Doctoral Thesis

New cross-coupling strategies for the synthesis of dialkyl ethers and saturated N-heterocycles

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New Cross-Coupling Strategies for the Synthesis of Dialkyl Ethers and Saturated N-Heterocycles

A thesis submitted to attain the degree of
DOCTOR OF SCIENCES of ETH ZURICH
(Dr. sc. ETH Zurich)

presented by
CAM-VAN VO

Master of Science, University of Pennsylvania
Born January 1st 1981
Citizen of Vietnam

accepted on the recommendation of
Prof. Dr. Jeffrey W. Bode, examiner
Prof. Dr. Erick M. Carreira, co-examiner

2014
Acknowledgement

It has been seven years since the day I left Vietnam for this amazing journey. I am so lucky to travel through three different continents for the Ph.D, to work with many outstanding scientists in professional environments, to learn not only science but also different cultures and meet many interesting people along the way. It has enriched my life day by day.

One of the questions I received most is why I joined the Bode group. It was because Jeff was nice and I found myself confident in this group. I owe the deepest gratitude to my advisor – Prof. Jeffrey W. Bode. I thank him for accepting me into his group, encouraging and supporting me both in my study and my research. I feel like growing up everyday in his group. He has always taught me to understand why and what I am doing, to be independent in science, and to push myself further “aim high and reach high”. I am grateful that he never left me “drowning” in my research problems, and was always opened for discussion and new ideas.

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I never thought that I would come to Switzerland – an amazingly peaceful country (just a bit too cold in winter), and to ETH – a perfect place for science. Here, I have chance to work with many talented colleagues. I express my gratitude to all Bode group members. Thanks to all of your collaborations, helps and humors, most of the time in the lab is joyful to me. I had a great opportunity to work with my dear labmates (Dmitry Mazunin, Gabriel Schäfer, the Awesome Team – Ayodele Ogunkoya, Ivano Pusterla, Michael Lüscher, Thomas Pieth and Claudia Murar). I have learned a lot especially from Noda-san – a live chemistry encyclopedia and a running machine, from Ivano – a perfectionist chemist, from Sheng-Ying (Fly) – the “Office” trouble-shooter and others for countless number of other things.

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One cannot success without the support of his family. To my beloved husband – Dung Hong, I could not imagine how I could survive through those years without your support. I am so grateful and lucky to have you in my life. Thank you for always being there when I need you most, always being gentle to me (even when I was not nice to you). Thank you for believing in me, sharing all the difficulties and happiness with me. I am happy that from now on we no longer stay so far from each other. Last but not least, I am deeply thankful to my parents – Tham Vo and Anh-Nguyet Ngo – for their unconditional loves, for raising me to believe everything is possible. To my brother – Thinh Vo, thank you for taking care of our parents all the time I am not at home. I wish you a bright future.

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Zurich, Switzerland

November 28th, 2013
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<tr>
<td>(11R)-(+)</td>
<td>(11aR)-(+)\text{-}10,11,12,13-tetrahydrodiindeno[7,1-de:1',7'-fg][1,3,2]dioxaphosphocin-5-bis[(R)-1-phenylethyl]amine, N-Di[(R)-1-phenylethyl]-[((R)-1,1′-spirobiindane-7,7′-diyl]-phosphoramidite</td>
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<td>dba</td>
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<td>DIAD</td>
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<td>(N,N)-diisopropylethylamine</td>
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<td>DMA</td>
<td>dimethylacetamide</td>
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<td>DMAP</td>
<td>4-((N,N)-dimethylamino) pyridine</td>
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DMF  dimethylformamide
DMSO  dimethyl sulfoxide
Dpe-Phos  bis-[2-(diphenylphosphino)phenyl]ether
EDTA  ethylenediaminetetraacetic acid
Et  ethyl
HFIP  hexafluoroisopropanol
LDA  lithium diisopropylamide
Me  methyl
MEM  β-methoxyethoxymethyl
MOM  methoxymethyl
Ms  methanesulfonyl
MS  molecular sieve
n-BuLi  n-butyllithium
n-Pr  n-propyll
NFBS  N-fluorobenzenesulfonimide
Ns  4-nitrobenzenesulfonyl
Ph  phenyl
RuPhos  2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
s-Bu  sec-butyl
SnAP  Tin (Sn) Amine Protocol
t-AmOH  tert-pentanol
\begin{itemize}
\item \textit{t-Bu} \quad \textit{tert}-butyl
\item \textbf{TBAF} \quad \textit{tetrabutylammonium fluoride}
\item \textbf{TBAT} \quad \textit{tetrabutylammonium triphenyldifluorosilane}
\item \textbf{TEA} \quad \textit{triethylamine}
\item \textbf{TEMPO} \quad \textit{2,2,6,6-tetramethylpiperidine 1-oxyl}
\item \textbf{TES} \quad \textit{triethyilsilyl}
\item \textbf{TFA} \quad \textit{trifluoroacetic acid}
\item \textbf{THF} \quad \textit{tetrahydrofuran}
\item \textbf{TIPS} \quad \textit{triisopropylsilyl}
\item \textbf{TMEDA} \quad \textit{tetramethylethylene diamine}
\item \textbf{TMS} \quad \textit{trimethylsilyl}
\item \textbf{Tol} \quad \textit{toluene}
\item \textbf{Tr} \quad \textit{trityl (triphenylmethyl)}
\end{itemize}
# LIST OF COMMON TERMS

<table>
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<tr>
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<tr>
<td>[α]</td>
<td>specific optical rotation</td>
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<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>calcd</td>
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<tr>
<td>¹³C NMR</td>
<td>carbon-13 nuclear magnetic resonance</td>
</tr>
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<td>cat.</td>
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<td>δ</td>
<td>chemical shift</td>
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<td>J</td>
<td>coupling constant</td>
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<td>d</td>
<td>doublet</td>
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<tr>
<td>°C</td>
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<tr>
<td>d.r.</td>
<td>diastereometric ratio</td>
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<tr>
<td>EI</td>
<td>electron impact ionization</td>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
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<tr>
<td>equiv</td>
<td>equivalent(s)</td>
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<td>Fg</td>
<td>functional group</td>
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<td>ESI</td>
<td>electrospray ionization</td>
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<td>g</td>
<td>gram</td>
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<td>HPLC</td>
<td>high-performance liquid chromatography</td>
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<td>HRMS</td>
<td>high resolution mass spectrometry</td>
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<td>h</td>
<td>hour(s)</td>
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<td>IR</td>
<td>infrared</td>
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<td>i-</td>
<td>iso-</td>
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<tr>
<td>LA</td>
<td>Lewis Acid</td>
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<td>m/z</td>
<td>mass/charge</td>
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<td>mp</td>
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<td>MHz</td>
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<tr>
<td>Symbol</td>
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<td>min</td>
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<tr>
<td>M</td>
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<td>NMR</td>
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<td>o-</td>
<td>ortho-</td>
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<tr>
<td>p-</td>
<td>para-</td>
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<td>ppm</td>
<td>parts per million</td>
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<tr>
<td>$^1$H NMR</td>
<td>proton NMR</td>
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<tr>
<td>PTLC</td>
<td>preparative thin layer chromatography</td>
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<td>q</td>
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<td>t-</td>
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<tr>
<td>t</td>
<td>triplet</td>
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<tr>
<td>$R_f$</td>
<td>retardation factor</td>
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<tr>
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<td>room temperature</td>
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<td>supercritical fluid chromatography</td>
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<td>ν</td>
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<tr>
<td>WV</td>
<td>microwave irradiation</td>
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<td>UV</td>
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Abstract

The current practice of synthetic organic chemistry relies heavily on the use of general, predictable coupling reactions of preformed building blocks. Despite the remarkable success of metal-catalyzed cross-coupling reactions, several important chemical connections are currently not well served by the existing methods. In this Dissertation, new cross-coupling strategies for the synthesis of dialkyl ethers and substituted saturated N-heterocycles are described.

Our group has reported a cross-coupling strategy for the preparation of dialkyl ethers by BF$_3$•OEt$_2$-promoted reaction of potassium organotrifluoroborates and O-methoxymethyl (O-MOM) acetals. Despite the advantages of this process, several limitations of this approach were noted, namely poor regioselectivity and low reactivity of electron-deficient aryltrifluoroborates, heteroaryltrifluoroborates, and alkyltrifluoroborates. The first part of this Dissertation describes the development of a second-generation ether-forming cross-coupling reaction, in which hydroxamic acid-derived acetal were identified as a new reaction partner. This new reaction partner enables the reaction to proceed under even milder conditions, and with less reactive potassium organotrifluoroborates. A study of the mechanism identified a role of hydroxamate moiety to overcome above limitations and provided insight into the reaction pathway.

The second part involves the development of SnAP reagents for the transformation of aldehydes into saturated N-heterocycles. A new approach to saturated N-heterocycles – intramolecular C–C bond-forming radical cyclization of an imine bearing a nucleophilic carbon has been established as an alternative to cross-coupling reactions with saturated N-heterocycles. A family of SnAP reagents have been prepared on multi-gram scale from inexpensive starting materials. SnAP reagents condense with aldehydes, followed by cyclization with copper(II)triflate to afford various unprotected N-heterocycles with different ring sizes. The reactions accept a broad scope of aldehydes including aryl, heteroaryl, alkyl aldehydes and glyoxylate. Preliminary mechanistic studies indicated copper-mediated oxidation of carbon-tin bond to generate heteroatom-stabilized primary carbon radical followed by intramolecular cyclization to deliver the product.
Zusammenfassung


Part I.

Ether-Forming Cross-Coupling Reactions of Organotrifluoroborates and Acetals
1. Background and Introduction

The last three decades have witnessed the remarkable success of metal-catalyzed cross-coupling reactions in organic chemistry. A metal-catalyzed cross-coupling reaction is generally referred as the coupling of an organohalide and a nucleophile catalyzed by a transition metal complex. The most common nucleophiles are carbon-based nucleophiles including organoborons (Suzuki-Miyaura), organomagnesiums (Kumada), organostannanes (Stille), organozincs (Negishi), organosilanes (Hiyama), alkenes (Heck) or alkyne pronucleophiles (Sonagashira). Over the years, extensive research efforts have been made in the development of ligands, metals, reaction conditions and building block availability making this method one of the most useful tools for carbon-carbon bond construction in both academia and industry. Cross-coupling reactions are not just limited to C–C bond formation, they have expanded to include heteroatom-based nucleophiles, which have recently received much attention. The use of oxygen-based nucleophiles leads to the formation of ether bond, one of the most abundant linkages in natural and man-made organic compounds. Over 20% of the top 200 small-molecule pharmaceuticals and 75% of new chemical entities contained at least one ether linkage (Figure 1).

Figure 1. Selective bioactive ethers
1.1. Metal-Catalyzed C–O Bond Forming Cross-Coupling Reactions

1.1.1. Ullmann-type Coupling Reactions

The C–O bond forming cross-coupling reactions started in the early twentieth century (1904), long before the seminal idea of transition metal-catalyzed C–C bond cross-coupling reactions (1970s). Two years after the discovery of the dimerization of o-bromonitrobenzene promoted by superstoichiometric copper – known as the Ullmann reaction – in 1901, Ullmann extended the reaction to the synthesis of diphenyl ether by the coupling of potassium phenoxide and bromobenzene (Scheme 1a). For more than a century, Ullmann ether synthesis has been used extensively for the preparation of simple and stable diaryl ethers in both industry and academia. The reaction proceeds under quite harsh conditions, including the use of strong bases, stoichiometric copper reagents and high reaction temperatures (>200 °C). The substrate scope is limited to electron-deficient aryl halides. In the intervening 90 years, the original Ullmann ether synthesis was not much improved. In the 1990s, the introduction of new copper sources, ligands, bases and aryl donors improved dramatically the outcome of this transformation. In 1997, Buchwald introduced the use of catalytic copper(I) triflate with ethyl acetate and naphthoic acid as ligands and cesium carbonate as base (Scheme 1b). The coupling reaction of phenols and aryl halides could be obtained at lower temperature (110 °C). The reaction scope has been expanded to unactivated aryl halides and hindered phenols. Further improvements by other research groups on the choice of appropriate bases and solutions for the low solubility of copper salts have been made, allowing the coupling of most classes of aryl halides with a variety of phenols.

The first successful application of copper-mediated arylation of aliphatic alcohols was reported by Buchwald in 2002 (Scheme 1c). Phenanthroline and its tetramethylated derivatives were used as ligands. The reaction conditions accommodated a wide range of alcohols including primary, secondary aliphatic, allylic, benzylic and propargylic alcohols. On the observation that amino acids not only accelerated the coupling of themselves with aryl halides, but also promoted the coupling of amines and phenols with aryl halides, Ma
and coworkers investigated the copper-catalyzed arylation of aliphatic alcohols using amino acids as ligands (Scheme 1d).

The complex of catalytic Cul and N,N-dimethylglycine allowed the coupling of aryl halide and most type of alcohols to occur smoothly at 110 °C in good yields. The above conditions are also applicable to the synthesis of vinyl ethers.

Scheme 1. Ullmann-type coupling for aryl ether synthesis

1.1.2. Chan-Lam Cross-Coupling Reactions

In 1998, Chan, Lam and Evans independently reported the coupling of aryl boronic acids and N–H or O–H containing compounds in the presence of Cu(II) reagents to generate aryl amines or aryl ethers, later known as the Chan-Lam cross-coupling. The reaction is a significant improvement in copper-mediated C–O and C–N bond forming cross-coupling for its mild conditions (room temperature, in air), the use of commercially available boronic acids and high functional group tolerance. The reaction initially required
stoichiometric amount of copper (Scheme 2a). In 2001, the catalytic C–O Chan-Lam coupling was developed by Lam using oxygen as the co-oxidant (Scheme 2b). Other aryl boron derivatives such as arylboronate esters, triarylboroxines were demonstrated to be suitable coupling reagents. Batey and Quach in 2003 investigated the copper-catalyzed coupling reactions of alkenyl- and aryltrifluoroborates with alcohols (Scheme 2c). Organotrifluoroborates were observed to be better than boronic acids. More importantly, the coupling reaction accepted a variety of alcohols including primary and secondary aliphatic, allylic, and propargylic alcohols.

**Scheme 2.** Chan-Lam cross-coupling reactions for aryl ether synthesis

1.1.3. Buchwald-Hartwig Cross-Coupling Reactions

The coupling reactions of alcohols and aryl halides catalyzed by palladium have been challenging to develop compared to the ones catalyzed by copper. The tendency of the \( \text{L}_2\text{Pd}^{II}(\text{Ar})(\text{OR}) \) intermediate to undergo \( \beta \)-hydride elimination is higher than the corresponding copper intermediate. The slower rate of C–O reductive elimination relative to \( \beta \)-elimination explains the low yields observed in the coupling of certain substrates. The
research groups of Buchwald and Hartwig in 1996 simultaneously developed Pd-catalyzed coupling of aryl halides and alcohols lacking β-hydrogen using bidentate phosphine ligands (Scheme 3a-b).\(^{19}\) The coupling occurred with either activated aryl halides (electron-deficient aryl halides) or intramolecularly at high temperature (100 °C). Further improvements on reductive elimination rate were achieved by the use of sterically hindered electron-rich phosphines (Scheme 3c).\(^{20}\) These types of ligands allowed the coupling of unactivated aryl halides with a broad scope of alcohols (aliphatic, allylic, benzylic and propargylic alcohols).\(^{21}\)

Scheme 3. Buchwald-Hartwig coupling for aryl ether synthesis

Metal-catalyzed C–O bond cross-coupling reactions are well-suited for the synthesis of various aryl ethers. This approach is currently, however, not applicable for dialkyl ether synthesis.

1.2. Carbenoid O–H Insertion for Ether Synthesis

Transition metal-catalyzed insertion of carbenoid into the O–H bond of alcohol provides a direct and efficient strategy for ether synthesis.\(^{22}\) Carbenoids are generally
generated in situ from diazo precursors. The O–H insertion of diazocarbenoids can be traced back to the report of Yates in 1952 on the copper-catalyzed decomposition of diazoketones (Scheme 4a).\(^{23}\) In this reaction, ethanol reacted with \(\alpha\)-diazoketone in the presence of catalytic amount of copper metal to afford \(\alpha\)-ethoxy ketone with good yield. \(\text{Rh}_2(\text{OAc})_4\) was first used by Teyssie in 1973 to generate a rhodium-carbenoid intermediate from diazo carboxylate, followed by O–H insertion to deliver ethers (Scheme 4b).\(^{24}\) Intensive studies on rhodium oxygen-hydrogen insertion of carbenoids have been done to expand the substrate scope to various alcohols, phenols and thiols.\(^{25}\) Limitations of rhodium-carbenoids in O–H insertion such as competing C–H insertion, \(\beta\)-elimination led to the reinvestigation of the O–H bond insertion of diazo compounds catalyzed by copper, especially for developing the enantioselective processes.

![Scheme 4](image)

**Scheme 4.** Copper- and rhodium-catalyzed O–H bond insertion

In 2006, Fu and Maier described the first copper/bisazaferrocene-catalyzed enantioselective O–H insertion generating \(\alpha\)-alkoxy carbonyl compounds in good ee (Scheme 5a).\(^{26}\) Different \(\alpha\)-aryl-\(\alpha\)-diazo esters could insert into O–H bonds of a wide range of alcohols (primary, secondary aliphatic, benzylic, allylic alcohols and phenols) in good yields. The enantioselectivity of this transformation depends on the choice of alcohols. Selectivity was observed to decrease in the case of allylic alcohols and phenols. The research group of Zhou later reported the use of chiral spiro bisoxazolines as ligands to improve the copper-catalyzed enantioselective insertion of diazocarbonyl compounds into O–H bonds of phenols (Scheme 5b).\(^{27}\) With the same type of ligands, they further developed the enantioselective iron/spiro bisoxazoline-catalyzed O–H insertion in 2010.\(^{28}\) The reactions proceeded smoothly with a broad scope of alcohols (aliphatic, benzylic and allylic alcohols) in good to excellent yields and enantioselectivity (Scheme 5c).
Sulfonylhydrazones are stable and versatile intermediates, which can be prepared from the condensation of aldehydes and hydrazines. They decompose under thermal conditions in the presence of base, leading to the formation of diazo compounds. In 2010, the research group of Barluenga and Valdés investigated the thermal decomposition of diazo compounds in the presence of alcohols and developed a simple method for the conversion of tosylhydrazones into ethers (Scheme 6). The reaction was proposed to occur through an insertion of the in situ carbene into the O–H bond of alcohol, under thermal condition (110–160 °C) or by microwave irradiation. The reaction is quite general; diazo intermediates can be generated from either aromatic or aliphatic hydrazones; all types of alcohols including allylic, benzylic, aliphatic alcohols and phenols can be used successfully.
1.3. Strategies for Dialkyl Ether Synthesis

Despite the prevailing occurrence of dialkyl ethers in organic compounds, reactions for their preparation are limited to a few harsh and unsavory methods, exemplified by the Williamson ether synthesis (Scheme 7). A particularly challenging task is the preparation of highly substituted alkyl ethers formed from two chiral secondary or tertiary alcohols. The use of Williamson ether synthesis or $S_N1$-type reactions of unstablized carbocations are often limited by the steric hindrance sensitivity and the competing elimination reaction under strongly basic conditions.

Unlike the well-established metal-catalyzed cross-coupling reactions for aryl ether synthesis, the efficient C–O bond forming cross-coupling for dialkyl ether synthesis still remains challenging. The use of Csp$^3$-electrophiles and aliphatic oxygen-based nucleophiles generally results in slower oxidation addition and reductive elimination relative to the Csp or sp$^2$ analogues. Slow oxidative addition and/or reductive elimination lead to the formation of side products from $\beta$-hydride elimination or homocoupling reaction (Scheme 8a). Metal-catalyzed insertion of diazo compounds into O–H bond of alcohols provides a direct method to access alkyl ethers from a wide range of alcohols in good yield and enantioselectivity. However, it is only efficient for stabilized $\alpha$-diazo carbonyl compounds (Scheme 8b). The transformation of tosylhydrazones into ethers under thermal conditions provides a nice method to access highly substituted aryl alkyl ethers from readily carbonyl compounds and alcohols. The limitation of this method is the high reaction temperature ($110–160 ^\circ C$) (Scheme 8c).
The other approach to the formation of ether bond is the C–C bond forming disconnection rather than the traditional C–O bond-forming disconnection (Figure 2). Based on this concept, several methods have been developed including metal-catalyzed cross-coupling reactions of alkoxyalkylmetallic nucleophiles with organohalides and acetal-based nucleophilic addition.

Scheme 8. Dialkyl ether synthesis via C–O cross coupling and O–H insertion

Alternatives Approaches to Dialkyl Ethers

The other approach to the formation of ether bond is the C–C bond forming disconnection rather than the traditional C–O bond-forming disconnection (Figure 2). Based on this concept, several methods have been developed including metal-catalyzed cross-coupling reactions of alkoxyalkylmetallic nucleophiles with organohalides and acetal-based nucleophilic addition.

Figure 2. Approaches for ether synthesis
1.3.1. Metal-Catalyzed C–C Bond Forming Cross-Coupling for Ether Synthesis

Molander and coworkers in 2008 first reported the Suzuki coupling reactions of potassium alkoxymethyltrifluoroborates with aryl chlorides for the preparation of alkyl benzyl ethers (Scheme 9a). The use of stable potassium alkoxymethyltrifluoroborates overcomes the limitations of the corresponding air-sensitive alkoxymethylboronate esters. Potassium alkoxymethyltrifluoroborates can be easily prepared via direct nucleophilic substitution of potassium halomethyltrifluoroborates with the corresponding alkoxides. Under the optimized conditions with catalytic Pd(OAc)$_2$, RuPhos as ligand and CsCO$_3$, different alkyl benzyl ethers were successfully prepared in good yields. With appropriate ligands for palladium, the scope of this coupling has been broadened to other electrophiles such as benzyl chlorides, aryl/heteroaryl pseudohalides and other organoborons such as alkoxyethyltrifluoroborates and dioxolanylethyltrifluoroborates (Scheme 9b–d). To dates, there is no example on α-substituted alkoxymethyltrifluoroborates to afford more substituted dialkyl ethers.

Scheme 9. Cross coupling of alkoxyalkyltrifluoroborates and halides by Molander
In a further exploration of alkoxymethyltrifluoroborate activity, Molander and coworkers developed an ether-forming Minisci reaction (Scheme 10). Potassium alkoxymethyltrifluoroborates served as radical precursors to generate oxygen-stabilized primary carbon-centered radicals under oxidative conditions, which subsequently add to the protonated heteroarene leading to the formation of ether product after the second oxidation.

![Scheme 10. Direct alkoxyalkylation of heteroarenes (Minisci reaction) by Molander](image)

### 1.3.2. Acetal-based Ether Synthesis

Acetals are known as protecting groups for carbonyl or alcohol functional groups. They are generally stable and do not react with nucleophilic reagents under basic conditions. However, under acidic conditions acetals act as strong electrophiles toward various nucleophiles via the formation of oxocarbenium ions as the reactive intermediates. They are considered as synthetic equivalents of carbonyl functional groups. The addition of a nucleophile to oxocarbenium ion leads to the formation of ether. Since the first report of Mukaiyama on the titanium-promoted aldol-type reactions of acetals and silyl enol ethers, there have been a number of publications describing acid-mediated C–C bond forming reactions of acetals. A variety of active carbon nucleophiles including silyl enol ethers, cyanides, allylic silanes have been used to add into oxocarbenium ions. These reactive intermediates were generally generated from the interaction of Lewis acids such as trimethylsilyl trifluoromethanesulfonate (TMSOTf), TiCl₄, SnCl₄, BF₃•Et₂O and the Lewis-basic oxygens of acetals. The reactions were mostly conducted at low temperatures (−78 °C) due to the poor stability of the oxocarbenium ions. The use of organometallic reagents as nucleophiles has been much less investigated.
Grignard Reagents

Activated α,β-unsaturated acetals react with Grignard reagents in the presence of titanium tetrachloride to afford allyl ethers in high yields.\(^{48}\) The reaction was proposed to proceed through a six-membered ring transition state. In the case of mixed acetals containing 2,4-dichlorophenoxyl group, TiCl\(_4\) was not required as the preferential binding of 2,4-dichlorophenoxyl group to magnesium facilitates the addition of nucleophile to the acetal (Scheme 11).\(^ {49}\)

![Scheme 11](image)

**Scheme 11.** Nucleophilic addition of Grignard reagents to acetals by Mukayama

Organocoppers

In the presence of BF\(_3\)•OEt\(_2\), organocoppers (RCu) and organocuprates (R\(_2\)CuLi) react quickly with acetals at \(-78{^\circ}\text{C}\) to give various dialkyl ethers.\(^{50}\) The reactions work well with either acetals or ketals regardless of the increasingly steric hindrance. A broad range of copper nucleophiles including primary, secondary aliphatic and aromatic cuprates could be used successfully in this transformation (Scheme 12a).

![Scheme 12](image)

**Scheme 12.** Nucleophilic addition of organocuprates to acetals
In a study of chemoselective deprotection of acetals in the presence of ketals using triethylsilyl trifluoromethanesulfonate (TESOTf) and 2,4,6-collidine, Fujioka and coworkers observed the formation of pyridinium-type salts 1 as the intermediates (Scheme 12b). These salts were reactive toward nucleophiles including water and other heteroatom-based nucleophiles (alcohols, thiols, azides, ect.), and are rather stable even at 0 °C compared to the less stable oxocarbenium ions. They further expanded the scope of nucleophiles to carbon-based nucleophiles including high-order cuprates and Gilman reagents. The reactions successfully proceeded with primary and secondary Gilman reagents to access different patterns of dialkyl ethers (Scheme 12b).

**Organoboron Reagents**

Organoborons exhibit wide-ranging utility in synthetic chemistry. Unlike other active organometallics such as organomagnesiums and organolithiums, organoborons possess milder and predictable reactivity. They are stable, easily prepared and easily handled. Since the discovery of the Suzuki-Miyaura coupling reactions, thousands of organoborons have become commercially available and are reagents of choice in coupling reactions. Despite these advantages, the addition of organoborons into oxocarbenium ions is not quite common.

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**Scheme 13.** Nucleophilic addition of organoborons to acetals
In 2010, Kobayashi reported the addition of allylboronates to acetals and ketals using InOTf as the dual catalyst (Scheme 13a).\textsuperscript{56} InOTf both serves as a Lewis acid to activate electrophilic acetal and transmetallates with allylboronate to form allylindium as the active nucleophile. The reactions occurred at room temperature, accommodated various aromatic, aliphatic acetals and ketals as electrophiles. With the same concept of nucleophilic addition to activated electrophilic acetals, Schaus used a chiral Bronsted and Lewis acid system (tartaric acid derived/Ce(OTf)_4) to catalyze the enantioselective addition of vinyl-, arylboronates to chromene acetals (Scheme 13b).\textsuperscript{56} Initial mechanistic studies indicated that the interaction of chiral Bronsted acid, Lewis acid and boron leads to the formation of an “ate-complex” boronate, which serves as the active Lewis acid facilitating the formation of cyclic oxocarbenium ion. The stereoselective addition of the chiral tetravalent boronate to cyclic oxocarbenium ion leads to the formation of ether. The efficiency of this reaction is limited to intrinsic nucleophilic partners such as cinnamyl and \(\pi\)-rich arenes. The research group of A. Doyle has recently developed an alternative to nucleophilic addition to acetals – nickel-catalyzed cross-coupling reactions of aryl- and heteroarylboronic acids with chromene acetals. The reactions enable chromene acetals to couple with a broader range of organoborons (Scheme 13c).\textsuperscript{57} In this transformation, the complexation of boron to the Lewis-basic oxygens of acetal promotes \(\text{Csp}^3\text{–O}\) oxidative addition of Ni to generate the Ni complex, followed by the transmetallation and arylboronic acid and reductive elimination to deliver the ether product. A range of aryl/heteroaryl boronic acids were suitable as coupling partners regardless of the electronic nature of the substituents on the phenyl ring.

1.4. Ether-Forming Cross-Coupling Reactions of Organotrifluoroborates and Acetals

The broad application of trivalent organoborons, particularly boronic acids and esters, in organic chemistry has clearly proven the popularity of the Suzuki coupling reactions. However, most of them are often consumed directly in the coupling reactions after purchased or prepared. It is rare to find a trivalent organoborons that survive intact through a lengthy, multiple-step synthesis.\textsuperscript{58} They are susceptible to reagents such as
oxidant, nucleophiles and bases. Some of boronic acids such as alkyl-, vinyl- or alkynyl boronic acids are not stable under atmospheric conditions or undergo the equilibrium formation of boroxines.\textsuperscript{59} The sensitivity of trivalent organoboron relies in the vacant orbital of boron, which can be attacked by oxidants, water or nucleophiles.\textsuperscript{60} In contrast to trivalent organoborons, tetravalent organotrifluoroborates with the strong boron-fluoride bonds are electron-rich species.\textsuperscript{61} They are usually crystalline compounds, stable toward air, moisture and other nucleophiles. They are easily accessed through one-pot synthetic routes; many of them are now commercially available.\textsuperscript{62,63} Organotrifluoroborates have been used widely as boronic acid equivalents in Suzuki reactions.

### 1.4.1. Nucleophilic Addition of Organotrifluoroborates to Iminium Ions

Unlike boronic acids, organotrifluoroborates however have not been used in addition to oxocarbenium ions for ether synthesis.\textsuperscript{64} This contrasts with the powerful addition to iminium ions, pioneered by Petasis\textsuperscript{65} and further developed by Batey,\textsuperscript{66} Langlois\textsuperscript{67} and Raeppel\textsuperscript{68} in the synthesis of substituted amines (Scheme 14).

\begin{scheme}
\textbf{Scheme 14.} Nucleophilic addition of organoborons to iminium ions
\end{scheme}
1.4.2. Ether-Forming Cross-Coupling Reactions of Organotrifluoroborates and Acetals

In our own efforts to provide a general chemical method for the preparation of dialkyl ethers under mild conditions from readily available starting materials, our group developed the BF$_3$•OEt$_2$-promoted reactions of potassium organotrifluoroborates and O-methoxymethyl (O-MOM) acetals for dialkyl ether synthesis (Scheme 15). O-MOM acetals are easily prepared from alcohols under mild conditions. The two components undergo regioselective coupling in the presence of BF$_3$•OEt$_2$ to give ethers. Alkynyl-, aryl-, and vinyltrifluoroborates were suitable substrates. The chemistry could be extended to substituted acetals that lead to secondary–secondary ethers in good to excellent yields. The mechanism of this reaction involves the formation of organodifluoroborane III, which serves as the active Lewis acid, from the interaction of organotrifluoroborate II and BF$_3$•OEt$_2$. The less sterically hindered oxygen of acetal I binds to organodifluoroborane III to generate the oxocarbenium ion V as the electrophile and the organodifluoroborane VI as the nucleophile. The nucleophilic transfer from organodifluoroborane VI to oxocarbenium ion V delivers dialkyl ether product VIII.

Scheme 15. Ether-forming cross coupling of organotrifluoroborates and O-MOM acetals
1.5. Conclusions

Over 150 years since the report of Williamson for ether synthesis, the synthetic chemistry community has been aiming at new ether-forming methods to overcome the harsh conditions of the original methodology, and to improve the generality and applicability from available building blocks. Metal-catalyzed C–O bond forming cross-coupling reactions of alcohols and organometallics for the synthesis of aryl ethers have been investigated and utilized widely. This strategy, however, is not suited for the synthesis of dialkyl ethers. Alternative approaches to access dialkyl ethers including carbenoid O–H bond insertion, metal-catalyzed C–C bond forming cross-coupling and acetal-based ether synthesis have drawn much attention of chemists and provided more options in the toolbox of ether synthesis. Regardless of these achievements, highly substituted dialkyl ethers are still challenging targets. A chemical method that can provide the predictability, the use of stable and preformed materials remains to be discovered and exploited.
2. Second-Generation Ether-Forming Cross-Coupling Reactions of Organotrifluoroborates and Acetals

In 2009 our group reported a cross-coupling strategy for the preparation of dialkyl ethers: the BF$_3$•OEt$_2$-promoted cross-coupling reactions of potassium organotrifluoroborates and O-MOM acetals.$^{69}$ The reaction is quite general with readily available, easily-handled reagents. The coupling occurs regioselectively under mild conditions and with good substrate scope to provide sterically demanding primary–secondary and secondary–secondary ethers, which would be difficult to prepare via the common Williamson ether synthesis.

![Scheme 16. Limitations of organotrifluoroborate and O-MOM acetal coupling](image)

In further exploring the applicability of this methodology for more substituted acetals and other classes of potassium organotrifluoroborates, we noted several limitations. First, as the substrates became more substituted the regioselectivity of the reaction eroded and the formation of undesired side products 2 increased. Second, modestly electron-deficient aryltrifluoroborates were poor substrates and heteroaryltrifluoroborates did not react. Third, a relatively large excess of potassium organotrifluoroborate (4.0 equiv) and BF$_3$•OEt$_2$ (4.0 equiv) along with a precomplexation step were required (Scheme 16). This part of the

Dissertation will describe the development of a second-generation ether-forming cross-coupling reactions of organotrifluoroborates and acetalts and further studies on the substrate scope, mechanism, and reactivity patterns of this transformation.

2.1. Identification of New Reaction Partner

The goals of our studies were to identify the conditions and reagents that:

1. improve the regioselectivity of challenging substrates (highly substituted acetals).
2. accommodate electron-deficient aryltrifluoroborates, heteroaryltrifluoroborates.
3. reduce the requirement for a large excess of organotrifluoroborate and Lewis acid.

A survey of alternative Lewis acids, reaction conditions and the addition of transition metals did not offer a general solution to the challenging substrates or address the regiochemical issues. We therefore turned to the optimization of the leaving group to provide a more robust and operationally-friendly process. In the first generation, the reactions proceeded best with alkynyltrifluoroborates, less efficiently with alkenyl- or aryltrifluoroborates and not at all with heteroaryl- and alkyltrifluoroborates. Moderate or low yields were observed with more hindered examples such as secondary-secondary acetals. In the case of alkenyl- or aryltrifluoroborates or more hindered acetal substrates used, the formation of methyl ether side products significantly increased. The use of mixed acetals of more acidic alcohols, such as phenol derivatives, led to diminished or completely reversed regioselectivity (eq 1).

\[
\text{PhO} \rightarrow \text{MeO} \quad \text{Ph} \quad \text{BF}_3 \quad \text{Ph} \quad \text{BF}_3 \quad \text{K} \quad 2.0 \text{equiv BF}_3 \cdot \text{OEt}_2 \quad \text{Ph} \quad \text{BF}_3 \quad \text{K} \quad \text{PhO} \quad \text{CH}_3 \text{CN, 0 °C} \quad \text{PhO} \quad \text{CN, 0 °C} \\
\begin{array}{c}
\text{desired product} \\
0% \ \\
\text{undesired product} \\
92%
\end{array} 
\]

This result indicated that the preferential binding of boron to phenoxy group (OPh) relative to methoxy group (OMe) of the acetal might cause the reversed regioselectivity, and that the regioselectivity could be improved by modifying the affinity of the leaving group to boron. With this in mind, we investigated alternative leaving groups (OY in Table 1) to
improve the selectivity and reactivity of the reaction. The coupling reaction of potassium phenyltrifluoroborate with unsymmetrical acetals of cyclohexanol 3, which could be prepared from commercially available cyclohexyl chloromethyl ether and corresponding alcohols (eq 2), were chosen as the model reaction. The efficiency of the alternative leaving groups was evaluated by the yield of desired ether product and by the ratio of desired product to the side product.

Figure 3. Boron chelation hypothesis

Unsymmetrical acetals containing chelating leaving groups were first investigated (Figure 3). We revisited O-methoxyethoxymethyl (O-MEM) acetal 7 (Y = methoxyethyl), which was used previously in our initial report but not much beneficial compared to O-MOM acetal 6.69 As expected, acetal 7 gave similar results compared to 6 (entry 2). In contrast, acetals derived of glycolic acid 8, 9 and 2-pyridinylmethyl 10 gave higher yields with no side product observed (entries 3–5), of which acetal 10 gave excellent yield (entry 5). Based on the observed reversed regioselectivity of O-MOM acetal of phenol (eq 1), we anticipated that the difference in electronic properties would also contribute to the improved regioselectivity in simple cases. Indeed, the reaction of acetal 11 (Y = OPh) gave no side product (entry 6) but did not improve the reaction yield. To offer a site of chelation while maintaining the electronics of phenol, we tested acetal 12; no side product was observed, but the yield was not improved (entry 7). We turned to N-hydroxylated derivatives (entries 8, 9), which have similar acidity as phenol while offering improved chelation of the Lewis acid. We were pleased to observe excellent yield and no side product with hydroxamic acid-derived acetal 14 (entry 9).
Table 1. Screening of leaving groups

<table>
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<tr>
<th>entry</th>
<th>acetal</th>
<th>% yield 4 (4:5)</th>
<th>entry</th>
<th>acetal</th>
<th>% yield 4 (4:5)</th>
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<td>9</td>
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<td>90 (1:0)</td>
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<td>10</td>
<td>85 (1:0)</td>
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</table>

A further evaluation of the leaving group efficiency toward the outcome of the reactions was performed using acetals 10 and 14 and selected potassium alkynyl-, alkenyl-, heteroaryl-, and alkyltrifluoroborates (Table 2). Superior results in terms of reactivity, chemical yield, and regioselectivity were observed with both pyridinylmethylhydroxyl and hydroxamate leaving groups (acetals 10 and 14, respectively). No side product was detected in both cases. A heteroaryltrifluoroborate salt yielded the desired product, albeit in lower yield. An alkyl derivative gave only recovered starting materials or deprotected alcohol. Based on these results, the hydroxamic acid-derived acetal 14 was chosen for further optimization. This acetal not only provided the best yields with different nucleophiles, but also should be electronically and sterically tunable by changing the substituents, facilitating further optimization of the reactions involving weaker nucleophiles or hindered acetals.
Table 2. Coupling reactions of various mixed acetals and potassium organotrifluoroborates

<table>
<thead>
<tr>
<th>entry</th>
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2.2. Optimization of Reaction Conditions

Table 3. Optimization of reaction conditions

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<th>entry</th>
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<th>time (min)</th>
<th>yield (%)</th>
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</tr>
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</table>

In the first generation, precomplexation of potassium organotrifluoroborates (4.0 equiv) with BF<sub>3</sub>•OEt<sub>2</sub> (4.0 equiv) was necessary prior to the addition of acetals. The reaction typically required 2 h at rt for completion. We investigated the coupling of potassium phenyltrifluoroborates and hydroxamic acid-derived acetal 14 under milder and simpler
conditions – lower temperatures, shorter reaction times, lower equivalences of nucleophile and Lewis acid and without precomplexation (Table 3). With the hydroxamate leaving group, the reactions occurred without the requirement of precomplexation or excess nucleophile (entries 5, 6). Using 2.0 equiv of nucleophile and BF$_3$$\cdot$OEt$_2$, the reactions were completed within minutes at 0 °C. With 1.2 equiv each of the nucleophile and BF$_3$$\cdot$OEt$_2$ also delivered the desired product in excellent yield with longer reaction times (2.5 h).

2.3. Exploration of Substrate Scope*

With the optimized reaction conditions in hand, we explored the cross-coupling reactions of potassium organotrifluoroborates with hydroxamic acid-derived acetal of cyclohexanol 14 (Scheme 17). While the coupling of electron-deficient halogenated aryltrifluoroborates and O-MOM acetals proved problematic, the hydroxymic acid-derived acetal delivered the desired ethers in good to excellent yields (17–20). The reactions with ortho substituted aryl nucleophiles (21) were less efficient, presumably due to the steric hindrance. Carbonyl functional groups such as ketones and esters were well tolerated regardless of the presence of Lewis acid in the reaction (23–24). With hydroxamate as the leaving group, the scope of nucleophiles was expanded to potassium heteroaryltrifluoroborates; the reactions occurred in good yields with oxygen- and sulfur-containing heteroaryltrifluoroborates (25-26) (compared to no detected product with O-MOM acetals). Currently, nitrogen-containing heteroaryltrifluoroborates do not afford the desired products but acetal deprotection product as the major product. For maximum efficiency, premixing of the heteroaryltrifluoroborates and BF$_3$$\cdot$OEt$_2$ is recommended. Potassium alkenyltrifluoroborates gave mixed results; reactions worked well with trans disubstituted alkenes (28, 29) but were inefficient with other substitution patterns (30, 31).

* The results described in this Section were in the collaboration with Dr. T. A. Mitchell at the University of Pennsylvania.
Scheme 18. Direct comparison of hydroxamic acid-derived and O-MOM-derived acetals.

A direct comparison of reactions using hydroxamic acid-derived acetals and O-MOM acetals was performed to demonstrate the advantages of hydroxamate leaving group. In addition to the operationally friendlier procedure, superior results were obtained in all of the cases with hydroxamate leaving group (Scheme 18). The reactions of new coupling partners – hydroxamic-acid derived acetals still proceeded best with alkynyltrifluoroborates and significantly improved in the case of the challenging substituted acetals (32–36). Secondary-secondary dialkyl ether (32) was obtained in excellent yield (95%) compared to one from corresponding O-MOM acetal (52% yield). Tertiary-primary dialkyl ether (35) was afforded in better yield with hydroxamic-acid derived acetals. Again, the direct comparison indicated clearly the improvement in reactivity toward the less efficient nucleophiles including electron-deficient aryltrifluoroborates (38, 39) and alkenyltrifluoroborates (29, 40). Heteroaryltrifluoroborate, which was inactive in the first generation, reacted with hydroxamic acid-derived acetal to afford the ether in decent yield (44).
In summary, we have described the development of the second-generation ether-forming cross-coupling reactions of potassium organotrifluoroborates and acetals. A survey of reaction partner identified hydroxamate as the new leaving group that improved the regioselectivity and product yield. This leaving group enables the reaction to occur rapidly under milder conditions (0 °C, 5–60 min) and expanded the substrate scope to more sterically hindered acetals and less reactive nucleophiles such as electron-deficient halogenated aryltrifluoroborates and heteroaryltrifluoroborates.

**Scheme 17.** Preparation of dialkyl ethers from acetal 14 and potassium organotrifluoroborates
3. Mechanistic Investigations

The mechanistic investigations were performed to explain the success of this reaction, in particular the superior regioselectivity and reactivity provided by hydroxamic acid-derived acetals. The results of these experiments would also provide insight into the mechanism, which may support the continued development of this transformation and related reactions.

Scheme 19. Proposed Mechanism

In our initial report, the role of BF$_3$•OEt$_2$ in the reaction was confirmed by $^{11}$B NMR spectroscopy to abstract fluoride from organotrifluoroborate II generating organodifluoroborane III as the active Lewis acid (Scheme 19). Organodifluoroborane III binds to the oxygens of hydroxamate leaving group facilitating the formation of oxocarbenium ion V and hydroxamate organofluoroboron complex VI. The chelation capability of hydroxamate group to boron leads to the preferential binding and improves the regioselectivity of the hydroxamic acid-derived acetals compared to O-MOM acetals. This postulate, however, could not fully explain the improvements in the substrate scope and reactivity toward less reactive potassium organotrifluoroborates. We hypothesized that the
hydroxamate organofluoroboron complex VI was the active nucleophile in the reaction and that hydroxamate played a role in promoting the nucleophilicity. This could explain both the higher reactivity and the faster reaction times. To test this hypothesis, we independently prepared boron complex VI. The preformed phenyldifluoroborane 46 was treated with N-methyl N-((trimethylsilyl)oxy)acetamide 45 in dichloromethane at room temperature, delivering a colorless crystal, whose structure was confirmed by X-ray crystallography (Scheme 20a). Boron complex (±) 47 was an air stable and readily handled compound, although it was susceptible to gradual hydrolysis.

![Scheme 20. Preparation of (±) 47 and its reactivity.](image)

Treating (±) 47 with acetal 14 gave no product. In the presence of BF₃•OEt₂, full conversion was observed (Scheme 20b). It was assumed that acetal 14 was not electrophilic enough to react with complex (±) 47 and that BF₃•OEt₂ served as a Lewis acid to generate the oxocarbenium ion, which is trapped by phenyl transfer from (±) 47. Further attempt to employ (±) 47 as a nucleophile with other more reactive electrophiles including benzaldehyde, acetylchloride and Meerwein salt was not successful; no desired product was observed.

**Crossover Experiments with Boron Complexes**

An alternative explanation of the improved reactivity of the hydroxamic acid-derived acetics could be the improved stability of oxocarbenium ion intermediate as a result of its reversible formation. To test this hypothesis, three crossover experiments were performed. First, boron complex 47 was added into the coupling reaction of O-MOM acetal 6 and
preformed phenyldifluoroboranes 46. The reaction was quenched prior to completion (5 min at 0 °C) to look for the presence of acetal 14, which could be indicative of the reversible formation of oxocarbenium ion. A significant amount of acetal 14 was indeed detected (Scheme 21a). To further confirm this postulate, the second crossover experiment was carried out. Two structurally different hydroxamic acid-derived acetals with similar reactivity (14 and 48) were exposed to preformed phenyldifluoroborane 46. The reaction was quenched prior to completion (5 min at 0 °C), crossover acetals 49 and 50 were observed (Scheme 21b). This experiment confirmed that the formation of oxocarbenium ion is reversible. As in a control experiment, ether products were stable under reaction conditions and crossover acetals were confirmed not formed by the fragmentation of ether products (Scheme 21c).

Scheme 21. Crossover experiments


$^1$H NMR Study of Reaction Mechanism

We have explained the role of hydroxamate moiety as a chelation trap to improve the regioselectivity and as a reversible leaving group to stabilize the key oxocarbenium intermediate leading to the improved reactivity. The following studies would provide more information about the reaction mechanism.

![Scheme 22. Proposed mechanism](image)

$^1$H NMR analysis of reaction mixture using different ratios of acetal 14 and phenyldifluoroborane 46. If the reaction proceeded via the proposed mechanism (Scheme 22), maximum yield should be observed in the case where excess or equimolar phenyldifluoroborane was used (case A, B and C); 50% and 10% of maximum yield should be observed in case D with 0.5 equivalent and case E with 0.1 equivalent of phenyldifluoroborane, respectively. However, the maximum yield was not observed without the excess phenyldifluoroborane (case C); only 12% product yield was formed. Traces of product was detected in case E. The results indicated that an excess amount of phenyldifluoroborane 46 was necessary for the reaction to go to completion and achieve the maximum yield. The excess phenyldifluoroborane might involve in promoting the formation of oxocarbenium ion and complex 47 via fluoride abstraction. Additional $^1$H NMR experiments were performed to test this hypothesis. A catalytic amount of “unreactive” alkyl difluoroborane 52, which was known not to transfer the alkyl group, was added into the reaction with equimolar phenyldifluoroborane (Scheme 23). This catalyst would serve to abstract fluoride. The obtained results were identical with either 1.2 equiv 46 (case F) or 1.0
equiv 46 and 0.2 equiv 52 (case G), confirming that the role of excess organodifluoroborane is to serve as a catalyst.

Scheme 23. $^1$H NMR Study of the Reaction Mechanism

Revised Mechanism

A revised mechanism of this transformation was proposed based on the above data (Scheme 24). An irreversible interaction of potassium organotrifluoroborate and BF$_3$•OEt$_2$ generates organodifluoroboranes B and potassium tetrafluoroborate. B serves as a Lewis acid and binds to the hydroxamate moiety. The excess organodifluoroborane D abstracts a second fluoride from the boron complex to open a coordination site on boron, which rapidly coordinates to oxygen of hydroxamate group to generate the five-membered ring boron complex G. The complex reversibly dissociates to form oxocarbenium ion H and boron complex I. The R$^3$ group transferring to H ion could be either from complex I or organotrifluoroborate F to deliver irreversibly diakyl ether K. It is not clear at this moment that I or F is the actual nucleophile in this transformation; further studies to evaluate their relative nucleophilicities are necessary.
4. Conclusions and Outlook

Despite the wide occurrence of ether bonds in organic compounds, effective ether-forming reactions that can offer the generality, predictability and applicability from available building blocks are quite limited. While the development of metal-catalyzed C–O bond forming cross-coupling reactions can partly solve this problem in aryl ether synthesis, general and convenient cross-coupling reactions for dialkyl ether synthesis remain scarce. In our own efforts, our group reported a first-generation ether-forming cross-coupling reactions of potassium organotrifluoroborates and acetals to access steric dialkyl ethers. This part of my Dissertation described the development of the second generation of this transformation to expand the substrate scope and improve reactivity. We have identified hydroxamate as a new leaving group that can improve the regioselectivity and reactivity of more substituted acetals and less reactive organotrifluoroborates. It also allows the reactions to proceed under milder conditions including lower temperature and much shorter reaction times. An exploration of substrate scope and a direct comparison to reactions with previously used O-MOM acetals were performed to demonstrate the superior of the new hydroxamic acid-derived acetals. The isolation and characterization of a likely intermediate, combined with crossover experiments and NMR studies have identified the role of
hydroxamate leaving group as a reversible leaving group and a chelation trap in improving the efficiency of this transformation, as well as the need for a slight excess of organodifluoroborane to serve as a catalyst.

**Outlook**

Ether-forming cross-coupling reaction of potassium organotrifluoroborates and acetals provides a versatile synthesis of dialkyl ethers, which are often difficult to access by conventional methods. The use of stable, commercially available organoboron reagents as a synthetic handle with simple procedure makes it a promising method for modular synthesis of complex molecules. The take-home messages from the development of this transformation are stabilized oxocarbenium ion intermediate could be achieved by the modification of the leaving group of acetals and that hydroxamate is a good and reversible leaving group. Based on these postulates, other nucleophiles could be used to add into oxocarbenium ion to obtain other dialkyl ether patterns (**Outlook 1**); other type of reactive intermediates such as iminium ion, benzyllic cation could be generated and stabilized by the reversibility of hydroxamate leaving group (**Outlook 2**); modification of leaving group could lead to the increasing the nucleophilicity of the boron complex (**Outlook 3**).

**Outlook 1 – Dialkyl ether synthesis from other nucleophiles**

Arenes and alkenes are among the most abundant organic feedstocks. Direct functionalization of those compounds is important not only in fine chemical preparation but also in industrial processes. Friedel-Craft acylation or alkylation is a process in which the arene acts as nucleophile to add to an acyl or alkyl cation. With the same concept, oxocarbenium ion generated from the corresponding hydroxamic acid-derived acetal could be trapped by an arene, ultimately delivered an alkyl benzyl ether (Scheme 25a). As a proof of concept, the Bode group in 2011 reported Friedel-Craft benzylation of activated and inactivated arenes, in which hydroxamate was used as a reversible leaving group to stabilize benzylcations (Scheme 25b).71
Part I. Ether-Forming Cross-Coupling Reactions of Organotrifluoroborates and Acetals

Scheme 25. Addition of arenes to oxocarbenium ions

An electron-rich alkene could serve as the nucleophile to add into an oxocarbenium ion (Prins reaction) generating another cation, which could undergo nucleophilic substitution or elimination to afford other dialkyl ethers (Scheme 26).

Scheme 26. Addition of alkenes to oxocarbenium ions

Outlook 2 – Saturated cyclic amine synthesis

Nucleophilic addition to imines is a powerful method to prepare amines. Saturated cyclic amines are valuable building blocks in both natural and man-made molecules. A direct synthesis of substituted cyclic amines is in demand.

Scheme 27. Saturated cyclic amine synthesis
Outlook 3 – Modification of hydroxamate moiety

Although the use of hydroxamic acid-derived acetals has improved the outcome of this transformation in comparison to O-MOM acetals, the nucleophilic transferring of certain groups remains challenging including alkyltrifluoroborates (not reactive), heteroaryltrifluoroborates (reactive but low yields). Modification of the leaving group may promote the nucleophilicity of leaving group-organoboron complex. A suitable leaving group would not only increase the reactivity of nucleophiles, but also facilitate the development of the asymmetric version of ether-forming cross-coupling reaction.

Scheme 28. Modification of hydroxamate moiety and strategy for asymmetric ether synthesis
5. References


42. Dioxolannes are decomposed by very basic reagents such as t-BuLi


63. There are 401 commercially available potassium organotrifluoroborates and 1795 ones with reported procedures for preparation: a result of Reaxys performed in November 4th, 2013.


Part II.

SnAP Reagents for the Transformation of Aldehydes into Saturated N-Heterocycles
1. Background and Introduction

The phenomenal success of metal-catalyzed cross-coupling reactions has revolutionized the synthesis of new bioactive small molecules. The robustness of the reaction conditions and the ready commercial availability of both building blocks and ligands make this method one of the most powerful tools to attach an aromatic or heteroaromatic ring to an organic molecule. Together with recent advances in parallel synthesis, it is not surprising to observe the increasing number of aromatic rings contained in new bioactive compounds. The increase of aromatic ring count statistically affects other important physical properties such as lipophilicity, aqueous solubility, plasma protein binding and CyP450 inhibition. A study of 245 preclinical Pfizer compounds in 2008 showed that the addition of aromatic ring resulted in a significant increase of logP leading to the poor permeability and oral absorption. Plasma protein binding that represents drug potency in vivo increased as a function of aromatic ring count in an analysis of 7,856 GSK compounds. A high aromatic ring count also leads to a higher inhibition of CyP450 associated with the toxicity and drug-drug interactions. In the light of these well-recognized limitations in solubility, pharmacokinetics and bioavailability of high-aromatic-ring-count molecules, scientists tend to favor saturated building blocks, especially saturated N-heterocycles. Saturated structures with out-of-phase substituents allow the exploration of more diverse chemical space, without significantly increasing molecular weight (Figure 1).

![Figure 1. Isomers of dimethylpyridine and dimethylpiperidine](image-url)
While the supply of aromatic building blocks is big, the supply of saturated N-heterocycles is quite limited. Unlike their aromatic counterparts, saturated N-heterocycles cannot be easily derivatized by cross-coupling reactions. Strategies for facile constructing substituted saturated N-heterocycles are consequently in demand.

### Figure 2. Common saturated N-heterocycles

#### 1.1. Direct Functionalization of Saturated N-Heterocycles

To date, most reports have focused on functionalization of the C–H bond adjacent to nitrogen.\(^7\)\(^8\)

#### 1.1.1. α-Lithiation with Diamine

In 1989, Beak and Lee reported the pioneering direct α-functionalization of nitrogen-containing heterocycles.\(^9\) The process involved α-deprotonation of Boc-protected N-heterocycles with an alkyllithium/diamine complex to generate dipole-stabilized carbanions, followed by the addition of electrophiles to provide α-substituted derivatives. An asymmetric version was later developed with the use of chiral diamine \((-\text{-})\)-sparteine (Figure 3).\(^10\) Extensive work on ligand design and reaction condition optimization performed by O’Brien and others enabled to access different enantiomers of α-substituted saturated N-heterocycles by using \((+\text{-})\)-sparteine surrogates and other chiral diamine ligands.\(^11\) Chiral organolithium complex was configurationally stable at low temperature and added stereospecifically to electrophiles with the retention of stereochemistry. Sparteine-mediated
α-functionalization was most successful with pyrrolidines. Asymmetric functionalization of 
N-Boc piperidines was calculated computationally to proceed with lower enatioselectivity  
and with a higher activation barrier compared to that of Boc-pyrrolidine.$^{12}$

![Figure 3. α-Lithiation with achiral and chiral diamines](image)

Due to the poor configurational stability of lithium complex at temperatures higher 
than −30 °C, the electrophiles were limited to reactive ones such as benzophenone, alkyl  
chloroformate, CO$_2$, Me$_2$SO$_4$, TMSCl.$^{13}$ To expand the electrophile scope, transmetallation  
of the lithium complex to other metals such as copper and zinc were used to generate more  
stable organometallic complex (Scheme 1). Dieter et al developed a method involving the  
transmetallation of the lithium complex to copper, followed by trapping with less reactive  
electrophiles such as vinyl iodide, α,β-unsaturated ketones, propargyl mesylates.$^{14}$ In 2006,  
Campos and coworkers successfully generated the configurationally stable organozinc via  
transmetallation of lithium complex to ZnCl$_2$, followed by Negishi coupling to access a  
variety of enatioenriched 2-arylpyrrolidines.$^{15}$ This method was also applied for the  
preparation of 2-arylpiperidines,$^{16}$ and recently for selective β-arylation of piperidines.$^{17,18}$

![Scheme 1. α-Lithiation followed by transmetallation](image)
1.1.2. C–H Functionalization

Metal-catalyzed C–H Functionalization

Murai and coworkers in 2001 reported the first directed sp$^3$ C–H activation of N-2-pyridyl cyclic amines with alkenes in the presence of a low-valent metal, Ru$_3$(CO)$_{12}$, to access α-alkylated saturated cyclic amines. Directing groups such as pyridine, pyrimidine or oxazoline were crucial for the success of reaction. The coordination of the nitrogen on the directing group with the ruthenium complex promoted the site-selective C–H bond cleavage. The reaction proceeded well with a range of mono- and disubstituted alkenes. Based on the same concept, the research groups of Sames and later Maes developed sp$^3$ C–H bond arylation of pyrrolidines and piperidines, using aryl boronate esters as coupling partners (Scheme 2). The use of readily available organoborons provided a variety of substituted pyrrolidines and piperidines. This approach was not successful for larger ring-size or other types of N-heterocycles. Other limitations include the difficulty of removing the directing group, and over arylation on unsubstituted cyclic amines.

Scheme 2. Nitrogen directed ruthenium catalyzed C–H activation by Murai and Sames

Schafer and coworkers recently developed a new route for the synthesis of α-substituted unprotected piperidines, piperazines and azepanes using the unique reactivity of tantalum–amidate complex for activating the C–H bonds adjacent to nitrogen (Scheme 3). In this transformation, Ta-amidate complex selectively activates sp$^3$ C–H bond by β-
hydrogen abstraction forming the tantallaaziridine complex, which undergoes alkene insertion leading to the generation of the α-alkylated cyclic amine.

Scheme 3. Direct C–H activation by Schafer

Radical-based C–H Functionalization

The pioneering work of Curran and Snieckus in 1990 on the formation of α-amino radicals via 1,5-hydrogen transfer inspired other research groups to develop radical-based α-functionalization of cyclic amine (Scheme 4a-b). Nakamura and coworkers developed an iron-catalyzed C–C bond formation at α-position of acyclic and cyclic amines with Grignard or zinc reagents (Scheme 4c). The reactions proceeded under mild conditions in the presence of an iron catalyst and provided α-aryl pyrrolidines, piperidines and azepanes.

Scheme 4. Radical-based C–H activation
Recently, MacMillan reported a photoredox α-amino C–H arylation. An α-amino radical was generated under the photoredox conditions and trapped with electron-deficient arenes or heteroarenes as radical coupling partners (Scheme 5).

**Scheme 5.** Photoredox C–H functionalization by MacMillan

**Intramolecular Redox C–H Functionalization**

A contribution to the functionalization of pyrrolidines using intramolecular redox C–H functionalization was reported by the Maulide research group (Scheme 6). A variety of Grignard reagents (alkyl, aryl, alkenyl, allylic) or potassium alkynyltrifluoroborates were employed to provide a variety α-substituted pyrrolidines. This procedure was sensitive to the nature of the cyclic amines. It worked well with pyrrolidines but poorly with others. N-phenylcarboxamide is critical for the reaction success; it serves as hydride acceptor and directs the addition of Grignard reagents to the α-position.

**Scheme 6.** Redox C–H functionalization by Maulide

### 1.2. Alternatives to Direct Functionalization of Saturated N-Heterocycles

While direct functionalization is largely used for cyclic amines with one heteroatom, cyclization is often used for constructing ones containing additional heteroatoms. Nucleophilic substitution of amino alcohols/thiols/amines with dihalo derivatives is used
frequently for preparing morpholines, thiomorpholines or piperazines. The intrinsic limitation of this approach is low yield due to the competing elimination reaction. A multiple-step synthesis such as alkylation followed by lactamization/esterification and reduction, reductive amination or ring closing metathesis followed by reduction could finally deliver desired products (Figure 4). Besides the lengthy synthesis, the complexity of the final products of these procedures is derived from the very first starting materials.

**Figure 4.** Common approaches to saturated N-heterocycle synthesis

### 1.2.1. Nucleophilic Substitution

To attenuate the side reactions caused by strongly basic conditions of substitution reactions, Aggarwal and coworkers used a softer electrophile – a vinyl sulfonium salt – instead of dihalo compounds with milder bases to provide a range of N-protected mono/disubstituted morpholines, thiomorpholines, piperazines in good yields (Scheme 7). Vinyl selenium salt was also used for the same purpose. However, the removal of protecting group on nitrogen – N-tosyl in most cases – was problematic.

**Scheme 7.** Vinyl sulfonium salts for N-heterocycle synthesis by Aggarwal
1.2.2. Metal-Mediated Hydroamination

Hydroamination reactions involve direct C–N bond formation by the addition of an amine to an unsaturated C–C bond. The transformation is thermodynamically feasible with a high activation barrier due to the electrostatic repulsion of electron-rich double bond and nucleophilic nitrogen. Rare-earth metals, alkaline earth metals, recently group 4 and late transition metals have been employed to activate the reagents (Table 1).\textsuperscript{33} Rare-earth metals and group 4 elements are highly efficient for intramolecular hydroamination of unactivated alkenes with a pendant primary or secondary amines to construct pyrrolidines and piperidines with high enatioselectivity. The formation of larger ring-sized cyclic amines is not effective.

Table 1. Comparison of catalyst’s efficiency on hydroamination

<table>
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<th>Catalyst</th>
<th>Advantages</th>
<th>Disadvantages</th>
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| Rare-earth Metal Catalyst (Y, La, Sm, Lu) | • Most active catalysts  
• Non-activated alkenes  
• High TON and stereoselectivity  
• 5–7 membered N-heterocycles  
(5 > 6 >> 7) | • Air and moisture sensitive  
• High temperature (>120 °C) for steric substituted aminoalkenes  
• Thorp–Ingold effect required in many cases |
| Alkaline Earth Metal Catalyst (Li, Ca, Mg) | • Comparable to rare-earth metal catalyst                                   | • Scope limited to 5 and 6 membered rings                                    |
| Group 4 Metal Catalyst (Ti, Zr, Ta)   | • Less air and moisture sensitive  
• Commercially available (pre)catalysts  
• Non-activated alkenes  
• Functional group tolerance | • Scope limited to 5 and 6 membered rings  
• Thorp–Ingold effect required in many cases |
| Late Transition Metal Catalyst (Rh, Pd, Ir, Au) | • Least air and moisture sensitive  
• Activated alkenes  
• Functional group tolerance | • Best for intermolecular                                                     |
With the same concept, Schafer and coworkers in 2012 reported an asymmetric synthesis of substituted cyclic amines with multiple heteroatoms such as morpholines and piperazines (Scheme 8). \(^{34}\) Titanium-amidate complex catalyzes regioselective hydroamination with functionalized oxygen- and nitrogen-containing aminoalkynes, followed by enantioselective reduction using Noyori-Ikariya catalyst generated substituted morpholines, piperazines in high yields and enantioselectivity.

**Scheme 8.** Asymmetric hydroamination followed by reduction by Schafer

### 1.2.3. Metal-Mediated Arylation

Palladium-catalyzed alkene aminoarylation has emerged as a useful method to prepare 2-(arylmethyl)pyrrolidines and other N-heterocycles. \(^{35}\) In 2004, Wolfe and coworkers reported Pd-catalyzed stereoselective synthesis of cis-2,5- and trans-2,3-disubstituted pyrrolidines from γ-aminoalkenes and aryl halides (Scheme 9a). \(^{36}\) The reactions have excellent diastereoselectivity, and enantiomerically enriched substrates are converted into products without any loss of optical purity. The insertion of a palladated amine into the C–C double bond in the syn fashion determines the stereochemical outcome of the products. To access the trans-2,5-pyrrolidines, cyclic carbamate substrates were used (Scheme 9b). \(^{37}\) This approach was also successful for the diastereoselective synthesis of cis-3,5-disubstituted morpholines, \(^{38}\) piperazines, \(^{39}\) and saturated 1,4-benzodiazepines. \(^{40}\) For the enantioselective synthesis of monosubstituted pyrrolidines, the monodentate phosphoramidite ligand \((R)\)-Siphos-PE was found to be effective (Scheme 9c). \(^{41}\) Electron-rich, electron-poor and electron-neutral aryl bromides and iodides were suitable coupling partners to provide a variety of 2-(arylmethyl)pyrrolidines.
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Scheme 9. Palladium-catalyzed arylamination by Wolfe

By taking advantage of the high oxidation state palladium(IV) complexes, the research group of Michael developed C–H activation carboamination of aminoalkenes for the construction of 2-(arylmethyl) five-, six-, and seven-membered saturated N-heterocycles (Scheme 10). The coupling partners – arenes – were used as solvent. The cyclization was facilitated in the presence of substituents offering a Thorp–Ingold effect. In contrast to Pd(0)/Pd(II)-catalyzed alkene aminoarylation, Pd(II)/Pd(IV)-catalyzed reactions involve the anti aminopalladation.

Scheme 10. Pd(IV) C–H activation arylamination by Michael

Besides palladium, copper, osmonium and hypervalent iodine were also used to catalyze the intramolecular alkene carboamination.
1.2.4. \( \text{sp}^3 \) C–H Amination

Scheme 11. Directed \( \text{sp}^3 \) C–H intramolecular amination by Chen

In 2011, the Chen and Daugulis research groups simultaneously reported the first metal-catalyzed intramolecular directed amination of non-activated \( \text{sp}^3 \) C–H bonds at \( \delta \)-position for the synthesis of \( N \)-protected pyrrolidines (Scheme 11).\(^{46, 47} \) The nitrogen protecting group – picolinamide – served as the directing group for C–H activation leading to the formation of kinetically favored six-membered palladacycle intermediate which followed by C–N reductive elimination to provide the cyclic amine.

Scheme 12. Direct \( \text{sp}^3 \) C–H intramolecular amination by Betley

In 2013, Betley and Hennessey reported the iron-catalyzed \( \text{sp}^3 \) C–H bond amination of organoazides for the synthesis \( N \)-heterocycles (Scheme 12).\(^{48} \) Inspired by activity of heme-iron in Nature, they developed iron dipyrrinato catalyst 1 that mimics the electronic structure of the well-known cytochrome P450 reactive iron-oxo intermediate in the direct C–H oxidation. In this transformation, the Fe(II) catalyst reduces azide to generate Fe(III) radical imido, which either undergoes direct C–H insertion or hydrogen abstraction and radical rebound to afford the Fe(III) product complex. Catalyst turn-over was achieved by \textit{in situ} \( N \)-Boc protection. Like other \( \text{sp}^3 \) C–H bond functionalization methods, selectivity is a concern. More activated C–H bonds at benzylic, allylic, or tertiary sites are more reactive.
Rearrangements of aldehydes into saturated N-heterocycles play an important role in the regioselectivity. In many cases, it is not easy to rationalize the dominant factor to determine the product outcome.

1.2.5. Ring Transformation

Ring transformations have not been much used for the general preparation of substituted N-heterocycles. In most cases, transformations are substrate specific; substituents on cyclic amines are usually set prior to the ring transformation. Recently, the synthesis of substituted morpholines, thiomorpholines and piperazines via catalytic ring expansion of 3-oxetanone-derived spirocycles have been reported by Carreira and coworkers (Scheme 13).

3-Oxetanone-derived spirocycles, generated from the condensation of 3-oxetanone and \( \beta \)-heteroatom-substituted amino compounds, undergo Lewis acid-catalyzed ring expansion to provide substituted saturated N-heterocycles. The elegance of the transformation lies in that changing heteroatom-substituted amino compound \( 2 \) leads to the formation of different substituted N-heterocycles.

Scheme 13. Ring expansion of 3-oxetanone-derived spirocycles

1.3. Conclusions

The shift in interest towards saturated N-heterocycles raises the need for the synthetic methods that could offer the generality and applicability from readily available building blocks. Despite extensive efforts, few methods are practical and scalable for a variety of substituted saturated N-heterocycles. Direct functionalization of saturated cyclic amines is conceptually ideal, but is not yet a general and applicable approach. Lithiation, followed by addition to electrophile or metal-catalyzed cross-coupling reaction is the most reliable method but still suffers from laborious conditions and is largely restricted to
constructing α-functionalized pyrrolidines and piperidines. Other classes of saturated N-heterocycles with different ring sizes or additional heteroatoms are not accommodated. The requirement of protecting groups on nitrogen, which are difficult to remove in most cases, limits the use of emerging methods. For the synthesis of those containing more than one heteroatom, several approaches have been reported, recently focusing on the simplicity and generality to obtain different substituted patterns of N-heterocycles.
2. One-Step Synthesis of Substituted Thiomorpholines

Morpholines, thiomorpholines and piperazines are increasingly common scaffolds for the synthesis of biologically active small molecules.\textsuperscript{51} Unlike their heteroaromatic counterparts, they cannot be easily elaborated by metal-catalyzed cross-coupling reactions. Direct functionalization of simple N-heterocycles, hydroamination and carboamination are mostly used for constructing substituted pyrrolidines or piperidines, but not well-suited for morpholines, thiomorpholines and piperazines. For the synthesis of those compounds, nucleophilic substitution or multiple-step synthesis are often used. The lengthy synthesis and the requirement of difficult-to-remove protecting group on nitrogen are major limitations of those methods. Some efforts have been made to develop new chemical transformations as alternatives to cross-coupling reaction that could offer generality and applicability from available building blocks targeting substituted saturated N-heterocycles. In the course of developing such chemical transformation, our research group sought to provide a new strategy, which could offer the direct transformation of widely available functional groups such as halides, aldehydes or boronic acids to unprotected N-heterocycles.

2.1. Discovery and Optimization of Reaction Conditions

2.1.1. Reaction Discovery

The preparation of 3-substituted (thio)morpholines from aldehydes was selected as the starting point, as there are very few methods for their synthesis.\textsuperscript{31,32,50-52}

![Figure 5. Retrosynthetic Analysis](image-url)
We envisioned that 3-substituted (thio)morpholine would be generated via an intramolecular C–C bond-forming cyclization of an imine, which could be prepared via the condensation of aldehyde and 2-aminoethanethiol or aminoethanol (Figure 5).

**Intramolecular Mannich Reaction**

![Scheme 14. Intramolecular Mannich reaction approach](image)

The first attempt to cyclize of the imine adduct was intramolecular Mannich reaction (Scheme 14). The trifluoroacetic salt of amine 3 condensed with benzaldehyde to deliver the corresponding imine 4. Imine 4 was heated at 40 °C, no cyclization product was detected and imine 4 was fully recovered (Scheme 15a). Strong base – LDA was added into imine solution to generate lithium enolate, which presumably added into the pendant imine. However, no cyclization occurred but recovered starting material (Scheme 15b).

![Scheme 15.](image)
In an attempt to increase the acidity of the α-proton, ethyl thioester derived amine 5 was used instead of ethyl ester derivative. Lactamization occurred more rapidly than imine condensation (Scheme 16).

**Scheme 16.**

Imidazol-2-ylidenes – a class of N-heterocyclic carbenes (NHCs) – are known to catalyzed the transesterification beween esters and alcohols through the formation of activated carboxylates. We envisioned that the addition of a catalytic amount of imidazol-2-ylidene 7 would lead to the formation of activated carboxylate 8, which is a structural ketone and contains more acidic α-protons. Ethoxide could act as a base to generate enolate that subsequently adds into the imine (Scheme 17a).

**Scheme 17.** N-heterocyclic carbene catalyzed intramolecular Mannich reaction approach

To test this idea, 10 mol % of N,N-bismesitylimidazolylidene (IMes) was added into the solution of imine 4 in CH2Cl2. At different temperatures and reaction times imine 4 did not cyclize, and was mostly recovered (Scheme 17b). A control experiment was performed
to explain the reaction failure by either the unsuccessful activated carboxylate formation or the challenging imine addition (Scheme 17c). An N-Boc protected amine 9 was subjected to the IMes catalyzed transesterification with methanol. The formation of methyl ester 11 would be the indicative of the successful formation of the activated carboxylate 10. However, no transesterification product 11 was observed, only recovered amine 9.

We turned to the idea of enhancing the electrophilicity of unactivated imine without using electron-deficient protecting group on nitrogen. Two-point binding Lewis acid could not only activate the electrophilicity of imine, but also stabilize the formed enolate by chelation and consequently facilitate the cyclization. Various Lewis acids including Cu(OTf)$_2$, Zn(OTf)$_2$, Sc(OTf)$_3$ and AgOTf were added in either catalytic or equimolar quantities into the cyclization reactions of imine 4. No cyclization product was detected, only recovered starting material (Scheme 18).

**Scheme 18.**

**Intramolecular Imine Addition of in situ Anion**

The fluorine–silicon bond is one of the most thermodynamically stable bonds (135 kcal/mol). The formation of this bond could be the driving force for the in situ anion generation from the silylated imine, which would subsequently undergo nucleophilic addition to the Lewis acid activated imine. Condensation of 2-((((trimethylsilyl)methyl)thio)ethanamine 12 and $p$-trifluoromethylbenzaldehyde gave the corresponding imine 13, which was subjected to cyclization reactions with different fluoride sources (TBAF, Me$_4$NF, TBAT, CsF, KHF$_2$) and Lewis acids (BF$_3$•OEt$_2$, TiF$_4$, ZnF$_2$, CeF$_3$,$\text{CuF}_2$, CuF(PPPh$_3$)•2MeOH). In most cases, desilylated imine 14 was detected; there was no cyclization product. This indicated that the formation of in situ anion was successful, but the nucleophilic imine addition was
unproductive (Scheme 19a). An N-acyliminium ion 16 formed in situ from the corresponding aminal 15 derivative was presumably much more electron deficient, and could be trapped by a pendant nucleophile. This approach proved unsuccessful; mainly, the formation of hydrolysis and desilylation product 17 was observed (Scheme 19b).

Scheme 19. Intramolecular imine addition of in situ anion approach from organosilanes

Organostannanes are known to undergo the reversible stannane/lithium transmetallation to generate organolithiums. The resulting organolithiums were generally not isolated but reacted with appropriate electrophiles such as aldehydes, ketones or alkyl halides. The equilibrium shifts towards the formation of organolithiums when the substituent on stannane is more electronegative such as vinyl, allyl, α-alkoxyalkyl, α,α'-dithioalkyl groups. With these precedents, we tested the intramolecular imine addition of in situ anion generated from organostannane. Imine 19 was subjected to the cyclization conditions with n-BuLi and Cu(OTf)$_2$ as Lewis acid. No cyclized product was observed (Scheme 20).

Scheme 20. Intramolecular imine addition of in situ anion approach from organostannanes
Initial attempts to cyclize the imine via intramolecular nucleophilic addition were unproductive. This is presumably due to the long-standing challenging C–C bond-forming addition to unactivated primary imines lacking electron withdrawing $N$-sulfonyl or $N$-aryl groups.61

**Intramolecular Radical Cyclization**

The carbon-nitrogen double bond has recently attracted attention as radical acceptor for intra- and intermolecular carbon-carbon bond construction.62 In contrast to ionic imine additions, a radical imine addition occurs under non-polar conditions with uncharged free radical species. This approach may provide a solution for the problematic ionic imine addition. Inspired by the reports of Nagaoka (2005)63 and Inoue (2011)64 on the radical $\alpha$-C–H functionalization of ethers and acetals (Scheme 21a–b), we envisioned that a carbon-centered radical adjacent to oxygen could be generated under reported conditions and subsequently adds into the imine. A phenyl imine with a pendant O-MOM acetal 22 was exposed to diphenylketones as radical initiator under UV light or to triethylborane and air. A productive cyclization, however, did not occur (Scheme 21c).

**Scheme 21.** Radical cyclization approach

**Organostannanes – Initially Successful Cyclization**

Inspired by reports from the group of Kagoshima on the intermolecular addition of organostannanes to $N$-phenyl or $N$-para-methoxyphenyl imines using the stoichiometric Cu(OTf)$_2$ in 2004,65 we examined the cyclization of stannylated imine 19 (Scheme 22).
Under the reported conditions at room temperature, no cyclization product 20 was detected. At 60 °C a small amount of cyclized product was obtained (15% isolated yield).

Scheme 22. Efforts in copper-mediated cyclization of stannylated imines

2.1.2. Optimization of Reaction Conditions

Aminotributylmethylstannane 18 (SnAP TM) was obtained in quantitative yield by S-alkylation of 2-aminoethanethiol with commercially available tributyl(iodomethyl)stannane (eq. 1).

Condensation with p-trifluoromethylbenzaldehyde gave the corresponding imine 19. Further optimization of cyclization conditions including work-up conditions, solvents, temperatures and reaction times was carried out to improve the reaction efficiency. Under the initial cyclization conditions, the reaction occurred with the appearance of sticky deep blue precipitate – a complex of copper and product. This complex was slowly soluble in CH₂Cl₂ layer after 2–3 h vigorous stirring in sat. aq. NaHCO₃ solution to release the free substituted thiomorpholine 20. Isolated yields were not reproducible in different batches. Various work-up conditions including sat. aq. NaHCO₃, sat. aq. NH₄Cl, 10% aq. NH₄OH and aq. EDTA solution were tested to break the copper complex more efficiently. A mixture of sat. aq. NaHCO₃ and 10% aq. NH₄OH (5:3) gave the best results, with 15 min for breaking

* SnAP = tin (Sn) amine protocol; TM = thiomorpholine
the copper complex and yield consistency. With reliable work-up conditions established, optimization of other reaction parameters was performed (Table 2). The optimization was unproductive until hexafluoroisopropanol (HFIP) was found to improve significantly the yield (55% yield) and diminished the formation of side products (entry 4). Other polar solvents (MeOH, t-BuOH) failed to give similar improvement and we attributed the beneficial effects of HFIP acidity to activation of the imine by protonation. Anhydrous conditions, which deterred imine hydrolysis, could be conveniently achieved by the addition of anhydrous CaSO₄ to the reaction mixture. To further improve the reactivity, monodentate and bidentate ligands for copper including 1,10-phenanthroline, 2,6-di-tert-butylpyridine, 2,6-lutidine, and pyridine were tested, with 2,6-lutidine offering the best results (entry 10). Using this ligand in a mixture of HFIP and CH₂Cl₂ or ClC₂H₄Cl as solvent, the cyclization was complete after 2 h at 60 °C or 12 h at room temperature (entry 11–12).

**Table 2. Optimization of reaction conditions**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>additive</th>
<th>temp. (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ClC₂H₄Cl</td>
<td>–</td>
<td>rt</td>
<td>nr</td>
</tr>
<tr>
<td>2</td>
<td>ClC₂H₄Cl</td>
<td>–</td>
<td>60</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>–</td>
<td>95</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>HFIP</td>
<td>–</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>ClC₂H₄Cl</td>
<td>HCl</td>
<td>60</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>t-BuOH</td>
<td>KHCO₃</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>1:1 ClC₂H₄Cl:HFIP</td>
<td>1,10-phenanthroline</td>
<td>60</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>1:1 ClC₂H₄Cl:HFIP</td>
<td>2,6-diBu-pyridine</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>1:1 ClC₂H₄Cl:HFIP</td>
<td>pyridine</td>
<td>60</td>
<td>38</td>
</tr>
<tr>
<td>10</td>
<td>1:1 ClC₂H₄Cl:HFIP</td>
<td>2,6-lutidine</td>
<td>60</td>
<td>75</td>
</tr>
<tr>
<td>11</td>
<td>4:1 ClC₂H₄Cl:HFIP</td>
<td>2,6-lutidine</td>
<td>60</td>
<td>74</td>
</tr>
<tr>
<td>12</td>
<td>4:1 CH₂Cl₂:HFIP</td>
<td>2,6-lutidine</td>
<td>rt</td>
<td>76</td>
</tr>
</tbody>
</table>
2.2. Synthesis of Substituted Thiomorpholines

With the optimal reaction conditions in hand, we explored the transformation of various aldehydes into N-unprotected 3-thiomorpholines with SnAP TM (Scheme 23).

![Scheme 23. Conversion of aldehydes into unprotected 3-thiomorpholines]

The reaction occurred smoothly with a broad scope of aldehydes (aryl-, heteroaryl-, alkylaldehydes). There is no significant effect of the electronics of aryl rings on reaction efficiency. Electron-poor, electron-rich, and electron-neutral substituents gave good yields (20-32). Substituents at ortho position on the aryl ring gave lower yield due to the steric hindrance (29). Functional groups including organohalides, protected alcohols, amines, and esters were tolerated under the reaction conditions. The reactions succeeded with meta- or para-heteroaryl substrates but failed with ortho-heteroaryl aldehydes (further discussed in Part II Section 3.1). Imines prepared from aliphatic aldehydes such as pivalaldehyde,

\* The results described in this Section were in the collaboration with Mr. Gediminas Mikutis during his project research at ETH Zurich 2012.
isobutyraldehyde, glyoxal, and chloral also afforded thiomorpholine products in good to moderate yields (37-40). Products from unbranched aliphatic aldehydes were observed but in lower yields, presumably due to facile enamine formation.

More substituted SnAP reagents 41 and 42 were prepared from rac-cysteine ethyl ester and rac-penicillamine methyl ester to investigate the formation of multi substituted thiomorpholines. Under the standard conditions, these reagents coupled with representative aldehydes to give more substituted thiomorpholines 43-46 in good yields and high diastereoselectivity (Figure 6). The cis relative stereochemistry was confirmed by X-ray crystallography of (±) 43. The high diastereoselectivities observed in these cases is presumably due to equilibration of an initially formed diastereomeric mixture to the thermodynamically favored cis-product.

![SnAP Cys and SnAP Pen](image)

**Figure 6.** SnAP reagents for the synthesis of disubstituted thiomorpholine

In summary, we have described the discovery of SnAP reagents for the transformation of aldehydes into N-protected 3-thiomorpholines. The reactions generally proceed with a broad scope of aldehydes including electron-rich, electron-poor aryl, heteroaryl, alkyl aldehydes and glyoxylates. The mild reaction conditions, simple execution, functional group tolerance and the ability to use commercially available building blocks as synthetic handle reflect the convenience of metal-catalyzed cross-coupling reactions, provide an access to various unprotected 3-thiomorpholines not currently accessible by conventional methods.
3. Mechanistic and Racemization Studies

3.1. Mechanistic Studies

Compared to the addition of carbanions to carbonyl groups of aldehydes and ketones, the addition to imines is often difficult due to their poor electrophilicity and the tendency of enolizable imines to undergo deprotonation rather than addition. The common strategies to increase the electrophilicity of imines are the use of electron-withdrawing groups on nitrogen or the formation of iminium ion. Lewis acids have also been employed, but are not generally efficient. Organostannanes – mostly allylstannane – have been used as nucleophiles in imine addition. The mild basicity of organostannanes minimizes the imine enolization. In the report of Kagoshima group on the Cu(II)-mediated intermolecular addition of α-thioalkyl stannanes to N-phenyl or N-para-methoxyphenyl imines, the reaction mechanism was proposed to be a nucleophilic addition, in which Cu(OTf)$_2$ served as a Lewis acid to activate the imines.

![Scheme 24](image-url)

**Scheme 24.** Possible mechanisms

For the intramolecular cyclization of imine bearing a pendant α-thioalkylstannane nucleophile that we discovered, several possible mechanisms were proposed (Scheme 24).
First, the reaction could proceed through the nucleophilic addition, in which Cu(OTf)\(_2\) activates the imine and \(\alpha\)-thiomethylstannane acts as the nucleophile (Scheme 24a). Second, the nucleophilic sulfur could add to the copper-activated imine to generate a cyclic sulfonium ion. Destannylation of the cyclic sulfonium ion leads to the formation of sulfur ylide, which rapidly undergoes 1,2-alkyl transfer to deliver the copper-thiomorpholine complex (Stevens rearrangement, Scheme 24b). Or the reaction could proceed through radical mechanism, in which copper(II) oxidizes stannane compound to generate the nucleophilic \(\alpha\)-thiocarbon-centered radical, which undergoes the addition to the imine (Scheme 24c). We tested the possibility of an ionic mechanism (case a and \(b\)), in which Cu(OTf)\(_2\) serves as a Lewis acid to activate imine toward the intramolecular nucleophilic imine addition. Other metal salt and Lewis acid including Zn(OTf)\(_2\) and BF\(_3\)•OEt\(_2\) were tested instead of Cu(OTf)\(_2\), but failed to promote the cyclization (Scheme 25a). 2-pyridylaldehyde and related substrates, which should chelate to Cu(II) and presumably enhance the imine electrophilicity, showed poor reactivity (Scheme 25b). These results led us to consider the other mechanism.

Organostannanes are well known to form carbon-centered radicals under oxidative conditions,\(^{67}\) suggesting a mechanism in which Cu(II) acts as an oxidant. To test this hypothesis, TEMPO (1.5 equiv) was added into reaction. No cyclization product was detected and TEMPO-trapped compound 49 was observed. Further reduction of 49 to amine 50 allowed us to isolate and characterize this adduct (Scheme 26).
Scheme 26. Experiments supporting a role for Cu(OTf)$_2$ as an oxidant rather than a Lewis acid and radical related mechanism

On the basis of these results, we proposed a mechanism for cyclization featuring the generation and cyclization of a carbon radical (Scheme 27). Iminotributylstannane I undergoes protonation with HFIP and one-electron oxidation with Cu(OTf)$_2$ leading to the formation of Cu(I) and radical cation II. The α-thio radical II cyclizes with the pendant imine to form radical cation III, which is reduced by Cu(II) generating copper(II)-product complex IV. The generation of a sulfur-stabilized primary carbon-centered radical, followed by the 6-endo-trig cyclization to form the stable aminyl radical is the key for the success of this transformation.

Scheme 27. Proposed Mechanism

Although radical cyclization is well known for the formation of 5-exo-trig products, reaction preferred exclusively 6-endo-trig products. The presence of 5-exo-trig products is not observed. The high regioselectivity is presumably due to the formation of the more stable nitrogen-centered radical, which is reduced by copper (I) species, and the formation of stronger C–C bond over the C–N bond (10 kcal/mol stronger). The observed 6-endo
cyclization, rather than the competing 5-exo cyclization, is consistent with prior studies on ring closures of imines with pendant vinyl and aryl radicals. The reaction of carbon radicals with imines may be related to the recent work of Molander and Baran on oxidative C–C bond formation between aromatic N-heterocycles and radicals generated from organoboronic acids or their derivatives. In these transformations, a stoichiometric amount of oxidant is needed to reform the aromatic ring. In principle, our cyclization should be catalytic in Cu(II) but we believe that coordination of the unprotected thiomorpholine product to the Cu(II) leads to catalyst inhibition.

The radical mechanism provides the explanations for the minimal effects of electronics of the aryl imines on the outcome of the cyclization, the success of reactions with electron-rich aliphatic imines and the functional group tolerance.

### 3.2. Racemization Studies *

The substituted SnAP reagent – SnAP Cys, prepared from rac cysteine ethyl ester, coupled with p-trifluoromethylbenzaldehyde to give 3,5-disubstituted thiomorpholine in high yield and excellent diastereoselectivity (>20:1 dr) (Scheme 28). We envisioned that a substrate-controlled asymmetric synthesis could be achieved with chiral SnAP reagents.

![Scheme 28](image.png)

To test this hypothesis, we prepared SnAP L-Cys 51 via S-alkylation of L-cysteine ethyl ester with tributyl(iodomethyl)-stannane (Scheme 29a). Under the standard conditions, SnAP L-Cys condensed with p-trifluorobenzaldehyde, followed by cyclization to give the 3,5-disubstituted thiomorpholine in excellent diastereoselectivity (>20:1 dr) but eroded enantioselectivity (43% ee) (Scheme 29b). The erosion of optical purity raised the concern

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* The results described in this Section were in the collaboration with Mr. Christian Bold during his project research at ETH Zurich 2013.
about the racemization. The determination of the optical purity of starting materials and reaction intermediates, as well as the optical stability of product under reaction conditions were performed. The results of these experiments would provide the explanation for the eroded enantioselectivity and might support the continued development of the asymmetric synthesis of substituted saturated N-heterocycles using SnAP reagents.

For the ease of analysis, silicon surrogates of stannylated compounds have been prepared (Scheme 30). The observed optical purity of these compounds would reflect the optical purity of L-Cysteine ethyl ester and SnAP L-Cys reagent. The non-significantly difference of the 52 and 55 enantiomeric excess implies that the erosion of substituted thiomorpholine optical purity was originated from SnAP reagent impurity, and the racemization might occur under basic conditions of S-alkylation step. To further confirm imine formation and cyclization have no effect on stereochemical outcome of product, we next varied the reaction conditions in the imine formation reaction and cyclization to observe the change of the product enantiomeric excess. Condensation in different solvents, temperatures, with different dehydrating reagents (Table 3) and cyclization in different equivalences of 2,6-lutidine to vary reaction pH (Table 4) gave no significant difference in product optical purity.
Part II. SnAP Reagents for the Transformation of Aldehydes into Saturated N-Heterocycles

Scheme 30.

Table 3. Effect of imine formation conditions on the optical purity of cyclized product

<table>
<thead>
<tr>
<th>imine formation conditions</th>
<th>CH$_2$Cl$_2$, MS 4A</th>
<th>THF, MgSO$_4$</th>
<th>PhMe, Na$_2$SO$_4$</th>
<th>AcCN, CaSO$_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>% ee 52</td>
<td>43</td>
<td>42</td>
<td>42</td>
<td>43</td>
</tr>
</tbody>
</table>

Table 4. Effect of cyclization conditions on the optical purity of cyclized product

<table>
<thead>
<tr>
<th>cyclization conditions</th>
<th>2,6-lutidine</th>
<th>0.50 equiv</th>
<th>1.0 equiv</th>
<th>3.0 equiv</th>
</tr>
</thead>
<tbody>
<tr>
<td>temperature</td>
<td>23 °C</td>
<td>23 °C</td>
<td>50 °C</td>
<td></td>
</tr>
<tr>
<td>reaction time</td>
<td>2 h</td>
<td>2 h</td>
<td>12 h</td>
<td></td>
</tr>
<tr>
<td>% ee 52</td>
<td>41</td>
<td>42</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>
We have described the initial mechanistic studies on the transformation of aldehydes into unprotected 3-thiomorpholines with SnAP reagents. The reactions involve the intramolecular radical addition of imines bearing stannylated alkyl nucleophiles. The oxidative generation of a sulfur-stabilized primary carbon-centered radical is crucial for the success of this transformation. The use of radical cyclization overcomes the long-standing problem of the poor electrophilicity of unactivated imines in nucleophilic addition. We anticipate that this cyclization could be extended to the formation of other ring size heterocycles and other heteroatoms such as oxygen, nitrogen could stabilize the initially formed carbon-centered radical.

We also investigated the possibility of the substrate-controlled asymmetric synthesis of multisubstituted thiomorpholines. Imine formation and cyclization conditions almost have no effect on the stereochemical outcome of cyclized products. With SnAP reagents containing acidic protons like SnAP Cys, racemization might occur during the preparation of SnAP reagents. These results support the possibility of the asymmetric transformation of aldehydes into saturated N-heterocycles with chiral SnAP reagents.
4. One-Step Synthesis of Substituted Morpholines and Piperazines*

Morpholines and piperazines are important units found in various bioactive molecules. Morpholine and its derivatives are present in antimicrobial, anti-inflammatory, antitumor, antitubercular agents and others. They are found in combinatorial synthesis as substituents of small molecule scaffolds to improve the physical and pharmacokinetic properties. The piperazine moiety is considered a ‘privileged structure’ and has also been used frequently in combinatorial libraries. Despite the importance of these building blocks in drug discovery, their application in medicinal chemistry is so far limited, possibly due to the lack of commercially available diverse structures. Like other saturated cyclic amines, there are limited convenient and predictable synthetic methods to prepare them. Most of the synthetic approaches are quite lengthy and tedious.

Figure 7. Morpholine and piperazine moieties in nature and drug discovery

* The results described in this Chapter were in the collaboration with Mr. Michael U. Luescher in his doctoral study at ETH Zurich 2013.
In an effort to expand the SnAP reagent concept for the synthesis of other saturated N-heterocycles, we reasoned that heteroatoms such as oxygen and nitrogen should suitably stabilize the primary carbon-centered radical and lead to the formation of substituted morpholines and piperazines. Based on these assumptions, we designed a series of SnAP reagents suitable for the synthesis of unprotected mono- and disubstituted morpholines and piperazines (Figure 8). All the SnAP reagents were prepared on a multigram scale from inexpensive starting materials, by straightforward and efficient routes (Scheme 31).

**Figure 8.** SnAP reagents for morpholine and piperazine synthesis

**Scheme 31.** Preparation of selected SnAP reagents for morpholine and piperazine synthesis
With these SnAP reagents in hand, we first explored the transformation of various aldehydes into monosubstituted morpholines and piperazines. A single reaction protocol was used for all the SnAP reagents and substrates as for the purposes of evaluation. The transformation was examined using a series of aryl, heteroaryl and aliphatic aldehydes. The reactions generally retained efficiency toward a broad range of aldehydes (aryl, heteroaryl and alkyl aldehydes) and occurred in better yields compared to the ones in thiomorpholine synthesis. With the use of anhydrous solvents and reagents, CaSO\textsubscript{4} was left out without any deterioration of reaction productivity.

In the synthesis of morpholines, the reaction proceeded well with electron-rich, electron-poor and electron-neutral aryl aldehydes (Scheme 32, 63-66). Steric hindrance played a role in retarding the cyclization, and promoting the formation of destannylated side product. In the case of 2,4,6-mesitaldehyde, the yield dropped to less than 5% (at 60 °C in 12 h) (67). Meta- and para-heteroaryl aldehydes coupled with SnAP M 57 in excellent yields (68 and 69). Functional groups, including organohalide, protected amine, ester and alkene were well tolerated under the reaction conditions. Imines prepared from secondary aliphatic aldehydes and glyoxylate afforded morpholines in good yields (70-72).

Scheme 32. Conversion of aldehydes into unprotected 3-morpholines
In addition to the conventional aldehydes examined, more exotic aldehydes such as unprotected indole-3-carboxaldehyde, 3-furaldehyde, 1-methyl pyrazole-4-carboxaldehyde and cyclopropylcarboxaldehyde were included in the transformation of aldehydes into 3-pipazines using SnAP Pip reagent 60 to investigate the reaction efficiency (Scheme 33). The reactions occurred smoothly in good yields and with functional group tolerance. Reaction with 2-chloro 4-fluorobenzaldehyde surprisingly gave excellent yield regardless the presence of chloro substituent at ortho position (74). We assumed that the electron-deficient aryl ring increases the imine electrophilicity and benefits the cyclization. The unprotected indole core was tolerated in the reaction conditions to give the cyclized product in moderate yield (78).

Scheme 33. Conversion of aldehydes into unprotected 3-pipazines

We next investigated the methyl substituted SnAP reagents in the synthesis of disubstituted morpholines (SnAP 2-Me-M 58, SnAP 3-Me-M 59) and piperazines (SnAP 2-Me-Pip 61, SnAP 3-Me-Pip 62). Under standard conditions, these reagents coupled with representative aldehydes to give 2,5- and 3,5-disubstituted morpholines, piperazines in good to moderate yields (Scheme 34).
Scheme 34. Conversion of aldehydes into disubstituted morpholines and piperazines

The cyclization of the imine presumably occurs through a six-membered ring transition-state in which the interaction of substituent and R group (and N-Boc group in case of piperazine) would determine the thermodynamically favored stereochemical outcome of cyclized product (Figure 9). Consequently, the bulkier the R group, the better the diastereoselectivity; for instance, the reaction of quinoline-4-carboxaldehyde gave higher diastereoselectivity than that of ethyl glyoxalate (Scheme 34, 86 vs 85). SnAP 3-Me-M and SnAP 3-Me-Pip gave better diastereoselectivity than SnAP 2-Me-M or SnAP 2-Me-Pip due to the more severe interaction. While cis 2,5-disubstituted morpholine with two substituents at equatorial positions was formed as the major diastereomer, trans 2,5-disubstituted piperazine was observed as the major product in the reaction of SnAP 2-Me-Pip. This is presumaly due to the interaction of Boc group on the nitrogen and methyl group that overrides the 1,3-diaxial interaction, leading to the formation of favored trans 2,5-disubstituted piperazine.
In summary, we have successfully extended SnAP reagents for the cross-coupling with aldehydes to afford unprotected mono- and disubstituted morpholines and piperazines. The studies demonstrated that a sulfur-stabilized radical is not ultimately necessary for the success of the reaction, and that oxygen and nitrogen could play the role in stabilizing the primary carbon-centered radical. The cyclization occurred in mild conditions mediated by copper(II). The reaction has broad scope of aldehydes with high productivity and selectivity.
5. One-Step Synthesis of Medium Ring Saturated N-Heterocycles

New synthetic methods for the preparation of saturated N-heterocycles are mainly used for 5- and 6-membered rings; there are limited reports or examples on the synthesis of larger ring derivatives. Direct lithiation followed by transmetallation and metal-catalyzed cross-coupling is successful on pyrrolidines and piperidines, but much less efficiently for the elaboration of larger rings or those containing additional heteroatoms (Scheme 35a).\textsuperscript{16} C–H functionalization of N-benzyl protected cyclic amines via the formation of α-amino radicals has been applied to N-benzyl azepanes, as reported by Ito\textsuperscript{23} and Nakamura (Scheme 35b).\textsuperscript{24} Wolfe et al. reported alkene aminoarylation for the preparation of substituted 2-carboaryl 1,4-tetrahydrobenzodiazepines (Scheme 35c).\textsuperscript{40} While direct functionalization on simple saturated N-heterocycle cores are promising but challenging approaches, most preparations of diazepanes and related structures are currently via multiple-step ring cyclization followed by reduction, such as nucleophilic substitution,\textsuperscript{78} reductive amination,\textsuperscript{79} lactamization or ring-closing metathesis (Scheme 35d).\textsuperscript{80}

\textbf{Scheme 35.} Reported methods for the medium ring saturated N-heterocycle synthesis

\textsuperscript{*} The results described in this Chapter were in the collaboration with Mr. Michael U. Luescher in his doctoral study at ETH Zurich 2013.
We have described the development of SnAP reagents for the synthesis of saturated 6-membered N-heterocycles. The generation of a heteroatom-stabilized primary radical followed by the cyclization with the pendant imine to form aminyl radical is key for the success of this transformation. The facile 6-endo-trig cyclization, which is favored over the expected 5-exo-trig cyclization, encouraged us to explore the preparation of more challenging saturated N-heterocycles with larger ring sizes (7, 8 and 9).

5.1. SnAP Reagents for Medium Ring N-Heterocycle Synthesis

SnAP reagents suitable for the synthesis of 7, 8, and 9-membered ring N-heterocycles including oxazepanes, tetrahydrobenzoxazepines, diazepanes, tetrahydrobenzodiazepines, oxazocanes and others were prepared on a multigram scale by efficient routes (Scheme 36). These SnAP reagents are easily handled, air- or moisture-stable liquids (Figure 10).
Part II. SnAP Reagents for the Transformation of Aldehydes into Saturated N-Heterocycles

Scheme 36. Preparation of selected SnAP reagents

With these new SnAP reagents, we explored the transformation of various aldehydes into substituted 7-, 8- and 9-membered N-heterocycles. The operationally simple reaction protocol were used for all the substrates: combination of the SnAP reagent with the aldehyde gives the corresponding imine, which is cyclized with stoichiometric Cu(OTf)₂ and 2,6-lutidine in CH₂Cl₂/HFIP 4:1 at rt for 12 h.

5.2. Synthesis of 7-Membered Saturated N-Heterocycles

The transformation of aldehydes to substituted 7-membered ring N-heterocycles using SnAP reagents 93–97 was examined using a series of aryl, heteroaryl, and aliphatic
aldehydes (Scheme 37). Both oxygen- or nitrogen-based SnAP reagents have similar activities toward various aldehydes. They react well with both electron-rich, electron-poor aryl and heteroaryl aldehydes to give moderate to good yields of 7-endo products. Imines prepared from aliphatic aldehydes including piperidine-4-carboxaldehyde (105), pivaldehyde (116) and cyclopropanecarboxaldehyde (117) all afforded the products in good yields. Functional groups suitable for further elaboration including esters, cyanides, organohalides, protected amines and free hydroxyl groups were tolerated under the reaction conditions. The major side products observed in these reactions were the protodestannylated imines, which were believed formed by competing hydrogen atom transfer from HFIP. The formation of benzannulated products was accomplished using SnAP reagents 95 and 97. The presence of benzene as a tether increases the rate of cyclization, presumably due to the pre-align reacting groups. Indeed, diminished formation of destannylated products and high yields were observed in the synthesis of the tetrahydrobenzodiazepines (114–117) using SnAP BDA 97.

Scheme 37. Conversion of aldehyde into 7-membered saturated N-heterocycles
More substituted oxazepanes were prepared using SnAP PhOA 94 to demonstrate the applicability of SnAP reagent concepts in the preparation of saturated N-heterocycles with more complex patterns of substitution (Figure 11). The presence of a phenyl group on the SnAP OA not only did not interfere the reactions, but also facilitated the cyclization, presumably due to the Thorp-Ingold effect. SnAP PhOA 94 coupled with o-tolylaldehyde to give cyclized products in excellent yields (at 60 °C in 12 h) regardless of the steric hindrance (118). The reactions also proceeded well with aldehydes containing free hydroxyl group or cyanide (119 and 120).

![Figure 11. Synthesis of disubstituted 4,6-oxazepane](image)

### 5.3. Synthesis of 8- and 9-Membered Saturated N-Heterocycles

The successful synthesis of 7-membered ring N-heterocycles encouraged us to explore the preparation of 8 and 9-membered N-heterocycles using SnAP reagents (Scheme 38). The transformation still retained the efficiency toward a broad range of aldehydes, including aromatic and aliphatic aldehydes, although the cyclization yields were somewhat lower – as anticipated. Protodestannylation of the imine was observed again to be the major side product. In these cases, the electronics of the aldehydes had a strong influence on the cyclization. Electron-rich aldehydes such as para-anisaldehyde afforded mostly the protodestannylated imine. Higher dilution (0.02 M), the addition of CaSO₄ to scavenge water, or heat (60 °C) did not improve the ratio of product and protodestannylated side product. Introducing an aromatic ring as the tether – SnAP BOAC 100 – facilitated the cyclization; the corresponding saturated N-heterocycles were isolated in good yields with a broad substrate scope including electron-rich aldehydes (130, 133).
We also evaluated the formation of 9-membered ring products with SnAP reagents and chose SnAP BOAN 101 for initial attempts. The desired heterocyclic compounds were isolated in low to moderate yields but with a broad substrate scope with respect to the aldehydes (134–137). Further efforts to improve the efficiency of these challenging cyclizations by variation of the ligand and oxidant are currently ongoing. It is remarkable, however, that this process can easily access 8 and 9-membered rings, even in cases where the SnAP reagents contain no backbone elements that favor cyclization.

5.4. Gram-scale Synthesis using SnAP Reagents

A gram scale synthesis of 3-trifluorophenyl 1,4-oxazepane using SnAP OA 93 (5 g) was performed to demonstrate the ease and scalability of our protocol. Reactions were carried out under standard laboratory techniques, with all the reagents and solvents used
as purchased. Formation of HCl salt from the crude product was used in purification to afford the desired product (75% yield and > 98% purity). No column chromatography was required.

Scheme 39. Gram-scale synthesis of substituted 1,4-oxazepane

In summary, we have disclosed the use of SnAP reagents for the transformation of aldehydes into medium ring saturated N-heterocycles (7-, 8- and 9-membered rings). Bench-stable SnAP reagents, broad substrate scope and exceptional functional group tolerance are all inherited from the previous investigations on 6-membered ring synthesis. The transformation proceeds smoothly with 7-membered ring heterocycles with readily available aldehydes. The protocol should be scalable with a gram-scale synthesis. Although the yields of substituted 8 and 9-membered ring heterocycles are modest under the current conditions, 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.
6. Conclusions and Outlook

The current practice of synthetic organic chemistry relies heavily on the use of general and predictable coupling reactions of preformed building blocks. Based on this concept, many synthetic methods including peptide synthesis and metal-catalyzed cross-coupling reactions have been developed and contributed enormously in the synthesis of new drugs and materials. The recent shift in interest towards saturated N-heterocycles and the lack of their commercial supply raises the need for new synthetic methods that could offer the generality and applicability from available building blocks to access a diverse collection of saturated N-heterocycles. Despite extensive efforts, few methods are practical and scalable.

In our own efforts, we have developed SnAP reagents for the direct transformation of aldehydes into unprotected saturated N-heterocycles (Figure 12). A family of SnAP reagents with different substitution patterns have been prepared. They are easily handled, air- and moisture-stable liquids that can be stored for several months without decomposition. Their efficiency and applicability in coupling with aldehydes have been proven through extent studies on the preparation of different types of saturated N-heterocycles, including thiomorpholines, morpholines, piperazines and their 7,8, and 9-membered ring derivatives. The reaction accepts an outstanding scope of aldehydes including aryl-, heteroaryl-, and aliphatic aldehydes, occurs in good yields and diastereoselectivity, as well as good functional group tolerance. The conversion of aldehydes into saturated N-heterocycles proceeds in mild conditions, with an operationally simple and scalable protocol. SnAP reagents were prepared in multigram scale from inexpensive starting materials, by straightforward and efficient routes (Scheme 40).

The transformation involved an intramolecular C–C bond-forming radical cyclization of an imine bearing a pendant nucleophilic carbon. The generation of a heteroatom-stabilized carbon-centered radical is key for the success of this transformation. The use of radical cyclization overcomes the challenging nucleophilic addition to unactivated imine.

Given the importance of saturated N-heterocycles in drug discovery and the lack of reliable synthetic methods for their preparation, we believe that SnAP reagents and their
transformation will enhance the toolbox of synthetic chemists in the synthesis of a wide range of *unprotected* saturated N-heterocycles.

**Figure 12.** SnAP Reagent Concept and SnAP reagents
This part of my Dissertation has described some first achievements in the development of SnAP reagents and their use in the preparation of substituted saturated N-heterocycles. These achievements should pave the way for the further studies in this topic including an expansion of SnAP reagents into even more exotic patterns (Outlook 1), development of asymmetric catalytic version of this transformation (Outlook 2) and the seek for surrogates of toxic organostannanes (Outlook 3).
**Outlook 1**

Spirocyclic structures are found in a wide range of natural compounds. They are also interesting scaffolds for the exploration of chemical space in drug discovery. The complexity of these molecules represents at the quaternary carbon-centered linkage of the two fused rings. Given the facile transformation of aldehydes into saturated N-heterocycles, we envisioned that the cyclization of the corresponding imines prepared from the condensation of SnAP reagents and ketones could provide those types of cyclic compounds.

**Outlook 2**

Our current mechanistic evidences favored a radical pathway for this transformation. In principle, the cyclization should be catalytic in Cu(II), but the strong coordination of nitrogen of the cyclic amine is believed to inhibit the turnover of Cu(II). The additional of sacrificial metal salt or the use of a ligand that binds strongly copper is expected to turn over copper. With the catalytic version, a screening of chiral ligands should lead to the asymmetric synthesis of saturated N-heterocycles.
Outlook 3

Scheme 43. Surrogates for organostannanes

One of the limitations of SnAP reagent concept is the use of toxic organostannanes. The current mechanistic evidence suggested the formation of a heteroatom-stabilized primary carbon-centered radical that followed the intramolecular radical imine addition. This type of radical could be generated from other non-stannylated radical precursor such as organosilane, organoboron, Barton esters or acetals.
7. References


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Synthesis of Pyrrolidines: Catalytic Oxidative Cyclization

Aminoacetoxylation.

15945 Carboamination Reactions: Divergent Reactivity of a Pd(IV) Species.

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61. *Reviews on nucleophilic imine addition*: Bloch, R.: (a) Additions of Organometallic Reagents to


Part III.

Experimental Procedures and Characterization Data
1. General Methods

All reactions were carried out under N$_2$ in dried glassware. N,N-Dimethylformamide (DMF), diethylether, acetonitrile and tetrahydrofuran (THF) were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Dichloromethane was distilled from CaH$_2$; hexafluoroisopropanol (HFIP) was distilled from molecular sieves 4A. BF$_3$•OEt$_2$ was distilled over CaH$_2$ prior to use. Cu(OTf)$_2$ and K$_2$CO$_3$ were dried at 110 °C under high vacuum (ca. 0.1 mmHg) for 2 h and stored in desiccator. All other chemicals were purchased from Acros, Aldrich, Fluka, Merck, ABCR, Maybridge, Fluorochem, TCI or Alfa Aesar and used as purchased unless stated otherwise. Thin layer chromatography was performed using EMD glass plates (silica gel F$_{254}$, Art 5715, 0.25 mm), visualized by fluorescence quenching under UV light, and stained with potassium permanganate or nynhydrin. Flash column chromatography was performed with Silicycle Silica Flash (230-400 mesh) using forced flow of 0.3–0.5 bar. Infrared (IR) spectra were recorded on a JASCO FT:IR-4100 spectrophotometer and reported as wavenumber (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 (δ) downfield from tetramethysilane (with the CHCl$_3$ peak at 7.26 ppm used as a standard). $^{13}$C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethysilane (with the central peak of CHCl$_3$ at 77.16 ppm used as a standard). NMR coupling constants (J) are reported in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, double of doublet; ddd, double of doublet of doublet; dt, doublet of triplet; t, triplet; q, quartet; quint, quintet; sext, sextet; m, multiplet. High-resolution mass spectrometric measurements (HRMS) were performed by the mass spectrometry service of the LOC at the ETH Zurich on Agilent 1200 (LC-MS), Bruker maXis for ESI-Q-TOF or Waters Micromass AutoSpec Ultima MassLynx 4.0 (GC-MS). Melting points (mp) were measured on an Electrothermal Mel-Temp melting point apparatus and are uncorrected. Gas-chromatography/mass spectrometry (GCMS) was performed using an Agilent 7820A (GC) coupled with an Agilent 5975 MSD series (MS) system. Optical rotations were measured using a Jasco P-2000 Polarimeter, operating at the sodium D line (589 nm) with
a 100 mm path length cell, and were reported as followed \([\alpha]_D^T\) (concentration in g/100 mL, solvent). Supercritical Fluid Chromatography (SFC) was performed using pumps and photodiode array detector from JASCO: Daicel Chiralpak columns (4.6 x 250 mm) with \(\text{CO}_2:i\text{PrOH}\) gradient elution from 5% to 50% \(i\)-PrOH; oven temperature at 40 °C; outlet pressure at 100 bar; flow rate of 3.0 mL/min; detection wavelength at 220 nm.

2. Part I: Ether-Forming Cross-Coupling Reactions of Potassium Organotrifluoroborates and Acetals

2.1. Preparation of Acetals

2.1.1. Preparation of \(N\)-methyl acetohydroxamic acid

\(N\)-Acetoxy-\(N\)-methylacetamide 53. To a suspension of \(N\)-methylhydroxylamine hydrochloride (8.0 g, 94 mmol) in \(\text{CH}_2\text{Cl}_2\) (250 mL) was added \(\text{NEt}_3\) (42 mL, 0.30 mol) at 0 °C. After 30 min at 0 °C, to the reaction mixture was added a solution of acetyl chloride (15 mL, 0.11 mol) in \(\text{CH}_2\text{Cl}_2\) (50 mL) over 60 min. After 4 h at 23 °C, the reaction was quenched with \(\text{H}_2\text{O}\) (50 mL) and stirred for 15 min. The mixture was extracted with \(\text{CH}_2\text{Cl}_2\) (3 x 50 mL), washed with \(\text{H}_2\text{O}\) (3 x 50 mL) and aq. sat. \(\text{NaCl}\) (20 mL), dried with \(\text{Na}_2\text{SO}_4\), and concentrated.\(^1\) Crude \(N\)-acetoxy-\(N\)-methylacetamide 53 (11 g) was used for the next step without further purification.

\(N\)-methyl acetohydroxamic acid 54. To the solution of crude \(N\)-acetoxy-\(N\)-
methylacetamide 53 (11 g, 86 mmol) in methanol (170 mL) was added sat. NaOMe in methanol (8.6 mL) and DMAP (0.5 g, 4.3 mmol). After refluxing at 60 °C for 4 h, the mixture was concentrated. Purification by flash column chromatography (EtOAc:MeOH 91:9) delivered 54 (6.9 g, 83% over 2 steps): 1H NMR δ 2.09 (s, 3H), 3.20 (s, 3H), 9.27 (bs, 1H); spectra data was consistent with a previous report.

2.1.2. Preparation of mixed acetals derived of c-hexanol

2-(2-Methoxyethoxy)methoxy)cyclohexane 7. To a solution of cyclohexanol (0.21 mL, 2.0 mmol) in CH2Cl2 (10 mL) was added (i-Pr)2NEt (0.90 mL, 6.0 mmol), followed by 2-methoxyethoxymethyl chloride (0.47 mL, 4.0 mmol) dropwise at 0 °C. After 18 h at 23 °C, the reaction was quenched with aq. sat. NH4Cl (10 mL) and stirred for 15 min. The mixture was extracted with CH2Cl2 (3 x 20 mL), washed with H2O (20 mL) and aq. sat. NaCl (20 mL), dried with Na2SO4, filtered and concentrated. Purification by flash column chromatography (hexanes:EtOAc 90:10) delivered 7 (0.30 g, 80%) as a colorless liquid: Rf = 0.5 (hexanes:EtOAc 2:1); IR (thin film) ν 2932, 2857, 1451, 1111, 1046, 933 cm⁻¹; 1H NMR (500 MHz, CDCl3) δ 1.18-1.34 (m, 5H), 1.52-1.54 (m, 1H), 1.72-1.73 (m, 2H), 1.88-1.90 (m, 2H), 3.39 (s, 3H), 3.53-3.54 (m, 3H), 3.70 (t, J = 4.5, 2H), 4.77 (s, 2H); 13C NMR (125 MHz, CDCl3) δ 24.3, 25.8, 32.3, 39.1, 66.7, 72.0, 75.2, 93.5; CI-HRMS calcd for C10H20O3H [M + H] 189.1491, found 189.1497.

General procedure for the preparation of mixed acetals derived of c-hexanol

To a solution of alcohol YOH (1.0 equiv) in 0.2 M CH₂Cl₂ was added DMAP (0.20 equiv), (i-Pr₂)₂NEt (20 equiv) at 0 °C, followed by cyclohexyl chloromethyl ether (2.0 equiv) dropwise. The reaction was warmed to rt and allowed to stir for 24 h. Another portion of (i-Pr₂)₂NEt (20 equiv) and cyclohexyl chloromethyl ether (2.0 equiv) was added at 0 °C. After 24 h at rt, the reaction was quenched with aq. sat. NH₄Cl and stirred for 15 min. The mixture was extracted with Et₂O, washed with 0.5 N HCl (10 mL), H₂O and aq. sat. NaCl, dried with Na₂SO₄, filtered and concentrated. Purification by flash column chromatography delivered corresponding mixed acetals.

**Ethyl 2-(cyclohexyloxymethoxy)acetate 8.** Purification by flash column chromatography (hexanes:EtOAc 95:5) delivered 8 (1.0 g, 91%) as a colorless liquid: Rᵣ = 0.5 (hexanes:EtOAc 4:1); IR (thin film) ν 2993, 2857, 1757, 1737, 1205, 1062 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.24-1.39 (m, 8H), 1.52-1.54 (m, 1H), 1.71-1.73 (m, 2H), 1.84-1.89 (m, 2H), 3.58 (t, J = 4.5, 9.5, 1H), 4.18-4.24 (m, 4H), 4.81 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 14.3, 24.2, 25.7, 61.0, 64.3, 75.6, 93.0, 170.4; ESI-HRMS calcd for C₁₁H₂₀O₄Na [M + Na] 239.1259, found 239.1253.

**2-(Cyclohexyloxymethoxy)-N,N-dimethylacetamide 9.** Purification by flash column chromatography (hexanes:EtOAc 50:50) delivered 9 (0.12 g, 89%) as a colorless liquid: Rᵣ = 0.3 (hexanes:EtOAc 1:1); IR (thin film) ν 2932, 2856, 1660, 1501, 1450, 1055, 934 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.17-1.34 (m, 5H), 1.40-1.42 (m, 1H), 1.60-1.62 (m, 2H), 1.77-1.79 (m, 2H), 2.95 (s, 3H), 2.96 (s, 3H), 3.56-3.60 (m, 1H), 4.24 (s, 2H), 4.82 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 24.1, 25.6, 32.6, 35.4, 36.1, 65.4, 75.5, 93.1, 168.9. EI-HRMS calcd for C₁₁H₂₁NO₃ [M] 215.1521, found 215.1513.

**2-((Cyclohexyloxymethoxy)methyl)pyridine 10.** Purification by flash column chromatography (hexanes:EtOAc 99:1) delivered 10 (1.9 g, 81%) as a colorless liquid: Rᵣ = 0.3 (hexanes:EtOAc 2:1); IR (thin film) ν 2932, 2856, 1592, 1436, 1056, 757 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.12-1.27 (m, 5H), 1.40-1.42 (m, 1H), 1.60-1.62 (m, 2H), 1.77-1.79 (m, 2H), 3.50 (tt, J = 3.5, 9.0, 1H), 4.63 (s, 2H), 4.77 (s, 2H), 7.04-

Part III. Experiment Procedures and Characterization Data

7.06 (m, 1H), 7.30-7.31 (m, 1H), 7.54-7.57 (m, 1H), 8.44-8.45 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 24.0, 25.4, 32.5, 70.1, 75.2, 93.1, 121.2, 122.1, 136.4, 149.0, 158.2; Cl-HRMS calcd for C$_{13}$H$_{19}$NO$_2$H [M + H] 222.1494, found 222.1502.

1-(Cyclohexyloxymethoxy)-2-methoxybenzene 11. Purification by flash column chromatography (hexanes:Et$_2$O 99:1) delivered 11 (0.51 g, 83%) as a colorless liquid: $R_f$ = 0.4 (hexanes:Et$_2$O 10:1); IR (thin film) $\nu$ 2933, 2856, 1599, 1495, 1220, 1145, 1089, 1005, 988, 873 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.19-1.34 (m, 5H), 1.51-1.56 (m, 1H), 1.71-1.73 (m, 2H), 1.89-1.91 (m, 2H), 3.69 (tt, $J$ = 4.0, 9.0, 1H), 6.99 (t, $J$ = 7.5, 1H), 7.06 (d, $J$ = 7.5, 2H), 7.28 (t, $J$ = 7.5, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 24.2, 25.7, 32.8, 76.5, 91.6, 116.4, 121.7, 129.5, 157.8; Cl-HRMS calcd for C$_{13}$H$_{18}$O$_2$ [M] 206.1307, found 206.1302.

1-(Cyclohexyloxymethoxy)-2-methoxybenzene 12. Purification by flash column chromatography (hexanes:EtOAc 96:4) delivered 12 (1.9 g, 90%) as a colorless liquid: $R_f$ = 0.4 (hexanes:EtOAc 4:1); IR (thin film) $\nu$ 2932, 2856, 1594, 1504, 1251, 1084, 993, 743 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.20-1.37 (m, 5H), 1.51-1.57 (m, 1H), 1.70-1.72 (m, 2H), 1.89-1.92 (m, 2H), 3.77 (tt, $J$ = 3.5, 8.5, 1H), 3.87 (s, 3H), 5.33 (s, 2H), 6.88-6.98 (m, 3H), 7.23-7.26 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 24.1, 25.7, 32.6, 55.8, 76.1, 92.4, 111.7, 116.5, 120.9, 122.1, 147.1, 149.6; ESI-HRMS calcd for C$_{14}$H$_{20}$O$_3$Na [M + Na] 259.1310, found 259.1306.

2-(Cyclohexyloxymethoxy)isoindoline-1,3-dione 13. Purification by flash column chromatography (hexanes:EtOAc 90:10) delivered 13 (0.52 g, 94%) as white crystals: $R_f$ = 0.4 (hexanes:EtOAc 4:1); mp = 59 °C; IR (thin film) $\nu$ 2933, 2857, 1792, 1733, 1610, 1452, 1132, 965, 700 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.23-1.37 (m, 5H), 1.56-1.60 (m, 1H), 1.74-1.76 (m, 2H), 1.97-1.99 (m, 2H), 4.07-4.08 (m, 1H), 1.73-7.84 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 24.1, 25.7, 31.8, 76.1, 96.7, 123.6, 129.2, 134.5, 163.8. ESI-HRMS calcd for C$_{15}$H$_{17}$NO$_4$Na [M + Na] 298.1055 found 298.1070.
Part III. Experiment Procedures and Characterization Data

\[ N-(\text{Cyclohexyloxymethoxy})-N\text{-methylacetamide 14.} \] Purification by flash column chromatography (hexanes:EtOAc 70:30) delivered 14 (0.49 g, 84%) as a colorless liquid: \( R_f = 0.5 \) (hexanes:EtOAc 2:1); IR (thin film) \( \nu = 2934, 2857, 1675, 1410, 1375, 1094, 953, 914 \) cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta = 1.22\text{-}1.39 \) (m, 5H), 1.54-1.55 (m, 1H), 1.73-1.76 (m, 2H), 1.89-2.03 (m, 2H), 2.12 (s, 3H), 3.27 (s, 3H), 3.60-3.64 (m, 1H), 5.00 (s, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta = 20.7, 23.9, 25.5, 32.4, 35.6, 77.3, 97.2, 173.1; \) CI-HRMS calcd for C\(_{10}\)H\(_{19}\)NO\(_3\)H [M + H] 202.1443, found 202.1446.

2.1.3. Preparation of hydroxamic acid-derived acetals

A solution of alcohol (2.0 equiv) and paraformaldehyde (2.0 equiv) in TMSCl (0.2 mL) was allowed to stir for 1 h at rt and concentrated to give the corresponding crude chloromethyl ether directly used for the next step without further purification.\(^6\) A solution of obtained chloromethyl ether in 0.2 M CH\(_2\)Cl\(_2\) was added to a solution of \( N\)-methyl acetohydroxamic acid 54 (1.0 equiv), (i-Pr)\(_2\)NEt (8.0 equiv), and DMAP (0.10 equiv) in 0.4 M CH\(_2\)Cl\(_2\) at 0 °C. After 24 h at rt, the reaction was quenched with sat. aq. NH\(_4\)Cl and stirred for 15 min. The mixture was extracted with EtOAc, washed with sat. aq. NH\(_4\)Cl, H\(_2\)O, sat. aq. NaCl, dried with Na\(_2\)SO\(_4\), filtered, and concentrated.\(^5\) Purification by flash column chromatography delivered corresponding hydroxamic-acid derived acetals.

\[ N\text{-methyl-N-}^\text{(octyloxymethoxy)acetamide 55.} \] Purification by flash column chromatography (hexanes:EtOAc 75:25) delivered 55 (0.80 g, 72%) as a colorless liquid: \( R_f = 0.5 \) (hexanes:EtOAc 50:50); IR (thin film) \( \nu = 3493, 1677, 1101 \) cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta = 0.88 \) (t, \( J = 6.5 \) Hz, 3H), 1.22-1.40 (m, 10H), 1.58-1.64 (m, 2H), 2.13 (s, 3H), 3.27 (s, 3H), 3.68 (t, \( J = 6.5 \) Hz, 1H), 4.95 (s, 2H); \(^{13}\)C NMR

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(125 MHz, CDCl$_3$) $\delta$ 14.0, 20.6, 22.6, 26.0, 29.2, 29.3, 29.6, 31.7, 35.5, 70.3, 99.6, 173.1; ESI-HRMS calcd for C$_{12}$H$_{26}$NO$_3$Na [M + Na] 254.1732, found 254.1741.

$N$-methyl-$N$-((1-phenylethoxy)methoxy)acetamide 56. Purification by flash column chromatography (hexanes:EtOAc 75:25) delivered 56 (0.44 g, 46%) as a colorless liquid: $R_f = 0.5$ (hexanes:EtOAc 50:50); IR (thin film) $\nu$ 3488, 1672, 1086, 760, 703 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.51 (d, $J = 6.5$ Hz, 3H), 2.11 (s, 3H), 3.27 (s, 3H), 4.79 (d, $J = 7.5$ Hz, 1H), 4.87 (q, $J = 6.5$ Hz, 1H), 4.93 (d, $J = 7.5$ Hz, 1H), 7.28-7.39 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 20.6, 23.7, 35.5, 76.2, 96.6, 126.4(2), 128.0, 128.6(2), 142.1, 173.1; ESI-HRMS calcd for C$_{12}$H$_{18}$NO$_3$ [M + H] 224.1287, found 224.1292.

$N$-methyl-$N$-((2-methylpentan-2-yl)oxy)methoxy)acetamide 57.

Purification by flash column chromatography (hexanes:EtOAc 70:30) delivered 57 (0.51 g, 72%) as a colorless liquid: $R_f = 0.5$ (hexanes:EtOAc 50:50); IR (thin film) $\nu$ 3543, 1673, 1099 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.92 (t, $J = 7.0$ Hz, 3H), 1.23 (s, 6H), 1.30-1.40 (m, 2H), 1.46-1.52 (m, 2H), 2.12 (s, 3H), 3.29 (s, 3H), 5.02 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 14.4, 17.1, 20.6, 26.1(2), 35.5, 43.9, 77.6, 93.9, 172.9; ESI-HRMS calcd for C$_{10}$H$_{21}$NO$_3$Na [M + Na] 226.1419, found 226.1419.

$N$-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)methoxy)-$N$-methylacetamide 58. Purification by flash column chromatography (hexanes:EtOAc 75:25) delivered 58 (1.8 g, 87%) as a colorless liquid: $R_f = 0.4$ (hexanes:EtOAc 70:30); IR (thin film) $\nu$ 3493, 1677, 1091 cm$^{-1}$; $[\alpha]^{25}_D = -36.622$ (0.49, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.77 (d, $J = 6.5$ Hz, 3H), 0.80-1.06 (m, 9H), 1.24-1.29 (m, 1H), 1.35-1.45 (m, 1H), 1.62-1.70 (m, 2H), 2.08-2.20 (m, 2H), 2.12 (s, 3H), 3.29 (s, 3H), 3.32-3.39 (m, 1H), 4.97 (d, $J = 7.0$ Hz, 1H), 5.11 (d, $J = 7.0$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 15.9, 20.6, 20.9, 22.1, 22.9, 25.3, 31.4, 34.1, 35.2, 41.7, 48.1, 80.8, 99.3, 172.9; ESI-HRMS calcd for C$_{14}$H$_{27}$NO$_3$Na [M + Na] 280.1889, found 280.1902.
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\[ \text{N-methyl-N-}((\text{trans-4-}) \text{methylcyclohexyl(oxy)methoxy})\text{propionamide 48.} \]

Purification by flash column chromatography (hexanes:EtOAc 80:20) delivered 48 (0.34 g, 30%) as a colorless liquid: \( R_f = 0.3 \) (hexanes:Et\(_2\)O 2:1); IR (thin film) \( \nu \) 1096, 1672, 1454 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.89 (d, \( J = 4 \), 3H), 0.96 (qd, \( J = 2.8 \), 12, 6H), 1.26-1.40 (m, 3H), 1.72-1.76 (m, 2H), 1.98-2.02 (m, 2H), 2.43 (q, \( J = 7.6 \), 2H), 3.28 (s, 3H), 3.55 (tt, \( J = 4.4 \), 11, 1H), 5.0 (s, 2H); \(^{13}\)C NMR (100 MHz, d-DMSO) \( \delta \) 8.4, 21.5, 24.9, 31.1, 31.9, 32.5, 35.2, 76.9, 96.3, 174.4; EI-HRMS calcd for C\(_{12}\)H\(_{23}\)NO\(_3\) [M] 229.1678, found 229.1656.

\[ \text{N-methyl-N-}((1r,4r)-4\text{-methylcyclohexyl(oxy)methoxy})\text{acetamide 50.} \]

Purification by flash column chromatography (hexanes:EtOAc 80:20) delivered 50 (0.69 g, 32%) as a colorless liquid: \( R_f = 0.4 \) (hexanes:EtOAc 2:1); IR (thin film) \( \nu \) 2930, 2865, 1675, 1409, 1375, 1096, 951 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.89 (d, \( J = 6.8 \), 3H), 0.96 (qd, \( J = 3.2 \), 12, 2H), 1.26-1.38 (m, 3H), 1.73-1.76 (m, 2H), 1.98-2.03 (m, 2H), 2.12 (s, \( J = 3 \)H), 3.28 (s, 3H), 3.54 (tt, \( J = 4.0 \), 11.2, 1H), 5.01 (s, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 20.7, 21.8, 31.8, 32.5, 33.2, 35.6, 78.1, 97.3, 173.2; EI-HRMS calcd for C\(_{11}\)H\(_{21}\)NO\(_3\) [M] 216.1594, found 216.1593.

\[ \begin{align*}
\text{R}^1 & \text{O} \quad \text{R}^2 \text{O} \quad \text{R}^3 \text{Me} \\
\text{Me} & \text{O} \quad \text{O} \quad \text{N} \quad \text{Me} \\
\text{O} & \text{Me} \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{Me} \\
\end{align*} \]

To a solution of O-MOM acetal (1.0 equiv, 1.0 mmol) and 2,2'-bipyridyl (3.0 equiv, 3.0 mmol) in 0.1 M CH\(_2\)Cl\(_2\) was added TESOTf (2.0 equiv, 2.0 mmol) at 0 °C dropwise. The reaction was allowed to stir for 30 min at 0 °C. After the disappearance of O-MOM acetal on TLC, \( N \)-methyl acetohydroxamic acid 54 (2.5 equiv, 2.5 mmol) was added. After 4 h at 23 °C, the reaction was quenched with aq. sat. NaHCO\(_3\) and stirred for 15 min. The mixture was extracted with CH\(_2\)Cl\(_2\), washed with H\(_2\)O and aq. sat. NaCl, dried over Na\(_2\)SO\(_4\), filtered
and concentrated. Purification by flash chromatography delivered the corresponding hydroxamic-acid derived acetals.

\( \text{N-(1-(2,4-dimethylpentan-3-yl)oxy)ethoxy-N-methylacetamide} \) 59.

Purification by flash column chromatography (hexanes:Et<sub>2</sub>O 95:5) delivered 59 (64 mg, 28%) as a colorless liquid: \( R_f = 0.4 \) (hexanes:Et<sub>2</sub>O 4:1); IR (thin film) \( \nu \) 2962, 2936, 2875, 1678, 1470, 1096, 1005 cm<sup>-1</sup>. \( ^1\)H NMR (500 MHz, CDCl<sub>3</sub>) \( \delta \) 0.89 (d, \( J = 6.5, 12\)H), 1.33 (d, \( J = 5.5, 3\)H), 1.81 (sept, \( J = 6.5, 2\)H), 2.32 (s, 3H), 3.01 (bs, 1H), 3.31 (s, 3H), 4.94 (q, \( J = 5.5, 1\)H). \( ^{13}\)C NMR (125 MHz, CDCl<sub>3</sub>) \( \delta \) 18.0, 18.5, 19.6, 20.1, 20.6, 21.0, 30.4, 35.2, 88.6, 104.1, 174.3. ESI-HRMS calcd C<sub>12</sub>H<sub>25</sub>NO<sub>3</sub>Na for \([M + Na]\) 254.1732, found 254.1736.

\( \text{Cholesteroxymethoxy-N-methylacetamide} \) 60.

Purification by flash column chromatography (hexanes:Et<sub>2</sub>O 94:6) delivered 60 (0.26 g, 11%) as white solid: \( R_f = 0.3 \) (hexanes:Et<sub>2</sub>O 4:1); mp = 106 °C; \([\alpha]_{D}^{25} = 31.8484 \) (0.50, CHCl<sub>3</sub>); IR (thin film) \( \nu \) 1094, 1404, 1681 cm<sup>-1</sup>. \( ^1\)H NMR (400 MHz, CDCl<sub>3</sub>) \( \delta \) 0.68 (s, 3H), 0.83-1.61 (m, 33H), 1.78-2.04 (m, 5H), 2.12 (s, 3H), 2.26-2.35 (m, 2H), 3.28 (s, 3H), 3.53 (tt, \( J = 4.0, 8.0, 1\)H), 5.02 (s, 2H), 5.37 (d, \( J = 8.0, 1\)H). \( ^{13}\)C NMR (100 MHz, CDCl<sub>3</sub>) \( \delta \) 12.0, 18.9, 19.5, 20.8, 21.2, 22.7, 23.0, 24.0, 24.4, 28.1, 28.3, 28.8, 32.0, 32.1, 35.9, 36.3, 36.8, 37.2, 39.4, 39.7, 39.9, 42.5, 50.3, 56.2, 56.9, 77.4, 79.1, 97.4, 122.5, 149.2, 173.1. ESI-HRMS calcd for C<sub>31</sub>H<sub>53</sub>NO<sub>3</sub>H [M + H] 488.4098, found 488.4099.

---

A solution of methylmethylsulfide of the corresponding alcohol (2.2 equiv) and \( \text{SO}_2\text{Cl}_2 \) (2.2 equiv) in 0.15 M \( \text{CH}_2\text{Cl}_2 \) was stirred at 0 °C for 1 h and concentrated to deliver the corresponding crude chloromethyl ether.\(^8\) To a solution of \( \text{N-methyl acetohydroxamic acid} \) 54 (1.0 equiv) in 0.4 M \( \text{CH}_2\text{Cl}_2 \) was added \((i-\text{Pr})_2\text{NET} \) (8.0 equiv), crude chloromethyl ether in 0.4 M \( \text{CH}_2\text{Cl}_2 \), and DMAP (0.10 equiv) at 0 °C. After 20 h at rt, the reaction was quenched slowly with sat. aq. \( \text{NH}_4\text{Cl} \) and stirred for 15 min. The mixture was extracted with EtOAc, washed with sat. aq. \( \text{NH}_4\text{Cl} \), \( \text{H}_2\text{O} \), sat. aq. \( \text{NaCl} \), and dried with \( \text{Na}_2\text{SO}_4 \), filtered, and concentrated. Purification by flash column chromatography delivered the corresponding hydroxamic acid-derived acetal.

\[
\text{N-methyl-N-[(phenoxymethoxy)acetamide 61.} \quad \text{Purification by flash column chromatography (hexanes:EtOAc 70:30) delivered 61 (0.28 g, 72%) as a colorless liquid: } R_f = 0.5 \text{ (hexanes:EtOAc 50:50); } \text{IR (thin film) } \nu = 3488, 1675, 1223, 760, 693 \text{ cm}^{-1}; \quad \text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3 \text{) } \delta = 2.08 \text{ (s, 3H), 3.25 \text{ (s, 3H), 5.50 \text{ (s, 2H)}, 7.02-7.10 \text{ (m, 3H), 7.30-7.37 \text{ (m, 2H);} \text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3 \text{) } \delta = 20.6, 35.4, 95.7, 115.5(2), 122.4, 129.5(2), 156.5, 173.2; \text{ESI-HRMS calcd for C}_{10}\text{H}_{13}\text{NO}_3\text{Na} [M + Na] 218.0793, found 218.0799.}
\]

\[
\text{(E)-N-[(3,7-dimethylocta-2,6-dienyloxy)methoxy]-N-methylacetamide 62. Purification by flash column chromatography (hexanes:EtOAc 80:20) delivered 62 (80 mg, 31%) as a colorless liquid: } R_f = 0.6 \text{ (hexanes:EtOAc 50:50); } \text{IR (thin film) } \nu = 3483, 1675, 1086 \text{ cm}^{-1}; \quad \text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3 \text{) } \delta = 1.60 \text{ (s, 3H), 1.68 \text{ (s, 3H), 1.69 \text{ (s, 3H), 2.03-2.16 \text{ (m, 4H), 2.13 \text{ (s, 3H), 3.28 \text{ (s, 3H), 4.25 \text{ (d, J = 7.0 Hz, 1H), 4.95 \text{ (s, 2H), 5.08 \text{ (t, J = 6.5 Hz, 1H), 5.33 \text{ (t, J = 6.5 Hz, 1H);} \text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3 \text{) } \delta = 16.5, 17.7, 20.7, 25.7, 26.3, 35.6, 39.6, 65.8, 98.3, 119.4, 123.8, 131.8, 141.9, 173.3; \text{ESI-HRMS calcd for C}_{14}\text{H}_{26}\text{NO}_3 [M + H] 256.1913, found 256.1914.}}}
\]

2.1.4. Preparation of O-MOM acetals

To a solution of the corresponding alcohol (10 equiv) in dimethoxymethane (2 mL) was added LiBr (0.20 equiv) and para-toluenesulfonic acid monohydrate (p-TSA) (0.1 equiv) at rt. After 12 h at rt, the reaction was quenched with aq. sat. NaHCO₃ and stirred for 15 min. The mixture was diluted with Et₂O. Organic layer was separated, washed with aq. sat. NaHCO₃, H₂O and aq. sat. NaCl, dried with Na₂SO₄, filtered, and concentrated. Purification by flash column chromatography delivered the corresponding O-MOM acetal.

(Methoxymethoxy)cyclohexane 6. Purification by flash column chromatography (hexanes:EtOAc 96:4) delivered 6 (2.2 g, 44%) as a colorless liquid: Rₖ = 0.4 (hexanes:EtOAc 10:1); IR (thin film) ν 2933, 2857, 1449, 1142, 1106, 1044 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.24-1.36 (m, 5H), 1.52-1.55 (m, 1H), 1.72-1.77 (m, 2H), 1.86-2.17 (m, 2H), 3.36 (s, 3H), 3.51 (tt, J = 3.5, 8.0, 1H), 4.68 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 24.2, 25.7, 32.8, 55.1, 75.2, 94.4; CI-HRMS calcd for C₉H₁₆O₂ [M] 144.1150, found 144.1145.

Cholesterol-MOM 63. Purification by flash column chromatography (hexanes:EtOAc 95:5) delivered 63 (2.5 g, 58%) as a white solid: Rₖ = 0.5 (hexanes:EtOAc 1:1); mp = 67 °C; [α]²⁵ –35.677 (0.50, CHCl₃); IR (thin film) ν 2934, 1465, 1379, 1149, 1106, 1049 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.68 (s, 3H), 0.85-1.58 (m, 33H), 1.78-2.03 (m, 5H), 2.23-2.37 (m, 2H), 3.37 (s, 3H), 3.42 (tt, J = 4.0, 8.0, 1H), 4.69 (s, 2H), 5.35-5.36 (m, 1H); ¹³C NMR (120 MHz, CDCl₃) δ 12.0, 18.8, 19.5, 21.2, 22.7, 22.9, 23.9, 24.4, 28.2, 28.4, 29.1, 32.0, 32.1, 35.9, 36.4, 36.9, 37.4, 39.6, 39.7, 39.9, 42.5, 50.4, 55.3, 56.3, 56.9, 77.4, 94.9, 121.9, 140.9; CI-HRMS calcd for C₂₉H₅₀O₂ [M] 430.3806, found 430.3810.

To a solution of the corresponding alcohol (1.0 equiv) in 0.5 M CH\(_2\)Cl\(_2\) was added (i-Pr)\(_2\)NEt (6.0 equiv) at 0 °C followed by methyl chloromethyl ether or methyl chloroethyl ether (2.0 equiv). After 1h at rt, the reaction was quenched with sat. aq. NH\(_4\)Cl and stirred for 15 min. The mixture was diluted with Et\(_2\)O, washed with H\(_2\)O and sat. aq. NaCl, dried with NaSO\(_4\), filtered, and concentrated.\(^\text{10}\) Purification by flash column chromatography delivered the corresponding O-MOM acetal.

**((Methoxymethoxy)benzene 64.** Purification by flash column chromatography (hexanes:EtOAc 95:5) delivered (methoxymethoxy)benzene 64 (1.3 g, 94%) as a colorless liquid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.50 (s, 3H), 5.20 (s, 3H), 7.01-7.08 (m, 3H), 7.30-7.34 (m, 2H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 56.0, 94.6, 116.4, 122.0, 129.6, 157.4; spectra data was consistent with previous report.\(^\text{11}\)

**2,4-Dimethyl-3-pentanol-methoxyethyl ether 65.** Purification by flash column chromatography (hexanes:EtOAc 98:2) delivered 65 (0.58 g, 66%) as a colorless liquid: \(R_f = 0.7\) (hexanes:EtOAc 10:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 0.92-1.08 (m, 12H), 1.31 (d, \(J = 5.0, 3H\)), 1.80-1.87 (m, 2H), 3.04 (d, \(J = 5.0, 1H\)), 3.32 (s, 1H), 4.65 (q, \(J = 5.5, 1H\)), \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 18.2, 18.5, 19.6, 20.5, 20.6, 30.5, 30.9, 52.3, 87.7, 101.5; spectra data was consistent with a previous report.\(^\text{12}\)

**((E)-1-(methoxymethoxy)-3,7-dimethylocta-2,6-diene / Geraniol-MOM 66.** Purification by flash column chromatography (hexanes:Et\(_2\)O 20:1) delivered 66 (1.80 g, 91%) as a colorless liquid: \(R_f = 0.4\) (hexanes:Et\(_2\)O 4:1); IR (thin film) ν 2926, 1670, 1444, 1378, 1104, 1049, 920 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.60 (s, 3H), 1.68 (bs, 6H), 2.03-2.14 (m, 4H), 3.38 (s, 3H), 4.07 (dd, \(J\)

\(^{10}\) Berliner, M. A.; Belecki, K. J. Org. Chem. 2005, 70, 9618–9621
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$= 0.4, 6.8, 2H), 4.63 \text{(s, 2H), } 5.09 \text{(tt, } J = 0.4, 6.8, 1H), 5.36 \text{(tq, } J = 1.2, 6.8, 1H);$ $^{13}\text{C NMR (100 MHz, CDCl}_3\text{)} \delta 16.5, 17.8, 25.8, 26.5, 39.7, 55.3, 63.3, 63.8, 95.6, 120.3, 124.1, 131.8, 141.0; \text{Cl-HRMS calcd for C}_{22}\text{H}_{22}\text{O}_2[M] 1986.1620, \text{found 198.1615.}$

2.2. Preparation of Ethers

*General non-premixing procedure (Procedure A)*

\[
\begin{align*}
R^1\text{O} & \quad R^3 \quad (1.0 \text{ equiv}) \\
R^1 & \quad R^2 \quad \text{+} \\
R^4 & \quad \text{BF}_3\text{K} \quad (2.0 \text{ equiv}) \\
\text{BF}_3\text{OEt}_2 (2.0 \text{ equiv}) & \quad 0.07 \text{ M CH}_2\text{Cl}_2 \\
& \quad 0 \text{ C}, 5\rightarrow 60 \text{ min}
\end{align*}
\]

To a solution of corresponding acetal (1.0 equiv) and potassium organotrifluoroborate (2.0 equiv) in CH$_3$CN or CH$_2$Cl$_2$ was added BF$_3$•OEt$_2$ (2.0 equiv) dropwise at 0 $^\circ$C. After stirring for 5 to 60 min at 0 $^\circ$C, the reaction was quenched with aq. sat. NaHCO$_3$. The mixture was extracted with CH$_2$Cl$_2$, washed with H$_2$O and aq. sat. NaCl, dried with Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography delivered the product.

*General premixing procedure (Procedure B)*

\[
\begin{align*}
R^1\text{O} & \quad R^3 \quad (1.0 \text{ equiv}) \\
R^1 & \quad R^2 \quad \text{+} \\
R^4 & \quad \text{BF}_3\text{K} \quad (4.0 \text{ equiv}) \\
\text{BF}_3\text{OEt}_2 (4.0 \text{ equiv}) & \quad 0.07 \text{ M CH}_2\text{Cl}_2 \\
& \quad 0\rightarrow 23 \text{ C}, 60\rightarrow 120 \text{ min}
\end{align*}
\]

To a suspension of potassium organotrifluoroborate (4.0 equiv) in CH$_2$Cl$_2$ was added BF$_3$•OEt$_2$ (4.0 equiv) dropwise at 0 $^\circ$C. After 30 min at 0 $^\circ$C, a solution of corresponding acetal (1.0 equiv) in CH$_2$Cl$_2$ was added dropwise to the mixture. After stirring for 60 to 120 min at 23 $^\circ$C, the reaction was quenched with aq. sat. NaHCO$_3$. The mixture was extracted with CH$_2$Cl$_2$, washed with H$_2$O and aq. sat. NaCl, dried with Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography delivered the product.
(3-Methoxyprop-1-yn-1-yl)benzene (eq 1) was prepared according to procedure B from acetal 64 (28 mg, 0.20 mmol), potassium phenylethynyltrifluoroborate (83 mg, 0.40 mmol) and BF$_3$•OEt$_2$ (50 µL, 0.40 mmol). Purification by flash column chromatography (hexanes:EtOAc 99:1) afforded (3-methoxyprop-1-yn-1-yl)benzene as a colorless liquid (27 mg, 92%); $^1$H NMR (400 MHz, CDCl$_3$) δ 3.46 (s, 3H), 4.33 (s, 2H), 7.26-7.32 (m, 3H), 7.44-7.47 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 57.8, 60.6, 85.0, 86.5, 122.8, 128.4, 128.5, 131.9; spectra data was consistent with a previous report.$^{13}$

Table 1. Screening of leaving groups

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<th>entry</th>
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<th>% yield 4 (4:5)</th>
<th>entry</th>
<th>acetal</th>
<th>% yield 4 (4:5)</th>
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</thead>
<tbody>
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<td>74 (6:1)</td>
<td>6</td>
<td><img src="image2" alt="entry 6 acetal" /></td>
<td>61 (1:0)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="entry 2 acetal" /></td>
<td>74 (4:1)</td>
<td>7</td>
<td><img src="image4" alt="entry 7 acetal" /></td>
<td>66 (1:0)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="entry 8 acetal" /></td>
<td>79 (1:0)</td>
<td>8</td>
<td><img src="image6" alt="entry 13 acetal" /></td>
<td>68 (1:0)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="entry 9 acetal" /></td>
<td>85 (1:0)</td>
<td>9</td>
<td><img src="image8" alt="entry 14 acetal" /></td>
<td>90 (1:0)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="entry 10 acetal" /></td>
<td>85 (1:0)</td>
<td></td>
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(Cyclohexyloxymethyl)benzene 4 was prepared according to procedure B from acetals 6–14 (0.20 mmol), potassium phenyltrifluoroborate (0.15 g, 0.80 mmol) and BF$_3$•OEt$_2$ (0.10 mL, 0.80 mmol). Purification by flash column chromatography (hexanes:EtOAc 99:1) afforded 4 as a colorless liquid. $^1$H NMR (500 MHz, CDCl$_3$) δ 1.21-1.40 (m, 5H), 1.54-1.57 (m, 1H), 1.77-1.78 (m, 2H), 1.95-1.97 (m, 2H), 3.36 (tt, J = 3.5, 8.5, 13) Cai, M.; Sha, J.; Xu, Q. *Tetrahedron* 2007, 63, 4642–4647
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1H), 4.56 (s, 2H), 7.26-7.28 (m, 2H), 7.32-7.36 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 24.3, 25.9, 32.4, 69.8, 76.9, 127.4, 127.6, 128.4, 139.5; spectra data was consistent with a previous report.\(^\text{14}\)

Isolated yield and ratio of product 4 and regio byproduct 5 determined from $^1$H NMR intergration are reported in Table 1.

Table 2. Coupling reactions of various mixed acetals and potassium organotrifluoroborates

<table>
<thead>
<tr>
<th>entry</th>
<th>R-BF$_3$K</th>
<th>% yield 15 (15:16)</th>
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<tr>
<td>1</td>
<td>1.0 equiv</td>
<td>74 (6:1)</td>
</tr>
<tr>
<td>2</td>
<td>4.0 equiv</td>
<td>85 (1:0)</td>
</tr>
<tr>
<td>3</td>
<td>1.0 equiv</td>
<td>58 (6:1)</td>
</tr>
<tr>
<td>4</td>
<td>4.0 equiv</td>
<td>28 (1:0)</td>
</tr>
<tr>
<td>5</td>
<td>4.0 equiv</td>
<td>_</td>
</tr>
</tbody>
</table>

(3-(Cyclohexyloxy)prop-1-ynyl)benzene 43 (Table 2, entry 2) was prepared according to the procedure A from acetals 6, 10, 14 (0.20 mmol), potassium phenylethynyltrifluoroborate (83 mg, 0.40 mmol) and BF$_3$•OEt$_2$ (50 µL, 0.40 mmol). Purification by flash column chromatography (hexanes:EtOAc 99:1) afforded 43 as a colorless liquid. $R_f$ = 0.8 (hexanes:EtOAc 10:1); IR (thin film) ν 2932, 2856, 2236, 1598, 1490, 1086, 1360, 1086 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 1.23-1.39 (m, 3H), 1.54-1.57 (m, 1H), 1.76-1.78 (m, 2H), 1.97-1.99 (m, 2H), 3.54 (tt, J = 3.5, 8.5, 1H), 4.40 (s, 2H), 7.30-7.31 (m, 3H), 7.44-7.46 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 24.2, 25.8, 32.1, 55.8, 76.8, 85.5, 86.1, 122.9, 128.3, 128.4, 131.8; CI-MS calcd for C$_{15}$H$_{18}$OH [M + H] 215.1436, found 215.1434. Isolated yield and ratio of product 43 and regio side product determined from $^1$H NMR intergration are reported in Table 2.

(E)-(Undec-2-enyloxy)cyclohexane 29 (Table 2, entry 3) was prepared according to procedure B from acetal 6, 10, 14 (0.20 mmol), potassium (E)-decenyltrifluoroborate (0.20 g, 0.80 mmol) and BF$_3$•OEt$_2$ (0.10 mL, 0.08 mmol). Purification by flash column chromatography (hexanes:EtOAc 99:1) afforded 29 as a colorless liquid. R$_f$ = 0.3 (hexanes:EtOAc 10:1); IR (thin film) ν 2927, 2854, 1672, 1451, 1361, 1106, 1065 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 0.87 (t, $J$ = 6.5, 5H), 1.17-1.38 (m, 18H), 1.52-1.54 (m, 1H), 1.72-1.74 (m, 2H), 1.90-1.92 (m, 2H), 2.00-2.04 (t, $J$ = 7.0, 2H), 3.25 (tt, $J$ = 4.0, 9.0, 1H), 3.94 (d, $J$ = 6.0, 2H), 5.52-5.57 (m, 1H), 5.64-5.69 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 14.2, 22.8, 24.4, 25.9, 29.2, 29.4, 29.6, 32.0, 32.4, 32.5, 68.7, 76.9, 127.1, 134.2; CI-HRMS calcd for C$_{17}$H$_{32}$OH [M + H] 253.2531, found 253.2536. Isolated yield and ratio of product 29 and regio side product determined from $^1$H NMR intergration are reported in Table 2.

2-(Cyclohexyloxymethyl)benzo[b]thiophene 44 (Table 2, entry 4) was prepared according to procedure B from acetal 6, 10, 14 (0.20 mmol), potassium benzothiophenyltrifluoroborate (0.19 g, 0.80 mmol) and BF$_3$•OEt$_2$ (0.10 mL, 0.80 mmol). Purification by flash column chromatography (hexanes: benzene 1:1), then by preparative thin layer chromatography (benzene: EtOAc 100:1) afforded 44 as a colorless liquid. R$_f$ = 0.4 (hexanes:benzene 1:1); IR (thin film) ν 2927, 2854, 1449, 1437, 1091, 835, 745, 727s cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 1.21-1.40 (m, 5H), 1.54-1.55 (m, 1H), 1.75-1.77 (m, 2H), 1.95-1.97 (m, 2H), 3.43 (tt, $J$ = 4.0, 9.5, 1H), 4.03 (s, 2H), 7.19 (s, 1H), 7.26-7.34 (m, 3H), 7.71 (d, $J$ = 7.5, 1H), 7.80 (d, $J$ = 7.5, 1H); $^{13}$C NMR (125 MHz, acetone-d6) δ 24.2, 25.9, 32.3, 65.2, 121.8, 122.5, 123.5, 124.2, 124.3, 139.7, 140.2, 143.8; CI-HRMS calcd for C$_{15}$H$_{18}$OSH [M + H] 247.1154, found 247.1153. Isolated yield and ratio of product 4 and regio side product determined from $^1$H NMR intergration are reported in Table 2.

Scheme 17

Below ethers were prepared according to General Procedure A described in Part III Section 2.2.
**1-Bromo-3-(cyclohexyloxymethyl)benzene 17.** Purification by flash column chromatography (hexanes:EtOAc 96:4) afforded 17 as a colorless liquid (50 mg, 93%); R<sub>f</sub> = 0.9 (hexanes:EtOAc 4:1); IR (thin film) ν 2931, 2855, 1570, 1448, 1083, 773, 866, 671 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.28-1.40 (m, 5H), 1.52-1.55 (m, 1H), 1.74-1.77 (m, 2H), 1.93-1.95 (m, 2H), 3.35 (tt, <i>J</i> = 3.5, 9.5, 1H), 4.51 (s, 2H), 7.20 (t, <i>J</i> = 7.5, 1H), 7.27 (d, <i>J</i> = 7.5, 1H), 7.39 (d, <i>J</i> = 7.5, 1H), 7.51 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 24.2, 25.9, 32.3, 69.0, 77.4, 886, 671 cm<sup>-1</sup>; CI-HRMS calcd for C<sub>13</sub>H<sub>17</sub>BrOH [M + H] 269.0541, found 269.0554.

**1-Bromo-4-(cyclohexyloxymethyl)benzene 18.** Purification by flash column chromatography (hexanes:EtOAc 96:4) afforded 18 as a colorless liquid (53 mg, 98%); R<sub>f</sub> = 0.9 (hexanes:EtOAc 4:1); IR (thin film) ν 2930, 2855, 1593, 1486, 1087, 803 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.25-1.38 (m, 5H), 1.52-1.56 (m, 1H), 1.75-1.76 (m, 2H), 1.92-1.94 (m, 2H), 3.34 (tt, <i>J</i> = 3.5, 9.0, 1H), 4.49 (s, 2H), 7.22 (d, <i>J</i> = 8.0, 2H), 7.45 (d, <i>J</i> = 8.0, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 24.2, 25.9, 32.3, 69.0, 77.2, 121.2, 129.2, 131.5, 138.5; CI-HRMS calcd for C<sub>13</sub>H<sub>17</sub>BrOH [M + H] 269.0541, found 269.0530.

**1-Chloro-3-(cyclohexyloxymethyl)benzene 19.** Purification by flash column chromatography (hexanes:EtOAc 96:4) afforded 19 as a colorless liquid (29 mg, 65%); R<sub>f</sub> = 0.8 (hexanes:EtOAc 4:1); IR (thin film) ν 2932, 2856, 1449, 1360, 1105, 777, 703, 683 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.26-1.39 (m, 5H), 1.54-1.55 (m, 1H), 1.75-1.77 (m, 2H), 1.93-1.96 (m, 2H), 3.35 (tt, <i>J</i> = 3.5, 9.5, 1H), 4.51 (s, 2H), 7.21-7.27 (m, 3H), 7.35 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 24.2, 25.9, 29.9, 32.3, 69.1, 77.4, 125.5, 127.6, 129.7, 134.4, 141.6; CI-HRMS calcd for C<sub>13</sub>H<sub>17</sub>ClOH [M + H] 225.1046, found 225.1045.

**1-Fluoro-3-(cyclohexyloxymethyl)benzene 20.** Purification by flash column chromatography (hexanes:EtOAc 99:1) afforded 20 as a colorless liquid (32 mg, 77%); R<sub>f</sub> = 0.5 (hexanes:EtOAc 10:1); IR (thin film) ν 2932, 2856, 1591, 1488, 1449, 1254, 1073, 781, 684 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.28-1.40 (m, 5H), 1.52-1.59 (m, 1H), 1.75-1.78 (m, 2H), 1.93-1.96 (m, 2H), 3.35 (tt, <i>J</i> = 3.5, 9.5, 1H), 4.54 (s,
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1-(Cyclohexyloxymethyl)-2-methylbenzene 21. Purification by flash column chromatography (hexanes:EtOAc 98:2) afforded 21 as a colorless liquid (12 mg, 30%); Rf = 0.4 (hexanes:EtOAc 10:1); IR (thin film) ν 2930, 2855, 1450, 1361, 1085, 742 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.21-1.40 (m, 5H), 1.54-1.55 (m, 1H), 1.76-1.78 (m, 2H), 1.97-2.05 (m, 2H), 2.34 (s, 3H), 3.36 (tt, J = 4.0, 9.5, 1H), 4.53 (s, 2H), 7.15-7.19 (m, 3H), 7.34-7.35 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 18.9, 24.3, 26.0, 32.4, 68.4, 77.4, 125.9, 127.6, 128.5, 130.2, 136.7, 137.2; CI-HRMS calcd for C₁₄H₂₀OH [M + H] 205.1592, found 205.1602.

1-(Cyclohexyloxymethyl)-4-methylbenzene 22. Purification by flash column chromatography (hexanes:EtOAc 98:2) afforded 22 as a colorless liquid (37 mg, 91%); Rf = 0.5 (hexanes:EtOAc 10:1); IR (thin film) 2931, 2856, 1684, 1609, 1266, 1092, 816 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 1.21-1.40 (m, 5H), 1.54-1.55 (m, 1H), 1.76-1.78 (m, 2H), 1.95-1.97 (m, 2H), 2.35 (s, 3H), 3.36 (tt, J = 3.5, 9.0, 1H), 4.53 (s, 2H), 7.16 (d, J = 8.0, 2H), 7.26 (d, J = 8.0, 2H); ¹³C NMR (125 MHz, CDCl₃) 21.4, 24.4, 26.1, 32.5, 69.7, 76.9, 127.8, 129.2, 136.5, 137.1; CI-HRMS calcd for C₁₄H₂₀O₂ [M] 203.1436, found 203.1433.

1-(4-(Cyclohexyloxymethyl)phenyl)ethanone 23. Purification by flash column chromatography (hexanes:EtOAc 98:2) afforded 23 as a colorless liquid (29 mg, 63%); Rf = 0.3 (hexanes:EtOAc 10:1); IR (thin film) ν 2931, 2856, 1684, 1609, 1266, 1092, 816 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.21-1.39 (m, 5H), 1.52-1.54 (m, 1H), 1.75-1.77 (m, 2H), 1.94-1.96 (m, 2H), 2.58 (s, 3H), 3.36 (tt, J = 4.0, 9.0, 1H), 4.60 (s, 2H), 7.44 (d, J = 8.0, 2H), 7.92 (d, J = 8.0, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 21.2, 25.9, 26.8, 32.3, 69.2, 77.5, 127.3, 128.5, 136.3, 145.2; ESI-HRMS calcd for C₁₅H₂₀O₂H [M + H] 233.1542, found 233.1539.
Methyl 4-(cyclohexyloxymethyl)benzoate 24. Purification by flash column chromatography (hexanes:EtOAc 98:2) afforded 24 as a colorless liquid (33 mg, 67%); Rf = 0.3 (hexanes:EtOAc 10:1); IR (thin film) ν 2932, 2856, 1732, 1614, 1449, 1278, 1105, 843 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.21-1.40 (m, 5H), 1.52-1.54 (m, 1H), 1.75-1.77 (m, 2H), 1.93-1.95 (m, 2H), 3.35 (tt, J = 3.5, 9.0, 1H), 3.90 (s, 3H), 4.59 (s, 2H), 7.41 (d, J = 8.0, 2H), 8.0 (d, J = 8.0, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 24.2, 25.9, 32.3, 69.2, 77.5, 127.1, 129.2, 129.8, 144.9, 167.2; ESI-HRMS calcd C₁₅H₂₀O₃Na [M + Na] 271.1310, found 271.1305.

(E)-(3-(cyclohexyloxy)prop-1-enyl)benzene 28. Purification by flash column chromatography (hexanes:Et₂O 99:1) afforded 28 as a colorless liquid (23 mg, 53%); Rf = 0.5 (hexanes:Et₂O 1:1); IR (thin film) ν 3025, 2931, 2855, 1495, 1448, 1361, 1089, 691 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.23-1.36 (m, 5H), 1.54-1.58 (m, 1H), 1.76-1.78 (m, 2H), 1.95-1.97 (m, 2H), 3.35 (tt, J = 3.5, 7.5, 1H), 4.18 (dd, J = 1.5, 6.0, 2H), 6.35 (td, J = 6.0, 16.0, 1H), 6.63 (d, J = 16.0, 1H), 7.23 (t, J = 7.5, 1H), 7.32 (t, J = 7.5, 2H), 7.44 (t, J = 7.5, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 23.8, 25.9, 32.3, 68.0, 76.4, 126.4, 127.4, 127.8, 128.6, 130.6, 137.3; ESI-HRMS calcd for C₁₅H₂₀ONa [M + Na] 239.1412, found 239.1410.

Below ethers were prepared according to General Procedure B described in Part III Section 2.2.

2-(Cyclohexyloxymethyl)thiophene 25. Purification by flash column chromatography (hexanes:benzene 1:1) afforded 25 as a colorless liquid (17 mg, 67%); Rf = 0.3 (hexanes:benzene 1:1); IR (thin film) ν 2931, 2855, 1536, 1449, 1083, 697 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.20-1.35 (m, 5H), 1.54-1.58 (m, 1H), 1.74-1.75 (m, 2H), 1.92-1.94 (m, 2H), 3.38 (tt, J = 4.0, 9.5, 1H), 4.70 (s, 2H), 6.95-6.97 (m, 2H), 7.25-7.26 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 24.3, 25.9, 32.3, 64.5, 76.8, 125.4, 125.7, 126.7, 142.5; CI-HRMS calcd for C₁₁H₁₆OS [M] 196.0922, found 196.0923.
2-(Cyclohexyloxymethyl)furan 26. Purification by flash column chromatography (hexanes:EtOAc 99:1) afforded 26 as a colorless liquid (33 mg, 67%); Rf = 0.5 (hexanes:EtOAc 10:1); IR (thin film) ν 2932, 2856, 1450, 1359, 1150, 1082, 733 cm\(^{-1}\); \(^1\)H NMR (500 MHz, acetone-d6) δ 1.23-1.28 (m, 5H), 1.48-1.50 (m, 1H), 1.69-1.70 (m, 2H), 1.84-1.86 (m, 2H), 3.32-3.37 (m, 1H), 4.44 (s, 2H), 6.32 (d, J = 3.0, 2H), 6.37 (t, J = 2.0, 3.0, 2H), 7.49 (s, 1H); \(^{13}\)C NMR (125 MHz, acetone-d6) δ 24.3, 26.3, 32.5, 62.0, 76.7, 108.9, 110.8, 143.0, 153.8; CI-HRMS calcd for C\(^{11}\)H\(^{16}\)O \([\text{M}]\) 180.1150, found 180.1142.

Scheme 18

(3-(Octyloxy)prop-1-ynyl)benzene 32 was prepared according to:

Procedure B: Purification by flash column chromatography (hexanes:EtOAc 95:15) afforded 32 as a colorless liquid (94 mg, 77%). Procedure A: Purification by flash column chromatography (hexanes:EtOAc 95:15) afforded 32 as a colorless liquid (83 mg, 85%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 0.88 (t, J = 6.5 Hz, 3H), 1.21-1.45 (m, 10H), 1.59-1.69 (m, 2H), 3.58 (t, J = 6.5 Hz, 2H), 4.36 (s, 2H), 7.27-7.34 (m, 3H), 7.42-7.49 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 14.3, 22.8, 26.3, 29.4, 29.6, 29.8, 32.0, 58.9, 70.5, 85.7, 86.1, 123.0, 128.4(2), 128.5, 131.9(2); spectral data was consistent with a previous report.\(^{12}\)

(3-(1-Phenylethoxy)prop-1-yn-1-yl)benzene 33 was prepared according to:

Procedure B: Purification by flash column chromatography (hexanes:EtOAc 95:5) afforded 33 as a colorless liquid (66 mg, 56%). Procedure A. Purification by flash column chromatography (hexanes:EtOAc 95:5) afforded 33 as a colorless liquid (58 mg, 61%).

IR (thin film) ν 3061, 2237, 1095, 1071, 757, 701, 691 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 1.52 (d, J = 6.5 Hz, 3H), 4.12 (d, J = 16.0 Hz, 1H), 4.31 (d, J = 16.0 Hz, 1H), 4.73 (q, J = 6.5 Hz, 1H), 7.26-7.48 (m, 10H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 24.0, 56.5, 76.9, 85.5, 86.0, 122.9, 126.7(2), 127.9, 128.4(2), 128.5, 128.7(2), 131.9(2), 142.8; CI-HRMS calcd for C\(^{17}\)H\(^{16}\)O [M] 236.1201, found 236.1194.
(3-(2-Methylpentan-2-yl)oxy)prop-1-yn-1-yl)benzene 34 was prepared according to: **Procedure B**: Purification by flash column chromatography (hexanes:EtOAc 95:5) afforded 34 as a colorless liquid (49 mg, 45%). **Procedure A**: Purification by flash column chromatography (hexanes:EtOAc 95:5) afforded 34 as a colorless liquid (53 mg, 61%).

IR (thin film) ν 3057, 2238, 1069, 756, 691 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.93 (t, J = 7.5 Hz, 3H), 1.24 (s, 6H), 1.35-1.45 (m, 2H), 1.49-1.55 (m, 2H), 4.28 (s, 2H), 7.26-7.32 (m, 3H), 7.41-7.46 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 14.8, 17.4, 17.4, 25.7(2), 42.8, 50.9, 76.5, 84.7, 87.3, 123.2, 128.30, 128.31(2), 131.9(2); CI-HRMS calcd for C₁₁H₂₁O [M + H] 217.1592, found 217.1595.

(3-(2,4-Dimethylpentan-3-yloxy)but-1-ynyl)benzene 35 was prepared according to: **Procedure B**: Purification by flash column chromatography (hexanes: Et₂O 99:1) afforded 35 as a colorless liquid (51 mg, 52%). **Procedure A**: Purification by flash column chromatography (hexanes: Et₂O 99:1) afforded 35 as a colorless liquid (93 mg, 95%).

¹H NMR (500 MHz, CDCl₃) δ 0.96-1.04 (m, 12H), 1.53 (d, J = 6.5, 3H), 1.82-1.94 (m, 2H), 3.15 (t, J = 5.5, 1H), 4.50 (q, J = 6.5, 2H), 7.26-7.31(m, 2H), 7.42-7.44 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 17.9, 18.7, 20.7, 20.8, 22.8, 30.5, 31.0, 67.0, 84.5, 88.1, 91.2, 123.3, 128.2, 128.3, 131.6; spectra data was consistent with a previous report.¹²

(3-Methoxyprop-1-yn-1-yl)benzene 36 was prepared according to: **Procedure A**: Purification by flash column chromatography (hexanes: EtOAc 99:1) afforded 36 as a colorless liquid (32 mg, 38%): IR (thin film) ν 3061, 2917, 2237, 1597, 1213, 1034 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.93 (s, 2H), 6.98-7.08 4(m, 3H), 7.29-7.36 (m, 5H), 7.44-7.47 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 56.8, 84.1, 87.3, 115.1, 121.6, 122.4, 128.4, 128.8, 129.6, 131.9, 157.9; El-HRMS calcd for C₁₅H₁₂O [M] 208.0883, found 208.0882.

(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)methyl)benzene 37 was prepared according to: **Procedure B**: Purification by flash column
chromatography (hexanes: EtOAc 99:1) afforded 37 as a colorless liquid (70 mg, 57%).

Procedure A: Purification by flash column chromatography (hexanes: EtOAc 99:1) afforded 37 as a colorless liquid (78 mg, 79%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 0.69-1.02 (m, 12H), 1.25-1.42 (m, 2H), 1.60-1.70 (m, 2H), 2.16-2.24 (m, 1H), 2.27-2.35 (m, 1H), 3.17 (ddd, $J = 4.0, 10.5, 10.5$ Hz, 1H), 4.40 (d, $J = 11.5$ Hz, 1H), 4.66 (d, $J = 11.5$ Hz, 1H), 7.31-7.37 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 16.2, 21.2, 22.6, 23.4, 25.7, 31.8, 34.8, 40.5, 48.5, 70.6, 78.9, 127.6, 128.0(2), 128.5(2), 139.3; spectral data was consistent with a previous report.$^{15}$

1-Bromo-4-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)methyl)benzene 38 was prepared according to:

Procedure B: Purification by flash column chromatography (hexanes: EtOAc 99:1) afforded 38 as a colorless liquid (60 mg, 37 %). Procedure A: Purification by flash column chromatography (hexanes: EtOAc 99:1) afforded 38 as a colorless liquid (80 mg, 62 %).

$^1$H NMR (500 MHz, CDCl$_3$) δ 0.70-1.02 (m, 12H), 1.24-1.41 (m, 2H), 1.60-1.70 (m, 2H), 2.12-2.20 (m, 1H), 2.22-2.32 (m, 1H), 3.16 (ddd, $J = 4.0, 10.5, 10.5$ Hz, 1H), 4.34 (d, $J = 12.0$ Hz, 1H), 4.60 (d, $J = 12.0$ Hz, 1H), 7.20 (d, $J = 8.0$ Hz, 2H), 7.45 (d, $J = 8.0$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 16.3, 21.2, 22.5, 23.4, 25.7, 31.7, 34.7, 40.4, 48.5, 69.8, 79.1, 121.3, 129.6(2), 131.5(2), 138.4; spectral data was consistent with a previous report.$^{16}$

1-Chloro-3-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)methyl)benzene 39 was prepared according to

Procedure B: Purification by flash column chromatography (hexanes: EtOAc 99:1) afforded 39 as a colorless liquid (42 mg, 30%). Procedure A: Purification by flash column chromatography (hexanes: EtOAc 99:1) afforded 39 as a colorless liquid (54 mg, 47%).

IR (thin film) ν 3066, 1109, 778, 682 cm$^{-1}$; [α]$^{25}_D$ -71.9194 (0.30, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 0.70-1.03 (m, 12H), 1.23-1.43 (m, 2H), 1.60-1.70 (m, 2H), 2.15-2.21 (m, 1H), 2.25-2.33 (m, 1H), 3.16 (ddd, $J = 4.0, 10.5, 10.5$ Hz, 1H), 4.37 (d, $J = 12.0$ Hz, 1H), 4.62 (d, $J =

12.0 Hz, 1H), 7.20-7.30 (m, 3H), 7.34 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 16.2, 21.2, 22.5, 23.4, 25.7, 31.7, 34.7, 40.4, 48.4, 69.7, 79.1, 125.9, 127.6, 127.9, 129.7, 134.3, 141.4; Cl-HRMS calcd for C$_{17}$H$_{26}$OCl [M + H] 281.1672, found 281.1788.

(1S,2R,4R)-1-Isopropyl-4-methyl-2-((E)-undec-2-enyloxy)cyclohexane 40 was prepared according to:

Procedure B: Purification by flash column chromatography (hexanes: EtOAc 99:1) afforded 40 as a colorless liquid (99 mg, 64%). Procedure A: Purification by flash column chromatography (hexanes: EtOAc 99:1) afforded 40 as a colorless liquid (89 mg, 72%).

$^1$H NMR (500 MHz, CDCl$_3$) δ 0.74-1.02 (m, 15H), 1.18-1.44 (m, 14H), 1.57-1.67 (m, 2H), 2.00-2.10 (m, 3H), 2.18-2.26 (m, 1H), 3.05 (ddd, $J = 3.5$, 10.0, 10.5 Hz, 1H), 3.82 (dd, $J = 6.5$, 11.5 Hz, 1H), 4.05 (d, $J = 6.0$, 11.5 Hz, 1H), 5.51-5.59 (m, 1H), 5.62-5.70 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 14.2, 16.4, 21.1, 22.5, 22.8, 23.5, 25.6, 29.2, 29.38, 29.42, 29.6, 31.7, 32.0, 32.4, 34.7, 40.7, 48.4, 69.5, 78.4, 127.2, 134.2; spectral data was consistent with a previous report.

(E)-(3-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)prop-1-yn-1-yl)benzene 41 was prepared according to: Procedure B: Purification by flash column chromatography (hexanes: EtOAc 99:1) afforded 41 as a colorless liquid (12 mg, 9%). Procedure A: Purification by flash column chromatography (hexanes: EtOAc 99:1) afforded 41 as a colorless liquid (22 mg, 20%).

IR (thin film) ν 3054, 2227, 1068, 755, 690 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 1.61 (s, 3H), 1.69 (s, 3H), 1.72 (s, 3H), 2.03-2.17 (m, 4H), 4.16 (d, $J = 7.0$ Hz, 1H), 4.36 (s, 2H), 5.07-5.14 (m, 1H), 5.35-5.41 (m, 1H), 7.27-7.35 (m, 3H), 7.42-7.49 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 16.6, 17.8, 25.8, 26.5, 39.8, 57.6, 66.1, 85.6, 86.1, 120.2, 122.9, 124.1, 128.4(2), 128.5, 131.9(3), 141.8; Cl-HRMS calcd for C$_{19}$H$_{25}$O [M + H] 269.1905, found 269.1900.

(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-3-((3-phenylprop-2-yn-1-yl)oxy)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-
cyclopenta[a]phenanthrene 42 was prepared according to:

Procedure B: Purification by flash column chromatography (hexanes: EtOAc 99:1) afforded 42 as a white solid (98 mg, 39%). Procedure A: Purification by flash column chromatography (hexanes: EtOAc 99:1) afforded 42 as a white solid (196 mg, 97%).

mp = 108 °C; $[\alpha]_{25}^{25} -37.4064$ (0.47, CHCl$_3$); IR (thin film) $\nu$ 2933, 2867, 1642, 1465, 1080, 754 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.68 (s, 3H), 0.86-1.59 (m, 33H), 1.81-1.91 (m, 2H), 1.96-2.03 (m, 3H), 2.24-2.31 (m, 1H), 2.43 (dd, $J = 2.4$, 4.8, 1H), 2.46 (dd, $J = 2.4$, 4.8, 1H), 3.45 (tt, $J = 4.8$, 11.2, 1H), 4.42 (s, 2H), 5.37-5.38 (m, 1H), 7.30-7.32 (m, 3H), 7.43-7.46 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 12.0, 18.9, 19.5, 21.2, 22.7, 22.9, 23.9, 24.4, 28.2, 28.4, 32.0, 32.1, 35.9, 36.3, 36.9, 37.3, 39.0, 39.6, 39.9, 42.4, 50.3, 56.1, 56.3, 56.9, 85.6, 86.0, 122.0, 122.9, 128.4(2), 131.9, 148.0; ESI-HRMS calcd for C$_{19}$H$_{24}$NO [M + NH$_4$] 518.4356, found 518.4367.

2.3. Mechanism Investigations

2.3.1. Preparation of 5-membered ring boron complex

$N$-methyl-$N$-((trimethylsilyl)oxy)acetamide 45. To a solution of $N$-hydroxy-$N$-methylacetamide 45 (0.50 g, 5.6 mmol) in THF (12 mL) was added NH(SiMe$_3$)$_2$ (1.5 mL, 6.7 mmol) at 0 °C. Reaction was warmed to 23 °C, allowed to stir in 2 h and concentrated to remove volatiles. Purification by bulb-to-bulb distillation under high vacuum, at 50 °C delivered 45 (0.70 g, 77%) as a colorless liquid:$^{17}$ IR (thin film) $\nu$ 2961, 2903, 1679, 1409, 1375, 1339, 1254, 1174, 944, 848 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.25 (s, 9H), 2.07 (s, 3H), 3.2 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 9.3, 20.8, 38.0, 174.5; El-HRMS calcd for C$_9$H$_{15}$NO$_2$Si [M] 161.0872, found 161.0870.

2-Fluoro-4,5-dimethyl-2-phenyl-1,3,4,2-dioxazaborol-4-ium-2-uide (±)-47. To a suspension of potassium phenyltrifluoroborate (0.39 g, 2.1 mmol) in CH$_2$Cl$_2$ (25 mL) was added BF$_3$•Et$_2$O (0.25 mL, 2.0 mmol) at 0 °C. After 30 min at 0 °C, to the

reaction mixture was added a solution of 45 (0.32 g, 2.0 mmol) in CH₂Cl₂ (5 mL). The reaction was allowed to stir in 1h at 23 °C and concentrated to give the crude product. To a solution of crude product in CH₂Cl₂ (1.5 mL) was triturated with Et₂O (7 mL) to deliver (±)-47 as colorless white solid: mp = 150 °C; IR (thin film) ν 1652, 1595, 1470, 1433, 1220, 1079, 1061, 942, 749, 707 cm⁻¹; ¹H NMR (400 MHz, CD₃CN) δ 2.14 (s, 3H), 3.52 (s, 3H), 7.25-7.29 (m, 3H), 7.46-7.48 (m, 2H); ¹³C NMR (100 MHz, CD₃CN) δ 13.2, 36.8, 128.1, 128.4, 132.7, 132.8, 162.8; ¹⁹F NMR (373 MHz, CD₃CN, CHF₃ as standard) -139.20 (t, J = 56.3, 1F); EI-HRMS calcd for C₉H₁₁BFNO₂ [M] 195.0867, found 195.0862.

Figure 1.

2.3.2. Crossover experiments

Experiment 1

To a suspension of potassium phenyltrifluoroborate (37 mg, 0.20 mmol) in CH₂Cl₂ (2 mL) was added BF₃•Et₂O (25 µL, 0.20 mmol) dropwise at 0 °C. After 1h at 0°C, the obtained phenyldifluoroborane 46 solution was added to a solution of acetal 6 (29 mg, 0.20 mmol) and (±)-47 (40 mg, 0.20 mmol) in CH₂Cl₂ (1 mL). The reaction was quenched after 5 min with sat. aq. NaHCO₃ (5 mL) and stirred for 15 min. The mixture was extracted with CH₂Cl₂ (10 mL), washed with H₂O (5 mL), sat. aq. NaCl (5 mL), dried with Na₂SO₄, and filtered. The obtained solution was analyzed by GCMS. GC conditions: Agilent column 19091S-433 (30 m x 250 µm); flow 0.5 mL/min; oven temperature 50 °C to 300 °C (ramp 15 °C/min).
Experiment 2

To a suspension of potassium phenyltrifluoroborate (28 mg, 0.15 mmol) in CH₂Cl₂ (2 mL) was added BF₃•Et₂O (20 µL, 0.15 mmol) dropwise at 0°C. After 1 h at 0 °C, the obtained phenyldifluoroborane 46 solution was added to a solution of acetals 14 (20 mg, 0.10 mmol) and 48 (23 mg, 0.10 mmol) in CH₂Cl₂ (1 mL). The reaction was quenched after 5 min with sat. aq. NaHCO₃ (5 mL) and stirred for 15 min. The mixture was extracted with CH₂Cl₂ (10 mL), washed with H₂O (5 mL), sat. aq. NaCl (5 mL), dried with Na₂SO₄, and filtered. The obtained solution was analyzed by GCMS. GC conditions: Agilent column 19091S-433 (30 m x 250 µm); flow 0.5 mL/min; oven temperature 50 °C to 300 °C (ramp 15 °C/min).
Experiment 3

To a solution of 50 (22 mg, 0.10 mmol), ether 51 (20 mg, 0.10 mmol) and potassium p-ethylphenyltrifluoroborate (42 mg, 0.20 mmol) in CH₂Cl₂ (1.5 mL) was added BF₃•Et₂O (25 µL, 0.20 mmol) at 0 °C. After stirring for 60 min at 23 °C, the reaction was quenched with aq. sat. NaHCO₃ (5 mL). The mixture was extracted with CH₂Cl₂ (10 mL), washed with H₂O (5 mL), sat. aq. NaCl (5 mL), dried with Na₂SO₄, and filtered. The obtained solution was analyzed by GCMS. GC conditions: Agilent column 19091S-433 (30 m x 250 µm); flow 0.5 mL/min; oven temperature 50 °C to 300 °C (ramp 15 °C/min). The remaining organic solution was concentrated. Crude ¹H-NMR, GC chromatogram showed that there was no crossover product.

2.3.3. ¹H NMR experiments

Experiment 1

Solutions containing various amounts of phenyldifluoroborane (1.00, 0.50, 1.20, 0.01 equiv) in CD₂Cl₂ were prepared by adding BF₃•OEt₂ (9.0, 5.0, 10.5, 2.0 µL, 0.07, 0.035, 0.14, 0.007 mmol) dropwise into a suspension of potassium phenyltrifluoroborate (13.0, 7.0, 15.6, 2.0 mg; 0.07, 0.035, 0.14, 0.007 mmol) in CD₂Cl₂ (0.60 mL) in separated flasks. Reactions were allowed to stir for 1 h at 0 °C. To the solutions of phenyldifluoroborane 46 in CD₂Cl₂ was added acetal 14 (14 mg, 0.07 mmol) and diphenylmethane (11.6 µL, 0.07
mmol) as internal standard in CD$_2$Cl$_2$ (0.40 mL) at 0 °C. The final solutions were quickly transferred to dried NMR tubes. Percentage of acetal 14 conversions and product yields were measured at rt using $^1$H NMR (Varian 300 MHz) against the internal peak at 3.99 ppm (2H). Below, the table reports raw data:

<table>
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<th>Time (min)</th>
<th>Ratio of acetal 14 and PhBF$_2$ 46</th>
<th>A: 1:2</th>
<th>B: 1:1.2</th>
<th>C: 1:1</th>
<th>D: 1:0.5</th>
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<td>71</td>
<td>12</td>
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</table>
H¹ NMR Observation:

5 min at 23 °C

180 min at 23 °C
Experiment 2

Solutions containing various amounts of phenyldifluoroborane 46 (1.20, 1.00, 1.00 equiv) and 3-phenylpropyldifluoroborane 52 (0.00, 0.20, 0.00 equiv) in CD$_2$Cl$_2$ were prepared by adding BF$_3$•OEt$_2$ (11.0, 11.0, 9.0 µL; 0.084, 0.084, 0.07 mmol) dropwise into a suspension of potassium phenyltrifluoroborate (15.6, 13.0, 13.0 mg; 0.084, 0.084, 0.07 mmol) and potassium 3-phenylpropyltrifluoroborate (0.00, 3.20, 0.00 mg; 0.00, 0.014, 0.00 mmol) in CD$_2$Cl$_2$ (0.60 mL) in separated flasks. Reactions were allowed to stir for 1 h at 0 °C. To the solutions of organodifluoroborane in CD$_2$Cl$_2$ was added acetal 14 (14 mg, 0.07 mmol) and diphenylmethane (11.6 µL, 0.07 mmol) as internal standard in CD$_2$Cl$_2$ (0.40 mL) at 0 °C. The final solutions were quickly transferred to dried NMR tubes. The reactions were performed at 23 °C; percentage of acetal 14 conversions and product yields were measured using H$^1$-NMR (Varian 300 MHz) against the internal peak at 3.99 ppm (2H). Below, the table reports raw data:

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<th>time (min)</th>
<th>ratio of acetal 14:PhBF$_2$ 46:Ph(CH$_2$)$_3$BF$_2$ 52</th>
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$^1$H NMR Observation:

5 min at 23 °C

180 min at 23 °C
3. Part II: SnAP Reagents for the Transformation of Aldehydes into Saturated N-Heterocycles

3.1. Preparation of tributyl(iodomethyl)stannane

\[
\text{Bu}_3\text{SnH} \quad \xrightarrow{1. \text{ LDA}, (\text{CH}_2\text{O})_n, 0 \degree \text{C to rt}} \quad \xrightarrow{2. \text{ CH}_3\text{SO}_2\text{Cl, -78 \degree \text{C to rt}}} \quad \text{Bu}_3\text{SnCl} \quad \text{138} \quad \xrightarrow{\text{NaI, acetone, 16 h, rt}} \quad \text{Bu}_3\text{SnI} \quad \text{139}
\]

\text{Tributyl(chloromethyl)stannane 138.} \quad ^{18} \text{To a stirred solution of } N,N\text{-diisopropylamine (32.1 mL, 227 mmol, 1.20 equiv) in THF (420 mL) at 0 \degree \text{C was added } n\text{-BuLi (1.6 M in hexanes, 136 mL, 218 mmol, 1.15 equiv) over 30 min. The solution was stirred for 30 min at 0 \degree \text{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 \degree \text{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 \degree \text{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}_2\text{O (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}_2\text{O (2 x 100 mL) and brine (200 mL), dried over anhydrous Na}_2\text{SO}_4, \text{filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes) afforded chloride 138 (57.1 g, 89% yield) as clear, colorless liquid.} ^{1}H \text{ NMR (400 MHz, CDCl}_3): \delta 3.06 (s, J^{(117/119}\text{Sn-}^1\text{H}) = 16.2 \text{ Hz, 2H}, 1.59-1.44 \text{ (m, 6H), 1.32 (sext, J = 7.3 Hz, 6H), 1.08-0.95 \text{ (m, 6H), 0.90 (t, J = 7.3 Hz, 9H);} ^{13}\text{C 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.} ^{19} \]

**Part III. Experiment Procedures and Characterization Data**

**129**

**Tributyl(iodomethyl)stannane 139.**

To a stirred solution of the chloride 138 (54.9 g, 162 mmol, 1.00 equiv) in acetone (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 iodide 139 (68.6 g, 98% yield) as clear, colorless liquid. 

\[ ^1 \text{H} \text{NMR (400 MHz, CDCl}_3): \delta 1.95 (s, J_{\text{Sn-1}H} = 17.8 \text{ Hz, 2H}) 1.62 - 1.44 (m, 6H), 1.33 ( sext, J = 7.2 \text{ Hz, 6H}), 1.08 - 0.95 (m, 6H), 0.91 (t, J = 7.2 \text{ Hz, 9H}); ^13 \text{C NMR (100 MHz, CDCl}_3): \delta 29.0, 27.4, 13.8, 10.8. \]

These spectral characteristics were identical to those previously reported.

**3.2. General Procedures for the Preparation of Saturated N-Heterocycles**

**General procedure for the preparation of substituted saturated heterocycles**

To a solution of the amino tributylstannane – SnAP 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 MS 4A (ca. 50 mg). The reaction mixture was stirred at rt for 2 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, to a solution of 2,6-lutidine (0.50 mmol, 1.00 equiv) in HFIP (2.0 mL) was added Cu(OTf)\(_2\) (0.50 mmol, 1.00 equiv) and stirred at rt for 1 h, during which 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.

---

(20) Commercially available. Decompose at room temperature over time. Can be stored neat at −10 °C for weeks.

h. The reaction was quenched at rt with a mixture of sat aq NaHCO$_3$ (5 mL) and 10% aq NH$_4$OH (3 mL), and stirred vigorously for 15 min. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 5 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)

- Precolumn for flash column chromatography: anhydrous KF (ca. 2–3 cm).
- Column for flash column chromatography: 30 mm column with ca. 8 cm silica gel.
- Sample loading: dry loading in 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: 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.$^{22}$
- 2,6-Lutidine is sometimes hard to separate from the desired heterocyclic compound by column chromatography. Therefore, the unpurified reaction mixture can be adsorbed onto silica gel and put onto the high vacuum for a prolonged time to remove 2,6-lutidine before the flash column chromatographic purification.
- If desired, further purification could be carried out by salt formation of the N-heterocycle to remove any trace of tin impurities.

3.3. One-Step Synthesis of Substituted Thiomorpholines

3.3.1. Preparation of SnAP reagents

2-(((Tributylstannyl)methyl)thio)ethanamine 18. To a solution of 139 (2.38 g, 5.52 mmol, 1.00 equiv) in EtOH (40 mL) was added 2-aminoethanethiol (448 mg, 5.52 mmol, 1.00 equiv), followed by a solution of K$_2$CO$_3$ (457 mg, 3.31 mmol, 0.60 equiv) in H$_2$O (3 mL) at rt. The reaction mixture was refluxed at 70 °C. After 12 h, the mixture was concentrated under reduced pressure to remove solvent; the resulting residue was dissolved in H$_2$O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic solutions were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford 18 (2.07 g, 98%) as a clear, colorless liquid. IR (thin film) $\nu$ 2955, 2925, 2852, 1629, 1578, 1463, 1375, 874 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.89 (t, $J$ = 6.1 Hz, 2 H), 2.57 (t, $J$ = 6.1 Hz, 2 H), 1.88 (t, $J$ = 20.4 Hz, 2 H), 1.57 – 1.47 (m, 6 H), 1.36 – 1.26 (m, 6 H), 0.96 – 0.86 (m, 15 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 42.4, 39.7, 29.0, 27.3, 13.7, 9.5, 8.1; ESI-HRMS calcd for C$_{15}$H$_{36}$NSSn [M + H] 382.1585, found 382.1582.

Ethyl 2-amino-3-(((tributylstannyl)methyl)thio)propanoate 41. To a solution of iodide 139 (432 mg, 1.00 mmol, 1.00 equiv) in EtOH (8 mL) was added ethyl cysteine hydrochloride (187 mg, 1.00 mmol, 1.00 equiv), followed by a solution of K$_2$CO$_3$ (166 mg, 1.20 mmol, 1.20 equiv) in H$_2$O (2 mL) at rt. The reaction mixture was refluxed at 70 °C. After 12 h, the mixture was concentrated under reduced pressure to remove the solvent; the resulting residue was dissolved in H$_2$O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic solutions were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (2:1 hexanes:EtOAc) afforded 41 (227 mg, 81% yield) as a clear, colorless liquid. IR (thin film) $\nu$ 3377, 2956, 2925, 2852, 1737, 1375, 1244, 1182, 1087, 864 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.19 (q, $J$ = 7.1 Hz, 2 H), 3.67 (dd, $J$ = 8.0, 4.5 Hz, 1H), 2.89 (dd, $J$ = 13.4, 4.5 Hz, 1H), 2.70 (dd, $J$ = 13.4, 8.0 Hz, 1H), 1.92 (dd, $J$ = 35.0, 9.3 Hz, 2H), 1.69 (s, 4H), 1.58 – 1.44 (m, 5H), 1.38 – 1.23 (m, 10H), 0.99 – 0.84 (m, 15H); $^{13}$C NMR
Part III. Experiment Procedures and Characterization Data

(101 MHz, CDCl$_3$) $\delta$ 174.6, 61.2, 53.2, 43.9, 29.1, 27.4, 14.4, 13.8, 9.7, 9.2; ESI-HRMS calcd for C$_{18}$H$_{40}$NO$_2$SSn [M + H] 454.1797, found 454.1798.

**Methyl 2-amino-3-methyl-3-(((tributylstannyl)methyl)thio)butanoate 42.**

To a solution of iodide 139 (432 mg, 1.00 mmol, 1.00 equiv) in EtOH (8 mL) was added methyl penicillamine hydrochloride (199 mg, 1.00 mmol, 1.00 equiv), followed by a solution of K$_2$CO$_3$ (166 mg, 1.20 mmol, 1.20 equiv) in H$_2$O (2 mL) at rt. The reaction mixture was refluxed at 70 °C. After 12 h, the mixture was concentrated under reduced pressure to remove the solvent; the resulting residue was dissolved in H$_2$O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic solutions were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (10:1 $\rightarrow$ 4:1 CH$_2$Cl$_2$:Et$_2$O) afforded 42 (228 mg, 52% yield) as a clear, colorless liquid. IR (thin film) $\nu$ 2956, 2926, 1738, 1462, 1376, 1231, 1166, 1121 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.72 (s, 3H), 3.51 (s, 1H), 1.80 (dd, $J$ = 34.4, 8.6 Hz, 3H), 1.57 (s, 2H), 1.54 – 1.45 (m, 6H), 1.38 – 1.26 (m, 10H), 1.20 (s, 3H), 0.99 – 0.86 (m, 15H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.0, 60.0, 51.8, 49.9, 29.1, 27.4, 25.1, 22.1, 13.8, 9.8, 3.5; ESI-HRMS calcd for C$_{19}$H$_{42}$NO$_2$SSn [M + H] 468.1953, found 468.1941.

3.3.2. Optimization of reaction conditions

To a mixture of Cu(OTf)$_2$ (0.05 mmol, 1.00 equiv), additive (0.50 mmol, 1.00 equiv) and CaSO$_4$ (10 mg) in solvent (0.5 mL) were added, followed by a solution of imine 19 (0.05 mmol, 1.00 equiv) in solvent (0.5 mL) and stirred at T (°C) in t (h). The reaction was quenched with sat. aq. NaHCO$_3$ (2 mL), followed by 10 % aq. NH$_4$OH (1 mL), and stirred vigorously in 15 min. The mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL), washed with H$_2$O (10 mL) and brine, dried over Na$_2$SO$_4$, filtered and concentrated. To the residue was added
Part III. Experiment Procedures and Characterization Data

benzylmethylether (6.56 µL, 0.05 mmol) as an internal standard; the product 20 yield was calculated based on ¹H-NMR integration.

Table 2. Optimization of reaction conditions

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3.3.3. Preparation of substituted 3-thiomorpholines

Substituted 3-thiomorpholines were prepared according to the General Procedure described in Part III Section 3.2. For R = heteroaryl, reaction was done with a mixture of 4:1 ClC₂H₄Cl:HFIP as solvent at 60 °C in 2 h.

3-(4-(Trifluoromethyl)phenyl)thiomorpholine 20. IR (thin film) ν 3266, 2911, 2832, 1618, 1417, 1325, 1162, 1121, 1067, 1018, 840 cm⁻¹; ¹H NMR ¹H NMR (400 MHz, CDCl₃) δ 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), 3.46 (dt, J = 12.0, 3.2 Hz, 1H), 3.18 (td, J = 12.0, 2.2 Hz, 1H), 2.91 (ddd, 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 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 148.2, 130.1 (q, $J_{CF}$ = 32.3 Hz), 127.1 (q, $J_{CF}$ = 3.8 Hz), 124.2 (q, $J_{CF}$ = 273.3 Hz), 62.6, 49.1, 35.0, 27.6.; ESI-HRMS calcd for C$_{11}$H$_{13}$F$_3$NS [M + H] 248.0716, found 248.0710.

3-Phenylthiomorpholine 23. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40 – 7.25 (m, 5H), 3.94 (dd, $J$ = 10.6, 2.3 Hz, 1H), 3.46 (dt, $J$ = 12.0, 3.1 Hz, 1H), 3.18 (td, $J$ = 12.0, 2.3 Hz, 1H), 2.98 – 2.80 (m, 2H), 2.54 – 2.38 (m, 2H), 1.70 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 144.3, 128.8, 127.9, 126.7, 63.1, 49.3, 34.9, 27.6. Spectra data was consistent with a previous report. $^{23}$

3-(Naphthalen-2-yl)thiomorpholine 24. IR (thin film) $\nu$ 3323, 3052, 2908, 2808, 1486, 1334, 1330, 128.3, 127.9, 127.7, 126.2, 125.9, 125.0, 125.0, 63.0, 49.2, 34.9, 27.6; ESI-HRMS calcd for C$_{14}$H$_{16}$NS [M + H] 230.0998, found 230.0996.

3-(4-Bromophenyl)thiomorpholine 25. IR (thin film) $\nu$ 3303, 3092, 2825, 1846, 1312, 1120, 1072, 1009, 825, 753 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.47 – 7.43 (m, 2H), 7.26 – 7.22 (m, 2H), 3.90 (dd, $J$ = 10.6, 2.3 Hz, 1H), 3.44 (dt, $J$ = 12.0, 3.0 Hz, 1H), 3.16 (td, $J$ = 12.0, 2.3 Hz, 1H), 2.89 (td, $J$ = 12.0, 3.0 Hz, 1H), 2.77 (dd, $J$ = 13.3, 10.6 Hz, 2H), 2.47 – 2.39 (m, 2H), 1.70 (s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.2, 131.7, 128.3, 121.4, 62.3, 49.0, 34.9, 27.4; ESI-HRMS calcd for C$_{10}$H$_{13}$BrNS [M + H] 257.9947, found 257.9951.

3-(4-Bromophenyl)thiomorpholine 26. IR (thin film) $\nu$ 3322, 2908, 2824, 1592, 1566, 1474, 1415, 1311, 1121, 789 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.58 – 7.52 (m, 1H), 7.43 – 7.36 (m, 1H), 7.32 – 7.25 (m, 1H), 7.18 (t, $J$ = 7.8 Hz, 1H),

3.89 (dd, $J = 10.5, 2.2$ Hz, 1H), 3.43 (dt, $J = 12.0, 3.1$ Hz, 1H), 3.14 (td, $J = 12.0, 2.2$ Hz, 1H), 2.94 – 2.83 (m, 1H), 2.78 (dd, $J = 13.0, 10.5$ Hz, 1H), 2.50 – 2.38 (m, 2H), 1.77 (s, NH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 143.2, 131.7, 128.3, 121.4, 62.3, 49.0, 34.9, 27.4; ESI-HRMS calcd for C$_{10}$H$_{13}$BrNS [M + H] 257.9947, found 257.9948.

3-(4-Fluorophenyl)thiomorpholine 27. IR (thin film) $\nu$ 3302, 2909, 2821, 1602, 1504, 1442, 1416, 1313, 1220, 1120, 1017, 985, 837 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.04 – 6.98 (m, 2H), 7.35 – 7.30 (m, 2H), 3.89 (dd, $J = 10.6, 2.3$ Hz, 1H), 3.44 (dt, $J = 12.1, 3.0$ Hz, 1H), 3.16 (td, $J = 12.1, 2.3$ Hz, 1H), 2.89 (td, $J = 12.0, 3.0$ Hz, 1H), 2.79 (dd, $J = 13.3, 10.6$ Hz, 1H), 2.48 – 2.40 (m, 2H), 1.77 (s, NH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 162.2 (d, $J_{CF} = 245.6$ Hz), 140.0 (d, $J_{CF} = 3.1$ Hz), 128.1 ($J_{CF} = 8.0$ Hz), 115.4 ($J_{CF} = 21.3$ Hz), 62.2, 49.2, 35.0, 27.4; ESI-HRMS calcd for C$_{10}$H$_{13}$FNS [M + H] 198.0748, found 198.0748.

3-(p-Tolyl)thiomorpholine 28. IR (thin film) $\nu$ 3320, 2918, 2820, 1512, 1447, 1415, 1312, 1210, 1019, 819 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.14 (d, $J = 8.0$, 2H), 7.14 (d, $J = 8.0$, 2H), 3.90 (dd, $J = 10.5, 2.3$ Hz, 1H), 3.44 (dt, $J = 12.0, 3.0$ Hz, 1H), 3.17 (td, $J = 12.0, 2.3$ Hz, 1H), 2.90 (td, $J = 12.0, 3.0$, 1H), 2.83 (dd, $J = 13.0, 10.5$ Hz, 1H), 2.49 – 2.39 (m, 2H), 2.33 (s, 3H), 1.76 (s, NH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 141.3, 137.4, 129.3, 126.5, 62.7, 49.2, 34.9, 27.5, 21.1; ESI-HRMS calcd for C$_{11}$H$_{16}$NS [M + H] 194.0998, found 194.0993.

3-(o-Tolyl)thiomorpholine 29. IR (thin film) $\nu$ 3319, 2910, 2826, 1488, 1446, 1308, 1293, 1119, 1018, 983, 761, 739 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50 – 7.46 (m, 2H), 7.23 – 7.12 (m, 2H), 4.14 (dd, $J = 10.4, 2.2$ Hz, 1H), 3.48 (dt, $J = 12.0, 3.0$ Hz, 1H), 3.20 (td, $J = 12.0, 2.2$ Hz, 1H), 2.93 (td, $J = 12.0, 3.0$ Hz, 1H), 2.80 (dd, $J = 13.5, 10.4$ Hz, 1H), 2.48 – 2.41 (m, 2H), 2.38 (s, 3H), 1.72 (s, NH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 142.2, 134.8, 130.5, 127.2, 126.4, 125.6, 58.9, 49.5, 33.7, 27.6, 19.3; ESI-HRMS calcd for C$_{11}$H$_{16}$NS [M + H] 194.0998, found 194.1002.
3-(4-Methoxyphenyl)thiomorpholine 30. IR (thin film) ν 3331, 2923, 2819, 1515, 1415, 1248, 1107, 1032, 984, 825, 781 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.27 (dt, J = 8.8, 2.5 Hz, 2H), 6.86 (dt, J = 8.8, 2.5 Hz, 2H), 3.87 (dd, J = 10.5, 2.2 Hz, 1H), 3.79 (s, 3H), 3.43 (dt, J = 12.0, 3.1 Hz, 1H), 3.16 (td, J = 12.0, 2.2 Hz, 1H), 2.89 (td, J = 12.0, 3.1 Hz, 1H), 2.81 (dd, J = 13.1, 10.6 Hz, 1H), 2.47-2.39 (m, 2H), 1.79 (s, NH); ¹³C NMR (101 MHz, CDCl₃) δ 159.1, 136.6, 127.6, 113.9, 62.4, 55.3, 49.3, 34.9, 27.4; ESI-HRMS calcd for C₁₁H₁₆NOS [M + H] 210.0948, found 210.0949.

3-(4-N,N-dimethylaminophenyl)thiomorpholine 31. IR (thin film) ν 3316, 2917, 2803, 1612, 1520, 1444, 1347, 1164, 818 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.22 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 3.83 (dd, J = 10.7, 2.3 Hz, 1H), 3.44 (dt, J = 12.0, 3.1 Hz, 1H), 3.16 (td, J = 12.0, 2.3 Hz, 1H), 2.93 (s, 1H), 2.92 (m, 2H), 2.48 – 2.38 (m, 2H), 1.91 (s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 150.2, 132.3, 127.3, 112.6, 62.5, 49.4, 40.6, 34.9, 27.4; ESI-HRMS calcd for C₁₂H₁₉N₂S [M + H] 223.1264, found 223.1263.

Methyl 4-(thiomorpholin-3-yl)benzoate 32. IR (thin film) ν 3324, 2929, 2860, 1725, 1455, 1277, 1120, 1098, 743 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 4.00 (dd, J = 10.6, 2.2 Hz, 1H), 3.91 (s, 3H), 3.46 (dt, J = 12.0, 3.1 Hz, 1H), 3.17 (td, J = 12.0, 2.2 Hz, 1H), 2.93 (td, J = 12.0, 3.1 Hz, 1H), 2.81 (dd, J = 13.1, 10.6 Hz, 1H), 2.51 – 2.41 (m, 2H), 1.71 (s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 149.1, 130.0, 129.6, 126.6, 62.7, 52.1, 48.9, 34.8, 27.4; ESI-HRMS calcd for C₁₂H₁₆NO₂S [M + H] 238.0897, found 238.0896.

3-(Quinolin-4-yl)thiomorpholine 33. IR (thin film) ν 3288, 2909, 2830, 1589, 1508, 1301, 1121, 778, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.86 (d, J = 4.5 Hz, 1H), 8.17 – 8.09 (m, 2H), 7.70 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.60 – 7.51 (m, 2H), 4.71 (dd, J = 10.3, 2.3 Hz, 1H), 3.54 (dt, J = 12.0, 3.1 Hz, 1H), 3.28 (td, J = 12.0, 2.3 Hz, 1H), 2.96 (ddd, J = 13.3, 11.7, 3.1 Hz, 1H), 2.83 (dd, J = 13.3, 10.3 Hz, 1H), 2.66 (dt, J = 13.3, 2.3 Hz, 1H), 2.50 (dq, J = 13.2, 2.3 Hz, 1H), 1.98 (s, NH); ¹³C NMR (100 MHz, CDCl₃) δ
3-(Thiophen-3-yl)thiomorpholine 34. IR (thin film) ν 3304, 3100, 2907, 2818, 1446, 1415, 1313, 1119, 990, 841, 760 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.27 (dd, J = 5.0, 3.0 Hz, 1H), 7.21 – 7.15 (m, 1H), 7.06 (dd, J = 5.0, 1.3 Hz, 1H), 4.05 (dd, J = 10.5, 2.3 Hz, 1H), 3.42 (dt, J = 12.2, 3.1 Hz, 1H), 3.14 (td, J = 12.2, 2.3 Hz, 1H), 2.91 – 2.77 (m, 2H), 2.55 (dt, J = 13.1, 2.3 Hz, 1H), 2.45 – 2.37 (dq, J = 13.1, 2.3 Hz, 1H), 1.84 (s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 145.3, 126.1, 125.9, 120.6, 58.3, 48.9, 34.4, 27.5; ESI-HRMS calcd for C₈H₁₂NS₂ [M + H] 186.0406, found 186.0406.

3-(Pyridin-4-yl)thiomorpholine 35. IR (thin film) ν 3278, 2908, 2817, 1597, 1411, 1316, 1122, 994, 822, 622 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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), 3.45 (dt, J = 12.0, 2.4 Hz, 1H), 3.15 (td, J = 12.0, 2.4 Hz, 1H), 2.89 (td, J = 13.0, 3.0 Hz, 1H), 2.76 (dd, J = 13.0, 10.5 Hz, 1H), 2.53 – 2.40 (m, 2H), 1.97 (s, NH); ¹³C NMR (101 MHz, CDCl₃) δ 152.4, 150.2, 121.6, 61.6, 48.6, 34.5, 27.4; ESI-HRMS calcd for C₉H₁₃N₂S [M + H] 181.0794, found 181.0795.

3-(Thiophen-3-yl)thiomorpholine 36. IR (thin film) ν 3281, 2908, 2822, 1423, 1316, 1121, 1020, 712 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.61 (d, J = 1.8 Hz, 1H), 8.52 (dd, J = 4.8, 1.8 Hz, 1H), 7.70 (dt, J = 7.8, 2.2 Hz, 1H), 7.28 – 7.24 (m, 1H), 3.98 (dd, J = 10.6, 2.3 Hz, 1H), 3.46 (dt, J = 12.0, 3.2 Hz, 1H), 3.18 (td, J = 12.0, 2.3 Hz, 1H), 2.95 – 2.87 (m, 1H), 2.83 (dd, J = 13.4, 10.6 Hz, 1H), 2.51 – 2.42 (m, 2H), 1.78 (s, NH); ¹³C NMR (100 MHz, CDCl₃) 149.3, 148.6, 139.5, 134.1, 123.6, 60.5, 49.0, 34.8, 27.4; ESI-HRMS calcd for C₉H₁₃N₂S [M + H] 181.0794, found 181.0794.

3-(tert-Butyl)thiomorpholine 37. IR (thin film) ν 2954, 2924, 1476, 1363, 1320, 1124, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.40 (dt, J = 12.3, 2.7 Hz, 1H), 3.01
3-Isopropylthiomorpholine 38. IR (thin film) ν 3418, 2959, 2924, 1644, 1464, 1287, 1212, 955 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 67.1, 49.7, 34.4, 28.7, 27.9, 26.5.

Ethyl thiomorpholine-3-carboxylate 39. IR (thin film) ν 3343, 2979, 2914, 2849, 1734, 1447, 1370, 1306, 1243, 1188, 1029, 750 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 171.7, 61.4, 58.8, 47.0, 29.7, 27.7, 14.3; ESI-HRMS calcd for C₇H₁₄NO₂S [M + H] 176.0740, found 176.0739.

3-(Trichloromethyl)thiomorpholine 40. IR (thin film) ν 3338, 2915, 2813, 1734, 1447, 1370, 1306, 1243, 1188, 1029, 750 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.60 – 3.49 (m, 1H), 3.15 (td, J = 12.0, 2.7 Hz, 1H), 3.04 (dt, J = 13.2, 1.8 Hz, 1H), 2.86 – 2.71 (m, 1H), 2.38 (dq, J = 13.2, 2.7 Hz, 1H), 2.19 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 102.3, 71.9, 48.9, 28.9, 27.4; ESI-HRMS calcd for C₅H₉Cl₃NS [M + H] 219.9516, found 219.9511.

cis-Ethyl 5-(4-(trifluoromethyl)phenyl)thiomorpholine-3-carboxylate 43. IR (thin film) ν 3317, 2993, 2916, 1722, 1618, 1325, 1245, 1122, 1015, 851 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 4.30 – 4.16 (m, 2H), 4.06 (d, J = 10.6 Hz, 1H), 3.79 (dd, J = 10.6, 2.5 Hz, 1H), 2.90 (d, J = 13.0 Hz, 1H), 2.85 – 2.67 (m, 2H), 2.53 – 2.41 (m, 2H), 1.28 (q, J = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 170.9, 147.3 (d, J_CF = 1.2 Hz), 138
130.4 (q, $J_{CF} = 32.5$ Hz), 127.2, 125.8 (q, $J_{CF} = 3.8$ Hz), 124.2 (q, $J_{CF} = 272.1$ Hz), 63.1, 61.6, 60.7, 34.5, 28.9, 14.3; ESI-HRMS calcd for C$_{14}$H$_{17}$F$_3$NO$_2$S [M + H] 320.0927, found 320.0937.

**Figure 4.**

cis-Ethyl 5-(4-methoxyphenyl)thiomorpholine-3-carboxylate 44. IR (thin film) $\nu$ 3333, 2979, 2908, 2833, 1733, 1611, 1512, 1246, 1033, 831 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.30 (m, 2H), 6.95 – 6.83 (m, 2H), 4.32 – 4.14 (m, 2H), 3.96 (dd, $J = 10.6, 2.1$ Hz, 1H), 3.89 – 3.75 (m, 4H), 2.98 – 2.68 (m, 3H), 2.56 – 2.36 (m, 2H), 1.30 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.1, 159.4, 135.8, 127.9, 114.1, 63.0, 61.5, 61.1, 55.4, 34.5, 28.9, 14.3; ESI-HRMS calcd for C$_{14}$H$_{20}$NO$_3$S [M + H] 282.1159, found 282.1156.

**Figure 4.**

cis-3-Ethyl 5-(tert-butyl)thiomorpholine-3-carboxylate 45. IR (thin film) $\nu$ 3367, 2957, 1737, 1476, 1367, 1303, 1200, 1177, 1162, 1034 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.19 (qd, $J = 7.1, 0.7$ Hz, 2H), 3.63 (dd, $J = 10.9, 2.3$ Hz, 1H), 2.75 (dd, $J = 13.1, 2.3$ Hz, 1H), 2.67 – 2.51 (m, 2H), 2.47 – 2.42 (m, 2H), 2.08 (s, 1H), 1.28 (t, $J = 7.1$ Hz, 4H), 0.95 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.7, 67.4, 61.4, 61.2, 34.5, 29.3, 28.0, 26.5, 14.3; method ESI-HRMS calcd for C$_{11}$H$_{22}$NO$_2$S [M + H] 232.1366, found 232.1363.

**Figure 4.**

cis-3-Methyl 2,2-dimethyl-5-(4-(trifluoromethyl)phenyl)thiomorpholine-3-carboxylate 46. IR (thin film) $\nu$ 3331, 2959, 2929, 1737, 1619, 1325, 1164, 1068, 1018, 841 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61 (d, $J = 8.3$ Hz, 2H), 7.54 (d, $J = 8.3$ Hz, 2H), 4.07 (d, $J$
= 10.6 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.73 (d, \( J = 3.0 \) Hz, 3H), 2.97 (dd, \( J = 13.4, 11.1 \) Hz, 1H), 2.46 (dd, \( J = 13.4, 2.6 \) Hz, 1H), 2.07 (s, 1H), 1.55 (s, 3H), 1.39 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 170.9, 147.0, 130.2 (q, \( J = 32.4 \) Hz), 127.1, 125.8 (q, \( J = 3.8 \) Hz), 124.2 (d, \( J = 272.0 \) Hz), 70.3, 62.4, 52.0, 39.9, 33.0, 27.5, 22.7; ESI-HRMS calcd for C\(_{15}\)H\(_{19}\)F\(_{3}\)NO\(_2\)S [M + H] 334.1084, found 334.1087.

3.4. Mechanistic Investigations and Racemization Studies

3.4.1. Mechanistic Investigations

To a solution of 2,6-lutidine (29 µL, 0.24 mmol, 1.00 mmol) in HFIP (1.0 mL) was added Cu(OTf)\(_2\) (91 mg, 0.24 mmol, 1.00 equiv) and stirred at rt for 1 h. A solution of imine 19 (132 mg, 0.24 mmol, 1.00 equiv) in CH\(_2\)Cl\(_2\) (4 mL), followed by TEMPO (56 mg, 0.36 mmol, 1.50 equiv) and stirred at rt for 12 h. Imine 49 was detected by HRMS (ESI-HRMS calcd for C\(_{20}\)H\(_{30}\)F\(_3\)N\(_2\)OS [M+H] 403.2031, found 403.2029). To the reaction mixture was added a solution of NaBH\(_3\)CN (72 mg, 0.36 mmol, 1.50 equiv) in MeOH (1 mL), followed by AcOH (9 µL). After 4 h at rt, the reaction was quenched with sat. aq. NaHCO\(_3\) (3 mL), followed by 10 % aq. NH\(_4\)OH (1 mL), stirred vigorously in 15 min. The mixture was extracted with CH\(_2\)Cl\(_2\) (3 x 30 mL), washed with H\(_2\)O (3 x 30 mL) and brine, dried with Na\(_2\)SO\(_4\), filtered and concentrated. Purification by flash column chromatography delivered amine 50; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.57 (d, \( J = 8.0 \) Hz, 2H), 7.47 (d, \( J = 8.0 \) Hz, 2H), 4.77 (s, 2H), 3.88 (s, 2H), 2.97 – 2.80 (m, 4H), 1.80 (s, 1H), 1.44 (d, \( J = 2.8 \) Hz, 4H), 1.25 (s, 2H), 1.14 (s, 6H), 1.06 (s, 6H); ESI-HRMS calcd for C\(_{20}\)H\(_{32}\)F\(_3\)N\(_2\)OS [M+H] 405.2182, found 405.2192.
3.4.2. Racemization studies

Preparation of chiral SnAP L-Cis

Chiral SnAP L-Cis 51. To a solution of iodide 139 (649 mg, 1.50 mmol, 1.00 equiv) in EtOH (12 mL) was added L-cysteine ethyl ester hydrochloride (281 mg, 1.50 mmol, 1.00 equiv), followed by a solution of K₂CO₃ (248 mg, 1.80 mmol, 1.20 equiv) in H₂O (2 mL) at rt. The reaction mixture was refluxed at 70 °C. After 12 h, the mixture was concentrated under reduced pressure to remove the solvent; the resulting residue was dissolved in H₂O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic solutions were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (2:1 hexanes:EtOAc) afforded 51 (577 mg, 85% yield) as a clear, colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 4.20 (q, J = 7.1 Hz, 2H), 3.68 (dd, J = 8.0, 4.5 Hz, 1H), 2.89 (dd, J = 13.4, 4.5 Hz, 1H), 2.70 (dd, J = 13.4, 8.0 Hz, 1H), 1.96, 1.88 (2d, J = 9.3 Hz, 2H), 1.78 (s, 2H), 1.57 – 1.42 (m, 3H), 1.40 – 1.23 (m, 13H), 1.00 – 0.83 (m, 15H); ¹³C NMR (101 MHz, CDCl₃) δ 174.6, 61.2, 53.2, 43.9, 29.1, 27.4, 14.4, 13.8, 9.7, 9.2. The spectra were consistent with ones of rac. SnAP Cys.

Preparation of enantioenriched cis-ethyl 5-(4-(trifluoromethyl)phenyl)thiomorpholine-3-carboxylate

cis-Ethyl 5-(4-(trifluoromethyl)phenyl)thiomorpholine-3-carboxylate 52 was prepared with the general procedure (described in Part III Section 3.2) from chiral SnAP L-Cys 51
and p-trifluoromethylbenzaldehyde. 43% ee determined by SFC (column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient: 5% i-PrOH in CO$_2$ to 50% i-PrOH in CO$_2$ over 10 min; acquisition time 13 min; flow: 3.0 mL/min; detection wavelength 254 nm: $t_R$ = 3.67 min and 4.95 min.

Preparation of silicon surrogates

(R)-Ethyl 2-(((benzyloxy)carbonyl)amino)-3-mercaptopropanoate 53. To a suspension of L-cysteine ethyl ester hydrochloride (31 mg, 0.16 mmol, 1.00 equiv) and anhydrous NaHCO$_3$ (42 mg, 0.48 mmol, 3.00 equiv) in CH$_2$Cl$_2$ (1.5 mL) was added benzyloxy carbonyl chloride (CbzCl) (28 mg, 0.165 mmol, 1.00 equiv). The reaction was allowed to warm up to rt and stir in 18 h. The reaction was diluted with CH$_2$Cl$_2$ (25 mL) and quenched by H$_2$O (25 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 25 mL). The combined organic layer was washed with H$_2$O, brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. Purification by flash column chromatography (hexanes:EtOAC 4:1) afforded 53 (rotamers 1:1 by $^1$H NMR intergration, 41 mg, 87% yield) as a cloudy, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.28 (m, 5H), 5.70 (d, $J$ = 6.0 Hz, 1H x 0.5), 5.62 (d, $J$ = 7.5 Hz, 1H x 0.5), 5.13 (2 s, 2H), 4.77 – 4.54 (m, 1H), 4.32 – 4.09 (m, 2H), 3.46 (dd, $J$ = 14.3, 4.6 Hz, 1H x 0.5), 3.32 (dd, $J$ = 14.3, 6.0 Hz, 1H x 0.5), 3.09 – 2.92 (m,
Part III. Experiment Procedures and Characterization Data

1H), 1.38 (t, J = 8.9 Hz, 1H), 1.28 (2 t, J = 7.1 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 170.4, 170.1, 170.0, 155.8, 136.3, 136.2, 135.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 127.1, 69.6, 67.3, 67.2, 62.2, 62.1, 55.3, 53.9, 33.4, 27.3, 14.3, 14.2. The spectra were consistent with previous report.24 SFC (column: Daicel Chiralpak ADH (4.6 x 250 mm); gradient: 5–50% i-PrOH in CO2 over 10 min; acquisition time 13 min; flow: 3.0 mL/min; detection wavelength 254 nm: tR = 8.56 min.

(R)-Ethyl 2-amino-3-(((trimethylsilyl)methyl)thio)propanoate 54. To a solution of L-cysteine ethyl ester hydrochloride (93 mg, 0.50 mmol, 1.00 equiv) and (chloromethyl)trimethylsilane (69.3 µL, 0.50 mmol, 1.00 equiv) in EtOH (4 mL) was added, followed by a solution of K2CO3 (83 mg, 0.60 mmol, 1.20 equiv) in H2O (2 mL) at rt. The reaction mixture was refluxed at 70 °C. After 12 h, the mixture was concentrated under reduced pressure to remove the solvent; the resulting residue was dissolved in H2O (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic solutions were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to afford pure 54 as an yellow oil in quantitative yield. IR (thin film) ν 3433, 2955, 1736, 1644, 1249, 1184, 1025, 845 cm−1; 1H NMR (400 MHz, CDCl3) δ 4.20 (q, J = 7.1 Hz, 2H), 3.65 (dd, J = 7.8, 4.6 Hz, 1H), 2.91 (dd, J = 13.4, 4.6 Hz, 1H), 2.74 (dd, J = 13.4, 7.8 Hz, 1H), 1.92 – 1.70 (m, 4H), 1.29 (t, J = 7.1 Hz, 3H), 0.14 – 0.08 (m, 9H); 13C NMR (101 MHz, CDCl3) δ 174.4, 61.3, 53.7, 41.7, 18.9, 14.4, -1.4; ESI-HRMS calcd for C9H21Na1N1O2S1Si1 [M + Na] 258.0954, found 258.0958.

(R)-Ethyl 2-(((benzyloxy)carbonyl)amino)-3-(((trimethylsilyl)methyl)thio)propanoate 55. To a suspension of silylated

**L-cysteine ethyl ester 54** (40 mg, 0.17 mmol, 1.00 equiv) and anhydrous NaHCO₃ (29 mg, 0.34 mmol, 2.00 equiv) in CH₂Cl₂ (2 mL) was added benzoxycarbonylchloride (CbzCl) (29 mg, 0.17 mmol, 1.00 equiv). The reaction was allowed to warm up to rt and stir in 18 h. The reaction was diluted with CH₂Cl₂ (25 mL) and quenched by H₂O (10 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL). The combined organic layer was washed with H₂O, brine, dried over anhydrous Na₂SO₄, filtered and concentrated. Purification by flash column chromatography (hexanes:EtOAC 10:1) afforded 55 (50 mg, 80% yield) as a colorless oil. IR (thin film) ν 3358, 2956, 1725, 1513, 1340, 1249, 1211, 1051, 1027 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.28 (m, 5H), 5.57 (d, J = 7.7 Hz, 1H), 5.20 – 5.04 (m, 2H), 4.63 – 4.52 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.05 – 2.83 (m, 2H), 1.81 (q, J = 11.9 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.07 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 171.2, 155.9, 136.4, 128.7, 128.3, 128.2, 67.2, 61.8, 53.3, 38.6, 19.2, 14.3, -1.7; ESI-HRMS calcd for C₁₇H₂₈N₂O₄Si₁ [M + H] 370.1503, found 370.1506. 44% ee determined by SFC (column: Daicel Chiralpak ADH (4.6 x 250 mm)); gradient: 5–50% i-PrOH in CO₂ over 10 min; acquisition time 13 min; flow: 3.0 mL/min; detection wavelength 254 nm: tᵣ = 4.28 and 4.78 min.
3.5. One-Step Synthesis of Substituted Morpholines and Piperazines

3.5.1. Preparation of SnAP reagents

SnAP M (SnAP Morpholine)

2-((Tributylstannyl)methoxy)ethanol 140. Sodium hydride (480 mg of a 60% suspension in mineral oil, 12.0 mmol, 1.20 equiv) was washed with pentane (3 x 3 mL), dried and suspended in DMSO/THF (1:10, 20 mL). The suspension was cooled to 0 °C, followed by the dropwise addition of commercially available ethylene glycol (1.80 mL, 30.0 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 (137; 4.32 g, 10.0 mmol, 1.00 equiv) in THF (10 mL) over 10 min. The suspension was allowed to warm to rt and heated at 55 °C for 15 h. The reaction was slowly quenched with H₂O (20 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 H₂O (2 x 10 mL), brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc 10:1) afforded 140 (2.59 g, 71% yield) as clear, colorless liquid. IR (thin film): ν 3407, 2955, 2924, 2870, 1462, 1375, 1096, 1070, 873 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.77 (s, J(117/119Sn-H) = 7.2 Hz, 2H), 3.72–3.64 (m, 2H), 3.48–3.41 (m, 2H), 1.91 (t, J = 6.2 Hz, 1H), 1.56–1.42 (m, 6H), 1.39–1.21 (m, 6H), 1.01–0.78 (m, 15H); ¹³C NMR (100 MHz, CDCl₃): δ 76.5, 62.6, 61.9, 29.3, 27.4, 13.9, 9.2; Rf = 0.30 (cyclohexane/EtOAc 10:1); ESI-HRMS calcd for C₁₅H₃₄Na₂O₂Sn₁ [M + Na] 389.1476, found 389.1480.
2-(2-((Tributylstannyl)methoxy)ethyl)isoindoline-1,3-dione 141. To a solution of 140 (2.53 g, 6.90 mmol, 1.00 equiv) in Et₂O (35 mL) at rt was added Et₃N (1.90 mL, 13.8 mmol, 2.00 equiv) in one portion followed by the dropwise addition of methanesulfonyl chloride (600 µL, 7.60 mmol, 1.10 equiv) over 5 min. The reaction mixture was stirred at rt and monitored by TLC. After 1 h, the reaction was slowly quenched with H₂O (30 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 (2 x 10 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 further purification.

To a solution of the mesylate in DMF (70 mL) was added potassium phthalimide (1.91 g, 10.3 mmol, 1.50 equiv) in one portion at rt. The reaction mixture was stirred vigorously at 100 °C for 3 h. The reaction was cooled to rt after the disappearance of the mesylate by TLC, slowly quenched with H₂O (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O (3 x 50 mL), brine (2 x 30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc 40:1 to 20:1) afforded the phthalimide protected SnAP M 141 (2.80 g, 82% yield, 2 steps) as clear, colorless liquid. IR (thin film): ν 3475, 2955, 2925, 2870, 1776, 1714, 1466, 1392, 1357, 1097, 1039, 874 cm⁻¹;¹H NMR (400 MHz, CDCl₃): δ 7.84 (dd, J = 5.5, 3.0 Hz, 2H), 7.70 (dd, J = 5.5, 3.0 Hz, 2H), 3.87 (t, J = 5.7 Hz, 2H), 3.71 (s, J¹¹⁷¹¹⁹Sn¹⁻H) = 7.8 Hz, 2H), 3.57 (t, J = 5.7 Hz, 2H), 1.54–1.29 (m, 6H), 1.28–1.12 (m, 6H), 0.93–0.69 (m, 15H);¹³C NMR (100 MHz, CDCl₃): δ 168.4, 133.9, 132.4, 123.3, 72.0, 62.2, 37.4, 29.2, 27.4, 13.8, 9.0; ESI-HRMS calcd for C₂₃H₃₇N₁Na₁O₃Sn₁ [M + Na] 518.1692, found 518.1691.

SnAP M (SnAP Morpholine) 57. To a solution of the phthalimide protected SnAP M 141 (2.50 g, 5.05 mmol, 1.00 equiv) in EtOH (20 mL) was added hydrazine monohydrate (2.50 mL, 50.5 mmol, 10.0 equiv). The reaction mixture heated to reflux 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 M 57 in quantitative yield.
(1.82 g) as clear, colorless liquid. IR (thin film): ν 3372, 2955, 2924, 2870, 1581, 1463, 1375, 1091, 873 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.73 (s, J(¹¹⁷/¹¹⁹Sn-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; ESI-HRMS calcd for C₁₅H₃₆N₁O₁Sn₁ [M + H] 366.1816, found 366.1813.

**SnAP 2-Me-M (SnAP 2-Methyl Morpholine)**

1-(Tritylamino)propan-2-ol 142. Trityl chloride (3.56 g, 12.8 mmol, 1.00 equiv) in CH₂Cl₂ (13 mL) was added dropwise to a solution of 1-amino-2-propanol (1.00 ml, 12.8 mmol, 1.00 equiv) and triethylamine (3.57 mL, 25.6 mmol, 2.00 equiv) in CH₂Cl₂ (13 ml) at 0 °C. The resulting clear, colorless solution was allowed to warm to room temperature and stirred for 16 h followed by the addition of H₂O (10 mL) in one portion. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were washed with H₂O (2 x 5 mL), brine (2 x 5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc 4:1) afforded the trityl protected amino alcohol 142 (3.75 g, 92% yield) as a colorless solid. IR (thin film): ν 3567, 3392, 3057, 2967, 2925, 2852, 1595, 1490, 14481079, 1033 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.49–7.44 (m, 6H), 7.31–7.25 (m, 6H), 7.23–7.17 (m, 3H), 3.91–3.67 (m, 1H), 2.89–2.51 (m, 1H), 2.23–2.11 (m, 2H), 1.93–1.45 (m, 1H), 1.12 (d, J = 6.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 145.9, 128.8, 128.0, 126.5, 70.7, 67.8, 51.3, 20.9; R₇ = 0.26 (cyclohexane/EtOAc 4:1); ESI-HRMS calcd for C₂₂H₂₃N₁O₁Na₁Sn₁ [M + Na] 340.1672, found 340.1667.

2-((Tributylstannyl)methoxy)-N-tritylpropan-1-amine 143. Sodium hydride (132 mg of a 60% suspension in mineral oil, 3.31 mmol, 1.50 equiv) was washed with pentane (3 x 2 mL) and suspended in DMF (11 mL). The suspension was cooled to 0 °C and alcohol 142 (0.700 g, 2.21 mmol, 1.00 equiv) in DMF
(11 mL) was added dropwise over 10 min. The resulting suspension was allowed to warm to rt. After 1 h, the reaction mixture was re-cooled to 0 °C and tributyl(iodomethyl)stannane (139; 1.05 g, 2.43 mmol, 1.10 equiv) was added dropwise over 10 min. The resulting suspension was allowed to warm to rt over 1 h and stirred for 3 h. The reaction mixture was cooled to 0 °C and slowly quenched with sat aq NH₄Cl (5 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 (2 x 10 mL), brine (2 x 10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/EtOAc 100:0 to 97:3) afforded trityl protected SnAP 2Me-M 143 (1.34 g, 98% 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, 6H), 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 (cyclohexane/EtOAc 10:1); ESI-HRMS calcd for C₃₅H₅₁N₁Na₁O₁Sn₁ [M + Na] 644.2892, found 644.2892.

Me₂O-SnBu₃
NH₂

2-((Tributylstannyl)methoxy)propan-1-amine 58. Trityl protected SnAP 2Me-M 143 (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 4 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 58 (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.

SnAP 3-Me-M (SnAP 3-Methyl Morpholine)

1-((Tributylstanny1)methoxy)propan-2-amine 59. 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 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 (139; 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 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 the desired SnAP 3Me-M 59 (1.40 g, 87% yield) as 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; Rf = 0.17 (EtOAc/MeOH 10:1); ESI-HRMS calcd for C₁₆H₃₈N₁O₁Sn₁ [M + H] 380.1973, found 380.1973.
Part III. Experiment Procedures and Characterization Data

SnAP Pip (SnAP Piperazine)

**tert-Butyl (2-(1,3-dioxoisoindolin-2-yl)ethyl)carbamate 145.** A flame dried 25 mL flask was charged with bromide 144 (515 mg, 2.30 mmol, 1.00 equiv) in DMF (12 mL) at rt. Potassium phthalimide (469 mg, 2.53 mmol, 1.10 mmol) was added at rt in one portion. The reaction mixture was stirred vigorously at rt for 24 h. The cloudy, colorless suspension was diluted with EtOAc (100 mL) and washed with H₂O (3 x 30 mL), sat aq NaHCO₃ (2 x 15 mL) and brine (2 x 15 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield a colorless solid that is usually used without further purification in the next step. Purification by flash chromatography (cyclohexane/EtOAc 4:1) to obtain analytically pure spectra afforded 145 (604 mg, 91% yield) as a colorless solid. ¹H NMR (400 MHz, CDCl₃): δ 7.88–7.81 (m, 2H), 7.74–7.67 (m, 2H), 4.89 (br s, NH), 3.87–3.77 (m, 2H), 3.47–3.35 (m, 2H), 1.33 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 168.6, 156.1, 134.1, 132.2, 123.5, 79.6, 39.7, 38.2, 28.4. These spectral characteristics were identical to those previously reported.²⁵

**tert-Butyl (2-(1,3-dioxoisoadolin-2-yl)ethyl)((tributylstannyl)methyl)carbamate 146.** Sodium hydride (138 mg of a 60% suspension in mineral oil, 3.45 mmol, 2.00 equiv) was washed with pentane (3 x 2 mL) and suspended in DMF (6 mL). The suspension was cooled to 0 °C and carbamate 145 (500 mg, 1.73 mmol, 1.00 equiv) in DMF (6 mL) was added dropwise over 10 min. The resulting suspension was allowed to warm to rt. After 30 min, the reaction mixture was re-cooled to 0 °C and tributyl(iodomethyl)stannane (139; 1.48 g, 3.45 mmol, 2.00 equiv) was added dropwise over 10 min. The resulting suspension was allowed to warm to rt over 3 h, and then stirred at rt for 3 h. The reaction mixture was cooled to 0 °C

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and slowly quenched with sat aq NH₄Cl (5 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 (2 x 10 mL), brine (2 x 10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/EtOAc 10:1) recovered unreacted tributyl(iodomethyl)stannane (139) and afforded phthalimide protected SnAP Pip (720 mg, 71% yield, rotamers 3:1) as a pale yellow liquid.

IR (thin film): \( \nu = 2954, 2923, 2871, 2852, 1775, 1717, 1680, 1393, 1162, 1137 \); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.87–7.80 \) (m, 2H), \( 7.73–7.69 \) (m, 2H \( \times \) 0.75), \( 7.69–7.65 \) (m, 2H \( \times \) 0.25), 3.90–3.83 (m, 2H), 3.48 (t, \( J_{\text{Sn}-1\text{H}} = 5.9 \text{ Hz} \), 2H \( \times \) 0.75), 3.42 (t, \( J = 5.4 \text{ Hz} \), 2H \( \times \) 0.25), 3.07 (s, \( J_{\text{Sn}-1\text{H}} = 17.5 \text{ Hz} \), 2H \( \times \) 0.25), 2.83 (s, \( J_{\text{Sn}-1\text{H}} = 27.0 \text{ Hz} \), 2H \( \times \) 0.75), 1.54–1.37 (m, 6H), 1.32–1.23 (m, 6H), 1.23 (s, 9H \( \times \) 0.25), 1.19 (s, 9H \( \times \) 0.75), 0.91–0.78 (m, 15H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 168.4, 168.1, 155.5, 155.4, 134.0, 133.7, 132.5, 132.4, 123.4, 123.3, 79.6, 79.3, 53.6, 48.3, 46.7, 35.6, 33.5, 33.1, 29.2, 28.3, 28.2, 27.6, 27.5, 13.9, 13.8, 10.7, 9.7; ESI-HRMS calcd for C\(_{28}\)H\(_{47}\)N\(_2\)O\(_4\)Sn\(_1\) [M + H] 595.2557, found 595.2556.

SnAP Pip (SnAP Piperazine) 60. A 25 mL flask equipped with a reflux condenser was charged with the phthalimide protected SnAP Pip (420 mg, 0.71 mmol, 1.00 equiv) in ethanol (7 mL) and heated to reflux. Hydrazine monohydrate (345 µL, 7.1 mmol, 10.0 equiv) was added dropwise at reflux. After the addition, the reaction mixture was stirred at reflux for 20 min while colorless solid crashed out. The suspension was allowed to cool to rt and was poured into a mixture of EtOAc (50 mL) and H₂O (15 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 and concentrated under reduced pressure to afford pure SnAP Pip (311 mg, 95% yield, rotamers 7:3). 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, \( J_{\text{Sn}-1\text{H}} = 17.2 \text{ Hz} \), 2H \( \times \) 0.3), 2.88–2.76 (m, 2H and 2H \( \times \) 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; ESI-HRMS calcd for C\(_{20}\)H\(_{45}\)N\(_2\)O\(_2\)Sn\(_1\) [M + H] 465.2501, found 465.2487.
SnAP 2- or 3-Me-Pip (SnAP 2- or 3-Methyl-Piperazine)

*t tert-Butyl (1-((triisopropylsilyl)oxy)propan-2-yl)carbamate 147.* Imidazole (1.46 g, 21.4 mmol, 1.50 equiv) was added in one portion to a solution of tert-Butyl (1-hydroxypropan-2-yl)carbamate (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 (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 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 (cyclohexane/EtOAc 25:1) afforded the desired product 147 (4.11 g, 87% yield) as clear, pale yellow liquid. IR (thin film): ν 3451, 3354, 2963, 2943, 2894, 2867, 1719, 1706, 1497, 1462, 1365, 1174, 1114, 1060 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) δ 155.6, 79.2, 66.7, 48.0, 28.6, 18.1, 17.8, 12.1; Rf = 0.35 (cyclohexane/EtOAc 20:1); ESI-HRMS calcd for C₁₇H₃₇N₁Na₁O₃Si₁ [M + Na] 354.2435, found 354.2436.

**SnAP 2-Me-Pip (SnAP 2-Methyl Piperazine)**

*t tert-Butyl (tributylstannyl)methyl(1-((triisopropylsilyl)oxy)propan-2-yl)carbamate 148.* 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 147 (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 (139; 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 (3 x 10 mL), brine (2 x 10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc 100:0 to 96:4) afforded the alkylated product 148 (1.65 g, 86% yield, rotamers 3:1) as 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 (cyclohexane/EtOAc 20:1); ESI-HRMS calcd for C₃₀H₆₅N₃Na₁O₃Si₁Sn₁ [M + Na] 658.3653, found 658.3651.

**tert-Butyl** (1-(1,3-dioxoisindolin-2-yl)propan-2-yl)((tributylstannyl)methyl) carbamate 150. 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 148 (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 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 149 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 alcohol 149, triphenylphosphine (713 mg, 2.72 mmol, 1.15 equiv), and phthalimide (400 mg, 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
(cyclohexane/EtOAc 25:1) afforded the phthalimide protected SnAP 2Me-Pip 150 (1.15 g, 80% yield, 2 steps, rotamers 4:1) as 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 (cyclohexane/EtOAc 10:1); m.p. = 68–70°C; ESI-HRMS calcd for C₂₉H₄₈N₂Na₁O₄Sn₁ [M + Na] 631.2534, found 631.2531.

SnAP 2Me-Pip (SnAP 2-Methyl-Piperazine) 61. The phthalimide protected SnAP 2Me-Pip 150 (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 2Me-Pip 61 (448 mg, 95% yield, rotamers 7:3) as 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; ESI-HRMS calcd for C₂₁H₄₇N₂O₂Sn₁ [M + H] 479.2658, found 479.2656.
**SnAP 3-Pip (SnAP 3-Methyl Piperazine)**

**tert-Butyl (2-((triisopropylsilyl)oxy)propyl)carbamate 151.** Imidazole (1.94 g, 28.5 mmol, 2.00 equiv) was added in one portion to a solution of tert-butyl (2-hydroxypropyl)carbamate (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 TIPSCI (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 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 (cyclohexane/EtOAc 25:1) afforded the desired product 151 (4.03 g, 85% yield) as clear, pale yellow liquid.

**IR** (thin film): ν 3461, 3368, 2965, 2943, 2893, 2868, 1721, 1709, 1506, 1464, 1366, 1174, 1124, 1070 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 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); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 156.3, 79.2, 67.9, 48.2, 28.6, 21.4, 18.3, 18.2, 12.6; R$_f$ = 0.35 (cyclohexane/EtOAc 20:1); ESI-HRMS calcd for C$_{17}$H$_{37}$N$_1$Na$_1$O$_3$Si$_1$ [M + Na] 354.2435, found 354.2435.

**tert-Butyl (2-((tributylstannyl)methyl)(2-((triisopropylsilyl)oxy)propyl)carbamate 152.** 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 151 (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 (139; 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 NH$_4$Cl (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 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 (cyclohexane/EtOAc 100:0
to 96:4) afforded the alkylated product 152 (1.85 g, 97% yield, rotamers 7:3) as clear, colorless liquid. IR (thin film): ν 2956, 2925, 2868, 1678, 1464, 1365, 1164, 1136 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 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; R\(_f\) = 0.49 (cyclohexane/EtOAc 20:1); ESI-HRMS calcd for C\(_{30}\)H\(_{65}\)N\(_1\)Na\(_1\)O\(_3\)Si\(_1\)Sn\(_1\) [M + Na] 658.3653, found 658.3652.

tert-Butyl (2-(1,3-dioxoisindolin-2-yl)propyl)((tributylstannyl)methyl)carbamate 154. 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 152 (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 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 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 triisopropylsilyl and to afford the desired alcohol 153 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 alcohol 153, triphenylphosphine (713 mg, 2.72 mmol, 1.15 equiv), and phthalimide (400 mg, 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 (cyclohexane/EtOAc 25:1) afforded the phthalimide protected SnAP 3Me-Pip 154 (1.19 g, 83% yield, 2 steps, rotamers 3:1) as pale yellow oil. IR (thin film): ν 2955, 2923, 2871, 2853, 1712, 1678, 1394, 1380, 1365, 1161 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ
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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; \( R_f = 0.43 \) (cyclohexane/EtOAc 10:1);

ESI-HRMS calcd for \( C_{29}H_{48}N_2NaO_4Sn_1 \) [M + Na] 631.2534, found 631.2531.

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\text{SnAP 3Me-Pip} \quad \text{(SnAP 3-Methyl-Piperazine) 62. The phthalimide protected SnAP 3Me-Pip 154 (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 \( \text{H}_2\text{O} \) (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 \( \text{Na}_2\text{SO}_4 \), filtered, and concentrated under reduced pressure to afford pure SnAP 3Me-Pip 62 (471 mg, 98% yield, rotamers 2:1) as colorless oil. IR (thin film): \( \nu \) 2956, 2924, 2871, 1676, 1457, 1365, 1163 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 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; ESI-HRMS calcd for \( C_{21}H_{47}N_2O_2Sn_1 \) [M + H] 479.2658, found 479.2655.

3.5.2. Preparation of substituted morpholines and piperazines

All the substituted morpholines and piperazines were prepared according to the General Procedure described in Part III Section 3.2.

\[ \text{3-Phenylmorpholine 63} \quad \text{\(^1\)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, \( J = 10.1, 3.2 \text{ Hz, 1H} \)), 3.91–3.85 (m, 1H), 3.82 (dd, \( J = 11.1, 3.2 \text{ Hz, 1H} \)), 3.66 (td, \( J = 11.1, 2.7 \text{ Hz, 1H} \)), 3.40 (dd, \( J = 11.1, 10.1 \text{ Hz, 1H} \)), 3.13 (td, \( J = 11.7, 3.2 \text{ Hz, 1H} \)), 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.}^{26}

3-(4-Methoxyphenyl)morpholine 64. IR (thin film): $\nu$ 3319, 2955, 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, $J = 10.2, 3.2$ Hz, 1H), 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, NfH); $^{13}$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 (cyclohexane/EtOAc/MeOH 10:10:1); m.p. = 54–55 °C; ESI-HRMS calcd for C$_{11}$H$_{16}$N$_1$O$_2$ [M + H] 194.1176, found 194.1179.

Methyl 4-(morpholin-3-yl)benzoate 65. 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 (cyclohexane/EtOAc 1:2); m.p. = 69–70 °C; ESI-HRMS calcd for C$_{12}$H$_{16}$N$_1$O$_3$ [M + H] 222.1125, found 222.1128.

3-(3-Bromophenyl)morpholine 66. IR (thin film): $\nu$ 3316, 2957, 2850, 1594, 1567, 1474, 1448, 1424, 1105, 782 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.58 (dd, $J = 1.8, 1.8$ Hz, 1H), 7.42–7.39 (m, 1H), 7.30 (d, $J = 7.8$ Hz, 1H), 7.19 (d, $J = 7.8, 7.8$ Hz, 1H), 3.88 (td, $J = 10.0, 3.2$ Hz, 2H), 3.80 (dd, $J = 11.0, 3.2$ Hz, 1H), 3.64 (td, $J = 11.0, 2.7$ Hz, 1H), 3.34 (dd, $J = 11.0, 10.0$ Hz, 1H), 3.11 (td, $J = 11.5, 3.2$ Hz, 1H), 3.02–2.96 (m, 1H), 1.75 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 143.1, 131.0, 130.4, 130.2, 126.0, 122.8, 73.6, 67.3, 60.1, 46.5; R$_f$ = 0.35 (CH$_2$Cl$_2$/EtOAc 1:1); ESI-HRMS calcd for C$_{10}$H$_{13}$Br$_1$N$_1$O$_1$ [M + H] 242.0175, found 242.0181.

3-(Benzo[b]thiophen-3-yl)morpholine 68. 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, 2H).
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 (cyclohexane/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.

3-(Pyridin-4-yl)morpholine 69. $^1$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, Hz, 1H), 2.05 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 150.2, 149.2, 149.2, 122.3, 73.0, 67.3, 59.5, 46.1. These spectral characteristics were identical to those previously reported.\(^\text{27}\)

tert-Butyl 4-(morpholin-3-yl)piperidine-1-carboxylate 70. 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.

3-(Bicyclo[2.2.1]hept-5-en-2-yl)morpholine 71. Mixture of diastereomers. IR (thin film): $\nu$ 3333, 3057, 2959, 2849, 1448, 1332, 1311, 1105, 775 cm$^{-1}$; $^1$H NMR of major diastereomer (400 MHz, CDCl$_3$): $\delta$ 6.18 (dd, J = 5.7, 2.9 Hz, 1H), 5.94 (dd, J = 5.7, 2.9 Hz, 1H), 3.92 (dd, J = 11.5, 3.1 Hz, 1H), 3.83–3.76 (m, 1H), 3.60–3.52 (m, 1H), 3.32 (dd, J = 11.5, 10.0 Hz, 1H), 2.95–2.75 (m, 4H), 2.51 (br s, NH), 2.25 (td, J = 10.0, 3.1 Hz, 1H), 2.04–1.93 (m, 1H), 1.92–1.82 (m, 1H), 1.46–1.40 (m, 1H), 1.26–1.19 (m, 1H), 0.91–0.80 (m, 1H); $^{13}$C NMR of major diastereomer (100 MHz, CDCl$_3$): $\delta$ 138.3, 131.7, 71.5, 67.1,

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59.7, 49.7, 46.0, 43.6, 42.2, 41.5, 29.7; R_f = 0.43 (CH_2Cl_2/MeOH 13:1); ESI-HRMS calcd for C_{11}H_{18}N_3O_1 [M + H] 180.1310, found 180.1393.

**Ethyl morpholine-3-carboxylate 72.** IR (thin film): ν 3418, 2982, 2863, 1732, 1457, 1373, 1208, 1102, 856 cm^{-1}; ^1H 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 (s, 1H), 1.27 (t, J = 7.1 Hz, 3H); ^13C NMR (100 MHz, CDCl_3): δ 171.4, 68.6, 63.8, 61.3, 57.0, 44.4, 14.3; R_f = 0.30 (cyclohexane/EtOAc/MeOH 10:10:1); ESI-HRMS calcd for C_7H_14N_1O_3 [M + H] 160.0968, found 160.0970.

**tert-Butyl 3-(4-(trifluoromethyl)phenyl)piperazine-1-carboxylate 73.** IR (thin film): ν 3317, 2978, 2939, 2857, 2812, 1685, 1620, 1418, 1327, 1167, 1125, 1067 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): 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, CDCl_3): 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 (cyclohexane/EtOAc/MeOH 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-(2-chloro-4-fluorophenyl)piperazine-1-carboxylate 74.** IR (thin film): ν 3315, 2976, 2928, 2858, 1693, 1490, 1419, 1168, 1127 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): 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, CDCl_3): 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; R_f = 0.18 (cyclohexane/TBME 1:1); ESI-HRMS calcd for C_{15}H_{21}ClF_3N_2O_2 [M + H] 315.1270, found 315.1271.
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**tert-Butyl 3-(4-methoxyphenyl)piperazine-1-carboxylate** 75. IR (thin film): ν 3321, 2974, 2931, 2834, 1692, 1514, 1417, 1248, 1171 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) : δ 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); \(^1^\)C NMR (100 MHz, CDCl\(_3\)) : δ 159.3, 154.9, 133.9, 128.2, 114.0, 79.8, 59.8, 55.4, 51.3, 46.3, 44.0, 28.6; R\(_f\) = 0.17 (cyclohexane/EtOAc 1:1); m.p. = 121–123 °C; ESI-HRMS calcd for C\(_{16}\)H\(_{25}\)N\(_2\)O\(_3\) [M + H] 293.1860, found 293.1863.

**tert-Butyl 3-(benzo[d][1,3]dioxol-5-yl)piperazine-1-carboxylate** 76. IR (thin film): ν 3324, 2975, 2897, 2817, 1691, 1489, 1419, 1251, 1171, 1126, 1038 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) : δ 6.92 (d, J = 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); \(^1^\)C NMR (100 MHz, CDCl\(_3\)) : δ 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 (cyclohexane/EtOAc 1:1); m.p. = 150–152 °C; ESI-HRMS calcd for C\(_{16}\)H\(_{23}\)N\(_2\)O\(_4\) [M + H] 307.1652, found 307.1656.

**tert-Butyl 3-(furan-3-yl)piperazine-1-carboxylate** 77. IR (thin film): ν 3320, 2976, 2929, 2859, 1690, 1420, 1249, 1168, 1124 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) : 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 = 10.2, 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); \(^1^\)C NMR (100 MHz, CDCl\(_3\)) : δ 154.8, 143.3, 139.3, 126.0, 109.1, 80.0, 51.9, 50.2, 45.7, 44.1, 28.6; R\(_f\) = 0.16 (cyclohexane/EtOAc 1:1); m.p. = 97–98 °C; ESI-HRMS calcd for C\(_{13}\)H\(_{21}\)N\(_2\)O\(_3\) [M + H] 253.1547, found 253.1553.

**tert-Butyl 3-(1H-indol-3-yl)piperazine-1-carboxylate** 78. IR (thin film): ν 3298, 2977, 2928, 2860, 1671, 1456, 1424, 1248, 1170, 1127 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) : δ 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,
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1H), 4.08 (br s, 1H), 3.18–2.86 (m, 4H), 1.81 (br s, NH), 1.49 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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; R$_f$ = 0.19 (CH$_2$Cl$_2$/MeOH 95:5); ESI-HRMS calcd for C$_{17}$H$_{24}$N$_3$O$_2$ [M + H] 302.1863, found 302.1864.

**tert-Butyl 3-(1-methyl-1H-pyrazol-4-yl)piperazine-1-carboxylate 79.** IR (thin film): $\nu$ 3421, 3299, 2976, 2932, 2860, 1684, 1419, 1250, 1167 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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), 2.76 (br s, 1H), 1.99 (br s, NH), 1.45 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.8, 137.5, 128.0, 122.5, 79.9, 51.5, 50.8, 45.7, 44.0, 39.1, 28.5; R$_f$ = 0.15 (CH$_2$Cl$_2$/MeOH 95:5); ESI-HRMS calcd for C$_{13}$H$_{23}$N$_4$O$_2$ [M + H] 267.1816, found 267.1820.

1-(tert-Butyl) 3-ethylpiperazine-1,3-dicarboxylate 80. IR (thin film): $\nu$ 3553, 3341, 2978, 2931, 2865, 1738, 1698, 1421, 1366, 1250, 1168 cm$^{-1}$; $^1$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; R$_f$ = 0.17 (cyclohexane/EtOAc 1:1); ESI-HRMS calcd for C$_{12}$H$_{22}$N$_4$Na$_1$O$_4$ [M + Na] 281.1472, found 281.1476.

**tert-Butyl 3-(tert-butyl)piperazine-1-carboxylate 81.** IR (thin film): $\nu$ 2964, 2869, 1696, 1419, 1365, 1246, 1173 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.2, 79.6, 64.3, 46.5, 44.9, 44.2, 32.8, 28.6, 26.6; R$_f$ = 0.21 (cyclohexane/TBME 4:1); ESI-HRMS calcd for C$_{13}$H$_{27}$N$_2$O$_2$ [M + H] 243.2067, found 243.2072.

**tert-Butyl 3-cyclopropylpiperazine-1-carboxylate 82.** IR (thin film): $\nu$ 3448, 3297, 3081, 2978, 2931, 2861, 1696, 1421, 1267, 1177 cm$^{-1}$; $^1$H NMR (400 MHz,
CDCl$_3$: $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.0, 79.7, 60.8, 45.9, 28.6, 14.5, 2.8, 2.2; $R_f = 0.19$ (CH$_2$Cl$_2$/MeOH 95:5); ESI-HRMS calcd for C$_{12}$H$_{22}$N$_2$NaO$_2$ [M + Na] 249.1573, found 249.1579.

**trans-N,N-Dimethyl-4-(6-methylmorpholin-3-yl)aniline** 83. Diastereomeric ratio of $\geq 5:1$. IR (thin film): $\nu$ 2967, 2929, 2889, 2849, 2802, 1615, 1523, 1336, 1098 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 150.4, 128.2, 128.1, 112.7, 74.0, 72.3, 59.5, 53.5, 40.8, 19.1; $R_f = 0.31$ (CH$_2$Cl$_2$/MeOH 95:5); ESI-HRMS calcd for C$_{13}$H$_{21}$N$_2$O$_1$ [M + H] 221.1648, found 221.1654.

**Figure 5.**

**trans-Ethyl 6-methylmorpholine-3-carboxylate** 84. Diastereomeric ratio of $> 10:1$. IR (thin film): $\nu$ 3565, 3460, 3329, 2977, 2936, 2904, 2858, 1739, 1448, 1372, 1285, 1197, 1105, 1042 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.6, 72.6, 69.1, 61.2, 57.0, 51.7, 18.7, 14.2; $R_f = 0.20$ (cyclohexane/EtOAc 1:2); ESI-HRMS calcd for C$_{9}$H$_{16}$N$_1$O$_3$ [M + H] 174.1125, found 174.1133.
**cis-Ethyl 5-methylmorpholine-3-carboxylate 85.** Diastereomeric ratio of ≥ 5:1. IR (thin film): ν 3586, 3460, 3327, 2966, 2851, 1738, 1458, 1379, 1284, 1209, 1103, 1027 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 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); ¹³C NMR (100 MHz, CDCl₃): δ 170.4, 73.2, 68.2, 61.2, 57.7, 50.0, 17.5, 14.2; Rf = 0.25 (cyclohexane/EtOAc 1:2); EI-HRMS calcd for C₈H₁₅N₁O₃ [M] 173.1052, found 173.1051.

**cis-3-Methyl-5-(quinolin-4-yl)morpholine 86.** Diastereomeric ratio of > 10:1. IR (thin film): ν 3388, 3299, 3063, 2967, 2847, 1590, 1509, 1328, 1101 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 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; Rf = 0.17 (cyclohexane/EtOAc 1:2); ESI-HRMS calcd for C₁₄H₁₇N₂O₁ [M] 229.1335, found 229.1334.

**tert-Butyl 2-methyl-5-(o-tolyl)piperazine-1-carboxylate 87.** Diastereomeric ratio of 5:1. Cis diastereomer: IR (thin film): ν 3502, 2974, 2932, 2868, 2822, 1691, 1412, 1171 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 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 = 11.5, 3.6 Hz, 1H), 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); ¹³C NMR (100 MHz, CDCl₃): 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, 47.1, 45.9, 45.7, 44.4, 28.6, 19.3, 19.2, 15.5, 15.2; Rf = 0.59 (cyclohexane/EtOAc 1:1); ESI-HRMS calcd for C₁₇H₂₇N₂O₂ [M + H] 291.2067, found 291.2074. trans diastereomer: IR (thin film): ν 2971, 2927, 2868, 1685, 1411, 1456, 1162 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 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); ¹³C NMR (100 MHz, CDCl₃): 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 (cyclohexane/EtOAc 1:1); ESI-HRMS calcd for C_{17}H_{27}N_{2}O_{2} [M + H] 291.2067, found 291.2074.

**Figure 6.**

**tert-Butyl 5-(4-(1H-1,2,4-triazol-1-yl)phenyl)-2-methylpiperazine-1-carboxylate 88.** Diastereomeric ratio of 8:3. **Cis diastereomer:** IR (thin film): ν 3433, 2976, 2931, 1681, 1523, 1410, 1170 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.54 (s, 1H), 8.08 (s, 1H), 7.64 (d, J = 7.6 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 4.34 (br s, 1H × 0.45), 4.20 (br s, 1H × 0.55), 3.99 (d, J = 11.5 Hz, 1H × 0.55), 3.80 (d, J = 12.0 Hz, 1H × 0.45), 3.73 (d, J = 9.5 Hz, 1H), 3.07 (dd, J = 11.5, 3.7 Hz, 1H), 2.98–2.74 (m, 2H), 1.71 (br s, NH), 1.46 (s, 9H), 1.32 (d, J = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 155.0, 154.6, 152.7, 142.3, 141.0, 136.5, 128.5, 120.2, 79.8, 60.3, 60.1, 50.6, 46.9, 45.6, 28.6, 15.4, 15.0; R_f = 0.22 (EtOAc/MeOH 99:1); ESI-HRMS calcd for C_{18}H_{25}N_{5}Na_{1}O_{2} [M + Na] 366.1900, found 366.1905. **trans diastereomer:** IR (thin film): ν 3421, 2976, 1647, 1523, 1417, 1162 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.54 (s, 1H), 8.10 (s, 1H), 7.66–7.58 (m, 4H), 4.23 (dd, J = 14.0, 2.2 Hz, 1H), 4.17–3.96 (m, 2H), 3.49 (dd, J = 14.0, 4.2 Hz, 1H), 2.95 (br d, J = 9.7 Hz, 1H), 2.54 (dd, J = 13.0, 2.6 Hz, 1H), 1.95 (br s, NH), 1.46 (s, 9H), 1.28 (d, J = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 155.0, 152.7, 142.0, 135.9, 129.0, 120.1, 80.0, 54.2, 47.4, 45.0, 41.7, 28.6, 15.7; R_f = 0.11 (EtOAc/MeOH 99:1); ESI-HRMS calcd for C_{18}H_{25}N_{5}Na_{1}O_{2} [M + Na] 366.1900, found 366.1899.

**1-(tert-Butyl) 3-ethyl 6-methylpiperazine-1,3-dicarboxylate 89.** Diastereomeric ratio of 3:2. **Major diastereomer:** IR (thin film): ν 3353, 2976,
2931, 1733, 1415, 1167, 1094 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 172.9, 154.7, 79.7, 61.2, 55.6, 46.5, 46.2, 39.3, 28.5, 15.1, 14.4; \(R_f = 0.15\) (cyclohexane/EtOAc 1:2); ESI-HRMS calcd for \(\text{C}_{13}\text{H}_{25}\text{N}_{2}\text{O}_{4}\) [M + H] 273.1809, found 273.1815. **Minor diastereomer:** IR (thin film): \(\nu\) 3343, 2976, 2932, 1740, 1693, 1409, 1168 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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), 1.19 (d, \(J = 6.8\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 171.1, 154.9, 80.0, 61.3, 57.8, 49.6, 46.2, 41.1, 28.5, 14.9, 14.3; \(R_f = 0.30\) (cyclohexane/EtOAc 1:2); ESI-HRMS calcd for \(\text{C}_{13}\text{H}_{25}\text{N}_{2}\text{O}_{4}\) [M + H] 273.1809, found 273.1817.

cis-\(\text{tert-Butyl}\) 3-methyl-5-(pyridin-3-yl)piperazine-1-carboxylate 90.

Diastereomeric ratio of > 10:1. IR (thin film): \(\nu\) 3420, 2975, 2868, 1652, 1522, 1408, 1169, 1049 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 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 \(\text{C}_{15}\text{H}_{24}\text{N}_{3}\text{O}_{2}\) [M + H] 278.1863, found 278.1867.

cis-\(1-(\text{tert-Butyl})\) 3-ethyl 5-methylpiperazine-1,3-dicarboxylate 91.

Diastereomeric ratio of > 10:1. IR (thin film): \(\nu\) 3446, 2977, 2932, 2872, 1739, 1697, 1420, 1267, 1165, 1136 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 170.7, 154.6, 80.2, 61.3, 57.6, 50.4, 50.2, 45.6, 28.5, 19.2, 14.3; \(R_f = 0.36\) (cyclohexane/EtOAc 1:1); ESI-HRMS calcd for \(\text{C}_{13}\text{H}_{25}\text{N}_{2}\text{O}_{4}\) [M + H] 273.1809, found 273.1816.
Part III. Experiment Procedures and Characterization Data

**cis-tert-Butyl 3-cyclopropyl-5-methylpiperazine-1-carboxylate** 92.

Diastereomeric ratio of > 10:1, colorless oil. IR (thin film): ν 3502, 3311, 3080, 3005, 2974, 2930, 2855, 1692, 1422, 1264, 1239, 1173, 1132 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.26–3.65 (m, 2H), 2.70–2.60 (m, 1H), 2.52 (br s, 1H), 2.33 (br s, 1H), 1.86–1.69 (m, 2H), 1.43 (s, 9H), 1.04 (d, J = 6.3 Hz, 3H), 0.74–0.63 (m, 1H), 0.53–0.42 (m, 2H), 0.27–0.17 (m, 1H), 0.17–0.10 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 154.8, 79.6, 61.2, 50.8, 50.0–48.2 (m), 28.6, 19.5, 14.4, 2.7, 2.1; Rᵣ = 0.25 (EtOAc/MeOH 20:1); ESI-HRMS calcd for C₁₃H₂₅N₂O₂ [M + H] 241.1911, found 241.1916.

3.6. One-step Synthesis of Medium Ring Saturated N-Heterocycles

3.6.1. Preparation of SnAP reagents

**SnAP OA** (SnAP 1,4-Oxazepane) and **SnAP OAC** (SnAP 1,4-Oxazocane)

3-(Tributylstannyl)methoxypropan-1-ol 155. 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 (139; 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 155 (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; ESI-HRMS calcd for C₁₆H₃₆O₂Na₁Sn₁ [M + Na] 403.1632, found 403.1635.

2-(3-((Tributylstannyl)methoxy)propyl)isoindoline-1,3-dione 156.

To a solution of 155 (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 (20 mL), brine (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 156 (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; ESI-HRMS calcd for C_{24}H_{39}N_{1}Na_{1}O_{3}Sn_{1} [M + Na] 532.1848, found 532.1854.

SnAP OA (SnAP 1,4-Oxazepane) 93. To a solution of 156 (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 CH_{2}Cl_{2} and filtered over Celite. The organic filtrate was concentrated under reduced pressure to afford pure SnAP OA 93 in quantitative yield (860 mg) as clear, colorless liquid. IR (thin film): ν 2955, 2924, 2870, 2853, 1576, 1463, 1375, 1338, 1089 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 3.70 (s, J\(^{117/119}\)Sn-\(^1\)H) = 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); \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 73.9, 62.2, 40.1, 33.8, 29.3, 27.4, 13.9, 9.2; ESI-HRMS calcd for C_{16}H_{38}N_{1}O_{1}Sn_{1} [M + H] 380.1972, found 380.1975.

SnAP OAC (SnAP 1,4-Oxazocane)

4-((Tributylstannyl)methoxy)butan-1-ol 157. 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 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 (139; 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 H\(_2\)O (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H\(_2\)O (20 mL), brine (20 mL), dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. Purification by flash column chromatography (pentane/EtOAc 10:1 to 5:1) afforded 157 (7.64 g, 97% yield) as clear, colorless liquid. IR (thin film): ν 3357, 2954, 2924, 1462, 1375, 1085, 1069, 958, 873 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 3.72 (s,
$J^{(117\text{a}119)}\text{Sn-H)} = 7.2 \text{ Hz, 2H}, 3.66-3.57 \text{ (m, 2H), 3.37 (t, } J = 5.0 \text{ Hz, 2H), 2.47 (t, } J = 5.8 \text{ Hz, 1H), 1.65 (d, } J = 5.0 \text{ Hz, 4H), 1.59-1.40 \text{ (m, 6H), 1.39-1.22 \text{ (m, 6H), 1.02-0.70 \text{ (m, 15H); }}^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta 75.9, 62.9, 62.3, 30.7, 29.3, 27.4, 27.2, 13.9, 9.1; \text{ ESI-HRMS calcd for C}_{17}\text{H}_{38}\text{Na}_1\text{O}_2\text{Sn}_1\text{ [M + Na] 417.1789, found 417.1776.}$

**2-(4-((Tributylstannyl)methoxy)butyl)isoindoline-1,3-dione 158.**

To a solution of 157 (7.64 g, 19.4 mmol, 1.00 equiv) in Et$_2$O (100 mL) was added Et$_3$N (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 H$_2$O (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H$_2$O (2 x 20 mL), brine (20 mL), dried over anhydrous Na$_2$SO$_4$, 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 H$_2$O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H$_2$O (3 x 50 mL), brine (2 x 50 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (pentane/EtOAc 20:1) afforded 158 (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$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 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); $^{13}$C NMR (100 MHz, CDCl$_3$): 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; ESI-HRMS calcd for C$_{25}$H$_{41}$N$_3$Na$_1$O$_3$Sn$_1$ [M + Na] 546.0205, found 546.0208.

**SnAP OAC (SnAP 1,4-Oxazocane) 99.** To a solution of 158 (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
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 obtain pure SnAP OAC 99 in quantitative yield (1.10 g) as clear, colorless liquid. IR (thin film): ν 3330, 2955, 2869, 2853, 1574, 1463, 1376, 1317, 1087, 873 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.71 (s, J(¹¹⁷/¹¹⁹Sn-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 C₁₇H₄₀N₂O₂Sn₁ [M + H] 394.2129, found 394.2130.

SnAP PhOA (SnAP 3-Phenyl 1,4-oxazepane)

1-Phenyl-3-(((tributylstannyl)methoxy)propan-1-amine 94. 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 3-amino-3-phenylpropan-1-ol (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 (139; 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 NH₄Cl (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 (2 x 10 mL), brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc 4:1 + 0.1% Et₃N v/v) afforded the pure SnAP PhOA 94 (1.26 g, 76% yield) as clear, pale yellow liquid. IR (thin film): ν 3384, 2955, 2925, 2870, 1455, 1376, 1087 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.28 (m, 4H), 7.26-7.20 (m, 1H), 7.26-7.20 (m, 1H), 4.07 (dd, J = 7.3, 6.3 Hz, 1H), 3.68 (s, J(¹¹⁷/¹¹⁹Sn-¹H) = 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, NH₂), 1.60-1.42 (m, 6H), 1.35-1.26 (m, 6H), 0.96-0.81 (m,
15H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 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$_{22}$H$_{42}$N$_1$O$_1$Sn$_1$ [M + H] 456.2287, found 456.2300.

**SnAP BOA (SnAP 2,3,4,5-Tetrahydro-1,4-benzoxazepine)**

**SnAP BOAN (SnAP 2,3,4,5,6,7-Hexahydrobenzo[h][1,4]oxazonine)**

SnAP BOA (SnAP 2,3,4,5-Tetrahydro-1,4-benzoxazepine)

A solution of 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 iodide 139 (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 x 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 (cyclohexane/EtOAc 30:1) afforded 159 (3.56 g, 69% yield) as clear, colorless liquid. IR (thin film): ν 3366, 2955, 2925, 2871, 2852, 1603, 1588, 1617, 1502 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(117/119Sn-1H) = 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, 159.4, 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$_{38}$Na$_1$O$_2$Sn$_1$ [M + Na] 451.1633, found 451.1630.
2-(2-(Tributylstannyl)methoxy)benzyl)isoindoline-1,3-dione 160. Diisopropyl azodicarboxylate (1.14 mL, 5.81 mmol, 1.00 equiv) was added dropwise over 10 min to a solution of benzyl alcohol 159 (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 NaHCO₃ (2 x 20 mL), brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc 20:1) afforded the phthalimide protected SnAP BOA 160 (2.13 g, 66% yield) as clear, colorless liquid. IR (thin film): ν 2955, 2925, 2871, 2851, 1773, 1719, 1391 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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(¹¹⁷/¹¹⁹Sn-¹H) = 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); ¹³C NMR (100 MHz, CDCl₃): 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, 13.9, 9.4; ESI-HRMS calcd for C₂₈H₃₉N₁Na₁O₃Sn₁ [M + Na] 580.1849, found 580.1836.

SnAP BOA (SnAP 2,3,4,5-Tetrahydro-1,4-benzoazepine) 95. Phthalimide protected SnAP BOA 160 (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 95 (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, J(¹¹⁷/¹¹⁹Sn⁻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.

SnAP BOAN (SnAP 2,3,4,5,6,7-Hexahydrobenzo[h][1,4]oxazonine)

3-(2-((Tributylstannyl)methoxy)phenyl)propan-1-ol 161.

Tributyl(iodomethyl) stannane (139; 1.38 g, 3.21 mmol, 1.05 equiv) in acetone (3 mL) was added dropwise over 5 min to a suspension of 2-(3-hydroxypropyl)phenol (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 (cyclohexane/EtOAc 15:1) afforded 161 (1.24 g, 89% yield) as clear, colorless liquid. IR (thin film): δ 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, J⁽¹¹⁷/¹¹⁹Sn⁻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, CDCl₃): δ 159.6, 130.0, 129.9, 127.2, 120.2, 110.5, 62.5, 58.4, 33.0, 29.2, 27.5, 26.4, 13.8, 9.3; ESI-HRMS calcd for C₂₂H₄₆Na₁O₂Sn₁ [M + Na] 479.1946, found 479.1946.

2-(3-((Tributylstannyl)methoxy)phenyl)propyl)isoindoline-1,3-dione 162. Diisopropyl azodicarboxylate (450 µL, 2.22 mmol, 1.05 equiv) was added dropwise over 15 min to a clear, colorless solution of alcohol 161 (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 H₂O (2 x 10 mL) and brine (15 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and
concentrated to yield colorless oil. Purification by flash column chromatography (cyclohexane/EtOAc 25:1) afforded the phthalimide protected SnAP BOAN 162 (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-\(^1\)H) = 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\(_1\)O\(_3\)Sn\(_1\) [M + Na] 608.2163, found 608.2169.

SnAP BOAN (SnAP 2,3,4,5,6,7-Hexahydrobenzo[h][1,4]oxazonine) 101.

Phthalimide protected SnAP BOAN 162 (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 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 BOAN 101 (855 mg, 100% yield) as colorless oil. IR (thin film): ν 3372, 3297, 2955, 2925, 2871, 2852, 1600, 1715, 1489, 1455, 1207, 1002 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): 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, J\(^{117/119}\)Sn-\(^1\)H) = 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); \(^13\)C NMR (100 MHz, CDCl\(_3\)): 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 C\(_{22}\)H\(_{42}\)N\(_1\)O\(_3\)Sn\(_1\) [M + H] 456.2287, found 456.2287.
**SnAP DA (SnAP 1,4-Diazepane)**

**tert-Butyl (3-chloropropyl)((tributylstannyl)methyl)carbamate 163.**

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 (139; 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 (cyclohexane/EtOAc 100:0 to 98:2) afforded the alkylated product 163 (rotomers 1:2 by ¹H NMR integration) (554 mg, 54% yield) as clear, colorless liquid. IR (thin film): ν 2956, 2923, 2871, 2853, 1679, 1365, 1162 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.61-3.46 (m, 2H), 3.46-3.15 (m, 2H), 3.12-3.00 (s, 2H × 0.33), 2.82 (s, J(¹¹⁷/¹¹⁹Sn-¹H) = 25.8 Hz, 2H × 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); ¹³C NMR (100 MHz, CDCl₃): δ 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; Rᶠ = 0.59 (cyclohexane/EtOAc 10:1); ESI-HRMS calcd for C₂₄H₄₄Cl₁N₁Na₁O₂Sn₁ [M + Na] 520.1972, found 520.1976.

**tert-Butyl (3-(1,3-dioxoisooindolin-2-yl)propyl)((tributylstannyl)methyl) carbamate 164.** Chloride 163 (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 (cyclohexane/EtOAc 15:1) afforded the phthalimide protected SnAP DA 164 (rotamers 3:7 by $^1$H NMR integration, 397 mg, 81% yield) as clear, colorless liquid. IR (thin film): ν 2955, 2924, 2871, 2853, 1773, 1716, 1679, 1395, 1161 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 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 × 0.30), 2.81 (s, J($^{117/119}$Sn-$^1$H) = 26.2 Hz, 2H × 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$_3$): δ 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.

SnAP DA (SnAP 1,4-Diazepane) 96. Phthalimide protected SnAP DA 164 (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 96 (rotamers 3:5 by $^1$H NMR integration, 1.02 g, 95% yield) as colorless oil. IR (thin film): ν 3370, 2956, 2924, 2871, 2853, 1677, 1578, 1481, 1467, 1163 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 3.28-3.20 (m, 2H), 3.01 (s, 2H × 0.38), 2.78 (s, J($^{117/119}$Sn-$^1$H) = 26.2 Hz, 2H × 0.62), 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$_3$): δ 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$_{43}$N$_2$O$_2$Sn$_1$ [M + H] 479.2658, found 479.2662.
Part III. Experiment Procedures and Characterization Data

SnAP BDA (SnAP 2,3,4,5-Tetrahydro-1,4-benzodiazepine)

**tert-Butyl (2-(hydroxymethyl)phenyl)carbamate 165.**

To a solution of (Boc)_2O (2.27 g, 10.4 mmol, 1.04 equiv) in THF (20 mL) was added 2-aminobenzyl alcohol (1.26 g, 10.0 mmol, 1.00 equiv) in one portion at rt. The reaction mixture was stirred at 40 °C for 15 h. The solvent was removed under reduced pressure. Purification by flash column chromatography (pentane/EtOAc 9:1 to 6:1) afforded 165 (2.69 g, 97% yield) as clear, colorless liquid. ^1H NMR (400 MHz, CDCl₃): δ 7.92 (d, J = 7.8 Hz, 1H), 7.61 (s, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 4.70 (d, J = 6.0 Hz, 2H), 1.97 (t, J = 6.0 Hz, 1H), 1.53 (s, 9H); ^13C NMR (100 MHz, CDCl₃): δ 153.5, 138.2, 129.4, 129.0, 129.1, 123.3, 121.3, 80.6, 64.5, 28.5. The spectral data were consistent with the previous report. ^28

**tert-Butyl (2-((triisopropylsilyl)oxy)methyl)phenyl)carbamate 166.**

To a solution of 165 (2.27 g, 9.56 mmol, 1.00 equiv) in CH₂Cl₂ (48 mL) at 0 °C was added imidazole (976 mg, 14.34 mmol, 1.50 equiv), followed by the slow addition of TIPSCI (2.31 mL, 10.52 mmol, 1.10 equiv). The reaction mixture was stirred at 40 °C for 15 h before slowly quenched with H₂O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H₂O (30 mL), brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (pentane/EtOAc 30:1) afforded 166 (3.35 g, 92% yield) as clear, colorless liquid. IR (thin film): ν 3363, 2942, 2866, 1732, 1592, 1529, 1452, 1233, 1161, 1056, 881, 790 cm⁻¹; ^1H NMR (400 MHz, CDCl₃): δ 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); 13C NMR (100 MHz, CDCl3): δ 153.2, 138.9, 128.8, 128.0, 127.9, 122.2, 119.7, 79.9, 66.0, 28.5, 18.1, 11.9; ESI-HRMS calcd for C21H37N1Na1O3Si1 [M + Na] 402.2435, found 402.2426.

*tert-Butyl* ((tributylstannyl)methyl)(2(((triisopropylsilyl)oxy)methyl)phenyl) carbamate 167. 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 166 (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 (139; 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 167 (1.63 g, 91% yield) as clear, colorless liquid.

IR (thin film): ν 2956, 2923, 2867, 1682, 1461, 1365, 1162, 1108, 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, 61.3, 36.7, 29.3, 28.4, 27.6, 18.3, 13.8, 12.2, 11.0; ESI-HRMS calcd for C34H65N1Na1O3Si1Sn1 [M + Na] 706.3654, found 706.3650.

*tert-Butyl* (2-(hydroxymethyl)phenyl)((tributylstannyl)methyl)carbamate 168. To a solution of 167 (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 168 (rotamers, 1.20 g, 96% yield) as clear, colorless liquid.
liquid. IR (thin film): ν 3418, 2956, 2922, 2870, 1681, 1455, 1375, 1162, 1044, 995, 872, 761 \text{cm}^{-1}; ^1H NMR (500 MHz, CDCl$_3$): 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); $^{13}$C NMR (126 MHz, CDCl$_3$): 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 C$_{25}$H$_{45}$N$_3$Na$_2$O$_3$Sn$_1$ [M + Na] 550.2318, found 550.2321.

**tert-Butyl (2-((1,3-dioxoisindolin-2-yl)methyl)phenyl)((tributylstannyl)methyl) carbamate 169.** To a solution of 168 (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 equiv) 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 169 (1.32 g, 88% yield) as clear, colorless liquid. IR (thin film): ν 2955, 2922, 2870, 1774, 1720, 1680, 1390, 1366, 1159 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 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); $^{13}$C NMR (100 MHz, CDCl$_3$): 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 C$_{33}$H$_{48}$N$_2$Na$_2$O$_3$Sn$_1$ [M + Na] 679.2535, found 679.2524.

**SnAP BDA** (SnAP 2,3,4,5-Tetrahydro-1,4-benzodiazepine) 97. To a solution of phthalimide protected SnAP BDA 169 (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 CH$_2$Cl$_2$ and filtered over Celite. The organic filtrate was concentrated under reduce pressure to obtain pure SnAP BDA 97 in quantitative yield (315 mg) as clear, colorless liquid. IR (thin film): ν
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2955, 2921, 2870, 2853, 1681, 1455, 1417, 1161, 995, 872, 760 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{25}\)H\(_{47}\)N\(_2\)O\(_2\)Sn\(_1\) [M + H] 527.2658, found 527.2659.

**SnAP-DAC** (SnAP 1,4-Diazocane)

**tert-Butyl (4-((triisopropylsilyl)oxy)butyl)carbamate 170.** Imidazole (1.35 g, 19.8 mmol, 1.50 equiv) was added in one portion to a solution of tert-butyl N-(4-hydroxybutyl)carbamate (2.50 g, 13.2 mmol, 1.00 equiv) in CH\(_2\)Cl\(_2\) (66 mL) at rt. The resulting solution was cooled to 0 °C and treated with TIPSCI (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 CH\(_2\)Cl\(_2\) (50 mL), washed with sat aq NH\(_4\)Cl (2 x 15 mL), H\(_2\)O (15 mL), brine (20 mL), dried over Na\(_2\)SO\(_4\), filtered over a short plug of silica gel and concentrated to yield the desired product 170 next to triisopropylsilanol as impurity. 100 °C under high vacuum (ca. 0.1 mmHg) for 2 h afforded the pure 170 (3.88 g, 85% yield) as colorless oil. IR (thin film): \(\nu\) 3461, 2942, 2867, 1698, 1522, 1175, 1106 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 156.1, 79.0, 63.1, 40.6, 30.4, 28.6, 26.7, 18.2, 12.1; ESI-HRMS calcd for C\(_{18}\)H\(_{38}\)N\(_4\)Na\(_1\)O\(_3\)Si\(_1\) [M + Na] 368.2591, found 368.2597.

**tert-Butyl ((tributylstannyl)methyl)(4-((triisopropylsilyl)oxy)butyl)carbamate 171.** 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 a solution of 170 (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 iodide 139 (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 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 10 mL), brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc 50:1) afforded 171 (Rotamers 1:2 by ¹H NMR integration, 5.37 g, 97% yield) as clear, colorless liquid. IR (thin film): ν 2955, 2925, 2867, 1676, 1464, 1162, 1110 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.70 (t, J = 6.2 Hz, 2H), 3.24−3.12 (m, 2H), 3.04 (s, 2H × 0.33), 2.82 (s, J(¹¹⁷/¹¹⁹Sn−¹H) = 25.9 Hz, 2H × 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₃₁H₆₇N₁Na₁O₃Si₁Sn₁ [M + Na] 672.3809, found 672.3801.

**tert-Butyl**\(\text{((tributylstannyl)methyl)(4-((triisopropylsilyl)oxy)butyl)carbamate 172.}\) 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 171 (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/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 (cyclohexane/EtOAc 9:1) afforded 172 (rotamers 12:19 by ¹H NMR integration, 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 × 0.39), 2.81 (s, J(¹¹⁷/¹¹⁹Sn−¹H) = 25.7 Hz, 2H × 0.61), 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); $^{13}$C NMR (100 MHz, CDCl$_3$): 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 C$_{22}$H$_{47}$N$_3$Na$_1$O$_3$Sn$_1$ [M + Na] 516.2474, found 516.2475.

**tert-Butyl (4-(1,3-dioxoisindolin-2-yl)butyl)((tributylstannyl)methyl) carbamate 173.** Methanesulfonyl chloride (156 µL, 2.01 mmol, 1.10 equiv) was added dropwise over 5 min to a solution of 172 (900 mg, 1.83 mmol, 1.00 equiv) and Et$_3$N (510 µL, 3.66 mmol, 2.00 equiv) in Et$_2$O (9 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred for further 2 h before poured into H$_2$O (10 mL). The layers were separated and the aqueous layer was extracted with Et$_2$O (2 x 10 mL). The combined organic layers were washed with H$_2$O (2 x 5 mL), brine (10 mL), dried over Na$_2$SO$_4$, 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 H$_2$O (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 H$_2$O (3 x 20 mL), brine (2 x 20 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford yellow oil. Purification by flash column chromatography (cyclohexane/EtOAc 15:1) afforded the phthalimide protected SnAP DAC 173 (rotamers 1:2 by $^1$H NMR integration, 1.10 g, 97% yield, 2 steps) as clear, colorless liquid. IR (thin film): ν 2954, 2925, 2871, 2853, 1716, 1676, 1395, 1162 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 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 × 0.33), 2.78 (s, $J^{(117/119}Sn^{-1}$H) = 25.9 Hz, 2H × 0.66), 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); $^{13}$C NMR (100 MHz, CDCl$_3$): 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 C$_{30}$H$_{50}$N$_2$Na$_1$O$_4$Sn$_1$ [M + Na] 645.2690, found 645.2689.
SnAP DAC (SnAP 1,4-Diazocane) **98.** Phthalimide protected SnAP DAC **173** (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 **98** (rotamers ca. 1:2 by $^1$H NMR integration, 180 mg, 99% yield) as colorless oil. IR (thin film): $\nu$ 3308, 2955, 2924, 2871, 2854, 1676, 1481, 1464, 1162 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.21-3.09 (m, 2H), 3.02 (s, 2H $\times$ 0.33), 2.79 (s, $J$(Sn-$^1$H) = 26.0 Hz, 2H $\times$ 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$_3$): $\delta$ 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$_2$O$_2$Sn$_1$ [M + Na] 515.2634, found 515.2625.

SnAP BOAC (SnAP 1,3,4,6-Tetrahydro-5H-benz[f][2,5]oxazocine)

(2-(((Tributylstannyl)methoxy)methyl)phenyl)methanol **174.** 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. Iodide **139** (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 NH$_4$Cl (20 mL) and H$_2$O (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 H$_2$O (2 x 10 mL), brine (20
(2.90 g, 85% yield) as colorless liquid. IR (thin film): \(\nu\) 3419, 2954, 2923, 2870, 2852, 1456, 1039 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.40-7.27 (m, 4H), 4.64 (d, \(J = 6.4\) Hz, 2H), 4.52 (s, 2H), 3.77 (s, \(J(^{117/119}\text{Sn}{}^{-1}\text{H}) = 15.8\) 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 140.9, 136.5, 130.4, 129.8, 127.9, 77.3, 64.3, 62.0, 29.2, 27.4, 13.8, 9.1; ESI-HRMS calcd for C\(_{21}\)H\(_{38}\)Na\(_1\)O\(_2\)Sn\(_1\) [M + Na] 465.1789, found 465.1792.

2-(2-(((Tributylstannyl)methoxy)methyl)benzyl)isoindoline-1,3-dione

Potassium phthalimide (351 mg, 1.89 mmol, 1.10 equiv) was added in one portion to a solution of 174 (760 mg, 1.72 mmol, 1.00 equiv) and triethylamine (290 \(\mu\)L, 2.07 mmol, 1.20 equiv) in Et\(_2\)O (9 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred for further 2 h before poured into H\(_2\)O (10 mL). The layers were separated and the aqueous layer was extracted with Et\(_2\)O (2 x 10 mL). The combined organic layers were washed with H\(_2\)O (2 x 5 mL), brine (10 mL), dried over Na\(_2\)SO\(_4\), 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 H\(_2\)O (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 H\(_2\)O (3 x 20 mL), brine (2 x 20 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure to afford yellow oil. Purification by flash column chromatography (cyclohexane/TBME 10:1) afforded the phthalimide protected SnAP BOAC 175 (883 mg, 90% yield, 2 steps) as clear, colorless liquid. IR (thin film): \(\nu\) 2954, 2923, 2870, 2851, 1771, 1716, 1392 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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, \(J(^{117/119}\text{Sn}{}^{-1}\text{H}) = 15.8\) Hz, 2H), 1.55-1.43 (m, 6H), 1.29 (sext, \(J = 7.3\) Hz, 6H), 0.94-0.85 (m, 15H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C_{29}H_{41}N_1Na_1O_3Sn_1 [M + Na] 594.2006, found 594.2008.

**SnAP BOAC 100.** The phthalimide protected SnAP BOAC 175 (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 H_2O (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_2SO_4, filtered, and concentrated under reduced pressure to afford pure SnAP BOAC 100 (1.72 g, 97% yield) as colorless oil. IR (thin film): 2955, 2925, 2870, 2852, 1456, 1059 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): δ 7.35-7.20 (m, 4H), 4.46 (s, 2H), 3.86 (s, 2H), 3.76 (s, J^{(117/119}Sn-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, CDCl_3): 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 C_{21}H_{40}N_1O_1Sn_1 [M + H] 442.2130, found 442.2133.

### 3.6.2. Preparation of saturated medium ring N-heterocycles

All the saturated N-heterocycles were prepared according to the General Procedure described in Part III Section 3.2.

**3-(4-(Trifluoromethyl)phenyl)-1,4-oxazepane 102.** IR (thin film): ν 3316, 2946, 1455, 1417, 1333, 1162, 1112, 1070, 763 cm^{-1}; ^1H 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); ^13C 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_3N_1O_1 [M + H] 246.1106, found 246.1105.
Ethyl 1,4-oxazepane-3-carboxylate 103. IR (thin film): ν 3348, 2937, 2858, 1735, 1466, 1370, 1207, 1163, 1025 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 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$_3$): δ 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 104. IR (thin film): ν 3321, 2938, 2855, 1592, 1473, 1424, 1336, 1137, 1105, 997, 782 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 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$_3$): δ 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 105. IR (thin film): ν 3442, 2933, 2857, 1690, 1426, 1365, 1280, 1246, 1169, 867, 769 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 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$_3$): δ 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$_{29}$N$_2$O$_3$ [M + H] 285.2173, found 285.2169.

3-(4-(Trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine 106. 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 107.** IR (thin film): $\nu$ 3340, 2979, 2933, 1735, 1489, 1454, 1301, 1188, 1021 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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), 3.95 (dd, $J = 7.6$, 2.7 Hz, 1H), 2.08 (br s, NH), 1.30 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 108.** IR (thin film): $\nu$ 3263, 3034, 2954, 2919, 2812, 1721, 1281 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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), 3.74 (dd, $J = 12.0$, 9.1 Hz, 1H), 1.93 (br s, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 109.** IR (thin film): $\nu$ 3263, 3034, 2954, 2919, 2812, 1871, 1227 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 159.6, 149.5, 149.1, 135.9, 134.9, 134.5, 129.5, 128.7, 123.9, 121.1, 78.4, 64.0, 52.1; ESI-HRMS calcd for C$_{14}$H$_{13}$N$_2$O$_1$ [M + H] 227.1179, found 227.1179.

**tert-Butyl 3-(4-(trifluoromethyl)phenyl)-1,4-diazepane-1-carboxylate 110.** 1:1 rotamers by $^1$H NMR integration; m.p. = 92–93 °C; IR (thin film): $\nu
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3327, 2976, 2933, 2839, 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, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 155.8, 155.5, 146.7, 146.4, 129.8 (q, JₐCF = 31.7 Hz), 127.4, 127.2, 125.6, 124.3 (q, JₐCF = 272.2 Hz), 79.8, 79.7, 64.7, 64.5, 56.8, 56.6, 47.1, 46.8, 46.4, 45.7, 30.2, 30.1, 28.7; ESI-HRMS calcd for C₁₇H₂₄F₃N₂O₂ [M + H] 345.1784, found 345.1788.

1-tert-Butyl 3-ethyl 1,4-diazepane-1,3-dicarboxylate 111. 1:1 rotamers by ¹H NMR integration; IR (thin film): ν 3352, 2977, 2933, 1736, 1695, 1471, 1365, 1165 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), 3.80-3.53 (m, 2H), 3.28-3.14 (m, 3H), 2.71-2.56 (m, 1H), 1.93-1.67 (m, 3H), 1.46 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 155.8, 155.5, 146.7, 146.4, 129.8 (q, JₐCF = 31.7 Hz), 127.4, 127.2, 125.6, 124.3 (q, JₐCF = 272.2 Hz), 79.8, 79.7, 64.7, 64.5, 56.8, 56.6, 47.1, 46.8, 46.4, 45.7, 30.2, 30.1, 28.7; ESI-HRMS calcd for C₁₃H₂₅N₂O₄ [M + H] 273.1809, found 273.1809.

tert-Butyl 3-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1,4-diazepane-1-carboxylate 112. 1:1 rotamers by ¹H NMR integration; IR (thin film): ν 3526, 3114, 2974, 2928, 2852, 1684, 1523, 1168 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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), 3.88-3.75 (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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₈H₂₆N₅O₂ [M + H] 344.2081, found 344.2080.

tert-Butyl 3-(4-methoxyphenyl)-1,4-diazepane-1-carboxylate 113. 1:1 rotamers by ¹H NMR integration; IR (thin film): ν 3526, 3330, 2973, 2933, 2835, 1691, 1247, 1173 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 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),
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3.80-3.76 (m, 3H), 3.28-3.14 (m, 2H), 2.90 (dd, \( J = 13.8, 10.2 \) Hz, \( 1H \times 0.5 \)), 2.80 (dd, \( J = 13.8, 10.7 \) Hz, \( 1H \times 0.5 \)), 2.74-2.65 (m, 1H), 2.11-2.00 (m, \( 1H \times 0.5 \)), 1.99-1.86 (m, \( 1H \times 0.5 \)), 1.88-1.75 (m, 1H), 1.77 (br s, NH), 1.50-1.45 (m, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 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, 46.2, 45.6, 29.9, 29.9, 28.7, 28.7; ESI-HRMS calcd for C\(_{17}\)H\(_{27}\)N\(_2\)O\(_3\) [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 114.** 4:6 rotamers by \(^1\)H NMR integration; IR (thin film): \( \nu \) 3318, 2978, 2933, 1695, 1390, 1322, 1166, 1126, 910, 839, 768 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.74-7.44 (m, 4H), 7.44-7.15 (m, 4H), 4.51 (d, \( J = 13.7 \) Hz, \( 1H \times 0.6 \)), 4.41-4.17 (m, \( 1H \) and \( 1H \times 0.4 \)), 4.01 (s, 2H), 3.02-2.71 (m, 1H), 1.94 (br s, NH), 1.57 (s, 3H), 1.44 (s, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 154.2, 145.8, 142.4, 138.3, 129.7 (q, \( J_{CF} = 34.0 \) Hz), 129.1, 128.3, 127.7, 127.3, 126.9, 125.6 (q, \( J_{CF} = 3.7 \) Hz), 124.2 (q, \( J_{CF} = 273.2 \) Hz), 80.6, 65.1, 64.2, 57.1, 55.8, 52.9, 28.6, 28.4; ESI-HRMS calcd for C\(_{21}\)H\(_{24}\)F\(_3\)N\(_2\)O\(_2\) [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 115.** Rotamers; IR (thin film): \( \nu \) 3342, 2977, 2932, 1737, 1698, 1494, 1455, 1388, 1317, 1163, 1041, 861, 760 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 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 C\(_{17}\)H\(_{25}\)F\(_3\)N\(_2\)O\(_2\) [M + H] 321.1809, found 321.1814.

**tert-Butyl 3-(tert-butyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-1-carboxylate 116.** 4:6 rotamers by \(^1\)H NMR integration; IR (thin film): \( \nu \) 3425, 2963, 1697, 1494, 1391, 1366, 1170, 758 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.42-7.05 (m, 4H), 4.60(d, \( J = 12.3 \) Hz, \( 1H \times 0.6 \)), 4.44 (d, \( J = 12.3 \) Hz, \( 1H \times 0.4 \)), 3.97-3.94 (m, \( 1H \times 0.4 \)), 3.94-3.89 (m, \( 1H \times 0.6 \)), 3.83 (t, \( J = 11.6 \) Hz, 1H), 2.75-2.39 (m, 2H), 1.49-1.26 (m, 9H), 0.98 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 154.4, 154.2, 142.9,
tert-Butyl 3-cyclopropyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-1-carboxylate 117. Rotamers; IR (thin film): ν 3420, 2976, 2930, 1697, 1494, 1389, 1325, 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.

cis 5-Phenyl-3-(o-tolyl)-1,4-oxazepane 118. d.r. ≥ 9:1; 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), 7.37-7.30 (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); 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 C₁₇H₂₅N₂O₁ [M + H] 268.1696, found 268.1707.

cis 4-(5-Phenyl-1,4-oxazepan-3-yl)phenol 119. d.r. ≥ 10:1; m.p. = 122–125 °C; IR (thin film): ν 3247, 3059, 3025, 2940, 2855, 1613, 1515, 1454, 1233, 1131 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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; ESI-HRMS calcd for C₁₇H₂₆N₂O₂ [M + H] 270.1489, found 270.1494.

cis 4-(5-Phenyl-1,4-oxazepan-3-yl)benzonitrile 120. d.r. = 9:1; m.p. = 114–117 °C; IR (thin film): ν 2940, 2857, 2227, 1607, 1131 cm⁻¹; ¹H NMR
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\[ \text{(400 MHz, CDCl}_3\text{): } \delta \text{ 7.65-7.57 (m, 2H), 7.56-7.52 (m, 2H), 7.44-7.39 (m, 2H), 7.36-7.30 (m, 2H), 7.28-7.23 (m, 1H), 4.21 (dd, } J = 9.5, 3.2 \text{ Hz, 1H), 4.17 (dd, } J = 9.5, 3.9 \text{ Hz, 1H), 4.07-3.90 (m, 3H), 3.60 (dd, } J = 12.3, 9.5 \text{ Hz, 1H), 2.31-2.11 (m, 2H), 1.77 (br s, NH); } ^1\text{C NMR (100 MHz, CDCl}_3\text{): } \delta \text{ 146.7, 145.9, 132.5, 128.9, 128.2, 127.5, 126.6, 118.9, 111.6, 78.2, 69.1, 65.7, 62.2, 40.9; ESI-HRMS calcd for } C_{18}H_{19}N_2\text{O}_1\text{ [M + H]} \text{ 279.1492, found 279.1494.}
\]

\[ \text{cisp}(\text{Furan-3-yl)-5-phenyl-1,4-oxazepane 121. d.r. > 10:1; m.p. = 70–73 °C; IR (thin film): } \nu \text{ 2938, 2854, 1457, 1134, 1021 cm}^{-1}; ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta \text{ 7.44-7.38 (m, 3H), 7.36-7.29 (m, 3H), 7.27-7.22 (m, 1H), 6.41 (dd, } J = 1.8, 0.7 \text{ Hz, 1H), 4.16-4.09 (m, 2H), 4.08-3.92 (m, 3H), 3.62 (dd, } J = 12.0, 10.0 \text{ Hz, 1H), 2.23-2.07 (m, 2H), 1.83 (br s, NH); } ^1\text{C NMR (100 MHz, CDCl}_3\text{): } \delta \text{ 146.1, 143.2, 139.3, 128.8, 127.3, 126.6, 125.2, 109.4, 78.2, 68.8, 62.8, 57.9, 40.8; ESI-HRMS calcd for } C_{15}H_{18}N_1\text{O}_2\text{ [M + H]} \text{ 244.1332, found 244.1331.}
\]

\[ \text{tert-Butyl 3-(4-(trifluoromethyl)phenyl)-1,4-diazocane-1-carboxylate 122. 1:1 rotamers by } ^1\text{H NMR integration; IR (thin film): } \nu \text{ 3343, 2929, 2858, 1689, 1406, 1365, 1423, 1165, 1125, 1107, 1067, 831 cm}^{-1}; ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta \text{ 7.62-7.53 (m, 2H), 7.53-7.43 (m, 2H), 4.09-3.94 (m, 1H and } 1H \times 0.5), 3.92-3.78 (m, 1H), 3.70 (d, } J = 14.3 \text{ Hz, } 1H \times 0.5), 3.28-3.12 (m, 1H and } 1H \times 0.5), 3.09-2.99 (m, 1H \times 0.5), 2.97-2.62 (m, 2H), 2.07-1.93 (m, 1H \times 0.5), 1.90-1.75 (m, 1H and } 1H \times 0.5), 1.73-1.57 (m, 3H), 1.56-1.46 (m, 9H); ^1\text{C NMR (101 MHz, CDCl}_3\text{): } \delta \text{ 155.7, 155.3, 147.6, 129.6 (dd, } J_{CF} = 34.2, 19.2 \text{ Hz), 127.2, 127.1, 125.7, 125.5, 124.5 (q, } J_{CF} = 277 \text{ Hz, } 19.2 \text{ Hz), 79.8, 79.6, 63.2, 62.0, 56.7, 56.3, 48.9, 48.7, 48.4, 48.2, 29.6, 28.8, 28.7, 28.6, 26.0, 24.4; ESI-HRMS calcd for } C_{18}H_{26}F_3N_2O_2\text{ [M + H]} \text{ 359.1941, found 359.1938.}
\]
**Part III. Experiment Procedures and Characterization Data**

**tert-Butyl 3-(2-chloro-4-fluorophenyl)-1,4-diazocane-1-carboxylate 123.** 4:6 rotamers by $^1$H NMR integration; IR (thin film): $\nu$ 3343, 2976, 2930, 2863, 1690, 1489, 1167 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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, 29.0, 28.8, 28.7, 28.1, 26.5, 24.8; ESI-MS 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 124.** 1:1 rotamers; IR (thin film): $\nu$ 3340, 2975, 2929, 2862, 1686, 1408, 1165, 1144 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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-MS calcd for C$_{20}$H$_{28}$N$_{3}$O$_{2}$ [M + H] 342.2176, found 342.2180.

**1-tert-Butyl 3-ethyl 1,4-diazocane-1,3-dicarboxylate 125.** 4:6 rotamers by $^1$H NMR integration; IR (thin film): $\nu$ 3352, 2975, 2932, 1732, 1695, 1466, 1413, 1365, 1168, 1048, 873, 772 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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, 26.4, 25.4, 14.4, 14.3; ESI-HRMS calcd for C14H27N2O4 [M + H] 287.1965, found 287.1962.

3-(4-(Trifluoromethyl)phenyl)-1,4-oxazocane 126. IR (thin film): ν 3340, 2922, 2859, 1617, 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 C13H16F3N1O1 [M + Na] 282.1076, found 282.1082.

Methyl 4-(1,4-oxazocan-3-yl)benzoate 127. 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): δs 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 128. IR (thin film): ν 3342, 2918, 2859, 1720, 1504, 1486, 1438, 1247, 1116, 1039, 929, 809 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ 6.96 (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 C\textsubscript{13}H\textsubscript{18}N\textsubscript{3}O\textsubscript{3} [M + H] 236.1281, found 236.1284.

**4-(4-(Trifluoromethyl)phenyl)-3,4,5,6-tetrahydro-1H-benzo[\textit{f}][1,4]oxazocine 129.** m.p. = 62–63 °C; IR (thin film): v 3312, 3062, 3018, 2923, 2854, 1619, 1326, 1165, 1123, 1067 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta 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), 7.07 (d, J = 14.9 Hz, 1H), 4.94 (d, J = 14.9 Hz, 1H), 4.14 (d, J = 14.9 Hz, 1H), 3.92-3.85 (m, 2H), 1.69 (br s, NH); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \delta 159.1, 158.8, 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\textsubscript{17}H\textsubscript{17}F\textsubscript{3}N\textsubscript{1}O\textsubscript{1} [M + H] 308.1257, found 308.1254.

**4-(4-Methoxyphenyl)-3,4,5,6-tetrahydro-1H-benzo[\textit{f}][1,4]oxazocine 130.** IR (thin film): v 3315, 3010, 2930, 2835, 1611, 1512, 1247 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta 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); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \delta 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\textsubscript{17}H\textsubscript{20}N\textsubscript{1}O\textsubscript{2} [M + H] 270.1489, found 270.1493.

**4-(1-Methyl-1H-pyrazol-4-yl)-3,4,5,6-tetrahydro-1H-benzo[\textit{f}][1,4]oxazocine 131.** IR (thin film): v 3394, 3306, 2935, 2859, 1651, 1444, 1114 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta 7.39 (s, 1H), 7.31 (s, 1H), 7.30-7.27 (m, 2H), 7.22-7.17 (m, 1H), 7.16-7.11 (m, 1H), 5.09 (d, J = 15.0 Hz, 1H), 4.94 (d, J = 15.0 Hz, 1H), 4.61 (d, J = 13.9 Hz, 1H), 4.15-4.09 (m, 2H), 3.94-3.83 (m, 2H), 3.85 (s, 3H), 2.00 (br s, NH); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \delta 138.2, 138.1, 137.7, 131.3, 128.3, 128.0, 127.5, 127.2, 122.0, 77.6, 73.5, 52.1, 50.7, 39.0; ESI-HRMS calcd for C\textsubscript{17}H\textsubscript{20}N\textsubscript{1}O\textsubscript{2} [M + H] 244.1444, found 244.1447.
Ethyl 3,4,5,6-tetrahydro-1H-benzo[f][1,4]oxazocine-4-carboxylate 132: ν 3345, 2979, 2871, 1733, 1447, 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 C₁₃H₁₇N₃NaO₃ [M + Na] 258.1101, found 258.1102.

4-(tert-Butyl)-3,4,5,6-tetrahydro-1H-benzo[f][1,4]oxazocine 133. 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, 1H), 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, 73.0, 72.6, 65.8, 51.5, 33.7, 26.8; ESI-HRMS calcd for C₁₄H₂₂N₁O₁ [M + H] 220.1696, found 220.1693.

3-(4-(Trifluoromethyl)phenyl)-2,3,4,5,6,7-hexahydrobenzo[h][1,4]oxazonine 134. IR (thin film): ν 3373, 3065, 3020, 2926, 2868, 1618, 1581, 1491, 1453, 1326, 1164, 1122, 1067 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 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), 3.00-2.92 (m, 1H), 2.83-2.76 (m, 1H), 2.61-2.54 (m, 1H), 1.98-1.79 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 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 C₁₈H₁₉F₃N₁O₁ [M + H] 322.1413, found 322.1409.
Part III. Experiment Procedures and Characterization Data

Ethyl 2,3,4,5,6,7-hexahydrobenzo[h][1,4]oxazonine-3-carboxylate 135. IR (thin film): ν 3370, 2979, 2925, 2856, 1733, 1491, 1449, 1219, 1186, 1023 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 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, 1H), 1.27 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₄H₂₀N₂O₃ [M + H] 250.1438, found 250.1436.

3-(3-Bromophenyl)-2,3,4,5,6,7-hexahydrobenzo[h][1,4]oxazonine 136. IR (thin film): ν 3368, 3060, 3016, 2924, 2865, 1490, 1220, 1012 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 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); ¹³C NMR (100 MHz, CDCl₃): δ 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 C₁₇H₁₉BrN₂O₂ [M + H] 332.0645, found 332.0639.

3-(Pyridin-3-yl)-2,3,4,5,6,7-hexahydrobenzo[h][1,4]oxazonine 137. IR (thin film): ν 3364, 3029, 2923, 2855, 1578, 1490, 1222, 1016 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 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); ¹³C NMR (100 MHz, CDCl₃): δ 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 C₁₈H₁₉N₂O₁ [M + H] 255.1492, found 255.1490.
3.6.3. Gram-scale synthesis of substituted 1,4-oxazepane

A 200 mL, flame dried flask equipped with stir bar, rubber septum, and N₂ balloon was charged with a solution of SnAP OA 93 (5.00 g, 13.2 mmol, 1.00 equiv) and MS 4A (ca. 1.0 g) in CH₂Cl₂ (65 mL). 4-(Trifluoromethyl)benzaldehyde (1.80 mL, 13.2 mmol, 1.00 equiv) was added at rt. The reaction was stirred at rt for 2 h and filtered through a layer of Celite (0.3−0.5 cm) rinsing with CH₂Cl₂. The filtrate was concentrated under reduced pressure to afford the imine.

Separately, a 500 mL, flame dried flask equipped with stir bar, rubber septum, and N₂ balloon was charged with a solution of 2,6-lutidine (1.53 mL, 13.2 mmol, 1.00 equiv) in HFIP (55 mL). Cu(OTf)₂ (4.78 g, 13.2 mmol, 1.00 equiv) was added at rt and the reaction was stirred 1 h, during which a homogeneous suspension was formed. A solution of the imine (13.2 mmol, 1.00 equiv) in CH₂Cl₂ (210 mL) was added and the resulting mixture was stirred at rt for 12 h. The reaction was quenched at rt with sat aq NaHCO₃ (50 mL), 10% aq NH₄OH (25 mL) that were added one after the other. The resulting mixture was stirred vigorously for 15 min. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were washed with H₂O (2 x 40 mL) and brine (80 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure by rotary evaporation at 40 °C, 375 mmHg and then at 55 °C, ca. 0.1 mmHg (vacuum pump) for 2 h to remove the 2,6-lutidine. The resulting orange oil was dissolved in CH₃CN (300 mL) and washed with hexanes (6 x 20 mL) to remove the tin residues. The combined hexanes layers were extracted with acetonitrile (3 x 15 mL). The combined acetonitrile layers were concentrated under reduced pressure to afford orange oil that was dissolved in TBME (20 mL) and cooled to 0 °C. HCl (8 mL of a 4.0 M solution in 1,4-dioxane, 32.0 mmol, 2.42 equiv) was added over 5 min and the resulting mixture was allowed to warm to rt over 2 h before concentrated under reduced pressure to afford orange solid. This solid was suspended in TBME (50 mL) and filtered over a glass-sintered filter (TBME rinse, 10 x 20 mL) to afford pure 102•HCl (2.79 g, 75% yield) as colorless solid.
Appendix: NMR Spectra
PART I: ETHER-FORMING CROSS-COUPLING REACTIONS OF ORGANOTRIFLUOROBORATES AND ACETALS

Compound 6
Compound 7
Compound 8
Appendix: NMR Spectra

Part I

Compound 9
Compound 10
Compound 11

[Diagram of NMR spectra for Compound 11]
Compound 12
Compound 13

[Diagram of NMR spectrum for Compound 13]
Compound 14
Compound 17
Appendix: NMR Spectra

Part I

Compound 18
Compound 19
Compound 20
Appendix: NMR Spectra

Part I

Compound 21
Appendix: NMR Spectra

Part I

Compound 22
Appendix: NMR Spectra

Part I

Compound 23
Compound 25
Compound 26
Compound 28
Compound 29
Compound 36

[Image of NMR spectrum]

2F-125-58 80K Samples 10-1.5 1.24 40
600 MHz 2 1 9 1 3 1 1 1 1 1 1 1 1

[Image of NMR spectrum]
Appendix: NMR Spectra

Part I

Compound 41
Appendix: NMR Spectra

Part I

Compound 42
Appendix: NMR Spectra

Part I

Compound 43
Appendix: NMR Spectra

Part I

Compound 44
Compound 47
Appendix: NMR Spectra

Part I

Compound 48

[Diagram of NMR spectra for Compound 48]
Compound 55

[Chemical structure diagram]

NMR Spectra

[Chemical shift graphs]
Compound 57
Appendix: NMR Spectra

Part I

Compound 58

[Diagram of NMR spectra for Compound 58]
Compound 59
Compound 60
Appendix: NMR Spectra

Part I

Compound 61

![NMR Spectrum Diagram]

The spectrum shows resonances at various chemical shifts. The structure of Compound 61 is also depicted, showing the presence of aromatic and nitro groups.
Appendix: NMR Spectra

Part I

Compound 62
Appendix: NMR Spectra

Part I

Compound 63
Part II: SnAP REAGENTS FOR THE TRANSFORMATION OF ALDEHYDES INTO SATURATED N-HETEROCYCLES

Compound 18
Appendix: NMR Spectra

Part II

Compound 20
Compound 24
Appendix: NMR Spectra

Part II

Compound 25

NMR Spectra

Chemical Shifts:
- 7.46 ppm
- 7.41 ppm
- 7.30 ppm
- 7.25 ppm
- 7.18 ppm
- 7.10 ppm
- 4.08 ppm
- 3.85 ppm
- 2.00 ppm
- 1.18 ppm

Structural Formula:

\[
\begin{align*}
\text{NH} & \quad \text{S} \\
\text{Br} & \quad \text{NH} & \quad \text{S} \\
\end{align*}
\]
Appendix: NMR Spectra

Part II

Compound 26
Compound 27
Appendix: NMR Spectra

Part II

Compound 28
Compound 29
Appendix: NMR Spectra

Part II

Compound 30

- 139.097
- 136.656
- 127.850
- 113.191
- 77.156
- 25.307
- 43.299
- 14.228

- 2.00
t 1.51
1.18
0.84
0.50
Appendix: NMR Spectra

Part II

Compound 31
Appendix: NMR Spectra

Part II

Compound 32
Compound 33
Appendix: NMR Spectra

Part II

Compound 34
Compound 35
Appendix: NMR Spectra

Part II

Compound 36
Compound 37
Appendix: NMR Spectra

Part II

Compound 38

[Diagram of NMR spectrum for Compound 38]
Appendix: NMR Spectra

Part II

Compound 39
Appendix: NMR Spectra

Part II

Compound 40
Compound 41
Appendix: NMR Spectra

Part II

Compound 42

[Detailed NMR spectra images with chemical structure diagrams]
Appendix: NMR Spectra

Part II

Compound 43
Compound 44
Compound 45
Compound 46

[Diagram of NMR spectrum and molecular structure]
Compound 50
Compound 54

\[
\text{Me}_3\text{Si} - \text{S} - \text{H}_2\text{N} - \text{CO}_2\text{Et}
\]
Compound 55

[Diagram of NMR spectrum]
Appendix: NMR Spectra

Part II

Compound 57

[Image of NMR spectrum for Compound 57]
Compound 58
Compound 59

\[
\begin{align*}
\text{Me} &\quad \text{NH}_2 \\
\text{O} &\quad \text{SnBu}_3
\end{align*}
\]
**Appendix: NMR Spectra**

**Part II**

<table>
<thead>
<tr>
<th>Compound 60</th>
</tr>
</thead>
</table>

![NMR Spectra](image-url)
Compound 61
Compound 62
Compound 64
Compound 65
Compound 66
Compound 68
Appendix: NMR Spectra

Part II

Compound 70

[Diagram of NMR spectrum for Compound 70]
Compound 71

Appendix: NMR Spectra
Part II
Compound 72
Compound 73
Compound 74

[Diagram of compound 74 with NMR spectrum]
Appendix: NMR Spectra

Compound 75

NMR Spectra of Compound 75
Compound 76
Compound 77
Appendix: NMR Spectra
Part II

Compound 78
Appendix: NMR Spectra

Part II

Compound 79
Appendix: NMR Spectra

Part II

Compound 80
Compound 81
Compound 82
Compound 83
Compound 84
Compound 85

Appendix: NMR Spectra
Part II

290
Appendix: NMR Spectra

Part II

Compound 86

[Image of NMR spectrum with chemical structure and peak assignments]

[Graph showing chemical shifts in ppm]

[Table of NMR peak assignments]
Compound 87

major diastereomer
5:4 rotamers by $^1$H NMR integration
Compound 87

![NMR Spectra](image-url)
Appendix: NMR Spectra

Part II

Compound 88

Major diastereomer
5:4 rotamers by $^1$H NMR integration
Compound 88
Compound 89

major diastereomer
Compound 90
Compound 91
Compound 92
Appendix: NMR Spectra

Part II

Compound 93

\[ \text{Bu}_3\text{Sn} - \text{O} - \text{NH}_2 \]
Compound 94

Bu₃Sn
H₂N
Ph

Appendix: NMR Spectra
Part II
Compound 95
Compound 96

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

Part II

Compound 97
Compound 98

Rotamers (ca. 1:2 by $^1$H NMR integration)
Appendix: NMR Spectra

Part II

Compound 99

Bu₃SnOCH₂NH₂
Appendix: NMR Spectra

Part II

Compound 100
Compound 101
Appendix: NMR Spectra

Part II

Compound 102
Compound 103
Compound 104

[Chemical Structure Image]

NMR Spectra

[Signal Peaks and Chemical Shifts]
Compound 105
Appendix: NMR Spectra

Part II

Compound 106
Compound 107
Compound 108
Appendix: NMR Spectra

Part II

Compound 109
Appendix: NMR Spectra

Part II

Compound 110

Rotamers (1:1 by $^1$H NMR integration)
Compound 111

Rotamers (1:1 by $^1$H NMR integration)
Compound 112

Rotamers (1:1 by $^1$H NMR integration)
Appendix: NMR Spectra

Compound 113

Rotamers (1:1 by $^1$H NMR integration)
Appendix: NMR Spectra

Part II

Compound 114

Rotamers (4:6 by $^1$H NMR integration)
Appendix: NMR Spectra

Part II

Compound 115

Rotamers
Appendix: NMR Spectra  
Part II  

Compound 116

Rotamers (4:6 by $^1$H NMR integration)
Appendix: NMR Spectra

Part II

Compound 117

[Diagram of NMR spectrum for Compound 117 with rotamers labeled]

[Detailed spectral data and assignments]
Appendix: NMR Spectra

Part II

Compound 118
Appendix: NMR Spectra

Part II

Compound 119
Appendix: NMR Spectra

Part II

Compound 120
Appendix: NMR Spectra

Part II

Compound 121

[Diagram of NMR spectrum for Compound 121]
Compound 122

Rotamers (1:1 by $^1$H NMR integration)
Compound 123

Rotamers (4:6 by $^1$H NMR integration)
Compound 124

Rotamers (1:1 by $^1$H NMR integration)
Compound 125

Rotamers (4:6 by $^1$H NMR integration)
Appendix: NMR Spectra

Compound 126

The NMR spectra show the chemical shifts of the protons and carbon atoms in the molecule. The spectra are divided into two sections: one for the proton spectrum (H) and another for the carbon spectrum (C). The proton spectrum is depicted in the upper section, with peaks at different chemical shifts indicating the presence of various protons. The carbon spectrum, shown in the lower section, displays the chemical shifts of the carbon atoms, with peaks at various positions corresponding to different carbon functionalities in the molecule.

The structure of compound 126 is also shown, highlighting the bonds and atoms, including the nitrogen (N), oxygen (O), and CF$_3$ groups. The peaks in the spectra correspond to these functional groups, providing insights into the chemical structure and composition of the compound.
Appendix: NMR Spectra

Part II

Compound 127
Compound 128
Compound 129
Appendix: NMR Spectra

Part II

Compound 130
Appendix: NMR Spectra

Part II

Compound 131
Compound 132
Compound 133
Compound 134
Compound 135
Appendix: NMR Spectra

Part II

Compound 136
Compound 137
Compound 140

[Diagram of NMR spectrum for Compound 140]
Compound 141
Compound 142

[Diagram of NMR spectrum with chemical structure and peaks labeled]
Compound 143
Appendix: NMR Spectra

Part II

Compound 146

[Diagram of NMR spectrum for Compound 146]
Compound 147
Appendix: NMR Spectra

Part II

Compound 148

[Diagram of NMR spectrum with spectral data]

[Labelings and values for proton and carbon spectra]
Appendix: NMR Spectra

Part II

Compound 150
Compound 151
Appendix: NMR Spectra

Part II

Compound 152

- Structure diagram with labels: Boc, Me, OTIPS, SnBu₃
- NMR spectra with chemical shift values
Appendix: NMR Spectra

Part II

Compound 154
Compound 155

\[
\text{Bu}_3\text{Sn} - \text{O} - \text{Bu} \quad \text{OH}
\]
Compound 156
Appendix: NMR Spectra

Part II

Compound 158
Compound 159
Compound 160

[Diagram of NMR spectrum for Compound 160]
Compound 161

[Image of NMR spectrum for Compound 161]
Compound 162

![NMR Spectra](image)
Compound 163
Appendix: NMR Spectra

Part II

**Compound 164**

![NMR Spectra of Compound 164](image)

Rotamers (3:7 by $^1$H NMR integration)
Compound 166
Appendix: NMR Spectra

Part II

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Compound 167

\[
\text{Boc} \quad \text{SnBu}_3 \\
\text{OTIPS}
\]
Compound 168

![NMR Spectrum of Compound 168]
Compound 169
Appendix: NMR Spectra

Part II

Compound 170
Appendix: NMR Spectra

Part II

Compound 171
Compound 172

Rotamers (3:2 by 1H NMR integration)
Compound 173

Rotamers (2:1 by $^1$H NMR integration)
Compound 174
Appendix: NMR Spectra

Part II

Compound 175

[Diagram of NMR spectrum and structure of Compound 175]