hz, 1H), 4.51 (d, J = 6.9 Hz, 1H), 4.34–4.20 (m, 1H), 4.12 (br s, 1H), 3.44–3.32 (m, 1H), 3.24 (s, 3H), 3.18–3.04 (m, 1H), 2.86 (br s, NH), 2.37 (s, 3H), 2.27–2.09 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 140.4, 139.9,
137.3, 129.2, 127.9, 125.2, 114.9, 95.4, 77.6, 59.1, 55.8, 43.8, 32.5, 11.2; R<sub>t</sub> = 0.10 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH 9:1); ESI-HRMS calcd for C<sub>16</sub>H<sub>22</sub>N<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> 288.1707, found 288.1708.

2-(Benzo[b]thiophen-3-yl)-3-(methoxymethoxy)pyrrolidine (3.23d). Purification by flash column chromatography (EtOAc:MeOH 98:2) afforded 3.23d in a diastereomeric ratio of 2:5 (7 mg, 5%, trans diastereomer) as a colorless oil and (18 mg, 14%, cis diastereomer) as a colorless oil. **trans diastereomer:** IR (thin film): ν 3066, 2931, 2858, 1672, 1459, 1428, 1380, 1150, 1105, 920 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.00–7.91 (m, 1H), 7.89–7.80 (m, 1H), 7.43–7.31 (m, 3H), 4.75 (d, J = 6.9 Hz, 1H), 4.70 (d, J = 6.9 Hz, 1H), 4.62 (d, J = 2.7 Hz, 1H), 4.38–4.31 (m, 1H), 3.38 (s, 3H), 3.33–3.24 (m, 2H), 2.07 (d, J = 13.5 Hz, 1H), 2.00–1.92 (m, 1H), 1.78 (br s, NH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 141.1, 138.0, 124.5, 124.2, 123.0, 122.4, 95.8, 82.4, 63.7, 55.7, 45.2, 31.8; R<sub>t</sub> = 0.34 (EtOAc:MeOH 95:5); ESI-HRMS calcd for C<sub>14</sub>H<sub>18</sub>N<sub>1</sub>O<sub>2</sub>S<sub>1</sub> [M + H]<sup>+</sup> 264.1053, found 264.1054.

Benzyl 4-(methoxymethoxy)-1,8-diazaspiro[4.5]decane-8-carboxylate (3.23e). Purification by flash column chromatography (EtOAc:MeOH 9:1) afforded 3.23e as pale yellow oil (16 mg, 10%). IR (thin film): ν 3300, 2961, 2924, 2853, 1695, 1434, 1260, 1095, 1020, 910 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.40–7.32 (m, 5H), 5.13 (s, 2H), 4.68 (d, J = 6.9 Hz, 1H), 4.58 (d, J = 6.9 Hz, 1H), 3.92–3.68 (m, 3H), 3.45–3.32 (m, 2H), 3.35 (s, 3H), 3.23–3.11 (m, 1H), 3.07–2.93 (m, 1H), 2.12–2.03 (m, 1H), 1.94–1.86 (m, 1H), 1.85–1.76 (m, 1H), 1.68–1.45 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 155.3, 137.0, 128.6, 128.1, 128.0, 95.5, 82.5, 67.2, 63.5, 55.9, 42.7, 41.1, 40.7, 33.9, 30.8, 30.3; R<sub>t</sub> = 0.18 (EtOAc:MeOH 95:5); ESI-HRMS calcd for C<sub>18</sub>H<sub>22</sub>N<sub>3</sub>O<sub>4</sub> [M + H]<sup>+</sup> 335.1965, found 335.1970.
trans-tert-Butyl (2-(4-(trifluoromethyl)phenyl)pyrrolidin-3-yl)carbamate (3.24a).

Purification by flash column chromatography (EtOAc) afforded 3.24a as a colorless solid (87 mg, 53%). IR (thin film): v 3330, 2978, 2932, 2872, 1698, 1507, 1326, 1164, 1124, 1068 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl3): \(\delta\) 7.55 (d, \(J = 8.2\) Hz, 2H), 7.49 (d, \(J = 8.2\) Hz, 2H), 4.51–4.26 (m, 2H + NHBoc), 3.31–3.16 (m, 1H), 3.03 (dd, \(J = 8.7, 8.6\) Hz, 1H), 2.36–2.24 (m, 1H), 2.04 (br s, NH), 1.79–1.65 (m, 1H), 1.19 (s, 9H); \(^13\)C NMR (100 MHz, CDCl3): \(\delta\) 155.2, 144.3, 129.4 (q, \(J_{\text{CF}} = 13.3\) Hz), 128.2, 127.2 (q, \(J_{\text{CF}} = 27.4\) Hz), 124.9 (q, \(J_{\text{CF}} = 3.8\) Hz), 79.3, 65.0, 53.8, 44.0, 32.3, 28.2; \(R_f = 0.25\) (EtOAc); m.p. = 113–116°C; ESI-HRMS calcd for C\(_{16}\)H\(_{22}\)F\(_3\)N\(_2\)O\(_2\) [M + H]\(^+\) 331.1628, found 331.1625.

trans-Methyl 4-(3-(tert-butoxycarbonyl)amino)pyrrolidin-2-yl)benzoate (3.24b).

Purification by flash column chromatography (CH\(_2\)Cl\(_2\):MeOH 95:5) afforded 3.24b as a colorless oil (53 mg, 33%). IR (thin film): v 2982, 1713, 1276, 1262, 1170, 0909, 750 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl3): \(\delta\) 7.98 (d, \(J = 8.4\) Hz, 2H), 7.43 (d, \(J = 8.3\) Hz, 2H), 4.45–4.30 (m, 2H + NHBoc), 3.90 (s, 3H), 3.25 (ddd, \(J = 9.7, 8.6, 4.1\) Hz, 1H), 3.05 (dd, \(J = 8.7, 8.6\) Hz, 1H), 2.29 (dddd, \(J = 13.0, 8.7, 6.8, 4.1\) Hz, 1H), 1.81–1.73 (m, 1H + NH), 1.22 (s, 9H); \(^13\)C NMR (100 MHz, CDCl3): \(\delta\) 167.3, 155.3, 145.7, 129.5, 129.0, 127.7, 79.3, 64.8, 53.9, 52.2, 44.0, 32.4, 28.3; \(R_f = 0.24\) (CH\(_2\)Cl\(_2\):MeOH 95:5); ESI-HRMS calcd for C\(_{17}\)H\(_{25}\)N\(_2\)O\(_4\) [M + H]\(^+\) 321.1809, found 321.1807.

trans-tert-Butyl ((2S,3R)-2-(4-methyl-3-nitrophenyl)pyrrolidin-3-yl) carbamate (3.24c). Purification by flash column chromatography (CH\(_2\)Cl\(_2\):MeOH 95:5) afforded 3.24c as a colorless oil (37 mg, 26%). IR (thin film): v 3335, 2987, 2930, 1700, 1528, 1365, 1276, 1261, 1169, 750 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl3): \(\delta\) 8.03 (s, 1H), 7.48 (d, \(J = 7.9\) Hz, 1H), 7.26–7.21 (m, 1H), 4.55–4.43 (m, NHBoc), 4.40–4.25 (m, 2H), 3.32–3.19 (m, 1H), 3.13–2.97 (m, 1H), 2.56 (s, 3H), 2.39–2.21 (m, 1H), 1.86–1.74 (m, 1H), 1.67 (s, NH), 1.21 (s, 9H); \(^13\)C NMR (100 MHz, CDCl3): \(\delta\) 155.2, 149.2, 139.7, 132.7, 132.3, 132.2, 123.7, 79.4, 64.3, 53.8, 43.9, 32.0, 28.2,
20.2; $R_f = 0.27$ (CH$_2$Cl$_2$:MeOH 95:5); ESI-HRMS calcd for C$_{16}$H$_{24}$N$_3$O$_4$ [M + H]$^+$ 322.1761, found 322.1762.

**trans-tert-Butyl (2-(3-bromopyridin-4-yl)pyrrolidin-3-yl)carbamate (3.24d).** Purification by flash column chromatography (EtOAc) afforded **3.24d** as a colorless oil (32 mg, 19%). IR (thin film): $\nu$ 3426, 2979, 2931, 2851, 1645, 1365, 1252, 1168 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.63 (s, 1H), 8.47 (d, $J = 5.0$ Hz, 1H), 7.63–7.52 (m, 1H), 4.71–4.59 (m, 1H), 4.52–4.31 (m, 1H + NHBoc), 3.25 (ddd, $J = 9.5$, 8.2, 5.1 Hz, 1H), 3.14–2.95 (m, 1H), 2.36 (dddd, $J = 13.5$, 9.5, 7.2, 5.1 Hz, 1H), 1.87–1.74 (m, 1H), 1.59 (s, 1H), 1.27–1.23 (m, NH), 1.20 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.8, 151.5, 148.5, 148.0, 124.2, 122.9, 79.3, 64.4, 51.8, 43.7, 32.7, 28.2; $R_f = 0.27$ (CH$_2$Cl$_2$:MeOH 95:5); ESI-HRMS calcd for C$_{14}$H$_{21}$BrN$_3$O$_2$ [M + H]$^+$ 342.0812, found 342.0807.

**Benzyl 4-((tert-butoxycarbonyl)amino)-1,8-diazaspiro[4.5]decane-8-carboxylate (3.24e).** Purification by flash column chromatography (EtOAc:MeOH 9:1) afforded **3.24e** as a colorless oil (30 mg, 15%). IR (thin film): $\nu$ 3303, 2975, 2936, 1694, 1533, 1432, 1366, 1245, 1166, 1089, 1017, 911 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38–7.29 (m, 5H), 5.53 (br s, NHBoc), 5.12 (s, 2H), 4.09 (s, 1H), 3.77–3.33 (m, 4H), 3.23–3.12 (m, 1H), 3.12–3.00 (m, 1H), 2.38 (s, 1H), 1.82–1.63 (m, 3H), 1.63–1.50 (m, 2H), 1.43 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.7, 155.2, 136.9, 128.6, 128.1, 128.0, 79.8, 67.3, 63.9, 56.5, 41.5, 40.7, 33.8, 31.4, 30.1, 28.5; $R_f = 0.16$ (EtOAc:MeOH 9:1); ESI-HRMS calcd for C$_{21}$H$_{32}$N$_3$O$_4$ [M + H]$^+$ 390.2387, found 390.2393.
7.4 Experimental Section for Chapter 4

7.4.1 Preparation of Radical Clock SnAP and Reference SnAP Reagents

(1-(Tritylamino)cyclopropyl)methanol (4.4). Trityl chloride (3.35 g, 12.0 mmol, 1.05 equiv) in DMF (10 mL) was added dropwise to a solution of amino alcohol 4.3 (995 mg, 11.4 mmol, 1.00 equiv) and NEt₃ (1.75 mL, 12.5 mmol, 1.10 equiv) in DMF (65 mL) at 0°C. The resulting pale yellow suspension was warmed to 40°C and stirred for 18 h followed by the addition of H₂O (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H₂O (5 x 20 mL), brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to yield 4.4 (2.82 g, 75% yield) as colorless oil that is usually used without further purification in the next step. Purification by preparative TLC (hexanes:EtOAc 5:1) was performed to afford analytically pure material for characterization. IR (thin film): ν 3341, 3083, 3055, 2929, 2874, 1490, 1447, 1027 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.53–7.45 (m, 6H), 7.29–7.23 (m, 6H), 7.23–7.17 (m, 3H), 2.90 (br s, 1H), 2.33 (s, 2H), 1.58 (br s, 1H), 0.75–0.62 (m, 2H), 0.34–0.18 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 147.4, 129.1, 127.8, 126.6, 70.9, 68.3, 39.0, 13.0; Rf = 0.30 (hexanes:EtOAc 5:1); ESI-HRMS calcd for C₂₃H₂₃N₁Na₁O₁ [M + Na]⁺ 352.1672, found 352.1670.

1-(([(Tributylstannyl)methoxy]methyl)-N-tritylcyclopropan-1-amine (4.5). Sodium hydride (197 mg of a 60% suspension in mineral oil, 4.94 mmol, 1.30 equiv) was washed with pentane (3 x 3 mL) and suspended in DMF (20 mL). The suspension was cooled to 0°C and
Trtl-protected amino alcohol 4.4 (1.25 g, 3.80 mmol, 1.00 equiv) in DMF (5 mL) was added dropwise over 10 min. The resulting suspension was allowed to warm to rt. After 60 min, the reaction mixture was re-cooled to 0°C and tributyl(iodomethyl)stannane (1.96 g, 4.56 mmol, 1.20 equiv) was added dropwise over 10 min. The resulting suspension was allowed to warm to rt over 3 h and stirred at rt for 3 h. The reaction mixture was cooled to 0°C and slowly quenched with sat aq NH₄Cl (50 mL). EtOAc (30 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with H₂O (5 x 30 mL), brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexanes:EtOAc 100:0 to 97:3) recovered unreacted tributyl(iodomethyl)stannane and afforded Trtl-protected radical clock SnAP 4.5 (1.71 g, 71% yield) as a pale yellow oil.

IR (thin film): ν 3057, 2955, 2923, 2870, 2850, 1490, 1448, 1069 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.55–7.47 (m, 6H), 7.25–7.20 (m, 6H), 7.18–7.14 (m, 3H), 3.34 (s, 2H), 3.08 (br s, 1H), 1.99 (s, 2H), 1.50–1.40 (m, 6H), 1.29–1.22 (m, 6H), 0.91–0.79 (m, 15H), 0.70–0.62 (m, 2H), 0.20–0.15 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 147.9, 129.2, 127.6, 126.3, 80.9, 70.9, 61.7, 37.0, 29.3, 27.4, 13.9, 12.7, 9.2; Rf = 0.82 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C₃₆H₅₁N₁O₁Sn₁ [M + Na]⁺ 656.2892, found 656.2884.

1-(((Tributylstannyl)methoxy)methyl)cyclopropan-1-amine 4.6. Trtl-protected radical clock SnAP 4.5 (1.15 g, 1.82 mmol, 1.0 equiv) was dissolved in CH₂Cl₂:2,2,2-trifluoroethanol:AcOH (7:2:1 v/v, 37 mL) and stirred at rt for 4 h. The clear colorless solution was diluted with CH₂Cl₂ (50 mL) and slowly set to pH ~ 8 with sat aq NaHCO₃ (80 mL) at 0°C. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with H₂O (2 x 30 mL), brine (2 x 50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexanes:EtOAc 4:1) afforded radical clock SnAP M 4.6 (590 mg, 83% yield) as a pale yellow oil. IR (thin film): ν 3057, 2955, 2923, 2870, 2853, 1462, 1076 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.76 (s, 2H), 3.21 (s, 2H), 1.61 (br s, NH₂), 1.58–1.46 (m, 6H), 1.34–1.27 (m, 6H), 0.98–0.86 (m, 15H), 0.61–0.57 (m, 2H), 0.49–0.44 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 83.4, 62.4, 34.1, 29.3, 27.5, 13.9, 12.4, 9.3; Rf = 0.26 (hexanes:EtOAc 4:1); ESI-HRMS calcd for C₁₇H₃₈N₁O₁Sn₁ [M + H]⁺ 392.1973, found 392.1967.
(R)-N-((R)-1-((4-Methoxybenzyl)oxy)but-3-en-2-yl)-2-methylpropane-2-sulfinamide (4.10). Vinylmagnesium bromide (1.0 M in THF; 12.7 mL, 12.7 mmol, 3.00 equiv) was added dropwise to a solution of the sulfinyl imine 4.9 (1.20 g, 4.23 mmol, 1.00 equiv) in toluene (20 mL) at −78°C. The reaction mixture was stirred at this temperature for 3 h before being quenched at −78°C with sat aq NH₄Cl (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H₂O (2 x 15 mL), brine (2 x 30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexanes:EtOAc 4:1) afforded 4.10 (1.28 g, 97% yield) as a colorless oil. IR (thin film): ν 3433, 2979, 2957, 1644, 1613, 1514, 1249 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.28–7.22 (m, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.64 (ddd, J = 17.3, 10.3, 7.0 Hz, 1H), 5.33 (dt, J = 17.3, 1.2 Hz, 1H), 5.22 (dt, J = 10.3, 1.2 Hz, 1H), 4.52 (d, J = 11.6 Hz, 1H), 4.41 (d, J = 11.6 Hz, 1H), 4.13–4.04 (m, 1H), 3.83 (d, J = 3.5 Hz, 1H), 3.79 (s, 3H), 3.54 (dd, J = 9.7, 4.3 Hz, 1H), 3.43 (dd, J = 9.7, 8.0 Hz, 1H), 1.21 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 159.4, 135.8, 129.9, 129.6, 118.7, 114.0, 72.6, 72.4, 56.7, 55.6, 55.4, 22.7; Rᵣ = 0.30 (hexanes:EtOAc 4:1); ESI-HRMS calcd for C₁₆H₂₆N₂O₃S₁ [M + H]⁺ 312.1628, found 312.1624.

(R)-2-(Tritylamino)but-3-en-1-ol (4.12). Trityl chloride (1.29 g, 4.62 mmol, 1.20 equiv) in DMF (5 mL) was added dropwise to a solution of amino alcohol hydrochloride 4.11 (476 mg,
3.85 mmol, 1.00 equiv) and NEt₃ (1.18 mL, 8.48 mmol, 2.20 equiv) in DMF (8 mL) at 0°C. The resulting pale yellow suspension was warmed to rt and stirred for 18 h followed by the addition of H₂O (50 mL) and EtOAc (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H₂O (5 x 20 mL), brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to yield **4.12** (1.12 g, 88% yield) as colorless oil that is usually used without further purification in the next step. Purification by preparative TLC (hexanes:EtOAc 8:1) was performed to afford analytically pure material for characterization. IR (thin film): ν 3419, 3330, 3083, 3058, 3030, 2932, 1595, 1490, 1448 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.58 (d, J = 8.0 Hz, 6H), 7.33–7.25 (m, 6H), 7.24–7.17 (m, 3H), 5.57 (ddd, J = 17.1, 10.4, 6.5 Hz, 1H), 5.15 (dt, J = 17.1, 1.5 Hz, 1H), 5.01 (dt, J = 10.4, 1.5 Hz, 1H), 3.27 (q, J = 5.3 Hz, 1H), 3.19 (dd, J = 10.7, 4.1 Hz, 1H), 2.71 (dd, J = 10.7, 5.3 Hz, 1H), 1.92 (br s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 146.8, 139.7, 128.9, 127.9, 126.5, 115.7, 71.3, 64.6, 56.9; R_f = 0.14 (hexanes:EtOAc 5:1); ESI-HRMS calcd for C₂₃H₂₃N₁Na₁O₁ [M + Na]⁺ 352.1672, found 352.1667.

(R)-1-((Tributylstannyl)methoxy)-N-tritylbut-3-en-2-amine (4.13). Sodium hydride (80 mg of a 60% suspension in mineral oil, 1.97 mmol, 1.30 equiv) was washed with pentane (3 x 3 mL) and suspended in DMF (6 mL). The suspension was cooled to 0°C and Trtl-protected amino alcohol **4.12** (500 mg, 1.52 mmol, 1.00 equiv) in DMF (4 mL) was added dropwise over 10 min. The resulting suspension was allowed to warm to rt. After 60 min, the reaction mixture was re-cooled to 0°C and tributyl(iodomethyl)stannane (785 mg, 1.82 mmol, 1.20 equiv) was added dropwise over 5 min. The resulting suspension was allowed to warm to rt over 3 h and stirred at rt for 3 h. The reaction mixture was cooled to 0°C and slowly quenched with sat aq NH₄Cl (20 mL). EtOAc (20 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with H₂O (5 x 30 mL), brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexanes:EtOAc 40:1) recovered unreacted tributyl(iodomethyl)stannane and afforded Trtl-protected vinyl SnAP **4.13** (624 mg, 65% yield) as a pale yellow oil. IR (thin film): v 3433, 2955, 2924, 1638, 1085, 1456 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.58–7.53 (m, 6H), 7.26–7.23 (m, 6H), 7.20–7.12 (m, 3H), 5.68 (ddd, J = 17.1, 10.3, 6.8 Hz, 1H), 5.03 (ddd, J = 17.1, 1.9, 1.2 Hz, 1H), 4.86 (ddd, J = 10.3, 1.9, 1.2 Hz, 1H), 3.42–3.34 (m, 2H), 3.20–3.10 (m, 1H), 2.92 (dd, J = 8.9, 4.7 Hz, 1H), 2.46 (s, 1H), 2.27 (dd, J = 8.9, 4.7 Hz, 1H), 1.50–1.40 (m, 6H), 1.32–1.20 (m, 6H), 0.92–0.79 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 147.2, 140.8, 129.1, 127.8, 126.3, 113.9, 78.2, 71.2, 62.2, 55.7,
29.3, 27.4, 13.8, 9.1; R<sub>f</sub> = 0.80 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C<sub>36</sub>H<sub>52</sub>N<sub>2</sub>O<sub>2</sub>T<sub>1</sub> [M + H]<sup>+</sup> 634.3073, found 634.3070.

(R)-1-((Tributylstannyl)methoxy)but-3-en-2-amine (4.14). Trt-protected vinyl SnAP 4.13 (600 g, 0.95 mmol, 1.0 equiv) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>:2,2,2-trifluoroethanol:AcOH (7:2:1 v/v, 20 mL) and stirred at rt for 4 h. The clear colorless solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and slowly set to pH ~ 8 with sat aq NaHCO<sub>3</sub> (50 mL) at 0°C. The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The combined organic layers were washed with H<sub>2</sub>O (2 x 30 mL), brine (2 x 50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexanes:EtOAc 1:1) afforded vinyl SnAP M 4.14 (252 mg, 68% yield) as a colorless oil. IR (thin film): ν 3394, 3080, 2956, 2925, 2870, 1644, 1463, 1376, 1081 cm<sup>-1</sup>; 1<sup>H</sup>NMR (400 MHz, CDCl<sub>3</sub>): δ 5.80 (ddd, J = 17.3, 10.4, 6.2 Hz, 1H), 5.21 (dt, J = 17.3, 1.5 Hz, 1H), 5.08 (dt, J = 10.4, 1.5 Hz, 1H), 3.80 – 3.66 (m, 2H), 3.58 – 3.50 (m, 1H), 3.33 (dd, J = 9.0, 4.0 Hz, 1H), 3.16 (dd, J = 9.0, 7.8 Hz, 1H), 1.55 – 1.45 (m, 8H), 1.35 – 1.22 (m, 6H), 0.98 – 0.80 (m, 15H); 13<sup>C</sup>NMR (100 MHz, CDCl<sub>3</sub>): δ 139.6, 114.9, 80.5, 62.6, 53.9, 29.3, 27.4, 13.9, 9.2; R<sub>f</sub> = 0.20 (hexanes:EtOAc 1:1); ESI-HRMS calcd for C<sub>17</sub>H<sub>38</sub>N<sub>1</sub>O<sub>1</sub>T<sub>1</sub> [M + H]<sup>+</sup> 392.1973, found 392.1971.

1-((Tributylstannyl)methoxy)butan-2-amine (S4.1). Sodium hydride (80 mg of a 60% suspension in mineral oil, 1.97 mmol, 1.30 equiv) was washed with pentane (3 x 3 mL) and suspended in DMF (6 mL). The suspension was cooled to 0°C and 2-amino-1-butanol (144 μL, 1.52 mmol, 1.00 equiv) in DMF (4 mL) was added dropwise over 10 min. The resulting suspension was allowed to warm to rt. After 60 min, the reaction mixture was re-cooled to 0°C and tributyl(iodomethyl)stannane (785 mg, 1.82 mmol, 1.20 equiv) was added dropwise over 5 min. The resulting suspension was allowed to warm to rt over 3 h and stirred at rt for 3 h. The reaction mixture was cooled to 0°C and slowly quenched with sat aq NH<sub>4</sub>Cl (20 mL). EtOAc (20
mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with H₂O (5 x 30 mL), brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (EtOAc) afforded SnAP Et-M S4.1 (524 mg, 88% yield) as a pale yellow oil. IR (thin film): ν 2960, 2925, 2870, 2855, 1456, 1091 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.79–3.64 (m, 2H), 3.29 (dd, J = 9.0, 3.8 Hz, 1H), 3.09 (dd, J = 9.0, 7.7 Hz, 1H), 2.88–2.77 (m, 1H), 1.64–1.36 (m, 11H), 1.33–1.26 (m, 6H), 0.95–0.87 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 81.1, 62.5, 52.6, 29.3, 27.5, 27.2, 13.9, 10.7, 9.2; Rf = 0.12 (EtOAc); ESI-HRMS calcd for C₁₇H₄₀N₁O₁Sn₁ [M + H]+ 394.2126, found 394.2122.

1-(Ethoxymethyl)-N-tritylcyclopropan-1-amine (4.15). Sodium hydride (73 mg of a 60% suspension in mineral oil, 1.82 mmol, 1.50 equiv) was washed with pentane (3 x 3 mL) and suspended in DMF (6 mL). The suspension was cooled to 0°C and Trtl-protected amino alcohol 4.4 (400 mg, 1.21 mmol, 1.00 equiv) in DMF (2 mL) was added dropwise over 10 min. The resulting suspension was allowed to warm to rt. After 60 min, the reaction mixture was re-cooled to 0°C and ethyl iodide (117 μL, 1.46 mmol, 1.20 equiv) was added dropwise over 2 min. The resulting suspension was allowed to warm to rt over 3 h and stirred at rt for 3 h. The reaction mixture was cooled to 0°C and slowly quenched with sat aq NH₄Cl (20 mL). EtOAc (20 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with H₂O (5 x 30 mL), brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexanes:EtOAc 25:1) afforded 4.15 (312 mg, 72% yield) as a colorless oil. IR (thin film): ν 2984, 2940, 2908, 1742, 1373, 1240, 1046 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.58–7.50 (m, 6H), 7.28–7.17 (m, 9H), 3.12 (q, J = 7.0 Hz, 2H), 2.19 (s, 2H), 1.59 (br s, NH), 1.12 (t, J = 7.0 Hz, 3H), 0.73–0.64 (m, 2H), 0.30–0.16 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 147.8, 129.2, 127.6, 126.3, 76.1, 71.0, 65.9, 36.9, 15.3, 12.9; Rf = 0.38
hexanes:EtOAc 10:1); ESI-HRMS calcd for C_{25}H_{27}N_{1}Na_{1}O_{1} [M + Na]^+ 380.1985, found 380.1982.

1-(Ethoxymethyl)cyclopropan-1-amine (4.16). Trt-protected 4.15 (160 g, 0.45 mmol, 1.0 equiv) was dissolved in CH_2Cl_2:2,2,2-trifluoroethanol:AcOH (7:2:1 v/v, 9 mL) and stirred at rt for 4 h. The clear colorless solution was diluted with CH_2Cl_2 (50 mL) and slowly set to pH ~ 8 with sat aq NaHCO_3 (20 mL) at 0°C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with H_2O (2 x 30 mL), brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated affording 4.16 (19 mg, 36% yield) as a colorless oil. IR (thin film): ν 3340, 2980, 2885, 2870, 1740, 1232, 1044 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): δ 3.55 (q, J = 7.0 Hz, 2H), 3.38 (br s, NH_2), 2.66 (s, 2H), 1.26–1.20 (m, 3H), 0.88–0.83 (m, 2H), 0.61–0.54 (m, 2H); ^13C NMR (100 MHz, CDCl_3): δ 77.0, 66.6, 34.2, 15.3, 11.4; R_f = 0.14 (CH_2Cl_2:MeOH 95:5); ESI-HRMS calcd for C_6H_14N_1O_1 [M + H]^+ 116.1070, found 116.1067.

7.4.2 Radical Clock Experiments

To a solution of the amino tributylstannane – radical clock SnAP 4.6 (0.50 mmol, 1.00 equiv) in CH_2Cl_2 (2.5 mL) at rt was added 4-methyl-3-nitrobenzaldehyde (0.50 mmol, 1.00 equiv) and molecular sieves 4Å (ca. 50 mg). The reaction mixture was stirred at rt for 6 h and filtered through a short layer of Celite (CH_2Cl_2 rinse). The filtrate was concentrated under reduced pressure to afford the pure imine.

Separately, 2,6-lutidine (0.50 mmol, 1.00 equiv) was added in one portion to a suspension of HFIP (2.0 mL) and anhydrous Cu(OTf)_2 (0.50 mmol, 1.00 equiv) and stirred at rt for 1 h, during which time a homogeneous suspension was formed. A solution of the imine (0.50 mmol, 1.00 equiv) in CH_2Cl_2 (8.0 mL) was added in one portion and the resulting mixture was stirred at rt for 12 h. The reaction was quenched at rt with 10% aq NH_4OH (5 mL), and stirred vigorously for 15 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were washed with H_2O (3 x 5 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated affording the crude material.

The crude material was dissolved in MeOH (2.0 mL) and cooled to 0°C after which NaBH_4 (2.5 mmol, 5.0 equiv) was added in portions. The reaction mixture was stirred at rt for 6 h before quenched at rt with H_2O (5 mL). EtOAc (10mL) was added and the layers were separated after
which the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with H$_2$O (3 x 5 mL) and brine (10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated. Purification using flash column chromatography (hexanes:EtOAc 5:1) afforded the fragmented products **4.7** (2.5 mg, ca. 2% yield) and **4.8** (11.0 mg, 9% yield) as colorless oils.

![Structure of 4.7](image)

**(3R,5S)-3-Ethyl-5-(4-methyl-3-nitrophenyl)morpholine (4.7).** IR (thin film): ν 2963, 2932, 2878, 2848, 1528, 1454, 1349, 1105 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.03 (d, $J = 1.8$ Hz, 1H), 7.52 (dd, $J = 7.9$, 1.8 Hz, 1H), 7.29 (d, $J = 7.9$ Hz, 1H), 4.01 (dd, $J = 10.2$, 3.2 Hz, 1H), 3.84 (dd, $J = 10.9$, 3.0 Hz, 1H), 3.78 (dd, $J = 11.0$, 3.2 Hz, 1H), 3.28–3.14 (m, 2H), 2.96–2.85 (m, 1H), 2.56 (s, 3H), 1.89 (br s, NH), 1.50–1.27 (m, 2H), 0.94 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): 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 calcd for C$_{13}$H$_{19}$N$_2$O$_3$ [M + H]$^+$ 251.1390, found 251.1394.

![Structure of 4.8](image)

**(3S,5R)-3-(4-Methyl-3-nitrophenyl)-5-vinylmorpholine (4.8).** IR (thin film): ν 2988, 2849, 1738, 1528, 1275, 1261, 1102 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.06 (d, $J = 1.8$ Hz, 1H), 7.55 (dd, $J = 7.9$, 1.8 Hz, 1H), 7.30 (d, $J = 7.9$ Hz, 1H), 5.77 (ddd, $J = 17.3$, 10.4, 6.8 Hz, 1H), 5.35 (dt, $J = 17.3$, 1.4 Hz, 1H), 5.23–5.12 (m, 1H), 4.07 (dd, $J = 10.2$, 3.2 Hz, 1H), 3.81 (td, $J = 10.4$, 3.2 Hz, 2H), 3.65–3.50 (m, 1H), 3.33–3.19 (m, 2H), 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 calcd for C$_{13}$H$_{17}$N$_2$O$_3$ [M + H]$^+$ 249.1234, found 249.1231.

**Note:** The morpholines 4.7 and 4.8, which were detected and isolated in the radical clock experiment, were also prepared using SnAP 3-Et-M S4.1 and SnAP reagent 4.14 using the standard SnAP protocol described in chp. 7.2.3. The spectral characteristics of these morpholines were identical to those obtained in the radical clock experiment, confirming their structure.
7.4.3 Identification of Residual Tin Species

The reaction (0.5 mmol scale) was performed according to the standard procedure for the synthesis of substituted morpholines described in chp. 7.2.2. The crude product was dissolved in CH$_3$CN (50 mL) and washed with hexanes (5 x 5 mL). The combined hexanes layers were extracted with CH$_3$CN (3 x 2 mL) and concentrated to yield almost pure tributyl((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)stannane (S4.2; 175 mg, 77% yield) as pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 4.20 (hept, J = 6.2 Hz, 1H), 1.71–1.48 (m, 6H), 1.40–1.27 (m, 6H), 1.26–1.05 (m, 6H), 0.92 (t, J = 7.3 Hz, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 73.0, 27.6, 27.0, 15.9, 13.7; C–F carbons not observed. These spectral characteristics were identical to those previously reported.\textsuperscript{14}

The combined CH$_3$CN layers were concentrated under reduced pressure to afford an orange oil that was re-dissolved in MTBE (2-methoxy-2-methylpropane; 2 mL). HCl (4M in dioxane; 1 mL) was slowly added and the resulting solution was stirred at rt for 1 h. The mixture was concentrated under reduced pressure to obtain an orange solid that was triturated with pentane (3 x 3 mL) and MTBE (5 x 3 mL) to yield 3-(4-(trifluoromethyl)phenyl)morpholine hydrochloride (115 mg, 86% yield) as colorless solid.

7.5 Experimental Section for Chapter 5

SnAP M 5.1, and SnAP Pip 5.6 were prepared as described in chp. 7.2.2 and SnAP TM 5.3 was prepared according to a literature known procedure.¹⁵

7.5.1 Preparation of Morpholines, Thiomorpholines and Piperazines with SnAP Reagents and Substoichiometric Cu(OTf)₂.

GENERAL PROCEDURE FOR THE IMINE FORMATION: To a solution of the amino tributylstannane – SnAP reagent (0.50 mmol, 1.00 equiv) in CH₂Cl₂ (2.5 mL) at rt was added the corresponding aldehyde (0.50 mmol, 1.00 equiv) and molecular sieves 4Å (ca. 100 mg/mmol). The reaction mixture was stirred at rt for 2–6 h and filtered through a short layer of Celite (CH₂Cl₂ rinse). The filtrate was concentrated under reduced pressure to afford the pure imine.

PROCEDURE FOR MORPHOLINES: Separately, (±)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline) (0.05 mmol, 10 mol %) and anhydrous Cu(OTf)₂ (0.05 mmol, 10 mol %) were dissolved in HFIP (2 mL) and stirred at rt for 6 h, during which time a dark green suspension was formed. A solution of the imine (0.50 mmol, 1.00 equiv) in HFIP (3 mL) was added in one portion and the resulting mixture was stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (20mL), treated with a solution of 12% aq NH₄OH and brine (1:1, 5 mL), and stirred vigorously for 15 min at rt. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 2 mL). The combined organic layers were washed with H₂O (2 x 2 mL) and brine (5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography afforded the corresponding morpholine product.

PROCEDURE FOR THIOMORPHOLINES: Separately, (±)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline) (0.10 mmol, 20 mol %) and anhydrous Cu(OTf)₂ (0.10 mmol, 20 mol %) were dissolved in HFIP (4.0 mL) and stirred at rt for 6 h, during which time a dark green suspension was formed. A solution of the imine (0.50 mmol, 1.00 equiv) in HFIP (6.0 mL) was added in one portion and the resulting mixture was stirred at rt for 24 h. The reaction mixture was diluted with CH₂Cl₂ (30mL), treated with a solution of 12% aq NH₄OH and brine (1:1, 10 mL), and stirred vigorously for 15 min at rt. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 2 mL). The combined organic layers were washed with H₂O (2 x 2 mL) and brine (5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography afforded the corresponding thiomorpholine product.

PROCEDURE [A] FOR PIPERAZINES: Separately, anhydrous Cu(OTf)$_2$ (0.05 mmol, 10 mol %) was dissolved in CH$_3$CN:HFIP (1:2, 3.0 mL), 2,6-lutidine (0.05 mmol, 10 mol %) was added and the resulting bluish solution was stirred at room temperature for 5 h. A solution of the imine (0.50 mmol, 1.00 equiv) in HFIP (2.0 mL) was added in one portion and the resulting mixture was stirred at rt for 24 h. The reaction mixture was diluted with CH$_2$Cl$_2$ (20mL), treated with a solution of 12% aq NH$_4$OH and brine (1:1, 5 mL), and stirred vigorously for 15 min at rt. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 2 mL). The combined organic layers were washed with H$_2$O (2 x 2 mL) and brine (5 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. Purification by flash column chromatography afforded the corresponding piperazine product.

PROCEDURE [B] FOR PIPERAZINES: Separately, (±)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline) (0.05 mmol, 10 mol %) and anhydrous Cu(OTf)$_2$ (0.05 mmol, 10 mol %) were dissolved in TFE (2 mL) and stirred at rt for 6 h, during which time a dark green suspension was formed. A solution of the imine (0.50 mmol, 1.00 equiv) in TFE (3 mL) was added in one portion and the resulting mixture was stirred at rt for 24 h. The reaction mixture was diluted with CH$_2$Cl$_2$ (20mL), treated with a solution of 12% aq NH$_4$OH and brine (1:1, 5 mL), and stirred vigorously for 15 min at rt. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 2 mL). The combined organic layers were washed with H$_2$O (2 x 2 mL) and brine (5 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. Purification by flash column chromatography afforded the corresponding piperazine product.

PROBING ENANTIOSELECTIVITY USING (S)-PHBOX LIGAND: Separately, (S)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline) (0.10 mmol, 20 mol %) and anhydrous Cu(OTf)$_2$ (0.10 mmol, 20 mol %) were dissolved in HFIP (2.0 mL) and stirred at rt for 6 h, during which time a dark green suspension was formed. A solution of the imine (0.50 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (8.0 mL) was added in one portion and the resulting mixture was stirred at rt for 20 h. The reaction mixture was treated with a solution of 12% aq NH$_4$OH and brine (1:1, 10 mL), and stirred vigorously for 15 min at rt. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 2 mL). The combined organic layers were washed with H$_2$O (2 x 2 mL) and brine (5 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. Purification by flash column chromatography afforded the corresponding enantioenriched products.
Notes on the purification of substituted heterocycles (0.50 mmol scale)

- Column for flash Column chromatography: 20 mm column with ca. 8–9 cm silica gel.
- Sample loading: Dry loading on silica gel.
- Solvent: Appropriate solvent mixture with 0.1% Et$_3$N v/v.
- If desired, most of the tin byproducts can be removed before the flash column chromatography to simplify the purification by column chromatography and afford more pure heterocycles: the crude product was dissolved in acetonitrile and washed several times with a small amount of hexanes. The combined hexanes layers were extracted with a small amount of acetonitrile. The combined acetonitrile layers concentrated under reduced pressure to afford the crude product with much less tin residues compared to the original one.$^{16}$
- If desired, further purification could be carried out by salt formation of the N-heterocycle to remove any trace of tin impurities.

Additional information

- Cu(OTf)$_2$ from Strem used for the cyclization afforded the best results with various results and lower yields using Cu(OTf)$_2$ from other suppliers.
- Product heterocycles are detected by TLC in the unpurified reaction mixture using both, potassium permanganate and ninhydrin$^{17}$ stains. The product is visible with both developing agents. Using the ninhydrin stain, the products show up as pink/purple spots on TLC.

- Some of the aldehydes and imines are not soluble in CH$_2$Cl$_2$ (0.15 M) at rt, which is the standard condition for imine formation. In these cases, acetonitrile (0.15 M) was used as solvent.

17. 0.300 g Ninhydrin, 1.0 mL AcOH, 100 mL EtOH
The reaction is not very sensitive to oxygen or H₂O and can be conducted in standard glassware without degassed, extra dry solvents or without pre-dried Cu(OTf)₂ with only slightly diminished yields.

- The indicated time (6 h at room temperature) for the complex formation with Cu(OTf)₂ and racemic Phenyl BOX ligand in HFIP or TFE is crucial to obtain the active catalyst.

- The reactions should be kept below 30°C to prevent catalyst deactivation during the process of the reaction - heating is detrimental!

- 2,6-Lutidine is sometimes hard to separate from the desired heterocyclic products using flash column purification. Therefore, the unpurified reaction mixture can be adsorbed onto silica gel and put onto the high vacuum for a prolonged time to remove most of the 2,6-lutidine before the flash column chromatographic purification.

![Reaction Progress Images](Image)

**3-(4-Methoxyphenyl)morpholine (5.4a).** Purification by flash column chromatography (hexanes:EtOAc 1:3) afforded 5.4a (79 mg, 82% yield) as colorless solid. ¹H NMR (400 MHz, CDCl₃): δ 7.34–7.28 (m, 2H), 6.90–6.84 (m, 2H), 3.87 (dd, J = 10.2, 3.2 Hz, 2H), 3.82–3.75 (m, 4H), 3.64 (td, J = 11.1, 2.6 Hz, 1H), 3.37 (dd, J = 11.1, 10.2 Hz, 1H), 3.12 (td, J = 11.6, 3.2 Hz, 1H), 2.99 (dt, J = 11.6, 2.0 Hz 1H), 1.69 (br s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 159.3, 132.9, 128.4, 114.0, 73.9, 67.3, 60.1, 55.4, 46.8. These spectral characteristics were identical to those previously reported. To probe the enantioselectivity using enantiomerically pure (S)-PhBox, HFIP:CH₂Cl₂ (1:4, 0.05 M) was used as solvent instead of HFIP. The preparation of the catalyst

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(20 mol %) was carried out in HFIP and the imine was added as a solution in CH₂Cl₂. The absolute configuration was not determined. Chiral HPLC: column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: 4% iPrOH in hexane + 0.1 % Et₃N, flow: 1.00 mL/min; detection: 254 nm.

![Chromatogram](image1)

**3-(2-Methoxyphenyl)morpholine (5.4b).** 20 mol % Cu(OtF)₂ / rac. PhBox in HFIP (0.05M) was used. Purification by flash column chromatography (hexanes:EtOAc 1:3) afforded 5.4b (74 mg, 76% yield) as a colorless oil. IR (thin film): ν 3316, 2957, 2909, 2848, 1668, 1600, 1232, 1215, 1184, 1108, 1049 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.47 (dd, J = 7.5, 1.7 Hz, 1H), 7.26–7.21 (m, 1H), 6.99–6.92 (m, 1H), 6.86 (dd, J = 8.3, 1.0 Hz, 1H), 4.31 (dd, J = 9.6, 3.1 Hz, 1H), 3.94 (dd, J = 10.9, 3.1 Hz, 1H), 3.90–3.84 (m, 1H), 3.83 (s, 3H), 3.67–3.59 (m, 1H), 3.36 (dd, J = 10.9, 9.6 Hz, 1H), 3.18–3.10 (m, 1H), 3.04–2.97 (m, 1H), 2.16 (br s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 157.0, 128.7, 128.5, 127.5, 120.8, 110.4, 72.2, 67.5, 55.4, 54.2, 46.9; Rᵣ = 0.19 (hexanes:EtOAc 1:3); ESI-HRMS calcd for C₁₁H₁₆N₂O₂ [M + H]⁺ 216.0995, found 216.0996.

![Molecule](image2)

**3-(2-Chloro-4-fluorophenyl)morpholine (5.2).** Purification by flash column chromatography (hexanes:EtOAc 1:1) afforded 5.2 (83 mg, 77% yield) as a colorless oil. IR
(thin film): ν 3313, 2961, 2912, 2889, 2852, 1676, 1603, 1490, 1335, 1232, 1105 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.65 (dd, J = 8.6, 6.3 Hz, 1H), 7.09 (dd, J = 8.6, 2.6 Hz, 1H), 7.03–6.93 (m, 1H), 4.35 (dd, J = 9.6, 3.1 Hz, 1H), 3.91 (dd, J = 11.1, 3.1 Hz, 2H), 3.91–3.84 (m, 1H), 3.64 (ddd, J = 11.1, 2.6 Hz, 1H), 3.24 (dd, J = 11.1, 9.6 Hz, 1H), 3.15 (ddd, J = 11.1, 3.1 Hz, 1H), 3.07–2.93 (m, 1H), 1.78 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 161.8 (d, J$_{CF}$ = 249.4 Hz), 134.0 (d, J$_{CF}$ = 3.4 Hz), 133.8 (d, J$_{CF}$ = 10.1 Hz), 129.7 (d, J$_{CF}$ = 8.6 Hz), 116.9 (d, J$_{CF}$ = 24.7 Hz), 114.4 (d, J$_{CF}$ = 20.7 Hz), 71.9, 67.4, 56.0, 46.6; R$_f$ = 0.19 (hexanes:EtOAc 1:1); ESI-HRMS calcd for C$_{10}$H$_{12}$Cl$_1$F$_1$N$_1$O$_1$ [M + H]$^+$ 216.0586, found 216.0582.

3-(3-Nitrophenyl)morpholine (5.4c). Purification by flash column chromatography (hexanes:EtOAc 1:1) afforded 5.4c (83 mg, 80% yield) as a colorless oil. IR (thin film): ν 2957, 2911, 2851, 1666, 1527, 1353, 1106 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.36–8.26 (m, 1H), 8.14 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.51 (dd, J = 7.8 Hz, 1H), 4.05 (dd, J = 10.0, 3.2 Hz, 1H), 3.93–3.87 (m, 1H), 3.84 (dd, J = 11.2, 3.2 Hz, 1H), 3.67 (ddd, J = 11.2, 2.7 Hz, 1H), 3.37 (dd, J = 11.2, 10.0 Hz, 1H), 3.15 (ddd, J = 11.4, 3.2 Hz, 1H), 3.07–2.97 (m, 1H), 1.77 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 148.6, 143.0, 133.6, 129.6, 123.0, 122.4, 73.4, 67.3, 59.8, 46.3; R$_f$ = 0.13 (hexanes:EtOAc 1:1); ESI-HRMS calcd for C$_{10}$H$_{13}$N$_2$O$_3$ [M + H]$^+$ 209.0921, found 209.0917.

3-(Pyridin-2-yl)morpholine (5.4d). 20mol% Cu(OTf)$_2$ / rac. PhBox in HFIP (0.05M) was used. Purification by flash column chromatography (EtOAc:MeOH 9:1) afforded 5.4d (55 mg, 68% yield) as a colorless oil. IR (thin film): ν 3274, 2956, 2922, 2852, 1670, 1592, 1435, 1206, 1106 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.57 (d, J = 4.7 Hz, 1H), 7.72–7.64 (m, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.24–7.18 (m, 1H), 4.15 (d, J = 9.6 Hz, 1H), 4.08 (d, J = 11.4 Hz, 1H), 3.92 (d, J = 11.4 Hz, 1H), 3.72–3.63 (m, 1H), 3.62–3.54 (m, 1H), 3.22–3.13 (m, 1H), 3.10 (d, J = 12.4 Hz, 1H), 2.00 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 158.4, 149.6, 136.9, 122.9, 121.8, 72.0, 67.2, 60.2, 45.5; R$_f$ = 0.16 (EtOAc:MeOH 9:1); ESI-HRMS calcd for C$_9$H$_{13}$N$_2$O$_1$ [M + H]$^+$ 165.1022, found 165.1024.
3-(Pyridin-3-yl)morpholine (5.4e). 20mol% Cu(OTf)$_2$ / rac. PhBox in HFIP (0.05M) was used. Purification by flash column chromatography (EtOAc:MeOH 9:1) afforded 5.4e (63 mg, 77% yield) as a colorless oil. IR (thin film): ν 3276, 2955, 2913, 2850, 1646, 1577, 1424, 1107 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.65 (d, $J = 2.2$ Hz, 1H), 8.56 (dd, $J = 4.8$, 1.7 Hz, 1H), 7.80–7.73 (m, 1H), 7.30–7.29 (m, 1H), 3.99 (dd, $J = 10.0$, 3.2 Hz, 1H), 3.91 (d, $J = 11.2$ Hz, 1H), 3.84 (dd, $J = 11.2$, 3.2 Hz, 1H), 3.73–3.65 (m, 1H), 3.42 (dd, $J = 11.2$, 10.0 Hz, 1H), 3.20–3.12 (m, 1H), 3.06–3.01 (m, 1H), 1.73 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 149.5, 149.2, 136.1, 134.9, 123.6, 73.5, 67.3, 58.3, 46.5; R$_f$ = 0.19 (EtOAc:MeOH 9:1); ESI-HRMS calcd for C$_9$H$_{13}$N$_2$O$_1$ [M + H]$^+$ 165.1022, found 165.1023.

3-(Thiophen-3-yl)morpholine (5.4f). Purification by flash column chromatography (hexanes:EtOAc 1:6) afforded 5.4f (62 mg, 73% yield) as a colorless oil. IR (thin film): ν 3101, 2956, 2889, 2850, 1669, 1449, 1320, 1104 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.29 (dd, $J = 5.0$, 3.0 Hz, 1H), 7.24–7.21 (m, 1H), 7.07 (dd, $J = 5.0$, 1.3 Hz, 1H), 4.05 (dd, $J = 9.9$, 3.2 Hz, 1H), 3.89 (dd, $J = 11.0$, 3.2 Hz, 1H), 3.89–3.82 (m, 1H), 3.63 (dd, $J = 11.0$, 2.8 Hz, 1H), 3.41 (dd, $J = 11.0$, 9.9 Hz, 1H), 3.10 (dd, $J = 11.5$, 11.0, 3.2 Hz, 1H), 3.02–2.93 (m, 1H), 1.82 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 141.8, 126.5, 126.0, 121.5, 73.2, 67.5, 56.3, 46.6; R$_f$ = 0.14 (hexanes:EtOAc 1:6); ESI-HRMS calcd for C$_8$H$_{12}$N$_1$O$_1$S$_1$ [M + H]$^+$ 170.0634, found 170.0632.

3-(4-(1H-1,2,4-Triazol-1-yl)phenyl)morpholine (5.4g). Purification by flash column chromatography (EtOAc:MeOH 9:1) afforded 5.4g (72 mg, 63% yield) as a colorless solid. IR (thin film): ν 3309, 3115, 2956, 2914, 2851, 1522, 1279, 1102 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.54 (s, 1H), 8.09 (s, 1H), 7.64 (d, $J = 8.6$ Hz, 2H), 7.54 (d, $J = 8.6$ Hz, 2H), 3.99 (dd, $J = 10.0$, 3.2 Hz, 1H), 3.95–3.74 (m, 2H), 3.71–3.60 (m, 1H), 3.43–3.32 (m, 1H), 3.24–3.08 (m, 1H), 3.02 (d, $J = 11.7$ Hz, 1H), 2.03 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 152.8, 141.0, 136.6, 128.7, 120.3, 73.6, 67.3, 60.0, 46.5; R$_f$ = 0.21 (EtOAc:MeOH 9:1); m.p. = 116–119°C;
ESI-HRMS calcd for C$_{12}$H$_{15}$N$_2$O$_1$ [M + H]$^+$ 231.1240, found 231.1239.

![Diagram](image)

3-(1-Methyl-1H-pyrazol-4-yl)morpholine (5.4h). 20mol% Cu(OTf)$_2$ / rac. PhBox in HFIP (0.05M) was used. Purification by flash column chromatography (EtOAc:MeOH 85:15) afforded 5.4h (51 mg, 62% yield) as a colorless oil. IR (thin film): ν 3297, 2950, 2851, 1679, 1651, 1447, 1104 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.43 (s, 1H), 7.33 (s, 1H), 3.91 (dd, J = 9.8, 3.2 Hz, 1H), 3.87 (s, 3H), 3.86–3.80 (m, 2H), 3.65–3.57 (m, 1H), 3.38 (dd, J = 11.1, 9.8 Hz, 1H), 3.11–3.02 (m, 1H), 2.99–2.90 (m, 1H), 1.70 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 137.7, 128.1, 121.6, 73.5, 67.5, 51.8, 46.4, 39.1; R$_f$ = 0.12 (EtOAc:MeOH 85:15); ESI-HRMS calcd for C$_8$H$_{13}$N$_3$O$_1$ [M + H]$^+$ 168.1131, found 168.1130.

![Diagram](image)

3-(5-Methylisoxazol-3-yl)morpholine (5.4i). Purification by flash column chromatography (EtOAc) afforded 5.4i (56 mg, 67% yield) as colorless solid. IR (thin film): ν 3314, 2959, 2916, 2853, 1605, 1455, 1107 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 5.99 (d, J = 0.9 Hz, 1H), 4.10 (dd, J = 9.3, 3.3 Hz, 1H), 3.96 (dd, J = 11.1, 3.3 Hz, 1H), 3.89–3.80 (m, 1H), 3.66–3.59 (m, 1H), 3.55 (dd, J = 11.1, 9.3 Hz, 1H), 3.10–3.01 (m, 1H), 3.01–2.93 (m, 1H), 2.40 (d, J = 0.9 Hz, 3H), 2.07 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 169.8, 163.4, 100.1, 71.0, 67.6, 52.2, 45.6, 12.4; R$_f$ = 0.15 (EtOAc); m.p. = 50–52°C; ESI-HRMS calcd for C$_8$H$_{13}$N$_2$O$_2$ [M + H]$^+$ 169.0972, found 169.0972.

![Diagram](image)

Ethyl morpholine-3-carboxylate (5.4j). Purification by flash column chromatography (hexanes:EtOAc 1:6) afforded 5.4j (48 mg, 60% yield) as a colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$): δ 4.20 (q, J = 7.1 Hz, 2H), 3.99 (dd, J = 11.2, 3.2 Hz, 1H), 3.80–3.68 (m, 2H), 3.59 (ddd, J = 11.1, 7.9, 2.9 Hz, 1H), 3.53 (dd, J = 7.2, 3.5 Hz, 1H), 3.02 (ddd, J = 12.2, 4.9, 2.9 Hz, 1H), 2.86 (ddd, J = 12.2, 8.0, 3.2 Hz, 1H), 1.95 (br s, NH), 1.27 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 171.4, 68.6, 63.8, 61.3, 57.0, 44.4, 14.3. These spectral characteristics were identical to those previously reported. To probe the enantioselectivity using enantiomerically pure (S)-PhBox, HFIP:CH$_2$Cl$_2$ (1:4, 0.05 M) was used as solvent instead of...
HFIP. The preparation of the catalyst (20 mol %) was carried out in HFIP and the imine was added as a solution in CH$_2$Cl$_2$. The absolute configuration was not determined. Chiral HPLC: column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: 10% iPrOH in hexane + 0.1 % Et$_3$N, flow: 1.00 mL/min; detection: 254 nm.

**Benzyl 4-(morpholin-3-ylmethyl)piperidine-1-carboxylate (5.4k).** Purification by flash column chromatography (EtOAc:MeOH 4:1) afforded 5.4k (51 mg, 32% yield) as a colorless oil. IR (thin film): ν 2953, 2925, 2854, 1683, 1436, 1203, 1134 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41–7.27 (m, 5H), 5.12 (s, 2H), 4.17 (s, 2H), 3.86–3.78 (m, 1H), 3.76 (dd, $J = 11.3, 3.0$ Hz, 1H), 3.55–3.42 (m, 1H), 3.18–3.07 (m, 1H), 3.02–2.93 (m, 1H), 2.92–2.84 (m, 2H), 2.84–2.69 (m, 2H), 1.91 (br s, NH), 1.77–1.60 (m, 2H), 1.60–1.47 (m, 1H), 1.27–1.10 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.4, 137.1, 128.6, 128.1, 128.0, 73.1, 67.8, 67.1, 52.0, 46.2, 44.3, 44.2, 39.3, 32.8, 32.1, 29.9; R$_f$ = 0.09 (EtOAc:MeOH 9:1); ESI-HRMS calcd for C$_{18}$H$_{27}$N$_2$O$_3$ [M + H]$^+$ 319.2016, found 319.2019.
(S)-3-Phenylmorpholine (5.14). Purification by flash column chromatography (hexanes:EtOAc:MeOH 20:20:1) afforded 5.14 (56 mg, 68% yield) as a colorless solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42–7.36 (m, 2H), 7.36–7.30 (m, 2H), 7.30–7.24 (m, 1H), 3.92 (dd, $J = 10.1, 3.2$ Hz, 1H), 3.91–3.85 (m, 1H), 3.82 (dd, $J = 11.1, 3.2$ Hz, 1H), 3.66 (td, $J = 11.1, 2.7$ Hz, 1H), 3.40 (dd, $J = 11.1, 10.1$ Hz, 1H), 3.13 (td, $J = 11.7, 3.2$ Hz, 1H), 3.03–2.97 (m, 1H), 1.83 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 140.7, 128.6, 127.9, 127.3, 73.8, 67.4, 60.7, 46.8. These spectral characteristics were identical to those previously reported.\textsuperscript{18} Chiral HPLC: column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: 4% iPrOH in hexane + 0.1 % Et$_3$N, flow: 0.80 mL/min; detection: 254 nm.
3-(o-Tolyl)morpholine (5.15). Purification by flash column chromatography (Hexanes:EtOAc 1:2) afforded 5.15 (63 mg, 71% yield) as a colorless oil. IR (thin film): ν 3319, 2956, 2925, 2852, 1459, 1334, 1108, 756 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.58 (dd, J = 7.3, 1.6 Hz, 1H), 7.24–7.11 (m, 3H), 4.15 (dd, J = 9.9, 3.0 Hz, 1H), 3.92–3.84 (m, 1H), 3.81 (dd, J = 11.1, 3.0 Hz, 1H), 3.72–3.62 (m, 1H), 3.34 (dd, J = 11.1, 9.9 Hz, 1H), 3.22–3.10 (m, 1H), 3.07–2.98 (m, 1H), 2.39 (s, 3H), 1.70 (br s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 138.6, 135.6, 130.5, 127.4, 126.7, 126.4, 72.6, 67.5, 56.9, 47.1, 19.4; Rₚ = 0.18 (Hexanes:EtOAc 1:2); ESI-HRMS calcd for C₁₇H₁₈N₂O₁ [M + H]+ 178.1226, found 178.1225. To probe the enantioselectivity using enantiomerically pure (S)-PhBox, HFIP:CH₂Cl₂ (1:4, 0.05 M) was used as solvent instead of HFIP. The preparation of the catalyst (20 mol %) was carried out in HFIP and the imine was added as a solution in CH₂Cl₂. The absolute configuration was not determined. Chiral HPLC: column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: 8% iPrOH in hexane + 0.1 % Et₃N, flow: 0.8 mL/min; detection: 254 nm.

3-(4-Methoxyphenyl)thiomorpholine (5.5a). Purification by flash column chromatography (hexanes:EtOAc 3:1) afforded 5.5a (65 mg, 62% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.27 (dd, J = 8.8, 2.5 Hz, 2H), 6.86 (dd, J = 8.8, 2.5 Hz, 2H), 3.87
(dd, J = 10.5, 2.2 Hz, 1H), 3.79 (s, 3H), 3.44–3.42 (m, 1H), 3.18–3.15 (m, 1H), 2.91–2.87 (m, 1H), 2.81 (dd, J = 13.1, 10.5 Hz, 1H), 2.47–2.39 (m, 2H), 1.79 (br s, NH); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.2, 136.7, 127.8, 114.0, 62.5, 55.4, 49.4, 35.0, 27.6. These spectral characteristics were mostly identical to those previously reported.$^1$

$N$-$(4$-(Thiomorpholin-3-yl)phenyl)acetamide (5.5b). Purification by flash column chromatography (EtOAc) afforded 5.5b (58 mg, 49% yield) as pale yellow solid. IR (thin film): ν 3299, 3190, 3118, 3056, 2913, 2819, 1667, 1601, 1538, 1515, 1411, 1315 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.45 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.15 (br s, NH), 3.90 (dd, J = 10.5, 1.7 Hz, 1H), 3.48–3.40 (m, 1H), 3.22–3.10 (m, 1H), 2.94–2.84 (m, 1H), 2.80 (dd, J = 13.4, 10.5 Hz, 1H), 2.48–2.39 (m, 2H), 2.17 (s, 3H), 1.67 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 168.3, 140.4, 137.4, 127.3, 120.2, 62.6, 49.3, 35.0, 27.6, 24.8; R$_f$ = 0.17 (EtOAc); m.p. = 156–159$^\circ$C; ESI-HRMS calcd for C$_{12}$H$_{17}$N$_2$O$_3$S$_1$ [M + H]$^+$ 237.1056, found 237.1058.

3-(2-Bromophenyl)thiomorpholine (5.5c). Purification by flash column chromatography (hexanes:EtOAc 4:1) afforded 5.5c (61 mg, 47% yield) as a colorless oil. IR (thin film): ν 3290, 2907, 2831, 2802, 1654, 1467, 1438, 1293, 1120, 1022, 986 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.59–7.51 (m, 2H), 7.34–7.28 (m, 1H), 7.16–7.09 (m, 1H), 4.34 (dd, J = 9.9, 2.7 Hz, 1H), 3.51–3.41 (m, 1H), 3.27–3.17 (m, 1H), 2.96–2.87 (m, 1H), 2.70 (dd, J = 13.0, 9.9 Hz, 1H), 2.66–2.60 (m, 1H), 2.49–2.42 (m, 1H), 1.77 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 142.9, 133.1, 129.1, 128.0, 127.8, 123.3, 61.4, 49.4, 33.4, 27.7; R$_f$ = 0.41 (hexanes:EtOAc 1:1); ESI-HRMS calcd for C$_{10}$H$_{13}$Br$_1$N$_1$S$_1$ [M + H]$^+$ 257.9947, found 257.9945.

3-(Thiomorpholin-3-yl)benzonitrile (5.5d). Purification by flash column chromatography (hexanes:EtOAc 3:2) afforded 5.5d (48 mg, 47% yield) as a colorless oil. IR (thin film): ν 3323, 2908, 2827, 2341, 1479, 1416, 1311, 1292, 1121 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.70 (s, 1H), 7.64–7.59 (m, 1H), 7.59–7.54 (m, 1H), 7.47–7.40 (m, 1H), 3.98 (dd, J =
10.6, 2.3 Hz, 1H), 3.49–3.41 (m, 1H), 3.22–3.11 (m, 1H), 2.96–2.84 (m, 1H), 2.77 (dd, J = 13.3, 10.6 Hz, 1H), 2.50–2.40 (m, 2H), 1.74 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 145.8, 131.6, 131.3, 130.5, 129.6, 118.8, 112.9, 62.2, 49.0, 35.0, 27.5; $R_f = 0.18$ (hexanes:EtOAc 3:2); ESI-HRMS calcd for C$_{11}$H$_{13}$N$_2$S$_1$ [M + H]$^+$ 205.0794, found 205.0797.

3-(4-(Trifluoromethyl)phenyl)thiomorpholine (5.5e). Purification by flash column chromatography (hexanes:EtOAc 4:1) afforded 5.5e (82 mg, 66% yield) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 4.00 (dd, J = 10.5, 2.2 Hz, 1H), 3.47–3.45 (m, 1H), 3.20–3.17 (m, 1H), 2.91 (dd, J = 13.3, 11.7, 3.2 Hz, 1H), 2.80 (dd, J = 13.3, 10.5 Hz, 1H), 2.51–2.40 (m, 2H), 1.76 (br s, NH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 148.2, 130.1 (q, $J_{CF} = 32.3$ Hz), 127.1, 125.7 (q, $J_{CF} = 3.8$ Hz), 124.2 (q, $J_{CF} = 273.3$ Hz), 62.6, 49.1, 35.0, 27.6. These spectral characteristics were mostly identical to those previously reported.$^1$ To probe the enantioselectivity using enantiomerically pure (S)-PhBox, HFIP:CH$_2$Cl$_2$ (1:4, 0.05 M) was used as solvent instead of HFIP. The preparation of the catalyst (20 mol %) was carried out in HFIP and the imine was added as a solution in CH$_2$Cl$_2$. The absolute configuration was not determined. Chiral HPLC: column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: 10% iPrOH in hexane + 0.1 % Et$_3$N, flow: 0.8 mL/min; detection: 254 nm.

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3-(Pyridin-4-yl)thiomorpholine (5.5f). Purification by flash column chromatography (hexanes:EtOAc 1:3) afforded 5.5f (52 mg, 58% yield) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.55 (dd, $J = 4.4$, 1.6 Hz, 2H), 7.28 (dd, $J = 4.4$, 1.6 Hz, 2H), 3.94 (dd, $J = 10.5$, 2.6 Hz, 1H), 3.46–3.44 (m, 1H), 3.17–3.14 (m, 1H), 2.90–2.87 (m, 1H), 2.76 (dd, $J = 13.0$, 10.5 Hz, 1H), 2.53–2.40 (m, 2H), 1.97 (br s, NH); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 152.5, 150.2, 121.7, 61.7, 48.7, 34.6, 27.5. These spectral characteristics were mostly identical to those previously reported.$^1$

3-(Quinolin-2-yl)thiomorpholine (5.5g). Purification by flash column chromatography (EtOAc) afforded 5.5g (49 mg, 43% yield) as pale yellow oil. IR (thin film): ν 3298, 3057, 2908, 2846, 1670, 1598, 1503, 1426, 1308, 1117 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.14 (d, $J = 8.5$ Hz, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.80 (d, $J = 8.1$ Hz, 1H), 7.70 (ddd, $J = 8.4$, 6.9, 1.4 Hz, 1H), 7.52 (ddd, $J = 8.1$, 6.9, 1.4 Hz, 1H), 7.45 (d, $J = 8.5$ Hz, 1H), 4.30 (dd, $J = 10.5$, 2.5 Hz, 1H), 3.61–3.52 (m, 1H), 3.26 (ddd, $J = 12.7$, 11.8, 2.5 Hz, 1H), 3.01–2.86 (m, 2H), 2.82–2.73 (m, 1H), 2.51–2.42 (m, 1H), 2.02 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 161.9, 147.8, 137.0, 129.7, 129.5, 127.7, 127.6, 126.5, 119.3, 63.2, 48.3, 33.3, 27.7; R$_t$ = 0.17 (EtOAc); ESI-HRMS calcd for C$_{13}$H$_{15}$N$_2$S$_1$ [M + H]$^+$ 231.0950, found 231.0951.

3-(1-Methyl-1H-benzo[d]imidazol-2-yl)thiomorpholine (5.5h). Purification by flash column chromatography (EtOAc) afforded 5.5h (67 mg, 57% yield) as a colorless oil. IR (thin film): ν 2920, 2849, 1653, 1472, 1458, 1281 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.76–7.70 (m, 1H), 7.36–7.32 (m, 1H), 7.32–7.24 (m, 2H), 4.36 (dd, $J = 10.8$, 2.5 Hz, 1H), 3.85 (s, 3H), 3.56–3.48 (m, 1H), 3.26–3.15 (m, 2H), 2.82 (ddd, $J = 13.4$, 12.0, 3.1 Hz, 1H), 2.74–2.67 (m, 1H), 2.46–2.39 (m, 1H), 1.59 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.7, 142.3, 135.9, 122.9, 122.3, 119.8, 109.4, 54.5, 48.0, 31.3, 30.1, 27.7; R$_t$ = 0.14 (EtOAc); ESI-HRMS calcd for C$_{12}$H$_{18}$N$_2$S$_1$ [M + H]$^+$ 234.1059, found 234.1060.
**Ethyl thiomorpholine-3-carboxylate (5.5i).** Purification by flash column chromatography (hexanes:EtOAc 1:1) afforded 5.5i (47 mg, 54% yield) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.20 (q, \(J = 7.1\) Hz, 2H), 3.64 (dd, \(J = 9.0, 3.0\) Hz, 1H), 3.38--3.35 (m, 1H), 3.02 (ddd, \(J = 10.9, 10.2, 2.6\) Hz, 1H), 2.90--2.72 (m, 2H), 2.67 (ddd, \(J = 13.0, 10.2, 2.6\) Hz, 1H), 2.50--2.39 (m, 1H), 1.98 (br s, NH), 1.28 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 171.7, 61.4, 58.8, 47.0, 29.7, 27.7, 14.3. These spectral characteristics were mostly identical to those previously reported.\(^1\)

**3-Isopropylthiomorpholine (5.5j).** Purification by flash column chromatography (EtOAc) afforded 5.5j (32 mg, 44% yield) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.40--3.36 (m, 1H), 3.02--2.98 (m, 1H), 2.79--2.66 (m, 1H), 2.59--2.55 (m, 1H), 2.50--2.48 (m, 1H), 2.43--2.41 (m, 1H), 2.35 (d, \(J = 13.2\) Hz, 1H), 1.59 (m, 1H + NH), 0.92 (t, \(J = 6.1\) Hz, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 63.3, 49.0, 33.5, 30.5, 28.1, 18.8, 18.7. These spectral characteristics were mostly identical to those previously reported.\(^1\)

**tert-Butyl 3-(4-methoxyphenyl)piperazine-1-carboxylate (5.7a).** Purification by flash column chromatography (hexanes:EtOAc 1:1) afforded 5.7a (103 mg, 71% yield) as a colorless solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.35--7.29 (m, 2H), 6.90--6.58 (m, 2H), 4.03 (br s, 2H), 3.80 (s, 3H), 3.64 (dd, \(J = 10.5, 2.5\) Hz, 1H), 3.09--3.00 (m, 1H), 2.95--2.80 (m, 2H), 2.71 (br s, 1H), 1.76 (br s, NH), 1.46 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.3, 154.9, 133.9, 128.2, 114.0, 79.8, 59.8, 55.4, 51.3, 46.3, 44.0, 28.6. These spectral characteristics were identical to those previously reported.\(^1\)
**tert-Butyl 3-(4-hydroxyphenyl)piperazine-1-carboxylate (5.7b).** Purification by flash column chromatography (EtOAc) afforded 5.7b (107 mg, 77% yield) as a pale yellow oil. IR (thin film): ν 3286, 2977, 2928, 2858, 1675, 1614, 1518, 1426, 1270, 1252, 1169, 1130 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.25–7.09 (m, 2H), 6.81–6.68 (m, 2H), 4.03 (s, 2H), 3.62 (dd,  J = 10.7, 3.1 Hz, 1H), 3.11–3.02 (m, 1H), 2.99–2.82 (m, 2H), 2.81–2.53 (m, 1H), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 155.9, 155.1, 132.9, 128.3, 115.7, 80.2, 59.8, 51.0, 46.2, 43.8, 28.6;  Rᵣ = 0.16 (EtOAc); ESI-HRMS calcd for C₁₅H₂₃N₂O₃ [M + H]⁺ 279.1703, found 279.1700.

**tert-Butyl 3-(2-chloro-4-fluorophenyl)piperazine-1-carboxylate (5.7c).** Purification by flash column chromatography (hexanes:TBME 1:1) afforded 5.7c (120 mg, 76% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.70–7.54 (m, 1H), 7.11 (dd,  J = 8.5, 2.6 Hz, 1H), 6.99 (dd,  J = 8.5, 2.6 Hz, 1H), 4.32–3.92 (m, 3H), 3.13–3.02 (m, 1H), 2.99–2.82 (m, 2H), 2.58 (dd,  J = 12.7, 10.2 Hz, 1H), 1.73 (br s, NH), 1.47 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 161.8 (d,  J_CF = 249.7 Hz), 154.8, 134.9 (d,  J_CF = 3.5 Hz), 133.7 (d,  J_CF = 11.7 Hz), 129.2 (d,  J_CF = 8.7 Hz), 117.0 (d,  J_CF = 24.6 Hz), 114.4 (d,  J_CF = 20.7 Hz), 80.0, 56.0, 50.2, 46.2, 43.5, 28.6. These spectral characteristics were identical to those previously reported.¹⁸

**tert-Butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate (5.7d).** Purification by recrystallization (hexanes:CH₂Cl₂) afforded 5.7d (110 mg, 57% yield) as a colorless solid. IR (thin film): ν 3481, 3324, 2978, 2930, 2858, 2824, 1696, 1613, 1401, 1362, 1266, 1169, 1090 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.79 (d,  J = 7.8 Hz, 2H), 7.42 (d,  J = 7.8 Hz, 2H), 4.05 (br s, 2H), 3.77–3.64 (m, 1H), 3.13–3.02 (m, 1H), 2.98–2.83 (m, 2H), 2.73 (br s, 1H), 1.59 (br s, NH), 1.46 (s, 9H), 1.34 (s, 12H); ¹³C NMR (100 MHz,
CDCl$_3$): δ 154.9, 144.7, 135.2, 128.8, 126.5, 84.0, 79.9, 60.6, 50.9, 46.2, 43.7, 28.6, 25.0; R$_f$ = 0.32 (hexanes:EtOAc 1:1); m.p. = 135–138°C; ESI-HRMS calcd for C$_{21}$H$_{34}$BN$_2$O$_4$ [M + H]$^+$ 389.2606, found 389.2606.

**tert-Butyl 3-(pyridin-2-yl)piperazine-1-carboxylate (5.7e).** Purification by flash column chromatography (EtOAc:MeOH 9:1) afforded 5.7e (100 mg, 76% yield) as a colorless oil. IR (thin film): ν 3312, 2973, 2957, 2926, 2854, 1692, 1419, 1247, 1171, 1125 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.62–8.53 (m, 1H), 7.72–7.60 (m, 1H), 7.34 (d, J = 6.6 Hz, 1H), 7.23–7.16 (m, 1H), 4.20 (s, 1H), 4.01 (s, 1H), 3.86 (dd, J = 10.4, 3.3 Hz, 1H), 3.14–3.03 (m, 1H), 2.95–2.81 (m, 3H), 1.87 (br s, NH), 1.47 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 160.0, 154.9, 149.5, 136.8, 122.7, 121.6, 80.0, 60.2, 49.9, 45.5, 44.3, 28.6; R$_f$ = 0.21 (EtOAc:MeOH 9:1); ESI-HRMS calcd for C$_{14}$H$_{22}$N$_3$O$_2$ [M + H]$^+$ 264.1707, found 264.1703.

**tert-Butyl 3-(pyridin-2-yl)piperazine-1-carboxylate (5.7f).** Purification by flash column chromatography (EtOAc) afforded 5.7f (105 mg, 83% yield) as a colorless oil. IR (thin film): ν 3587, 2960, 2919, 2849, 1685, 1457, 1420, 1260, 1168, 1099, 1019 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.85 (s, 1H), 7.61 (s, 1H), 4.08 (d, J = 12.4 Hz, 1H), 3.98–3.68 (m, 2H), 3.19–2.90 (m, 3H), 2.89–2.77 (m, 1H), 1.63 (br s, NH), 1.47 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 154.8, 151.3, 135.0, 80.1, 51.8, 44.8, 29.9, 28.6, 28.5; R$_f$ = 0.27 (EtOAc); ESI-HRMS calcd for C$_{12}$H$_{20}$N$_3$O$_3$ [M + H]$^+$ 254.1499, found 254.1496.

**tert-Butyl 3-(pyridin-2-yl)piperazine-1-carboxylate (5.7g).** Purification by flash column chromatography (EtOAc) afforded 5.7g (106 mg, 79% yield) as a colorless oil. IR (thin film): ν 3309, 2963, 2920, 2850, 1685, 1419, 1261, 1167, 1126 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.74 (s, 1H), 7.83 (s, 1H), 4.27–3.87 (m, 3H), 3.08–2.94 (m, 2H), 2.94–2.74 (m, 2H), 1.57 (br s, NH), 1.47 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 154.7, 152.8, 140.4, 139.7, 80.3, 53.1, 51.9, 50.8, 45.6, 44.6, 43.3, 28.6; R$_f$ = 0.26 (EtOAc); ESI-HRMS calcd for C$_{12}$H$_{20}$N$_3$O$_3$S$_1$
[M + H]$^+$ 270.1271, found 270.1272.

**tert-Butyl 3-(pyridin-2-yl)piperazine-1-carboxylate (5.7h).** Purification by flash column chromatography (EtOAc:MeOH 9:1) afforded 5.7h (91 mg, 58% yield) as a colorless oil. IR (thin film): ν 3327, 2962, 2918, 2850, 1694, 1457, 1417, 1261, 1099, 1017 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.79–7.71 (m, 1H), 7.38–7.33 (m, 1H), 7.32–7.27 (m, 2H), 4.34 (d, $J = 11.8$ Hz, 1H), 4.17–3.98 (m, 2H), 3.87 (s, 3H), 3.15 (d, $J = 10.7$ Hz, 2H), 2.99–2.75 (m, 2H), 1.60 (br s, NH), 1.48 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 154.8, 153.0, 142.3, 136.0, 123.0, 122.4, 119.9, 109.4, 80.2, 52.4, 45.5, 30.2, 29.9, 28.6; R$_f$ = 0.31 (EtOAc:MeOH 9:1); ESI-HRMS calcd for C$_{17}$H$_{25}$N$_4$O$_2$ [M + H]$^+$ 317.1972, found 317.1967.

**tert-Butyl 3-(1-methyl-1H-pyrazol-4-yl)piperazine-1-carboxylate (5.7i).** Purification by flash column chromatography (EtOAc:MeOH 9:1) afforded 5.7i (88 mg, 66% yield) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.43 (s, 1H), 7.32 (s, 1H), 4.16–3.80 (m, 2H), 3.85 (s, 3H), 3.71 (dd, $J = 10.1$, 2.9 Hz, 1H), 2.99 (br d, $J = 11.2$ Hz, 1H), 2.95–2.85 (m, 1H), 2.83–2.79 (m, 1H), 2.76 (br s, 1H), 1.99 (br s, NH), 1.45 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 154.8, 137.5, 128.0, 122.5, 79.9, 51.5, 50.8, 45.7, 44.0, 39.1, 28.5. These spectral characteristics were identical to those previously reported.$^{18}$

**tert-Butyl 3-(benzo[b]thiophen-3-yl)piperazine-1-carboxylate (5.7j).** Purification by flash column chromatography (hexanes:EtOAc 3:2) afforded 5.7j (95 mg, 60% yield) as a colorless oil. IR (thin film): ν 3321, 2975, 2929, 2858, 1692, 1426, 1252, 1171, 1126 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.94 (d, $J = 7.2$ Hz, 1H), 7.87 (d, $J = 7.8$ Hz, 1H), 7.45 (s, 1H), 7.44–7.32 (m, 4H), 4.30 (br s, 1H), 4.21–3.98 (m, 2H), 3.17–3.07 (m, 1H), 3.06–2.91 (m, 2H), 2.91–2.75 (m, 1H), 1.93 (br s, NH), 1.50 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 154.8, 140.8, 137.7,
136.6, 124.7, 124.2, 123.1, 122.6, 121.9, 80.0, 55.1, 50.5, 46.3, 44.4, 28.6; \( R_f = 0.15 \) (hexanes:EtOAc 1:1); ESI-HRMS calcd for \( \text{C}_{17}\text{H}_{23}\text{N}_{2}\text{O}_{2}\text{S} \) \([\text{M + H}]^+\) 319.1475, found 319.1473.

**1-(tert-Butyl) 3-ethyl piperazine-1,3-dicarboxylate (5.7k).** Purification by flash column chromatography (hexanes:EtOAc 1:2) afforded 5.7k (68 mg, 56% yield) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 4.16 (q, \( J = 7.1 \) Hz, 3H), 3.66 (br d, \( J = 12.4 \) Hz, 1H), 3.38 (dd, \( J = 8.6, 3.5 \) Hz, 1H), 3.30–2.83 (m, 3H), 2.75–2.64 (m, 1H), 2.23 (br s, NH), 1.42 (s, 9H), 1.24 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 171.2, 154.6, 80.0, 61.2, 56.9, 45.8, 44.3, 43.5, 28.4, 14.2. These spectral characteristics were identical to those previously reported.\(^{18}\)

**tert-Butyl 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)piperazine-1-carboxylate (5.7l).** Purification by flash column chromatography (EtOAc:MeOH 9:1) afforded 5.7l (63 mg, 34% yield as rotamers) as a pale yellow oil. IR (thin film): \( \nu \) 2955, 2926, 2870, 2854, 1693, 1421, 1365, 1249, 1170 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 4.30–3.97 (m, 3H), 3.95–3.76 (m, 1H), 3.00–2.93 (m, 1H), 2.86–2.78 (m, 1H), 2.74–2.67 (m, 1H), 2.74–2.41 (m, 3H), 2.40–2.32 (m, 1H), 1.73 (br d, \( J = 12.7 \) Hz, 1H), 1.70 (br d, \( J = 12.7 \) Hz, 1H), 1.59 (br s, NH), 1.48 (s, 9H), 1.47 (s, 9H), 1.32–1.27 (m, 1H), 1.25–1.16 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 155.0, 154.9, 79.9, 79.6, 59.1, 48.0, 47.1, 45.7, 45.1, 44.2, 43.7, 39.4, 28.6, 28.4, 28.4; \( R_f = 0.19 \) (EtOAc:MeOH 9:1); ESI-HRMS calcd for \( \text{C}_{19}\text{H}_{36}\text{N}_{3}\text{O}_{4} \) \([\text{M + H}]^+\) 370.2700, found 370.2698.

**tert-Butyl 3-(4-(trifluoromethyl)phenyl)piperazine-1-carboxylate (5.16).** Purification by flash column chromatography (hexanes:TBME 1:1) afforded 5.16 (74 mg, 45% yield) as a pale yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.60 (d, \( J = 8.3 \) Hz, 2H), 7.53 (d, \( J = 8.3 \) Hz, 2H), 4.05 (br s, 2H), 3.77 (br d, \( J = 10.1 \) Hz, 1H), 3.08 (br d, \( J = 7.7 \) Hz, 1H), 2.99–2.80 (m, 2H), 2.80–2.61 (m, 1H), 1.77 (br s, NH), 1.47 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 154.8, 145.7, 130.2 (q, \( J_{\text{CF}} = 32.6 \) Hz), 127.5, 125.6 (q, \( J_{\text{CF}} = 3.7 \) Hz), 124.2 (q, \( J_{\text{CF}} = 272.1 \) Hz), 80.1, 60.0,
51.1, 46.1, 43.8, 28.6. These spectral characteristics were identical to those previously reported.\(^\text{16}\) Chiral HPLC: column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: 10% iPrOH in hexane, flow: 1.00 mL/min; detection: 254 nm.

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**tert-Butyl 3-(4-fluorophenyl)piperazine-1-carboxylate (5.30).** Purification by flash column chromatography (hexanes:EtOAc 2:1) afforded \textbf{5.30} (110 mg, 79% yield) as a colorless oil. IR (thin film): ν 2972, 2934, 2874, 2837, 1692, 1608, 1513, 1247, 1168 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.40–7.32 (m, 2H), 7.06–6.93 (m, 2H), 4.02 (br s, 2H), 3.67 (dd, \(J = 10.6, 3.1\) Hz, 1H), 3.05 (d, \(J = 8.1\) Hz, 1H), 2.97–2.80 (m, 2H), 2.78–2.55 (m, 1H), 1.86 (br s, NH), 1.46
(s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.4 (d, $J_{CF} = 246.0$ Hz), 154.8, 137.5 (d, $J_{CF} = 3.1$ Hz), 128.7 (d, $J_{CF} = 8.0$ Hz), 115.4 (d, $J_{CF} = 21.1$ Hz), 79.9, 59.7, 51.2, 46.2, 44.0, 28.6; $R_f = 0.18$ (hexanes:EtOAc 1:1); ESI-HRMS calcd for C$_{15}$H$_{21}$F$_2$N$_2$NaO$_2$ [M + Na]$^+$ 303.1479, found 303.1485.

### 7.5.2 Preparation of SnAP Reagents for the Synthesis of $\alpha$-bis-substituted Morpholines

**IMPORTANT:** The first two products in this reaction sequence (tributylstannyl alcohol and tributylstannyl mesylate) are unstable. These compounds decompose within minutes at rt. The tributylstannyl mesylate is slightly more stable and can be stored in solution at 0°C for approximately one day. It is important to follow the procedure, including the reaction times, the solvents for the extractions and the temperature of the water bath. The reaction sequence up to the stable phthalimide protected SnAP reagent should be done as fast as possible in one go!

![Diagram of the reaction sequence](image)

**2-(2-(1-(Tributylstannyl)ethoxy)ethyl)isoindoline-1,3-dione (5.8).** Sodium hydride (907 mg of a 60% suspension in mineral oil, 22.7 mmol, 1.10 equiv) was washed with pentane (3 x 2 mL) and suspended in DMF (30 mL). The suspension was cooled to 0°C and N-(2-hydroxyethyl)phthalimide (4.73 g, 24.7 mmol, 1.20 equiv) in DMF (12 mL) was added dropwise over 10 min. The resulting mixture was stirred at 0°C for ca. 2–3 h while the tributylstannyl mesylate compound was prepared as quickly as possible.
To a stirred solution of \textit{N},\textit{N}-diisopropylamine (3.35 mL, 23.7 mmol, 1.15 equiv) in THF (50 mL) at 0°C was added \textit{n}-BuLi (1.6 M in hexanes, 14.4 mL, 23.1 mmol, 1.12 equiv) over 5 min. The light yellow solution was stirred for 30 min at 0°C before tributyltin hydride (5.55 mL, 20.6 mmol, 1.00 equiv) was added dropwise over 5–10 min. The resulting yellow solution was stirred for 30 min at 0°C before cooled to –78°C. Acetaldehyde (1.27 mL, 22.7 mmol, 1.10 equiv) was slowly added and the resulting reaction mixture was stirred at –78°C for 0.5 h before being poured cold onto sat aq NH$_4$Cl (40 mL). The layers were separated and the aqueous layer was extracted with Et$_2$O (3 x 30 mL). The combined organic layers were washed with H$_2$O (1 x 20 mL) and brine (3 x 20 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure at 0–20°C to afford the tributylstannyl alcohol as a colorless oil that was used in the next step immediately.

The resulting tributylstannyl alcohol was dissolved in CH$_2$Cl$_2$ (200 mL) and cooled to –78°C. Et$_3$N (8.60 mL, 61.8 mmol, 3.00 equiv) was added followed by the slow addition of methanesulfonyl chloride (3.20 mL, 41.2 mmol, 2.00 equiv) over 5–10 min. The resulting mixture was stirred at –78°C for 15–20 min before being poured cold onto sat aq NH$_4$Cl (50 mL). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (1 x 20 mL). The combined organic layers were washed with H$_2$O (2 x 40 mL) and brine (2 x 40 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure at 0–20 °C to afford the tributylstannyl mesylate as a colorless oil.

This tributylstannyl mesylate was added neat and slowly to the previously prepared mixture of sodium hydride and \textit{N}-(2-hydroxyethyl)phthalimide in DMF at 0°C. The ice bath was removed and stirring was continued for 16 h. The reaction mixture was re-cooled to 0°C, slowly quenched with sat aq NH$_4$Cl (10 mL), diluted with H$_2$O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H$_2$O (2 x 50 mL), brine (3 x 50 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure at 40°C to afford the crude phthalimide protected SnAP 6-Me-M reagent. Purification by flash column chromatography (hexanes:EtOAc 15:1) afforded 5.8 (4.40 g, 42% yield) as a clear, colorless liquid. IR (thin film): ν 2956, 2925, 2871, 2853, 1775, 1715, 1467, 1392, 1090, 1025 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.84 (dd, $J = 5.5, 3.0$ Hz, 2H), 7.70 (dd, $J = 5.5, 3.0$ Hz, 2H), 3.94–3.77 (m, 3H), 3.69 (dt, $J = 9.6, 5.5$ Hz, 1H), 3.53 (ddd, $J = 9.6, 7.3, 5.5$ Hz, 1H), 1.50–1.32 (m, 6H), 1.42 (d, $J = 7.3$ Hz, 3H), 1.27–1.17 (m, 6H), 0.88–0.75 (m, 15H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 168.3, 133.9, 132.3, 123.3, 71.9, 66.8, 38.1, 29.3, 27.5, 20.1, 13.8, 8.8; $R_f$ = 0.39 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C$_{24}$H$_{46}$N$_7$O$_3$Sn$_1$ [M + H]$^+$ 510.2029, found 510.2032.
2-(1-(Tributylstannyl)ethoxy)ethan-1-amine (5.10). Phthalimide protected SnAP 6-Me-M 5.8 (1.60 g, 3.15 mmol, 1.00 equiv) in EtOH (14 mL) was heated to reflux. Hydrazine monohydrate (1.53 mL, 31.5 mmol, 10.0 equiv) was added dropwise at reflux over 5 min. The resulting reaction mixture was stirred for further 30 min at reflux while colorless solid crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (30 mL) and H₂O (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with H₂O (3 x 10 mL), brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford pure SnAP 6-Me-M 5.10 (1.08 g, 91% yield) as colorless oil. IR (thin film): ν 2955, 2924, 2871, 2853, 1577, 1464, 1293, 1091 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.83 (q, J = 7.4 Hz, 1H), 3.50 (dt, J = 9.2, 5.2 Hz, 1H), 3.29 (dt, J = 9.2, 5.2 Hz, 1H), 2.83 (t, J = 5.2 Hz, 2H), 1.57–1.44 (m, 6H), 1.49 (d, J = 7.4 Hz, 3H), 1.40 (br s, NH), 1.36–1.26 (m, 6H), 0.97–0.82 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 72.8, 72.1, 42.5, 29.4, 27.6, 20.5, 13.9, 9.0; R₇ = 0.09 (EtOAc); ESI-HRMS calcd for C₁₆H₃₈N₁O₁Sn₁ [M + H]⁺ 380.1973, found 380.1971.

**IMPORTANT:** The first two products in this reaction sequence (tributylstannyl alcohol and tributylstannyl mesylate) are unstable. These compounds decompose within minutes at rt. The tributylstannyl mesylate is slightly more stable and can be stored in solution at 0°C for approximately one day. It is important to follow the procedure, including the reaction times, the solvents for the extractions and the temperature of the water bath. The reaction sequence up to the stable phthalimide protected SnAP reagent should be done as fast as possible in one go!
2-(2-(1-(Tributylstannyl)propoxy)ethyl)isoindoline-1,3-dione (5.9). Sodium hydride (907 mg of a 60% suspension in mineral oil, 22.7 mmol, 1.10 equiv) was washed with pentane (3 x 2 mL) and suspended in DMF (30 mL). The suspension was cooled to 0°C and N-(2-hydroxyethyl)phthalimide (4.73 g, 24.7 mmol, 1.20 equiv) in DMF (12 mL) was added dropwise over 10 min. The resulting mixture was stirred at 0°C for ca. 2–3 h while the tributylstannyl mesylate compound was prepared as quickly as possible.

To a stirred solution of N,N-diisopropylamine (3.35 mL, 23.7 mmol, 1.15 equiv) in THF (50 mL) at 0°C was added n-BuLi (1.6 M in hexanes, 14.4 mL, 23.1 mmol, 1.12 equiv) over 5 min. The light yellow solution was stirred for 30 min at 0°C before tributyltin hydride (5.55 mL, 20.6 mmol, 1.00 equiv) was added dropwise over 5–10 min. The resulting yellow solution was stirred for 30 min at 0°C before cooled to −78°C. Propionaldehyde (1.64 mL, 22.7 mmol, 1.10 equiv) was slowly added and the resulting reaction mixture was stirred at −78°C for 0.5 h before being poured cold onto sat aq NH₄Cl (40 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 30 mL). The combined organic layers were washed with H₂O (1 x 20 mL) and brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure at 0–20°C to afford the tributylstannyl alcohol as a colorless oil that was used in the next step immediately.

The resulting tributylstannyl alcohol was dissolved in CH₂Cl₂ (200 mL) and cooled to −78°C. Et₃N (8.60 mL, 61.8 mmol, 3.00 equiv) was added followed by the slow addition of methanesulfonyl chloride (3.20 mL, 41.2 mmol, 2.00 equiv) over 5–10 min. The resulting mixture was stirred at −78°C for 15–20 min before being poured cold onto sat aq NH₄Cl (50 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (1 x 20 mL). The combined organic layers were washed with H₂O (2 x 40 mL) and brine (2 x 40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure at 0–20°C to afford the tributylstannyl mesylate as a colorless oil.

This tributylstannyl mesylate was added neat and slowly to the previously prepared mixture of sodium hydride and N-(2-hydroxyethyl)phthalimide in DMF at 0°C. The ice bath was removed and stirring was continued for 16 h. The reaction mixture was re-cooled to 0°C, slowly quenched with sat aq NH₄Cl (10 mL), diluted with H₂O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O (2 x 50 mL), brine (3 x 50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure at 40°C to afford the crude phthalimide protected SnAP 6-Et-M reagent. Purification by flash column
chromatography (hexanes:EtOAc 15:1) afforded 5.9 (3.34 g, 31% yield) as a clear, colorless liquid. IR (thin film): ν 2955, 2926, 2871, 2853, 1776, 1715, 1466, 1392, 1086, 1032 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.87–7.81 (m, 2H), 7.73–7.67 (m, 2H), 3.94–3.79 (m, 2H), 3.71 (dt, J = 6.4 Hz & J(¹¹⁷/¹¹⁹Sn⁻¹H) = 5.1 Hz, 1H), 3.67–3.61 (m, 1H), 3.55 (ddd, J = 9.5, 7.0, 5.5 Hz, 1H), 1.86–1.68 (m, 2H), 1.50–1.35 (m, 6H), 1.28–1.18 (m, 6H), 0.88–0.80 (m, 15H), 0.80–0.76 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.3, 133.9, 132.3, 123.3, 79.3, 67.4, 38.2, 29.3, 27.6, 27.3, 13.8, 12.1, 9.3; Rᵣ = 0.29 (hexanes:EtOAc 10:1); ESI-HRMS calcd for C₂₅H₄₁N₁Na₁O₃Sn₁ [M + Na]⁺ 546.2005, found 546.19967.

2-(1-(Tributylstannyl)propoxy)ethan-1-amine (5.11). Phthalimide protected SnAP 6-Et-M 5.9 (1.60 g, 3.06 mmol, 1.00 equiv) in EtOH (13 mL) was heated to reflux. Hydrazine monohydrate (1.48 mL, 30.6 mmol, 10.0 equiv) was added dropwise at reflux over 5 min. The resulting reaction mixture was stirred for a further 30 min at reflux while colorless solid crashed out. The colorless suspension was allowed to cool to rt and poured into a mixture of EtOAc (30 mL) and H₂O (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with H₂O (3 x 10 mL), brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford pure SnAP 6-Et-M 5.11 (1.04 g, 86% yield) as colorless oil. IR (thin film): ν 3371, 2956, 2925, 2871, 2852, 1577, 1458, 1071 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.73 (dt, J = 6.6 Hz & J(¹¹⁷/¹¹⁹Sn⁻¹H) = 3.6 Hz, 1H), 3.46–3.39 (m, 1H), 3.36–3.29 (m, 1H), 2.83 (br s, 2H), 1.94–1.75 (m, 2H), 1.54–1.41 (m, 6H), 1.45 (br s, NH₂), 1.36–1.26 (m, 6H), 0.95 (t, J = 7.3 Hz, 3H), 0.92–0.85 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 79.4, 73.3, 42.6, 29.4, 27.7, 27.7, 13.9, 12.4, 9.4; Rᵣ = 0.09 (EtOAc); ESI-HRMS calcd for C₁₇H₄₆N₁O₁Sn₁ [M + Na]⁺ 394.2129, found 394.2126.
7.5.3 Preparation of α-bis-substituted Morpholines

α-Bis-substituted morpholines were prepared according to the general procedure for the preparation of morpholines described in chp. 7.5.1.

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\begin{align*}
\text{trans-2-Methyl-3- (6 - phenyl - 2,3 - dihydroimidazo [2,1-b] thiazol-5-yl) morpholine (5.12a).} & \quad 20\text{mol}\% \text{ Cu(OTf)}_2 / \text{rac. PhBox in HFIP (0.05M) was used. Purification by flash column chromatography (EtOAc) afforded 5.12a (103 mg, 68\% yield) as a colorless oil. IR (thin film): } \nu \text{ cm}^{-1}; \quad ^1H \text{ NMR (400 MHz, CDCl}_3): \delta \text{ ppm}; \quad ^{13}C \text{ NMR (100 MHz, CDCl}_3): \delta \text{ ppm}; \quad \text{Rf = 0.16 (EtOAc); ESI-HRMS calcd for C}\quad_{16}H_{20}N_3O_1S_1 \quad [M + H]^+ \text{ 302.1322, found 302.1320.} \\
\text{trans-2-Methyl-3- (3-phenylisoxazol-5-yl)morpholine (5.12b).} & \quad \text{Purification by flash column chromatography (hexanes:EtOAc 1:1) afforded 5.12b (96 mg, 79\% yield) as a colorless oil. IR (thin film): } \nu \text{ cm}^{-1}; \quad ^1H \text{ NMR (400 MHz, CDCl}_3): \delta \text{ ppm}; \quad ^{13}C \text{ NMR (100 MHz, CDCl}_3): \delta \text{ ppm}; \quad \text{Rf = 0.26 (hexanes:EtOAc 1:1); ESI-HRMS calcd for C}\quad_{14}H_{17}N_2O_2 \quad [M + H]^+ \text{ 245.1285, found 245.1287.} \\
\text{trans-Ethyl 4-(2-methylmorpholin-3-yl)benzoate (5.12c).} & \quad \text{Purification by flash column chromatography (hexanes:EtOAc 1:2) afforded 5.12c (110 mg, 94\% yield) as a colorless oil. IR}
\end{align*}
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(thin film): v 2952, 2854, 1723, 1436, 1279, 1113 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.02–7.95 (m, 2H), 7.48–7.40 (m, 2H), 3.93 (ddd, J = 11.2, 3.4, 1.3 Hz, 1H), 3.90 (s, 3H), 3.84–3.76 (m, 1H), 3.56–3.47 (m, 2H), 3.15–3.04 (m, 1H), 2.96 (ddd, J = 11.7, 2.7, 1.3 Hz, 1H), 1.99 (br s, NH), 0.91 (d, J = 5.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 167.0, 146.5, 129.9, 128.3, 77.7, 67.9, 67.5, 52.2, 46.6, 18.2; Rᵣ = 0.14 (hexanes:EtOAc 1:1); ESI-HRMS calcd for C₁₃H₁₈N₁O₃ [M + H]⁺ 236.1281, found 236.1283.

**trans-2-Ethyl-3-(quinolin-4-yl)morpholine (5.13a).** Purification by flash column chromatography (EtOAc) afforded 5.13a (93 mg, 77% yield) as a colorless oil. IR (thin film): v 3309, 2959, 2935, 2852, 1587, 1508, 1331, 1116 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.90 (d, J = 4.6 Hz, 1H), 8.22 (br s, 1H), 8.14 (dd, J = 8.4, 0.8 Hz, 1H), 7.73 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.64 (br s, 1H), 7.59 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 4.39 (br s, 1H), 4.05 (ddd, J = 11.2, 3.3, 1.3 Hz, 1H), 3.92–3.81 (m, 1H), 3.49 (br s, 1H), 3.25–3.15 (m, 1H), 3.04 (ddd, J = 11.7, 2.7, 1.3 Hz, 1H), 1.67 (br s, NH), 1.37–1.26 (m, 1H), 1.08–0.96 (m, 1H), 0.78 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 150.5, 148.6, 147.2, 130.6, 129.3, 127.4, 126.8, 123.1, 120.0, 84.0, 68.1, 58.7, 46.9, 25.4, 10.2; Rᵣ = 0.16 (EtOAc); ESI-HRMS calcd for C₁₃H₁₈N₁O₃ [M + H]⁺ 243.1492, found 243.1491. To probe the enantioselectivity using enantiomerically pure (S)-PhBox, HFIP:CH₂Cl₂ (1:4, 0.05 M) was used as solvent instead of HFIP. The preparation of the catalyst (20 mol %) was carried out in HFIP and the imine was added as a solution in CH₂Cl₂. The absolute configuration was not determined. Chiral HPLC: column: Daicel Chiralpak OJH (4.6 × 250 mm); eluent: 4% iPrOH in hexane + 0.1 % Et₃N, flow: 1.00 mL/min; detection: 254 nm.
**trans-3-(4-(1H-1,2,4-Triazol-1-yl)phenyl)-2-ethylmorpholine (5.13b).** Purification by flash column chromatography (EtOAc) afforded 5.13b (113 mg, 87% yield) as a colorless solid. IR (thin film): ν 3429, 3313, 3115, 2960, 2919, 2850, 1522, 1279, 1114 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.54 (s, 1H), 8.10 (s, 1H), 7.67–7.60 (m, 2H), 7.56–7.48 (m, 2H), 3.98 (dd, J = 11.2, 3.4, 1.4 Hz, 1H), 3.85–3.73 (m, 1H), 3.58 (d, J = 8.7 Hz, 1H), 3.36–3.27 (m, 1H), 3.18–3.04 (m, 1H), 2.96 (ddd, J = 11.6, 2.7, 1.3 Hz, 1H), 1.74 (br s, NH), 1.35 – 1.16 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 152.8, 141.9, 140.9, 136.6, 129.7, 120.2, 82.9, 68.0, 65.4, 46.7, 25.1, 10.0; Rₜ = 0.14 (EtOAc); m.p. = 119–121°C; ESI-HRMS calc'd for C₁₄H₁₅N₂O₁ [M + H]⁺ 259.1553, found 259.1554. To probe the enantioselectivity using enantiomerically pure (S)-PhBox, HFIP:CH₂Cl₂ (1:4, 0.05 M) was used as solvent instead of HFIP. The preparation of the catalyst (20 mol %) was carried out in HFIP and the imine was added as a solution in CH₂Cl₂. The absolute configuration was not determined. Chiral HPLC: column: Daicel Chiralpak OJH (4.6 × 250 mm); eluent: 10% iPrOH in hexane, flow: 1.00 mL/min; detection: 254 nm.
trans-2-Ethyl-3-(o-tolyl)morpholine (5.13c). To probe the enantioselectivity using enantiomerically pure (S)-PhBox, HFIP:CH₂Cl₂ (1:4, 0.05 M) was used as solvent instead of HFIP. The preparation of the catalyst (20 mol%) was carried out in HFIP and the imine was added as a solution in CH₂Cl₂. The absolute configuration was not determined. Purification by flash column chromatography (hexanes:EtOAc 1:1) afforded 5.13c (84 mg, 82% yield) as a colorless oil. IR (thin film): ν 3319, 2958, 2935, 2854, 1462, 1332, 1115 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.45 (d, J = 7.2 Hz, 1H), 7.23–7.09 (m, 3H), 3.97 (ddd, J = 11.2, 3.3, 1.3 Hz, 1H), 3.82 (d, J = 8.8 Hz, 1H), 3.81–3.74 (m, 1H), 3.45–3.36 (m, 1H), 3.16–3.06 (m, 1H), 2.95 (ddd, J = 11.8, 2.7, 1.3 Hz, 1H), 2.39 (s, 3H), 1.66 (br s, NH), 1.35–1.14 (m, 3H), 0.83 (t, J = 7.4 Hz, 3H), ¹³C NMR (100 MHz, CDCl₃): δ 139.7, 136.2, 130.5, 127.5, 127.3, 126.4, 83.8, 68.2, 60.7, 47.1, 24.8, 20.1, 10.4; Rᵣ = 0.23 (hexanes:EtOAc 1:1); ESI-HRMS calcd for C₁₃H₂₀N₁O₁ [M + H]⁺ 206.1539, found 206.1542. Chiral HPLC: column: Daicel Chiralpak ODH (4.6 × 250 mm); eluent: 4% iPrOH in hexane + 0.1% Et₃N, flow: 0.45 mL/min; detection: 254 nm.
7.5.3 Preparation of Bisoxazoline Ligands

**tert-Butyl (S)-3-(2,5-difluorophenyl)-2-((diphenylmethylene)amino)propanoate (5.17).** A procedure from the literature was applied to prepare **5.17**. Purification by flash column chromatography (hexanes:EtOAc 20:1) afforded **5.17** (2.08 g, 97% yield) as a colorless oil. IR (thin film): \( \nu \) 3059, 2978, 1732, 1623, 1497, 1152 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.62–7.53 (m, 2H), 7.42–7.28 (m, 6H), 6.90–6.81 (m, 3H), 6.79 (d, \( J = 6.6 \text{ Hz} \), 2H), 4.20 (dd, \( J = 8.9, 4.7 \text{ Hz} \), 1H), 3.32–3.22 (m, 1H), 3.15 (dd, \( J = 13.4, 9.2 \text{ Hz} \), 1H), 1.44 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 171.0, 170.4, 158.4 (dd, \( J_{CF} = 241.5, 2.3 \text{ Hz} \)), 157.5 (dd, \( J_{CF} = 242.0, 2.5 \text{ Hz} \)), 139.5, 136.3, 130.4, 128.9, 128.6, 128.3, 128.1, 127.8, 127.3 (dd, \( J_{CF} = 18.4, 8.0 \text{ Hz} \)), 118.6 (dd, \( J_{CF} = 23.7, 5.0 \text{ Hz} \)), 116.0 (dd, \( J_{CF} = 25.4, 8.7 \text{ Hz} \)), 114.4 (dd, \( J_{CF} = 24.0, 8.5 \text{ Hz} \)), 81.6, 66.0, 32.8, 28.2; \( R_t = 0.25 \) (hexanes:EtOAc 10:1); ESI-HRMS calcd for \( C_{26}H_{28}F_2N_1O_2 \left[ M + H \right]^+ \) 422.1926, found 422.1293. Chiral HPLC: column: Daicel Chiralpak ODH (4.6 × 250 mm); eluent: 0.8% iPrOH in hexane, flow: 1.0 mL/min; detection: 254 nm.

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(S)-2-Amino-3-(2,5-difluorophenyl)propanoic acid hydrochloride (5.18). TFA (21.5 mL, 279 mmol, 51.1 equiv) was added dropwise to a solution of the protected amino acid 5.17 (2.30 g, 5.46 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (21.5 mL) at 0°C and stirring was continued for 18 h at rt. The mixture was concentrated under reduced pressure to afford an oil that was dissolved in Et$_2$O (500 mL) and washed with 4M aq HCl (10 x 150 mL). The aqueous phases were combined and concentrated under reduced pressure to afford pure 5.18 (1.28 g, 99% yield) as colorless solids. IR (thin film): ν 3433, 3075, 3014, 2251, 2126, 1661, 1054 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$): δ 13.82 (br s, COOH), 8.63 (br s, NH$_3^+$), 7.34–7.13 (m, 3H), 4.10 (t, $J = 6.9$ Hz, 1H), 3.18 (d, $J = 6.9$ Hz, 2H); $^{13}$C NMR (100 MHz, DMSO-d$_6$): δ 170.0, 157.9 (dd, $J_{CF} = 240.0, 2.0$ Hz), 157.0 (dd, $J_{CF} = 240.0, 2.2$ Hz), 124.1 (dd, $J_{CF} = 18.8, 8.4$ Hz), 118.3 (dd, $J_{CF} = 24.5, 4.5$ Hz), 116.7 (dd, $J_{CF} = 25.0, 8.9$ Hz), 115.7 (dd, $J_{CF} = 23.9, 8.7$ Hz), 51.9, 29.2; ESI-HRMS calcd for C$_9$H$_{10}$F$_2$N$_1$O$_2$ [M + H]$^+$ 202.0674, found 202.0676.

(S)-2-Amino-3-(2,5-difluorophenyl)propan-1-ol (5.19). BH$_3$ (1.0 M in THF; 15.3 mL, 15.3 mmol, 3.00 equiv) was added dropwise to a suspension of the amino acid hydrochloride
(1.20 g, 5.05 mmol, 1.00 equiv) in THF (15 mL) at rt. The resulting suspension was heated to reflux for 3 h, then cooled to 0°C, quenched with MeOH (15 mL), and concentrated under reduced pressure. MeOH (20 mL) and 2 M aq HCl (40 mL) were added followed by stirring for 1 h at rt before the mixture was concentrated under reduced pressure. The resulting solids were suspended in CH₂Cl₂ (50 mL) and set to pH ca. 9–10 with 5 M aq NaOH. The organic phase was separated, dried with Na₂SO₄, and concentrated to afford pure 5.19 (880 mg, 93% yield) as a brown oil. IR (thin film): ν 3358, 3190, 2927, 2868, 1596, 1496, 1426, 1192, 1052 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.97 (td, J = 8.9, 4.6 Hz, 1H), 6.94–6.84 (m, 2H), 3.59 (dd, J = 10.7, 3.9 Hz, 1H), 3.36 (dd, J = 10.7, 6.9 Hz, 1H), 3.19–3.05 (m, 1H), 2.76 (ddd, J = 13.6, 5.6, 1.5 Hz, 1H), 2.57 (ddd, J = 13.6, 8.2, 1.4 Hz, 1H), 2.15 (br s, NH₂); ¹³C NMR (100 MHz, CDCl₃): δ 158.6 (dd, J₉CF = 242.5, 2.3 Hz), 157.4 (dd, J₉CF = 240.0, 2.5 Hz), 127.6 (dd, J₉CF = 18.6, 7.7 Hz), 117.8 (dd, J₉CF = 23.6, 5.2 Hz), 116.4 (dd, J₉CF = 25.6, 8.8 Hz), 114.6 (dd, J₉CF = 24.0, 8.6 Hz), 66.0, 53.1, 34.3; ESI-HRMS calcd for C₉H₁₂F₂N₁O₁ [M + H]⁺ 188.0881, found 188.0883.

(4S,4'S) - 2,2' - (Propane-2,2-diyl) bis (4-(2,5-difluorobenzyl) - 4,5 - dihydrooxazole) (5.20). A procedure from the literature was applied to prepare 5.20.²⁰ Purification by flash column chromatography (hexanes:EtOAc 3:2) afforded 5.20 (311 mg, 45% yield) as a colorless oil. IR (thin film): v 3398, 3076, 2984, 2938, 1655, 1495, 1426, 1201, 1175978 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.01–6.91 (m, 4H), 6.91–6.83 (m, 2H), 4.41 (dq, J = 9.4, 6.3 Hz, 2H), 4.23 (t, J = 9.0 Hz, 2H), 3.97 (dd, J = 8.6, 6.7 Hz, 2H), 2.97 (dd, J = 13.9, 5.6 Hz, 2H), 2.76 (dd, J = 13.9, 6.7 Hz, 2H), 1.44 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 169.8, 158.5 (dd, J₉CF = 242.0, 2.3 Hz), 157.3 (dd, J₉CF = 240.1, 2.5 Hz), 126.3 (dd, J₉CF = 18.6, 8.0 Hz), 118.5 (dd, J₉CF = 23.8, 5.0 Hz), 116.3 (dd, J₉CF = 25.7, 8.7 Hz), 114.7 (dd, J₉CF = 24.1, 8.6 Hz), 72.1, 65.8, 38.7, 34.2, 24.2; Rf = 0.28 (hexanes:EtOAc 1:1); ESI-HRMS calcd for C₂₃H₂₃F₄N₂O₂ [M + H]⁺ 435.1690, found 435.1691.

**tert-Butyl (S) - 2 - ((diphenylmethylene) amino) - 3 - (3-fluoro - 4 - methylphenyl)propanoate (5.21).** A procedure from the literature was applied to prepare 5.21. Purification by flash column chromatography (hexanes:EtOAc 30:1) afforded 5.21 (3.50 g, 75% yield) as a colorless oil. IR (thin film): $\nu$ 3058, 2978, 2930, 1730, 1662, 1278, 1254, 1152 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.60–7.55 (m, 2H), 7.42–7.27 (m, 6H), 6.98 (t, $J = 7.9$ Hz, 1H), 6.79–6.65 (m, 4H), 4.10 (dd, $J = 9.0$, 4.4 Hz, 1H), 3.18 (dd, $J = 13.5$, 4.4 Hz, 1H), 3.10 (dd, $J = 13.5$, 9.0 Hz, 1H), 2.21 (d, $J = 1.8$ Hz, 3H), 1.44 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.8, 170.6, 161.2 (d, $J_{CF} = 244.5$ Hz), 139.6, 138.1 (d, $J_{CF} = 7.5$ Hz), 136.5, 131.0 (d, $J_{CF} = 5.5$ Hz), 130.3, 128.9, 128.5, 128.1, 127.8, 125.4 (d, $J_{CF} = 3.2$ Hz), 122.5 (d, $J_{CF} = 17.3$ Hz), 116.3 (d, $J_{CF} = 22.0$ Hz), 81.4, 67.8, 39.2, 28.2, 14.3; $R_f = 0.30$ (hexanes:EtOAc 10:1); ESI-HRMS calcd for C$_{27}$H$_{29}$F$_3$N$_2$O$_2$ [M + H]$^+$ 418.2177, found 418.2174.
(S)-2-Amino-3-(2,5-difluorophenyl)propanoic acid hydrochloride (5.23). TFA (60 mL, 0.78 mol, 46.4 equiv) was added dropwise to a solution of the protected amino acid 5.21 (7.00 g, 16.8 mmol, 1.00 equiv) in CH₂Cl₂ (70 mL) at 0°C and stirring was continued for 18 h at rt. The mixture was concentrated under reduced pressure to afford an oil that was dissolved in Et₂O (500 mL) and washed 4M aq HCl (10 x 150 mL). The aqueous phases were combined and concentrated under reduced pressure to afford pure 5.22 as colorless solids that were used in the next step without further purification.

NaHCO₃ (4.22 g, 50.3 mmol, 3.00 equiv) was added portionwise to the amino acid hydrochloride 5.22 in THF-H₂O (1:1, 85 mL) at rt. (Boc)₂O (4.39 g, 20.1 mmol, 1.20 equiv) was added in portions after the bubbling stopped. The mixture was stirred at rt for 18 h before set to a pH of ca. 2 with 1M aq HCl. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with H₂O (2 x 20 mL) and brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford pale orange solids. These solids were dissolved in little CH₂Cl₂ and hexanes was added dropwise until some solids started to crash out. The resulting suspension was stirred at rt for 2 h before filtered to afford pure Boc-protected amino acid 5.23 (3.95 g, 79% yield, rotamers 3:1) as colorless solids. IR (thin film): ν 3432, 3325, 2980, 2932, 1717, 1511, 1396, 1255, 1166 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.10 (t, J = 7.9 Hz, 1H), 6.89–6.78 (m, 2H), 6.03 (br s, 1H x 0.25), 4.95 (d, J = 7.5 Hz, 1H x 0.75), 4.58 (d, J = 6.8 Hz, 1H x 0.75), 4.38 (br s, 1H x 0.25), 3.15 (dd, J = 13.7, 5.2 Hz, 1H), 3.04 (dd, J = 14.0, 5.9 Hz, 1H x 0.75), 2.90 (br s, 1H x 0.25), 2.24 (d, J = 1.8 Hz, 3H), 1.50–1.25 (m, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 176.0, 161.3 (d, JCF = 245.1 Hz), 155.5, 135.4 (d, JCF = 6.7 Hz), 131.7 (d, JCF = 5.6 Hz), 124.9, 123.7 (d, JCF = 17.0 Hz), 116.0 (d, JCF = 22.3 Hz), 80.6, 54.3, 37.3, 28.4, 28.2, 14.4, 14.4; ESI-HRMS calcd for C₁₅H₂₀F₁₁N₁Na₁O₄ [M + Na]⁺ 320.1269, found 320.1277.

tert - Butyl (S)- (3-(3-fluor-4-methylphenyl) - 1 - (methyl(λ¹-oxidanyl)amino) - 1 - oxopropan-2-yl) carbamate (5.24). Carbonyldiimidazole (3.27 g, 20.2 mmol, 1.20 equiv) was added to a solution of the acid 5.23 (5.00 g, 16.8 mmol, 1.00 equiv) in THF-DMF (1:1, 40 mL) at
rt. A solution of DIPEA (3.08 mL, 117.7 mmol, 1.05 equiv), and N,O-dimethylhydroxylamine x HCl (1.80 g, 18.5 mmol, 1.10 equiv) in DMF (10 mL) was added dropwise after 10 min and the resulting mixture was stirred at rt for 36 h. 10% aq Citric acid (30 mL) was added dropwise and stirring was continued for 1 h at rt. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with H₂O (2 x 20 mL) and brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification using flash column chromatography (hexanes:EtOAc 3:1) afforded Weinreb amide 5.24 (5.72 g, 99% yield) as a colorless oil. IR (thin film): υ 3310, 2977, 2932, 1710, 1655, 1511, 1390, 1253, 1165 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.07 (t, J = 7.9 Hz, 1H), 6.82 (dd, J = 8.5, 4.9 Hz, 2H), 5.17 (d, J = 8.1 Hz, 1H), 4.94–4.67 (m, 1H), 3.70 (s, 3H), 3.18 (s, 3H), 3.01 (dd, J = 13.7, 5.8 Hz, 1H), 2.82 (dd, J = 13.8, 7.2 Hz, 1H), 2.22 (s, 3H), 1.39 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 172.2, 161.3 (d, JCF = 245.0 Hz), 155.3, 136.3 (d, JCF = 7.1 Hz), 131.4 (d, JCF = 5.6 Hz), 124.9 (d, JCF = 2.8 Hz), 123.2 (d, JCF = 17.0 Hz), 116.1 (d, JCF = 22.3 Hz), 79.8, 61.8, 51.6, 38.3, 32.3, 28.4, 14.3; Rf = 0.18 (hexanes:EtOAc 4:1); ESI-HRMS calcd for C₁₁H₂₅F₁₄N₂Na₂O₄ [M + Na]⁺ 363.1691, found 363.1701.

![ tert-Butyl (S)-(1-(3-fluoro-4-methylphenyl)-3-oxobutan-2-yl)carbamate (5.25). ]

Methyl lithium (1.6 M in Et₂O; 7.70 mL, 12.3 mmol, 2.10 equiv) was added dropwise to a solution of the Weinreb amide 5.24 (2.00 g, 5.88 mmol, 1.0 equiv) in THF (30 mL) at –30°C. The mixture was stirred for 3 h at this temperature before poured onto H₂O (200 mL) containing 1M aq HCl (12 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with H₂O (2 x 20 mL) and brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification using flash column chromatography (hexanes:EtOAc 5:1) afforded ketone 5.25 (1.18 g, 68% yield) as colorless solids. IR (thin film): υ 3423, 3060, 2977, 2931, 2910, 1683, 1502, 1367, 1253, 1165 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.09 (t, J = 7.9 Hz, 1H), 6.84–6.77 (m, 2H), 5.25–4.75 (m, 1H), 4.55–4.10 (m, 1H), 3.13–2.98 (m, 1H), 2.98–2.72 (m, 1H), 2.23 (s, 3H), 2.15 (s, 3H), 1.42 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 206.6, 161.4 (d, JCF = 244.5 Hz), 155.3, 135.8 (d, JCF = 7.4 Hz), 131.7 (d, JCF = 5.5 Hz), 124.7 (d, JCF = 3.1 Hz), 123.6 (d, JCF = 17.1 Hz), 115.9 (d, JCF = 22.4 Hz), 80.160.7, 37.0, 28.4, 28.0, 14.3; Rf = 0.14 (hexanes:EtOAc 4:1); ESI-HRMS calcd for C₁₆H₂₃F₁₄N₂Na₂O₃ [M + Na]⁺ 318.1476, found 318.1478.
tert-Butyl \((2S,3R)-(3\text{-fluoro}-4\text{-methylphenyl})\text{-3-hydroxybutan-2-yl}) \text{ carbamate (5.26).} \) NaBH₄ (794 mg, 21.0 mmol, 2.00 equiv) was added portionwise to a suspension of the amino ketone 5.25 (3.10 g, 10.5 mmol, 1.00 equiv) in MeOH (105 mL) at −20°C. The mixture was stirred at this temperature for 3 h before poured onto H₂O (100 mL) and EtOAc (100 mL). The combined organic phases were washed with H₂O (2 x 20 mL) and brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification using flash column chromatography (hexanes:EtOAc 4:1) afforded Boc-protected amino alcohol 5.26 (1.18 g, 68% yield, dr = 18:86 in favor of the desired diastereomer) as colorless solids. \(^1\)H NMR (400 MHz, CDCl₃): δ 7.09 (t, \(J = 7.7\) Hz, 1H), 6.96–6.81 (m, 2H), 4.56 (d, \(J = 7.9\) Hz, 1H), 3.94–3.69 (m, 2H), 2.87–2.69 (m, 2H), 2.23 (s, 3H), 1.37 (s, 9H), 1.22 (d, \(J = 6.4\) Hz, 3H); \(R_f = 0.15\) (hexanes:EtOAc 4:1); ESI-HRMS calcd for C₁₆H₂₅F₁N₁O₃ [M + H]⁺ 298.1813, found 298.1810. Chiral HPLC: column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: 3% iPrOH in hexane, flow: 1.0 mL/min; detection: 254 nm.
(2R,3S)-3-Amino-4-(3-fluoro-4-methylphenyl)butan-2-ol (5.27). TFA (4.87 mL, 63.6 mmol, 45.0 equiv) was added dropwise to the Boc-protected amino alcohol 5.26 (420 mg, 1.41 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (20 mL) at rt. The mixture was stirred at this temperature for 1 h before concentrated under reduced pressure. The resulting oil was dissolved in Et$_2$O (100 mL) and set to a pH of ca. 10 using 3M aq NaOH. The phases were separated and the aqueous phase was extracted with Et$_2$O (3 x 10 mL). The combined organic phases were washed with H$_2$O (2 x 10 mL) and brine (2 x 10 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification using flash column chromatography (EtOAc:MeOH 98:2) afforded amino alcohol 5.27 (181 mg, 65% yield) as colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.10 (t, $J$ = 8.0 Hz, 1H), 6.90–6.81 (m, 2H), 3.76 (dt, $J$ = 10.2, 5.1 Hz, 1H), 3.05–2.95 (m, 1H), 2.81 (dd, $J$ = 13.7, 3.8 Hz, 1H), 2.40 (dd, $J$ = 13.7, 10.1 Hz, 1H), 2.24 (s, 3H), 1.84 (br s, NH$_2$), 1.20 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 161.5 (d, $J_{CF}$ = 245.1 Hz), 139.0 (d, $J_{CF}$ = 7.2 Hz), 131.6 (d, $J_{CF}$ = 5.6 Hz), 124.6 (d, $J_{CF}$ = 3.2 Hz), 122.8 (d, $J_{CF}$ = 17.2 Hz), 115.7 (d, $J_{CF}$ = 21.9 Hz), 69.8, 57.5, 38.0, 17.8, 14.3, 14.3; R$_f$ = 0.18 (EtOAc:MeOH 98:2); ESI-HRMS calcd for C$_{11}$H$_{17}$F$_1$N$_1$O$_1$ [M + H]$^+$ 198.1289, found 198.1284.

(4S,4’S,5S,5’S)-2,2’- (Cyclohexane - 1,1- diyl) bis (4 - (3-fluoro-4-methylbenzyl) - 5 - methyl-4,5-dihydrooxazole) (5.29). Cyclohexane-1,1-dicarbonyl dichloride$^{21}$ (150 mg, 0.717 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (0.7 mL) was added dropwise to a solution of triethylamine (200 μL, 1.44 mmol, 2.00 equiv) and amino alcohol 5.27 (283 mg, 1.44 mmol, 2.00 equiv) in CH$_2$Cl$_2$ (1.3 mL) at 0°C. The resulting solution was stirred at rt for 18 h before quenched with 1M aq HCl (2 mL). The phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 3 mL). The combined organic phases were washed with sat aq NaHCO$_3$ (2 x 3 mL), H$_2$O (2 x 3 mL) and brine (10 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford the crude dicarboxamide 5.28, which was used in the next reaction without further purification.

Dicarboxamide 5.28 in CH₂Cl₂ (9 mL) was treated with triethylamine (440 µL, 3.16 mmol, 4.40 equiv) and methanesulfonyl chloride (122 µL, 1.58 mmol, 2.20 equiv) at 0°C. The mixture was stirred at rt for 2 h before poured onto sat aq NH₄Cl (10 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 3 mL). The combined organic phases were washed H₂O (2 x 3 mL) and brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude bismethanesulfonate, which was treated with a solution of KOH (698 mg, 12.4 mmol, 11.0 equiv) in MeOH (14 mL). The resulting solution was stirred for 18 h at rt before a mixture of CH₂Cl₂-H₂O (1:1, 50 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic phases were washed H₂O (2 x 10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude bisoxazoline ligand 5.29. Purification using flash column chromatography (hexanes:EtOAc 3:1) afforded pure 5.29 (64 mg, 36% yield) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.07 (t, J = 7.7 Hz, 2H), 6.89–6.82 (m, 4H), 4.26 (p, J = 6.2 Hz, 2H), 3.85 (dt, J = 8.5, 5.2 Hz, 2H), 2.99 (dd, J = 13.7, 5.2 Hz, 2H), 2.54 (dd, J = 13.7, 8.5 Hz, 2H), 2.22 (s, 6H), 2.10–1.98 (m, 2H), 1.96–1.86 (m, 2H), 1.72–1.56 (m, 2H), 1.51–1.37 (m, 4H), 1.08 (d, J = 6.3 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 167.6, 161.3 (d, J_CF = 244.5 Hz), 137.5 (d, J_CF = 7.4 Hz), 131.4 (d, J_CF = 5.4 Hz), 124.9 (d, J_CF = 3.2 Hz), 122.8 (d, J_CF = 17.2 Hz), 116.1 (d, J_CF = 20.0 Hz), 79.9, 73.9, 43.1, 40.8, 32.3, 25.6, 22.6, 21.1, 14.3; Rf = 0.38 (hexanes:EtOAc 3:1); ESI-HRMS calcd for C₃₀H₃₇F₂N₂O₂ [M + H]⁺ 495.2818, found 495.2811.
7.6 NMR Spectra

![NMR Spectra Image]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

NMR spectra showing chemical shifts and peaks for compounds Boc, SnBu₃, NH, and C(Ph)₃. The spectra are labeled with peak values and assignments. The diagram includes a structure of the compound with chemical labels.
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

S2.2
Chapter 7: Experimental Procedures and Characterization Data - NMR 253

$$\text{Me}_2\text{O} \rightarrow \text{SnBu}_3$$

2.11
2.12
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

NMR

\[ \text{Boc} \]
\[ \text{Me} \]
\[ \text{OTIPS} \]

S2.6
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

NORTIPS

Boc

N

SnBu3

Me

OTIPS

S2.7

1H (ppm)

10.0  9.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0  -0.5

13C (ppm)

-110 -100 -90 -80 -70 -60 -50 -40 -30 -20 -10  0  10  20  30  40  50  60  70  80  90  100  110  120  130  140  150  160  170  180  190  200  210

-98.24
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

- NMR

S2.8

[Chemical structure image]

[ Spectroscopic data graph with peaks labeled ]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 267

[Chemical structure image]

2.5g
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

2.5h

N
H
BocN

T1 (ppm)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
2.5i
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

2.6a

The image shows a 1H NMR spectrum of compound 2.6a. The spectrum displays resonances at various chemical shifts, indicating the presence of hydrogen atoms at different positions within the molecule. The peaks and integration of these resonances provide information about the chemical structure and purity of the compound.

The 13C NMR spectrum is also shown, providing additional structural information, with signals at specific chemical shifts characteristic of the functional groups present in 2.6a.
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

2.6c

N
Boc
MeO

1.00-1.60
3.00-3.80
6.00-6.80
7.00-7.80

113.2
115.2
119.2
124.2
139.4
144.0
151.4
26.60

T (ppm)
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 275

\[ \text{NMR spectrum for compound 2.6f} \]

\[ \text{Melting point: 145.8-152.2°C} \]

\[ \text{IR (KBr):} \]

\[ \text{Mass:} \]

\[ \text{H NMR (DMSO-d6, 400 MHz, ppm):} \]

\[ \text{C NMR (DMSO-d6, 100 MHz, ppm):} \]
2.6g

**Chemical Structure:**

```
  N
  |   N
  C= N
  |   H
  |   Me
Boc
```

**NMR Spectrogram:**

- **1H ppm:**
  - 0.82, 1.07
  - 1.12, 1.13, 1.17, 1.22, 1.24
  - 1.50, 1.52, 1.59
  - 1.94, 1.99
- **13C ppm:**
  - 17.34, 17.59
  - 27.13, 27.18
  - 34.57, 34.72
  - 61.86, 62.54
  - 103.17, 103.18
  - 117.79, 117.80
  - 127.99, 127.99
  - 153.13
  - 174.46
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

2.15a

$\text{EtO} \quad \text{O}_{\text{Me}}$
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 281

2.15b

[Chemical structure image]

[Titration graph]

[Resonance assignments]
2.16a

![NMR Spectrogram](image-url)
2.17a, major diastereomer
2.17a, minor diastereomer
2.17b, major diastereomer
5:4 rotamers (\(1^\text{H} \text{NMR integration}\))
2.17b, minor diastereomer
2.18a

\[
\begin{align*}
&\text{EtO} \\
&\text{O} \\
&\text{N} \\
&\text{Boc} \\
&\text{N} \\
&\text{H} \\
&\text{Me}
\end{align*}
\]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

2.18b

N
H
N
Boc

Me

N

1.01  1.12
0.80  0.85
0.46  0.54
0.35  0.43

3.77  3.79
3.77  3.79

2.26  2.28  2.28
2.26  2.28  2.28

-28.19
-19.55

NMR
2.19

\[ \text{Bu}_3\text{Sn} \xrightarrow{\text{O}} \text{OH} \]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

2.21

Bu$_3$Sn\[\text{O}\]N$_2$O

NMR spectrum

[Image of NMR spectrum]

[Chemical structure with peaks labeled]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

$$\text{Bu}_3\text{Sn} \xrightarrow{O} \text{NH}_2$$

2.23
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 297

2.27

\[
\text{O} \quad \text{SnBu}_3
\]

\[
\text{O} \quad \text{N}
\]

\[
\text{O} \quad \text{O}
\]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

2.29

[Image of NMR spectrum]

[Chemical structure image]

[Legend or annotations]
2.28

\[
\begin{align*}
\text{O} & \quad \text{SnBu}_3 \\
\text{O} & \quad \text{N}
\end{align*}
\]
2.31. Rotamers 2:1 (\(^1\)H NMR)
2.32, Rotamers 7:3 ($^1$H NMR)
2.33, Rotamers 5:3 (1H NMR)
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

NMR 305

2.34
S2.9

NHBoc

OTIPS
S2.11

### Experimental Procedures and Characterization Data - NMR

**Chemical Structure:**

![Chemical Structure](image)

**NMR Spectra:**

- **{0.0} - {9.0} ppm:**
  - Details of spectral peaks and assignments.
- **{11.0} - {15.0} ppm:**
  - Additional spectral details.

**Key Points:**

- Boc: tert-Butyloxycarbonyl
- SnBu₃: Tri-n-butyltin
- OH: Hydroxyl group

**Spectral Data:**

- **{0.0} - {9.0} ppm:**
  - Integration and peak assignment.
- **{11.0} - {15.0} ppm:**
  - Integration and peak assignment.

**Notes:**

- Detailed analysis and discussion of spectral data.

---

**References:**

- Boc: tert-Butyloxycarbonyl
- SnBu₃: Tri-n-butyltin
- OH: Hydroxyl group

---

**Conclusion:**

Further analysis and interpretation of spectral data for S2.11.

---

**Figures and Tables:**

- Detailed figures and tables for spectral analysis.

---

**Supplementary Information:**

- Additional data and information for further study.
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 309

Boc
N
SnBu₃

O=\text{N}=O

S2.12
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

Boc
N
NH₂
SnBu₃

2.35
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 311

S2.13

[Chemical structure image]

[Graphical spectrum image]
S2.15
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

![NMR Spectra](image)

**2.36b**

Formula: 

```
EtO
O
HN
```

Chemical shifts and integration data are shown on the NMR spectra.
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

BocN

HN

2.36d
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

- NMR

$\text{H}_2\text{N}$

$\text{O}$

$\text{F}_3\text{C}$

$\text{C}_2$ 2.37a
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

2.37b
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 325
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

2.38d

![NMR Spectrum Image]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

![NMR Spectrum Image]

**Compound: 2.39b**

**Chemical Structures:**

- EtO
- Boc
- O
- HN

**NMR Data:**

- δ 2.39 (b)
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 333

2.39c

\[
\text{HN}
\]

\[
\text{Boc}
\]

Chemical shift and coupling constant data for compound 2.39c.

NMR spectrum showing various peaks at different chemical shifts.

Additional chemical shift data provided below the spectrum.
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

2.40b
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 337

2.40c
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

- NMR

338

HN
N
Boc

2.40d
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

2.43b, 38%

MeO₂C—\(\text{NH}\)MeO

NMR spectrum with chemical shifts and proton percentages.
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

**2.44b, 42%**

![NMR spectrum](image)

![Compound structure](image)
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

2.45a

Chemical shifts and coupling constants for NMR spectra are not explicitly given in the image.
2.46a
2.46b

\[ \text{Br} \]

\[
\begin{align*}
&\text{O} \\
&\text{N} \\
&\text{H} \\
&\text{Br}
\end{align*}
\]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

2.46c

Chemical structure and NMR spectra.
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

2.7
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

NMR

2.8

1.00
2.05
2.10

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 10

163.23
139.14
131.01
129.97
77.48
76.84
64.23
62.82
21.36

-8.66
-7.26
-6.87

N
Me
Me

OH
Me
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

3.3

OAc

SnBu₃

N₃
OMOM
\[ \text{SnBu}_3 \]
OTBS

3.4
OMOM

SnBu₃

NH₂

3.6
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 365

NPhth NHBoc Ts

3.7
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

NHBoc

SnBu₃

NPhth

3.8
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 367

NH₂

SnBu₃

NHBoc

3.9

-7.26

1.00

0.08

2.25

2.55

3.00

3.40

3.76

4.25

4.82

4.97

5.08

5.50

5.90

6.16

6.56

7.00

7.40

7.68

8.00

8.38

8.55

9.00

9.48

10.00

f₁ (ppm)

10.50

11.00

11.50

12.10

12.68

13.00

13.50

14.00

14.50

15.00

15.50

16.00

16.50

17.00

17.50

18.00

18.50

19.00

20.00

f₂ (ppm)

200

100

0

-10

-20

-30

-40

-50

-60

-70

-80

-90

-100

-110

-120

-130

-140

-150

-160

-170

-180

-190

-200

-210

210
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

NMR

3.12
3.14
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 371
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

3.10a

[Chemical structure image]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 375

3.10b

[Chemical structure image]

NMR spectra with chemical shifts and assignments.
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

3.10b

[Chemical structure image]

[Graphical data]

376
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 379

[Diagram of NMR spectra with chemical shifts and elemental analysis data]

3.10d

-54.89

-95.02

77.48

54.94

135.47

11.97

-55.99

45.86

70.23

28.53

35.42

-76.67

-95.02

77.48

54.94

135.47

11.97

-55.99

45.86

70.23

28.53

35.42

-76.67
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

3.10d
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 381

![NMR Spectrogram](image-url)

**3.10e**
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

NMR
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 383

3.11a
3.11b
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

NMR

3.11d

NHBoc

N

H

S

1.00  0.92  2.02  0.98  1.00  2.04  1.01  2.06  1.02  2.08  1.03  2.10  1.10  3.00

10.0  9.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0  0.5

147.73  182.36  153.35  125.83  124.03  123.63  115.89  52.33  51.28  46.28  37.21  23.68  17.94  16.84  12.40  10.00

f1 (ppm)

210  200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10

f1 (ppm)
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

3.11f

NHBoc

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

-155.76

-7.26

-4.97

3.69 3.68 3.67 3.67 3.53 3.52 3.51

3.69 3.68 3.67 3.53 3.52 3.51

2.82 2.69 2.69 2.68 2.68 2.68 2.68

1.85 1.76 1.76 1.76 1.76 1.76 1.76

1.58 1.57 1.56 1.56 1.55 1.55 1.55

1.52 1.51 1.51 1.51 1.51 1.51 1.51

23.80

28.55

31.16

33.65

39.52

52.54

52.88

63.08

63.20

76.84

77.16

77.48

79.25

0.92

1.00

1.05

1.18

1.18

1.15

4.35

4.35

0.00

0.00

3.11f
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

3.19

OMOM

SnBu$_3$

NH$_2$

NMR spectrum showing chemical shifts and peak intensities for the compound OMOM. The spectrum includes peaks at various ppm values, indicating the presence of different chemical groups and their positions in the molecule.
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

- 3.20

NHBoc

NPhth

Ts

- 168.13
- 153.72
- 145.20
  134.19
  133.56
  132.11
  129.89
  129.55
  125.53

- 81.02
- 77.48
- 77.16
- 76.84
- 68.86

- 34.39
- 28.01
- 25.37
- 21.75

- 2.00
- 2.06
- 2.00
- 2.12

0.82
1.00

0.82
1.00

0.82
1.00

9.32
1.19

2.70
2.67
2.42
2.39
2.18
2.16

2.78
2.83
2.88
2.82
2.77
2.75
2.71
2.71
2.70
2.69
2.35
2.33
2.31
2.29
2.26
2.23
2.20
4.93
4.91
4.90
4.88
4.87
3.90
3.88
3.86
3.84

7.84
7.83
7.83
7.82
7.77
7.75
7.71
7.71
7.70
7.69
7.35
7.33
7.31
7.29
7.26
7.23
7.20
4.93
4.91
4.90
4.88
4.87
3.90
3.88
3.86
3.84

3.20

NHBoc

NPhth

Ts
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

NHBoc

SnBu₃

NPhth

3.21
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 399

NHBoc

\[
\text{SnBu}_3
\]

\[
\text{NH}_2
\]

3.22
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

- NMR

3.23c

OMOM

\[ \text{Me} \]

\[ \text{Ph} \]

\[ \begin{array}{c}
\text{3.23c}
\end{array} \]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

3.23c

OMOM

N

N

Ph

Me

NMR
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

3.24a

NHBoc

\[
\text{CF}_3
\]

\[
\text{NHBoc}
\]

\[
\text{CF}_3
\]
3.24b

NHBoc

CO₂Me

10.0  9.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0  -0.5

210  200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 411

3.24c

NHBoc

\[
\text{NHBoc} \quad \text{NO}_2 \\
\text{Me}
\]

NMR spectra and chemical shifts are shown.
3.24e
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

4.6

\[ \text{NH}_2 \text{SnBu}_3 \]

NMR spectra showing chemical shifts and peak assignments.
4.12
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

4.7

\[
\begin{align*}
\text{NH} & \\
\text{Me} & \\
\text{NO}_2 & \\
\text{Me} & \\
\end{align*}
\]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

**Crude!!**

- **Bu$_3$Sn$_2$O**
- **O**
- **SnBu$_3$**
- **Cu(II)**
- **Bu$_3$Sn-R**

**S4.2**
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR
5.2
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 435

5.4i

[Chemical structure image]

[Graph or spectrum image]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

5.4k
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

NMR

5.15
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

5.5d

Diagram showing NMR spectra with chemical shifts and peak assignments.
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 445

![NMR Spectrogram]

5.7e

![NMR Spectrogram]
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

5.7f

N

H

Boc

N

O

\[ \text{Chemical Shifts (ppm)} \]

NMR Spectra:

- 5.7f

Chemical Shifts:

- H NMR (DMSO-d6) δ 7.85 (d, J = 7.6 Hz), 7.61 (d, J = 7.6 Hz)
- 1H NMR (DMSO-d6) δ 4.09, 3.56, 3.34, 2.84, 2.35 (m, ArH), 1.63 (s, 9H, TMS)
- 13C NMR (DMSO-d6) δ 135.03 (C), 134.81 (C), 133.81 (C), 131.81 (C), 130.81 (C), 128.61 (C), 126.11 (C), 124.31 (C), 120.11 (C), 116.71 (C), 114.11 (C), 113.11 (C), 105.71 (C), 44.71 (C), 28.51 (CH3), 28.49 (CH3)
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

NMR

\[
\begin{align*}
\text{Boc} & \quad \text{N} \\
\text{N} & \quad \text{H} \\
\text{Boc} & \quad 5.7j
\end{align*}
\]
Crude tributylstannyl alcohol with HSnBu₃ as impurity!

Crude tributylstannyl mesylate with HSnBu₃ as impurity!
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 453

5.8
Crude tributylstannyl alcohol with HSnBu3 as impurity!

Crude tributylstannyl mesylate with HSnBu3 as impurity!
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 457

5.11

O
Me

SnBu3

NH2
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR 461

5.13a
Ph\(\equiv N\)\(\text{CO}_2\text{tBu}\)

![NMR Spectrum](image)

5.17
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

H₂N₉₅CO₂H x HCl

F

5.18
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

- NMR

BocHN

NOMe

5.24

1H (ppm)

10.0  9.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0  -0.5

13C (ppm)

110  200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

5.25
CHAPTER 7: EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA - NMR

BocHN

\[
\text{Me} \quad \text{F} \\
\text{Me} \\
\text{OH}
\]

5.26
Michael Umberto Luescher

Personal Information

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Education

2012 – present PhD candidate in Organic Chem., Department of Chem. and Applied Biosciences, ETH Zurich, Zurich, Switzerland (Prof. J. W. Bode)
2001 – 2004 Lab Technician Apprenticeship, Novartis Institutes for Biomedical Research, Basel, Switzerland

Research Experience

Oct. – Nov. 2016 Institute of Transformative Bio-Molecules in Nagoya (ITbM), Nagoya, Japan
Visiting PhD student in the research group Prof. Kenichiro Itami working on photoredox protocols towards a catal. enantioselective SnAP reaction.

2012 – present Swiss Federal Institute of Technology in Zurich (ETH Zurich), Zurich, Switzerland
Doctoral research with Prof. J. W. Bode working on the preparation of saturated, functionalized aza-heterocycles using SnAP (tin (Sn) amine protocol) reagents for applications drug development approaches. Developed new reagents, routes to access them, and reaction protocols to prepare the desired scaffolds using catal. procedures. Reagents are made comm. available in collaboration with Sigma-Aldrich.

2011 – 2012 University of Basel, Basel, Switzerland
Undergraduate research projects with Prof. Karl Gademann on studies towards ophiodilacone A and B involving investigations on phase-transfer reactions. Progress was made towards the stereoselective preparation of the target compound.

Summer 2011 Massachusetts Institute of Technology (MIT), Cambridge, United States of America
Research internship with Prof. Rick L. Danheiser investigating intramolecular nitrile Diels–Alder reactions and their application in pyridine synthesis. Model substrates were synthesized and the participation of the CN group in [4+2] cycloaddition reactions was investigated.

2004 – 2007 & Summer 2010 Novartis Institutes for Biomedical Research, Basel, Switzerland
Working as a lab technician on advanced S.A.R. studies through the complete preparation of small molecules as candidate drugs in the nervous system and oncology division including cGMP and GLP documentation.

Teaching and Coaching Experience

2012 – present Swiss Federal Institute of Technology in Zurich (ETH Zurich), Zurich, Switzerland
- Teaching and head teaching assistant of an org. chem. course (Fall Semester 2014 and 2015).
- Responsible for lab safety including the training of new lab members and organizing fire safety courses.
- Guiding a prospective laboratory technician in organic synthesis techniques, analytical methods and cGMP, GLP documentation.
Awards and Fellowships

2015
- SCNAT/SCS/SSFEC 2015 Chem. Travel Award
- Poster Prize at the Swiss Chemical Society Syngenta Symposium 2015

2016
- Award for the Best Group Contribution at the Syngenta Symposium for Talented PhD Students

2017
- Three-Year Postdoctoral HFSP (international human frontier science program organization) Cross-Discipl. Fellowship (CDF).

Publications

2. Geoghegan, K.; Luescher, M. U.; Bode J. W. “2-(((Tributylstannyl)methyl)thio)ethanamine, 2-((Tributylstannyl)methoxy)ethanamine and tert-Butyl (2-aminoethyl)((tributylstannyl)methyl) carbamate” e-EROS 2017, DOI: 10.1002/047084289X.

Conferences, Presentations and Workshops


Luescher, M. U.; Syngenta Workshop for Talented PhD Students, Syngenta AG, Stein, Switzerland, 2016


Luescher, M. U.; Bode J. W. “Catalytic One-Step Synthesis of Unprotected Piperazines, Morpholines and Thiomorpholines using SnAP Reagents” Oral Presentation, Swiss Chemical Society Fall Meeting, Lausanne, Switzerland, 2015
