The Synthesis of Novel N-Heterocyclic Scaffolds and Diazirine-Based Molecular Tags

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Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry in the Graduate School of Duke University

2016
ABSTRACT

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Abstract

N-Heterocycles are ubiquitous in biologically active natural products and pharmaceuticals. Yet, new syntheses and modifications of N-heterocycles are continually of interest for the purposes of expanding chemical space, finding quicker synthetic routes, better pharmaceuticals, and even new handles for molecular labeling. There are several iterations of molecular labeling; the decision of where to place the label is as important as of which visualization technique to emphasize.

Piperidine and indole are two of the most widely distributed N-heterocycles and thus were targeted for synthesis, functionalization, and labeling. The major functionalization of these scaffolds should include a nitrogen atom, while the inclusion of other groups will expand the utility of the method. Towards this goal, ease of synthesis and elimination of step-wise transformations are of the utmost concern. Here, the concept of electrophilic amination can be utilized as a way of introducing complex secondary and tertiary amines with minimal operations.

Molecular tags should be on or adjacent to an N-heterocycle as they are normally the motifs implicated at the binding site of enzymes and receptors. The labeling techniques should be useful to a chemical biologist, but should also in theory be useful to the medical community. The two types of labeling that are of interest to a chemist and
a physician would be positron emission tomography (PET) and magnetic resonance imaging (MRI).

Coincidentally, the 3-positions of both piperidine and indole are historically difficult to access and modify. However, using electrophilic amination techniques, 3-functionalized piperidines can be synthesized in good yields from unsaturated amines. In the same manner, 3-labeled piperidines can be obtained; the piperidines can either be labeled with an azide for biochemical research or an $^{18}$F for PET imaging research. The novel electrophiles, N-benzenesulfonyloxyamides, can be reacted with indole in one of two ways: 3-amidation or 1-amidomethylation, depending on the exact reaction conditions. Lastly, a novel, hyperpolarizable $^{15}$N$_2$-labeled diazirine has been developed as an exogenous and versatile tag for use in magnetic resonance imaging.
Dedication

This work is dedication to my family: past, present, and future.
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**Abbreviations**

Ac: acetate

Ar: arene

BINAP: 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl

bp: boiling point

Bu: butyl

Bn: benzyl

Bz: benzyol

calcd.: calculated

conc.: concentration

CNS: central nervous system

Cy: cyclohexyl

dba: dibenzylideneacetone

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE: 1,2-dichloroethane

DCM: dichloromethane

DDQ: 2,3-dichloro-5,6-dicyano-para-benzoquinone

DEAD: diethyl azodicarboxylate

Deoxo-Fluor: bis(2’-methoxyethyl)aminosulfur trifluoride

DIAD: diisopropyl azodicarboxylate
DIPA: diisopropylamine
DMA: \(N,N\)-dimethylacetamide
DMAD: dimethyl acetylenedicarboxylate
DMF: \(N,N\)-dimethylformamide
DMSO: dimethylsulfoxide
dr: diastereomeric ratio
EDCI: \(N\)-(3′-dimethylaminopropyl)-\(N′\)-ethylcarbodiimide hydrochloride
ee: enantiomeric excess
equiv.: equivalents
ESI: electron spray ionization
Et: ethyl
FTIR: Fourier transform infrared spectroscopy
GABA: G protein-coupled receptors
GCMS: gas chromatography-mass spectrometry
h: hour
HAOSA: hydroxylamine-O-sulfonic acid
HRMS: high resolution mass spectrometry
hv: light
IPNS: isopenicillin N synthase
IUPAC: International Union of Pure and Applied Chemistry
k-2.2.2: 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane

L-selectride: lithium tri-sec-butyl(hydrido)borate(1-)

lit.: literature

LAH: lithium aluminum hydride

LG: leaving group

mCPBA: *meta*-chloroperbenzoic acid

Me: methyl

MEK: methyl ethyl ketone

min: minutes

mp: melting point

MR: magnetic resonance

MRI: magnetic resonance imaging

MS: molecular sieves

MTBE: methyl *tert*-butyl ether

NCS: *N*-chlorosuccinimide

NIS: *N*-iodosuccinimide

NMR: nuclear magnetic resonance

Ns: 4-nitrobenzenesulfonyl

Nuc: nucleophile

PCC: pyridinium chlorochromate
PET: positron emission tomography
Ph: phenyl
PHIP: parahydrogen induced polarization
Phth: phthaloyl
Piv: pivaloyl
PKC: protein kinase C
PPA: polyphosphoric acid
Pr: propyl
Ref.: reference
Rf: retention factor
rs: regioselectivity
rt: room temperature
SABRE: signal amplification by reversible exchange
SABRE-SHEATH: SABRE in shield enables alignment transfer to heteronuclei
SAR: structure-activity relationship
Selectfluor: N-chloromethyl-N’-fluorotriethylenediammonium bis(tetrafluoroborate)
SERT: serotonin transporter
SPECT: single-photon emission tomography
T1: spin-lattice relaxation time
TLC: thin-layer chromatography
Ts: singlet state relaxation time

Ts: 4-toluenesulfonyl

TBAF: tetrabutylammonium fluoride

TBAI: tetrabutylammonium iodide

TBS: tert-butyldimethylsilyl

TEBAC: benzyltriethylammonium chloride

temp.: temperature

TFA: trifluoroacetic acid

TFAA: trifluoroacetic anhydride

THF: tetrahydrofuran

TMP: 2,2,6,6-tetramethypiperidine

TPD: 3-trifluoromethyl-3-phenyldiazirine

TSPO: translocator protein

Xtalfluor E: (diethylamino)difluorosulfonium tetrafluoroborate,
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Chapter 1: Synthesis of 3-functionalized and 3-labeled piperidines by radical cyclization

1. Synthesis of 3-functionalized and 3-labeled piperidines by radical cyclization

1.1 Introduction

Figure 1: Examples of piperidine-containing natural products, pharmaceuticals, and potential therapeutic compounds

Piperidine-based structures are ubiquitous in both natural products\(^1\)\(^-\)\(^5\) and pharmaceuticals (Figure 1).\(^6\)\(^-\)\(^16\) Piperidines occur not only as an isolated ring, but also in bicyclic systems and in more complex polycyclic alkaloids. Piperidine scaffolds can contain several stereogenic centers and substitution patterns, making them ideal targets of research for organic chemists and biologists alike. For example, slaframine is a toxic substance found in the fungus *Rhizoctonia leguminicola* of red clover hay,\(^17\) while prosophylline is a natural product isolated from various *Prosopis* species and possesses antibacterial and anesthetic properties.\(^18\) Nojirimycin was the first known azasugar discovered and has since become a common skeleton in antibiotics.\(^19\)\(^-\)\(^20\) Furthermore, the
common insecticide anabasin is a naturally occurring piperidine alkaloid found in *Nicotiana glauca*.

Potential pharmaceuticals containing the piperidine ring have been cited tens of thousands of times thus far in clinical and preclinical work, with much effort going into streamlining their respective syntheses. Of all N-heterocycles, piperidine is the most prevalent in FDA-approved small molecule drugs.\textsuperscript{16} For example, Alogliptin is a recently approved drug for diabetes first discovered in 2007.\textsuperscript{21} Pergolide was previously approved by the FDA as a treatment for Parkinson’s, but has since been linked to heart disease.\textsuperscript{22} Several piperidine-containing molecules are cited as ligands and potential therapeutics; however there are no $\sigma_1$ receptor ligands in clinical use today.\textsuperscript{23-25}

**1.1.1 Previous synthesis of functionalized piperidines**

The preparation of diversely functionalized piperidines as advanced intermediates or as biologically active compounds remains a challenge in chemical synthesis.\textsuperscript{26} While 2- and 6-substituted piperidines are generally regarded as well-studied,\textsuperscript{27,28} the synthesis of 3-, 4-, and 5-piperidines are lesser-known.\textsuperscript{26} Therefore, the focus herein will be on forming functionalized piperidines of the 3-, 4-, and 5-position varieties.

**1.1.1.1 Hydrogenation of pyridines**

From a retrosynthetic perspective, one of the simplest processes to piperidines is the direct reduction of pyridines. Interestingly, pyridine salts are much easier to
hydrogenate than basic pyridines. For instance, pyridine hydrochloride was reduced with Adam’s catalyst under 1 atm of hydrogen (Scheme 1, A). However, substituted basic pyridines require much more forcing conditions (Scheme 1, B). This approach is often a strenuous process with a limited functional group tolerance and problematic diastereoselectivity when using multi-substituted pyridine substrates.

![Scheme 1: Examples of hydrogenation to piperidines](image)

**1.1.1.2 Synthesis of piperidines by alkylation**

![Scheme 2: Examples of piperidine formation by alkylation](image)

Although the direct alkylation of primary amines is usually inefficient, the synthesis of piperidines by alkylation is facile. Primary benzylamine reacted with a linear bis-tosylate to form a chiral piperidine (Scheme 2, A). Furthermore, alkylation of
an acidic tosylamide by a modified Mitsunobu procedure was very efficient (Scheme 2, B).³²

1.1.1.3 Reductive amination

Reductive amination can be a valuable approach to piperidines, specifically azasugar derivatives. The introduction of an exogenous primary amine to a 1,5-dialdehyde under reducing conditions gives the expected piperidine (Scheme 3, A).³³ Normally, amino aldehydes and ketones are unstable, however if they are handled only briefly in a multistep fashion, intramolecular reductive amination can be successful (Scheme 3, B).³⁴

Scheme 3: Synthesis of azasugars by reductive elimination

1.1.1.4 Cycloadditions

Cycloadditions are not a common method to piperidines since the outcome and speed of the reaction is largely dependent on the substrate. Imino Diels-Alder reactions require electron-deficient imines and electron-rich dienes to form piperidine skeletons.³⁵
Furthermore the products will contain an unsaturation, and would therefore require either a reduction or addition to obtain the desired piperidine (Scheme 4).

Scheme 4: Piperidine synthesis from an imino Diels-Alder reaction

1.1.1.5 Transition metal-catalyzed methods

Transition metal-catalyzed cyclization from unsaturated amides has been described. In one example, Widenhoefer and co-workers used gold catalysis to form a spiro-structure in 88% yield (Scheme 5, A). Gold catalysis also enabled the synthesis of 3-hydroxypiperidines (Scheme 5, B). However, conditions for that protocol are not atom-efficient, plus some of the hydroxypyrrolidine byproducts were seen. Palladium can also catalyze the cyclization of unsaturated amides under oxygen at 60 psi. (Scheme 5, C).
1.1.1.6 The Hofmann–Löffler–Freytag reaction

Perhaps the earliest instance of radical cyclization comes from the homolytic cleavage of an appropriate N-chloramine in the presence of strong, concentrated acid. The generally accepted mechanism starts with protonation of the N-chloramine followed by homolytic cleavage of the N-Cl bond (Scheme 6). The aminyl radical abstracts a proton, generally in a 1,5-manner, but any close proton could be used. The alkyl radical propagates the cycle, but in a condensed mechanism a new C–Cl bond is made from the two existing radicals. Upon basic work-up the free amine intramolecularly attacks the alkyl chloride, forming a new heterocycle.
Scheme 6: Mechanism of the Hofmann-Löffler-Freytag reaction

The Hofmann-Löffler-Freytag reaction has been used to great effect in the synthesis of nitrogen-containing natural products. Baldwin and co-workers were able to access the tricyclic gelsemium alkaloid core by irradiating 1 (Scheme 7, A).\textsuperscript{39} Thelen and co-worker converted 3 to N-methylgranatanine 4 (Scheme 7, B).\textsuperscript{40} Although it seems that a 5- and a 7-membered ring should have been formed, molecular models show that formation of the two piperidine rings is indeed favored. The aminyl radical concept is further advanced in section 1.1.2.

Scheme 7: Examples of the Hofmann–Löffler–Freytag reaction in natural product synthesis
1.1.1.7 Aziridinium ring expansion to 3-functionalized piperidines

Scheme 8: Aziridinium intermediate first postulated in the rearrangement of isopropyl derivative 5 to \( n \)-propyl compound 6

The aziridinium intermediate was first postulated by Zirkle and co-workers in 1947, long after the existence of a sulfonium species had been announced.\textsuperscript{41} In their experiment, similar to one used to help prove the existence of a sulfonium intermediate, isopropyl compound 5 was treated with aqueous base and after extraction, \( n \)-propyl 6 was found (Scheme 8).\textsuperscript{41-42}

Scheme 9: Stereoselective rearrangement of an acyclic 1,2-aminochloroalkane

Although the initial experiment is still impressive today, the reaction scope and utility has been greatly expanded in recent years. Just as in the original discovery,\textsuperscript{41-42} Back and co-workers in 2003 rearranged a branched 1,2-aminoalcohol 7–8 stereoselectively to a linear 1,2-aminochloroalkane 9–10 (Scheme 9).\textsuperscript{43}
A. Mechanism of aziridinium rearrangement with trifluoroacetates

![Mechanism Diagram]

B. Catalytic method

![Catalytic Method Diagram]

Scheme 10: Rearrangement of 1,2-aminoalcohols utilizing a trifluoroacetate leaving group

1,2-Aminochloroalkanes are the most readily accessible aziridinium precursors, but the aziridinium rearrangement has been extended to other halogens and pseudohalogens. Additionally, several exogenous nucleophiles can be employed in the ring opening step toward the final desired compound. For example, 1,2-aminoalcohols can be efficient precursors of aziridinium rearrangement. For instance, compound 11 was acylated with TFAA under basic conditions and then rearranged via the aziridinium intermediate; hydrolysis furnished the rearranged 1,2-aminoalcohol 12 (Scheme 10, A).\textsuperscript{44} Cossy and co-workers further advanced the concept by developing a novel catalytic method, employing only 20 mol % TFAA in the first step and 30 mol % NaOH in the second step (Scheme 10, B).\textsuperscript{45}
Cyclic ring expansions and contractions were noticed for a series of chloropyrrolidines and chloropiperidines. Ring expansion was observed when chloropyrrolidine 13 was treated with base, giving 3-chloropiperidine 15 in unspecified yield (Scheme 11, A). In contrast, ring contraction was noticed when 3-chloropiperidine salts 16–17 here basified in the presence of benzylamine (Scheme 11, B). Although these two findings may seem to contradict each other, the reversibility of the chloride anion in the reaction eventually leads to the thermodynamic 3-chloropiperidine 15. Ring opening with a primary amine is not reversible, therefore kinetic products 18–19 are observed.

Scheme 11: Early studies on ring expansion and contraction via the aziridinium intermediate

Although the aziridinium pathway had been generally accepted for some time as the reaction pathway for the rearrangement of 1,2-aminohaloalkanes; it was not until 1966 that the reactive intermediate was isolated and characterized, two years after the
isolation of the 4-membered azidinium intermediate. The desired intermediate 21 was obtained using two different synthesis procedures; isolated compounds from both procedures exhibiting the same spectral characteristics and gave the same ratio of products 22–23 after hydrolysis in aqueous NaOH (Scheme 12).

![Scheme 12: Isolation of the aziridinium intermediate](image)

The data obtained in a follow-up study indicate that compound 15 reacts between $10^4$–$10^7$ times faster than cyclohexyl chloride (which cannot go through the aziridinium intermediate). Additionally, the rate of formation of the chloride ion in solution with 14 different nucleophiles is first order throughout the series, proving aziridinium formation to be rate-determining. The rate is also affected by pH. For instance, when the pH is moderate or high, the rate is a function of pH. If the pH is increased enough, no change from first-order kinetics is observed. When strong and irreversible nucleophiles are used, the pyrrolidine is the major product. However, moderate nucleophiles (e.g. OH and OAc) give mixtures of the pyrrolidine and piperidine products.
Several exogenous nucleophiles can be used if the initial nucleophile is poor and/or reversible. Formation of a new halogen bond is usually outcompeted when a stronger bond can be made.\textsuperscript{49} Dakanali unconventionally used an aziridinium in the synthesis of selective dopamine antagonist ecopipam (Scheme 13, A).\textsuperscript{53-54} 1,2-Aminochloroalkane 24 was reacted with a aryl Grignard reagent in the presence of CuCl to give rearranged amine 25 with a new C–C bond.\textsuperscript{54} NaN\textsubscript{3} in DMSO attacked a mixture of 26 and 27 with rearrangement and a 1,3-dipolar cyclization to give products 28 and 29 in an isolable mixture (Scheme 13, B).\textsuperscript{55} 1,2-aminobromoalkane 30 was attacked by DMF at 80 °C to give product 31 (Scheme 13, C).\textsuperscript{56} Although no rearrangement was observed, the aziridinium intermediate was postulated because alkyl bromides would not normally be displaced with DMF to form formate esters. Aminoalcohol 32 gave 33 in 81% yield after rearrangement of the aziridinium intermediate with KSCN (Scheme 13, D).\textsuperscript{57} Shreeve and co-workers noticed that when Deoxo-Fluor was reacted with some 1,2-aminoalcohol substrates, a deviation from their expected product was observed. The normal displacement aminofluoroalkane 35 and the aziridinium rearranged product 36 were synthesized together in high yield (Scheme 13, E).\textsuperscript{58}
Scheme 13: Aziridinium rearrangements with different leaving groups and nucleophiles

Cossy and co-workers extended the concept of aziridinium ring expansion to piperidines. In their study, they found that enantiopure hydroxypyrrolidines could be converted to enantiopure azidopiperidines and azidopyrrolidines. In their proposed mechanism, the hydroxyl group attacks XtalFluor E. The newly formed leaving group is
attacked by the nitrogen to give an aziridinium species. The aziridinium is attacked regioselectively by the azide to give mainly the 3-azidopiperidine (Table 1). The tandem use of radical cyclization and aziridinium rearrangement is discussed further in the next section.

Table 1: Enantiospecific ring expansion of hydroxypyrrolidines

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>products and yield</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>BnO₂N₃OH</td>
<td>BnO₂N₃, N₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BnO₂N₃, N₃</td>
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<tr>
<td></td>
<td></td>
<td>BnO₂N₃, N₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BnO₂N₃, N₃</td>
</tr>
<tr>
<td>2</td>
<td>TBSO₂N₃OH</td>
<td>TBSO₂N₃, N₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBSO₂N₃, N₃</td>
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<tr>
<td></td>
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<td>TBSO₂N₃, N₃</td>
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<tr>
<td></td>
<td></td>
<td>TBSO₂N₃, N₃</td>
</tr>
<tr>
<td>3</td>
<td>TrOH</td>
<td>TrN₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TrN₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TrN₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TrN₃</td>
</tr>
<tr>
<td>4</td>
<td>TBSO₂TrOH</td>
<td>TBSO₂TrN₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBSO₂TrN₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBSO₂TrN₃</td>
</tr>
</tbody>
</table>

1.1.2 Aminyl radical addition to unsaturated bonds

Even though the Hofmann–Löffler–Freytag reaction has been well-documented since the 1960’s, new information and starting materials for the reaction are continually of interest. At the same time, intermolecular addition of aminyl radicals to unsaturated
bonds was just beginning to be explored by Neale and Minisci.\textsuperscript{62-66} Although strong acids are known to cause N-chloramines to fragment into aminyl radicals,\textsuperscript{64} it was later found that a Lewis acid such as Fe(II), Ti(III), or Cu(I) can perform the same task. Hydroxylamine-O-sulfonic acid (HAOSA) with FeCl\textsubscript{2} aminochlorinated styrene (Scheme 14, A).\textsuperscript{64} In the presence of Fe(II) or Ti(III) salts, N-chloramines aminated benzene and other aromatic compounds (Scheme 14, B).\textsuperscript{65} One of the first examples of cyclization from an aminyl radical to a double bond resulted in the synthesis of N-methylindoline (Scheme 14, C).\textsuperscript{65}

\begin{center}
\textbf{Scheme 14: First examples of aminyl radical adding to olefins}
\end{center}

1.1.2.1 Aminyl radical addition to olefins vs. proton abstraction

1,5-Proton abstraction is faster than an intermolecular addition to an olefin.\textsuperscript{67} However, when intramolecular addition of an aminyl radial to an olefin is possible, that pathway is preferred over 1,5-proton abstraction (Scheme 15).\textsuperscript{68} Compound 37 cyclizes to 38 by addition rather than follow a Hofmann–Löffler–Freytag route to product 39.
Scheme 15: Olefin addition outcompetes proton abstraction

1.1.2.2 Tandem cyclization and aziridinium rearrangement to 3-chloropiperidines

Göttlich discovered a copper-catalyzed cyclization procedure for unsaturated N-chloramines. N-chloramine 40 first formed the expected pyrrolidine 41 in the reaction however 3-chloropiperidine 43 was the exclusive isolated product (Scheme 16). The rationale is that under nearly neutral conditions, the nitrogen of the initial pyrrolidine remains basic. The aziridinium 42 forms reversibly, leading to the thermodynamically favored piperidine 43. Göttlich and co-workers were able to extend this methodology to several unsaturated amine substrates.

Scheme 16: Example of the copper-catalyzed synthesis of 3-chloropiperidines

1.1.2.3 Iodide-catalyzed cyclization of N-chloramines to 3-chloropiperidines

While searching for other metal catalysts to induce the cyclization of unsaturated N-chloramines, Göttlich and co-workers serendipitously discovered that tetrabutylammonium iodide (TBAI) behaves as an efficient catalyst. The most likely mechanism seems to be catalytic iodide displacement of the N-chloramine 40 to give N-
iodoamine 44 (Scheme 17). This compound undergoes facile homolytic cleavage and aminoiolation to pyrrolidine 45. Aziridinium intermediate 46 is formed and displaced by chloride ions in solution to give compound 43.

Scheme 17: Proposed iodide-catalyzed mechanism

The reaction protocol developed here was further extended to the synthesis of several 3-chloropiperidines. Although gem-dimethyl precursors are the most efficient, several other substrates work as well. None of the 3-iodopiperidine was obtained by this protocol, as chloride is the superior nucleophile (Table 2).

Table 2: Gem-dimethyl examples of 3-chloropiperidines generated from catalytic iodide
1.1.2.4 Use of N-iodoamines in the total synthesis of azasugars

Use of the N-iodoamine was extended to the synthesis of fagomine azasugar derivatives. Starting from glucose derivative 47, alkene 48 was synthesized in 81% yield (Scheme 18). 48 underwent a series of Mitsunobu-type reactions to first obtain alcohol 49 then amine 50. The amine was treated with NIS to afford 51. The N-I bond formed in situ was quickly cleaved homolytically affording only the thermodynamic exo-iodopiperidine. Stereochemistry is conserved and the product was obtained in 70% diastereomeric excess. The mixture was not isolated but was instead cyclized directly to

Scheme 18: Synthesis of azasugars via N-iodoamines

Use of the N-iodoamine was extended to the synthesis of fagomine azasugar derivatives. Starting from glucose derivative 47, alkene 48 was synthesized in 81% yield (Scheme 18). 48 underwent a series of Mitsunobu-type reactions to first obtain alcohol 49 then amine 50. The amine was treated with NIS to afford 51. The N-I bond formed in situ was quickly cleaved homolytically affording only the thermodynamic exo-iodopiperidine. Stereochemistry is conserved and the product was obtained in 70% diastereomeric excess. The mixture was not isolated but was instead cyclized directly to
bicycle 52 or alkylated to 53 in 74% and 65% overall yield respectively. The fagomine azasugar derivative 54 was obtained after hydrogenolysis of 53 in 88% yield. Clearly the combination of N-I homolytic cleavage, intramolecular cyclization, and nucleophilic aziridinium ring-opening is a powerful combination with still untapped potential.

1.2 Synthesis of 3-functionalized piperidines

Recent progress made by Göttlich and co-workers attracted our attention as it preferentially formed the piperidine ring over the pyrrolidine ring without the use of transition metals or without harsh conditions.\(^{71}\) The thought is that an exogenous nucleophile can be added in a one-pot fashion to a 3-chloropiperidine to form a new 3-functionalized piperidine (Scheme 19). A particularly useful nucleophile would allow for several amino-functionalizations and be a biorthogonal chemical reporter. My studies started from the azide nucleophile, as it is the most versatile bioorthogonal chemical reporter in chemical biology,\(^{73,74}\) and is also one of the most multipurpose functional groups in organic synthesis.\(^{75}\) With the azide moiety, one would be able to explore the bioactive properties of piperidine-containing molecules and their targets in medicinal research. For instance, a 3-azidopiperidine would be able to covalently bond to fluorescent tags to reveal cellular targets.\(^{76}\) Additionally, azidopiperidines could be functionalized with an affinity tag for immunoprecipitation experiments.\(^{70,77-80}\) Azides are also one of the most powerful nucleophiles in existence and should easily and irreversibly react with the aziridinium intermediate in preference to chloride or iodide.\(^{81}\)
1.2.1 Optimization of 3-azidopiperidines

Optimization of 3-azidopiperidines was initiated by reacting \( N \)-chloramine 56 with NaI (iodide catalyst) and \( \text{NaN}_3 \) (exogenous nucleophile) in various solvents, concentrations, and temperatures (Table 3). In non-polar solvents, no reaction takes place at all (entries 1–2). DCM, allows for a 50\% overall conversion to desired product 58 and 3-chloropiperidine 59 but was perhaps hindered because of the low boiling point (entry 3). However, it was encouraging to see \( \text{NaN}_3 \) can act as an exogenous nucleophile in the desired way. In DCE at 75 °C, the reaction yield of 58 rose significantly; additionally the use of 5 mol \% NaI was found to be superior to 10 mol \% NaI (entries 4–5). Use of CHCl₃ at 50 °C was better still, although increasing the concentration proved worse (entries 6–7). A huge improvement was realized when MeCN was used as the solvent, as the byproducts 57 and 59 were completely eliminated (entry 8). Lowering the concentration and increasing the temperature to 80 °C led to an 89\% NMR yield (entry 9). Lowering the temperature to 60 °C led to a 94\% NMR yield with no byproducts, concluding the optimization table (entry 10).
### Table 3: Optimization of 3-azidopiperidines from unsaturated N-chloramines

<table>
<thead>
<tr>
<th>Entry</th>
<th>NaI (equiv)</th>
<th>Solvent</th>
<th>Conc. [M]</th>
<th>Temp. (°C)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>57</th>
<th>58</th>
<th>59</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>MTBE</td>
<td>0.18</td>
<td>50</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>Toluene</td>
<td>0.18</td>
<td>50</td>
<td>no reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.05</td>
<td>DCM</td>
<td>0.18</td>
<td>38</td>
<td>50% conversion&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>0.10</td>
<td>DCE</td>
<td>0.18</td>
<td>75</td>
<td>56 17</td>
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<tr>
<td>5</td>
<td>0.05</td>
<td>DCE</td>
<td>0.18</td>
<td>75</td>
<td>63 27</td>
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<tr>
<td>6</td>
<td>0.05</td>
<td>CHCl₃</td>
<td>0.30</td>
<td>50</td>
<td>65 17</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>0.05</td>
<td>CHCl₃</td>
<td>0.18</td>
<td>50</td>
<td>78 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.05</td>
<td>MeCN</td>
<td>0.18</td>
<td>50</td>
<td>69 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.05</td>
<td>MeCN</td>
<td>0.09</td>
<td>80</td>
<td>89 0</td>
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<tr>
<td>10</td>
<td>0.05</td>
<td>MeCN</td>
<td>0.09</td>
<td>60</td>
<td>94 0</td>
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</table>

Reactions ran at 0.2 mmol scale. No S<sub>2</sub>2 reaction was involved for the formation of 58 from 59 as NMR spectra analysis indicated both products have the same relative stereochemistry and both azide and chloride occupy the equatorial position in their chair conformations, respectively. <sup>a</sup> Yields determined by <sup>1</sup>H NMR spectroscopy with DMF as a quantitative internal standard. <sup>b</sup> Conversion is a combination of 58 and 59.

I next focused on developing a one-pot procedure starting directly from the unsaturated amine. By starting directly from the amine, an extra purification step can be avoided and the unstable N-chloramine will not have to be stored over the course of the experiments. When amine 60 (Scheme 20, entry 1) was treated with N-chlorosuccinimide in MeCN, the N-chloramine formation occurred cleanly within one hour. Treatment of this solution with NaI and NaN₃ afforded the desired product 61 in 99% NMR yield, comparable in yield to the original procedure in Table 3, although with
a longer reaction time. Not only is one step bypassed, but the amount of NaN₃ was lowered to 1.2 equivalents without detriment. N-Iodosuccinimide (NIS), which can effect an almost instantaneous cyclization to the 3-iodopiperidine gave a lower yield of 61, probably due to competitive decomposition at that time scale (entry 2). Lowering the temperature to 60 °C had no effect on the yield or time requirement for the reaction (entry 3). Thus 60 °C was chosen as the standard condition because lower temperatures usually mean higher selectivity and functional group tolerance.

\[
\begin{align*}
\text{Entry} & & \text{Me} & & \begin{array}{c}
\text{Me} \\
\text{N} \text{H} \\
\text{Bn}
\end{array} & & \begin{array}{c}
\text{Me} \\
\text{N} \text{Me} \\
\text{N} \text{N}_3
\end{array} \\
1 & & \begin{array}{c}
1. \text{NCS (1.0 equiv), MeCN, rt} \\
2. \text{NaN₃ (1.2 equiv), NaI, 80 °C, 48 h}
\end{array} & & \text{61 (99%)²} \\
2 & & 60 & & \begin{array}{c}
1. \text{NIS (1.0 equiv), MeCN, rt} \\
2. \text{NaN₃ (1.2 equiv), 80 °C, 48 h}
\end{array} & & \text{61 (82%)²} \\
3 & & 60 & & \begin{array}{c}
1. \text{NCS (1.0 equiv), MeCN, rt} \\
2. \text{NaN₃ (1.2 equiv), NaI, 60 °C, 48 h}
\end{array} & & \text{61 (99%)²}
\end{align*}
\]

a) Yields determined by ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard. b) NIS = N-iodosuccinimide.

**Scheme 20: Optimization of a one-pot synthesis to 3-azidopiperidines**

### 1.2.2 Substrate scope for the synthesis of 3-azidopiperidines

The generality of the reaction was then tested against various unsaturated amines. First, substrates with different nitrogen substituents were examined (Table 4, entries 1-3). Substrates 57, 62, and 60 all gave the expected endo ring-opened products in 90% yield or better. Disubstituted alkenes with different configurations also form the expected piperidines with high yield, regioselectivity, and diastereoselectivity (entries 4–
In particular, the cis and trans substrates gave only cis and trans piperidines respectively, although 66 does show some of the exo ring-opened product (entries 5–8). The trisubstituted alkene 74 afforded the expected piperidine in only 28% yield, indicating that steric bulk may affect the outcome of the transformation (entry 9). Next, those substrates with different substitutions on the pentenyl backbone, including spiro and fused compounds, were examined (entries 10–16). Substrate 76, without alkyl substitution, affords β-azido cyclc amines with low regioselectivity. Substrates 79, 82, and 85 showcase the effect a single methyl substitution at either the α-, β-, or γ- position has on the outcome of the reaction (entries 11–13). Spiro and fused substrates 88, 91, and 93 cleanly yield the six-membered ring in preference to the five-membered ring (entries 14–16). Finally, hexenyl substrate 95, under the same conditions also gave a fair yield of cyclized products, but with little regioselectivity (entry 17).
Table 4: One-pot synthesis of 3-azidopiperidines from unsaturated amines

<table>
<thead>
<tr>
<th>entry</th>
<th>amine</th>
<th>product</th>
<th>yield $^a$</th>
<th>A vs. B ring $^b$ (dr) $^c$</th>
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</thead>
<tbody>
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<td>1</td>
<td></td>
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<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

$^a$ yield in %

$^b$ A only

$^c$ (dr) = diastereomeric ratio
Reactions conditions: amine (1.0 equiv, 0.3 mmol, 0.1 M), NCS (1.0 equiv), MeCN, 24 °C, 1 h; then NaI (0.05 equiv), NaN₃ (1.2 equiv), 60 °C, 48 h. a) Isolated yields. b) rs = regioselectivity of endo vs exo ring opening products determined by ¹H NMR spectroscopy and GCMS analysis of the reaction mixture. c) dr = diastereomeric ratio

### 1.2.3 3-Azidopiperidine derivatization

In order to fully appreciate the applications of this new method, I first examined the use of azide as a versatile functional group by derivatizing 3-azidopiperidine 73 (Table 4). The Staudinger reaction of 73 with PPh₃ in THF/H₂O produced 98 in 91% yield (Scheme 21). Next, a modified Staudinger reaction was developed to directly access secondary amine 99 in a three step reaction. Hydrogenolysis is known to both reduce the azide functional group and deprotect a benzyl-protected amine. Accordingly, hydrogenolysis of 73 with Pd/C in ethanol affords 100 in 87% yield. The 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate (DMAD) gives 101 in 99% yield. 73 was then subjected to two of the most commonly used chemical biology transformations, azide-alkyne click chemistry and the Staudinger ligation. The reaction
of 73 with phenylacetylene in the presence of CuSO₄ and sodium ascorbate cleanly gives 102 in 92% yield, while the Staudinger ligation product 103 was formed neatly in 90% yield. These final two successful transformations suggest the potential applications of this one-pot synthesis of 3-azidopiperidines for molecular labeling of bioactive molecules containing the piperidine motif.

**Scheme 21: Derivatization of the azide functional group**

### 1.2.4 Synthesis of other 3-functionalized piperidines

Extending this methodology, the direct use of amines as nucleophiles was examined. Taking unsaturated amines 68 and 72 as model substrates 3-aminopiperidines 104–107 were formed in yields comparable to those observed when using NaN₃ as a nucleophile (Table 5, entries 1–2). Encouraged, other heteroatom nucleophiles were examined. With NaOAc as the nucleophile the desired 3-acetopiperidines 108 and 109
Table 5: Synthesis of 3-functionalized piperidines by using different N-, O-, and C-nucleophiles

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions for step 2</th>
<th>product from 68 (yield(^a))</th>
<th>product from 72 (yield(^b))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaI (5 mol%), 60 °C, 2 h; HN\textsubscript{Et\textsubscript{2}} (2.5 equiv), 60 °C, 24 h</td>
<td>104 (53%)</td>
<td>105 (89%)</td>
</tr>
<tr>
<td>2</td>
<td>NaI (5 mol%), 60 °C, 2 h; HN(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{2}NBoc (2.5 equiv), 60 °C, 48 h</td>
<td>106 (57%)</td>
<td>107 (91%)</td>
</tr>
<tr>
<td>3</td>
<td>NaI (5 mol%), NaOAc (1.2 equiv) 60 °C, 24 h</td>
<td>108 (55%)</td>
<td>109 (84%)</td>
</tr>
<tr>
<td>4</td>
<td>NaI (5 mol%), NaSCN (1.2 equiv), 60 °C, 48 h</td>
<td>110 (31%)</td>
<td>111 (83%)</td>
</tr>
<tr>
<td>5</td>
<td>NaI (5 mol%), NaCN (1.2 equiv), 60 °C, 48 h</td>
<td>112</td>
<td>114</td>
</tr>
</tbody>
</table>

\[112 : 113 = 1:1 \text{ (57\%)}\]  \[114 : 115 = 1:1 \text{ (83\%)}\]

Reaction conditions: 68 or 72 (1.0 equiv, 0.3 mmol, 0.1 M), NCS (1.0 equiv), MeCN, 24 °C, 1 h; then NaI (0.05 equiv), NaN\textsubscript{3} (1.2 equiv), 60 °C, 48 h. a) Isolated yields. b) Ratios determined by \(^1\text{H} NMR spectroscopy.
were readily synthesized, demonstrating the potential to synthesized azasugars (entry 3). When NaSCN was used readily formed an unusual cyclic thiourea 110. However compound 72 formed the expected 3-isothiocyanatopiperidine 111 in 83% yield (entry 4). The use of NaCN as a nucleophile gave a 1 to 1 mixture of the desired 3-cyanopiperidine (112 and 114) and the unexpected 3-succinylpiperidine (113 and 115) (entry 5). This outcome suggests that the succinimide (pKₐ = 14.7) byproduct formed after the chlorination step can serve as an effective nucleophile in the presence of a base such as NaCN (HCN pKₐ = 12.7).

Intrigued by the dual role of NCS as the chlorinating agent and as the nucleophile, I decided to further explore this atom-economic transformation in the reaction of 72 with NCS. Na₂CO₃ was added to the reaction as a non-nucleophilic base to deprotonate succinimide. With succinimide as the sole nucleophile in the reaction, 115 was synthesized in 77% yield (Scheme 22). To determine if other N-chloramides could promote the tandem chlorination and aziridinium ring-opening, chloramine-T (TsNCINa) and N-chloropyrrolidinone were applied to 72. Additional base was not required in the case of chloramine-T. Excitingly, both reactions worked to give sulfonamide 116 and amide 117. These results illustrate that even very weak nucleophiles can productively ring-open an aziridinium.
Scheme 22: One-pot synthesis of 3-amidopiperidines

1.2.5 Rapid synthesis of 3-fluoropiperidines

The fluoride nucleophile is not amenable to the reaction conditions of our previous research (Table 5). Fluoride ions are inherently nucleophilic but are strongly solvated in polar solvents, severely diminishing its nucleophilicity. Additionally, inorganic fluoride salts are insoluble in non-polar solvents, again lowering their effective nucleophilicity. t-BuOH is an exception however, and is known to actually liberate the nucleophilicity of the fluoride ions.93 When MeCN was replaced by t-BuOH in the general protocol, 3-fluoropiperidines were successfully obtained from various fluoride salts.94 The addition of silver salts proved advantageous as it precipitated chloride and iodide, thereby forcing the aziridinium intermediate to occur.95 Yields for this reaction range from around 70% to 80%. The reaction takes between 3 and 6 hours for complete conversion.94 However, with the desire to extend this protocol to $^{18}$F-labeled piperidines
for PET imaging (\(^{18}F\) half-life about 110 minutes), a more rapid method was needed. NIS accelerated the halogenation and cyclization step, but the fluorination step remained too slow. AgF was replaced with TBAF and AgOTf; as \([^{18}F]\)AgF would not be available but \([^{18}F]\)TBAF would be. This system led to a very rapid formation of the desired 3-fluoropiperidines without much loss in yield over the first method (Scheme 23). This new, rapid method could potentially be utilized for the development of novel \(^{18}F\)-labeled piperidines as PET imaging tools.

\[
\text{Scheme 23: Rapid synthesis of 3-fluoropiperidines}
\]

\textit{1.2.6 Attempt at an enantioselective synthesis of 3-functionalized piperidines}

So far the protocol has only resulted in racemic 3-functionalized piperidines, however many piperidine-based bioactive molecules are not racemic and contain one or more stereocenters. As benzyl groups can function as exocyclic moieties in the
cyclization reaction, I thought that an adjacent chiral center might encourage diastereoselectivity.\textsuperscript{97-98} If diastereomeric selectivity can be achieved, then separation of the diastereomers followed by hydrogenolysis of the exocyclic benzyl-derived moieties would furnish enantiopure piperidines. Simple (S)-\(\alpha\)-phenylethylamine was selected as a possible exocyclic moiety. Cyclization to the 3-chloropiperidine gave a 3 : 5 ratio of diastereomers 125 and 126 in 82\% yield, albeit with unknown relative or absolute stereochemistry (Figure 2, A). The \(^1\text{H}\) NMR spectrum of the crude mixture clearly shows two sets of peaks corresponding to the two diastereomers (Figure 2, B). This modest selectivity suggested that a bulkier or otherwise more effective substrate could provide a single diastereomer.
Figure 2: First attempt at substrate-controlled cyclization

2',6'-Dimethoxyacetophenone (127) was thought to be a superior choice to phenylethylamine because of its increased steric bulk. Oxime formation to 128 proceeded smoothly (Scheme 24, A). Commonly the reduction of oximes with LAH produces primary amines, even if the yields are only moderate. However, the LAH reduction of this molecule produced multiple products that cannot be determined or separated from one another. Additional attempts at the reduction of this compound with DIBAL, zinc and acetic acid, zinc and ammonium formate, or Raney nickel and ammonium formate do not effectively reduce the oxime and only starting material was recovered. In another attempt, imine 129 was formed with benzylamine in the presence
of TiCl₄ (Scheme 24, B). Yet again however, the reduction of this intermediate failed after multiple attempts. Neither hydrogenation with palladium on carbon, NaBH₄, or even LAH reduced this very stable imine.

**Scheme 24: Attempts at synthesizing a bulkier chiral amine**

Perhaps the reason why this compound would not reduce was because the molecule is too electron rich. NaBH₄ and LiAlH₄ are both small reducing reagents and should not be affected by the increased steric demand imposed by the two dimethoxy groups. If the reactivity was hindered only because of the electronics of the molecule, then an electron withdrawing group on the ring should help in the reduction process. Therefore, a synthetic route was devised where the aromatic ring would be more electron-withdrawing. Halogens are an intriguing functionality for this purpose because they are electron withdrawing and are inert to LAH reductions, unlike the nitro group. However, methyl ketones are reactive to electrophilic chlorination and bromination conditions; therefore a benzaldehyde starting material was now needed. At the same time the unsaturated primary amine 132 would need to be synthesized.
Dimethylpentenal (130) was transformed into oxime 131 in 99% yield (Figure 3, A). Oxime reduction with LAH gave 132 in 71% yield. 2,6-Dimethoxybenzaldehyde (133) was easily dichlorinated by a modified Yamamoto procedure to give compound 134.  

A. Synthesis of a larger exo-group for diastereoselectivity

B. NMR spectrum of piperidine ratios

Figure 3: Final attempt at substrate-controlled, diastereomeric piperidine formation
This now electron-neutral, but bulky benzaldehyde was made into an imine with MeLi and attacked with MeLi to give the piperidine precursor. Finally, using the standard cyclization procedure was afforded two diastereomeric piperidines. Unfortunately, the yield from this reaction was only 55% and the diastereomeric ratio was 5 to 4. Both of these numbers are lower now than when using phenylethylamine, completely disproving our theory of substrate control (Figure 3, B).

1.3 Toward the synthesis of azasugars by intramolecular cyclization

The best yields and regioselectivities achieved by the new cyclization procedure were obtained when using 3,3-geminal dimethyl piperidine precursors (Table 4). Although 3,3-geminal dimethyl substituted piperidines are rare and could find use in drug discovery, they are currently non-existent in known natural products and pharmaceuticals. Therefore a functionalizable group in the 3,3-position that could direct exclusive piperidine formation was desired. Acetals, a common protecting group for carbonyls, can fulfill this need. The prospect of a 3-position carbonyl installed on a piperidine ring then led me think of diversifiable azasugars as possible targets.
1.3.1 Attempts to use S,S'-acetals to direct regioselectivity

Scheme 25: Dithianes at the 3,3-position do not give good regioselectivity

The most well-known S,S'-acetals are 1,3-dithianes, so I set out to produce a 1,3-dithiane-containing substrate. 1,3-Dithiane was transformed to 137 in 58% yield using a one-pot procedure (Scheme 25). Reduction of 137 to amine 138 gave the first S,S'-acetal-containing substrate. However, when 138 was subjected to the standard azide protocol, no cyclization was seen. It can be safely assumed that NCS is deprotecting the dithiane and destroying the molecule. NIS is an even more effective deprotecting reagent than NCS, but N-iodoamine formation should be faster than deprotection. The N-iodoamine intermediate should cyclize immediately upon formation to the 3-iodopiperide so that deprotection will not occur. Indeed, the desired 3-iodopiperidine 139 was formed in
82% yield without any pyrrolidine byproduct. Unfortunately the regioselectivity was not great when irreversible nucleophiles (NaN₃, NaOAc, TBAF) were added to the reaction, proving that 1,3-dithianes are not the group we were hoping it would be.

Scheme 26: Forward synthesis of new S,S'-acetals

However, perhaps acyclic or bulkier S,S'-diphenyl acetal derivatives would provide better regioselectivity. Retrosynthetic analysis revealed that the piperidine precursors could originate from a 3,3-sigmatropic rearrangement of a dichlorovinylether to give a diversifiable α,α-dichloroaldehyde (Scheme 26). Going forward with this analysis, trichloroethanol and allyl bromide were coupled together under phase transfer conditions to give allyl ether 140. Then 140 was subjected to elimination and thermal rearrangement to form α,α-dichloroaldehyde 141. 141 was then substituted by various
thiols in aqueous base to give various \( \alpha,\alpha \)-disulphenyl aldehydes \(^{142-145}\). Reductive amination of the intermediates met with varied success to give compounds \(^{146-149}\); unfortunately hindered and/or electron rich \(^{144}\) could not be reduced under any condition attempted.\(^{111-113}\)

Cyclization experiments were then conducted (Table 6). Compound \(^{146}\) seemed the most likely to give the best regioselectivity, as it is acyclic and very large. Unfortunately, the outcome of the cyclization was a 2.6 : 1.3 : 1.0 mixture of the piperidine : SM : pyrrolidine, even smaller than that seen for the 1,3-dithiane case. \(^{147}\) and \(^{148}\) were unable to properly react, perhaps \(\text{S,S'}\) -dipropylacetals are easier to cleave by oxidation than the other \(\text{S,S'}\) -acetals. As steric bulk on the amine should force high regioselective piperidine formation, \(^{149}\) was subjected to the cyclization conditions.\(^{106}\) However, the regioselectivity found was only a 3 : 2 mixture of piperidine : pyrrolidine.

![Table 6: Regioselectivity outcomes when using S,S'-acetals](image)

**Table 6: Regioselectivity outcomes when using S,S'-acetals**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Regioselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{146}): R = Ph, R' = n-Bu</td>
<td>13 : 5</td>
</tr>
<tr>
<td>(^{147}): R = Pr, R' = n-Bu</td>
<td>No Cyclization</td>
</tr>
<tr>
<td>(^{148}): R = Pr, R' = t-Bu</td>
<td>No Cyclization</td>
</tr>
<tr>
<td>(^{149}): R = -(CH(_2))(_5), R' = t-Bu</td>
<td>3 : 2</td>
</tr>
</tbody>
</table>

**1.3.2 Attempts to use O,O'-acetals to direct regioselectivity**

\(\text{S,S'}\)-Acetals were then abandoned, but \(\text{O,O'}\)-acetals could still work. A route starting from acetates \(^{150-151}\) was attempted (Scheme 27). Compound \(^{150-151}\) were
alkylated to compounds 152–153. Bulkier base LiTMP seems to be better at this reaction. Amide 154 was obtained but could not be reduced under any circumstances. However, the 152–153 were reduced by LAH to the alcohols in moderate yield to obtain 155–156. These alcohols were oxidized to aldehydes 157–158 by PCC.114-115 The piperidine precursors 159–160 were obtained by following standard reductive amination conditions. Unfortunately only a 3 : 2 regioselectivity in favor of the piperidine was observed when diethyl acetal 159 was subjected to standard cyclization procedures. The same reaction was attempted with cyclic acetal 160, but the regioselectivity for piperidine formation was even lower (10 : 9).

\[\text{Scheme 27: Synthesis of } O,O\text{-acetals and their effect on piperidine formation}\]

a) 152: LiTMP, allyl bromide, THF (82%), 153: LDA, allyl bromide, THF (38%, 95% pure); b) KOH, EtOH; then EDCI, BnNH₂, Et₃N, DCM (13%); c) 155: LAH, Et₂O, 0 °C (48%, isolated with EtOH), 156: LAH, Et₂O, 0 °C (53%); d) 157: PCC, DCM, 4 Å MS (15%), 158: PCC, NaOAc, DCM, 3 Å MS (59%); e) 159: BnNH₂, DCM/EtOH, 160: BnNH₂, DCM/MeOH; f) 159: NaBH₄, DCM/EtOH (49% over 2 steps), 160: NaBH₄, DCM/MeOH (95% over 2 steps, 95% pure). g) NCS, MeCN; h) NaI, NaOAc, MeCN, 60 °C.
1.3.3 Conclusion on the use of acetals

Although the yields using β-substituted piperidine substrates is still high, it is now clear to us that the regioselectivity is not just dependent on the Thorpe-Ingold effect or on steric bulk. It seems that there is a large electronic effect involved that is hard to discern (Table 7). Since the regioselectivity of either S or O-acetals is not as high as using geminal dimethyl groups, this synthetic route will no longer be explored.

Table 7: Complete summary of acetal effects on piperidine selectivity

<table>
<thead>
<tr>
<th>Acetal</th>
<th>Cassette</th>
<th>Regioselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>146: R = SPh, R' = n-Bu</td>
<td>1. Cyclization</td>
<td>13 : 5</td>
</tr>
<tr>
<td>147: R = SPr, R' = n-Bu</td>
<td>2. NaOAc, MeCN</td>
<td>No cyclization</td>
</tr>
<tr>
<td>148: R = SPr, R' = t-Bu</td>
<td></td>
<td>No cyclization</td>
</tr>
<tr>
<td>149: R = S(CH₂)₂S-, R' = t-Bu</td>
<td></td>
<td>3 : 2</td>
</tr>
<tr>
<td>138: R = S(CH₂)₂S-, R' = i-Pr</td>
<td></td>
<td>4 : 1</td>
</tr>
<tr>
<td>160: R = O(CH₂)₂O-, R' = Bn</td>
<td></td>
<td>10 : 9</td>
</tr>
<tr>
<td>159: R = OEt, R' = Bn</td>
<td></td>
<td>3 : 2</td>
</tr>
<tr>
<td>60: R = Me, R' = Bn</td>
<td></td>
<td>&gt;20 : 1</td>
</tr>
</tbody>
</table>

1.4 Synthesis of labeled σ₁ receptor ligands

1.4.1 Introduction

Piperidines are ubiquitous structures; yet they are particularly noteworthy in sigma receptor ligands. The σ₁ receptors are generally located in the central nervous system (CNS) or in the endoplasmic reticulum in individual cells. The σ₁ receptor is known to be overexpressed in many cancer cell lines and is implicated in several neurodegenerative diseases. These receptors also regulate several processes involved in homeostasis and neuronal differentiation. Therfore, σ₁ receptor ligands are
often cited as possible therapeutic and diagnostic agents. The similar, but less studied \( \sigma_2 \) receptor is often ligated with the same types of small molecules, making the ratio of affinities (K’s) very important in determining the ligand’s efficacy and utility.

1.4.1.1 \(^{123}\)I-labeled piperidine-based \( \sigma_1 \) receptor ligands

Single-photon emission tomography (SPECT) is a gamma ray-emitting medical imaging technique that commonly uses radioisotope \(^{123}\)I in the form of Na\(^{123}\)I. However, \(^{123}\)I can also be incorporated into an organic molecule as a radiopharmaceutical, such as in \([^{123}\)I]iobenguane (Figure 4, 163). Waterhouse and co-workers used Na\(^{123}\)I to label four possible \( \sigma_1 \) receptor ligands with \(^{123}\)I from the corresponding tetrabutylltin precursors. The compound that showed the most promise out of the four is compound 164.

![Figure 4: \(^{123}\)I-labeled compounds for SPECT](image)

1.4.1.2 \(^{11}\)C-labeled piperidine-based \( \sigma_1 \) receptor ligand

Positron emission tomography (PET) is yet another imaging technique which uses ionizing energy. Though most associated with the \(^{18}\)F radioisotope, \(^{11}\)C is yet another commonly used isotope that decays by positron emission. Employing \( \sigma_1 \) receptor ligand data obtained by Berardi and co-workers, Zheng and co-workers developed a \(^{11}\)C-labeled synthesis which took about 15–20 min from start to finish using
$^{[11]}\text{C}\text{MeOTf}$ as the radioactive precursor (Scheme 28).\textsuperscript{128} Accounting for the half-life of $^{11}\text{C}$ (about 20 min), the decay corrected radiochemical yields were between 40\%–50\%.

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme28.png}
\end{center}

**Scheme 28: $^{11}\text{C}$-labeled $\sigma_1$-receptor ligands**

1.4.1.3 $^{18}\text{F}$-labeled $\sigma_1$ receptor ligands that do not involve the aziridinium intermediate

$^{11}\text{C}$ has a much shorter half-life than the more commonly used PET radioisotope $^{18}\text{F}$ (110 minutes). $^{18}\text{F}$ is also advantageous because it emits positrons that have the lowest energy of any other positron emitting isotope; this translates into sharper images during a PET scan.\textsuperscript{96} Several $^{18}\text{F}$-labeled $\sigma_1$ receptor ligands have been developed. An interesting $^{18}\text{F}$-benzothiazolone compound shows remarkable picomolar affinity for both sigma receptors (Table 8, A).\textsuperscript{116} When placed in mice the compound clearly entered the brain, reaching peak signal just a few minutes after injection. The other $^{18}\text{F}$-labeled $\sigma_1$ receptor ligands listed share a very similar skeleton; however their specific $K_i$'s and ratios can be tuned (Table 8, B–D).\textsuperscript{129–131} Interestingly, as time and research goes on, both the nanomolar affinity for the $\sigma_1$ receptor and the $K_i (\sigma_2)/K_i (\sigma_1)$ ratio between the two receptors has steadily increased.
Table 8: Recent $^{18}$F-labeled $\sigma_1$ receptor ligands and their affinity data

<table>
<thead>
<tr>
<th>Compound</th>
<th>Year</th>
<th>$K_i$ ($\sigma_1$) [nM]</th>
<th>$K_i$ ($\sigma_2$) [nM]</th>
<th>$K_i$ ($\sigma_2$)/$K_i$ ($\sigma_1$)</th>
<th>Ref. #</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2012</td>
<td>0.0025 ± 0.0009</td>
<td>0.96 ± 0.21</td>
<td>384</td>
<td>116</td>
</tr>
<tr>
<td>B</td>
<td>2013</td>
<td>5.4 ± 0.4</td>
<td>164 ± 20</td>
<td>30.4</td>
<td>129</td>
</tr>
<tr>
<td>C</td>
<td>2015</td>
<td>1.85 ± 1.59</td>
<td>291 ± 111</td>
<td>157</td>
<td>130</td>
</tr>
<tr>
<td>D</td>
<td>2016</td>
<td>1.47 ± 0.89</td>
<td>1304 ± 475</td>
<td>887</td>
<td>131</td>
</tr>
</tbody>
</table>

1.4.1.4 $^{18}$F$^-$ ring-opening of azetidinium and aziridinium intermediates for PET imaging

Azetidinium rings are the 4-membered analogs of aziridiniums and have similar reactivity. In their studies to visualize cyclin-dependent kinases, Mamat and co-workers attempted to synthesize $^{18}$F-labeled pyrido[2,3-$d$]pyrimidines. These compounds were heavily modified from the original studies, but azetidinium rings were nonetheless synthesized and converted to the respective labeled compounds (Scheme 29). Interestingly, the authors report that a similar synthesis using the aziridinium system was unsuccessful.
Scheme 29: Nucleophilic $^{18}$F-fluorination of an azetidinium ring

Consequently, Nag and co-workers utilized the aziridinium intermediate in their synthesis of monoamine oxidase-B inhibitors (Scheme 30, A).$^{134}$ A bicyclic aziridinium was ring-opened with $^{18}$F to give 3-$^{18}$F-fluoropiperidines.$^{135}$ The radiolabeled compounds were formed easily and reliably, but the compounds showed limited success during the *in vivo* studies. To my knowledge, there is only one example of an $^{18}$F-labeled $\sigma_1$ receptor ligand produced via the aziridinium intermediate. This $^{18}$F-labeled piperidine-based compound by Waterhouse and co-workers is a derivative of their earlier $^{123}$I-labeled $\sigma_1$ receptor ligand.$^{124, 136}$ 1,2-Aminomesylate gave the $^{18}$F-labeled piperidine in 15 min; this compound was tested in rodents and showed noteworthy uptake in various organs by PET imaging (Scheme 30, B).
Scheme 30: Examples of nucleophilic $^{18}$F-aziridinium ring-opening

1.4.2 $^{18}$F-labeling with the aminofluorination protocol

This exo-$^{18}$F-labeling of a piperidine should be surpassed by work that incorporated the $^{18}$F inside the piperidine ring. I therefore sought to utilize my own rapid aminofluorination on a known $\sigma_1$ receptor ligand. The target molecule in this study is one of the highly selective studied by Berardi and co-workers (Figure 5, 165). The original PET-imaging variation of the ligand is the same molecule labeled with a $^{11}$C isotope at the methoxy position 166. The $^{11}$C radioisotope only has a half-life of 20 minutes, much shorter than the half-life of $^{18}$F (110 minutes). $^{18}$F is also advantageous because it emits positrons that have the lowest energy of any other positron emitting isotope; this translates into sharper images during a PET scan. I therefore propose that $^{18}$F-labeled 167 can be achieved using the rapid aminofluorination protocol developed in scheme 21. The azide derivative 168 could be used to label the $\sigma_1$ receptor in a different capacity. For instance, a 3-azidopiperidine would be able to covalently bond to a fluorescent tag to reveal cellular targets.76
1.4.3 Initial synthetic route to 3-fluorinated $\sigma_1$ receptor ligand

**A. Literature retrosynthesis**

![Diagram of initial synthetic route to 3-fluorinated $\sigma_1$ receptor ligand]

**B. Revised retrosynthesis**

![Diagram of revised retrosynthesis to 3-fluorinated $\sigma_1$ receptor ligand]

Scheme 31: Literature and revised retrosynthetic analysis

Literature research of the unlabeled and $^{11}$C-labeled naphthalene derivatives reveals that the basic retrosynthetic analysis for the skeleton of the target has already
been completed (Scheme 31, A).\textsuperscript{7, 128} In the unlabeled ligand, the final step is an N-alkylation of the primary alkyl chloride with 3,3-dimethylpiperidine. However, since the aminofluorination (limited by \textsuperscript{18}F half-life) protocol necessitated that the penultimate structure be secondary amine \textsuperscript{169}; N-alkylation was not trusted to occur only once and reductive amination from aldehyde \textsuperscript{170} was favored instead (Scheme 31, B).\textsuperscript{94}

\textbf{Scheme 32: Initial synthetic route to piperidine precursor 169}

Tetralone \textbf{171} was attacked with a Grignard reagent and the resulting tertiary alcohol eliminated to give \textbf{172} in 21% yield (Scheme 32). Full aromatization to \textbf{173} could easily be achieved with DDQ. Deprotection of the silyl ether was obtained with HCl in 93% yield. Alcohol \textbf{174} was oxidized with PCC to give aldehyde \textbf{170}. Reductive

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{Scheme32.png}};
\end{tikzpicture}
\end{center}

\textsuperscript{a} Mg\textsuperscript{+}, (3'-bromopropoxy)(tert-butyl)dimethylsilane, THF, reflux; then AcOH (21%); b) DDQ, toluene (73%); c) HCl, H\textsubscript{2}O, EtOH (93%); d) PCC, DCM (78%); e) MeOH/DCM (3 : 1); then NaBH\textsubscript{4}, MeOH/DCM (1 : 1), 0 °C to rt (75% over two steps).
amination of 170 with 132 was achieved in a two-step manner in 75% yield. Overall efficiency to the piperidine precursor was just over 8%, already lower than the 9% overall yield reported for the synthesis of $^{11}$C-radiotracer 166. Therefore a new synthetic route was sought.

### 1.4.4 Revised synthetic route and biochemical outcome

The forward synthesis to labeled compounds 167–168 was reexamined and it was discovered that an acetal protecting group could replace the silyl ether protecting group. The new route would remove an oxidation step from the synthesis while still keeping the overall scheme intact. The new acetal protecting group is also more atom economical than the original silyl ether group. Notably, the Grignard reaction of tetralone 171 to 175 occurred in 73% yield. Oxidation to the naphthalene structure 176 was accomplished with DDQ in 97% yield. The resulting compound was deprotected using AcOH/H$_2$O at 60 °C; lower temperatures for extended periods of time did not effect deprotection. The two-step reductive amination to the target precursor 169 was completed in 75% yield. There are now less synthetic steps required and a higher overall yield (46% up to this point) than that previously reported for the $^{11}$C-labeled compound.
a) Mg\(^{2+}\), 2-(2′-bromoethyl)-1,3-dioxolane, THF, reflux; then AcOH (73%); b) DDQ, toluene (97%); c) AcOH, H\(_2\)O, 60 °C (86%); d) 132, MeOH/DCM (3 : 1); then NaBH\(_4\), MeOH/DCM (1 : 1), 0 °C to rt (75% over two steps).

Scheme 33: Revised synthesis to piperidine precursor 171

Initially it was thought that the new fluorine atom may actually make the ligand-receptor interaction stronger and that the azide substitution would have no effect.\(^{137-138}\) However, both the \(^{19}\)F-compound 177 and N\(_3\)-compound 168 needed to be tested biochemically to prove this hypothesis. Along with 177 and 168, the original ligand 165 and the 3-chloropiperidine 178 were needed as controls for the assays.

\(^{19}\)F compound 177 was synthesized in 80% yield using standard conditions, showcasing the potential use in PET imaging (Figure 6, A). 3-Chloro compound 178 was also synthesized in 80% yield while the N\(_3\) compound 168 was synthesized in only 53% yield. An attempt at original ligand 165 was made by subjecting 178 to NaBH\(_4\) in MeOH.\(^{139}\) Reduction was not seen, but instead substitution of the chloride by methoxide
gave 3-methoxypiperidine 179 in 55% yield. Therefore reduction with LAH was attempted, 165 was synthesized in 26% yield in this manner.\textsuperscript{103}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure6}
\caption{Synthesis and binding values of each ligand}
\end{figure}

These five compounds (165, 168, 177–179) were tested in a competitive binding assay.\textsuperscript{140} The results indicate that the new functionalities change the binding capacity for the $\sigma_1$ receptors substantially (Figure 6, B). All the compounds except for the chlorinated product 178 have $K_i$'s orders of magnitude higher than the original compound 165. The disappointing data for these compounds mean that $^{18}$F-labeled compound 167 should not be synthesized or advanced to PET imaging.
1.4.5 Synthesis of 2nd generation ligands and biochemical outcome

Further inquiry into what types of skeletons bind well to the \( \sigma_1 \) receptor reveals that the 3,3-geminal dimethyl group on the piperidine ring is not necessary, and many single methyl group derivatives at the 2, 3, or 4 position are also good binders.\(^7\), \(^{125}\), \(^{127}\) Perhaps an additional group at the 3’ position distorts the binding capacity. To alleviate this problem, I planned to construct the piperidine ring such that a single methyl and the new nucleophile (F, Cl, or N\(_3\); \(180-182\) will be on the same carbon in a 3,3-geminal fashion.

The general synthetic scheme will stay the same, only a new amine needed to be synthesized (Scheme 34, A). Starting with a Johnson–Claisen rearrangement, unsaturated ester \(184\) was synthesized in 57% yield (Scheme 33, B).\(^{141}\) Direct conversion of the ester to the amide using aqueous ammonia and catalytic NaCN proved difficult to scale, but nonetheless gave \(185\) in a 65% yield.\(^{142}\) However, reduction of the amide to the amine posed a challenge. LAH reduction on \(185\) was carried out, but the amine product is much more volatile than amine \(132\), and significant portions of the product were lost. Attempted isolation of the hydrochloride salt led to decomposition. The best way to obtain piperidine precursor \(183\) was a three-step reduction of \(185\) and aldehyde \(170\), which yielded the secondary amine \(183\) in 71%.
a) triethyl orthoacetate, propionic acid (57%); b) NH$_3$, MeOH/H$_2$O, NaCN, 45 °C (65%); c) LAH, THF; then 170, MeOH/DCM (3 : 1); then NaBH$_4$, MeOH/DCM (1 : 1), 0 °C to rt (73% over three steps).

Scheme 34: Proposed 2nd generation ligands and synthesis to precursor 183

The natural abundance $^{19}$F version, along with the N$_3$ and Cl derivatives were synthesized via the normal reaction conditions (182–184, Figure 7, A). Notably, the yields for 182–184 were all lower than in the 3,3-dimethyl case. Interestingly, the reaction with NaN$_3$ gave a mixture of piperidine and pyrrolidine rings 184 and 188 respectively, whereas the fluorination reaction gave only the piperidine product.

When subjected to the same biochemical scrutiny as the earlier generation of compounds, all the new compounds displayed strong nanomolar affinity for both sigma receptors (Figure 7, B).$^{140}$ All displayed a higher $K_i$ for $\sigma_1$ than for $\sigma_2$, though not greater than a four-fold difference. Out of all the other proteins tested (47 in total), the SERT transport protein was the only other potential target, although the $K_i$ was on average 10
times higher than for the $\sigma_1$ receptor. With this data in hand, we decided to push the limit of the aminofluorination protocol and continue on to the $^{18}$F-fluorination studies.

A. Synthesis of 2nd generation ligands

$$\begin{align*}
183 \quad \text{cyclization conditions} \\
\text{a, b = 180} \\
\text{c, d = 181} \\
\text{c, e = 182 and 186}
\end{align*}$$

B. Biochemical outcome for new ligands

<table>
<thead>
<tr>
<th>compound</th>
<th>X group</th>
<th>$K_i$ [nM]</th>
<th>SERT</th>
<th>$\sigma_1$</th>
<th>$\sigma_2$</th>
</tr>
</thead>
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<tr>
<td>165</td>
<td>H</td>
<td>319</td>
<td>16</td>
<td>62</td>
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<tr>
<td>180</td>
<td>F</td>
<td>239</td>
<td>38</td>
<td>56</td>
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<tr>
<td>181</td>
<td>Cl</td>
<td>198</td>
<td>17.5</td>
<td>61</td>
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<tr>
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<td>N$_3$</td>
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</tr>
<tr>
<td>186</td>
<td>N$_2$</td>
<td>235</td>
<td>63.5</td>
<td>115</td>
<td></td>
</tr>
</tbody>
</table>

a) NIS, t-BuOH, rt; b) AgOTf, TBAF, 70 °C, 30 min (27%) c) NCS, MeCN, rt, 1 h; d) NaI, 60 °C (50%); e) NaI, NaN$_3$, 60 °C (47%, 1.1 : 1 ratio of 182 to 186).

Figure 7: Synthesis and outcome for the 2nd generation receptor ligands

1.5 Conclusion

A general synthetic protocol for 3-functionalized piperidines has been achieved. The utility of 3-azidopiperidines with well-known azide transformations has been proven, while the efficacy of nitrile, acetate, amine, and isothiocyanate functionalities in the 3-position of a highly substituted piperidine can easily be imagined. Unfortunately an enantioselective method for the synthesis of 3-functionalized piperidines could not be achieved by substrate control. The synthesis of azasugars by use of acetals usually gave
high yields of cyclization, but regioselectivity remained low throughout. A fluorine atom can be quickly introduced to the 3-position of a piperidine ring with a modified procedure. The extension of this aminofluorination to the labeling of a confirmed \( \sigma_1 \) receptor ligand has been described. With this data in hand, collaborators are working toward applying the rapid aminofluorination to the synthesis of the desired \( ^{18}\text{F} \)-labeled \( \sigma_1 \) receptor ligand for PET imaging.

**1.6 Supplemental information**

**1.6.1 General information**

Glassware and stir bars were dried in an oven at 140 °C for at least 12 h and then cooled in a desiccator cabinet over Drierite prior to use. Unless otherwise noted, reactions were performed without exclusion of air or moisture. Optimization screens were performed in 1 dram reaction vials and substrate screens were performed in 2 dram reaction vials. Both reaction vials were sealed with Teflon caps. Plastic syringes or glass pipets were used to transfer liquid reagents. Reactions were stirred magnetically using Teflon-coated, magnetic stir bars. All reagents and solvents were purchased from commercial sources and used as received unless otherwise stated. \( N \)-chlorosuccinimide (NCS) was recrystallized from boiling water then dried under a vacuum and stored in a desiccator. \( N \)-iodosuccinimide (NIS) was recrystallized from boiling dioxane and MTBE, crushed under a mortar and pestle, filtered, washed with hexanes, and then stored in a dark vial. Sodium thiocyanate was dried under a vacuum at 60 °C prior to use. \( N \)-
chloropyrrolidinone was synthesized according to the method of Zhong.\textsuperscript{143} \textit{n}-BuLi was titrated using 1,3-diphenyl-2-propanone tosylhydrazone directly before use.\textsuperscript{144} Anhydrous toluene, THF, Et\textsubscript{2}O, and DCM were obtained from a DriSolve purification system when necessary. Organic solutions were concentrated \textit{in vacuo} using a rotary evaporator. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to KMnO\textsubscript{4} stain. Column chromatography was performed with silica gel (60 Å, standard grade). Melting points were determined in open capillary tubes using a Mel-Temp II apparatus and are uncorrected. Proton, carbon and fluorine nuclear magnetic resonance spectra were recorded at ambient temperature (unless otherwise stated) using a Varian INOVA 400 (400, 100, 376 MHz respectively) or Varian Unity (500, 125, 470 MHz respectively). All values for proton chemical shifts are reported in parts per million (\delta) and are referenced to the residual protium in CDCl\textsubscript{3} (\delta 7.24). All values for carbon chemical shifts are reported in parts per million (\delta) and are referenced to the carbon resonances in CDCl\textsubscript{3} (\delta 77.0). Chemical shifts for \textsuperscript{19}F NMR are reported in parts per million (\delta) and are referenced to the fluorine resonances of CFCl\textsubscript{3} (\delta 00.0). NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz), integration. Infrared spectroscopic data obtained using a Thermo Scientific Nicolet 380 and are reported in
wavenumbers (cm⁻¹). High-resolution mass spectra were obtained through the Duke University Mass Spectrometry Facility using an Agilent 1100 Series liquid chromatography-electrospray ionization mass spectrometer.

1.6.2 Experimental procedures and characterization data

**N-Benzyl-2,2,5-trimethylhex-4-en-1-amine (74).** NaBH(OAc)₃ (0.979 g, 4.62 mmol, 1.4 equiv) was added slowly to a solution of 2,2,5-trimethylhex-4-enal (0.465 g, 3.3 mmol, 1.0 equiv) and benzylamine (0.36 mL, 3.3 mmol, 1.0 equiv) in DCE (10 mL) and the suspension stirred for 8 h at room temperature. Then the reaction was quenched with aqueous NaOH (30 mL, 15%) and extracted with Et₂O (3 × 20 mL). The organic layers were combined, dried over Na₂SO₄, filtered, and the filtrate concentrated *in vacuo*. The crude mixture was distilled *in vacuo* (bp 123 °C at 8 Torr) to yield 74 as a colorless liquid (0.477 g, 62%). ¹H NMR (400 MHz, CDCl₃): δ 7.32–7.19 (m, 5H), 5.15–5.09 (m, 1H), 3.77 (s, 3H), 2.34 (s, 2H), 1.92 (d, J = 7.7 Hz, 2H), 1.68 (s, 3H), 1.58 (s, 3H), 1.23 (s, br, 1H), 0.86 (s, 6H).

**General Procedure for the One-Pot Azido-Cyclization Reactions**

To a solution of unsaturated amine (0.3 mmol, 1 equiv) in anhydrous MeCN (3 mL) was added NCS (0.3 mmol, 1 equiv). The reaction solution was allowed to stir in the dark for 2 h, after which NaN₃ (0.36 mmol, 1.2 equiv) and NaI (0.015 mmol, 0.05 equiv) were added. The solution was then immediately heated to 60 °C and allowed to stir for 48 h before the solution was cooled back down to room temperature. The reaction
mixture was diluted with an aqueous solution of NaOH (7 mL, 0.4M) and placed into a separatory funnel. The product(s) were then extracted with hexanes (4 × 10 mL). The hexane layers were combined and washed with an aqueous solution of NaOH (5 mL, 1.25M) followed by brine (15 mL). The organic layer was dried over Na\(_2\)SO\(_4\) and filtered. The filtrate was concentrated \textit{in vacuo}. The crude residue was then purified by either column chromatography or Kugelrohr distillation.

\textbf{5-Azido-1-butyl-3,3-dimethylpiperidine (58).} Isolation by Kugelrohr distillation; Clear liquid (57.8 mg, 92%); \(R_f = 0.55\) (10% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.57 (ddt, \(J = 11.4, 10.5, 4.5 \text{ Hz}, 1\)H), 2.98 (ddt, \(J = 10.5, 4.5, 1.7 \text{ Hz}, 1\)H), 2.38 (dt, \(J = 11.1, 1.7 \text{ Hz}, 1\)H), 2.35–2.23 (m, 2H), 1.74 (t, \(J = 10.5 \text{ Hz}, 1\)H), 1.71 (ddt, \(J = 12.5, 4.5, 1.7 \text{ Hz}, 1\)H), 1.65 (d, \(J = 11.1 \text{ Hz}, 1\)H), 1.47–1.37 (m, 2H), 1.32 (sextet, \(J = 7.3 \text{ Hz}, 2\)H), 1.09 (t, \(J = 12.0 \text{ Hz}, 1\)H), 1.01 (s, 3H), 0.93 (s, 3H), 0.90 (t, \(J = 7.3 \text{ Hz}, 3\)H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 65.0, 58.5, 57.9, 55.6, 42.8, 31.6, 29.4, 29.1, 25.6, 20.5, 14.0; FTIR (thin film), cm\(^{-1}\) 2954, 2929, 2092, 147; HRMS-ESI (m/z) calcd. for C\(_{11}\)H\(_{23}\)N\(_4\) ([M+H]\(^+\)): 211.1917; found: 211.1919.

\textbf{5-Azido-1-(tert-butyl)-3,3-dimethylpiperidine (63).} Isolation by Kugelrohr distillation; Clear liquid (55.3 mg, 90%); \(R_f = 0.56\) (10% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.48 (ddt, \(J = 11.1, 10.4, 4.3 \text{ Hz}, 1\)H), 3.16 (ddt, \(J = 10.4, 4.3, 1.9 \text{ Hz}, 1\)H), 2.50 (dt, \(J = 11.1, 1.9 \text{ Hz}, 1\)H), 1.84 (t, \(J = 10.4 \text{ Hz}, 1\)H), 1.78 (d, \(J = 11.1 \text{ Hz}, 1\)H), 1.71 (ddt, \(J = 12.3, 4.3, 1.9 \text{ Hz}, 1\)H), 1.07 (t, \(J = 11.7 \text{ Hz}, 1\)H), 1.03 (s, 9H), 0.99 (s, 3H), 0.93 (s,
3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 57.9, 56.7, 53.3, 51.5, 43.1, 31.5, 29.4, 26.4 (3C), 25.3; FTIR (thin film), cm$^{-1}$ 2089, 1362, 1251, 1225; HRMS-ESI (m/z) calcd. for C$_{11}$H$_{25}$N$_4$ ([M+H]$^+$): 211.1917; found: 211.1918.

5-Azido-1-benzyl-3,3-dimethylpiperidine (61). Isolation by Kugelrohr distillation; Clear liquid (69.6 mg, 95%); R$_f$ = 0.52 (10% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.36–7.22 (m, 5H), 3.61 (ddt, $J$ = 11.5, 10.5, 4.5 Hz, 1H), 3.52 (d, $J$ = 13.5 Hz, 1H), 3.47 (d, $J$ = 13.5 Hz, 1H), 2.99 (ddt, $J$ = 10.5, 4.5, 2.0 Hz, 1H), 2.36 (dt, $J$ = 10.8, 2.0 Hz, 1H), 1.83 (t, $J$ = 10.5 Hz, 1H), 1.74 (ddt, $J$ = 12.5, 4.5, 2.0 Hz, 1H), 1.72 (d, $J$ = 10.8 Hz, 1H), 1.13 (t, $J$ = 12.0 Hz, 1H), 1.05 (s, 3H), 0.91 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 138.5, 128.6 (2C), 128.2 (2C), 127.0, 64.7, 62.5, 58.1, 55.5, 42.8, 31.8, 29.2, 25.5; FTIR (thin film), cm$^{-1}$ 2092, 1254, 737, 697; HRMS-ESI (m/z) calcd. for C$_{14}$H$_{21}$N$_4$ ([M+H]$^+$): 245.1761; found: 245.1761.

3-Azido-1-isobutyl-3,5,5-trimethylpiperidine (65). Isolation by Kugelrohr distillation; Clear liquid (46.3 mg, 69%); R$_f$ = 0.75 (10% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ 2.58 (dt, $J$ = 11.9, 1.8 Hz, 1H), 2.32 (dt, $J$ = 10.9, 1.8 Hz, 1H), 2.03 (d, $J$ = 7.4 Hz, 2H), 1.93 (d, $J$ = 11.9 Hz, 1H), 1.76 (septet, $J$ = 6.6 Hz, 1H), 1.73 (d, $J$ = 10.9 Hz, 1H), 1.52 (dt, $J$ = 14.1, 1.8 Hz, 1H), 1.25 (s, 3H), 1.15 (d, $J$ = 14.1 Hz, 1H), 1.14 (s, 3H), 0.97 (d, $J$ = 6.6 Hz, 3H), 0.89 (s, 3H), 0.96 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 66.4, 66.1, 63.3, 60.4, 47.1, 31.3, 29.9, 26.8, 26.3, 25.9, 20.8, 20.6; FTIR (thin film), cm$^{-1}$ 2952,
cis-3-Azido-1-butyl-2-ethylpiperidine (69) and (isomer). Isolation by column chromatography (10% ethyl acetate–hexanes); Yellow liquid (39.6 mg, 63%, 6:1 ratio); Rf = 0.14 (20% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 3.73 (dt, J = 6.3, 3.3 Hz, 1H, 69), 3.12 (dt, J = 9.7, 4.3 Hz, 1H, isomer) 3.06 (ddd, J = 10.0, 5.2, 3.1 Hz, 1H, isomer), 2.80–2.69 (m, 1H, 69; m, 1H, isomer), 2.64 (dt, J = 9.0, 5.0 Hz, 1H, isomer), 2.56 (t, J = 7.6 Hz, 2H, 69), 2.42–2.28 (m, 2H, 69; m, 2H, isomer), 2.22 (q, J = 8.3 Hz, 1H, isomer), 1.94–1.84 (m, 1H, 69), 1.84–1.21 (m, 9H, 69; m, 9H, isomer), 1.01 (t, J = 7.4 Hz, 3H, isomer), 0.94 (t, J = 7.4 Hz, 3H, 69), 0.91 (t, J = 7.4 Hz, 3H, isomer), 0.90 (t, J = 7.2 Hz, 3H, 69); ¹³C NMR (125 MHz, CDCl₃, 69): δ 63.4, 58.9, 53.1, 49.8, 27.6, 27.4, 21.5, 20.7, 19.8, 14.0, 11.6; ¹³C NMR (125 MHz, CDCl₃, isomer): δ 68.5, 67.1, 56.5, 54.4, 31.3, 27.7, 27.2, 24.2, 23.2, 20.5, 11.4; FTIR (thin film), cm⁻¹: 2956, 2931, 2091, 1255; HRMS-ESI (m/z) calcd. for C₁₁H₂₃N₄ ([M+H]+): 211.1917; found: 211.1918.

cis-3-Azido-1-(tert-butyl)-2-ethylpiperidine (71). Isolation by column chromatography (1% ethyl acetate–1% NH₄OH–hexanes); Clear liquid (38.0 mg, 60%); Rf = 0.44 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 3.62 (dt, J = 11.7, 4.7 Hz, 1H), 3.18–3.13 (m, 1H), 2.85–2.78 (m, 1H), 2.46 (td, J = 12.9, 2.7 Hz, 1H), 1.86–1.76 (m, 1H), 1.62–1.38 (m, 5H), 1.11 (s, 9H), 0.97 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ
62.4, 57.3, 54.2, 38.2, 29.5 (3C), 25.9, 25.0, 17.4, 12.8; FTIR (thin film), cm⁻¹ 2970, 2094, 1254, 1219; HRMS-ESI (m/z) calcd. for C₁₁H₂₃N₄([M+H]+): 211.1917; found: 211.1916.

trans-3-Azido-1-butyl-2,5,5-trimethylpiperidine (71). Isolation by column chromatography (1% ethyl acetate–1% NH₄OH–hexanes); Clear liquid (51.4 mg, 76%); Rf = 0.59 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 3.06 (ddd, J = 11.9, 9.4, 4.7 Hz, 1H), 2.66 (ddd, J = 13.2, 9.0, 6.6 Hz, 1H), 2.42 (dd, J = 11.5, 2.3 Hz, 1H), 2.36 (ddd, J = 13.2, 8.5, 5.4 Hz, 1H), 1.96 (dq, J = 9.4, 6.1 Hz, 1H), 1.93 (d, J = 11.5 Hz, 1H), 1.78 (ddd, J = 12.6, 4.7, 2.3 Hz, 1H), 1.46–1.21 (m, 4H), 1.23 (t, J = 12.3 Hz, 1H), 1.19 (d, J = 6.1 Hz, 3H), 1.02 (s, 3H), 0.92 (s, 3H), 0.90 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 63.8, 62.5, 60.8, 52.7, 42.7, 31.0, 29.4, 27.2, 25.1, 20.6, 16.3, 14.0; FTIR (thin film), cm⁻¹ 2954, 2929, 2097, 1257; HRMS-ESI (m/z) calcd. for C₁₂H₂₅N₄ ([M+H]+): 225.2074; found: 225.2076.

trans-3-Azido-1-benzyl-2,5,5-trimethylpiperidine (73). Isolation by column chromatography (1% ethyl acetate–1% NH₄OH–hexanes); Clear liquid (69.3 mg, 89%); Rf = 0.37 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.35–7.20 (m, 5H), 4.12 (d, J = 13.9 Hz, 1H), 3.21 (ddd, J = 11.7, 9.3, 4.7 Hz, 1H), 3.08 (d, J = 13.9 Hz, 1H), 2.34 (dd, J = 11.5, 2.3 Hz, 1H), 2.06 (dq, J = 9.3, 6.1 Hz, 1H), 1.81 (ddd, J = 12.7, 4.7, 2.3 Hz, 1H), 1.74 (d, J = 11.5 Hz, 1H), 1.31 (d, J = 6.1 Hz, 3H), 1.28 (t, J = 12.2, 1H), 1.00 (s, 3H), 0.84 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 139.9, 128.4 (2C), 128.1 (2C), 126.1, 63.7, 62.4, 61.6, 57.4, 42.7, 31.0, 29.2, 24.9, 16.9; FTIR (thin film), cm⁻¹ 2095, 1255, 737, 697; HRMS-ESI (m/z) calcd. for C₁₅H₂₃N₄ ([M+H]+): 259.1917; found: 259.1911.
3-Azido-1-benzyl-2,2,5,5-tetramethylpiperidine (75). Isolation by column chromatography (1% ethyl acetate–1% NH₄OH–hexanes); Clear liquid (22.7 mg, 28%); Rf = 0.74 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.38–7.19 (m, 5H), 4.08 (d, J = 14.3 Hz, 1H), 3.47 (dd, J = 12.5, 4.7 Hz, 1H), 3.03 (d, J = 14.3 Hz, 1H), 2.10 (d, J = 12.1 Hz, 1H), 2.04 (dd, J = 12.1, 2.0 Hz, 1H), 1.62 (ddd, J = 12.9, 4.7, 2.0 Hz, 1H), 1.46 (t, J = 12.7 Hz, 1H), 1.31 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H), 0.84 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 141.1, 128.1 (2C), 128.0 (2C), 126.5, 65.1, 58.1, 57.5, 53.1, 38.9, 31.0, 29.3, 26.8, 25.1, 9.6; FTIR (thin film), cm⁻¹ 2953, 2097, 1452, 1254, 733, 697; HRMS-ESI (m/z) calcd. for C₁₆H₂₅N₄ ([M+H]+): 273.2074; found: 273.2068.

3-Azido-1-benzylpiperidine (77). Isolation by column chromatography (1% ethyl acetate–1% NH₄OH–hexanes); Clear liquid (19.3 mg, 30%); Rf = 0.22 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.36–7.23 (m, 5H), 3.53 (s, 2H), 3.49 (tt, J = 9.1, 4.1 Hz, 1H), 2.82 (ddt, J = 10.8, 4.1, 1.5 Hz, 1H), 2.62 (dtt, J = 11.3, 3.3, 1.5 Hz, 1H), 2.20–2.06 (m, 2H), 1.93 (dqt, J = 12.6, 4.1, 1.5 Hz, 1H), 1.82–1.73 (m, 1H), 1.64–1.52 (m, 1H), 1.45–1.34 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 137.9, 129.0 (2C), 128.2 (2C), 127.1, 62.9, 57.5, 57.3, 53.0, 29.5, 23.3; FTIR (thin film), cm⁻¹ 2089, 1256, 736, 697; HRMS-ESI (m/z) calcd. for C₁₂H₁₇N₄ ([M+H]+): 217.1448; found: 217.1446. These data are consistent with published data.¹⁴⁵

2-(Azidomethyl)-1-benzylpyrrolidine (78). Isolation by column chromatography (1% ethyl acetate–1% NH₄OH–hexanes); Clear liquid (25.0 mg, 38%); Rf = 0.29 (10% ethyl
acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36–7.21 (m, 5H), 4.00 (d, $J = 13.0$ Hz, 1H), 3.43 (d, $J = 13.0$ Hz, 1H), 3.27 (dd, $J = 12.4$, 5.9 Hz, 1H), 3.17 (dd, $J = 12.4$, 4.0 Hz, 1H), 3.00–2.94 (m, 1H), 2.80–2.72 (m,1H), 2.28–2.20 (m, 1H), 2.01–1.91 (m, 1H), 1.84–1.67 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 139.4, 128.7 (2C), 128.3 (2C), 127.1, 63.2, 59.4, 54.6, 54.5, 29.0, 23.1; FTIR (thin film), cm$^{-1}$ 2091, 1452, 1270, 736, 697; HRMS-ESI (m/z) calcd. for C$_{12}$H$_{17}$N$_4$ ([M+H]$^+$): 217.1448; found: 217.1448. These data are consistent with published data.$^{145}$

**cis-3-Azido-1-benzyl-5-methylpiperidine (82).** Isolation by column chromatography (1% ethyl acetate–1% NH$_4$OH–hexanes); Clear liquid (43.9 mg, 69%); $R_f$ = 0.37 (10% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36–7.23 (m, 5H), 3.54 (d, $J = 13.3$ Hz, 1H), 3.52 (d, $J = 13.3$ Hz, 1H), 3.46 (ddt, $J = 11.5$, 10.6, 4.4 Hz, 1H), 3.02 (ddt, $J = 10.6$, 4.4, 1.7 Hz, 1H), 2.78 (ddt, $J = 10.9$, 3.7, 1.7 Hz, 1H), 2.05 (dtt, $J = 12.6$, 4.4, 1.7 Hz, 1H), 1.83–1.69 (m, 1H), 1.78 (d, $J = 10.6$ Hz, 1H), 1.54 (t, $J = 10.9$ Hz, 1H), 0.94 (q, $J = 12.0$ Hz, 1H), 0.90 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 137.9, 129.0 (2C), 128.3 (2C), 127.1, 62.7, 60.5, 57.5, 57.4, 38.3, 29.9, 19.0; FTIR (thin film), cm$^{-1}$ 2090, 1263, 738, 697; HRMS-ESI (m/z) calcd. for C$_{13}$H$_{19}$N$_4$ ([M+H]$^+$): 231.1604; found: 231.1608.

**trans-5-Azido-1-benzyl-2-methylpiperidine (83) and cis-5-azido-1-benzyl-2-methyl-piperidine (83’).** Isolation by column chromatography (0.5% ethyl acetate–1% NH$_4$OH–hexanes); Clear liquid (14.5 mg, 21%, 3.3:1 ratio); $R_f$ = 0.28 (10% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.35–7.21 (m, 5H, 83; m, 5H, 83’), 4.04 (d, $J = 13.4$ Hz, 1H), 3.44 (d, $J = 13.4$ Hz, 1H), 3.27 (dd, $J = 12.4$, 5.9 Hz, 1H), 3.17 (dd, $J = 12.4$, 4.0 Hz, 1H), 3.00–2.94 (m, 1H), 2.80–2.72 (m,1H), 2.28–2.20 (m, 1H), 2.01–1.91 (m, 1H), 1.84–1.67 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 139.4, 128.7 (2C), 128.3 (2C), 127.0, 63.2, 59.4, 54.6, 54.5, 29.0, 23.1; FTIR (thin film), cm$^{-1}$ 2091, 1452, 1270, 736, 697; HRMS-ESI (m/z) calcd. for C$_{12}$H$_{17}$N$_4$ ([M+H]$^+$): 217.1448; found: 217.1448. These data are consistent with published data.$^{145}$

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Hz, 1H, 83), 3.87 (tt, J = 10.8, 4.0 Hz, 1H, 83), 3.84 (d, J = 13.4 Hz, 1H, 83'), 3.55–3.49 (m, 1H, 83'), 3.39 (d, J = 13.4 Hz, 1H, 83'), 3.19 (d, J = 13.4 Hz, 1H, 83), 3.06 (ddd, J = 10.8, 4.0, 2.0 Hz, 1H, 83), 2.68–2.59 (m, 2H, 83'), 2.08 (t, J = 10.8 Hz, 1H, 83), 2.31–2.26 (m, 1H, 83), 2.22–2.15 (m, 1H, 83), 1.79–1.52 (m, 2H, 83; m, 5H, 83'), 1.47–1.39 (m, 1H, 83), 1.18 (d, J = 6.1 Hz, 3H, 83), 1.12 (d, J = 6.3 Hz, 3H, 83'); 13C NMR (125 MHz, CDCl3, found 83 and 83'): δ 138.7, 128.9 (2C), 128.8 (2C), 128.3 (2C), 128.2 (2C), 126.9, 65.8, 60.1, 58.4, 57.5, 56.1, 55.7, 53.4, 35.5, 34.4, 20.0, 15.3; FTIR (thin film), cm⁻¹ 2096, 1453, 1063, 785, 759, 734, 697; HRMS-ESI (m/z) calcd. for C₁₃H₁₈N₄ ([M+H]⁺): 231.1604; found: 231.1603.

trans-3-Azido-1-benzyl-4-methylpiperidine (86) and 2-(azidomethyl)-1-benzyl-3-methylpyrrolidine (87). Isolation by column chromatography (0.1% ethyl acetate–1% NH₄OH–hexanes); Clear liquid (34.4 mg, 50%); Rᵥ = 0.30 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.36–7.21 (m, 5H, 86; m, 5H, 87), 4.04 (d, J = 13.2 Hz, 1H, 86), 3.53 (s, 2H, 86), 3.40 (dd, J = 12.6, 4.9 Hz, 1H, 87), 3.39 (d, J = 13.2 Hz, 1H, 87), 3.20 (dd, J = 12.6, 4.1 Hz, 1H, 87), 3.08 (ddd, J = 10.7, 4.2, 1.7 Hz, 1H, 86), 2.99 (td, J = 10.1, 4.2 Hz, 1H, 86), 2.94–2.90 (m, 1H, 87), 2.38–2.25 (m, 2H, 87), 2.16–2.07 (m, 1H, 87), 1.99–1.92 (m, 1H, 86; m, 1H, 87), 1.93 (t, J = 10.4 Hz, 1H, 86), 1.71–1.66 (m, 1H, 86), 1.42–1.32 (m, 2H, 86; m, 1H, 87), 1.06 (d, J = 6.0 Hz, 3H, 86), 1.04 (d, J = 6.9 Hz, 3H, 87); 13C NMR (125 MHz, CDCl₃, 86): δ 129.0 (2C), 128.7 (2C), 128.3 (2C), 127.2 (2C), 64.5, 62.7, 57.4, 52.9, 36.2, 32.7, 18.6; FTIR (thin film), cm⁻¹ 2925, 2093, 1454, 1256, 739, 698; HRMS-ESI (m/z) calcd. for C₁₂H₁₉N₄ ([M+H]⁺): 231.1604; found: 231.1602.
2-(Azidomethyl)-1-benzyl-3-methylpyrrolidine (87'). Isolation by column chromatography (0.1% ethyl acetate–1% NH₄OH–hexanes); Clear liquid (12.6 mg, 18%); R₇ = 0.38 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.36–7.21 (m, 5H), 3.99 (d, J = 13.1 Hz, 1H), 3.56 (d, J = 13.1 Hz, 1H), 3.25 (dd, J = 12.6, 6.1 Hz, 1H), 3.12 (dd, J = 12.6, 4.7 Hz, 1H), 2.98 (ddd, J = 9.1, 6.9, 2.0 Hz, 1H), 2.82 (ddd, J = 8.3, 6.1, 4.7 Hz, 1H), 2.36–2.24 (m, 2H), 1.86 (dtd, J = 12.1, 6.7, 2.0 Hz, 1H), 1.50 (dtd, J = 12.1, 10.1, 6.9 Hz, 1H), 1.04 (d, J = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 139.5, 128.7 (2C), 128.2 (2C), 126.9, 65.0, 59.9, 53.0, 52.0, 35.5, 32.9, 15.0; FTIR (thin film), cm⁻¹ 2925, 2093, 1452, 1309, 1271, 739, 699; HRMS-ESI (m/z) calcd. for C₁₂H₁₉N₄ ([M+H]⁺): 231.1604; found: 231.1601.

7-Azido-5-benzyl-5-azaspiro[2.5]octane (89). Isolation by column chromatography (0.5% ethyl acetate–1% NH₄OH–hexanes); Clear liquid (37.7 mg, 52%); R₇ = 0.20 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.35–7.22 (m, 5H), 3.62 (tt, J = 9.1, 4.1 Hz, 1H), 3.57 (d, J = 13.2 Hz, 1H), 3.50 (d, J = 13.2 Hz, 1H), 2.95 (dd, J = 10.7, 4.1 Hz, 1H), 2.26–2.19 (m, 1H), 2.22 (d, J = 11.2 Hz, 1H), 1.99 (d, J = 11.2 Hz, 1H), 1.63 (dd, J = 12.9, 9.1 Hz, 1H), 1.44 (dd, J = 12.9, 4.1 Hz, 1H), 0.43–0.32 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): δ 137.8, 128.9 (2C), 128.3 (2C), 127.1, 62.4, 61.0, 57.6, 56.8, 38.7, 16.4, 12.2, 10.3; FTIR (thin film), cm⁻¹ 2926, 2094, 1242, 740, 698; HRMS-ESI (m/z) calcd. for C₁₄H₁₉N₄ ([M+H]⁺): 243.1604; found: 243.1604.

6-(Azidomethyl)-5-benzyl-5-azaspiro[2.4]heptane (90). Isolation by column chromatography (0.5% ethyl acetate–1% NH₄OH–hexanes); Clear liquid (20.6 mg, 28%);
R^f = 0.24 (10% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.36–7.21 (m, 5H), 4.06 (d, \(J = 13.0\) Hz, 1H), 3.44 (d, \(J = 13.0\) Hz, 1H), 3.38 (dd, \(J = 12.4, 5.9\) Hz, 1H), 3.34 (dd, \(J = 12.4, 4.2\) Hz, 1H), 3.02 (dddd, \(J = 8.2, 6.2, 5.9, 4.2\) Hz, 1H), 2.59 (d, \(J = 9.1\) Hz, 1H), 2.51 (d, \(J = 9.1\) Hz, 1H), 2.06 (dd, \(J = 12.5, 8.2\) Hz, 1H), 1.65 (dd, \(J = 12.5, 8.2\) Hz, 1H), 0.59–0.40 (m, 4H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 139.2, 128.7 (2C), 128.3 (2C), 127.0, 64.4, 62.7, 59.7, 54.3, 38.4, 19.8, 14.1, 9.4; FTIR (thin film), cm\(^{-1}\) 2922, 2091, 1253, 738, 697; HRMS-ESI (m/z) calcd. for C\(_{14}\)H\(_{19}\)N\(_4\) ([M+H]^+): 243.1604; found: 243.1605.

3-Azido-1-benzyl-\textit{trans}-decahydroquinoline (92). Isolation by column chromatography (1% ethyl acetate–1% NH\(_4\)OH–hexanes); Yellow liquid (67.2 mg, 83%); R^f = 0.38 (10% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.36–7.21 (m, 5H), 4.09 (d, \(J = 13.6\) Hz, 1H), 3.40 (ddt, \(J = 11.6, 10.9, 4.4\) Hz, 1H), 3.22 (d, \(J = 13.6\) Hz, 1H), 2.97 (ddd, \(J = 10.9, 4.4, 2.2\) Hz, 1H), 2.29–2.21 (m, 1H), 1.98–1.92 (m, 1H), 1.88–1.78 (m, 1H), 1.86 (t, \(J = 10.9\) Hz, 1H), 1.74 (ddd, \(J = 10.7, 9.5, 3.6\) Hz, 1H), 1.71–1.63 (m, 2H), 1.38–1.23 (m, 3H), 1.17–1.05 (m, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 138.7, 128.9 (2C), 128.3 (2C), 126.9, 65.7, 57.3, 57.0, 56.5, 40.6, 37.7, 32.7, 30.3, 25.8, 25.5; FTIR (thin film), cm\(^{-1}\) 2922, 2091, 1253, 738, 697; HRMS-ESI (m/z) calcd. for C\(_{16}\)H\(_{23}\)N\(_4\) ([M+H]^+): 271.1917; found: 271.1917.

3-Azido-1-benzyl-\textit{cis}-decahydroquinoline (94). Isolation by column chromatography (0.5% ethyl acetate–1% NH\(_4\)OH–hexanes); Clear liquid (30.1 mg, 37%); R^f = 0.50 (10% ethyl acetate–hexanes); R^f = 0.50 (10% ethyl acetate–hexanes); \(^1\)H NMR
(400 MHz, CDCl₃): δ 7.33–7.21 (m, 5H), 3.74 (d, J = 13.6 Hz, 1H), 3.58 (d, J = 13.6 Hz, 1H), 3.48 (tt, J = 11.0, 5.0 Hz, 1H), 2.72 (dt, J = 11.1, 4.6 Hz, 1H), 2.66 (ddd, J = 11.0, 5.0, 1.2 Hz, 1H), 2.35 (t, J = 11.0 Hz, 1H), 2.06 (tq, J = 8.0, 4.6 Hz, 1H), 1.82–1.52 (m, 7H), 1.45–1.39 (m, 1H), 1.36–1.27 (m, 1H), 1.19–1.06 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 139.4, 128.4 (2C), 128.2 (2C), 126.9, 58.5, 58.2 (2C), 49.5, 34.5, 31.1, 29.9, 25.3, 21.0, 17.7; FTIR (thin film), cm⁻¹ 2925, 2091, 1253, 736, 697; HRMS-ESI (m/z) calcd. for C₁₆H₂₃N₄ ([M+H]⁺): 271.1917; found: 271.1917.

3-Azido-1-benzylazepane (96). Isolation by column chromatography (1% ethyl acetate–1% NH₄OH–hexanes); Clear liquid (21.2 mg, 31%); Rᶠ = 0.35 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.39–7.21 (m, 5H), 3.73 (d, J = 13.5 Hz, 1H), 3.66 (d, J = 13.5 Hz, 1H), 3.49 (tt, J = 7.8, 4.4 Hz, 1H), 2.87 (dd, J = 13.8, 4.4 Hz, 1H), 2.69 (dd, J = 13.8, 7.8 Hz, 1H), 2.63 (t, J = 6.0 Hz, 2H), 2.09–1.99 (m, 1H), 1.80–1.51 (m, 5H); ¹³C NMR (125 MHz, CDCl₃): δ 139.5, 128.6 (2C), 128.2 (2C), 127.0, 63.1, 61.4, 59.1, 55.9, 32.9, 29.0, 22.2; FTIR (thin film), cm⁻¹ 2922, 2089, 1452, 1251, 697; HRMS-ESI (m/z) calcd. for C₁₃H₁₅N₄ ([M+H]⁺): 231.1904; found: 231.1906.

2-(Azidomethyl)-1-benzylpiperidine (97). Isolation by column chromatography (1% ethyl acetate–1% NH₄OH–hexanes); Clear liquid (16.5 mg, 24%); Rᶠ = 0.25 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.38–7.20 (m, 5H), 4.00 (d, J = 13.5 Hz, 1H), 3.33 (d, J = 13.5 Hz, 1H), 3.50 (dd, J = 12.7, 5.8 Hz, 1H), 3.47 (dd, J = 12.7, 4.0 Hz, 1H), 2.77 (dt, J = 12.1, 4.3 Hz, 1H), 2.51 (ddt J = 8.6, 5.8, 4.0 Hz, 1H), 2.09 (ddd J = 12.1, 9.2, 3.4
Hz, 1H), 1.79–1.64 (m, 2H), 1.62–1.29 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 139.1, 128.7 (2C), 128.2 (2C), 126.9, 60.2, 58.5, 53.0, 51.5, 29.4, 25.0, 23.1; FTIR (thin film), cm$^{-1}$ 2933, 2092, 1270, 698; HRMS-ESI (m/z) calcd. for C$_{16}$H$_{19}$N$_4$ ([M+H]$^+$): 231.1904; found: 231.1906.

**Azide Functionalization Experiments**

**trans-1-Benzyl-2,5,5-trimethylpiperidin-3-amine (98).**$^{84,85}$ To a stirring solution of 73 (38.8 mg, 0.15 mmol, 1.0 equiv) in water (18.9 µL, 1.05 mmol, 7 equiv) and THF (3 mL), was added triphenylphosphine (59.0 mg, 0.225 mmol, 1.5 equiv) and brought to reflux. After 5 h, the reaction was cooled to room temperature, concentrated in vacuo, and the residue purified by column chromatography to produce 98 as a clear liquid (34.9 mg, 93%). R$_f$ = 0.14 (10% methanol–dichloromethane); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.35–7.17 (m, 5H), 4.10 (d, $J = 13.9$ Hz, 1H), 3.06 (d, $J = 13.9$ Hz, 1H), 2.63 (ddd, $J = 11.6$, 8.6, 4.4 Hz, 1H), 2.32 (dd, $J = 11.3$, 2.4 Hz, 1H), 1.81 (dq, $J = 8.6$, 6.0 Hz, 1H), 1.71 (d, $J = 11.3$ Hz, 1H), 1.59 (ddd, $J = 12.5$, 4.4, 2.4 Hz, 1H), 1.57 (s, br, 2H), 1.25 (d, $J = 6.0$ Hz, 3H), 0.97 (t, $J = 12.0$ Hz, 1H), 0.97 (s, 3H), 0.77 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 140.5, 128.4, 128.0, 126.4, 65.3, 64.4, 57.8, 51.7, 41.7, 30.7, 29.6, 25.3, 16.5; FTIR (thin film), cm$^{-1}$ 2949, 1452, 1368, 1122, 736, 697; HRMS-ESI (m/z) calcd. for C$_{16}$H$_{26}$N$_2$ ([M+H]$^+$): 233.2012; found: 233.2011.

**trans-1-Benzyl-N-isobutyl-2,5,5-trimethylpiperidin-3-amine (99).**$^{86,146}$ To a stirring solution of 73 (38.8 mg, 0.15 mmol, 1.0 equiv), in anhydrous DCM (1.5 mL), was
added a solution of trimethylphosphine in toluene (0.3 mL, 1.0M, 0.3 mmol, 2.0 equiv). The solution was allowed to stir for 1.75 h before isobutylaldehyde (34.0 µL, 0.375 mmol, 2.5 equiv) was added to the solution. After 4.25 h, the DCM and excess isobutylaldehyde were removed in vacuo and MeOH (2 mL) was added to the residue. To the resulting solution was added solid NaBH₄ (17.0 mg, 0.45 mmol, 3.0 equiv) at 0 °C and it was stirred for 10 min then allowed to warm to room temperature. After 1 h, the reaction mixture was quenched with a saturated aqueous solution of NaHCO₃. The reaction mixture was diluted with water (15 mL) and extracted with Et₂O (4 × 15 mL). The ether layers were combined, dried over K₂CO₃, and concentrated in vacuo. The crude residue was purified by column chromatography to give 99 as a yellow oil (23.1 mg, 54%). Rᵣ = 0.66 (20% methanol–dichloromethane); ¹H NMR (400 MHz, CDCl₃): δ 7.35–7.16 (m, 5H), 4.06 (d, J = 13.9 Hz, 1H), 3.08 (d, J = 13.9 Hz, 1H), 2.48 (dd, J = 11.3, 6.9 Hz, 1H), 2.37–2.27 (m, 1H), 2.30 (dd, J = 11.1, 2.4 Hz, 1H), 2.29 (dd, J = 11.3, 3.6 Hz, 1H), 1.95 (dq, J = 8.4, 6.0 Hz, 1H), 1.71 (ddd, J = 10.8, 4.5, 2.4 Hz, 1H), 1.70 (d, J = 11.1 Hz, 1H), 1.64 (septet, J = 6.6 Hz, 1H), 1.20 (d, J = 6.0 Hz, 3H), 0.94 (s, 3H), 0.92–0.87 (m, br, 2H), 0.88 (d, J = 6.6 Hz, 3H), 0.78 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 140.6, 128.4, 128.0, 126.4, 63.9, 62.7, 51.8 (2C), 55.9, 44.5, 30.6, 29.6, 28.9, 25.6, 20.8, 20.7, 16.2; FTIR (thin film), cm⁻¹ 2950, 1453, 1364, 1123, 735, 697; HRMS-ESI (m/z) calcd. for C₁₉H₃₃N₂ ([M+H⁺]: 289.2638; found: 289.2635.
trans-2,5,5-Trimethylpiperidin-3-amine (100). To a stirring solution of 73 (38.8 mg, 0.15 mmol, 1.0 equiv) in MeOH (3 mL) under nitrogen, was added palladium on carbon (23.2 mg, 10 wt. %, 22.5 µmol, 0.15 equiv). The reaction mixture was purged and refilled with hydrogen. After 2 h, the reaction mixture was diluted with MeOH and filtered through Celite. The filtrate was concentrated in vacuo to give 100 as a light yellow liquid (18.6 mg, 87%). 1H NMR (400 MHz, CDCl3): δ 2.51 (dd, J = 12.2, 2.5 Hz, 1H), 2.39 (d, J = 12.2 Hz, 1H), 2.36 (ddd, J = 11.5, 9.1, 4.1 Hz, 1H), 2.09 (dq, J = 9.1, 6.3 Hz, 1H), 1.56 (ddd, J = 12.9, 4.1, 2.5 Hz, 1H), 1.39 (s, br, 3H), 1.12 (d, J = 6.3 Hz, 3H), 0.96 (t, J = 12.2 Hz, 1H), 0.96 (s, 3H), 0.83 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 60.0, 58.2, 52.1, 47.9, 32.1, 29.5, 24.5, 19.2; FTIR (thin film), cm⁻¹ 2949, 2903, 1459, 789, 714, 606; HRMS-ESI (m/z) calcd. for C₈H₁₉N₂ ([M+H]^+): 143.1543; found: 143.1541.

Dimethyl 1-(trans-1'-benzyl-2',5',5'-trimethylpiperidin-3'-yl)-1H-1,2,3-triazole-4,5-dicarboxylate (101). To a stirring solution of 73 (38.8 mg, 0.15 mmol, 1.0 equiv) in toluene (1.5 mL) was added dimethyl acetylenedicarboxylate (55.3 µL, 0.45 mmol, 3.0 equiv). The reaction vessel was purged and refilled with nitrogen. The reaction was brought to reflux for 24 h then cooled to room temperature. The solvent was evaporated in vacuo and the crude residue purified by column chromatography to give 101 as a clear oil (59.6 mg, 99%). Rf = 0.25 (25% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 7.31–7.17 (m, 5H), 4.72 (ddd, J = 12.6, 9.8, 4.4 Hz, 1H), 4.16 (d, J = 13.7 Hz, 1H), 4.01 (s, 3H), 3.95 (s, 3H), 3.14 (d, J = 13.7 Hz, 1H), 3.00 (dq, J = 9.8, 6.0 Hz, 1H), 2.44 (dd, J = 11.6,
2.2 Hz, 1H), 1.98 (d, J = 11.6 Hz, 1H), 1.97 (t, J = 12.6 Hz, 1H), 1.79 (ddd, J = 12.6, 4.4, 2.2 Hz, 1H), 1.07 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 160.6, 159.3, 139.6, 138.8, 131.2, 128.3, 128.2, 126.8, 64.0, 62.6, 61.1, 57.3, 53.5, 52.6, 45.0, 31.2, 29.0, 24.2, 16.3; FTIR (thin film), cm$^{-1}$ 1731, 1213, 734, 698; HRMS-ESI (m/z) calcd. for C$_{21}$H$_{29}$N$_4$O$_4$ ([M+H]$^+$): 401.2183; found: 401.2178.

**trans-1-Benzyl-2,5,5-trimethyl-3-(4’-phenyl-1’H-1’,2’,3’-triazol-1’-yl)piperidine (102).** To a suspension of 73 (38.8 mg, 0.15 mmol, 1.0 equiv) in water (0.3 mL) and tert-butanol (0.3 mL) were added phenylacetylene (16.5 µL, 0.15 mmol, 1.0 equiv), sodium ascorbate (30.0 mg, 0.015 mmol, 0.1 equiv), and CuSO$_4$·5H$_2$O (0.8 mg, 0.003 mmol, 0.02 equiv). The solution was stirred vigorously and heated to 60 °C. After 15 h a solid had precipitated out of solution. The precipitate was filtered and washed with copious amounts of water to give 102 as a light pink solid (49.6 mg, 92%). $R_f$ = 0.54 (20% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.85–7.79 (m, 2H), 7.74 (s, 1H), 7.44–7.38 (m, 2H), 7.35–7.28 (m, 6H), 4.56 (ddd, J = 12.5, 9.8, 4.7 Hz, 1H), 4.17 (d, J = 13.8 Hz, 1H), 3.17 (d, J = 13.8 Hz, 1H), 2.66 (dq, J = 9.8, 6.0 Hz, 1H), 2.48 (dd, J = 11.7, 2.2 Hz, 1H), 1.96 (d, J = 11.7 Hz, 1H), 1.89 (ddd, J = 12.7, 4.7, 2.2 Hz, 1H), 1.80 (t, J = 12.6 Hz, 1H), 1.10 (s, 3H), 1.00 (d, J = 6.0 Hz, 3H), 0.86 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 147.6, 139.5, 130.7, 128.8, 128.4, 128.2, 128.1, 126.8, 125.6, 118.2, 64.1, 62.5, 62.1, 57.5, 45.2, 31.1, 29.1, 24.6, 16.3; FTIR (neat), cm$^{-1}$ 1370, 1049, 908, 766, 731, 693; HRMS-ESI (m/z) calcd. for C$_{23}$H$_{30}$N$_4$ ([M+H]$^+$): 361.2387; found: 361.2387.
**N-(trans-1’-Benzyl-2’,5’,5’-trimethylpiperidin-3’-yl)-2-(diphenylphosphoryl)benzamide (103).** To a stirring solution of 73 (38.8 mg, 0.15 mmol, 1.0 equiv) in MeCN (1.32 mL) and water (0.11 mL) was added methyl 2-(diphenylphosphino)benzoate (48.0 mg, 0.15 mmol, 1.0 equiv). After the solid was completely dissolved, the solution was heated to 37 °C. After 48 h, the reaction mixture was concentrated in vacuo and the crude residue was immediately purified by column chromatography to give 103 as a light yellow solid (72.4 mg, 90%). Rf = 0.32 (4% methanol–dichloromethane); 1H NMR (400 MHz, CDCl3): δ 8.97 (d, br, J = 8.9 Hz, 1H), 8.17–8.13 (m, 1H), 7.64 (tt, J = 7.6, 1.6 Hz, 1H), 7.62–7.52 (m, 5H), 7.51–7.42 (m, 5H), 7.35 (tt, J = 7.6, 1.6 Hz, 1H), 7.29–7.14 (m, 5H), 7.03–6.96 (m, 1H), 4.03 (d, J = 13.9 Hz, 1H), 3.84–3.75 (m, 1H), 2.99 (d, J = 13.9 Hz, 1H), 2.22 (dd, J = 11.2, 2.1 Hz, 1H), 2.01 (dq, J = 9.5, 6.0 Hz, 1H), 1.68 (d, J = 11.2 Hz, 1H), 1.00–0.90 (m, 2H), 0.92 (d, J = 6.0 Hz, 3H), 0.87 (s, 3H), 0.63 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 166.3 (d, J_P–C = 3.0 Hz), 141.6 (d, J_P–C = 7.7 Hz), 140.4, 133.6 (d, J_P–C = 12.2 Hz), 132.7, 132.4, 132.3 (d, J_P–C = 10.2 Hz), 132.2 (d, J_P–C = 10.2 Hz), 132.0 (d, J_P–C = 10.2 Hz), 131.6 (d, J_P–C = 107.5 Hz), 131.2 (d, J_P–C = 107.5 Hz), 129.8 (d, J_P–C = 12.0 Hz), 128.8 (d, J_P–C = 12.2 Hz), 128.7 (d, J_P–C = 12.2 Hz), 128.4, 128.0, 127.9 (d, J_P–C = 90.3 Hz), 126.4; FTIR (neat), cm⁻¹ 1650, 1118, 723, 693; HRMS-ESI (m/z) calcd. for C₃₄H₃₈N₂O₂P ([M+H]⁺): 537.2665; found: 537.2663.

**General procedure for entries 1–2 in Table 4:**
To a solution of unsaturated amine 68 or 72 (0.3 mmol, 1.0 equiv) in anhydrous MeCN (3 mL) was added NCS (0.3 mmol, 1.0 equiv). The reaction solution was allowed to stir in the dark for 1 h. Then NaI (0.015 mmol, 0.05 equiv) was added and the solution immediately heated to 60 °C. After 2.5 h, the amine nucleophile (0.75 mmol, 2.5 equiv) was added. The reaction was monitored by TLC until determined complete and was then diluted with EtOAc (40 mL). The organic layer was washed with aqueous solutions of NaOH (2 × 10 mL, 1.0M) followed by brine (10 mL). The organic layer was dried over Na2SO4, filtered, and the filtrate was concentrated in vacuo. The crude residue was then purified by either column chromatography or Kugelrohr distillation.

**cis-1-(tert-Butyl)-N,N,2-triethylpiperidin-3-amine (104).** Isolation by column chromatography (7.5% methanol–1% NH4OH–dichloromethane); White solid (38.4 mg, 53%); Rf = 0.19 (25% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 3.15 (dt, J = 8.0, 4.1 Hz, 1H), 2.86–2.80 (m, br, 1H), 2.65 (dq, J = 13.8, 7.1 Hz, 2H), 2.60 (dq, J = 13.8, 7.1 Hz, 2H), 2.60–2.49 (m, 2H), 1.78–1.71 (m, br, 1H), 1.54–1.36 (m, 5H), 1.12 (s, 9H), 0.96 (t, J = 7.1 Hz, 6H), 0.90 (t, J = 7.4 Hz, 3H); 13C NMR (125 MHz, CDCl3): δ 60.6, 56.1, 54.0, 42.1 (2C), 38.7, 29.9 (3C), 26.5, 24.1, 17.2, 12.9, 11.4 (2C); FTIR (thin film), cm⁻¹ 2967, 2931, 1215; HRMS-ESI (m/z) calcd. for C15H33N2 ([M+H]+): 241.2638; found: 241.2634.

**trans-1-Benzyl-N,N-diethyl-2,5,5-trimethylpiperidin-3-amine (105).** Isolation by Kugelrohr distillation; Clear liquid (77.4 mg, 89%); Rf = 0.16 (10% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 7.35–7.18 (m, 5H), 4.17 (d, J = 13.9 Hz, 1H), 3.01 (d, J = 13.9 Hz, 2H), 2.87 (t, J = 7.4 Hz, 2H), 2.64–2.53 (m, 2H), 1.78–1.71 (m, br, 1H), 1.54–1.36 (m, 5H), 1.12 (s, 9H), 0.96 (t, J = 7.4 Hz, 3H); 13C NMR (125 MHz, CDCl3): δ 60.6, 56.1, 54.0, 42.1 (2C), 38.7, 29.9 (3C), 26.5, 24.1, 17.2, 12.9, 11.4 (2C); FTIR (thin film), cm⁻¹ 2967, 2931, 1215; HRMS-ESI (m/z) calcd. for C15H33N2 ([M+H]+): 241.2638; found: 241.2634.
Hz, 1H), 2.55 (dq, J = 12.8, 7.1 Hz, 2H), 2.52 (ddd, J = 12.5, 11.2, 4.0 Hz, 1H), 2.30 (dq, J = 12.8, 7.1 Hz, 2H), 2.29 (dd, J = 11.2, 2.7 Hz, 1H), 2.06 (dq, J = 9.6, 6.0 Hz, 1H), 1.61 (d, J = 11.2 Hz, 1H), 1.43 (ddd, J = 12.5, 4.0, 2.7 Hz, 1H), 1.33 (d, J = 6.0 Hz, 3H), 1.05 (t, J = 7.1 Hz, 6H), 0.96 (s, 3H), 0.77 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 140.8, 128.4 (2C), 128.0 (2C), 126.3, 64.7, 60.5, 59.0, 58.5, 43.9 (2C), 35.5, 30.4, 30.1, 24.7, 17.1, 14.9 (2C); FTIR (thin film), cm⁻¹ 2966, 2926, 737, 697; HRMS-ESI (m/z) calcd. for C₁₉H₃₃N₂ ([M+H]⁺): 289.2638; found: 289.2644.

**tert-Butyl-4-(cis-1'-(tert-butyl)-2'-ethylpiperidin-3'-yl)piperazine-1-carboxylate (106).** Isolation by column chromatography (5% methanol–1% NH₄OH–dichloromethane); Yellow oil (63.5 mg, 53%); Rₐ = 0.39 (20% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 3.38 (t, J = 5.0 Hz, 4H), 3.24–3.19 (m, 1H), 2.80 (dt, J = 13.1, 3.6 Hz, 1H), 2.51 (ddd, J = 13.6, 11.8, 2.9 Hz, 1H), 2.43 (t, J = 5.0 Hz, 4H), 2.20 (dt, J = 11.8, 4.2 Hz, 1H), 1.80–1.74 (m, 1H), 1.61–1.25 (m, 5H), 1.45 (s, 9H), 1.10 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃, 60 °C): δ 154.8, 79.3, 64.9, 55.4, 54.2, 50.2 (2C), 44.2 (2C), 38.7, 29.7 (3C), 28.5 (3C), 26.1, 23.6, 17.8, 12.9; FTIR (thin film), cm⁻¹ 2967, 1699, 1365, 1250, 1171; HRMS-ESI (m/z) calcd. for C₂₀H₄₆N₄O₂ ([M+H]⁺): 354.3115; found: 354.3118.

**tert-Butyl-4-(trans-1'-benzyl-2',5',5'-trimethylpiperidin-3'-yl)piperazine-1-carboxylate (107).** Isolation by column chromatography (5% ethyl acetate–1% NH₄OH–hexanes); Clear oil (110.0 mg, 91%); Rₐ = 0.63 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.33–7.19 (m, 5H), 4.15 (d, J = 13.8 Hz, 1H), 3.45–3.31 (m, 4H), 3.01 (d, J =
13.8 Hz, 1H), 2.60–2.52 (m, 2H), 2.41 (ddd, J = 12.5, 9.7, 3.8, 1H), 2.37–2.32 (m, 2H), 2.30 (dd, J = 11.3, 2.3 Hz, 1H), 2.10 (dq, J = 9.7, 6.0 Hz, 1H), 1.61 (d, J = 11.3 Hz, 1H), 1.48–1.43 (m, 1H), 1.46 (s, 9H), 1.34 (d, J = 6.0 Hz, 3H), 1.05 (t, J = 12.5 Hz, 1H), 0.95 (s, 3H), 0.77 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), 60 °C): δ 154.9, 140.7, 128.5 (2C), 128.0 (2C), 126.4, 79.3, 64.7, 64.2, 59.9, 58.4, 48.8 (2C), 44.5 (2C), 35.8, 30.4, 30.0, 28.5 (3C), 24.7, 16.8; FTIR (thin film), cm\(^{-1}\) 1695, 1365, 1246, 1173, 1119; HRMS-ESI (m/z) calcd. for C\(_{24}\)H\(_{40}\)N\(_3\)O\(_2\) ([M+H]\(^+\)): 402.3114; found: 402.3114.

**General procedure for entries 3–4 in Table 4:**

To a solution of unsaturated amine 68 or 72 (0.3 mmol, 1.0 equiv) in anhydrous MeCN (3 mL) was added NCS (0.3 mmol, 1.0 equiv). The reaction solution was stirred in the dark for 1 h. Then, nucleophile (NaOAc or NaSCN, 0.36 mmol, 1.2 equiv) and NaI (0.015 mmol, 0.05 equiv) was added and the solution was then heated at 60 °C. After 48 h, the reaction was cooled to room temperature. The reaction mixture was diluted with water (10 mL) and extracted with hexanes (4 × 10 mL). The organic layers were combined and washed with aqueous solutions of NaOH (2 × 10 mL, 1M) followed by brine (10 mL). The organic layer was dried over Na\(_2\)SO\(_4\) and filtered. The filtrate was concentrated \textit{in vacuo} and the crude residue was then purified by either column chromatography or Kugelrohr distillation.

\textit{cis-1-(tert-Butyl)-2-ethylpiperidin-3-yl acetate} (108). Isolation by column chromatography (1% ethyl acetate–1% NH\(_4\)OH–hexanes); White solid (37.6 mg, 55%); R\(_f\)
= 0.56 (20% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.88 (dt, $J = 11.6, 5.0$ Hz, 1H), 3.27–3.21 (m, 1H), 2.83–2.77 (m, 1H), 2.48 (ddd, $J = 13.3, 11.9, 3.2$ Hz, 1H), 2.02 (s, 3H), 1.77–1.71 (m, 1H), 1.64–1.43 (m, 5H), 1.11 (s, 9H), 0.90 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.5, 73.9, 55.8, 54.0, 38.3, 29.6 (3C), 25.8, 25.4, 21.4, 17.5, 12.6; FTIR (thin film), cm$^{-1}$ 2959, 1733, 1366, 1240, 1217, 1030; HRMS-ESI (m/z) calcd. for C$_{13}$H$_{26}$NO$_2$ ([M+H]$^+$): 228.1958; found: 228.1958.

**trans-1-Benzyl-2,5,5-trimethylpiperidin-3-yl acetate (109).** Isolation by Kugelrohr distillation; White solid (69.2 mg, 84%); $R_f = 0.34$ (10% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36–7.19 (m, 5H), 4.74 (ddd, $J = 10.5, 8.8, 4.8$ Hz, 1H), 4.09 (d, $J = 13.8$ Hz, 1H), 3.12 (d, $J = 13.8$ Hz, 1H), 2.34 (ddd, $J = 11.3, 2.0$ Hz, 1H), 2.26 (dq, $J = 8.8, 6.1$ Hz, 1H), 2.06 (s, 3H), 1.77 (ddd, $J = 12.2, 4.8, 2.0$ Hz, 1H), 1.77 (d, $J = 11.3$ Hz, 1H), 1.16 (d, $J = 6.1$ Hz, 3H), 1.15 (dd, $J = 12.5, 10.5$ Hz, 1H), 1.01 (s, 3H), 0.82 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.4, 140.0, 128.4 (2C), 128.1 (2C), 126.6, 63.5, 60.7, 57.4, 42.6, 31.1, 29.1, 25.5, 21.3, 15.4; FTIR (thin film), cm$^{-1}$ 1734, 1368, 1238, 1029; HRMS-ESI (m/z) calcd. for C$_{17}$H$_{26}$NO$_2$ ([M+H]$^+$): 276.1958; found: 276.1964.

**cis-8-Ethyl-1,6-diazabicyclo[3.2.1]octane-7-thione (110).** Isolation by column chromatography (20% ethyl acetate–hexanes to 40% ethyl acetate–hexanes); Orange oil (15.6 mg, 31%); $R_f = 0.14$ (25% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.11 (s, br, 1H), 3.90 (dt, $J = 11.6, 8.0$ Hz, 1H), 3.68 (dt, $J = 9.9, 5.4$ Hz, 1H), 3.61 (tdd, $J = 6.3, 5.4, 1.0$ Hz, 1H), 3.31 (ddd, $J = 11.6, 9.2, 3.7$ Hz, 1H), 2.15–1.87 (m, 3H), 1.72–1.44 (m, 4H), 0.96
(t, J = 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 185.4, 68.9, 62.2, 46.7, 30.8, 28.4, 25.5, 9.7; FTIR (thin film), cm$^{-1}$ 3201, 2961, 1459, 1421, 1318, 1256; HRMS-ESI (m/z) calcd. for CsH$_{15}$N$_2$S ([M+H]$^+$): 171.0950; found: 171.0949.

**trans-1-Benzyl-3-isothiocyanato-2,5,5-trimethylpiperidine (111).** Isolation by column chromatography (1% ethyl acetate–1% NH$_4$OH–hexanes); Clear oil (68.3 mg, 83%); R$_f$ = 0.59 (10% ethyl acetate–hexanes); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.39–7.21 (m, 5H), 4.10 (d, J = 13.8 Hz, 1H), 3.57 (ddd, J = 11.6, 9.0, 4.4 Hz, 1H), 3.12 (d, J = 13.8 Hz, 1H), 2.34 (dd, J = 11.4, 2.0 Hz, 1H), 2.29 (dq, J = 9.0, 6.1 Hz, 1H), 1.90 (ddd, J = 12.9, 4.4, 2.0 Hz, 1H), 1.79 (d, J = 11.4 Hz, 1H), 1.45 (dd, J = 12.9, 11.6 Hz, 1H), 1.35 (d, J = 6.1 Hz, 3H), 0.96 (s, 3H), 0.84 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 139.7, 131.0, 128.6 (2C), 128.5 (2C), 127.1, 63.7, 62.5, 59.4, 57.6, 45.3, 31.2, 29.1, 25.1, 17.3; FTIR (thin film), cm$^{-1}$ 2055 (broad), 1452, 1365, 1125, 722, 697; HRMS-ESI (m/z) calcd. for CsH$_{18}$N$_2$S ([M+H]$^+$): 275.1576; found: 275.1579.

**General procedure for entry 5 in Table 2:**

To a solution of unsaturated amine 68 or 72 (0.3 mmol, 1.0 equiv) in anhydrous MeCN (3 mL) was added NCS (0.3 mmol, 0.01 equiv). The reaction solution was allowed to stir in the dark for 1 h, after which NaI (0.015 mmol, 0.05 equiv) was added and the solution immediately heated to 60 °C. After 2.5 h, NaCN (0.36 mmol, 1.2 equiv) was added. The reaction was monitored by TLC until determined complete. Then the reaction mixture was diluted with water (10 mL) and extracted with hexanes (4 $\times$ 10
mL). The hexane layers were combined and washed with aqueous solutions of NaOH (2 × 10 mL, 1M) followed by brine (10 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and the filtrate was concentrated in vacuo. The crude residue was then purified by column chromatography.

**cis-1-(tert-Butyl)-2-ethylpiperidin-3-carbonitrile (112).** Isolation by column chromatography (2% ethyl acetate–hexanes); Clear oil (9.0 mg, 15%, mass loss due to the volatility); $R_f$ = 0.46 (25% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.33 (dt, $J$ = 7.4, 4.7 Hz, 1H), 2.95–2.88 (m, br, 1H), 2.78 (dt, $J$ = 12.9, 4.2 Hz, 1H), 2.59 (ddd, $J$ = 13.9, 12.9, 3.0 Hz, 1H), 1.99–1.91 (m, br, 1H), 1.83 (qd, $J$ = 13.0, 4.5 Hz, 1H), 1.80–1.59 (m, 2H), 1.52–1.45 (m, br, 1H), 1.41–1.29 (m, 1H), 1.11 (s, 9H), 1.00 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 122.3, 54.7, 54.3, 38.1, 31.7, 29.6 (3C), 24.7, 24.0, 19.6, 12.5; FTIR (thin film), cm$^{-1}$ 2962, 1361, 1219, 1204; HRMS-ESI (m/z) calcd. for C$_{12}$H$_{23}$N$_2$ ([M+H]$^+$): 195.1856; found: 195.1856.

**1-(cis-1’-(tert-Butyl)-2’-ethylpiperidin-3’-yl) succinimide (113).** Isolation by column chromatography (25% ethyl acetate–1% NH$_4$OH–hexanes); Yellow oil (20.0 mg, 25%); $R_f$ = 0.51 (50% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.22 (dt, $J$ = 13.5, 4.1 Hz, 1H), 3.16–3.10 (m, 1H), 2.97–2.80 (m, 2H), 2.68–2.58 (m, 1H), 2.63 (s, br, 4H), 1.80–1.68 (m, 1H), 1.66–1.53 (m, 2H), 1.44 (qt, $J$ = 12.9, 4.2 Hz, 1H), 1.30–1.18 (m, 1H), 1.15 (s, 9H), 0.79 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 178.0 (2C), 56.3, 55.4, 54.2,
trans-1-Benzyl-2,5,5-trimethylpiperidine-3-carbonitrile (114). Isolation by column chromatography (2% ethyl acetate–1% NH₄OH–hexanes); Clear oil (30.7 mg, 42%); R_f = 0.62 (25% ethyl acetate–hexanes); ^1H NMR (400 MHz, CDCl₃): δ 7.26–7.21 (m, 5H), 4.11 (d, J = 13.7 Hz, 1H), 3.11 (d, J = 13.7 Hz, 1H), 2.64 (ddd, J = 12.6, 9.7, 4.1 Hz, 1H), 2.41 (dq, J = 9.7, 6.1 Hz, 1H), 2.36 (dd, J = 11.5, 2.3 Hz, 1H), 1.79 (ddd, J = 13.2, 4.1, 2.3 Hz, 1H), 1.78 (d, J = 11.5 Hz, 1H), 1.50 (t, J = 12.9 Hz, 1H), 1.42 (d, J = 6.1 Hz, 3H), 0.96 (s, 3H), 0.84 (s, 3H); ^13C NMR (125 MHz, CDCl₃): δ 139.2, 128.3 (2C), 128.2 (2C), 126.8, 121.9, 63.5, 58.9, 57.5, 41.1, 33.8, 30.4, 28.7, 24.2, 18.6; FTIR (thin film), cm⁻¹ 2953, 1453, 1127, 740, 698; HRMS-ESI (m/z) calcd. for C₁₆H₂₃N₂ ([M+H]^+): 243.1856; found: 243.1857.

N-(trans-1-Benzyl-2,5,5-trimethylpiperidin-3-yl)-succinimide (115). To a solution of unsaturated amine 72 (0.3 mmol, 1.0 equiv) in anhydrous MeCN (3 mL) was added NCS (0.3 mmol, 1.0 equiv). The reaction solution was allowed to stir in the dark for 1 h, after which NaI (0.015 mmol, 0.05 equiv) was added and the solution immediately heated to 60 °C. After 2.5 h, Na₂CO₃ (0.36 mmol, 1.2 equiv) was added. The reaction was monitored by TLC until determined complete. Then the reaction mixture was diluted with water (10 mL) and extracted with hexanes (4 × 10 mL). The hexane layers were combined and washed with aqueous solutions of NaOH (2 × 10 mL, 1M) followed by brine (10 mL). The organic layer was dried over Na₂SO₄, filtered, and the
filtrate was concentrated in vacuo. The crude residue was then purified by column chromatography (20% ethyl acetate–hexanes) to give 115 as a white solid (72.6 mg, 77%).

Rf = 0.40 (40% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 7.36–7.19 (m, 5H), 4.17 (ddd, J = 13.0, 10.1, 4.4 Hz, 1H), 4.14 (d, J = 13.8 Hz, 1H), 3.06 (d, J = 13.8 Hz, 1H), 3.01 (dq, J = 10.1, 6.1 Hz, 1H), 2.68 (s, br, 4H), 2.34 (dd, J = 11.5, 2.3 Hz, 1H), 2.07 (t, J = 12.6 Hz, 1H), 1.90 (d J = 11.5 Hz, 1H), 1.28 (ddd, J = 12.3, 4.4, 2.3 Hz, 1H), 1.06 (s, 3H), 1.02 (d, J = 6.1 Hz, 3H), 0.80 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 177.3 (2C), 140.4, 128.3 (2C), 128.1 (2C), 126.5, 64.2, 57.6, 57.0, 53.6, 39.7, 31.1, 29.2, 28.0 (2C), 24.5, 16.6; FTIR (thin film), cm⁻¹ 1699, 1390, 1369, 1193, 1148, 735; HRMS-ESI (m/z) calcd. for C19H27N2O2 ([M+H]+): 315.2067; found: 315.2072.

N-(trans-1-Benzyl-2,5,5-trimethylpiperidin-3-yl)-tosylsulfonamide (116). To a solution of 72 (21.7 mg, 0.1 mmol, 1.0 equiv) in anhydrous MeCN (1 mL) was added TsNCINa·3H2O (28.2 mg, 0.1 mmol, 1.0 equiv). The reaction solution was allowed to stir in the dark for 1 h. Then NaI (0.7 mg, 0.005 mmol, 0.05 equiv) was added and the reaction heated to 60 °C for 2 h. Then the reaction was cooled to temperature, diluted with DCM (10 mL), and filtered through Celite. The filtrate was concentrated in vacuo and the crude residue purified by column chromatography (10% ethyl acetate–hexanes) to give 116 as a colorless oil (29.6 mg, 77%). Rf = 0.32 (25% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 7.70 (d, J = 8.4 Hz, 2H), 7.33–7.20 (m, 7H), 4.34 (d, J = 9.5 Hz, 1H), 3.39 (d, J = 13.6 Hz, 1H), 3.15 (td, J = 9.5, 7.6, 4.4 Hz, 1H), 3.13 (d, J = 13.6 Hz, 1H),
2.42 (s, 3H), 2.27 (dd, J = 11.5, 1.5 Hz, 1H), 2.02 (dq, J = 7.6, 6.2 Hz, 1H), 1.74 (d, J = 11.5 Hz, 1H), 1.39 (ddd, J = 13.1, 4.4, 1.5 Hz, 1H), 1.12 (d, J = 6.2 Hz, 3H), 1.00 (dd, J = 13.1, 9.5 Hz, 1H), 0.83 (s, 3H), 0.76 (s, 3H); 13C NMR (125 MHz, CDCl3, 60 °C): δ 143.1, 139.8, 138.6, 129.6 (2C), 128.5 (2C), 128.2 (2C), 127.1 (2C), 126.8, 62.1, 61.2, 58.2, 54.8, 44.0, 30.7, 28.9, 26.2, 21.4, 14.2; FTIR (thin film), cm⁻¹ 1153, 732, 663, 564; HRMS-ESI (m/z) calcd. for C22H31N2O2S ([M+H]+): 387.2101; found: 387.2103.

1-(trans-1′-Benzyl-2′,5′,5′-trimethylpiperidin-3′-yl)pyrrolidin-2-one (117). To a solution of 72 (65.2 mg, 0.3 mmol, 1.0 equiv) in anhydrous MeCN (3 mL) was added N-chloro-2-pyrrolidinone (35.9 mg, 0.3 mmol, 1.0 equiv). The reaction solution was allowed to stir in the dark for 1 h. NaI (2.2 mg, 0.015 mmol, 0.05 equiv) was then added and the reaction heated to 60 °C for 2 h. Na₂CO₃ (38.2 mg, 0.36 mmol, 1.2 equiv) was then added and the reaction allowed to stir for an additional 72 h at 60 °C. The reaction was cooled to room temperature and diluted with EtOAc (40 mL). This solution was washed with aqueous solutions of NaOH (2 × 10 mL, 1M) followed by brine (10 mL). The organic layer was dried over Na₂SO₄ and filtered. The filtrate was concentrated in vacuo. The crude residue was then purified by column chromatography (25% ethyl acetate–hexanes) to give 117 as a slightly yellow solid (58.2 mg, 65%). Rf = 0.14 (40% ethyl acetate–hexanes); 1H NMR (500 MHz, CDCl3, 60 °C): δ 7.33–7.19 (m, 5H), 4.15 (d, J = 13.9 Hz, 1H), 4.14–4.06 (m, 1H), 3.39–3.24 (m, 1H), 3.29–2.24 (m, 1H), 3.04 (d, J = 13.9 Hz, 1H), 2.43–2.34 (m, 3H), 2.28–2.21 (m, 1H), 2.02–1.96 (m, 2H), 1.71 (d, J = 11.4 Hz, 1H), 1.40
(ddd, $J = 12.4, 4.6, 2.2$ Hz, 1H), 1.35 (dd, $J = 12.4, 12.3$ Hz, 1H), 1.14 (d, $J = 6.0$ Hz, 3H), 1.08 (s, 3H), 0.81 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 174.8, 140.2, 128.4 (2C), 128.1 (2C), 126.6, 64.8, 59.5, 58.1, 52.2, 43.2, 41.1, 31.5, 30.9, 29.5, 24.8, 18.6, 16.4; FTIR (thin film), cm$^{-1}$ 2949, 1684, 1420, 1283, 1268; HRMS-ESI (m/z) calcd. for C$_{19}$H$_{29}$N$_2$O ([M+H$^+$]): 301.2274; found: 301.2273.

(S)-2,2-dimethyl-N-(1’-phenylethyl)pent-4-en-1-amine (124). A solution of 130 (224 mg, 2 mmol, 1.0 equiv) and (S)-(−)-α-methylbenzylamine (0.26 mL, 2 mmol, 1.0 equiv) in DCM/MeOH (3:1, 40 mL) was stirred overnight under nitrogen. Then the solvent was removed in vacuo and a new solution of DCM/MeOH (1:1, 40 mL) was introduced. The solution was cooled to 0 °C and solid NaBH$_4$ (151 mg, 4.0 mmol, 2.0 equiv) was added. After 11 h, the reaction was warmed to room temperature, quenched with aqueous NaOH (2 mL, 15%), and extracted with EtOAc (100 mL). The organic layer was washed with brine (2 × 50 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo. The compound was purified by column chromatography (1% methanol–dichloromethane to 10% methanol–dichloromethane) to give 124 as a clear liquid (382 mg, 88%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.31–7.27 (m, 4H), 7.23–7.18 (m, 1H), 5.79–5.69 (m, 1H), 5.00–4.93 (m, 2H), 3.65 (q, $J = 6.5$ Hz, 1H), 2.26 (d, $J = 11.5$ Hz, 1H), 2.13 (d, $J = 11.5$ Hz, 1H), 2.03–1.92 (m, 2H), 1.30 (d, $J = 6.5$ Hz, 3H), 0.83 (s, 3H), another 0.83 (s, 3H).
**2,2-Dimethylpent-4-enal oxime (131).** To a solution of 132 (2.05 mL, 15 mmol, 1.0 equiv) in MeOH (50 mL) and H₂O (6 mL) was added Na₂CO₃ (1.91 g, 18 mmol, 1.2 equiv) and hydroxylamine hydrochloride (1.25 g, 18 mmol, 1.2 equiv). After 24 h, H₂O (50 mL) was added and the resulting solution was extracted with Et₂O (3 × 50 mL). The Et₂O layers were combined, washed with brine (2 × 50 mL), dried over Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo* to produce 131 as a clear liquid (1.88 g, 99%). Rᵣ = 0.55 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 8.01–7.72 (br, 1H), 7.34 (s, 1H), 5.76 (ddt, J = 16.9, 10.2, 7.4 Hz, 1H), 5.10–5.02 (m, 2H), 2.16 (dt, J = 7.4, 1.1 Hz, 2H), 1.09 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 158.5, 133.8, 118.1, 45.2, 36.6, 25.0; FTIR (neat), cm⁻¹ 2965, 1384, 914, 652; HRMS-ESI (m/z) calcd. for C₇H₁₄NO ([M+H]⁺): 128.1070; found: 128.1070.

**2,2-Dimethylpent-4-en-1-amine (132).** To a solution of LAH (418 mg, 11.0 mmol, 2.2 equiv) in THF (11 mL) was added a solution of 131 (636 mg, 5.0 mmol, 1.0 equiv) in THF (2 mL) dropwise over 15 min at 0 °C under nitrogen. The reaction was warmed to room temperature and allowed to stir here for 10 min. Then the reaction was brought to reflux. After 2 h, the reaction was cooled down to 0 °C and quenched with H₂O (0.5 mL) then aqueous NaOH (0.5 mL, 15%). After stirring for 1 h, the reaction was diluted with H₂O (50 mL) and filtered. The filtrate was extracted with Et₂O (4 × 25 mL). The organic layers were combined and extracted with aqueous HCl (4 × 20 mL, 0.5M). The aqueous layers were combined, basified with an aqueous solution of NaOH, and then extracted
with Et₂O (3 × 30 mL). The organic layers were combined, washed with brine (2 × 25 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo to produce 132 as a clear liquid (403 mg, 71%). ¹H NMR (500 MHz, CDCl₃): δ 5.85–5.76 (m, 1H), 5.04–4.99 (m, 2H), 2.44 (s, 2H), 1.96 (dt, J = 7.5, 1.1 Hz, 2H), 1.05–0.97 (br, 2H), 0.85 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 135.3, 116.9, 52.7, 44.0, 34.9, 24.6; FTIR (neat), cm⁻¹ 2955, 1471, 996, 910, 810, 732; HRMS-ESI (m/z) calcd. for C₇H₁₆N ([M+H]+): 114.1277; found: 114.1277.

3,5-Dichloro-2,6-dimethoxybenzaldehyde (134). To a stirring solution of NCS (2.80 g, 21 mmol, 2.1 equiv) in DCM (80 mL) under nitrogen at −78 °C was added solid ZrCl₄ (0.23 g, 1.0 mmol, 0.1 equiv) followed by solid 133 (1.66 g, 10 mmol, 1.0 equiv). The reaction was allowed to warm to room temperature overnight. Then the reaction was quenched with a concentrated aqueous solution of NaHCO₃ (10 mL). The aqueous layer was removed and the organic layer was washed with aqueous NaOH (10 mL, 0.25M) and aqueous Na₂S₂O₃ (10 mL, 10%). The organic layer was then dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The impure solid was recrystallized twice from boiling hexanes to give 134 as a white solid (1.61 g, 68%). Rf = 0.44 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 10.23 (s, 1H), 7.64 (s, 1H), 3.94 (s, 6H).

N-(1’-(3”’,5”’-Dichloro-2”’,6”’-dimethoxyphenyl)ethyl)-2,2-dimethylpent-4-en-1-amine (135). A solution of 134 (235 mg, 1.0 mmol, 1.0 equiv) and 132 (113 mg, 1.0 mmol, 1.0 equiv) in DCM/MeOH (3:1, 20 mL) was stirred for 10 h. Then the solvent was removed in vacuo and the residue placed under nitrogen for 10 h. To the residue was
added toluene (22 mL) and the solution cooled to −78 °C. BF₃·Et₂O (0.309 mL, 2.5 mmol, 2.5 equiv) was added quickly and the reaction stirred for 1 h. MeLi (3.6 mL, 0.7M in Et₂O) was added dropwise over 5 min and the reaction continued to stir at −78 °C for 3 h. Then the reaction was quenched with a saturated aqueous solution of NaHCO₃ (1 mL) and warmed to room temperature. The mixture was extracted with EtOAc (20 mL) and the organic layer washed with a saturated aqueous solution of NaHCO₃ (20 mL), water (20 mL) and brine (20 mL). The organic layer was then dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. To the residue was added aqueous HCl (30 mL, 2M) and the solution extracted with EtOAc (4 × 10 mL). The organic layer is made basic by washing with aqueous NaOH. The organic layer was then dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo to give 134 as a white solid (149 mg, 61%). ¹H NMR (400 MHz, CDCl₃): δ 7.30 (s, 1H), 5.82–5.71 (m, 1H), 5.07–4.95 (m, 2H), 4.16 (q, J = 7.0 Hz, 1H), 3.87 (s, 6H), 2.23 (d, J = 11.3 Hz, 1H), 2.10 (d, J = 11.3 Hz, 1H), 1.99–1.95 (m, 2H), 1.71 (s, br, 1H), 1.46 (d, J = 7.0 Hz, 3H), 0.83 (s, 3H), another 0.83 (s, 3H).

N-(2″-Allyl-1″,3″-dithian-2″-yl)methyl)propan-2-amine (138). To a stirring mixture of LAH (159 mg, 4.2 mmol, 1.4 equiv) in THF (10 mL) was added a solution of 137 (736 mg, 3.0 mmol, 1.0 equiv) in THF (2 mL) dropwise over 5 min at 0 °C under nitrogen. Then TMSCl (0.46 mL, 3.6 mmol, 1.2 equiv) as added dropwise over 3 min and the reaction slowly warmed to room temperature then to reflux. After stirring for 3 h, the reaction was cooled to 0 °C and quenched successively with H₂O (0.15 mL), aqueous
NaOH (0.15 mL, 15%), then H₂O (0.45 mL). The reaction was allowed to warm to room temperature and was then filtered and washed with Et₂O (50 mL). The organic layer was extracted with aqueous HCl (3 × 50 mL, 0.5M). The aqueous extracts were combined, washed with hexanes (50 mL), and then made basic with aqueous NaOH (40 mL, 2M). The mixture was then extracted with Et₂O (3 × 50 mL). The Et₂O washes from this step were combined, washed with brine (50 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude material was passed through a plug of silica to give 138 as a clear liquid (297 mg, 43%). ¹H NMR (400 MHz, CDCl₃): δ 5.89 (ddt, J = 17.0, 10.2, 7.2 Hz, 1H), 5.15 (dt, J = 17.0, 1.4 Hz, 1H), 5.12 (dt, J = 10.2, 1.2 Hz), 2.93 (s, 2H), 2.91–2.67 (m, 5H), 2.65 (ddd, J = 7.2, 1.4, 1.2 Hz, 2H), 2.05–1.82 (m, 2H), 1.05 (d, J = 6.2 Hz, 6H).

2,2-Bis(propylthio)pent-4-enal (143).¹ To a stirring, clear solution of propanethiol (0.66 mL, 7.31 mmol, 2.1 equiv) in aqueous NaOH (3.5 mL, 2M) was added neat 141 (532 mg, 3.48 mmol, 1.0 equiv) dropwise over 5 min. After stirring for 1 h, the reaction was diluted with H₂O (10 mL) and extracted with MTBE (2 × 15 mL). The organic layers were combined, washed with a concentrated aqueous solution of NaHCO₃ (5 mL) then brine (10 mL). The organic layer was dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude material was purified by Kugelrohr distillation to give 143 as a yellow liquid (537 mg, 66%). R₇ = 0.70 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 9.05 (s, 1H), 5.91 (m, 1H), 5.20–5.15 (m, 2H), 2.63–2.60 (m, 2H), 2.49–2.43 (m, 4H), 1.61–1.52 (m, 4H), 0.97 (t, J = 7.3 Hz, 6H).
**N-Butyl-2,2-bis(phenylthio)pent-4-en-1-amine (146).** To a stirring solution of 142 (174 mg, 0.58 mmol, 1.0 equiv) and butylamine (63.0 μL, 0.66 mmol, 1.1 equiv) in DCE (2 mL) at 0 °C was added NaBH(OAc)$_3$ (172 mg, 0.81 mmol, 1.4 equiv) and the reaction slowly warmed to room temperature. Then AcOH (3 drops) was added and the reaction stirred for 24 h. Then the reaction was diluted with Et$_2$O (15 mL) and washed with aqueous NaOH (5 mL, 2M), a saturated solution of NaHCO$_3$ (5 mL), then brine (5 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography (9% ethyl acetate–1% NH$_4$OH–90% hexanes) to give 146 as a clear liquid (29.8 mg, 14%). R$_f$ = 0.28 (10% ethyl acetate–hexanes on a triethylamine/dichloromethane-treated plate); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.64–7.61 (m, 4H), 7.39–7.30 (m, 6H), 6.06 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 5.11–5.07 (m, 1H), 5.01–4.95 (m, 1H), 2.64 (s, 2H), 2.52 (t, J = 7.0 Hz, 2H), 2.45–2.42 (m, 2H), 1.48–1.40 (m, 2H), 1.37–1.29 (2H), 0.89 (t, J = 7.3 Hz, 3H).

**N-(tert-Butyl)-2,2-bis(propylthio)pent-4-en-1-amine (148).** To a solution of 143 (232 mg, 1.0 mmol, 1.0 equiv) in Ti(Oi-Pr)$_4$ (0.37 mL, 1.25 mmol, 1.25 equiv) at 0 °C was added tert-butylamine (105 μL, 1.0 mmol, 1.0 equiv) under nitrogen. After stirring for 4 h, EtOH (1 mL) was added to the reaction followed by solid NaBH$_4$ (75.6 mg, 2.0 mmol, 2.0 equiv). After stirring for an additional 10 h, the reaction was quenched with H$_2$O (1 mL), filtered through Celite, and concentrated in vacuo. To the residue was added aqueous HCl (5 mL, 2M) and the solution washed with hexanes (4 × 10 mL). The
aqueous layer was then basified with aqueous NaOH (7 mL, 1M) and the solution extracted with EtOAc (2 × 10 mL). The organic layers were combined, washed with brine (2 × 10 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo to give 148 as a slightly yellow liquid (173 mg, 60%). Rᵣ = 0.71 (10% ethyl acetate–hexanes on a triethylamine/dichloromethane-treated plate); ¹H NMR (400 MHz, CDCl₃): δ 5.96–5.85 (m, 1H), 5.16–5.08 (m, 2H), 2.64 (s, 2H), 2.59–2.54 (m, 6H), 1.63–1.53 (m, 4H), 1.05 (s, 9H), 0.99 (t, J = 7.3 Hz, 6H).

**Ethyl 2,2-diethoxypent-4-enoate (152).** To a stirring solution of TMP (4.68 mL, 27.5 mmol, 1.1 equiv) in THF (30 mL) was added a solution of n-BuLi (10.5 mL, 26.25 mmol, 1.05 equiv, 2.5M in hexanes) dropwise over 15 min at 0 °C under nitrogen. After stirring for 1 h, 150 (4.47 mL, 25 mmol, 1.0 equiv) was added dropwise over 10 min. After 1 h, the reaction was cooled to ~40 °C and stirred for 10 min. Allyl bromide (2.60 mL, 30 mmol, 1.2 equiv) was then added to the reaction dropwise over 10 min. The reaction was slowly warmed to 0 °C over 2 h then placed in an ice bath and stirred for another 1 h. The reaction was then quenched with aqueous HCl (20 mL, 1M), warmed to room temperature, and extracted with hexanes (200 mL). The organic layer was then washed with aqueous HCl (3 × 20 mL, 1M), a saturated aqueous solution of NaHCO₃ (20 mL), and brine (20 mL). The organic layer was then dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. Kugelrohr distillation (4 Torr) of the crude material affords 152 as a colorless liquid (4.43 g, 82%). Rᵣ = 0.30 (10% ethyl acetate–hexanes); ¹H NMR
(400 MHz, CDCl₃): δ 5.69 (ddt, J = 16.7, 10.6, 7.2 Hz, 1H), 5.13–5.07 (m, 2H), 4.24 (q, J = 7.1 Hz, 2H), 3.60 (dq, J = 9.3, 7.1 Hz, 2H), 3.49 (dq, J = 9.3, 7.1 Hz, 2H), 2.67 (dt, J = 7.2, 1.3 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 6H). These data are consistent with published spectra.¹⁴⁷

**Ethyl 2-allyl-1,3-dioxane-2-carboxylate (153).** To a stirring solution of DIPA (1.54 mL, 11 mmol, 1.1 equiv) in THF (20 mL) was added a solution of n-BuLi (4.45 mL, 10.5 mmol, 1.05 equiv, 2.36M in hexanes) dropwise over 15 min at 0 °C under nitrogen. After 1 h, the reaction was cooled to −40 °C and stirred for 15 min. To the reaction was added a solution of 151 (1.60 g, 10 mmol, 1.0 equiv) in THF (5 mL) dropwise over 15 min and stirred for an additional 15 min. The reaction was warmed to 0 °C briefly then cooled back to −40 °C for 20 min. Allyl bromide (1.04 mL, 12 mmol, 1.2 equiv) was then added dropwise over 10 min and the reaction slowly warmed to 10 °C over 5 h. The reaction was then quenched with aqueous HCl (10 mL, 2M), warmed to room temperature, and extracted with hexanes (100 mL). The organic layer was then washed with aqueous HCl (2 × 10 mL, 2M), H₂O (10 mL), a saturated aqueous solution of NaHCO₃ (10 mL), and brine (40 mL). The organic layer was then dried over Na₂SO₄, filtered, and the filtrate concentrated *in vacuo*. Kugelrohr distillation (7 Torr) of the crude material afforded 153 as a slightly yellow liquid (767 mg, 38%). Rᵣ = 0.57 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 5.79 (ddt, J = 16.9, 10.4, 7.2 Hz, 1H), 5.11–
5.00 (m, 2H), 4.28 (q, \( J = 7.1 \) Hz, 2H), 4.01–3.96 (m, 2H), 3.89–3.82 (m, 2H), 2.53–2.50 (m, 2H), 2.15–2.03 (m, 1H), 1.37–1.30 (m, 1H), 1.31 (t, \( J = 7.0 \) Hz, 3H).

(2'-Allyl-1',3'-dioxan-2'-yl)methanol (156). To a stirring mixture of LAH (98.7 mg, 2.6 mmol, 2.0 equiv) in Et\(_2\)O (6 mL) at 0 °C was added a solution of 153 (260 mg, 1.3 mmol, 1.0 equiv) in Et\(_2\)O (2 mL) dropwise over 10 min under nitrogen. After 1.5 h, the reaction was quenched successively with H\(_2\)O (0.1 mL), aqueous NaOH (0.2 mL, 15%), H\(_2\)O (0.3 mL) and the reaction warmed to room temperature. The reaction was then filtered and washed with Et\(_2\)O (40 mL). The aqueous layer was removed and the organic layer washed with H\(_2\)O (5 mL), brine (10 mL), dried over Na\(_2\)SO\(_4\), filtered, and the filtrate concentrated \textit{in vacuo}. The crude residue was purified by column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) to give 156 as a clear liquid (110 mg, 53%). R\(_f\) = 0.33 (50% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 5.75 (ddt, \( J = 17.5, 10.0, 7.0 \) Hz, 1H), 5.16–5.08 (m, 2H), 4.02–3.87 (m, 4H), 3.56 (d, \( J = 6.4 \) Hz, 2H), 2.63–2.61 (m, 2H), 1.94–1.83 (m, 1H), 1.86 (t, \( J = 6.4 \) Hz, 1H), 1.61–1.53 (m, 1H).

\( N\)-Benzyl-2,2-diethoxypent-4-en-1-amine (159). A solution of 157 (61.0 mg, 0.354 mmol, 1.0 equiv) and benzylamine (37.9 mg, 0.354 mmol, 1.0 equiv) in DCM/EtOH (3:1, 6 mL) was stirred overnight under nitrogen. Then the solvent was removed \textit{in vacuo} and a new solution of DCM/EtOH (1:1, 40 mL) was introduced. The solution was cooled to 0 °C and solid NaBH\(_4\) (26.8 mg, 0.708 mmol, 2.0 equiv) was added followed by 2 drops of
H₂O. The reaction was then warmed to room temperature and stirred for 1.5 h when the reaction was quenched with aqueous NaOH (1 mL, 15%), and extracted with Et₂O (50 mL). The organic layer was washed with H₂O (2 × 5 mL), a concentrated aqueous solution of NaHCO₃ (5 mL), brine (5 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The compound was purified by column chromatography (1% methanol–dichloromethane to 10% methanol–dichloromethane) to give 159 as a clear liquid (45.3 mg, 49%). ¹H NMR (400 MHz, CDCl₃): δ 7.32–7.19 (m, 5H), 5.70 (ddt, J = 17.1, 10.2, 7.2 Hz, 1H), 5.13–5.01 (m, 2H), 3.77 (s, 2H), 3.47 (dq, J = 9.2, 7.0 Hz, 1H), 3.40 (dq, J = 9.2, 7.0 Hz, 1H), 2.64 (s, 2H), 2.54–2.51 (m, 2H), 1.40 (s, br, 1H), 1.13 (t, J = 7.0 Hz, 6H).

(3’-(6’’-Methoxy-3’’,4’’-dihydronaphthalen-1’’-yl)propoxy)tert-butyldimethylsilane (172). Vigorous mechanical stirring is carried out on Mg° turnings (3.34 g, 137.4 mmol, 5.5 equiv) for 1 day under a nitrogen atmosphere. Then, THF (60 mL) is added to the Mg° turnings followed by a single crystal of I₂. After 10 min of stirring, neat (3-bromopropoxy)tert-butyldimethylsilane (6.37 mL, 27.5 mmol, 1.1 equiv) is added dropwise over 15 min to the mixture. A solution of 171 (4.41 g, 25 mmol, 1.0 equiv) and THF (20 mL) is then made and added dropwise over 20 min to the reaction mixture. The reaction is brought to reflux and allowed to stir for 2 h. The reaction is cooled to room temperature and a saturated solution of aqueous NH₄Cl (20 mL) is slowly added to the reaction followed by H₂O (80 mL). The reaction is filtered through Celite and the filtrate is extracted with EtOAc (3 × 75 mL). The EtOAc layers are
combined and washed with saturated NH₄Cl (50 mL), brine (50 mL), and then dried over Na₂SO₄. The solution is filtered and the solvent removed in vacuo. AcOH (50 mL) is added to the resulting residue and stirred for 6 h. 15% aqueous NaOH (5 mL) was then added to the reaction and the resulting solution was extracted with hexanes (4 × 50 mL). The hexanes layers were combined and washed with saturated NaHCO₃ (50 mL) followed by brine (50 mL). The hexanes are removed in vacuo and the crude residue purified by column chromatography to give 172 as a yellow liquid (1.72 g, 21%). Rf = 0.74 (25% ethyl acetate–hexanes).

(3’-(6”-Methoxynaphthalen-1’”-yl)propoxy)tert-butyldimethylsilane (173). To a stirring solution of 172 (2.00 g, 6 mmol, 1 equiv) in toluene (100 mL), was added DDQ (2.04 g, 9 mmol, 1.5 equiv) under nitrogen. After stirring at room temperature for 3 h, the reaction mixture was filtered through filter paper and diluted with hexanes (100 mL). The resulting organic solution was washed with aqueous NaOH (2 × 50 mL, 1M), saturated NaHCO₃ (50 mL), and brine (50 mL). The organic layer was dried over Na₂SO₄ and filtered, and the filtrate concentrated in vacuo. The crude residue was purified by column chromatography to produce 173 as a yellow liquid (1.44 g, 73% yield). Rf = 0.64 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.97 (d, J = 9.8 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.33 (dd, J = 8.2, 7.0, Hz, 1H), 7.19–7.12 (m, 3H), 3.91 (s, 3H), 3.69 (t, J = 6.1 Hz, 2H), 3.09 (t, J = 7.9 Hz, 2H), 1.92 (tt, J = 7.9, 6.1 Hz, 2H), 0.92 (s, 9H), 0.06 (s, 6H);
FTIR (thin film), cm$^{-1}$ 2929, 1255, 1219, 1101, 835, 775; HRMS-ESI (m/z) calcd. for C$_{20}$H$_{31}$O$_2$Si ([M+H]$^+$): 331.2088; found: 331.2089.

**3-(6'-Methoxynaphthalen-1'-yl)propan-1-ol (174).** To a solution of 173 (526 mg, 1.59 mmol, 1.0 equiv) in EtOH (14.4 mL), was added aqueous 10% HCl (1.6 mL). After 48h, the solution was basified with a saturated solution of NaHCO$_3$ (20 mL) and diluted with H$_2$O (20 mL). The product was extracted with Et$_2$O (3 x 20 mL). The Et$_2$O layers were combined, washed with brine (2 x 20 mL), dried over MgSO$_4$, and filtered. The filtrate was concentrated *in vacuo* and purified by column chromatography to yield 174 as a white solid (319 mg, 93% yield). mp 50–53 °C; R$_f$ = 0.23 (25% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.97 (dt, $J = 8.9$, 0.8 Hz, 1H), 7.62 (dd, $J = 8.2$, 0.8 Hz, 1H), 7.36 (dd, $J = 8.2$, 7.1 Hz, 1H), 7.22–7.15 (m, 3H), 3.93 (s, 3H), 3.74 (t, $J = 6.3$ Hz, 2H), 3.14 (t, $J = 7.8$ Hz, 2H), 2.01 (tt, $J = 7.8$, 6.3 Hz, 2H), 1.45 (s, br, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 157.2, 138.0, 135.1, 127.2, 126.2, 125.6, 125.4, 123.9, 118.4, 106.6, 62.5, 55.3, 33.6, 29.2; FTIR (thin film), cm$^{-1}$ 1625, 1434, 1255, 1220, 1034.

**3-(6'-Methoxynaphthalen-1'-yl)propanal (170).**$^{114,149}$ To a solution of PCC (1.21 g, 5.6 mmol, 2 equiv) in DCM (15 mL) was added 3 Å molecular sieves (2.8 g crushed under mortar and pestle). The mixture was allowed to stir for 5 min when 174 (606 mg, 2.8 mmol, 1.0 equiv) was added under a nitrogen atmosphere. After 3 h, Et$_2$O (15 mL) is added and the mixture filtered through a plug of silica. Concentration of the filtrate *in vacuo* followed by filtration through another plug of silica produced 170 as a white solid
(469 mg, 78% yield). Rf = 0.43 (25% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 9.88 (t, J = 1.3 Hz, 1H), 7.89 (d, J = 9.1 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.36 (dd, J = 8.2, 7.2 Hz, 1H), 7.21–7.15 (m, 3H), 3.93 (s, 3H), 3.38 (t, J = 7.6 Hz, 2H), 2.90 (td, J = 7.6, 1.3 Hz, 2H); 13C NMR (125 MHz, CDCl3): δ 201.5, 157.3, 136.3, 135.2, 126.9, 126.2, 126.0, 124.8, 123.7, 118.7, 106.8, 55.2, 44.5, 25.1; FTIR (thin film), cm⁻¹: 1721, 1625, 1435, 1256, 1221; HRMS-ESI (m/z) calcd. for C14H15O2 ([M+H]+): 215.1067; found: 215.1068.

N-(3'-(6''-Methoxynaphthalen-1''-yl)propyl)-2,2-dimethylpent-4-en-1-amine (169). To a stirring solution of 132 (226 mg, 2.0 mmol, 1.0 equiv) in MeOH/DCM (1:3, 20 mL) was added a solution of 170 (429 mg, 2.0 mmol, 1 equiv) in MeOH/DCM (1:3, 20 mL). After 24 h, the solvent was removed in vacuo and a new solution of MeOH/DCM (1:1, 40 mL) was added to the residual liquid and cooled to 0 °C. NaBH₄ (151 mg, 4.0 mmol, 2 equiv) was added in small portions over 5 min to the reaction. The reaction was warmed to room temperature and stirred here for 12 h. Then an aqueous solution of NaOH (2mL, 15%) was added to quench and basify the reaction and the result was extracted with EtOAc (100mL). The organic layer was washed with a saturated aqueous solution of NaHCO₃ (20 mL), brine (2 × 20 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. Purification of the crude oil by column chromatography (1% methanol–dichloromethane to 10% methanol–dichloromethane) yields 169 as a viscous, clear oil (468 mg, 75%). Rf = 0.08 (25% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 7.98 (dt, J = 8.8, 1.0 Hz, 1H), 7.60 (dd, J = 8.2, 1.0 Hz, 1H), 7.35 (dd, J = 8.2,
7.1 Hz, 1H), 7.20–7.14 (m, 3H), 5.87–5.77 (m, 1H), 5.04-4.98 (m, 2H), 3.93 (s, 3H), 3.08 (t, J = 7.7 Hz, 2H), 2.69 (t, J = 7.1 Hz, 2H), 2.35 (s, 2H), 2.01 (dt, J = 7.5, 1.2 Hz, 2H), 1.91 (tt, J = 7.7, 7.1 Hz, 2H), 1.20 (s, br, 1H), 0.89 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 157.1, 138.6, 135.6, 135.1, 127.3, 126.2, 125.5, 125.4, 123.8, 118.2, 116.7, 106.6, 60.4, 55.2, 50.6, 44.8, 34.2, 31.2, 30.7, 25.5; FTIR (thin film), cm$^{-1}$ 2951, 1626, 1434, 1220. HRMS-ESI (m/z) calcd. for C$_{21}$H$_{30}$NO ([M+H]$^+$): 312.2322; found: 312.2322.

2-(2′-(6″-Methoxy-3″,4″-dihydronaphthalen-1″-yl)ethyl)-1,3-dioxolane (175). Vigorous mechanical stirring was carried out on Mg$^0$ turnings (2.01 g, 82.5 mmol, 5.5 equiv) for 1 day under a nitrogen atmosphere. Then, THF (25 mL) was added to the Mg$^0$ turnings followed by a single crystal of I$_2$. After 10 min of stirring, neat 2-(2-bromoethyl)-1,3-dioxolane (3.39 g, 18.75 mmol, 1.25 equiv) was added dropwise over 15 min. to the mixture. A solution of 171 (2.64 g, 15.0 mmol, 1 equiv) in THF (20 mL) was added dropwise over 15 min to the reaction mixture and brought to reflux for 24 h. The reaction was cooled to room temperature, and diluted with a saturated aqueous solution of NH$_4$Cl (20 mL) then with EtOAc (50 mL). The resulting suspension was filtered through Celite and the filtrate extracted with EtOAc (2 × 75 mL). The EtOAc layers were combined and washed with a saturated aqueous solution of NH$_4$Cl (20 mL), brine (2 × 25 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo. AcOH (40 mL) was added to the resulting residue and stirred for 1.5 h. H$_2$O (20 mL) was then added to the reaction and the resulting solution extracted with hexanes (4 × 50 mL). The hexanes
layers were combined and washed with a saturated aqueous solution of NaHCO₃ (2 × 50 mL), followed by brine (50 mL). The hexanes were removed in vacuo and the crude residue purified by column chromatography (5% ethyl acetate–hexanes to 10% ethyl acetate–hexanes) to give 175 as a white solid (2.85 g, 73%). Rᵣ = 0.46 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.20 (dd, J = 8.1, 0.9 Hz, 1H), 6.74–6.69 (m, 2H), 5.76 (tt, J = 4.7, 1.2 Hz, 1H), 4.02–3.96 (m, 2H), 3.93–3.86 (m, 2H), 3.80 (s, 3H), 2.71 (t, J = 8.0 Hz, 2H), 2.57–2.51 (m, 2H), 2.26–2.20 (m, 2H), 1.92–1.86 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 158.2, 138.5, 135.3, 127.8, 123.7, 122.4, 113.7, 110.8, 104.3, 64.9, 55.2, 32.7, 28.9, 26.9, 23.0; FTIR (thin film), cm⁻¹ 1605, 1497, 1248, 1132, 1033, 821; HRMS-ESI (m/z) calcd. for C₁₆H₂₁O₃ ([M+H]+): 261.1485; found: 261.1477.

2-(2′-(6′-Methoxynaphthalen-1′-yl)ethyl)-1,3-dioxolane (176). To a solution of 175 (1.95 g, 7.5 mmol, 1.0 equiv) in toluene (150 mL), was added DDQ (2.13 g, 9.375 mmol, 1.25 equiv) in one portion under nitrogen. After stirring at room temperature for 2 h, the reaction mixture was filtered and washed with hexanes (150 mL). The resulting organic solution was washed with aqueous NaOH (2 ×50 mL, 1.0 M), a saturated aqueous solution of NaHCO₃ (50 mL), and brine (50 mL). The organic layer was dried over Na₂SO₄ and filtered. The filtrate was concentrated in vacuo and the crude residue purified by column chromatography (2% ethyl acetate–hexanes to 5% ethyl acetate–hexanes) to produce 176 as a yellow oil (1.94 g, 97%). Rᵣ = 0.45 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.98 (dt, J = 9.1, 0.7 Hz, 1H), 7.61 (dd, J = 8.1, 0.7
Hz, 1H), 7.35 (dd,  J = 8.1, 7.1 Hz, 1H), 7.23–7.15 (m, 3H), 4.99 (t,  J = 4.6 Hz, 1H), 4.09–4.00 (m, 2H), 3.96–3.87 (m, 2H), 3.93 (s, 3H), 3.17 (m, 2H), 2.10 (m, 2H). 13C NMR (125 MHz, CDCl3): δ 157.2, 137.8, 135.1, 127.2, 126.2, 125.6, 125.4, 123.8, 118.4, 106.6, 104.0, 65.0, 55.3, 34.9, 27.1; FTIR (thin film), cm⁻¹: 1624, 1257, 1219, 1131, 1030; HRMS-ESI (m/z) calcd. for C16H19O3 ([M+H]⁺): 259.1329; found: 259.1332.

**Ethyl 4-methyl-4-pentenoate (184).** Using proper distillation glassware, a solution of 2-methylprop-2-en-1-ol (3.61 g, 50.0 mmol, 1.0 equiv), triethyl orthoacetate (27.5 mL, 150.0 mmol, 3.0 equiv), and propionic acid (0.22 mL, 3 mmol, 0.06 equiv) was heated under standard pressure to remove ethanol, then unreacted starting materials until the vapor temperature reads 148 °C. The reaction was then cooled to room temperature and then aqueous HCl (20 mL, 1M) was added. After stirring for 0.5 h, the solution was extracted with hexanes (2 × 40 mL). The organic layers were combined, washed with a saturated aqueous solution of NaHCO₃ (2 × 20 mL), H₂O (20 mL), then brine (20 mL). The organic layer was dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The residue was distilled [74–78 °C at 15 Torr] to give 184 as a clear liquid (4.04 g, 57%). 1H NMR (400 MHz, CDCl3): δ 4.75–4.73 (m, 1H), 4.70–4.68 (m, 1H), 4.13 (q,  J =7.2 Hz, 2H), 2.47–2.43 (m, 2H), 2.36–2.31 (m, 2H), 1.74 (s, 3H), 1.26 (t,  J = 7.2 Hz, 3H). These data are consistent with published spectra.

**4-Methyl-4-pentenamide (185).** To five separate vials, each reagent was added: 184 (711 mg, 5.0 mmol, 1.0 equiv), concentrated aqueous ammonia (7.5 mL), sodium
cyanide (24.5 mg, 0.5 mmol, 0.1 equiv), and MeOH (7.5 mL). The separate reactions were sealed with paraffin film, heated to 45 °C, and stirred for 48 h. Then the reactions were cooled to room temperature, combined, and concentrated in vacuo until approximately 25 mL of total volume remained. Brine (50 mL) was added and the resulting mixture extracted with DCM (4 × 50 mL). The organic layers were combined, dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The remaining solid was filtered and washed with hexanes to give 185 as a white solid (1.85 g, 65%). mp 84–85 °C; Rf = 0.40 (100% ethyl acetate); ¹H NMR (400 MHz, CDCl₃): δ 5.47 (s, br, 2H), 4.79–4.77 (m, 1H), 4.74–4.71 (m, 1H), 2.42–2.32 (m, 4H), 1.76 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 175.2, 144.3, 110.5, 34.0, 33.0, 22.4; FTIR (neat), cm⁻¹ 3348, 3177, 1627, 1414, 883, 646; HRMS-ESI (m/z) calcd. for C₆H₁₁NO ([M+H]+): 114.0913; found: 114.0914

N-(3′-(6″-Methoxynaphthalen-1″-yl)propyl)-4-methylpent-4-en-1-amine (183). A solution of 185 (566 mg, 5.0 mmol, 1.67 equiv) in THF (5 mL) was added dropwise over 5 min to a mixture of LAH (418 m, 11.0 mmol, 3.67 equiv) in THF (15 mL) under a nitrogen atmosphere at 0 °C. After stirring at 0 °C for 10 min, the reaction was stirred for an additional 2 h at room temperature. The reaction was cooled back to 0 °C and quenched slowly with water (0.4 mL), aqueous NaOH (0.4 mL, 15%), then water again (1.2 mL). The reaction was warmed to room temperature and stirred for 1 h. The reaction was filtered, washed with Et₂O (50 mL), the filtrate dried over Na₂CO₃, and concentrated in vacuo (<100 Torr at 22 °C). The resulting amine solution was added to a solution of 170
(0.6423 g, 3.0 mmol, 1.0 equiv) in DCM/MeOH (3:1, 60 mL) and stirred overnight in a closed vessel. The solvent was removed in vacuo and a new solution of DCM/MeOH (1:1, 60 mL) was introduced. The solution was cooled to 0 °C and solid NaBH₄ (227 mg, 6.0 mmol, 2.0 equiv) was added. After 30 min, the reaction was warmed to room temperature and stirred for an additional 2 h. Then, aqueous NaOH (5 mL, 15%) and water (100 mL) were added to quench the reaction and the solution was extracted with EtOAc (3 × 75 mL). The organic layers were combined and washed with saturated aqueous NaHCO₃ (100 mL) and brine (100 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. Preliminary treatment of the residue on silica followed by Kugelrohr distillation (0.4 Torr) gives **183** as a viscous, clear oil (585 mg, 73%). R_f = 0.08 (100% ethyl acetate on a triethylamine/dichloromethane-treated plate); ¹H NMR (400 MHz, CDCl₃): δ 7.96 (d, J = 9.2 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.35 (dd, J = 8.2, 7.1 Hz, 1H), 7.20–7.14 (m, 3H), 4.71–4.67 (m, 2H), 3.93 (s, 3H), 3.08 (t, J = 7.8 Hz, 2H), 2.72 (t, J = 7.2 Hz, 2H), 2.61 (t, J = 7.3 Hz, 2H), 2.04 (t, J = 7.6 Hz, 2H), 1.93 (tt, J = 7.8, 7.2 Hz, 2H), 1.72 (s, 3H), 1.63–1.52 (s, br, 1H), 1.63 (tt, J = 7.6, 7.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 157.2, 144.5, 137.2, 135.1, 127.1, 126.1, 125.7, 125.2, 123.8, 118.4, 110.6, 106.6, 55.2, 48.7, 48.6, 35.0, 30.3, 29.1, 25.9, 22.1; FTIR (thin film), cm⁻¹ 2952, 2769, 2359, 1626, 1443, 784; HRMS-ESI (m/z) calcd. for C₂₀H₂₈NO ([M+H]+): 298.2165; found: 298.2166.

5-Azido-1-(3′-(6′′-methoxynaphthalen-1′′-yl)propyl)-3,3-dimethylpiperidine (168). R_f = 0.36 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.97 (d, J = 8.7
Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.36 (dd, J = 8.3, 7.1 Hz, 1H), 7.21–7.15 (m, 3H), 3.93 (s, 3H), 3.62 (ddt, J = 11.6, 10.5, 4.4 Hz, 1H), 3.11–3.02 (m, 2H), 3.00 (ddt, J = 10.5, 4.4, 1.6 Hz, 1H), 2.46–2.34 (m, 3H), 1.92–1.84 (m, 2H), 1.79 (t, J = 10.5 Hz, 1H), 1.74 (ddt, J = 12.6, 4.4, 1.6 Hz, 1H), 1.69 (d, J = 11.1 Hz, 1H), 1.12 (t, J = 12.1 Hz, 1H), 1.08 (s, 3H), 0.95 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 157.2, 138.5, 135.1, 127.3, 126.2, 125.5, 125.4, 124.0, 118.3, 106.6, 64.9, 58.6, 57.5, 55.6, 55.3, 42.8, 31.7, 30.5, 29.4, 28.2, 25.7; FTIR (thin film), cm⁻¹ 2949, 2092, 1625, 1255, 1219; HRMS-ESI (m/z) calcd. for C21H29N4O ([M+H]+): 353.2336; found: 353.2333.

5-Fluoro-1-(3′-(6′-methoxynaphthalen-1′-yl)propyl)-3,3-dimethylpiperidine (177). Rf = 0.56 (25% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 7.99 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.35 (dd, J = 8.2, 7.1 Hz, 1H), 7.21–7.15 (m, 3H), 4.76 (dtt, J = 48.9, 8.6, 4.4 Hz, 1H), 3.93 (s, 3H), 3.14–3.02 (m, 2H), 2.94–2.85 (m, 1H), 2.42 (t, J = 7.0 Hz, 2H), 2.24 (d, J = 11.2 Hz, 1H), 2.21–2.13 (m, 1H), 1.93–1.85 (m, 3H), 1.74 (td, J = 13.8, 4.6 Hz, 1H), 1.36 (td, J = 13.0, 9.0 Hz, 1H), 1.02 (s, 6H); 13C NMR (125 MHz, CDCl3): δ 157.2, 138.6, 135.1, 127.3, 126.2, 125.5, 125.4, 124.0, 124.0, 118.3, 106.6, 87.8 (d, 1JF-C = 169.9 Hz), 65.0, 58.5 (d, 2JF-C = 23.8 Hz), 57.4, 55.2, 43.4 (d, 2JF-C = 16.5 Hz), 31.8 (d, 3JF-C = 8.0 Hz), 30.4, 28.9, 28.2, 26.9; 19F NMR (376 MHz) δ -182.0 to -182.9 (br, m); FTIR (thin film), cm⁻¹ 2948, 1625, 1472, 1256, 1219, 1002; HRMS-ESI (m/z) calcd. for C21H28FNO ([M+H]+): 330.2228; found: 330.2228.
5-Chloro-1-(3’-(6”-methoxynaphthalen-1”-yl)propyl)-3,3-dimethylpiperidine (178). \( R_f = 0.41 \) (10% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.97 (d, \( J = 8.8 \) Hz, 1H), 7.61 (d, \( J = 8.2 \) Hz, 1H), 7.36 (dd, \( J = 8.2, 7.1 \) Hz, 1H), 7.21–7.15 (m, 3H), 4.13 (ddt, \( J = 11.9, 10.6, 4.5 \) Hz, 1H), 3.93 (s, 3H), 3.18 (ddt, \( J = 10.6, 4.5, 1.7 \) Hz, 1H), 3.13–3.00 (m, 2H), 2.48–2.34 (m, 2H), 2.44 (dt, \( J = 11.1, 1.7 \) Hz, 1H), 1.97 (t, \( J = 10.6 \) Hz, 1H), 1.95 (ddt, \( J = 12.7, 4.5, 1.7 \) Hz, 1H), 1.91–1.84 (m, 2H), 1.71 (d, \( J = 11.1 \) Hz, 1H), 1.35 (t, \( J = 12.3 \) Hz, 1H), 1.09 (s, 3H), 0.93 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 157.2, 138.5, 135.1, 127.3, 126.2, 125.5, 125.4, 124.0, 118.3, 106.6, 64.7, 62.4, 57.3, 55.3, 54.3, 48.4, 33.3, 30.5, 29.4, 28.2, 25.3; FTIR (thin film), cm\(^{-1}\) 2949, 1625, 1471, 1433, 1256, 1220; HRMS-ESI (m/z) calcd. for C\(_{21}\)H\(_{29}\)ClNO ([M+H]\(^+\)): 346.1932; found: 346.1933.

3-Fluoro-1-(3’-(6”-methoxy-naphthalen-1”-yl)propyl)-3-methyl-piperidine (180). \( R_f = 0.15 \) (50% ethyl acetate–hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.98 (d, \( J = 8.8 \) Hz, 1H), 7.60 (d, \( J = 8.2 \) Hz, 1H), 7.35 (dd, \( J = 8.2, 7.0 \) Hz, 1H), 7.21–7.14 (m, 3H), 3.93 (s, 3H), 3.05 (td, \( J = 7.6, 2.6 \) Hz, 2H), 2.73–2.60 (br, m, 2H), 2.45 (t, \( J = 7.6 \) Hz, 2H), 2.20–2.11 (br, m, 1H), 1.93 (quintet, \( J = 7.6 \) Hz, 2H), 1.93–1.77 (m, 3H), 1.60–1.53 (m, 1H), 1.36 (d, \( J = 21.6 \) Hz, 3H), 0.98–0.85 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), 60 °C): \( \delta \) 157.2, 138.5, 135.2, 127.4, 126.2, 125.6, 125.4, 123.9, 118.3, 106.7, 62.3 (d, \( ^2J_{F-C} = 22.6 \) Hz), 58.1, 55.3, 53.3, 35.3 (d, \( ^2J_{F-C} = 21.2 \) Hz), 30.7, 28.1 (d, \( ^2J_{F-C} = 4.1 \) Hz), 25.2 (d, \( ^2J_{F-C} = 24.6 \) Hz), 22.3, (note that a carbon peak for C-F could not be found); FTIR (thin film), 1530, 1349, 1288, 1266, 1133; HRMS-ESI (m/z) calcd. for C\(_{20}\)H\(_{27}\)FNO ([M+H]\(^+\)): 316.2071; found: 316.2076.
3-Chloro-1-(3’-(6”-methoxynaphthalen-1”-yl)propyl)-3-methylpiperidine (181).

Rf = 0.26 (25% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 8.01 (d, J = 9.1 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 8.1, 7.1 Hz, 1H), 7.22–7.14 (m, 3H), 3.93 (s, 3H), 3.12–3.03 (m, 2H), 2.74–2.67 (m, 1H), 2.58–2.20 (br, m, 5H), 1.94–1.86 (br, m, 4H), 1.67–1.59 (br, m, 2H), 1.63 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 157.4, 138.6, 135.3, 127.6, 126.2, 125.6, 125.4, 124.0, 118.2, 107.0, 68.1, 66.3, 57.6, 55.3, 53.7, 40.3, 30.5, 30.0, 28.1, 23.2; FTIR (thin film), cm⁻¹: 2942, 1625, 1435, 1256, 1220, 1171; HRMS-ESI (m/z) calcd. for C₂₀H₂₇ClNO (\([\text{M+H}]^+\)) : 332.1776; found: 332.1777.

3-Azido-1-(3’-(6”-methoxynaphthalen-1”-yl)propyl)-3-methylpiperidine (182).

Rf = 0.50 (50% ethyl acetate–hexanes); 1H NMR (500 MHz, CDCl₃, 60 °C): δ 7.99 (d, J = 9.0 Hz, 1H), 7.59 (d, J 8.2 Hz, 1H), 7.34 (dd, J = 8.2, 7.0 Hz, 1H), 7.20–7.15 (m, 3H), 3.93 (s, 3H), 3.08 (td, J = 7.5, 2.6, 2H), 2.58–2.50 (br, m, 2H), 2.47–2.38 (m, 2H), 2.24–2.19 (m, 1H), 2.17 (d, J = 11.6 Hz, 1H), 1.92 (tt, J = 7.5, 7.3 Hz, 2H), 1.86–1.78 (m, 1H), 1.70–1.65 (m, 1H), 1.63–1.56 (m, 1H), 1.47–1.41 (m, 1H), 1.31 (s, 3H); 13C NMR (125 MHz, CDCl₃, 60 °C): δ 157.4, 138.6, 135.3, 127.6, 126.2, 125.6, 125.5, 124.0, 118.2, 107.0, 62.5, 60.1, 58.1, 55.3, 53.7, 35.3, 30.6, 28.1, 24.4, 22.5; FTIR (thin film), 2937, 2091, 1625, 1434, 1256, 1219; HRMS-ESI (m/z) calcd. for C₂₀H₂₇N₃O (\([\text{M+H}]^+\)) : 339.2179; found: 339.2179.

2-(Azidomethyl)-1-(3’-(6”-methoxynaphthalen-1”-yl)propyl)-2-methylpyrrolidine (186). Rf = 0.32 (50% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl₃): δ 7.96 (dt, J = 8.7, 0.9 Hz, 1H), 7.60 (dt, J = 8.2, 0.9 Hz, 1H), 7.35 (dd, J = 8.2, 7.0
Hz, 1H), 7.21–7.14 (m, 3H), 3.93 (s, 3H), 3.27 (d, J = 12.2 Hz, 1H), 3.16–2.97 (m, 3H), 3.03 (d, J = 12.2 Hz, 1H), 2.65 (dt, J = 11.9, 7.8 Hz, 1H), 2.53 (dt, J = 8.7, 8.1 Hz, 1H), 2.47 (dt, J = 11.9, 6.8 Hz, 1H), 1.98–1.87 (m, 3H), 1.83–1.73 (m, 2H), 1.56 (dt, J = 12.4, 7.8 Hz, 1H), 0.98 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 157.2, 138.6, 135.1, 127.3, 126.2, 125.5, 125.4, 123.6, 118.2, 106.6, 63.2, 58.2, 55.2, 51.3, 48.6, 36.5, 30.9, 30.4, 21.4, 18.6; FTIR (thin film), 2092, 1625, 1434, 1256, 1219, 1170; HRMS-ESI (m/z) calcd. for C₂₀H₂₇N₄O ([M+H]+): 339.2179; found: 339.2170.

1-(3’-(6”-Methoxynaphthalen-1”-yl)propyl)-3,3-dimethylpiperidine (165). To a stirring solution of 177 (27.7 mg, 0.08 mmol, 1.0 equiv) in THF (2 mL) was added solid LAH (30.4 mg, 0.8 mmol, 10.0 equiv) under a stream of nitrogen and the resulting mixture heated to reflux. After 24 h, the reaction was cooled to room temperature and quenched successively with H₂O (0.3 mL), aqueous NaOH (0.3 mL, 15%), and H₂O (0.6 mL). The result was filtered and washed with Et₂O (20 mL) then extracted with Et₂O (3 × 15 mL). The organic layers were combined, washed with brine (15 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography (2% methanol–dichloromethane) to give 165 as a clear oil (6.4 mg, 26%). ¹H NMR (400 MHz, CDCl₃): δ 8.00 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.20–7.14 (m, 3H), 3.93 (s, 3H), 3.07 (t, J = 7.7 Hz, 2H), 2.42–2.25 (m, br, 4H), 2.10–2.00 (m, br, 2H), 1.93–1.86 (m, br, 2H), 1.25–1.21 (m, br, 2H), 0.97 (s, 6H). These data are consistent with published spectra.⁷

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5-Methoxy-1-(3′-(6′′-methoxynaphthalen-1′′-yl)propyl)-3,3-dimethylpiperidine (179). To a solution of 177 (238 mg, 0.069 mmol, 1.0 equiv) in CHCl₃/MeOH (1:1, 2 mL) was added NaBH₄ (26.1 mg, 0.69 mmol, 10.0 equiv). The resulting solution was heated to reflux for 3 h then quenched with aqueous NaOH (3 drops, 15%) and diluted with H₂O (10 mL). The solution was extracted with hexanes (3 × 10 mL). The organic layers were combined, washed with brine (2 × 10 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography (5% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) to give 179 as a clear liquid (23.6 mg, 55%). Rf = 0.32 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.97 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.33 (dd, J = 8.1, 7.1 Hz, 1H), 7.19–7.12 (m, 3H), 3.91 (s, 3H), 3.45 (ddt, J = 10.7, 9.8, 4.5 Hz, 1H), 3.35 (s, 3H), 3.10–3.05 (m, 1H), 3.05 (t, J = 7.7 Hz, 2H), 2.45–2.33 (m, 3H), 1.91–1.82 (m, 2H), 1.75 (ddt, J = 12.3, 4.5, 1.7 Hz, 1H), 1.66 (d, J = 10.9 Hz, 1H), 1.66 (t, J = 10.0 Hz, 1H), 1.26–1.23 (m, 1H), 1.04 (s, 3H), 0.91 (s, 3H).
Chapter 2: Electrophilic amidation of indoles and pyrroles using \(N\)-benzenesulfonyloxyamides
2. Electrophilic amidation of indoles and pyrroles using \( N \)-benzenesulfonyloxyamides

2.1 Introduction

Figure 8: Examples of biologically important indoles and pyrroles

Indoles are one of the most prolific heterocycles of biological importance.\textsuperscript{152-160} The term “privileged scaffold” was actually first coined by Evans and co-workers in the late 1980’s when referring to indoles.\textsuperscript{161-162} Furthermore, indoles are one of only three heterocycles found in an amino acid (Figure 8, tryptophan). From that amino acid are derived all indole-based and some pyrrole-based natural products (e.g. serotonin, ibogamine and pyrrolnitrin). Several indole-based pharmaceuticals have been approved by the FDA, ranking at number 9 in the frequency of their occurrence versus all nitrogen heterocycles (e.g. sumatriptan).\textsuperscript{16} Comparatively, pyrroles are not as frequently found in pharmaceuticals or in nature as indoles.\textsuperscript{16} Yet, their chemical reactivity is similar, and many pyrroles of biological interest are used in chemical research.\textsuperscript{3, 163-164}
2.1.1 Indole aminal natural products

N,N'-Acetals, more often called aminals, can be found in nature. The aminal functional group is most commonly associated with indoles and indolines at the N-1 position (Figure 9). These types of motifs are difficult to access and have been targets in many total synthesis projects, as, many of these types of compounds have cytotoxic, fungicidal, or insecticidal properties.

Figure 9: Examples of aminal-containing natural products

2.1.2 Previous aminal syntheses

2.1.2.1 Synthesis of indole N,O-acetals

N,O-acetals are sometimes referred to as aminals although this is discouraged by IUPAC. The nucleoside adenosine is an example of a naturally occurring N,O-acetal (Figure 9). Li and co-workers developed a chiral synthesis of cyclic indole N,O-acetals in their synthesis toward a selective NS5a inhibitor. The addition of an aldehyde to an aminoalcohol in the presence of trifluoroacetic acid gave an N,O-acetal with high diastereoselectivity and yield (Scheme 35). The indoline could be oxidized by KMnO4 to give the fully aromatized indole in high yield and enantiopurity.
Scheme 35: Chiral synthesis of indole $N,O$-acetals

2.1.2.2 Synthesis of indole aminals using reducing conditions

**A. Direct reduction to aminal followed by rearrangement**

![Chemical reaction diagram]

**B. Tandem reduction and addition to an olefin**

![Chemical reaction diagram]

Scheme 36: Coupled amidine reduction reactions

The most common way to synthesize indole aminals is under reducing conditions. Reduction of amidine functional groups is a standard protocol which can be
coupled with other reactions if so desired. Nitro group reduction followed by acetal deprotection and imine formation produces an amidine (Scheme 36, A). Reduction of the amidine with NaBH₄ gives the aminal. Interestingly, this indole aminal can be rearranged in acid to give the thermodynamically more stable 3-aminomethyl indole. Amidine reduction can also be coupled with radical cyclization to give a trisubstituted aminal (Scheme 36, B). Furthermore, in their total synthesis of goniomitine, Beaudry and co-workers reduced compound 87, which contained an ester, an amide, and a nitrile in one step to form the necessary alcohol and aminal intermediate 88 (Scheme 37). The intermediate was not isolated, but instead was directly oxidized to furnish the final compound goniomitine.

Scheme 37: Reduction step to the aminal of goniomitine

2.1.2.3 Synthesis of indole aminals from iminium intermediates

Under normal Mannich conditions, indoles are aminomethylated at the C-3 position. However, iminium ions can be transferred to indoles and other NH-heterocycles under certain conditions to form aminals. For instance, dialkyl aminals in the presence of succinic anhydride and base transfer an aminal to a 3-substituted indole
(Scheme 38, entry 1). However when both the 1- and 3-positions of indole are open, selectivity could not be achieved (entry 2).

Scheme 38: Indole aminals from iminium ions

2.1.2.4 Synthesis of indole aminals using Lewis acid catalysis

Scheme 39: Aminomethylation of indoles with Lewis acids

Normally in the presence of Lewis acids, indoles are aminomethylated with aminals, hemiaminals, and \(N,O\)-acetals at the more thermodynamically stable 3-position.
For instance, indoles react with alkyl aminals in the presence of TMSCl to give 3-aminomethylatedindoles (Scheme 39, A).\textsuperscript{176} Trifluoromethyl hemiaminals also give 3-aminomethylatedindoles when using the Lewis acid BF$_3$·OEt$_2$ (Scheme 39, B).\textsuperscript{177} However, Sakai and co-worker discovered that when treated with a catalytic amount of Hf(OTf)$_4$, N,O-acetals give the aminal product instead (Scheme 39, C).\textsuperscript{178} Additionally, this method was successfully extended to other NH-heterocycles such as pyrroles and aza-indoles.

### 2.1.3 3-Aminated indoles and pyrroles in potential pharmaceuticals

Although in general indoles have been extensively synthesized and studied, 3-amino and 3-amidoindoles have not been. δ-Carbolines such as quindoline have been isolated from natural sources (Figure 10),\textsuperscript{179,180} but to the best of my knowledge, no 3-amino or 3-amidoindole natural product has ever been isolated. These compounds can be accessed synthetically, and many of them exhibit biological activity. Romagnoli and co-workers found several 3-aminindoles that exhibit cytotoxicity by inhibiting tubulin.\textsuperscript{181} A 3-guanidinoindole showed glucose-dependent insulin secretion in pancreatic β-cells, providing a promising new therapeutic for type 2 diabetes.\textsuperscript{182} Kumar and co-workers found a quinazolidinone with a 3-aminofunctional group to be a potent COX-II inhibitor.\textsuperscript{183} Furthermore, the compound was not found to be cytotoxic or ulcerogenic.
2.1.4 Previous syntheses to 3-aminoindoles

The first known methods to 3-amino and 3-amidoindoles were simply the reduction of 3-nitrosoindoles using zinc and hydrochloric acid, or alternatively hydrogenation using Adam’s catalyst.\textsuperscript{184-185} However, due to the instability of primary and secondary 3-aminoindoles outside the crystalline state, most modern methods produce either a tertiary 3-aminoindole or a 3-amidoindole.\textsuperscript{186-188} Recently, much effort has been spent on discovering new methods towards these unique scaffolds.

2.1.4.1 Early metal-free methods to 3-aminoindoles

In a similar path to standard electrophilic nitration and reduction, nitroethane in the presence of polyphosphoric acid (PPA) reacts with nucleophilic arenes to give aniline derivatives.\textsuperscript{189} Most examples were anisoles, but in one example the authors showed that a 3-amidoindole could be synthesized by this method (Scheme 40, A). Fu and co-workers synthesized 3-amido and 3-aminoindoles by utilizing a proven yet lengthy approach, the Curtius rearrangement (Scheme 40, B).\textsuperscript{190} Although not a standard method, but one of the initial methods developed nonetheless, is the synthesis of 3-
aminoidoles from anilines and diimmonium dibromides (Scheme 40, C).\textsuperscript{191} Diimmonium dibromides represent one of the first types of electrophilic amination reagents. Numerous 1-alkyl-3-aminoidoles were formed in this manner.

\begin{center}
\textbf{Scheme 40: Early methods toward 3-aminoidoles}
\end{center}

2.1.4.2 A three-component method

An interesting Cu-catalyzed 3-component reaction yields 3-aminoidoles after a two-step process (Scheme 41).\textsuperscript{192} Utilizing an \textit{ortho}-aminobenzaldehyde, a nucleophilic amine, and a terminal alkyne as its three components, the reaction first yields a 3-aminoidoline. This intermediate can be isomerized to give the desired 3-aminoidole in the presence of base and heat. The method was successfully expanded to the use of many secondary amines and electron-withdrawing alkynes; however the yields were not as good when using multifunctional arenes.
2.1.4.3 Buchwald-Hartwig method

Cirrincione and co-workers found that in highly specialized circumstances and under forcing conditions, a 3-bromoindole can be directly displaced by an amine to give 3-aminoindoles in moderate yields. However, if 3-haloindoles and anilines or amides are the desired disconnect, the Buchwald-Hartwig method is more generally used. Hartwig and co-workers observed that in principle, 3-haloindoles could undergo the desired reaction with anilines (Scheme 42, A). In their synthesis of pyrimidoindoles, Nagarajan and co-workers proved that 2- and 3-haloindoles with electron-withdrawing aldehydes at the 3- and 2-positions of indole respectively could be successfully cross-coupled to many primary amides (Scheme 42, B). Generally there are two problems with the Buchwald-Hartwig approach to 3-aminoindoles. The biggest hindrance is probably the fact that 3-haloindoles are unstable and cannot exist for more than a few days without some decomposition. Secondly, free NH-indoles have never been observed to efficiently give 3-aminoindoles, probably due to competitive cross-coupling.

Scheme 41: Cu-catalyzed 3-component method

![Scheme 41: Cu-catalyzed 3-component method](image-url)
2.1.4.4 Transition-metal catalyzed electrophilic amination

Transition metal-catalyzed annulative approaches starting from electrophilic amides and nucleophilic \(\sigma\)-alkynylanilines are the most widespread strategies in this category. For instance, Miura and co-workers used \(N\)-benzoyloxyamines in the presence
of a copper catalyst and base to synthesize both 3-aminobenzofurans and 3-aminoindoles (Scheme 43, A).\textsuperscript{197-198} Rhodium can be used instead when the electrophile is an $N$-pivaloyloxyamide (Scheme, 43, B).\textsuperscript{199} With these two examples, both 3-amino and 3-amidoindoles can be synthesized in high yield. In a double ring-forming annulation, Zhu and co-workers used palladium and oxidative conditions to successfully prepare 3-amidoindole derivatives (Scheme 43, C).\textsuperscript{200} All instances here show a high functional group tolerance.

**Table 9: Partial substrate scope for the zinc-mediated synthesis of 3-amidoindoles**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>78%</td>
</tr>
<tr>
<td>Cl</td>
<td>89%</td>
</tr>
<tr>
<td>F</td>
<td>72%</td>
</tr>
<tr>
<td>MeO$_2$S</td>
<td>89%</td>
</tr>
<tr>
<td>NC</td>
<td>80%</td>
</tr>
<tr>
<td>H</td>
<td>91%</td>
</tr>
</tbody>
</table>

Beller and co-workers found that in the presence of excess Zn$^{2+}$ salts, arylhydrazines and terminal propargylic amides react to form 3-amidoindoles in high yields (Table 9).\textsuperscript{201-202} Propargylic imides and sulfonamides can be used as well in this protocol. The authors also show that some of the new 3-amidoindoles are inhibitors of
the enzyme GSK-3β. However, one limitation here is that 2-methylindoles are the only presented products.

2.2 The amidation of indoles and pyrroles

Despite the before mentioned protocols, there still is not an electrophilic 3-amino or 3-amidoindole synthesis that uses simple indoles as substrates. Herein, I describe a direct 3-amidation of indoles using novel N-benzenesulfonyloxyamides as electrophilic amidation reagents. Additionally, pyrroles are amidated at both the 2- and 3-positions when subjected to the same protocol. Using an alternative protocol, indoles are N-amidomethylated, giving aminals.

The pKa of indole in DMSO is 21, meaning it can be deprotonated by a variety of strong bases to give the ambident indolide anion. According to resonance, chemoselectivity is a concern as electrophiles can add to this species at the 1- or 3-positions (N vs. C). Multiple studies show that alkylations and acylations of indole using non-coordinating cations such as Na⁺ in strongly solvating solvents (e.g. DMSO) result in the N-alkylated or N-acylated indole.²⁰³⁻²⁰⁵ Whereas alkylations and acylations of indole in the presence of strongly coordinating cations (e.g. Zn²⁺) in non-polar solvents result in the C-alkylated or C-acylated product.²⁰⁶⁻²⁰⁹
2.2.1 Synthesis of indole aminals

2.2.1.1 Limited success in the initial amidation of indoles

In the initial screening for suitable reaction conditions, indole (189) was deprotonated in the presence of Mg\(^{2+}\) or Zn\(^{2+}\) cations and screened against known electrophilic amines and amides. None of the known compounds worked immediately but a new type of electrophilic amide, N-toluenesulfonyloxyamide (191), did generate some of the desired 3-amidoindole 190 (Table 10). Electrophile 191 proved successful (entries 1–3), but that was superseded by N-nitrobenzenesulfonyloxyamide 192 (entries 4–6), then finally by N-benzenesulfonyloxyamide 193 (entries 7–8). The amount of ZnCl\(_2\) could be reduced (entries 6 and 8), while transmetalation to ZnCl\(_2\) is necessary to produce a clean reaction profile (entries 9–10). Increasing the amount of indole equivalents did not increase efficiency (entries 11–13). Although the yield at this stage was 60%, further tampering of the reaction did not give any better yields. Furthermore, indole was used in a 110% excess, and other indoles did not work very well in the reaction. More information was necessary for the complete optimization of 3-amidoindoles.
Table 10: Initial optimization for the synthesis of 3-amidoindoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole (equiv)</th>
<th>Solvent</th>
<th>ZnCl₂ (equiv)</th>
<th>Temp. (°C)</th>
<th>BzMeNOLG</th>
<th>190 (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ᵃ</td>
<td>2.1</td>
<td>Benzene</td>
<td>None</td>
<td>50</td>
<td>LG = Ts (191)</td>
<td>26%</td>
</tr>
<tr>
<td>2ᵇ</td>
<td>2.1</td>
<td>Benzene</td>
<td>2.5</td>
<td>50</td>
<td>191</td>
<td>5%</td>
</tr>
<tr>
<td>3</td>
<td>2.1</td>
<td>THF</td>
<td>2.5</td>
<td>50</td>
<td>191</td>
<td>49%</td>
</tr>
<tr>
<td>4</td>
<td>2.1</td>
<td>THF</td>
<td>2.5</td>
<td>50</td>
<td>LG = Ns (192)</td>
<td>56%</td>
</tr>
<tr>
<td>5</td>
<td>2.1</td>
<td>THF</td>
<td>2.5</td>
<td>50</td>
<td>LG = SO₂Ph (193)</td>
<td>58%</td>
</tr>
<tr>
<td>6</td>
<td>2.1</td>
<td>THF</td>
<td>2.5</td>
<td>40</td>
<td>192</td>
<td>54%</td>
</tr>
<tr>
<td>7</td>
<td>2.1</td>
<td>THF</td>
<td>1.2</td>
<td>40</td>
<td>192</td>
<td>53%</td>
</tr>
<tr>
<td>8</td>
<td>2.1</td>
<td>THF</td>
<td>1.2</td>
<td>40</td>
<td>193</td>
<td>60%</td>
</tr>
<tr>
<td>9ᵃ</td>
<td>2.1</td>
<td>THF</td>
<td>None</td>
<td>rt</td>
<td>193</td>
<td>55%</td>
</tr>
<tr>
<td>10ᵃ</td>
<td>2.1</td>
<td>Benzene</td>
<td>None</td>
<td>rt</td>
<td>193</td>
<td>19%</td>
</tr>
<tr>
<td>11</td>
<td>2.5</td>
<td>THF</td>
<td>1.5</td>
<td>40</td>
<td>193</td>
<td>51%</td>
</tr>
<tr>
<td>12</td>
<td>3.0</td>
<td>THF</td>
<td>1.5</td>
<td>40</td>
<td>193</td>
<td>52%</td>
</tr>
<tr>
<td>13</td>
<td>2.2</td>
<td>THF</td>
<td>1.2</td>
<td>40</td>
<td>193</td>
<td>59%</td>
</tr>
</tbody>
</table>

Reaction conditions: 189 (variable, in 1 mL of solvent), i-PrMgCl (variable, solution in THF), rt, 30 min; then ZnCl₂ (variable, solid), rt, 1 h; then BzMeOLG (1.0 equiv, 0.2 mmol, 0.2M), 24 h. a) Crude material contained many unanalyzed byproducts. b) Reactants were insoluble and caused the low yield. Yields determined using ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard.

2.2.1.2 Successful optimization of indole aminals

More information about what affects the reaction outcome was needed. Indole (189) was set as the limiting reagent and byproducts N-benzyllindole 195 and N-benzenesulfonylindole 196 were now being accounted for (Table 10). In the first
experiment, NaH in DMSO was used to test what the reaction outcome will be when using a non-coordinating cation in a strong solvent. An electrophilic amidation to a new N–N bond might seem irrational, but 1-aminoindoles have been synthesized before via monochloramine and hydroxylamine-O-sulfonic acid. Almost immediately after the reaction was started, 193 had disappeared and as expected, 3-amidated product 192 was completely absent from the products. The expected N–N product did not form either, however aminal 194 was observed (entry 1).

Since this reaction is much faster (< 1 h compared to 24 h) and less complicated (no transmetalation step), the aminal reaction was thought a superior basis for learning the complexities of the new amidation reactions (Table 1). Entries 2–4 show that an excess of base is required, ideally with an excess of 193 as well, to increase the yield of 194 and lower the amount of byproducts. Entries 5–8 switch the base to NaOt-Bu, which is easier to handle and less basic. The best yield was obtained when using 3.0 equivalents of NaOt-Bu and 1.5 equivalents of 193 (entry 5). Entry 6 was conducted in the presence of ZnCl₂ to test the effects of a coordinating cation in a highly polar solvent. Here, aminal 194 was still observed, but a marked decrease in product selectivity was seen. 3.0 equivalents of base and 1.5 equivalents of 193 is the optimal stoichiometry as evidenced by entries 7–11. Na⁺ and K⁺ cations support the formation of aminals at about the same efficiency; however Li⁺ cations are not as effective, probably because of their higher Lewis acidity.
The optimized protocol for the synthesis of aminals was scaled up to 0.4 mmol, resulting in a 78% yield of 194 (Table 12, entry 1). Surprisingly, indole reacted with electrophilic benzyl derivative 197 to give aminal 198 (entry 2). 2-Methylindole reacts with 193 to give 199 in only a 33% yield, suggesting either steric hindrance or benzylic radical abstraction as a factor.
Table 12: Aminal substrate scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>Electrophile</th>
<th>Yield</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Indole" /></td>
<td>193</td>
<td>78%</td>
<td><img src="image2" alt="Benzylaminoindole" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Indole" /></td>
<td>197</td>
<td>64%</td>
<td><img src="image4" alt="Benzylaminoindole" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Indole" /></td>
<td>193</td>
<td>33%</td>
<td><img src="image6" alt="Benzylaminoindole" /></td>
</tr>
</tbody>
</table>

Reaction conditions: indole derivative (1.0 equiv, 0.4 mmol, 0.2M), NaO-t-Bu (3.0 equiv, 1.2 mmol), rt, 30 min; then 193 or 197 (1.5 equiv, 0.6 mmol, 0.3M), rt, 1 h. Yields are isolated yields.

2.2.2 Synthesis of 3-amidoindoles and 2- and 3-amidopyrroles

2.2.2.1 Final optimization of 3-amidoindoles

Going forward with the 3-amidation reaction, the indole, base, and electrophile equivalents were set to 1.0, 3.0 and 1.5 respectively (Table 13). Purely changing the solvent (entries 1–4) did not give any 3-amidated product 190, but aminal formation was still fairly efficient in THF. Once ZnCl₂ was added to the reaction, 3-amidoindole 190 was once again observed and byproducts (194–196) were drastically reduced (entries 5–7). With more ZnCl₂, nucleophile 189 and electrophile 193 were both recovered in high amounts (entries 6–7). Then the zinc cation was replaced with magnesium and the result is the completely repression of 190, demonstrating just how important zinc is to the
reaction (entry 8). Complete consumption of 193 was noted when the solvent was changed to DMF, although almost no chemoselectivity was observed (entry 9). Adding a full 2.0 equivalents of ZnCl₂ nearly consumes all 189, solves the byproduct problem, and leads to a 73% yield of desired 3-amidoindole 190.

Table 13: Optimization table for the synthesis of 3-amidoindoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Transmetalation</th>
<th>189 (recovery)</th>
<th>194 (yield)</th>
<th>195 (yield)</th>
<th>196 (yield)</th>
<th>190 (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ᵃ</td>
<td>DMSO</td>
<td>None</td>
<td>12%</td>
<td>83%</td>
<td>0%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>2ᵇ</td>
<td>Benzene</td>
<td>None</td>
<td>8%</td>
<td>6%</td>
<td>8%</td>
<td>52%</td>
<td>0%</td>
</tr>
<tr>
<td>3ᵃ</td>
<td>t-BuOH</td>
<td>None</td>
<td>67%</td>
<td>8%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>4ᵃ</td>
<td>THF</td>
<td>None</td>
<td>14%</td>
<td>70%</td>
<td>0%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>5ᶜ</td>
<td>THF</td>
<td>ZnCl₂ (0.5 equiv)</td>
<td>39%</td>
<td>29%</td>
<td>12%</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>6ᵈ</td>
<td>THF</td>
<td>ZnCl₂ (1.0 equiv)</td>
<td>29%</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
<td>53%</td>
</tr>
<tr>
<td>7ᶜᵉ</td>
<td>THF</td>
<td>ZnCl₂ (2.0 equiv)</td>
<td>68%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>31%</td>
</tr>
<tr>
<td>8ᶜ</td>
<td>THF</td>
<td>MgCl₂ (2.0 equiv)</td>
<td>11%</td>
<td>10%</td>
<td>11%</td>
<td>18%</td>
<td>21%</td>
</tr>
<tr>
<td>9ᶜ</td>
<td>DMF</td>
<td>ZnCl₂ (1.0 equiv)</td>
<td>15%</td>
<td>2%</td>
<td>23%</td>
<td>18%</td>
<td>21%</td>
</tr>
<tr>
<td>10ᶜ</td>
<td>DMF</td>
<td>ZnCl₂ (2.0 equiv)</td>
<td>2%</td>
<td>0%</td>
<td>4%</td>
<td>0%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Reaction conditions: 189 (1.0 equiv, 0.2 mmol, 0.2M), NaOt-Bu (3.0 equiv, 0.6 mmol), rt, 30 min; then transmetalation, rt, 1 h; then 193 (1.5 equiv, 0.6 mmol, 0.3M), 24 h. a) Step 3 of reaction conducted at rt. b) 193 added as a solution in THF. c) Step 3 of reaction conducted at 60 °C. d) 0.77 equivalents of 193 remaining after 24 h. e) 0.90 equivalents of 193 remaining after 24 h. Yields determined using ¹H NMR spectroscopy with CH₂Br₂ as a quantitative internal standard.

2.2.2.2 Substrate scope for the 3-amidation of indoles

With these optimized conditions, the 3-amidation reaction was scaled up from 0.2 mmol to 0.4 mmol and tested on various indole substrates (Table 14). 190 was
obtained in 76% yield while 2-methylindole yielded 200 in 91% yield. Compared to 190 and 200, 201 was obtained in a moderate yield of 61%. Halogenated indoles were amidated in moderate yields to give products 202–204, suggesting that electron-withdrawing substituents will give lower yields. The different positions of the halogens also seem to have an effect. A styrene moiety was tolerated in the reaction and 205 was obtained in a 62% yield. This is important since electron-rich styrenes will react with many radicals and electrophiles.213,218 The electron-donating methoxy group aided the efficiency of amidation to give 206 in 87% yield. Conversely, the electron-withdrawing nitro group hindered the amidation efficiency and 207 was obtained in only a 45% yield. A free benzyl alcohol also inhibited the amidation reaction, but the desired product 208 was found in a 33% yield. Perhaps equilibrium is established between the indoline anion and the alkoxy anion which hinders the efficiency. At first it seemed that esters were not tolerated in the reaction as 209 could not be obtained, however ethyl indole-5-carboxylate was amidated in 55% yield to give 210. The reason for this discrepancy seems to be increased steric hindrance adjacent to the 3-position.
Table 14: 3-Amidoindole substrate scope

<table>
<thead>
<tr>
<th>R¹</th>
<th>Reaction conditions: indole (1.0 equiv, 0.4 mmol, 0.2M), NaOt-Bu (3.0 equiv, 1.2 mmol), rt, 30 min; then ZnCl₂ (2.0 equiv, 0.8 mmol), rt, 1 h; then 193 (1.5 equiv, 0.6 mmol, 0.3M), temperature, &lt; 24 h. Yields are isolated yields. a) Step 3 conducted at 80 °C instead of 60 °C. b) Step 3 conducted at room temperature instead of 60 °C. c) 78% recovery of indole starting material (ethyl 2-indole carboxylate).</th>
</tr>
</thead>
<tbody>
<tr>
<td>R¹</td>
<td>1. NaOt-Bu, DMF, 1 h</td>
</tr>
<tr>
<td></td>
<td>2. ZnCl₂, 30 min</td>
</tr>
<tr>
<td></td>
<td>3. 193, DMF, 60 °C</td>
</tr>
<tr>
<td>190 (76%)</td>
<td></td>
</tr>
<tr>
<td>200 (91%)</td>
<td></td>
</tr>
<tr>
<td>201 (61%)</td>
<td></td>
</tr>
<tr>
<td>202 (44%)</td>
<td></td>
</tr>
<tr>
<td>203 (53%)</td>
<td></td>
</tr>
<tr>
<td>204 (62%)</td>
<td></td>
</tr>
<tr>
<td>205 (62%)</td>
<td></td>
</tr>
<tr>
<td>206 (87%)</td>
<td></td>
</tr>
<tr>
<td>207 (45%)</td>
<td></td>
</tr>
<tr>
<td>208 (33%)</td>
<td></td>
</tr>
<tr>
<td>209 (0%)</td>
<td></td>
</tr>
<tr>
<td>210 (55%)</td>
<td></td>
</tr>
</tbody>
</table>

2.2.2.3 Substrate scope for the amidation of pyrroles

With this indole scope, application of the method to pyrroles was immediately envisioned. Pyrroles are also scaffolds in natural products and pharmaceuticals; plus the
direct C-amination and C-amidation of pyrroles is also absent from the literature. However, pyrrole regioselectivity is more difficult to predict than that of indoles because of the resonance contribution making all open positions nucleophilic. Non-coordinating cations of pyrrolide react at the 1-position while zinc pyrrolides give C-products (both 2- and 3-positions).\textsuperscript{204, 209} Electrophilic aromatic substitution reactions primarily give 2- or 2,5-disubstituted pyrroles.\textsuperscript{104, 219-220}

Aware of the possible complications, the amidation of pyrroles was commenced (Table 15). 2,5-Dimethylpyrrole was amidated using standard conditions to give 211 in a 68\% yield (entry 1). Importantly, no aminal formation was observed. 2-Amidation of pyrroles was found to be extremely facile when all 3-positions are blocked; the whole reaction occurring at room temperature to give 212 in 84\% yield (entry 2). Entries 3–4 attempt to establish the regioselectivity of the reaction. At 60 °C, three unique products are obtained. 3-Amidated pyrrole 213 was obtained in a higher amount than the 2-amidated product 214, but diamidated product 215 was also obtained. With almost no selectivity in products at 60 °C, the reaction was ran entirely at room temperature to determine whether regioselectivity is temperature dependent (entry 4). Although the lower temperature gives an excellent total yield (93\%), very little change in the ratio of products was observed. Finally, the stoichiometries of all the reagents were doubled in an attempt to heavily favor diamidation (entry 5). Pleasantly, diamidated 215 was obtained in 78\% yield as the sole product.
Table 15: Reactivity of pyrroles to amidation

Reaction conditions: pyrrole (1.0 equiv, 0.4 mmol, 0.2M), NaOt-Bu (3.0 equiv, 1.2 mmol), rt, 30 min; then ZnCl₂ (2.0 equiv, 0.8 mmol), rt, 1 h; then 193 (1.5 equiv, 0.6 mmol, 0.3M), 60 °C.  

- a) Step 3 conducted at room temperature instead of 60 °C.
- b) Reaction conditions: pyrrole (1.0 equiv, 0.4 mmol, 0.2M), NaOt-Bu (6.0 equiv, 2.4 mmol), rt, 30 min; then ZnCl₂ (4.0 equiv, 1.6 mmol), rt, 1 h; then 193 (3.0 equiv, 1.2 mmol, 0.6M), rt. Yields are isolated yields.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyrrole</th>
<th>Yield</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Pyrrole 1" /></td>
<td>68%</td>
<td><img src="image2" alt="Product 1" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Pyrrole 2" /></td>
<td>84%</td>
<td><img src="image4" alt="Product 2" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Pyrrole 3" /></td>
<td><img src="image6" alt="213 (29%)" /> <img src="image7" alt="214 (15%)" /> <img src="image8" alt="215 (29%)" /></td>
<td><img src="image9" alt="Product 3" /></td>
</tr>
<tr>
<td>4</td>
<td><img src="image10" alt="Pyrrole 4" /></td>
<td><img src="image11" alt="213 (42%)" /> <img src="image12" alt="214 (18%)" /> <img src="image13" alt="215 (33%)" /></td>
<td><img src="image14" alt="Product 4" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="image15" alt="Pyrrole 5" /></td>
<td><img src="image16" alt="213 (0%)" /> <img src="image17" alt="214 (0%)" /> <img src="image18" alt="215 (78%)" /></td>
<td><img src="image19" alt="Product 5" /></td>
</tr>
</tbody>
</table>
2.2.2.4 Electrophilic amide scope

Next, the electrophile scope was examined (Table 16). 225 was synthesized from 197 in 80% yield (entry 1). However no product could be observed when using secondary N-alkyl structures 216 and 217 (entries 2–3). An electrophilic N-phenyl derivative with an –OSO₂Ph leaving group could not be isolated, so an –OPNB group was substituted instead (218). However, none of the desired product was seen (entry 4).²²¹ It seems that only N-methyl or N-primary alkyl groups are compatible with the method. Electrophilic pivaloyl amide 219 gives the product 226 in moderate yield (entry 5). Acetamide derivative 220 does not react efficiently to product 227 (entry 6). It seems likely that the α-protons of 220 are being slowly deprotonated, then fragmenting into non-reactive acetamide byproducts.²²²⁻²²⁴ Electron-deficient trichloroacetamide 221 never gave any desired product (entry 7). At 0 °C, 221 decomposed immediately; while at −15 °C, it decomposed slowly. Nonetheless, standard carbamate protecting groups can be easily installed to give products 228 and 229 in 83% and 86% yield respectively (entries 8–9). Acrylamide 224 was not tolerated in the reaction and gave no desired material (entry 10). TLC analysis showed many spots and crude ¹H NMR showed that no alkene peaks survived, suggesting that an uncontrollable aza-Michael reaction occurred.
Table 16: Electrophile scope for the 3-amidation of indoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>R¹ =</th>
<th>R² =</th>
<th>Product and yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>197</td>
<td>Bn</td>
<td>Ph</td>
<td>225 (80%)</td>
</tr>
<tr>
<td>2</td>
<td>216</td>
<td>Cy</td>
<td>Ph</td>
<td>Not detected</td>
</tr>
<tr>
<td>3</td>
<td>217</td>
<td>s-Bu</td>
<td>Ph</td>
<td>Not detected</td>
</tr>
<tr>
<td>4ᵃ</td>
<td>218</td>
<td>Ph</td>
<td>Ph</td>
<td>Not detected</td>
</tr>
<tr>
<td>5ᵇ</td>
<td>219</td>
<td>Me</td>
<td>t-Bu</td>
<td>226 (60%)</td>
</tr>
<tr>
<td>6</td>
<td>220</td>
<td>Me</td>
<td>Me</td>
<td>227 (32%)</td>
</tr>
<tr>
<td>7ᶜ</td>
<td>221</td>
<td>Me</td>
<td>CCl₃</td>
<td>Not detected</td>
</tr>
<tr>
<td>8</td>
<td>222</td>
<td>Me</td>
<td>OMe</td>
<td>228 (86%)</td>
</tr>
<tr>
<td>9</td>
<td>223</td>
<td>Me</td>
<td>O-t-Bu</td>
<td>229 (83%)</td>
</tr>
<tr>
<td>10</td>
<td>224</td>
<td>Bn</td>
<td>HCCH₂</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

Reaction conditions: 2-methylindole (1.0 equiv, 0.4 mmol, 0.2M), NaOt-Bu (3.0 equiv, 1.2 mmol), rt, 30 min; then ZnCl₂ (2.0 equiv, 0.8 mmol), rt, 1 h; then electrophiles (1.5 equiv, 0.6 mmol, 0.3M), 60 °C. a) The leaving group is –OPNB not –OSO₂Ph. b) Step 3 conducted at 50 °C instead of 60 °C. c) Step 3 was run both at rt and at −15 °C and neither gave the desired product.

2.2.3 Biological data obtained

Biological testing of these new amidoindoles, amidopyrroles, and indole aminals is ongoing. However, some interesting data on binding affinity has already been received.¹⁴⁰ Compound 200 showed the greatest affinity for translocator protein (TSPO) with a Kᵢ of 234 nM (Figure 11). TSPO is a ubiquitous transmembrane receptor whose upregulation in normal cells is indicative of several disease states.²²⁵-²²⁶ One 3-amidated indole (202) and one 3-amidated pyrrole (211) showed high nanomolar affinity for serotonin receptor 5-HT2C. Currently, the 5-HT2C receptors are thought of as good
targets for managing psychiatric diseases. The results are even more startling when one considers that no theoretical basis for ligand efficiency was reviewed nor was compound optimization done outside of the substrate scope.

![Figure 11: Data on $K_i$ for specific receptors](image)

### 2.3 Synthesis of commercially unavailable materials

#### 2.3.1 Synthesis of commercially unavailable indoles

![Scheme 44: Synthesis of indole substrates](image)

Some of the desired indoles for the substrate scope are not commercially available. Compound 230 was synthesized using a Fischer esterification procedure that had not yet been disclosed for that compound (Scheme 44). Indole-5-carboxaldehyde
was separately subjected to a Wittig reaction and a reductive amination to obtain 231 and 232 respectively.

2.3.2 Synthesis of N-benzenesulfonyloxyamide and carbamates

The electrophilic amide scope also needed to be examined. First, the possibility of having several electrophilic N-alkyl and aryl substitutions was intriguing (Scheme 45, A). Hydroxamic acid intermediates 238–242 were synthesized in good yield using a protocol developed by MacMillan and co-workers.228 N-alkyl benzamide derivatives 193, 197, and 216–217 were easily obtained by acylation with benzenesulfonyl chloride. The phenyl derivative 243 rearranged upon formation in our hands, identical to the reported by Dhara and co-workers.221 However, a p-nitrobenzoyl derivative (218) could be synthesized without rearrangement.

Including non-benzyol-derived amides was also important for the scope of the reaction (Scheme 45, B). Carbamates 247–248 and urea 249 functionalities were also sought after. Using standard benzenesulfonylation conditions, 219–223 were synthesized. These compounds would test the influence of steric bulk (219), α-protons (220), and electronics (221–223). Unfortunately, urea 250 could not be isolated after several attempts. Electrophile 224 was also synthesized as a change from both standard substitutions (benzoyl and methyl) to find out if unsaturated amides would survive the 3-amidation protocol (Scheme 45, C).
2.4 Conclusions

To the best of my knowledge this is the first report of the direct and electrophilic 3-amidation of indoles. Additionally, this is the first instance of direct C-amidation of pyrroles. Simply by changing the solvent and cations in the standard protocol, amidomethylation can be favored instead. Indoles are generally commercially available, while the electrophilic N-benzenesulfonyloxyamides are easy to prepare at little expense. Although the reaction is sensitive to steric and electronic effects, the substrate
scope is still reasonably broad. Remarkably, no expensive transition metal catalysts or ligands are needed. Conceptually, this method makes the retrosynthetic analysis easier, as the anticipated disconnect is simply an indole and an amide; in contrast to an annulation, Buchwald-Hartwig, or some multi-step process. Finally, these compounds may prove to be promising lead compounds in receptor ligand design.

2.5 Supplemental Information

2.5.1 General information

Glassware and stir bars were dried in an oven at 140 °C for at least 12 h and then cooled in a desiccator cabinet over Drierite prior to use. Optimization and substrate screens were performed in microwave tubes sealed with Biotage Reseal™ septa. Plastic syringes or glass pipets were used to transfer liquid reagents. Unless otherwise noted, reactions were performed without exclusion of air or moisture. Unless otherwise stated, all reagents and solvents were used as received from commercial sources. Commercial indole was recrystallized from a solution of hexanes and benzene prior to use. The concentration of i-PrMgCl was determined by iodometric titration prior to use. DMF was distilled over MgSO₄ in batches and stored over 3 Å molecular sieves before use. Anhydrous THF and DCM were obtained from a DriSolve purification system when necessary. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet
light and/or exposure to KMnO₄ stain. The pH of the hydroxylamine formation reactions were monitored by allowing an altered (cut so only the relevant pH squares are used) EMD Millipore mColorpHast® pH strip to stir with the reactions. Organic solutions were concentrated in vacuo using a rotary evaporator. Column chromatography was performed with silica gel (60 Å, standard grade). Melting points were determined in open capillary tubes using a Mel-Temp II apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded at ambient temperature (unless otherwise stated) at 400 MHz or 500 MHz. All values for proton chemical shifts are reported in parts per million (δ) and are referenced to the residual protium in relevant deuterated solvent (δ 7.26 for CDCl₃ and δ 2.50 for (CD₃)₂SO). All values for carbon chemical shifts are reported in parts per million (δ) and are referenced to the carbon resonances in relevant deuterated solvent (δ 77.0 for CDCl₃ and δ 39.5 for (CD₃)₂SO). Infrared spectroscopic data are reported in wavenumbers (cm⁻¹) and only selected peaks are reported. High-resolution mass spectra were obtained using a liquid chromatography-electrospray ionization and Time-of-flight mass spectrometer. Low-resolution mass spectra were obtained using single quadruple gas chromatography-mass spectrometer.

2.5.2 Experimental procedures and characterization data

**Ethyl indole-5-carboxylate (230).** A stirring solution of indole-5-carboxaldehyde (806 mg, 5 mmol, 1.0 equiv) and concentrated aqueous H₂SO₄ (1 mL, 18 mmol, 3.6 equiv) in absolute EtOH (100 mL) was heated to reflux and stirred for 20 h.
The reaction was then cooled to room temperature, quenched with a saturated aqueous solution of NaHCO$_3$ (20 mL) and concentrated in vacuo to remove the EtOH. The resulting mixture was extracted with Et$_2$O (150 mL). The organic layer was washed with H$_2$O (40 mL), a saturated aqueous solution of NaHCO$_3$ (40 mL), and brine (40 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo to give a solid. The solid was filtered and washed with hexanes to give 230 as a tan solid (844 mg, 89%). $R_f$ = 0.36 (25% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.44–8.42 (m, 1H), 8.37 (s, br, 1H), 7.92 (dd, $J$ = 8.6, 1.4 Hz, 1H), 7.41 (d, $J$ = 8.6 Hz, 1H), 7.29–7.27 (m, 1H), 4.40 (q, $J$ = 7.1 Hz, 2H), 1.42 (t, $J$ = 7.1 Hz, 3H). These data are consistent with published spectra.$^{231}$

5-Vinylindole (231).$^{232}$ A solution of KOt-Bu (584 mg, 5.2 mmol, 2.6 equiv) and MePPh$_3$Br (1.14 g, 3.2 mmol, 1.6 equiv) in THF (10 mL) was stirred for 25 min under nitrogen. Neat indole-5-carboxaldehyde (290 mg, 2.0 mmol, 1.0 equiv) was then added over a stream of nitrogen and the reaction heated to 50 °C for 20 h. Then the reaction was cooled to room temperature, quenched with H$_2$O (50 mL), and extracted with Et$_2$O (3 × 20 mL). The organic layers where combined, washed with brine (20 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography (10% ethyl acetate–hexanes to 20% ethyl acetate–hexanes) to give 231 as a white solid (253 mg, 88%). $R_f$ = 0.39 (25% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.11 (s, br, 1H), 7.67 (s, 1H), 7.38–7.33 (m, 2H), 7.20–7.33 (m, 1H),
6.85 (dd, $J = 17.6, 10.7$ Hz, 1H), 6.56–6.54 (m, 1H), 5.72 (dd, $J = 17.6, 0.8$ Hz, 1H), 5.16 (dd, $J = 10.7, 0.8$ Hz, 1H). These data are consistent with published spectra.\textsuperscript{233}

\textbf{5-(Pyrrolidin-1'-ylmethyl)-1H-indole (232).} To a stirring solution of indole-5-carboxaldehyde (290 mg, 2.0 mmol, 1.0 equiv) and pyrrolidine (0.18 mL, 2.2 mmol, 1.1 equiv) in THF (8 mL) was added NaBH(OAc)\textsubscript{3} (593 mg, 2.8 mmol, 1.4 equiv) followed by AcOH (0.2 mL) at room temperature. After 24 h, the reaction was quenched with aqueous NaOH (2 mL, 15\%) and stirred for 1 h. Then the reaction was diluted with H\textsubscript{2}O (60 mL) and extracted with EtOAc (2 × 20 mL), then the organic layers were combined, washed with a concentrated solution of aqueous NaHCO\textsubscript{3} (10 mL), brine (10 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and the filtrate concentrated \textit{in vacuo}. The solid residue was filtered and washed with a solution of hexanes/Et\textsubscript{2}O (5:1, 20 mL) then hexanes (40 mL) to give 232 as a tan solid (323 mg, 81\%). $R_f = 0.25$ (5\% methanol–dichloromethane using a triethylamine/dichloromethane treated plate); \textsuperscript{1}H NMR (400 MHz, (CD\textsubscript{3})\textsubscript{2}SO): $\delta$ 10.99 (s, 1H), 7.42–7.41 (m, 1H), 7.32–7.28 (m, 2H), 7.03 (dd, $J = 9.8, 1.4$ Hz, 1H), 6.37–6.35 (m, 1H), 3.60 (s, 2H), 2.43–2.38 (m, 4H), 1.69–1.65 (m, 4H); \textsuperscript{13}C NMR (125 MHz, (CD\textsubscript{3})\textsubscript{2}SO): $\delta$ 135.0, 129.6, 127.5, 125.2, 122.2, 119.7, 110.9, 100.9, 60.3, 53.4 (2C), 23.1 (2C); FTIR (neat) cm\textsuperscript{-1} 2810, 1345, 866, 730; HRMS ESI (m/z) calcd. for C\textsubscript{13}H\textsubscript{17}N\textsubscript{2} ([M+H\textsuperscript{+}]): 201.1386; found: 201.1386.

\textbf{N-Benzylhydroxylamine hydrochloride (234).}\textsuperscript{234–235} To a stirring solution of benzaldehyde oxime (4.85 g, 40 mmol, 1.0 equiv) in MeOH (60 mL) containing an altered
pH strip were added solid NaBH₃CN (5.53 g, 88 mmol, 2.2 equiv) and aqueous HCl (about 50 mL, 2M) over 15 min in such a way that the pH of the solution stayed within 2–3 during the duration of the addition. After stirring for an additional 3.5 h, the reaction was quenched with aqueous 15% NaOH (until pH = 10) and the MeOH removed in vacuo. The remaining aqueous solution was extracted with DCM (3 × 100 mL). The organic layers were combined, washed with brine (100 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude residue was dissolved in Et₂O (75 mL) and gaseous HCl was piped into the solution generating a white precipitate. The precipitate was filtered and washed with Et₂O, then hexanes to obtain 234 as a white powder (4.40 g, 69%). mp 110–111 °C (lit.236 mp 110 °C); ¹H NMR (400 MHz, CDCl₃): δ 11.69 (s, 2H), 10.93 (s, 1H), 7.52–7.41 (m, 5H), 4.30 (s, 2H). These data are consistent with published spectra.237

N-Cyclohexylhydroxylamine (235).234-235 To a stirring solution of cyclohexanone oxime (4.53 g, 40 mmol, 1.0 equiv) in MeOH (60 mL) containing an altered pH strip were added solid NaBH₃CN (3.77 g, 60 mmol, 1.5 equiv) and aqueous HCl (about 30 mL, 2M) over 15 min in such a way that the pH of the solution stayed within 2–3 during the duration of the addition. After stirring for an additional 1 h, the reaction was quenched with aqueous 15% NaOH (until pH = 10) and the MeOH removed in vacuo. To the solid residue was added DCM (150 mL) and EtOAc (250 mL) and the mixture washed with a saturated aqueous solution of NaHCO₃ (20 mL) then brine (50 mL). The organic layer
was concentrated \textit{in vacuo} to give a solid. The solid was filtered, washed with MTBE, and then with hexanes to give \textbf{235} as short white needles (4.19 g, 91\%). mp 140–141 °C (lit.\textsuperscript{238} mp 140 °C); \textsuperscript{1}H NMR (500 MHz, (CD\textsubscript{3})\textsubscript{2}SO): δ 6.99 (s, 1H), 5.32 (s, 1H), 2.63–2.52 (m, 1H), 1.89–1.49 (m, 5H), 1.24–0.91 (m, 5H); \textsuperscript{13}C NMR (125 MHz, (CD\textsubscript{3})\textsubscript{2}SO): δ 59.9, 30.1 (2C), 26.0, 24.2 (2C); FTIR (neat) cm\textsuperscript{-1} 3244, 2927, 1520, 1454, 1369, 814; HRMS-ESI (m/z) calcd. for C\textsubscript{6}H\textsubscript{14}NO ([M+H]\textsuperscript{+}): 116.1070; found: 116.1070.

\textbf{\textit{N-(sec-Butyl)hydroxylamine (236).}}\textsuperscript{234-235} To a stirring mixture of hydroxylamine hydrochloride (4.17 g, 60 mmol, 1.2 equiv) and Na\textsubscript{2}CO\textsubscript{3} (6.36 g, 60 mmol, 1.2 equiv) in H\textsubscript{2}O/MeOH (6:5, 110 mL) was added MEK (4.48 mL, 50 mmol, 1.0 equiv). After 3 h, the reaction was diluted with H\textsubscript{2}O (100 mL) and extracted with Et\textsubscript{2}O (4 × 50 mL). The organic layers were combined, washed with brine (2 × 25 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and the filtrate concentrated \textit{in vacuo}. The residue was dissolved in MeOH (60 mL) and stirred. To the stirring solution were added an altered pH strip, followed by solid NaBH\textsubscript{3}CN (4.71 g, 75 mmol, 1.5 equiv) and aqueous HCl (about 40 mL, 2M) over 15 min in such a way that the pH of the solution stayed within 2–3 during the duration of the addition. After stirring for an additional 30 min, the reaction was quenched with aqueous 15\% NaOH (until pH = 10) and the MeOH removed \textit{in vacuo}. The remaining aqueous solution was diluted with H\textsubscript{2}O (100 mL) and extracted with DCM (3 × 100 mL). The organic layers were combined, washed with brine (50 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and the filtrate concentrated \textit{in vacuo} to give a solid. The solid was filtered and
washed with hexanes to obtain 236 as white plates (1.36 g, 30%). mp 62–63 °C (lit.\textsuperscript{238} mp 67 °C); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 5.27 (s, br, \textit{J} = 7.5 Hz, 2H), 2.90 (dqd, \textit{J} = 7.4, 6.4, 5.5 Hz, 1H), 1.58 (dqd, \textit{J} = 13.6, 7.5, 5.5 Hz, 1H), 1.31 (dqd, \textit{J} = 13.6, 7.5, 7.4 Hz, 1H), 1.07 (d, \textit{J} = 6.4 Hz, 3H), 0.91 (t, \textit{J} = 7.5 Hz, 3H). These data are consistent with published spectra.\textsuperscript{239}

\textbf{N-Hydroxy-N-methylbenzamide (238)}\textsuperscript{228} To a stirring suspension of \textit{N}-methylhydroxylamine hydrochloride (8.35 g, 100 mmol, 1.0 equiv) and NaHCO\textsubscript{3} (16.80 g, 110 mmol, 1.1 equiv) in THF/H\textsubscript{2}O (10:1, 165 mL) under N\textsubscript{2} was added benzoyl chloride (12.75 mL, 110 mmol, 1.1 equiv) dropwise over 20 min. After 20 h of stirring, the reaction was diluted with H\textsubscript{2}O (100 mL) and extracted with DCM (3 \times 60 mL). The organic layers were combined, washed with brine (100 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and the filtrate concentrated \textit{in vacuo}. The crude material was purified by column chromatography (20% ethyl acetate–hexanes to 100% ethyl acetate) to give 238 as an orange oil (14.10 g, 93%). \textit{R}_{f} = 0.23 (50% ethyl acetate–hexanes); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 8.86 (s, br, 1H), 7.52–7.51 (m, 2H), 7.48–7.46 (m, 1H), 7.43–7.40 (m, 2H), 3.38 (s, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 167.2, 132.5, 130.7, 128.4 (2C), 127.9 (2C), 38.2; FTIR (thin film) cm\textsuperscript{-1} 3152, 2873, 1598, 1571, 1388, 1217, 706; HRMS-ESI (m/z) calcd. for C\textsubscript{8}H\textsubscript{10}NO\textsubscript{2} ([M+H]\textsuperscript{+}): 152.0706; found: 152.0703.

\textbf{N-Benzyl-N-hydroxybenzamide (239)}\textsuperscript{228} To a stirring suspension of \textit{N}-benzylhydroxylamine hydrochloride (958 mg, 6 mmol, 1.0 equiv) and NaHCO\textsubscript{3} (1.01 g, 12 mmol, 2.0 equiv) in THF/H\textsubscript{2}O (10:1, 11 mL) under nitrogen was added benzoyl
chloride (0.77 mL, 6.6 mmol, 1.1 equiv) dropwise over 8 min. After 15 h of stirring, the reaction was diluted with H$_2$O (10 mL) and extracted with DCM (3 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo. Hexanes was added to the residue and the resulting white precipitate was filtered and washed with hexanes to give 239 as a white solid (1.23 g, 90%). R$_f$ = 0.19 (25% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.51 (s, br, 1H), 7.51–7.26 (m, 10H), 4.85 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 167.9, 135.2, 132.2, 131.1, 128.7 (2C), 128.5 (2C), 127.9 (3C), 127.3 (2C), 54.5; FTIR (neat) cm$^{-1}$ 3263, 1622, 1373, 1356, 1255; HRMS-ESI (m/z) calcd. for C$_{14}$H$_{14}$NO$_2$ ([M+H]$^+$): 228.1019; found: 228.1020.

**N-Cyclohexyl-N-hydroxybenzamide (240).** To a stirring suspension of N-cyclohexylhydroxylamine (2.30 g, 20 mmol, 1.0 equiv) and NaHCO$_3$ (1.85 g, 22 mmol, 1.1 equiv) in THF/H$_2$O (10:1, 44 mL) under nitrogen was added benzoyl chloride (2.56 mL, 22 mmol, 1.1 equiv) dropwise over 15 min. After stirring for 24 h, the reaction was diluted with H$_2$O (20 mL) and extracted with Et$_2$O (3 × 10 mL). The organic layers were combined, washed with brine (20 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo to give a solid. The solid was washed with hexanes to give 240 as a white solid (3.42 g, 78%). R$_f$ = 0.21 (25% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.37 (s, br, 1H), 7.53–7.43 (m, 5H), 3.79–3.71 (m, 1H), 1.97–1.74 (m, 7H), 1.20–1.06 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 166.4, 132.9, 130.6, 128.6 (2C), 127.4 (2C),
59.8, 29.8 (2C), 25.3 (2C), 24.9; FTIR (neat) cm⁻¹ 2852, 1432, 1160, 776, 693; HRMS-ESI (m/z) calcd. for C₁₃H₁₈NO₂ ([M+H]⁺): 220.1332; found: 220.1332.

**N-(sec-Butyl)-N-hydroxybenzamide (241)** To a stirring suspension of **N-(sec-butyl)hydroxylamine** (891 mg, 10 mmol, 1.0 equiv) and NaHCO₃ (924 mg, 11 mmol, 1.1 equiv) in THF/H₂O (10:1, 16.5 mL) under nitrogen was added benzoyl chloride (1.28 mL, 11 mmol, 1.1 equiv) dropwise over 5 min. After stirring for 14.5 h, the reaction was diluted with H₂O (10 mL) and extracted with Et₂O (2 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. Benzene (50 mL) was added to the residue and a solid was precipitated out using hexanes. The solid was filtered and washed with hexanes to give **241** as white crystals (1.24 g, 64%). Rᵣ = 0.61 (50% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 8.50 (s, br, 1H), 7.49–7.35 (m, 5H), 3.87 (dqd, br, J = 9.5, 6.5, 5.1 Hz, 1H), 1.87 (ddq, J = 13.9, 9.5, 7.4 Hz, 1H), 1.45 (dqd, J = 13.9, 7.4, 5.1 Hz, 1H), 1.30 (d, J = 6.5 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 167.1, 133.0, 130.5, 128.6 (2C), 127.5 (2C), 58.2, 26.7, 18.3, 10.8; FTIR (neat) cm⁻¹ 2971, 2870, 1424, 1170, 692; HRMS-ESI (m/z) calcd. for C₁₃H₁₈NO₂ ([M+H]⁺): 194.1176; found: 194.1175.

**N-Hydroxy-N-phenylbenzamide (242)** To a stirring suspension of **N-phenylhydroxylamine** (1.09 g, 10 mmol, 1.0 equiv) and NaHCO₃ (924 mg, 11 mmol, 1.1 equiv) in THF/H₂O (10:1, 16.5 mL) under nitrogen was added benzoyl chloride (1.28 mL, 11 mmol, 1.1 equiv) dropwise over 15 min. After stirring for 14.5 h, the reaction was...
diluted with H₂O (10 mL) and extracted with DCM (3 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The solid residue was washed with hexanes to give 242 as a white solid (2.13 g, 79%). Rₐ = 0.28 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.44–7.35 (m, 3H), 7.33–7.19 (m, 7H). These data are consistent with published spectra.²⁴⁰

N-Methyl-N-((phenylsulfonyl)oxy)benzamide (193). To a stirring solution of 238 (7.56 g, 50 mmol, 1.0 equiv) in pyridine (40 mL) at 0 °C was added benzenesulfonyl chloride (6.72 mL, 52.5 mmol, 1.05 equiv) dropwise over 15 min. After 2 h, the reaction was diluted with Et₂O (400 mL) and washed with a half-saturated aqueous solution of CuSO₄ (400 mL), aqueous solutions of citric acid (2 × 100 mL, 0.5 M), a saturated aqueous solution of NaHCO₃ (100 mL), brine (100 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. Hexanes was added and the resulting precipitate was washed with hexanes to obtain 193 as a white solid (11.82 g, 81%). Rₐ = 0.24 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.73–7.73 (m, 2H), 7.56 (tt, J = 7.5, 1.2 Hz, 1H), 7.41–7.23 (m, 7H), 3.53 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 171.2, 134.7, 133.2, 132.2, 131.3, 129.0 (4C), 128.3 (2C), 128.1 (2C), 40.5; FTIR (neat) cm⁻¹ 1690, 1449, 1378, 1191, 892; HRMS-ESI (m/z) calcd. for C₁₄H₁₄NO₄S ([M+H⁺]: 292.0638; found: 292.0637.

N-Benzyl-N-((phenylsulfonyl)oxy)benzamide (197). To a stirring solution of 239 (1.14 g, 5.0 mmol, 1.0 equiv) in pyridine (4 mL) at 0 °C was added benzenesulfonyl
chloride (0.67 mL, 5.25 mmol, 1.05 equiv) dropwise over 12 min. After 1 h, the reaction was diluted with Et₂O (50 mL), washed with a half-saturated aqueous solution of CuSO₄ (50 mL), aqueous solutions of citric acid (2 × 10 mL, 0.5M), a saturated aqueous solution of NaHCO₃ (10 mL), brine (20 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo to give a solid. The solid was washed with hexanes to give 197 as a white solid (1.67 g, 91%). Rf = 0.35 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.72–7.69 (m, 2H), 7.58 (tt, J = 7.5, 1.2 Hz, 1H), 7.42–7.23 (m, 12H), 5.10 (s, br, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 171.2, 134.6, 134.3, 133.3, 132.4, 131.3, 129.0 (4C), 128.6 (4C), 128.3, 128.2, 128.1 (2C), 55.9; FTIR (neat) cm⁻¹: 1689, 1375, 1321, 1189, 960, 889; HRMS-ESI (m/z) calcd. for C₂₀H₁₈NO₄S ([M+H]⁺): 368.0951; found: 368.0949.

N-Cyclohexyl-N-((phenylsulfonyl)oxy)benzamide (216). To a stirring solution of 240 (2.19 g, 10 mmol, 1.0 equiv) in pyridine (10 mL) at 0 °C was added benzenesulfonyl chloride (1.34 mL, 10.5 mmol, 1.05 equiv) dropwise over 15 min. After stirring for 1 h, the reaction was diluted with Et₂O (100 mL), washed with a half-saturated aqueous solution of CuSO₄ (100 mL), another half-saturated aqueous solution of CuSO₄ (20 mL), aqueous solutions of citric acid (2 × 20 mL, 0.5M), a saturated aqueous solution of NaHCO₃ (20 mL), brine (20 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography (20% ethyl acetate–hexanes) to give 216 as a colorless solid (2.74 g, 76%). Rf = 0.35 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.91–7.88 (m, 2H), 7.59 (tt, J = 7.5, 1.2 Hz,
N-(sec-Butyl)-N-((phenylsulfonyl)oxy)benzamide (217). To a stirring solution of 241 (966 mg, 5.0 mmol, 1.0 equiv) in pyridine (4 mL) at 0 °C was added benzenesulfonyl chloride (0.67 mL, 5.25 mmol, 1.05 equiv) dropwise over 5 min. After 1 h, the reaction was diluted with Et₂O (50 mL), washed with a half-saturated aqueous solution of CuSO₄ (50 mL), aqueous solutions of citric acid (2 × 10 mL, 0.5M), a saturated aqueous solution of NaHCO₃ (10 mL), brine (10 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude residue was purified by column chromatography (10% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) to give 217 as a white solid (813 mg, 49%). Rf = 0.21 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.92 (d, J = 7.6 Hz, 2H), 7.63–7.59 (m, 1H), 7.51–7.44 (m, 5H), 7.36 (t, J = 7.6 Hz, 2H), 4.02–3.93 (m, 1H), 1.96–1.84 (m, 1H), 1.60–1.49 (m, 1H), 1.32 (d, J = 6.6 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 172.9, 134.6, 134.5, 133.6, 131.6, 129.2 (2C), 128.9 (2C), 128.5 (2C), 128.2 (2C), 62.6, 27.0, 17.9, 11.2; FTIR (neat) cm⁻¹ 1694, 1450, 1381, 1193, 587, 565; HRMS-ESI (m/z) calcd. for C₁₇H₂₁NO₄S ([M+H]+): 334.1108; found: 334.1112.
N-((4”-Nitrobenzoyl)oxy)-N-phenylbenzamide (218). To a stirring solution of 242 (500 mg, 3.31 mmol, 1.0 equiv) and 4-nitrobenzoyl chloride (676 mg, 3.64 mmol, 1.1 equiv) in DCM (15 mL) under nitrogen was added Et₃N (0.92 mL, 6.62 mmol, 2.0 equiv) dropwise over 10 min. After stirring for 2.5 h, the reaction was diluted with H₂O (50 mL) and extracted with DCM (2 × 40 mL). The organic layers were combined and washed with an aqueous solution of HCl (2 × 20 mL, 0.5M), brine (20 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) to give 218 as a white solid (690 mg, 58%). Rf = 0.44 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 8.32 (d, J = 8.9 Hz, 2H), 8.29 (d, J = 8.9 Hz, 2H), 7.60–7.58 (m, 2H), 7.41–7.26 (m, 8H); ¹³C NMR (125 MHz, CDCl₃): δ 166.8, 162.4, 151.0, 140.5, 132.7, 132.6, 131.4, 131.3 (2C), 129.4 (2C), 128.9 (2C), 128.2 (2C), 127.4 (2C), 123.7 (2C); FTIR (neat) cm⁻¹: 1769, 1677, 1525, 1006, 860, 597; HRMS-ESI (m/z) calcd. for C₂₀H₁₄N₂O₄Na ([M+Na]⁺): 385.0795; found: 385.0793.

N-Hydroxy-N-methylpivalamide (244). To a stirring solution of N-methylhydroxylamine hydrochloride (2.19 g, 26.25 mmol, 1.05 equiv) and Et₃N (8.72 mL, 62.5 mmol, 2.5 equiv) in DCM (75 mL) was added trimethylacetyl chloride (3.08 mL, 25 mmol, 1.0 equiv) dropwise over 20 min in a nitrogen atmosphere. After 4 h, the reaction was diluted with DCM (200 mL), washed with an aqueous solution of HCl (3 × 50 mL, 1M), washed with H₂O (50 mL), washed with brine (50 mL), dried over Na₂SO₄, filtered,
and the filtrate concentrated in vacuo to give 244 as a white solid (1.82 g, 55%). R$_f$ = 0.36 (50% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.16 (s, br, 1H), 3.42 (s, 1H), 1.29 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 176.9, 38.3, 37.9, 27.1 (3C); FTIR (neat) cm$^{-1}$ 3189, 2957, 1591, 1190, 686, 545; HRMS-ESI (m/z) calcd. for C$_6$H$_{14}$NO$_2$ ([M+H]$^+$): 132.1019; found: 132.1020.

**2,2,2-Trichloro-N-hydroxy-N-methylacetamide (246).** To a stirring solution of N-methylhydroxylamine hydrochloride (1.75 g, 21 mmol, 1.05 equiv) and Et$_3$N (5.58 mL, 40 mmol, 2.0 equiv) in DCM (100 mL) was added 2,2,2-trichloroacetyl chloride (2.23 mL, 20 mmol, 1.0 equiv) dropwise over 10 min in a nitrogen atmosphere at −15 °C. After stirring for 0.5 h, the reaction was quenched with H$_2$O (100 mL) and the organic layer removed. The aqueous layer was extracted with DCM (100 mL). All the organic layers were combined, washed with an aqueous solution of HCl (2 × 40 mL, 0.5M), brine (40 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo. The crude solid was washed with hexanes to give 246 as a white solid (2.52 g, 65%). R$_f$ = 0.64 (50% ethyl acetate–hexanes); $^1$H NMR (400 MHz, (CD$_3$)$_2$SO): δ 10.64 (s, 1H), 3.29 (s, 3H); $^{13}$C NMR (125 MHz, (CD$_3$)$_2$SO): δ 158.7, 92.3, 38.9; FTIR (neat) cm$^{-1}$ 1645, 1403, 1201, 813, 791, 652; HRMS data could not be obtained. GCMS (m/z) calcd. for C$_3$H$_4$Cl$_3$NO$_2$ (M): 190.9; found: 190.9.

**Methyl hydroxy(methyl)carbamate (247).** To a stirring suspension of N-methylhydroxylamine hydrochloride (5.01 g, 60 mmol, 1.0 equiv) and NaHCO$_3$ (10.08 g,
120 mmol, 2.0 equiv) in THF/H₂O (10:1, 110 mL) under nitrogen was added methyl chloroformate (5.10 mL, 66 mmol, 1.1 equiv) dropwise over 15 min. After stirring for 17 h, the reaction was diluted H₂O (50 mL) and extracted with DCM (3 × 50 mL). The organic layers were combined, dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo to give 247 as a colorless liquid (4.94 g, 78%). Rᶠ = 0.12 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.28 (s, br, 1H), 3.76 (s, 3H), 3.21 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 158.7, 53.3, 38.0; FTIR (neat) cm⁻¹ 3290, 1671, 1361, 1165, 1044, 761; HRMS-ESI (m/z) calcd. for C₃H₇NO₃ ([M+H]⁺): 106.0499; found: 106.0499.

**tert-Butyl hydroxy(methyl)carbamate (248).** To a stirring suspension of N-methylhydroxylamine hydrochloride (1.67 g, 40 mmol, 1.0 equiv) and NaHCO₃ (3.36 g, 40 mmol, 2.0 equiv) in THF/H₂O (10:1, 33 mL) under nitrogen was added di-tert-butyl dicarbonate (5.24 g, 24 mmol, 1.2 equiv) portionwise over 5 min. After stirring for 17 h, the reaction was diluted H₂O (30 mL) and extracted with DCM (3 × 20 mL). The DCM layers were combined, washed with brine (30 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography (5% ethyl acetate–hexanes to 25% ethyl acetate–hexanes) to give 248 as a colorless oil (2.25 g 77%). Rᶠ = 0.62 (50% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 6.71–6.54 (m, br, 1H), 3.15 (s, 3H), 1.48 (s, 9H). These data are consistent with published spectra.
1,1-Diethyl-3-hydroxy-3-methylurea (249). To a stirring suspension of N-methylhydroxylamine hydrochloride (1.67 g, 20 mmol, 1.0 equiv) and NaHCO$_3$ (1.85 g, 22 mmol, 1.1 equiv) in THF/H$_2$O (10:1, 33 mL) under nitrogen was added diethylcarbamyl chloride (2.79 mL, 22 mmol, 1.1 equiv) dropwise over 15 min. After stirring for 22 h, the reaction was diluted with H$_2$O (100 mL) and extracted with EtOAc (3 × 60 mL). The organic layers were combined, washed with brine (2 × 40 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated _in vacuo_. The liquid residue was placed in a −20 °C freezer to produce a solid. The solid was washed with hexanes to give 249 as a white solid (1.40 g, 48%). $R_f = 0.36$ (50% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.78 (s, 1H), 3.35 (q, $J = 7.1$ Hz, 4H), 2.94 (s, 3H), 1.17 (t, $J = 7.1$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.5, 44.4, 41.3 (2C), 13.1 (2C); FTIR (thin film) cm$^{-1}$ 3269, 2975, 1623, 1434; HRMS-ESI (m/z) calcd. for C$_6$H$_{14}$N$_2$O$_2$Na ([M+Na]$^+$): 169.0947; found: 169.0947.

N-Methyl-N-((phenylsulfonyl)oxy)pivalamide (219). To a stirring solution of 244 (1.31 g, 10 mmol, 1.0 equiv) in pyridine (8 mL) at 0 °C was added benzenesulfonyl chloride (1.34 mL, 10.5 mmol, 1.05 equiv) dropwise over 15 min. After stirring for 2 h, the reaction was placed in a −20 °C freezer for 20 h. Then the reaction was warmed to room temperature and diluted with Et$_2$O (75 mL), washed with a half-saturated aqueous solution of CuSO$_4$ (100 mL), another half-saturated aqueous solution of CuSO$_4$ (20 mL), aqueous solutions of citric acid (2 × 20 mL, 0.5M), a saturated aqueous solution of
NaHCO₃ (20 mL), brine (20 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. To the residue was added hexanes and the mixture was placed in a −20 °C freezer until a solid had formed. The solid was washed with hexanes to give 219 as a white solid (1.59 g, 59%). Rₛ = 0.43 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 8.01–7.98 (m, 2H), 7.72–7.67 (m, 1H), 7.59–7.55 (m, 2H), 3.35 (s, 3H), 1.11 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 180.3, 134.6 (2C), 129.3 (2C), 129.0 (2C), 41.8, 39.5, 27.4 (3C); FTIR (neat) cm⁻¹ 1704, 1371, 1061, 543; HRMS-ESI (m/z) calcd. for C₁₂H₁₈NO₄S ([M+H]⁺): 272.0951; found: 272.0954.

**N-Methyl-N-((phenylsulfonyl)oxy)acetamide (220).** To a stirring suspension of N-methylhydroxylamine hydrochloride (1.67 g, 20 mmol, 1.0 equiv) and NaHCO₃ (3.36 g, 40 mmol, 2.0 equiv) in THF/H₂O (10:1, 33 mL) under nitrogen was added acetic anhydride (2.08 mL, 22 mmol, 1.1 equiv) dropwise over 15 min. After 4 h of stirring, the reaction was diluted with H₂O (20 mL) and extracted with EtOAc (5 × 20 mL). The organic layers were combined, washed with brine (2 × 10 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo to give a yellow residue. To the crude residue was added pyridine (4 mL) in a 0 °C ice bath and benzenesulfonyl chloride (1.15 mL, 9 mmol, 0.45 equiv) added dropwise over 5 min. After 1.5 h of stirring, the solution was diluted with Et₂O (50 mL), washed with a half-saturated aqueous solution of CuSO₄ (50 mL), aqueous solutions of citric acid (2 × 10 mL, 0.5M), a saturated aqueous solution of NaHCO₃ (10 mL), brine (10 mL), dried over Na₂SO₄, filtered, and the filtrate
concentrated in vacuo. The crude material was purified by column by column chromatography (10% ethyl acetate–hexanes to 30% ethyl acetate–hexanes) to give 220 as a colorless oil (1.28 g, 28%). \( \text{Rf} = 0.30 \) (25% ethyl acetate–hexanes); \(^1\text{H NMR (400 MHz, CDCl}_3\)): \( \delta \) 8.03–8.00 (m, 2H), 7.80–7.75 (m, 1H), 7.66–7.61 (m, 2H), 3.12 (s, 3H), 1.92 (s, 3H); \(^{13}\text{C NMR (100 MHz, CDCl}_3\)): \( \delta \) 175.8, 135.3, 133.7, 129.5 (2C), 129.2 (2C), 38.0, 20.8; FTIR (neat) cm\(^{-1}\) 1698, 1449, 1367, 1192, 1088, 552; HRMS-ESI (m/z) calcd. for C\(_9\)H\(_{12}\)NO\(_4\)S ([M+H]+): 230.0482; found: 230.0482.

\( 2,2,2\text{-Trichloro-N-methyl-N-((phenylsulfonyl)oxy)acetamide (221).}\) To a stirring solution of 246 (962 mg, 5 mmol, 1.0 equiv) in pyridine (4 mL) at 0 °C was added benzenesulfonyl chloride (0.67 mL, 5.25 mmol, 1.05 equiv) dropwise over 5 min. After 1 h of stirring, the reaction was warmed to room temperature. After stirring for an additional 1 h, the reaction was diluted with a half-saturated aqueous solution of CuSO\(_4\) (50 mL) and extracted with EtOAc (75 mL). The organic layer was washed with an aqueous solution of citric acid (2 \times 10 mL, 0.5M), a saturated solution of aqueous NaHCO\(_3\) (10 mL), and brine (10 mL). The organic layer was dried over Na\(_2\)SO\(_4\), filtered, and the filtrate concentrated in vacuo. Hexanes (20 mL) was added to the residue and placed in a −20 °C freezer until a solid had formed. The solid was washed with hexanes to give 221 as a white solid (1.63 g, 98%). \( \text{Rf} = 0.50 \) (25% ethyl acetate–hexanes); \(^1\text{H NMR (400 MHz, CDCl}_3\)): \( \delta \) 8.05–8.02 (m, 2H), 7.74 (tt, \( J = 7.5, 1.3 \) Hz, 1H), 7.62–7.57 (m, 2H), 3.80 (s, 3H); \(^{13}\text{C NMR (100 MHz, CDCl}_3\)): \( \delta \) 160.1, 135.3, 133.4, 129.4 (2C), 129.2 (2C), 90.5,
Methyl methyl((phenylsulfonyl)oxy)carbamate (222). To a stirring solution of 247 (1.05 g, 10 mmol, 1.0 equiv) in pyridine (8 mL) at 0 °C was added benzenesulfonyl chloride (1.34 mL, 10.5 mmol, 1.05 equiv) dropwise over 15 min. After stirring for 1 h, the reaction was placed in a −20 °C freezer for 20 h. Then the reaction was warmed to room temperature and diluted with Et₂O (75 mL), washed with a half-saturated aqueous solution of CuSO₄ (100 mL), another half-saturated aqueous solution of CuSO₄ (20 mL), aqueous solutions of citric acid (2 × 20 mL, 0.5M), a saturated aqueous solution of NaHCO₃ (20 mL), brine (20 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. To the residue was added hexanes and the mixture was placed in a −20 °C freezer until a solid had formed. The solid was washed with hexanes to give 222 as a beige solid (2.03 g, 83%). Rf = 0.24 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 8.01–7.97 (m, 2H), 7.70 (tt, J = 7.5, 1.2 Hz, 1H), 7.60–7.55 (m, 2H), 3.45 (s, 3H), 3.26 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 157.6, 134.6, 133.9, 129.5 (2C), 128.9 (2C), 53.7, 40.2; FTIR (neat) cm⁻¹ 1712, 1387, 1196, 1174, 749; HRMS-ESI (m/z) calcd. for C₉H₉ClNO₄S ([M+H]+): 331.9312; found: 331.9313.

tert-Butyl methyl((phenylsulfonyl)oxy)carbamate (223). To a stirring solution of 248 (1.47 g, 10 mmol, 1.0 equiv) in pyridine (8 mL) at 0 °C was added benzenesulfonyl chloride (1.34 mL, 10.5 mmol, 1.05 equiv) dropwise over 15 min. After stirring for 2 h,
the reaction was diluted with Et₂O (75 mL), washed with a half-saturated aqueous solution of CuSO₄ (100 mL), aqueous solutions of citric acid (2 × 20 mL, 0.5M), a cold aqueous solution of NaOH (20 mL, 0.5M), brine (20 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. To the residue was added hexanes and the mixture was placed in a −20 °C freezer until a solid had formed. The solid was washed with hexanes to give 223 as a white solid (2.04 g, 71%). Rᵣ = 0.56 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 8.00 (dd, J = 8.4, 1.2 Hz, 2H), 7.70 (tt, J = 7.5, 1.2 Hz, 1H), 7.57 (dd, J = 8.4, 7.5 Hz, 2H), 3.27 (s, 3H), 1.20 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 155.9, 134.4, 134.1, 129.6 (2C), 128.9 (2C), 83.4, 40.2, 27.5 (3C); FTIR (neat) cm⁻¹: 1720, 1372, 1328, 1150, 844, 556; HRMS-ESI (m/z) calcd. for C₁₂H₁₈NO₅ ([M+H]+): 310.0720; found: 310.0721.

**N-Benzyl-N-hydroxyacrylamide (251).** To a stirring suspension of N-benzylhydroxylamine hydrochloride (958 mg, 6 mmol, 1.0 equiv) and NaHCO₃ (1.01 g, 12 mmol, 2.0 equiv) in THF/H₂O (10:1, 22 mL) under nitrogen was added acryloyl chloride (0.54 mL, 6.6 mmol, 1.1 equiv) dropwise over 5 min. After stirring for 1 h, the reaction was diluted with H₂O (25 mL) and extracted with EtOAc (4 × 20 mL). The organic layers were combined, washed with brine (10 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The residue was placed in a −20 °C freezer until a solid had formed. The solid was washed with hexanes to give 251 as an off-white solid (1.00 g, 94%). Rᵣ = 0.33 (40% ethyl acetate–hexanes); ¹H NMR (400 MHz, (CD₃)₂SO): δ 10.08 (s, 1H), 7.37–7.26 (m, 5H), 4.76 (s, 2H), 6.89 (dd, J = 17.2, 10.4 Hz, 1H), 6.22 (dd, J =
17.2, 2.3 Hz, 1H); \(^1^3^C\) NMR (125 MHz, (CD\(_3\))\(_2\)SO): \(\delta\) 165.1, 136.9, 128.3 (2C), 128.0 (2C), 127.8, 127.2, 127.1, 51.5; FTIR (neat) cm\(^{-1}\) 2858, 1587, 1448, 1229, 962, 694; HRMS-ESI (m/z) calcd. for C\(_{10}\)H\(_{12}\)NO\(_2\): 178.0863; found: 178.0863.

**N-Benzyl-N-((phenylsulfonyl)oxy)acrylamide (224).** To a stirring solution of 251 (354 mg, 2.0 mmol, 1.0 equiv) and Et\(_3\)N (0.35 mL, 2.5 mmol, 1.25 equiv) in DCM (4 mL) at 0 °C under nitrogen was added benzenesulfonyl chloride (0.27 mL, 2.1 mmol, 1.05 equiv) dropwise over 3 min. After 30 min, the reaction was diluted with a solution of Et\(_2\)O/EtOAc (2:1, 30 mL) and the result washed with aqueous HCl (2 \(\times\) 10 mL, 0.5M) and a saturated aqueous solution of NaHCO\(_3\) (10 mL). The organic layer was dried over Na\(_2\)SO\(_4\), filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography (10% ethyl acetate–hexanes to 40% ethyl acetate–hexanes) to give 224 as white solid (314 mg, 49%). \(R_f = 0.42\) (25% ethyl acetate–hexanes); \(^1^H\) NMR (400 MHz, (CD\(_3\))\(_2\)SO): \(\delta\) 7.97–7.93 (m, 2H), 7.74–7.69 (m, 1H), 7.59–7.54 (m, 2H), 7.30–7.24 (m, 3H), 7.20–7.16 (m, 2H), 6.26 (d, \(J = 8.6\) Hz, 1H), 6.25 (d, \(J = 3.7\) Hz, 1H), 5.55 (dd, \(J = 8.6, 3.7\) Hz, 1H), 4.87 (s, br, 2H); FTIR (thin film) cm\(^{-1}\) 1680, 1385, 1191, 748; HRMS-ESI (m/z) calcd. for C\(_{16}\)H\(_{15}\)NO\(_3\)SNa ([M+Na\(^+\)]: 340.0614; found: 340.0614.

**General Procedure for Aminal Reactions**

To a solution of indole derivative (0.4 mmol, 1.0 equiv) in DMSO (2 mL) was added solid NaOt-Bu (115 mg, 1.2 mmol, 3.0 equiv) under a stream of nitrogen and the reaction stirred for 30 min. Then a solution of electrophilic amide (0.6 mmol, 1.5 equiv)...
in DMSO (2 mL) was added dropwise over 10 min. After stirring for an additional 1 h, the reaction was diluted with H$_2$O (20 mL) and extracted with Et$_2$O (2 × 20 mL). The organic layers were combined, washed with H$_2$O (10 mL), brine (10 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography to give pure aminals.

$N$-((1''H-Indol-1''-yl)methyl)benzamide (194). Column chromatography (10% ethyl acetate–hexanes to 30% ethyl acetate–hexanes) gives 194 as white crystals (77.7 mg, 78%). $R_f = 0.19$ (25% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.70 (dd, $J = 8.2$, 1.1 Hz, 2H), 7.64 (ddt, $J = 7.8$, 1.1, 0.8 Hz, 1H), 7.54 (ddd, $J = 8.2$, 0.9, 0.8 Hz, 1H), 7.48 (tt, $J = 7.2$, 1.1 Hz, 1H), 7.38–7.33 (m, 2H), 7.29 (d, $J = 3.2$ Hz, 1H), 7.23 (ddd, $J = 8.2$, 7.1, 1.1 Hz, 2H), 7.15 (ddd, $J = 7.8$, 7.1, 0.9 Hz, 1H), 7.10 (t, br, $J = 6.2$ Hz, 1H), 6.52 (dd, $J = 3.2$, 0.8 Hz, 1H), 5.76 (d, $J = 6.2$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.6, 135.5, 133.4, 132.0, 128.9, 128.6 (2C), 128.1, 127.0 (2C), 122.1, 121.1, 120.1, 109.4, 102.6, 50.4; FTIR (thin film) cm$^{-1}$ 3307, 1643, 1534, 1290, 736; HRMS-ESI (m/z) calcd. for C$_{16}$H$_{15}$N$_2$O ([M+H]$^+$): 251.1179; found: 251.1177.

$N$-((1''H-Indol-1''-yl)(phenyl)methyl)benzamide (198). Column chromatography (50% dichloromethane–hexanes to 100% dichloromethane) gives 198 as a white solid (83.3 mg, 64%). $R_f = 0.46$ (25% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.81–7.78 (m, 3H), 7.65 (d, $J = 7.4$ Hz, 1H), 7.55–7.51 (m, 1H), 7.46–7.38 (m, 6H), 7.34–7.31 (m, 2H), 7.21–7.11 (m, 3H), 6.99 (d, br, $J = 8.2$ Hz, 1H), 6.56 (d, $J = 3.1$ Hz, 1H);
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.8, 137.4, 135.7, 133.2, 132.1, 129.2, 129.0 (2C), 128.8, 128.7 (2C), 127.1 (2C), 126.5 (2C), 125.9, 122.2, 121.1, 120.3, 110.4, 102.8, 63.5; FTIR (thin film) cm$^{-1}$ 3295, 1640, 1528, 1306, 731; HRMS-ESI (m/z) calcd. for C$_{22}$H$_{18}$N$_2$ONa ([M+Na]$^+$): 349.1311; found: 349.1311.

$^{N}$-((2''-Methyl-1''H-indol-1''-yl)methyl)benzamide (199). Column chromatography (20% ethyl acetate–hexanes) gives 199 as a white solid (34.8 mg, 33%). $R_f$ = 0.30 (25% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.73–7.70 (m, 2H), 7.54–7.38 (m, 5H), 7.21–7.17 (m, 1H), 7.14–7.10 (m, 1H), 6.56 (t, br, $J = 5.9$ Hz, 1H), 6.29 (d, $J = 0.8$ Hz, 1H), 5.82 (d, $J = 5.9$ Hz, 2H), 2.55 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$, 60 °C): $\delta$ 167.0, 136.7, 136.2, 133.7, 131.9, 128.7, 128.6 (2C), 127.0 (2C), 121.4, 120.3, 120.0, 108.8, 101.8, 48.0, 12.6; FTIR (neat) cm$^{-1}$ 3274, 1638, 1552, 1398, 1292, 1086; HRMS-ESI (m/z) calcd. for C$_{17}$H$_{17}$N$_2$O ([M+H]$^+$): 265.1335; found: 265.1340.

General Procedure for Amidation of Indoles and Pyrroles

To a solution of indole or pyrrole derivative (0.4 mmol, 1.0 equiv) in DMF (2 mL) was added solid NaOtf-Bu (115 mg, 1.2 mmol, 3.0 equiv) under a stream of nitrogen and stirred for a 30 min. The reaction was then transferred by syringe to a flame-dried microwave tube containing ZnCl$_2$ (109 mg, 0.8 mmol, 2.0 equiv) and the resulting mixture stirred for 1 h. A solution of electrophilic amide (0.6 mmol, 1.5 equiv) in DMF (2 mL) was then added over 5 min to the reaction and the resulting mixture heated to the corresponding temperature (room temperature to 80 °C). When the reaction was
complete (monitored by TLC but never reacted longer than 24 h), it was quenched with an aqueous solution of NH₄Cl (1 mL, 1.8M) and stirred for 15 min. Then the reaction was diluted with EtOAc (20 mL) and washed with aqueous solutions of NH₄Cl (3 × 15 mL, 1.8M). The aqueous washes were combined and extracted with EtOAc (3 × 10 mL). All the organic layers were then combined and washed with aqueous NH₄Cl (4 × 10 mL, 1.8M), brine (10 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography to give pure amidated products.

**N-(1'H-Indol-3'-yl)-N-methylbenzamide (190).** Reaction conducted at 60 °C. Column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) gives 190 as a pearl-white foam (76.2 mg, 76%). Rf = 0.42 (50% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 8.40 (s, br, 1H), 7.60 (dd, J = 8.4, 1.5 Hz, 1H), 7.34–7.13 (m, 6H), 7.09–7.03 (m, 2H), 6.67 (s, br, 1H), 3.52 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 172.0, 136.1, 134.7, 129.4, 127.6 (2C), 127.5 (2C), 123.4, 122.7, 122.1, 121.1, 120.4, 117.1, 111.8, 38.0; FTIR (thin film), cm⁻¹ 3249, 1615, 1424, 741, 697; HRMS-ESI (m/z) calcd. for C_{16}H_{15}N₂O ([M+H]+): 251.1179; found: 251.1179.

**N-Methyl-N-(2'-methyl-1'H-indol-3'-yl)benzamide (200).** Reaction conducted at 60 °C. Column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) gives 200 as a tan solid (95.7 mg, 91%). Rf = 0.42 (50% ethyl acetate–hexanes); ¹H NMR (500 MHz, CDCl₃): δ 8.21 (s, br, 1H), 7.55–7.52 (m, 1H), 7.31–7.29 (m, 2H), 7.21–7.13
(m, 4H), 7.05–7.02 (m, 2H), 3.46 (s, 3H), 1.96 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 172.2, 136.3, 133.8, 129.4, 127.4 (2C), 127.3 (2C), 124.5, 121.8, 120.2, 118.5, 116.8, 110.9, 37.2, 10.7; FTIR (neat), cm$^{-1}$ 3234, 1613, 1376, 1214, 1093, 695; HRMS-ESI (m/z) calcd. for C$_{17}$H$_{17}$N$_2$O ([M+H]$^+$): 265.1335; found: 265.1335.

N-Methyl-N-(7'-methyl-1'H-indol-3'-yl)benzamide (201). Reaction conducted at 60 °C. Column chromatography (20% ethyl acetate–hexanes to 40% ethyl acetate–hexanes) gives 201 as a yellow solid (64.8 mg, 61%). $R_f = 0.42$ (50% ethyl acetate–hexanes); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.32 (s, br, 1H), 7.46 (d, $J = 7.8$ Hz, 1H), 7.31 (d, $J = 7.5$ Hz, 2H), 7.19–7.14 (m, 1H), 7.12 (dd, $J = 7.8$, 7.3 Hz, 1H), 7.08–7.03 (m, 2H), 7.03 (d, $J = 7.3$ Hz, 1H), 6.64 (s, br, 1H), 3.51 (s, 3H), 2.43 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 171.9, 136.1, 134.3, 129.4, 127.7 (2C), 127.5 (2C), 123.2, 123.0, 122.6, 121.0, 120.8, 120.6, 115.4, 38.0, 16.2; FTIR (thin film), cm$^{-1}$ 3264, 1623, 1385, 727; HRMS-ESI (m/z) calcd. for C$_{17}$H$_{16}$N$_2$ONa ([M+Na]$^+$): 287.1155; found: 287.1155.

N-(6'-Bromo-1'H-indol-3'-yl)-N-methylbenzamide (202). Reaction conducted at 60 °C. Column chromatography (20% ethyl acetate–hexanes to 40% ethyl acetate–hexanes) gives 202 as a yellow solid (58.4 mg, 44%). $R_f = 0.51$ (50% ethyl acetate–hexanes); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.86 (s, 1H), 7.42 (d, $J = 8.4$ Hz, 1H), 7.36 (d, $J = 1.3$ Hz, 1H), 7.28–7.26 (m, 3H), 7.20–7.16 (m, 1H), 7.08–7.04 (m, 2H), 6.64 (s, 1H), 3.48 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 172.1, 135.8, 135.4, 129.6, 127.6 (2C), 127.5 (2C), 123.7,
122.3, 122.1, 121.8, 118.8, 116.2, 114.8, 38.1; FTIR (thin film), cm⁻¹ 3220, 1617, 1381, 1069, 728; HRMS-ESI (m/z) calcd. for C₁₆H₁₄BrN₂O ([M+H]⁺): 329.0284; found: 329.0283.

\( \text{N-(5'-Chloro-1'H-indol-3'-yl)-N-methylbenzamide (203).} \) Reaction conducted at 60 °C. Column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) gives 203 as a white foam (63.1 mg, 53%). \( R_f = 0.24 \) (50% ethyl acetate–hexanes);

\(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 8.83 (s, 1H), 7.55 (s, 1H), 7.29–7.05 (m, 7H), 6.65 (s, 1H), 3.47 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 172.1, 135.8, 133.1, 129.6, 127.6 (2C), 127.5 (2C), 126.2, 124.3, 123.1, 122.7, 121.4, 117.0, 113.0, 38.0; FTIR (neat), cm⁻¹ 3241, 1621, 1376, 1295, 748, 700; HRMS-ESI (m/z) calcd. for C₁₆H₁₄ClN₂O ([M+H]⁺): 307.0609; found: 307.0609.

\( \text{N-(4'-Fluoro-1'H-indol-3'-yl)-N-methylbenzamide (204).} \) Reaction conducted at 60 °C. Column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) gives 204 as a pink foam (55.0 mg, 51%). \( R_f = 0.36 \) (50% ethyl acetate–hexanes);

\(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) 8.26 (s, br, 1H), 7.32 (d, \( J = 7.2 \) Hz, 2H), 7.18–7.03 (m, 5H), 6.84 (dd, \( J_{H-H} = 8.0 \) Hz and \( J_{F-H} = 10.4 \) Hz, 1H), 6.66 (s, 1H), 3.51 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 172.2, 155.7 (\( J_{F-C} = 246.5 \) Hz), 137.5 (\( J_{F-C} = 10.2 \) Hz), 136.3, 129.2, 127.7 (2C), 127.6 (2C), 123.1 (\( J_{F-C} = 7.4 \) Hz), 121.6, 120.1, 112.6 (\( J_{F-C} = 20.0 \) Hz), 108.0, 105.4 (\( J_{F-C} = 18.8 \) Hz), 38.7; FTIR (thin film), cm⁻¹ 3249, 1622, 1387, 1331, 1227, 737; HRMS-ESI (m/z) calcd. for C₁₆H₁₃FN₂ONa ([M+Na]⁺): 291.0904; found: 291.0904.
**N-Methyl-N-(5’-vinyl-1’H-indol-3’-yl)benzamide (205).** Reaction conducted at 60 °C. Column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) gives 205 as a white foam (68.6 mg, 62%). Rf = 0.43 (50% ethyl acetate–hexanes); 1H NMR (500 MHz, CDCl3): δ 8.28 (s, 1H), 7.58 (d, J = 1.5 Hz, 1H), 7.37 (dd, J = 8.5, 1.5 Hz, 1H), 7.33–7.30 (m, 2H), 7.23 (d, J = 8.5 Hz, 1H), 7.19–7.15 (m, 1H), 7.09–7.05 (m, 2H), 6.86 (dd, J = 17.5, 10.9 Hz, 1H), 6.65 (s, 1H), 5.75 (d, J = 17.5 Hz, 1H), 5.22 (d, J = 10.9 Hz, 1H), 3.52 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 172.0, 137.4, 136.0, 134.5, 130.5, 129.5, 127.7 (2C), 127.6 (2C), 123.6, 122.4, 121.7, 120.9, 116.0, 112.0, 38.0; FTIR (thin film), cm\(^{-1}\) 3234, 1614, 1383, 907, 726, 697; HRMS-ESI (m/z) calcd. for C18H17N2O ([M+H]\(^{+}\)): 277.1335; found: 277.1335.

**N-(5’-Methoxy-1’H-indol-3’-yl)-N-methylbenzamide (206).** Reaction conducted at 60 °C. Column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) gives 206 as a white foam (97.9 mg, 87%). Rf = 0.27 (50% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 7.99 (s, br, 1H), 7.33 (d, J = 7.3 Hz, 2H), 7.18 (d, J = 8.8 Hz, 1H), 7.17 (t, J = 7.3 Hz, 1H), 7.07 (t, J = 7.3 Hz, 2H), 6.98 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.8, 2.4 Hz, 1H), 6.69 (s, br, 1H), 3.87 (s, 3H), 3.51 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 172.0, 154.5, 136.0, 129.8, 129.4, 127.6 (2C), 127.5 (2C), 123.7, 121.8, 121.6, 112.8, 112.7, 98.8, 55.7, 37.9; FTIR (neat), cm\(^{-1}\) 3185, 1620, 1424, 1209, 695; HRMS-ESI (m/z) calcd. for C17H17N2O₂ ([M+H]⁺): 281.1285; found: 281.1284.
N-Methyl-N-(2′-methyl-5′-nitro-1′H-indol-3′-yl)benzamide (207). Reaction conducted at 80 °C. Column chromatography (20% ethyl acetate–hexanes to 100% ethyl acetate) gives 207 as yellow prisms (55.7 mg, 45%). Rf = 0.15 (50% ethyl acetate–hexanes); 1H NMR (400 MHz, (CD3)2SO): δ 11.65 (s, 1H), 8.40 (d, J = 2.2 Hz, 1H), 7.94 (dd, J = 8.9, 2.2 Hz, 1H), 7.39 (d, J = 8.9 Hz, 1H), 7.23–7.08 (m, 5H), 3.34 (s, 3H), 2.08 (s, 3H); 13C NMR (125 MHz, (CD3)2SO): δ 170.8, 141.0, 136.6, 136.5, 135.4, 129.4, 127.5 (2C), 126.7 (2C), 123.5, 119.5, 116.5, 113.2, 111.6, 36.9, 10.7; FTIR (neat), cm⁻¹ 3171, 1617, 1331, 1311, 1098, 1066; HRMS-ESI (m/z) calcd. for C17H16N3O3 ([M+H]+): 310.1186; found: 310.1186.

N-(5′-(Hydroxymethyl)-1′H-indol-3′-yl)-N-methylbenzamide (208). Reaction conducted at 40 °C. Column chromatography (40% ethyl acetate–hexanes to 75% ethyl acetate–hexanes) gives 208 as a tan foam (37.0 mg, 33%). Rf = 0.37 (75% ethyl acetate–hexanes); 1H NMR (400 MHz, (CD3)2SO): δ 10.87 (s, 1H), 7.44 (s, 1H), 7.27–7.05 (m, 6H), 5.08 (t, J = 5.7 Hz, 1H), 4.56 (d, J = 5.7 Hz, 2H), 3.36 (s, 3H); 13C NMR (125 MHz, (CD3)2SO): δ 170.8, 141.0, 136.6, 133.8, 133.7, 129.1, 127.4 (2C), 127.1 (2C), 122.9, 122.7, 121.3, 120.7, 114.8, 111.7, 63.6, 37.8; FTIR (thin film), cm⁻¹ 3283, 1617, 1331, 1311, 1098, 1066; HRMS-ESI (m/z) calcd. for C17H17N2O2 ([M+H]+): 281.1285; found: 281.1284.

Ethyl 3-(N-methylbenzamido)-1H-indole-5-carboxylate (210). Reaction conducted at 60 °C. Column chromatography (20% ethyl acetate–hexanes to 80% ethyl acetate–hexanes) gives 210 as a white foam (70.3 mg, 55%). Rf = 0.29 (50% ethyl acetate–hexanes); 1H NMR (500 MHz, CDCl3): δ 8.47 (s, br, 1H), 8.37 (s, 1H), 7.93 (d, J = 8.4 Hz,
(H), 7.34–7.03 (m, 6H), 6.76 (s, br, 1H), 4.42 (q, J = 7.1 Hz, 2H), 3.54 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 171.9, 167.3, 137.1, 135.9, 129.6, 128.6, 127.6 (4C), 124.2, 123.5, 123.1, 122.4, 120.6, 111.5, 60.9, 38.2, 14.5; FTIR (thin film), cm$^{-1}$ 3256, 1705, 1620, 1278, 1240, 1102; HRMS ESI (m/z) calcd. for C$_{19}$H$_{19}$N$_2$O$_3$ ([M+H]$^+$): 323.1390; found: 323.1386.

N-(2',5'-Dimethyl-1'H-pyrrol-3'-yl)-N-methylbenzamide (211). Reaction conducted at 60 °C. Column chromatography (20% ethyl acetate–hexanes to 40% ethyl acetate–hexanes) gives 211 as a yellow solid (61.9 mg, 68%). R$_f$ = 0.47 (50% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.40–7.37 (m, 2H), 7.30–7.15 (m, 4H), 5.68 (d, J = 2.5 Hz, 1H), 3.34 (s, 3H), 2.14 (s, 3H), 1.72 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 171.1, 136.6, 129.0, 128.1 (2C), 127.1 (2C), 125.1 (2C), 120.3, 103.5, 38.1, 13.0, 10.0; FTIR (thin film), cm$^{-1}$ 3271, 1614, 1573, 1372, 717, 695; HRMS ESI (m/z) calcd. for C$_{14}$H$_{17}$N$_2$O ([M+H]$^+$): 229.1335; found: 229.1336.

N-(4'-Ethyl-3',5'-dimethyl-1'H-pyrrol-2'-yl)-N-methylbenzamide (212). Reaction conducted at room temperature. Column chromatography (20% ethyl acetate–hexanes to 40% ethyl acetate–hexanes) gives 212 as a green oil prone to decomposition (85.7 mg, 84%). R$_f$ = 0.53 (50% ethyl acetate–hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.10 (s, br, 1H), 7.32–7.09 (m, 5H), 3.32 (s, 3H), 2.19 (q, J = 7.4 Hz, 2H), 2.07 (s, 3H), 1.55 (s, 3H), 0.87 (t, J = 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 171.3, 135.6, 129.6, 127.7 (2C), 127.3 (2C),
125.5, 120.1, 120.0, 111.4, 37.7, 17.5, 15.4, 10.7, 8.2; FTIR (thin film), cm⁻¹ 3280, 2959, 1630, 1380; HRMS-ESI (m/z) calcd. for C₁₀H₁₇N₂O (M+H⁺): 257.1648; found: 257.1649.

**N-(2',4'-Dimethyl-1'H-pyrrol-3'-yl)-N-methylbenzamide (213).** Reaction conducted at room temperature. Column chromatography (10% ethyl acetate–hexanes to 75% ethyl acetate–hexanes) gives 213 as a yellow oil which readily decomposes (38.6 mg, 42%). R_f = 0.47 (50% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.39 (s, br, 1H), 7.33–7.31 (m, 2H), 7.23–7.14 (m, 3H), 6.29 (s, 1H), 3.33 (s, 3H), 1.98 (s, 3H), 1.85 (s, 3H); FTIR (thin film), cm⁻¹ 3282, 1621, 1371, 720, 696; HRMS-ESI (m/z) calcd. for C₁₄H₁₇N₂O (M+H⁺): 229.1335; found: 229.1335. A reasonable ¹³C NMR spectrum could not be obtained before the compound decomposed.

**N-(3',5'-Dimethyl-1'H-pyrrole-2'-yl)-N-methylbenzamide (214).** Reaction conducted at room temperature. Column chromatography (10% ethyl acetate–hexanes to 75% ethyl acetate–hexanes) gives 214 as a yellow oil (16.3 mg, 18%). R_f = 0.54 (50% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.68 (s, br, 1H), 7.34–7.27 (m, 3H), 7.22–7.16 (m, 2H), 5.47 (s, 1H), 3.34 (s, 3H), 2.12 (s, 3H), 1.66 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 171.5, 135.7, 129.8, 127.7 (2C), 127.6 (2C), 126.4, 124.8, 112.7, 107.2, 107.2, 102.7, 37.7, 13.0, 10.0; FTIR (thin film), cm⁻¹ 3269, 1630, 1371, 720, 696; HRMS-ESI (m/z) calcd. for C₁₀H₁₇N₂O (M+H⁺): 229.1335; found: 229.1337.

**N,N'-(3',5'-Dimethyl-1'H-pyrrole-2',4'-diyl)bis(N-methylbenzamide) (215).** Reaction conducted at room temperature. Column chromatography (10% ethyl acetate–
hexanes to 75% ethyl acetate–hexanes) gives 215 as a white foam (47.1 mg, 33%). Rf = 0.17 (50% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl₃): δ 9.06 (s, 1H), 7.29–7.02 (m, 10H), 3.15 (s, 3H), 3.08 (s, 3H), 1.70 (s, 3H), 1.52 (s, 3H); 13C NMR (100 MHz, CDCl₃): δ 171.7, 171.5, 136.1, 135.5, 129.8, 129.2, 127.6 (2C), 127.4 (6C), 125.6, 124.2, 119.8, 108.7, 37.6 (2C), 10.0, 7.7; FTIR (thin film), cm⁻¹ 3201, 1614, 1361, 1090, 718, 695; HRMS-ESI (m/z) calcd. for C₂₂H₂₄N₃O₂ ([M+H]+): 362.1863; found: 362.1863.

**Diamidation procedure for the synthesis of N,N′-(3′,5′-Dimethyl-1′H-pyrrole-2′,4′-diyl)bis(N-methylbenzamide) (215).** To a solution of 2,4-dimethylpyrrole (38.1 mg, 0.4 mmol, 1.0 equiv) in DMF (2 mL) was added solid NaOt-Bu (231 mg, 2.4 mmol, 6.0 equiv) under a stream of nitrogen and stirred for a 30 min. The reaction was then transferred by syringe to a flame-dried microwave tube containing ZnCl₂ (218 mg, 1.6 mmol, 4.0 equiv) and the resulting mixture stirred for 1 h. A solution of 193 (1.2 mmol, 3.0 equiv) in DMF (2 mL) was then added over 5 min and the resulting mixture kept at room temperature for 22 h. The reaction was then quenched with an aqueous solution of NH₄Cl (1 mL, 1.8M) and stirred for 15 min. Then it was diluted with EtOAc (20 mL) and washed with aqueous solutions of NH₄Cl (3 × 15 mL, 1.8M). The aqueous washes were combined and extracted with EtOAc (3 × 10 mL). All the organic layers were then combined and washed with aqueous NH₄Cl (4 × 10 mL, 1.8M), brine (10 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated *in vacuo*. The crude material was purified
by column chromatography (50% ethyl acetate–hexanes to 100% ethyl acetate) to give pure 215 as a white foam (113.3 mg, 78%). Characterization data for 216 reported above.

**N-Benzyl-N-(2’-methyl-1’H-indol-3’-yl)benzamide (225).** Reaction conducted at 50 °C. Column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) gives 225 as a tan foam (109.0 mg, 80%). \( R_f = 0.53 \) (50% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 8.45 \) (s, 1H), 7.84 (d, \( J = 7.6 \) Hz, 2H), 7.53–7.48 (m, 1H), 7.45–7.40 (m, 4H), 7.34–7.29 (m, 2H), 7.26 (d, \( J = 8.0 \) Hz, 2H), 7.22 (d, \( J = 8.0 \) Hz, 1H), 7.12–7.08 (m, 1H), 7.01–6.94 (m, 2H), 6.77 (d, \( J = 7.6 \) Hz, 1H), 2.38 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta 166.8, 141.2, 135.5, 134.2, 133.5, 131.6, 128.6 \) (2C), 128.3 (2C), 126.9 (3C), 126.5 (3C), 121.1, 119.5, 118.3, 111.0, 110.8, 49.9, 11.8; FTIR (neat), cm\(^{-1}\) 3276, 1634, 1507, 1479, 1459, 694; HRMS-ESI (m/z) calcd. for C\(_{23}\)H\(_{20}\)N\(_2\)ONa ([M+Na]\(^+\)): 363.1468; found: 363.1467.

**N-Methyl-N-(2’-methyl-1’H-indol-3’-yl)pivalamide (226).** Reaction conducted at 50 °C. Column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) gives 226 as an orange solid (59.0 mg, 60%). \( R_f = 0.16 \) (25% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 8.03 \) (s, br, 1H), 7.39–7.37 (m, 1H), 7.32–7.29 (m, 1H), 7.19–7.11 (m, 2H), 3.21 (s, 3H), 2.33 (s, 3H), 1.07 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta 180.5, 134.0, 131.3, 125.3, 121.7, 120.0, 119.0, 117.6, 110.9, 40.3, 40.2, 28.7 \) (3C), 11.4; FTIR (thin film), cm\(^{-1}\) 3267, 1608, 1482, 1459, 1362, 742; HRMS-ESI (m/z) calcd. for C\(_{15}\)H\(_{21}\)N\(_2\)O ([M+H]\(^+\)): 245.1648; found: 245.1647.
**N-Methyl-N-(2’-methyl-1’H-indol-3’-yl)acetamide (227).** Reaction conducted at 60 °C. Column chromatography (20% ethyl acetate–hexanes to 100% ethyl acetate) gives 227 as a brown foam (26.0 mg, 32%). Rf = 0.39 (75% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 8.39–8.24 (m, br, 1H), 7.40–7.32 (m, 2H), 7.21–7.12 (m, 2H), 3.29 (s, 3H), 2.36 (s, 3H), 1.88 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 173.1, 134.0, 130.5, 124.2, 122.0, 120.2, 118.2, 116.7, 111.0, 36.3, 21.5, 10.7; FTIR (thin film), cm⁻¹ 3233, 1623, 1382, 1211, 741; HRMS-ESI (m/z) calcd. for C12H15N2O ([M+H]+): 203.1179; found: 203.1179.

**Methyl methyl(2’-methyl-1’H-indol-3’-yl)carbamate (228).** Reaction conducted at 50 °C. Column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) gives 228 as an orange foam (87.3 mg, 86%). Rf = 0.13 (25% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 7.86 (s, br, 1H), 7.40–7.36 (m, 1H), 7.29–7.26 (m, 1H), 7.17–7.08 (m, 2H), 3.83 (s, 0.6H), 3.64 (s, 2.4H), 3.31 (s, 3H), 2.31 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 157.6, 133.7, 130.3, 124.4, 121.4, 119.8, 116.9, 116.3, 110.9, 53.0, 37.8, 10.8; FTIR (thin film), cm⁻¹ 3200, 1682, 1164, 743; HRMS-ESI (m/z) calcd. for C12H15N2O2 ([M+H]+): 219.1128; found: 219.1127.

**tert-Butyl methyl(2’-methyl-1’H-indol-3’-yl)carbamate (229).** Reaction conducted at 60 °C. Column chromatography (10% ethyl acetate–hexanes to 30% ethyl acetate–hexanes) gives 229 as an orange foam (86.4 mg, 83%). Rf = 0.32 (25% ethyl acetate–hexanes); 1H NMR (400 MHz, CDCl3): δ 7.83–7.76 (m, br, 1H), 7.40 (d, J = 7.0 Hz, 1H), 7.27–7.24 (m, 1H), 7.16–7.07 (m, 2H), 3.25 (s, 3H), 2.31–2.27 (m, br, 3H), 1.56 (m, br, 2.6H),
1.34 (s, 6.4H); $^{13}$C NMR (125 MHz, (CD$_3$)$_2$SO, mixture of two rotamers (denoted major or minor or both)): δ 156.6 (minor), 156.3 (major), 134.1 (minor), 133.7 (major), 130.8 (minor), 129.8 (major), 124.7 (both), 121.4 (minor), 121.1 (major), 119.8 (minor), 119.5 (major), 117.2 (major), 117.0 (minor), 110.9 (minor), 110.7 (major), 80.0 (minor), 79.5 (major), 38.0 (minor), 37.2 (major), 28.4 (minor, 3C), 28.3 (major, 3C), 11.1 (major), 10.9 (minor); FTIR (neat), cm$^{-1}$ 3280, 1669, 1152, 1110, 762, 641; HRMS-ESI (m/z) calcd. for C$_{15}$H$_{20}$N$_2$O$_2$Na ([M+Na]$^+$): 283.1417; found: 283.1419.
Chapter 3. Diazirines as novel hyperpolarizable molecular tags for magnetic resonance imaging

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3. Diazirines as novel hyperpolarizable molecular tags for magnetic resonance imaging

3.1 Introduction

Magnetic resonance (MR) is one of the most widely used imaging techniques in medicine. MR has the advantage of high spatial resolution and without the cost of needing ionizing radiation, as in the case of SPECT and PET. MR is highly adept at tracking chemical reactions, allowing for the unique capability to reveal metabolic pathways and detect initial stages of disease states.

However, MR does have severe limitations in sensitivity. For instance, at 1.5 T (typical magnetic field for a clinical MR instrument) the thermal difference in population of the two nuclei spin states of $^1$H (spin = ½) is only 5 ppm; a fraction of the signal which would be produced if all the nuclei were of one spin state. If the magnetic field was increased to 21 T, the difference in population of the $^1$H spin states is still only 70 ppm. Because most of the human body consists of H$_2$O, almost all clinical MR instruments and probes are only able to measure or tune the proton signal arising from H$_2$O.$^{245}$ Furthermore, inquiry into other nuclei (e.g. $^{13}$C) in the human body generates additional signal-to-noise problems because of the large amounts of different organic chemicals around. Because of these technical limitations, exogenous organic probes which could track metabolic processes or disease states in real-time have not been successful (if based solely on the thermal distribution).
3.1.1 Hyperpolarization

A. Spin states of hydrogen

\[
\begin{align*}
\text{ortho-hydrogen} & \quad (\text{spin triplet}) \\
\text{para-hydrogen} & \quad (\text{spin singlet})
\end{align*}
\]

B. Distribution of spin states as a function of temperature

![Graph showing the distribution of spin states as a function of temperature]

Referenced from Fukutani.\textsuperscript{246}

Figure 12: Spin isomers of hydrogen

In order to address the insensitivity of MR and possibly allow for the use of low concentration probes \textit{in vivo}, several hyperpolarization techniques have been invented.\textsuperscript{247-253} Hyperpolarization is defined as nuclear spin polarization higher than the equilibrium Boltzmann distribution. Out of all the hyperpolarization techniques, parahydrogen induced nuclear polarization (PHIP) is of particular interest. Compared to the other available methods, PHIP is more economical and quicker. Parahydrogen is the lower energy spin singlet and the source of hyperpolarization transfer when using the PHIP technique (Figure 12, A). At room temperature, hydrogen is a statistical mixture
made of 3:1 triplet orthohydrogen to singlet parahydrogen. At cooler temperatures, the more thermodynamically stable singlet state dominates (Figure 12, B). Crucially, parahydrogen can be stored (in the absence of a paramagnetic material) for weeks, thereby providing easy access to large amounts of spin polarization.

3.1.1.1 Beginnings of parahydrogen induced polarization

**Scheme 46: Hydrogenation of acrylonitrile with parahydrogen**

PHIP was first hypothesized in 1986 by Wietekamp and Bowers. In fact in 1983, three years earlier, PHIP had been observed as a signal increase but was incorrectly attributed to another nuclear effect. However, by 1987, two separate groups had the experimental proofs for the signal enhancements. In one of the two examples, hydrogenation of acrylonitrile with parahydrogen using Wilkinson’s catalyst results in a large signal increase at the hydrogened positions (Scheme 46). This signal increase results because the pairwise transfer of parahydrogen to the substrate occurs with retention of the polarization.
3.1.1.2 Non-hydrogenative polarization transfer

(A) Schematic of polarization transfer using pyridine as a substrate. (B) Single scan NMR spectra. The $^1$H control (top) with 128-fold vertical expansion relative to the bottom $^1$H trace that was recorded immediately after polarization transfer. (C) Polarization of $^1$H decoupled $^{13}$C trace. (D) Polarization of $^1$H decoupled $^{15}$N trace. Spectra from Elliot and co-workers.258

**Figure 13: Schematic of hyperpolarization transfer and signal increases of different spin = $\frac{1}{2}$ nuclei of pyridine**

It was found that the hydrogens of coordinating ligands could be hyperpolarized in the presence of parahydrogen and Crabtree’s catalyst, this phenomenon was deemed “signal amplification though reversible exchange” or SABRE. Amplified pyridine signals were observed in this way (Figure 13).258-259 By reversible exchange of ligands, polarization could be transferred not just other to protons but to other spin = $\frac{1}{2}$ nuclei by the $J$-coupling mechanism (Figure 13, A). After just a few seconds of contact between the starting materials and the catalyst, a 550-fold increase in the proton signal of pyridine
was observed (Figure 13, B). However, the signal generated from polarization transfer to \( ^{13}\text{C} \) was even greater, an 823-fold increase (Figure 13, C). Finally, the naturally abundant (0.35%) \( ^{15}\text{N} \) in pyridine also exhibited a large signal increase (Figure 13, D).

![Chemical structures](image)

**Figure 14:** Other molecules that can reversibly bind the catalyst and become hyperpolarized

Importantly, this technique has been extended to other \( N \)-heterocycles (Figure 14). Sterically unencumbered picolines and lutidines are efficiently polarized. B-vitamin nicotinamide was efficiently polarized. Purine base adenine and nucleic acid adenosine were continuously polarized using a modified PHIP approach. However, the authors concede that continuous hyperpolarization will not be amenable to clinical applications. Additionally, tuberculosis drugs isoniazid and pyrazinamide were hyperpolarized in 230- and 960-fold proton signal enhancements respectively. Tessari and co-workers found that the lower limit of detection for hyperpolarized nuclei based on a series of spectra is less than 1\( \mu \text{M} \) in solution. When one considers the normal concentration of an organic NMR sample in deuterated solvent (10–100mM) or the
concentration of gadolinium contrast reagent required for acquiring MRI of tissues (0.25–1.0M!) hyperpolarization methods offer a clear advantage. 

3.1.1.3 Polarization transfer of parahydrogen to $^{13}$C- and $^{15}$N-labeled pyridines

Up to now, PHIP had only been treated to natural abundance spin $\frac{1}{2}$ ligands. However, to extend this method to exogenous probes for in vivo clinical work, two important issues must be addressed. First, the signal must persist for a longer time than the typical $T_1$ time frame. Additionally, the signal-to-noise ratio must be kept to a minimum (using isotopes that have low concentration in vivo). In the first example, $^{13}$C-labeled ($T_1$ in 10’s of seconds) nicotinamide was examined and a signal enhancement of $10^6$ was observed. The $T_1$ was not elaborated on, but a maximum signal-to-noise ratio of about $10^3$ for 148 µmol of substance was noted. $^{15}$N-labeled materials are more expensive than $^{13}$C-labeled compounds, and $^{15}$N has a lower sensitivity than $^{13}$C; however it is attractive because the $T_1$ is usually much longer. Hyperpolarization of $^{15}$N-labeled pyridine and nicotinamide was then studied, with the outcome being 10% overall $^{15}$N polarization (about 30,000-fold signal increase) and a $T_1 = 42$ s at 9.4 T.

3.1.1.4 Limiting nearby spin $> \frac{1}{2}$ nuclei increases hyperpolarization lifetime

Although the lower limit of detection for hyperpolarized nuclei in solution seems to be less than 1µM, this hyperpolarization dissipates within seconds in almost all cases due to $T_1$ relaxation mechanisms. Therefore, a major limit to hyperpolarization is the small window of time in which to do something useful with the material. Besides
choosing nuclei with longer $T_1$ lifetimes (e.g. $^{15}$N), the next most important way to improve lifetime is to remove other spin $\frac{1}{2}$ nuclei from the environment; nearby spin $\frac{1}{2}$ nuclei will couple with the hyperpolarized nuclei and dissipate the polarization. Moving protons further away or replacing protons with deuteriums greatly enhances the hyperpolarized lifetime (Figure 15).

![Chemical Structures]

*Figure 15: The type of polarized nuclei and the surrounding nuclei can have a profound influence on $T_1$*

### 3.1.2 Singlet state and hyperpolarization

However, nuclear singlet states have lifetimes ($T_S$) much longer than the spin-lattice relaxation time ($T_1$) and could support long-lived hyperpolarization. The singlet state is free from dipolar relaxation and most other modes that have an effect on $T_1$. The singlet state has a spin of 0, invisible to an NMR, however hyperpolarization can work on a singlet state system if the two nuclear sites are adjacent yet magnetically inequivalent. The spin-spin coupling ($J$-coupling) of the two nuclei must also be similar to the coupling of hydrogen ligated to the iridium catalyst (about 10 Hz).

#### 3.1.2.1 Singlet state hyperpolarized proton system

In 2004, Levitt and co-workers demonstrated the first instance of creating a nuclear singlet spin system with $T_S$ much greater than $T_1$. Using 2,3-dibromothiophene
as a model substrate, the authors were able to extend the lifetime from 17 s to 104 s (Figure 16).\textsuperscript{269} Similarly, a much higher ratio increase from $T_1$ to $T_S$ was seen when using a multi-deuterated compound.\textsuperscript{270} These two examples show how the two pairs of nuclei can be made magnetically inequivalent and thus amenable to the singlet state polarization. In the first example, the two protons are chemically inequivalent and thus would be different in the NMR. In the second example, the two protons are chemically equivalent but are diastereotopic. Therefore the two protons are magnetically inequivalent and are distinguishable in the NMR.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure16.png}
\caption{Difference in triplet and singlet magnetization lifetimes for pairs of protons}
\end{figure}

3.1.2.2 Singlet state hyperpolarized $^{13}$C$_2$-labeled system

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure17.png}
\caption{Common structures of $^{13}$C$_2$-labeled systems}
\end{figure}

Many researchers then set out to extend this method to $^{13}$C$_2$-labeled systems. The most common feature in this class are $^{13}$C$_2$-labeled ethynes with protons far removed.
from the ethyne group (Figure 17). Most reported singlet lifetimes ($T_s$) for these types of systems are around 15 min.

A much more complicated internal naphthalene system was also investigated. The isotopically-labeled structure was synthesized in 10 linear steps with a 15% overall yield (Figure 18). This compound exhibited the highest $T_s$ ever found for a material when the sample was degassed (4250 s, 380 s if not degassed). Although a compound such as this is not practical from a clinical perspective because of its size and the need to degas, it is important as a proof-of-concept. A much more practical solution was devised by Warren and co-workers with their 2,3-$^{13}\text{C}_2$-diacetyl compound. Normally the singlet would not be seen by NMR, but one of the carbonyls will become a hydrate in the presence of water, making the two carbons inequivalent.

![Chemical Structure](image)

Figure 18: Perdeuterated naphthalene has an extremely long singlet lifetime

3.1.2.3 Singlet state hyperpolarized $^{15}\text{N}_2$-nitrous oxide

So far only one example of a $^{15}\text{N}_2$-labeled singlet state hyperpolarized molecule is known, and it is not an organic compound. The nitrogens of $^{15}\text{N}_2\text{O}$ have a $J$-coupling of 8.1 Hz, making it close to the desired 10 Hz. Additionally, no nuclei with spin are around to dampen the hyperpolarized signal. When dissolved in degassed (CD$_3$)$_2$SO, the
singlet lifetime of $^{15}$N$_2$O was 26 min. The finding is useful since N$_2$O is highly soluble in biologically important solvents such as water, oil, and blood. As an experiment on clinical applicability, $^{15}$N$_2$O was dissolved in olive oil and the measured $T_s$ was still 19 min.

### 3.1.3 Diazirines as photoaffinity probes

The examples of hyperpolarization given are one-use, idealized systems. A general type of tag for NMR that is small and without signal-to-noise problems has yet to be found. Here, I look to chemical biology for examples of truly general tags which might be promising for hyperpolarization. There are several examples of photoaffinity based probes, the smallest and most general of which are diazirines.$^{276-278}$ Diazirines are three-membered rings with two sp$^2$ hybridized nitrogens bonded to a sp$^3$ hybridized carbon (Figure 19).

The use of diazirines as photoaffinity tags dates back to the 1970’s when Knowles and co-workers were studying photolysis. First theorized as good tags in 1973,$^{279}$ it was not until 1978 that Knowles and co-workers used a diazirine-based photoaffinity probe to label some fatty acids in the lipid bilayer.$^{280}$ Another improvement to diazirine-labeling was made in 1980 when it was discovered that 3-trifluoromethyl-3-phenyldiazone (TPD) was a much better carbene precursor than regular aliphatic diazirines (Figure 19).$^{281}$
3.1.3.1 Simple aliphatic diazirine probes

The diazine-based structure does not need to be complex in order to achieve results. Simple aliphatic azialcohols were able to label PKC subdomains, adenylate kinase, nicotinic ACh receptors, and Rho GTPase (Figure 20). Several of these azialcohols may be used on a single target, giving different locations for the new covalent bond. Some also show irreversible inhibition of the target enzyme after labeling.

3.1.3.2 Structures for drug discovery and drug mechanism elucidation

An early example of diazirine-based probes derived from known drugs was accomplished by Baldwin and co-workers. Their TPD-labeled penicillin derivative
(Figure 21) was found to be a substrate for isopenicillin N synthase (IPNS). A more recent example examines how chemotherapeutic agent etoposide interacts with topoisomerase II. For this work, the authors replace the sugar moiety of etoposide with a TPD moiety (Figure 22). The new diazirine compound was shown to have a similar mode of action as etoposide and displayed even more cytotoxicity to leukemia cells and easily underwent photolysis. Assays suggest that a new covalent bond between the new compound and topoisomerase II was formed, but so far the structure has not been isolated.

![Chemical structures](image)

**Figure 22: Etoposide and its TPD-labeled derivative**

In a similar manner, general anesthetic etomidate was modified separately with an azialcohol and a TPD moiety (Figure 23). The general anesthetic properties of the new and unmodified etomidates were about the same. With the azietomidate structure, photolabeling was able to confirm the binding pocket and binding sites of GABA. However, TPD-etomidate of the same chirality is not an efficient ligand. Interestingly, the other enantiomer bound to GABA at a completely different location as the other
two. Some useful SAR information was obtained about etomidate; plus the unexpected bonding sites of TPD-etomidate could implicate novel pathways.

![Figure 23: Structures of anesthetic etomidate and its diazirine-labeled derivatives](image)

3.1.3.3 Diazirine-labeled proteins

In a key study, Thiele and co-workers fed diazirine-labeled photo-leucine and photo-methionine to mammalian cells in the absence of normal amino acids leucine and methionine (Figure 24). Because of the close similarity between the new and native amino acids, the diazirine-labeled amino acids were incorporated into the standard proteins of the cells. After some time, the diazirines in the cells were photolyzed and after Western blotting, new protein-protein interactions were observed. This work inspired more targeted experimentation on protein-protein interactions.

![Figure 24: New photoreactive diazirine-labeled amino acids](image)

### 3.1.4 Standard diazirine syntheses

3.1.4.1 Synthesis of diazirines from ketones

The major synthetic pathway to diazirines starts from ketones. The ketones are transformed to diaziridines and subsequently oxidized to diazirines. Several synthetic
protocols exist for the conversion of ketones to diaziridines; however there are really only two classes of protocols. In the first class, condensation of the ketone with ammonia, followed by treatment with hydroxylamine-O-sulfonic acid (HAOSA) ≤ 0 °C gives the diaziridine (Scheme 47). The alternative method is technically the inverse addition of the former class. Thus, the ketone is transformed into an O-sulfonyl oxime in two steps, then addition of ammonia completes the diaziridine synthesis.

Scheme 47: Summary of syntheses for diazirines via ketones

Once the diaziridine has been synthesized, numerous oxidation reagents can be used for the final step. Perhaps the easiest and most common method is oxidation via I₂ (Scheme 47). Oxidation to the diazirine with Ag₂O can be accomplished. Oxalyl chloride and trimethylacetyl chloride are also efficient oxidizing agents. tert-Butyl hypochlorite can be used if overoxidation is not a concern. Transition metals are not normally used to oxidize a diaziridine to a diazirine, yet stoichiometric CrO₃ was
found to work on an adamantine structure. Catalytic RuO$_2$ with stoichiometric NaIO$_4$ was used to synthesize a TPD diazirine. Electrochemical oxidation on a Pt/Ti anode has also been accomplished.

3.1.4.2 The Graham reaction

The only method which can directly synthesize a diazirine without the diaziridine oxidation step is the Graham reaction. Graham discovered that hypohalite oxidation of amidines gives halodiazirines (Scheme 48). Initially, the Graham reaction was studied as a curiosity and was not considered synthetically useful. However, several diazirines can be made by the nucleophilic diazirine exchange process.

\[
\begin{align*}
\text{R} - \text{NH}_2 + \text{NaOX} &\rightarrow \text{R} \cdot \text{N} = \text{N} \cdot \text{X} \\
\text{R} \cdot \text{N} = \text{N} \cdot \text{X} + \text{Nuc} &\rightarrow \text{R} \cdot \text{N} = \text{N} \cdot \text{Nuc}
\end{align*}
\]

\text{Nuc} = \text{CN, F, ArO, MeO, R'}\text{NH}

\textbf{Scheme 48: Graham synthesis of diazirines}

3.1.4.3 Post-functional modifications

No matter which starting material or method that is utilized, the diazirine syntheses are fairly harsh and low-yielding. Therefore installation of the diazirine early in a synthesis is preferable to a late-stage diazirine synthesis. However, one worries about the stability of diazirines to chemical transformations. One of the earliest examinations of diazirine stability in chemical synthesis was accomplished by Church and Weiss in 1970. They discovered that small aliphatic diazirines are stable to several
standard transformations, such as the Jones reagent, TsCl in pyridine, and nucleophilic substitution in hot DMF.

\[
\text{Scheme 49: First post-functional transformations of small diazirines}
\]

Hatanaka and co-workers expanded on the post-functional modifications of diazirines in 1994 in their search for nitrated TPD analogs. Strong acid conditions did not affect the diazirine in any way. Even nitration in nitric acid and acetic anhydride afforded the desired TPD derivative in 88% yield (Scheme 50).^301

\[
\text{Scheme 50: Diazirines are stable to strong acid conditions}
\]

The same group pushed the boundaries even further to show the stability of diazirines under Friedel-Crafts conditions (Scheme 51). Interestingly, the diazirine was stable to both strong oxidizing conditions (permanganate) and reducing conditions.
(sodium borohydride). An Appel reaction was also successful, proving the stability of diazirines towards electrophiles.\textsuperscript{308} Diazirines are not stable to $h\nu < 350$ nm, strong reducing conditions (e.g. LAH), hydrogenation, or organometallic reagents.\textsuperscript{309}

![Chemical structure diagram]

Scheme 51: Diazirines are unaffected by electrophilic, oxidative, and reductive conditions

3.2 Diazirines as uniquely suited carriers of singlet state hyperpolarization

Nuclear singlet states have lifetimes ($T_s$) much longer than the spin-lattice relaxation time ($T_1$) and could support long-lived hyperpolarization.\textsuperscript{268} However, for hyperpolarization to work for a singlet state system, the two nuclear sites (spin = ½) in question must be adjacent, yet magnetically inequivalent at high field; they must be “equivalent” at low field. The spin-spin coupling ($J$-coupling) of the two nuclei must also be equal to about 10 Hz.\textsuperscript{268} Ideally, the two nuclei have long $T_1$’s, are distant from other spin = ½ nuclei, and have a low natural abundance. The atom $^{15}$N comes to mind as the spin = ½, the $T_1$’s are generally on the order of 100 s, and is only 0.36% natural abundant.
As stated before, diazirines have been used to great effect as photoaffinity labels in chemical biology. Diazirines are highly adept in this role for multiple reasons as demonstrated by the empirical evidence across many systems of interest. They are small, meaning there is a low chance of altering the reactivity of the diazirine-labeled molecule. They are remarkably stable to many chemical reactions or biological processes. Their photolysis generates N2 and a potent carbene intermediate (which will bond to a nearby molecule); however this will not occur without light or extreme heat. Withstanding their photolysis, their small size and stability would be highly prized in any labeling method.

Combining this information, if diastereotopic 15N2-labeled diazirine synthesized, they would have the ideal properties of a general molecular tag for MR. 15N2-labeled diazirines would have all the desirable labeling properties of regular diazirines in addition to containing the best isotope for long lived hyperpolarization (T1). Signal-to-noise problems inherent in observing 15N will be virtually eliminated because of the isotope labeling. By making the diazirine diastereotopic, all the physics requirements for single state hyperpolarization would in principle be fulfilled. By utilizing the singlet state, metabolic processes which are generally slower than spin-lattice relaxation could be observed with hyperpolarization still intact. Although all the desirable characteristics have been established theoretically for the 15N2-diazirine moiety, a diazirine with the
necessary values ($J_{N-N}$-coupling and chemical shift difference) for single state hyperpolarization can only be found empirically.

### 3.3 Exploration of diazirines suitable to singlet state hyperpolarization

#### 3.3.1 Decision to make 3-azibutanol the precursor diazirine

In order to achieve hyperpolarization, the two nitrogens of the diazirine ring must be diastereotopic; which means that there must be at least one stereogenic center in the molecule. However, we do not know how far away the stereogenic center should be or what kinds of functional groups should be included. In order to compensate for our lack of foundational knowledge in this regard, many different diazirine compounds must be quickly synthesized and then tested for compatibility with hyperpolarization. Fortunately, the isotopic labeling can be forgone until after a suitable compound has been identified.

![Figure 25: Two possible progenitors for the diazirine project](image)

There are two routes to consider: synthesize a larger diazirine compound with orthogonal handles that can undergo many modifications, or synthesize a small, simple diazirine with just one flexible functional group. Both pathways will be pursued, and
experience will dictate the best path. For the first method, an acetophenone derivative seemed reasonable, while 3-azibutanol can suffice for the second method (Figure 25).

To pursue the first idea, commercially available 4′-methoxyacetophenone (254) was treated with KH and TBSCI to obtain the silyl enol ether, this was immediately followed by a Rubottom oxidation to yield α-siloxyketone 255 (Scheme 52). The oxime 256 was easily obtained by reaction with hydroxylamine hydrochloride under basic conditions. However, the formation of an O-tosyloxime with TsCl in pyridine did not go as planned. A single compound was formed in the reaction, but the desired diazirine precursor was not the product. Isolation confirmed that the reaction had undergone a spontaneous Beckmann rearrangement to 257.

Scheme 52: Failed synthesis of larger diazirine 252

With the synthesis of larger diazirine 252 proving unlikely, the synthesis of small diazirine 3-azibutanol (254) was conducted. Church and Weiss first synthesized the compound in 1970 by using a slightly modified procedure, 254 was synthesized in
34% yield from 4-hydroxybutanone (Scheme 53). Although successful, 254 only has one functional group, so it was imperative to ensure successful functional group interconversion. The primary alkyl iodide 258 was synthesized in 42% yield from PPh₃ and I₂. Using another procedure by Church and Weiss, tosylate 259 was synthesized in 90% yield. These successive reactions demonstrated that the small diazirine strategy is best.

![Scheme 53: Small diazirine strategy proves successful](image_url)

### 3.3.2 Discovery of a diazirine-containing molecule amenable to single state hyperpolarization

#### 3.3.2.1 Electrophilic diazirines and the use of heteroatoms as nucleophiles

Diazirine electrophiles 258–259 were subjected to chiral nucleophilic reagents. However these electrophiles proved to be quite poor as primary amines, enolates, enamines, and malonates were all ineffective nucleophiles. However, cyclic 1-methylpiperazine was reported to be a good nucleophile for tosylate 259. Yet that compound does not have a stereogenic center. Therefore, 259 was reacted with three different nitrogen heterocycles with stereogenic centers to provide three diazirines for
testing (260–262, Scheme 54). As nitrogen heterocycles were proven to be good nucleophiles, perhaps thiols could work as well. Propanethiol was successfully reacted with 259 in the presence of base to give thioether 263 in 66% yield. A stereogenic center was installed when oxidation of 263 with mCPBA gave sulfoxide 264. These four stereogenic diazirines were tested for compatibility with singlet state hyperpolarization, but none were sufficient.

Scheme 54: Synthesis of chiral diazirines which were not compatible with singlet state hyperpolarization

3.3.2.2 Derivatization of nucleophilic diazirines leads to a target

With the incompatibility of compounds 260–262 and 264 toward singlet state hyperpolarization, more options were needed. However, carbon nucleophiles with
stereogenic centers remained unsuccessful. Since electrophilic diazirines were troublesome, perhaps a nucleophilic diazirine would work better. Westermann and co-workers reported that tosylate 259 can react with cyanide to produce a nitrile (a possible nucleophile). Indeed, NaCN in DMSO reacted with 259 to give 265 in 87% yield (Scheme 55).

![Scheme 55: Target compound for isotopic labeling identified](image)

a) TsCl, pyridine, 0 °C (90%); b) NaCN, DMSO, 70 °C (87%); c) KH, (EtO)₂CO, THF, 0 °C (87%); d) BnBr, K₂CO₃, DMF, 60 °C (91%); e) KOH, EtOH (92%).

The synthesis of diazirine-containing molecules by this route was very successful. The nitrile was acylated with diethyl carbonate to give stereogenic diazirine 266. This compound was alkylated in a facile manner with benzyl bromide to 267, while some of the ester was hydrolyzed to reveal acid 268. Compounds 266–268 were then tested in the NMR for their compatibility with hyperpolarization. The NMR tests revealed that functional groups can have a drastic effect on the ¹JNN and chemical shift;
only 268 has the correct values for single state hyperpolarization despite the similar structures of 266–268. Compound 268 has a $J_{\text{N-N}} = 17.5$ Hz and a chemical shift difference of 0.58 ppm at 8.5 T (21.2 Hz), making it a good target for isotopic labeling and singlet state hyperpolarization.

3.4 Design and synthesis of a novel hyperpolarizable $^{15}$N$_2$-diazirine for magnetic resonance imaging

3.4.1 Isotopically labeled target and retrosynthetic analysis

Although a target molecule with the right nitrogen nuclear values has been identified, the actual hyperpolarization tests must be conducted with $^{15}$N$_2$-labeled diazirines. Since this test would be a proof-of-concept, it should have the longest possible $T_S$. However, coupling of the methyl protons to the naturally abundant diazirines is strong and would quickly dissipate the hyperpolarized signal. A trideuteromethyl group will not have this undesired effect since deuterium has a nuclear spin = 1. The methylene protons adjacent to the diazirine do not couple well and do not need to be replaced. The methylene protons should actually remain since they provide a backup plan as polarization can be transferred to the methylene protons first then to the $^{15}$N$_2$-diazirine. The new structure 269 is therefore the real target (Figure 26).

![Figure 26: Hyperpolarization requirements beget compound 269 as the target](image-url)
Ideally, the synthetic procedures used to synthesize 268 would not need to be changed much. However, since a trideuteromethyl had to be installed while leaving the methylene protons untouched, it had to be installed before the diazirines. An exhaustive look at available trideuteromethyl compounds in combination with known carbonyl chemistry led me to believe that alkylating 1,3-dithiane with CD3I was the best course of action (Scheme 56).

![Scheme 56: Retrosynthetic analysis to isotopic target 269](image)

In fact, the first step did work well, but the deprotection of the 1,3-dithiane proved to be very difficult. Many different deprotection strategies were attempted but none were satisfactory.107 During the deprotection attempts, the molecule was either unscathed, overoxidized, or when the reaction did work, the desired molecule could not be extracted out of aqueous solution. A new synthetic scheme had to be developed.

![Scheme 57: Failed deprotection strategies to asymmetric ketone 270](image)
3.4.2 Detour from the initial scheme leads to synthesis of the desired compound

For the 1,3-dithiane deprotection to work, the compound must be resistant to oxidation, be more soluble in organic solvent than water, and be nonvolatile. In order for the subsequent diazirine formation to work, the compound must be somewhat water soluble and contain only the ketone as a strongly electrophilic site. Protecting groups were out of the question because time was of the essence. Tosylation and nitrile substitution steps occur after diazirine formation in the natural abundance synthesis of diazirine, however there was no reason the steps could not be switched.

It was postulated that ketonitrile 273 would be slightly water soluble (for diazirine formation) but not so water soluble that it could not be extracted with EtOAc (deprotection step). To test this hypothesis, unlabeled starting material 272 was subjected to deprotection strategies. A reported deprotection strategy with I₂ was found to be the best; the desired ketonitrile 273 was cleanly produced and extracted in 76% yield (Scheme 58).314 With 4-hydroxybutan-2-one, diazirine formation usually results in a 30% yield. However, the diazirine formation of 265 occurred at only 20% efficiency. The lower yield with the nitrile can probably be attributed to its lower solubility in aqueous conditions.

![Scheme 58: Testing the suitability of unlabeled nitrile in key steps](image-url)

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With this new information and new synthetic scheme, I set forth to synthesize target product 269. Alkylation of 1,3-dithiane with CD₃I followed by ethylene oxide ring opening smoothly a 271 in 84% yield (Scheme 59). The alcohol 271 was transformed into the nitrile 274 after two steps. The deprotection of 274 to 275 with I₂ and NaHCO₃ resulted in a 77% yield.³¹⁴ The reaction of 275 with ¹⁵N-labeled ammonia and ¹⁵N-labeled hydroxylamine-O-sulfonic acid gave diazirine 276 in 18% yield. When the acylation procedure was tried with 276, the reaction did not work. Eventually it was discovered that the unlabeled version probably has a slight impurity of DMSO from the previous reaction. When a small amount of DMSO was added to pure 276 and subjected to the acylation procedure, it gave compound 277 in 74% yield. Finally, the ethyl ester was deprotected used KOH in EtOH to give finally compound 269 in 90% yield. The NMR outcome was very promising. Work done by the Malcolmson and Warren labs reveals that 269 has a $T_1 = 5.8$ min and a $T_S = 23$ min. The singlet lifetime is nearly as long at that seen in N₂O ($T_S = 26$ min),²⁷⁵ but diazirine is the much more useful moiety.

![Chemical structures](image_url)

a) BuLi, CD₃I, 0 °C; b) BuLi, ethylene oxide, −15 °C (84% over 2 steps); c) TsCl, pyridine, 0 °C; d) NaCN, DMSO, 70 °C (83% over 2 steps); e) I₂, NaCO₃ (77%); f) ¹⁵NH₂OH, 0 °C; g) ¹⁵NH₂OSO₂H,
MeOH, 0 °C; h) I₂, Et₃N, MeOH, 0 °C (18% over 3 steps); i) KH, (EtO)₂CO, THF/DMSO (74%); j) KOH, EtOH (90%).

Scheme 59: Complete synthesis of isotopically labeled trideuteromethyl-¹⁵N₂-diazirine

3.5 Synthesis of biologically relevant diazirines

With the proof-of-concept for the singlet state hyperpolarization of ²⁶⁹ established, the future of hyperpolarizable ¹⁵N₂-diazirines will be in their application to MRI. Here, it is important that ¹⁵N₂-diazirines be installed on any compound of interest. The development of diazirine-based bioconjugation tools would expand the scope of hyperpolarization exponentially.³¹⁵-³¹⁶ Diazirine-containing amino acid derivatives could be used in a similar way.²⁹³ To examine the scope of this hyperpolarization method for application in chemical biology and clinical use, diazirine-containing bioconjugation tools and amino acids were explored.

3.5.1 Synthesis of accessible diazirine-based tags for bioconjugation

Diazirine-based compounds for bioconjugation with selected functional groups were pursued. First, tosylate ²⁵⁹ was reacted with NaN₃ in DMSO in 85% yield to give azide ²⁷⁸, as azide is one of the most commonly used biorthogonal handles in chemical biology.⁶⁹-⁷⁰, ⁷³-⁷⁴, ⁷⁷-⁸⁰ Azide was reduced by a Staudinger reaction to give amine ²⁷⁹; this can be used to form amides with biologically active compounds containing exposed carboxylic acid functional groups. Nitrile ²⁶⁵ was hydrolyzed to carboxylic acid ²⁸⁰, which can also be used to form amides with biologically active compounds containing a
free NH group. To gauge the efficiency of this type of reaction 280 was coupled to
dibenzylamine in 65% yield to form 281.

![Scheme 60: Synthesis of diazirine-containing bioconjugation tools](image)

3.5.2 Synthesis of diazirine-containing amino acid derivatives

![Scheme 61: Synthesis of diazirine-containing amino acid derivatives](image)

Diazirine-labeled amino acids were targeted. From previous experience it is
known that the photo-methionine is not a good candidate for hyperpolarization
experiments. However, slightly different functional groups can make a big difference.
Tosylate 259 could not be used to alkylate protected glycine 282. Yet alkylation of 282 with iodide 258 was successful. Eventually, a methyl ester derivative 284 and a primary amide derivative 286 were synthesized (Scheme 61).

![Scheme 62: Synthesis of diazirine-containing Michael acceptors](image)

Michael acceptors which could be used with 282 were considered in the synthesis of glutamic acid derivatives. First, two separate Michael acceptors were prepared. 287 was prepared from 268 by a tandem Mannich-decarboxylation-elimination reaction in 57% yield (Scheme 62).\textsuperscript{317} Diethylmalonate was alkylated with 259.\textsuperscript{318} The product was partially hydrolyzed and subjected to the Mannich-decarboxylation-elimination reaction to give 288 in 41% overall yield.

![Scheme 63: First step in diazirine-labeled glutamic acid derivatives](image)

For glutamic acid derivatives, Michael acceptors 287–288 were reacted with protected glycine 282 under phase-transfer conditions.\textsuperscript{319} Electrophile 287 reacted to
give product 289 in 99% yield and 1:1 dr. This is a good first-step in the synthesis of diazirine-based glutamic acid derivatives.

**3.6 Conclusion**

In an interesting collaborative project, theoretical physics, organometallics, and organic synthesis have come together to demonstrate the combined potency of single state hyperpolarization with $^{15}\text{N}_2$-labeled diazirines. The model compound exhibits a signal lifetime greater than most PET isotopes and this signal is observable even after 1 hour. Although not all diazirines are amenable to singlet state hyperpolarization, the hope is that one day many will be. Some biologically relevant diazirine-containing molecules have been synthesized here.

Until now, SABRE-SHEATH had not been used to induce singlet state hyperpolarization. Additionally, diazirines-based photoaffinity tags have never before been demonstrated to be a carrier of hyperpolarization, thereby providing a potential use for these already well-appreciated moieties. I have discovered and synthesized an $^{15}\text{N}_2$-diazirine which can perform the desired single state hyperpolarization. This synthesis was done with nearly no theoretical or empirical basis to aid in my efforts towards this goal. To the best of my knowledge, this is the first asymmetric deuterium labeling of a ketone and the first $^{15}\text{N}_2$-labeling of a diazirine.
3.7 Supplemental information

3.7.1 General information

Glassware and stir bars were dried in an oven at 140 °C for at least 12 h and then cooled in a desiccator cabinet over Drierite prior to use. Plastic syringes or glass pipets were used to transfer liquid reagents. Unless otherwise noted, reactions were performed without exclusion of air or moisture. Unless otherwise stated, all reagents and solvents were used as received from commercial sources. \( n \)-BuLi was titrated using 1,3-diphenyl-2-propanone tosylhydrazone directly before use.\(^{144}\) mCPBA was purified by the same method as Schwatz and Blumbergs.\(^{320}\) CD\(_3\)I was distilled under N\(_2\) directly before use.\(^{15}\)N-labeled HAOSA (\( ^{15} \)NH\(_2\)OSO\(_3\)H) was synthesized from \( ^{15} \)N-labeled hydroxylamine hydrochloride and chlorosulfonic acid directly before use.\(^{321}\) Anhydrous toluene, THF, Et\(_2\)O, and DCM were obtained from a DriSolve purification when necessary. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to KMnO\(_4\) stain. Organic solutions were concentrated \textit{in vacuo} using a rotary evaporator. Column chromatography was performed with silica gel (60 Å, standard grade). Nuclear magnetic resonance spectra were recorded at ambient temperature (unless otherwise stated) at 400 MHz or 500 MHz. All values for proton chemical shifts are reported in parts per million (\( \delta \)) and are referenced to the residual protium in relevant deuterated
solvent (δ 7.26 for CDCl$_3$, δ 3.31 for CD$_3$OD, and δ 2.50 for (CD$_3$)$_2$SO). All values for carbon chemical shifts are reported in parts per million (δ) and are referenced to the carbon resonances in relevant deuterated solvent (δ 77.0 for CDCl$_3$ and δ 49.0 for CD$_3$OD). Infrared spectroscopic data are reported in wavenumbers (cm$^{-1}$) and only selected peaks are reported. High-resolution mass spectra were obtained using a liquid chromatography-electrospray ionization and Time-of-flight mass spectrometer. Low-resolution mass spectra were obtained using single quadruple gas chromatography-mass spectrometer.

### 3.7.2 Experimental procedures and characterization data

2-((tert-Butyldimethylsilyl)oxy)-1-(4’-methoxyphenyl)ethan-1-one (255). To a stirring solution of 4’-methoxyacetophenone (3.00 g, 20 mmol, 1.0 equiv) and TBSCl (3.92 g, 26 mmol, 1.3 equiv) in THF (60 mL) under nitrogen at −78 °C was added solid KH (3.21 g, 80 mmol, 4.0 equiv, prepared by washing 30 wt % KH dispersed in mineral oil with pentanes) in one portion. The reaction was slowly warmed to room temperature over 15 h then heated to reflux for another 24 h. The reaction was cooled to room temperature then filtered through Celite and washed with hexanes (200 mL), and the filtrate concentrated in vacuo. Kugelrohr distillation (0.5 Torr) of the crude material provided the intermediate as a colorless oil that was subsequently added to a stirring mixture of NaH$_2$PO$_4$ (3.09 g, 25.72 mmol, 1.29 equiv) and hexanes (60 mL) under nitrogen at −15 °C. After stirring for 10 min, solid mCPBA (2.13 g, 14.15 mmol, 0.71
equiv) was added in one portion and the resulting mixture slowly warmed to room temperature over 24 h. The reaction was diluted with hexanes and filtered. The filtrate was washed with a half saturated aqueous solution of Na$_2$S$_2$O$_3$ (50 mL), a solution of aqueous Na$_2$HPO$_4$ (2 × 50 mL), brine (50 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated *in vacuo*. The crude residue was purified by column chromatography (2% ethyl acetate–hexanes to 10% ethyl acetate–hexanes) to give 255 as a clear liquid (2.09 g, 37%). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.93 (d, $J = 9.1$ Hz, 2H), 6.93 (d, $J = 9.1$ Hz, 2H), 4.86 (s, 2H), 3.87 (s, 3H), 0.93 (s, 9H), 0.12 (s, 6H).

**2-(3'-Methyl-3'H-diazirin-3'-yl)ethan-1-ol (253).** A saturated solution of aqueous ammonium hydroxide (25 mL, 450 mmol, 9.0 equiv) was added to 4-hydroxy-2-butanone (4.41 g, 50 mmol, 1.0 equiv) at 0 °C. After stirring for 10 min, solid hydroxylamine-O-sulfonic acid (5.00 g, 44 mmol, 0.88 equiv) was added in portions over the course of 30 min. After stirring for an additional 1 h, the reaction was warmed to room temperature and MeOH (150 mL) was added. The resulting suspension was filtered and the filtrate concentrated *in vacuo* until the amount of remaining liquid was approximately 50 mL. The remaining liquid was placed in a 0 °C ice bath and the pH adjusted to 9 with Et$_3$N (about 1 mL). Solid I$_2$ was slowly added to the reaction until the solution was consistently brown due to excess I$_2$. From here, the solution was warmed and allowed to stir for 30 min. Brine (100 mL) was added to the reaction and the resulting solution extracted with Et$_2$O (2 × 50 mL). The Et$_2$O layers were combined and
washed with a saturated aqueous solution of Na₂S₂O₅ (25 mL), dilute HCl (2 × 25 mL), a saturated aqueous solution of NaHCO₃ (25 mL), and brine (25 mL). The Et₂O layer was dried over MgSO₄, filtered, and the filtrate concentrated in vacuo to give 253 as a yellow liquid (1.39 g, 34%). R₆ = 0.43 (5% methanol–dichloromethane); ¹H NMR (400 MHz, CDCl₃): δ 3.54 (t, J = 6.3 Hz, 2H), 1.64 (t, J = 6.3 Hz, 2H), 1.42 (s, br, 1H), 1.07 (s, 3H); FTIR (neat), cm⁻¹ 3342, 2927, 1385, 1049, 1013. These data are consistent with published spectra.

3-(2'-Iodoethyl)-3-methyl-3H-diazirine (258). To a stirring solution of I₂ (3.05 g, 12 mmol, 1.2 equiv), PPh₃ (3.15 g, 12 mmol, 1.2 equiv), and imidazole (1.63 g, 24 mmol, 2.4 equiv) in DCM (30 mL) under nitrogen at 0 °C was added a solution of 253 (1.00 g, 10 mmol, 1.0 equiv) in DCM (10 mL) dropwise over 10 min. After 15 min, the reaction was warmed to room temperature and stirred for an additional 1.5 h. Then the reaction was quenched with MeOH (2 mL), then H₂O (2 mL), and the DCM evaporated in vacuo. To the residue was added H₂O (20 mL) and the result extracted with hexanes (4 × 40 mL). The hexanes layers were combined, washed with a dilute aqueous solution of HCl (2 × 25 mL), a saturated aqueous solution of NaHCO₃ (40 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude material was passed through a short plug of silica to give 258 as a slightly orange liquid (0.89 g, 42%). ¹H NMR (400 MHz, CDCl₃): δ 2.95 (t, J = 7.6 Hz, 2H), 2.03 (t, J = 7.6 Hz, 2H), 1.08 (s, 3H). These data are consistent with published spectra.
2-(3’-Methyl-3’H-diazirin-3’-yl)ethyl 4-methylbenzenesulfonate (259).\textsuperscript{322} To a stirring solution of 253 (0.50 g, 5.0 mmol, 1.0 equiv) in pyridine (4 mL) at 0 °C was added TsCl (1.00 g, 5.25 mmol, 1.05 equiv) portionwise over 10 min. The reaction was kept stirring for an additional 2 h then placed in a −20 °C freezer overnight. The reaction was then poured onto ice (30 g) and a concentrated solution of aqueous HCl (7.5 mL) and the result extracted with Et\textsubscript{2}O (20 mL). The Et\textsubscript{2}O layer was washed with a dilute aqueous solution of HCl (10 mL), a dilute aqueous solution of ice cold NaOH (10 mL), then brine (5 mL). The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and the filtrate concentrated \textit{in vacuo} to give 259 as a yellow solid (1.14 g, 90%). R\textsubscript{f} = 0.37 (25% ethyl acetate–hexanes); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.82 (d, J = 8.3 Hz, 2H), 7.38–7.35 (m, 2H), 3.95 (t, J = 6.4 Hz, 2H), 2.46 (s, 3H), 1.67 (t, J = 6.4 Hz, 2H), 1.00 (s, 3H); FTIR (neat), 1354, 1173, 900, 756, 661, 552. These data are consistent with published spectra.\textsuperscript{312,322}

2-Methyl-1-(2’-(3”-methyl-3”H-diazirin-3”-yl)ethyl)piperidine (260).\textsuperscript{325} A solution of 259 (203 mg, 0.8 mmol, 1.0 equiv) and 2-methylpiperidine (141 μL, 1.2 mmol, 1.5 equiv) in DMF (1.6 mL) was heated to 82 °C for 20 h. The reaction was then cooled to room temperature and diluted with Et\textsubscript{2}O (30 mL). The organic layer was washed with a saturated aqueous solution of NaOH (10 mL, 1.5%), brine (2 × 10 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and the filtrate concentrated \textit{in vacuo}. The crude material was purified by column chromatography (25% ethyl acetate–hexanes) to give 260 as a yellow liquid

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(65.4 mg, 45%). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 55.6, 51.8, 48.2, 34.5, 30.5, 26.0, 24.9, 23.8, 19.9, 18.8; FTIR (thin film), cm$^{-1}$ 2930, 2856, 1449, 1375.

3-Methyl-1-(2'-{(3''-methyl-3''H-diazirin-3''-yl)ethyl)piperidine  (261). A solution of 259 (203 mg, 0.8 mmol, 1.0 equiv) and 3-methylpiperidine (141 $\mu$L, 1.2 mmol, 1.5 equiv) in DMF (1.6 mL) was heated to 82 °C for 20 h. The reaction was then cooled to room temperature and diluted with Et$_2$O (30 mL). The organic layer was washed with a saturated aqueous solution of NaOH (10 mL, 1.5%), brine (2 $\times$ 10 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography (25% ethyl acetate–hexanes) to give 261 as a yellow liquid (78.7 mg, 45%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.76–2.67 (m, 2H), 2.20 (t, $J$ = 7.9 Hz, 2H), 1.79–1.43 (m, 9H), 1.00 (s, 3H), 0.82 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 61.9, 53.8, 53.2, 32.9, 32.0, 31.1, 25.4, 24.9, 19.9, 19.7; FTIR (thin film), cm$^{-1}$ 2927, 2853, 2764, 1458.

Methyl (2'-{(3''-methyl-3''H-diazirin-3''-yl)ethyl)-L-prolinate  (262). A solution of 259 (203 mg, 0.8 mmol, 1.0 equiv), Et$_3$N (220 $\mu$L, 1.6 mmol, 2.0 equiv), and methyl L-prolinate hydrochloride (199 mg, 1.2 mmol, 1.5 equiv) in DMF (1.6 mL) was heated to 82 °C for 4 h. The reaction was then cooled to room temperature and diluted with Et$_2$O (30 mL). The organic layer was washed with a saturated aqueous solution of NaOH (10 mL, 1.5%), brine (2 $\times$ 10 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography (25% ethyl acetate–hexanes).
hexanes) to give 262 as a yellow liquid (34.2 mg, 20%). $^1$H NMR (400 MHz, CDCl$_3$): δ 3.71 (s, 3H), 3.14–3.05 (m, 2H), 2.65–2.57 (m, 1H), 2.32–2.24 (m, 2H), 2.13–2.02 (m, 1H), 1.95–1.73 (m, 3H), 1.51 (t, $J = 7.8$ Hz, 2H), 1.00 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 174.4, 65.8, 53.1, 51.7, 49.3, 33.6, 29.2, 24.7, 23.1, 19.7; FTIR (thin film), cm$^{-1}$ 2952, 1732, 1196, 1169.

3-Methyl-3-(2′-(propylthio)ethyl)-3H-diazirine (263). A mixture of 259 (102 mg, 0.4 mmol, 1.0 equiv), propanethiol (72 μL, 0.8 mmol, 2.0 equiv), and K$_2$CO$_3$ (82.9 mg, 0.6 mmol, 1.5 equiv) in CHCl$_3$ (1 mL) was heated to 60 °C for 48 h. The reaction was then cooled to room temperature and diluted with hexanes (50 mL), washed with an aqueous solution of HCl (2 × 5 mL, 0.5M), an aqueous solution of NaOH (2 × 5 mL, 0.5M), brine (10 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography (2% ethyl acetate–hexanes) to give 263 as a clear liquid (63.3 mg, 66%). $^1$H NMR (400 MHz, CDCl$_3$): δ 2.44 (t, $J = 7.3$ Hz, 2H), 2.33 (t, $J = 7.8$ Hz, 2H), 1.63–1.54 (m, 4H), 1.03 (s, 3H), 0.96 (t, $J = 7.3$ Hz, 3H).

3-Methyl-3-(2′-(propylsulfinyl)ethyl)-3H-diazirine (264). To a stirring solution of 263 (41.9 mg, 265 μmol, 1.0 equiv) in DCM (3 mL) was added mCPBA (50.2 mg, 291 μmol, 1.1 equiv). After 15 min the reaction was diluted with EtOAc (20 mL), washed with a saturated aqueous solution of Na$_2$S$_2$O$_3$ (5 mL), a saturated aqueous solution of NaHCO$_3$ (5 mL), brine (5 mL), dried over Na$_2$SO$_4$, filtered, and the filtrate concentrated in vacuo. To the residue was added Et$_2$O, causing a precipitation. The precipitate was
filtered, washed with Et₂O, and the filtrate concentrated in vacuo to give 264 as a clear oil (21.6 mg, 47%). Rƒ = 0.29 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 2.72–2.65 (m, 3H), 2.59–2.40 (m, 3H), 1.88–1.84 (m, 2H), 1.82–1.74 (m, 2H), 1.08 (s, 3H), 1.07 (t, J = 7.4 Hz, 3H); FTIR (thin film), cm⁻¹ 2966, 2933, 1039, 1020.

3-(3′-Methyl-3′H-diazirin-3′-yl)propanenitrile (265).³¹² To a solution of 36 (2.00 g, 7.86 mmol, 1.0 equiv) in DMSO (20 mL) was added NaCN (0.77 g, 15.73 mmol, 2.0 equiv). The solution was heated to 70 °C and stirred for 20 h. The reaction was then cooled to room temperature, diluted with H₂O (20 mL), and extracted with Et₂O (3 × 25 mL). The organic layers were combined, washed with aqueous solutions of NaOH (2 × 20 mL, 1M), brine (10 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo to give 265 as a light pink liquid (0.75 g, 87%). Rƒ = 0.35 (100% hexanes); ¹H NMR (400 MHz, CDCl₃): δ 2.23 (t, J = 7.5 Hz, 2H), 1.75 (t, J = 7.5 Hz, 2H), 1.12 (s, 3H). These data are consistent with published spectra.³¹²

Ethyl 2-cyano-3-(3′-methyl-3′H-diazirin-3′-yl)propanoate (266). To a stirring suspension of KH (0.61 g, 15.2 mmol, 2.0 equiv, prepared by washing 30 wt % KH dispersed in mineral oil with pentanes) and diethyl carbonate (1.84 mL, 15.2 mmol, 2.0 equiv) in THF (19 mL) was added a solution of 265 (0.83 g, 7.6 mmol, 1.0 equiv) in THF (3.5 mL) over a period of 5 min under nitrogen at 0 °C. After 1.5 h, the reaction was warmed to room temperature and stirred for an additional 18 h. The reaction was then quenched with a saturated aqueous solution of NH₄Cl (6 mL), poured onto water (10 mL),
mL), and the products extracted with EtOAc (3 × 25 mL). The organic layers were combined and washed with an aqueous solution of HCl (20 mL, 1M), a saturated aqueous solution of NaHCO₃ (20 mL), brine (2 × 20 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The resulting crude liquid was purified by column chromatography (10% ethyl acetate–hexanes to 20% ethyl acetate–hexanes) to give 266 as a light yellow liquid (1.20 g, 87%). R_f = 0.37 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 4.30 (q, J = 7.1 Hz, 2H), 3.37 (dd, J = 8.1, 6.5 Hz, 1H), 2.03 (dd, J = 15.0, 8.1 Hz, 1H), 2.01 (dd, J = 15.0, 6.5 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.17 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 164.8, 115.7, 63.2, 35.2, 32.5, 23.4, 19.5, 13.8; FTIR (neat), cm⁻¹ 2359, 1742, 1255, 1192, 1022.

**Ethyl 2-benzyl-2-cyano-3-(3'-methyl-3'H-diazirin-3'-yl)propanoate (267).** To a stirring solution of 266 (54.4 mg, 0.3 mmol, 1.0 equiv) and K₂CO₃ (82.0 mg, 0.6 mmol, 2.0 equiv) in DMF (2 mL) was added BnBr (45 μL, 0.375 mmol, 1.25 equiv) and the reaction heated to 60 °C for 30 min. Then the reaction was cooled to room temperature, diluted with water (5 mL) and the resulting solution extracted with hexanes (3 × 7 mL). The organic layers were combined, washed with brine (2 × 5 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude liquid was purified by column chromatography (5% ethyl acetate–hexanes) to give 267 as a clear oil (73.7 mg, 91%). R_f = 0.50 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.36–7.21 (m, 5H), 4.25 (dq, J = 10.7, 7.2 Hz, 1H), 4.19 (dq, J = 10.7, 7.2 Hz, 1H), 3.09 (d, J = 13.4 Hz, 1H), 3.02 (d, J
= 13.4 Hz, 1H), 2.05 (d, J = 14.8 Hz, 1H), 1.92 (d, J = 14.8 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.17 (s, 3H); FTIR (thin film), cm⁻¹ 2361, 1740, 1445, 1257, 1223, 702.

2-Cyano-3-(3'-methyl-3'H-diazirin-3'-yl)propanoic acid (268). To a solution of 266 (1.44 g, 7.9 mmol, 1.0 equiv) in EtOH (1 mL, 190 proof) was added a solution of KOH (667 mg, 11.9 mmol, 1.5 equiv) in EtOH (12 mL, 190 proof) and the reaction allowed to stir overnight. The reaction was then concentrated in vacuo to remove the EtOH and then diluted with H₂O (30 mL). The aqueous solution was washed with Et₂O (10 mL), acidified to pH = 1 with an aqueous solution of HCl (2M), and then extracted with Et₂O (3 × 10 mL). The organic layers from the extraction were combined, washed with brine (5 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo to give 268 as a thick yellow oil (1.12 g, 92%). \(^1\)H NMR (400 MHz, (CD₃)₂SO): δ 12.94 (s, br, 1H), 3.17 (t, J = 7.6 Hz, 1H), 1.80 (d, J = 7.6 Hz, 2H), 1.01 (s, 3H); FTIR (neat), cm⁻¹ 2936, 1698, 1293, 1262, 1187, 911.

2-(2’-(Methyl-\(d_3\))-1’,3’-dithian-2’-yl)ethan-1-ol (271). To a stirring solution of 1,3-dithiane (3.97 g, 33 mmol, 1.0 equiv) in THF (60 mL) was added \(n\)-BuLi (13.9 mL, 34.65 mmol, 1.05 equiv, 2.5M in hexanes) dropwise over 10 min under a nitrogen atmosphere at -40 °C. The reaction was slowly warmed to 0 °C and CD₃I was added dropwise over 10 min to it. The reaction stirred at 0 °C for 4 h, then at room temperature for 10 h, then at -15 °C for 45 min. \(n\)-BuLi (13.2 mL, 33 mmol, 1.0 equiv, 2.5M in hexanes) was added dropwise over 10 min to the reaction followed by a solution of ethylene
oxide (11 mL, ≈ 33 mmol, ≈ 1 equiv, 2.5–3.3M in THF). The reaction was allowed to warm to room temperature over 1.5 h, quenched with an aqueous solution of HCl (20 mL, 2M), and extracted with Et₂O (2 × 100 mL). The organic layers were combined, washed with a saturated aqueous solution of NaHCO₃ (100 mL), brine (2 × 50 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude residue was purified by column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) to give 271 as a light yellow liquid (4.97 g, 84%). Rf = 0.22 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 3.84 (t, J = 5.9 Hz, 2H), 2.99 (ddd, J = 14.7, 10.1, 3.0 Hz, 2H), 2.80 (ddd, J = 14.7, 6.6, 3.2 Hz, 2H), 2.29 (s, br, 1H), 2.27 (t, J = 5.9 Hz, 2H), 2.04 (dt, J = 14.0, 6.6, 3.0 Hz, 1H), 1.90 (dt, J = 14.0, 10.1, 3.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 58.6, 46.7, 42.5, 26.0 (2C), 24.4, (note that a carbon peak for CD₃ could not be found); FTIR (thin film), cm⁻¹: 3373, 2904, 1421, 1275, 1042, 905; HRMS-ESI (m/z) calcd. for C₇H₁₂D₃OS₂ ([M+H]⁺): 182.0747; found: 182.0743.

3-(2’-(Methyl-d₃)-1’,3’-dithian-2’-yl)propanenitrile (274).³¹², ³²⁵ To a solution of 271 (4.90 g, 27 mmol, 1.0 equiv) in pyridine (25 mL) was added solid TsCl (5.40 g, 28.35 mmol, 1.05 equiv) portionwise over 15 min 0 °C. The reaction was stirred at 0 °C for 2 h then placed in a −20 °C freezer for 24 h. Then the reaction was warmed to room temperature, added to a mixture of ice (200 g) and concentrated aqueous HCl (50 mL), then extracted with Et₂O (250 mL). The organic layer was then washed with cold aqueous HCl (2 × 50 mL, 0.5M), cold aqueous NaOH (50 mL, 0.5M), a concentrated
aqueous solution of NaHCO₃ (25 mL), brine (25 mL), and the solvent removed in vacuo. To the residue was added DMSO (60 mL) and NaCN (2.65 g, 54 mmol, 2.0 equiv) and the result was heated to 70 °C with stirring for 4 h. The reaction was then cooled to room temperature, diluted with H₂O (75 mL), and extracted with Et₂O (3 × 60 mL). The organic layers were combined, washed with aqueous NaOH (2 × 40 mL, 1M), brine (40 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude residue was purified by column chromatography (10% ethyl acetate–hexanes to 25% ethyl acetate–hexanes) to give 274 as a clear liquid (4.26 g, 83%). Rᵣ = 0.44 (25% ethyl acetate–hexanes);

₁H NMR (400 MHz, CDCl₃): δ 2.89 (ddd, J = 14.8, 10.2, 3.0 Hz, 2H), 2.77 (ddd, J = 14.8, 6.4, 3.3 Hz, 2H), 2.54 (t, J = 8.0 Hz, 2H), 2.33 (t, J = 8.0 Hz, 2H), 2.03 (dtt, J = 14.0, 6.4, 3.0 Hz, 1H), 1.89 (dtt, J = 14.0, 10.2, 3.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 119.5, 47.2, 36.3, 26.3 (2C), 24.4, 13.3, (note that a carbon peak for CD₃ could not be found); FTIR (neat), cm⁻¹ 2907, 2244, 1421, 1277, 1039, 908; HRMS-ESI (m/z) calcd. for C₈H₁₁D₃NS₂ ([M+H]⁺): 191.0750; found: 191.0751.

4-Oxopentanenitrile-5,5,5-d₃ (275).³¹⁴ To a solution of 274 (4.00 g, 21 mmol, 1.0 equiv) in acetone/H₂O (75 mL / 7.5 mL) at 0 °C was added solid NaHCO₃ (12.35 g, 147 mmol, 7 equiv) followed by I₂ (15.99 g, 63 mmol, 3.0 equiv) at 0 °C. After 2 h, the reaction was warmed to rt and an additional amount of I₂ (5.33 g, 21 mmol, 1.0 equiv) was added. After 1 h, the reaction was quenched with an aqueous solution of Na₂S₂O₅ (250 mL, 10%) and extracted with EtOAc (4 × 200 mL). The organic layers were combined and washed
with an aqueous solution of sodium thiosulfate (40 mL, 10%), an aqueous solution of NaOH (80 mL, 1M), brine (100 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated \textit{in vacuo}. The crude residue was purified by column chromatography (10% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) to give 275 as a light yellow liquid (1.62 g, 77%). \( R_f = 0.14 \) (25% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) 2.83 \((t, J = 7.2 \text{ Hz}, 2\text{H}), 2.58 \((t, J = 7.2 \text{ Hz}, 2\text{H}); \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 204.0, 118.8, 37.5, 27.8 (septet, \(^1J_{D-C} = 19.5 \text{ Hz} \), 10.5; FTIR (neat), cm\(^{-1}\) 2249, 1710, 1412, 1360, 1175; HRMS data could not be obtained. GCMS (m/z) calcd. for C₅H₄D₃NO (M): 100.1; found: 100.1.

\textbf{3-(3''-(Methyl-\textit{d}_3)-3'H-diazipirin-3''-yl-1',2''-\textit{15}N₂)propanenitrile (276).} To stirring neat 275 (1.502 g, 15 mmol, 1.0 equiv) at 0 °C was added an aqueous solution of \(^{15}\)NH₂OH (2.7 mL, 37.5 mmol, 2.5 equiv, 14M). After 10 min, to the preceding solution was added a solution of \(^{15}\)NH₂OSO₃H (1.71 g, 15 mmol, 1.0 equiv) in MeOH (9 mL) dropwise over 5 min. After 40 min, the reaction was warmed to room temperature. After stirring for 1 h at room temperature, the reaction was poured into MeOH (60 mL), filtered, and then most of the solvent removed \textit{in vacuo} (\( \approx 20 \text{ mL remaining} \)). This solution was cooled to 0 °C and Et₃N (1 mL) was added, followed by the portionwise addition of I₂ (until reaction is persistent brown). The reaction stirred for an additional 40 min at 0 °C then at rt for 30 min. Brine (50 mL) was added and the reaction extracted with Et₂O (2 × 25 mL). The organic layers were combined and washed with an aqueous solution of Na₂SO₃ (2 × 25 mL, 10%), an aqueous solution of HCl (2 × 10 mL, 0.25M), a
saturated aqueous solution of NaHCO₃ (2 × 10 mL), then brine (10 mL). The organic layer was dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude residue was purified by column chromatography (10% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) to give 276 as a clear liquid (303 mg, 18%). Rₓ = 0.50 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 2.23 (t, J = 7.5 Hz, 2H), 1.75 (t, J = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 118.4, 30.7, 24.2 (t, ¹J₁₅N‒C = 9.0 Hz), 18.4 (septet, ¹J₁D‒C = 19.2 Hz), 12.1; FTIR (neat), cm⁻¹ 2251, 1538, 1445, 1426, 755; HRMS data could not be obtained. Parent mass could not be seen by GCMS.

**Ethyl 2-cyano-3-(3′-(methyl-d₃)-3′H-diazirin-3′-yl-1′,2′⁻¹⁵N₃)propanoate (277).** To a stirring suspension of KH (90 mg, 2.25 mmol, 5.0 equiv, prepared by washing 30 wt % KH dispersed in mineral oil with pentanes) in anhydrous THF (0.5 mL) was added diethyl carbonate (0.22 mL, 1.8 mmol, 4.0 equiv) and DMSO (40 μL) under nitrogen. A solution of 276 (52 mg, 0.45 mmol, 1.0 equiv) in THF (0.5 mL) was then added dropwise to the reaction over 20 min and the resulting solution stirred overnight. Then the reaction was quenched with a saturated aqueous solution of NH₄Cl (2 mL), an aqueous solution of HCl (5 mL, 2M), and extracted with EtOAc (3 × 7.5 mL). The organic layers were combined, washed with brine (5 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude residue was purified by column chromatography (10% ethyl acetate–hexanes) to give 277 as a clear liquid (62 mg, 74%). Rₓ = 0.54 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 4.30 (q, J = 7.2 Hz, 2H), 3.37 (dd, J = 8.1,
2.04 (ddt, \(J = 15.0, 8.3, 3^J_{15N-H} = 0.6\) Hz, 1H), 1.99 (ddt, \(J = 15.0, 6.5, 3^J_{15N-H} = 0.6\) Hz, 1H), 1.34 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 164.8, 115.7, 63.2, 35.2, 32.5, 23.2\) (t, \(1^J_{15N-C} = 9.1\) Hz), 19.2–18.4 (m, CD\(_3\)), 11.7; FTIR (thin film), cm\(^{-1}\) 1745, 1262, 1213, 1030; HRMS-ESI (m/z) calcd. for C\(_8\)H\(_9\)D\(_3\)N\(_2\)O\(_2\) ([M+H]+): 187.1053; found: 187.1053.

2-Cyano-3-(3′-(methyl-ds)-3′H-diazirin-3′-yl-1′,2′-\(^{15}\)N\(_2\))propanoic acid (269).\(^{326}\) To a stirring solution of 278 (60.0 mg, 0.32 mmol, 1.0 equiv) in EtOH (1 mL, 190 proof) was added a solution of KOH (53.9 mg, 0.96 mmol, 3.0 equiv) in EtOH (1 mL, 190 proof) dropwise over 3 min. After 24 h, the reaction was concentrated in vacuo. To the residue was added H\(_2\)O (5 mL) and the solution washed with Et\(_2\)O (5 mL). The aqueous layer was acidified with an aqueous solution of HCl (5 mL, 2M) and extracted with Et\(_2\)O (3 \times 7.5 mL). The organic extracts were combined, dried over Na\(_2\)SO\(_4\), filtered, and the filtrate concentrated in vacuo to give 269 as a green oil (45.7 mg, 90%). \(R_f = 0.35\) (5% methanol–dichloromethane); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 8.22\) (s, br, 1H), 3.47 (dd, \(J = 8.3, 6.1\) Hz, 1H), 2.09 (ddt, \(J = 15.0, 8.3, 3^J_{15N-H} = 0.6\) Hz, 1H), 2.03 (ddt, \(J = 15.0, 6.1, 3^J_{15N-H} = 0.6\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 169.7, 115.2, 35.1, 32.6, 23.2\) (t, \(1^J_{15N-C} = 8.8\) Hz), 19.2–18.4 (m, CD\(_3\)); FTIR (thin film), cm\(^{-1}\) 3502 (br), 2924 (br), 2360, 1739, 1263 (br), 1216 (br); HRMS-ESI (m/z) calcd. for C\(_6\)H\(_3\)D\(_3\)N\(_2\)O\(_2\) ([M-H]): 157.0594; found: 157.0593.

3-(3′-Methyl-3′H-diazirin-3′-yl)ethylazide (278).\(^{312}\) NaN\(_3\) (1.52 g, 23.4 mmol, 2.0 equiv) was added to a solution of 259 (3.00 g, 11.7 mmol, 1.0 equiv) in DMSO (28 mL).
The resulting solution was heated to 50 °C and stirred for 2 h. The solution was then cooled to room temperature, diluted with H₂O (40 mL) and extracted with Et₂O (3 × 25 mL). The organic layers were combined and washed with an aqueous solution of NaOH (20 mL, 0.5M), another aqueous solution of NaOH (20 mL, 1.0M), brine (10mL), dried over Na₂SO₄, filtered, and the filtrated concentrated in vacuo to give 278 as a pale yellow liquid (1.24 g, 85%). Rₛ = 0.29 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 3.21 (t, J = 6.9 Hz, 2H), 1.62 (t, J = 6.9 Hz, 2H), 1.08 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 46.2, 33.9, 24.0, 19.8; FTIR (neat), cm⁻¹ 2094, 1452, 1387, 1350, 1265.

2-(3′-Methyl-3'H-diazirin-3'-yl)-ethylamine (279). To a stirring solution of 278 (606 mg, 4.8 mmol, 1.0 equiv) in THF/H₂O (9:1 17.1 mL) was added PPh₃ (1.44 g, 5.5 mmol, 1.15 equiv) at room temperature. After 4.25 h, the solution was acidified with an aqueous solution of HCl (10 mL, 2M) and the THF removed in vacuo. The remaining solution was washed with DCM (50 mL, then 2 × 25 mL), basified with an aqueous solution of NaOH (20 mL, 2M), and extracted with Et₂O (6 × 25 mL). The extraction layers were combined, dried over Na₂SO₄, filtered, and the filtrated concentrated in vacuo to give 279 as a pale yellow liquid (116 mg, 24%). Rₛ = 0.38 (10% methanol–5% triethylamine–dichloromethane on a triethylamine/dichloromethane-treated plate) ¹H NMR (400 MHz, CDCl₃): δ 2.57 (t, J = 6.9 Hz, 2H), 1.54 (t, J = 6.9 Hz, 2H), 1.28 (s, br, 2H), 1.04 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 37.8, 36.9, 24.5, 20.1; FTIR (neat) cm⁻¹ 2925, 2856, 1588, 1446, 1386, 837.
3-(3'-Methyl-3'H-diazirin-3'-yl)propanoic acid (280). A solution of 265 (535 mg, 5.8 mmol, 1.0 equiv) in 10% aqueous NaOH (10 mL) was refluxed under nitrogen for 4.5 h then cooled to room temperature. The reaction was diluted with H₂O (6 mL) and washed with hexanes (12 mL). The aqueous solution was then acidified with aqueous HCl (15 mL, 2M) and extracted with EtOAc (20 mL). The organic layer was then washed with brine (10 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. Kugelrohr distillation (0.5 Torr) of the crude material provided 280 as a colorless liquid (560 mg, 75%). Rₚ = 0.38 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 2.24 (t, J = 7.7 Hz, 2H), 1.72 (t, J = 7.7 Hz, 2H), 1.05 (s, 3H). These data are consistent with published spectra.³ⁱ²

N,N-Dibenzyl-3-(3'-methyl-3'H-diazirin-3'-yl)propanamide (281). To a stirring solution of 280 (38 mg, 0.3 mmol, 1.0 equiv) and dibenzylamine (69 μL, 0.36 mmol, 1.2 equiv) in DCM (0.5 mL) was added EDCI (104 mg, 0.54 mmol, 1.8 equiv) at room temperature. After 13 h, the reaction was quenched with aqueous HCl (5 mL, 1M) and extracted with EtOAc (3 × 5 mL). The organic layers were combined and washed with a saturated aqueous solution of NaHCO₃ (5 mL), brine (5 mL), dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. The crude material was purified by column chromatography (10% ethyl acetate–hexanes) to give 281 as a pale yellow oil (60 mg, 65%). Rₚ = 0.22 (10% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.40–7.12 (m,
10H), 4.61 (s, 2H), 4.41 (s, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.85 (t, J = 7.5 Hz, 2H), 1.03 (s, 3H); FTIR (thin film), cm\(^{-1}\) 2922, 1648, 1444, 1207, 731, 699.

**Methyl 2-(((diphenylmethylene)amino)-4-(3'-methyl-3'H-diazirin-3'-yl)butanoate (283).** A mixture of 258 (315 mg, 1.5 mmol, 1.0 equiv), 282 (380 mg, 1.5 mmol, 1.0 equiv), TEBAC (34.2 mg, 0.15 mmol, 0.1 equiv), and K\(_2\)CO\(_3\) (622 mg, 4.5 mmol, 3.0 equiv) in MeCN (2 mL) was stirred at room temperature for 1 h then heated to 50 °C. After 24 h, the reaction was cooled to room temperature, diluted with Et\(_2\)O (25 mL), washed with H\(_2\)O (2 × 10 mL), brine (10 mL), dried over Na\(_2\)SO\(_4\), filtered, and the filtrated concentrated in vacuo. The crude material was purified by column chromatography (1% ethyl acetate–hexanes to 50% ethyl acetate–hexanes on triethylamine/dichloromethane-treated silica gel) to give 283 as a yellow liquid (206 mg, 41%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.60–7.58 (m, 2H), 7.48–7.28 (6H), 7.14–7.11 (m, 2H), 3.99–3.95 (m, 1H), 1.82–1.76 (m, 2H), 1.38–1.30 (m, 1H), 1.25–1.17 (m, 1H), 0.95 (s, 3H).

**Methyl 2-amino-4-(3'-methyl-3'H-diazirin-3'-yl)butanoate hydrochloride (284).** A mixture of 283 (36 mg, 107 μmol, 1.0 equiv) in aqueous HCl (0.3 mL, 2M) and Et\(_2\)O (0.3 mL) was stirred vigorously at room temperature for 2 h. Then the reaction was diluted with H\(_2\)O (0.5 mL) and washed multiple times with Et\(_2\)O (0.5 mL at a time). The aqueous layer was concentrated in vacuo and the residue washed with Et\(_2\)O (5 mL). The residue was dissolved in MeOH (2 mL) then concentrated in vacuo to give 284 as a clear
film (20.6 mg, 93%). \(^1\)H NMR (400 MHz, CD\(_3\)OD): δ 4.88 (s, 3H), 4.04 (t, J = 6.5 Hz, 1H), 3.84 (s, 3H), 1.89–1.72 (m, 2H), 1.62–1.43 (m, 2H), 1.04 (s, 3H).

2-((3’-Methyl-3’H-diazirin-3’-yl)methyl)acrylonitrile (287).\(^{317}\) To stirring neat 268 (1.12 g, 7.31 mmol, 1.0 equiv) at room temperature was added a solution of Et\(_3\)NH (75.6 μL, 7.31 mmol, 1.0 equiv) in aqueous 37% formalin solution (60.5 μL, 8.04 mmol, 1.1 equiv) dropwise over 1 min. After stirring overnight, the reaction was diluted with H\(_2\)O (10 mL) and extracted with Et\(_2\)O (2 × 10 mL). The organic layers were combined, washed with an aqueous solution of HCl (2 × 5 mL, 1M), brine (10 mL), dried over Na\(_2\)SO\(_4\), filtered, and the filtrate concentrated in vacuo to produce 287 (0.51 g, 57%) as a yellow liquid. \(R_f = 0.46\) (25% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 6.01 (t, J = 0.8 Hz, 1H), 5.86 (t, J = 1.3 Hz, 1H), 2.24 (dd, J = 1.3, 0.8 Hz, 2H), 1.14 (s, 3H); FTIR (neat), cm\(^{-1}\) 2226, 1590, 1434, 1405, 949.

Methyl 4-cyano-2-((diphenylmethylene)amino)-5-(3’-methyl-3’H-diazirin-3’-yl)pentanoate (289).\(^{319}\) To a stirring mixture of 287 (81.1 mg, 0.67 mmol, 1.0 equiv), TEBAC (15.3 mg, 67 μmol, 0.1 equiv), K\(_2\)CO\(_3\) (92.6 mg, 0.67 mmol, 1.0 equiv), in MeCN (1 mL) was added solid 282 (170 mg, 0.67 mmol, 1.0 equiv) and the reaction heated to 50 °C for 2 h. Then the reaction was placed in a −20 °C freezer. After 24 h, the reaction was warmed to room temperature, diluted with H\(_2\)O (5 mL) and extracted with Et\(_2\)O (3 × 12 mL). The organic layers were combined, washed with brine (2 × 5 mL), dried over Na\(_2\)SO\(_4\), filtered, and the filtrate concentrated in vacuo to give 289 as a thick yellow oil.
(249 mg, 99%, 1.3:1 dr) $^1$H NMR (400 MHz, CDCl$_3$, mixture of two diastereomers (denoted major or minor)): δ 4.28 (dd, $J = 9.9, 3.6$ Hz, 1H, major), 4.18 (t, $J = 6.3$ Hz, 1H, minor), 3.72 (s, 3H, minor), 3.68 (s, 3H, major), 2.68–2.53 (s, 1H, major; s, 1H, minor), 1.12 (s, 3H, major), 1.10 (s, 3H, minor).
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Biography

Gerardo “Jerry” X. Ortiz Jr. was born April 25, 1988 in Northwest Indiana to Gerardo X. Ortiz Sr. and Martha Ortiz. He is the eldest brother to David M. Ortiz and Melanie M. Ortiz. After graduation from Merrillville High School in June 2006, Jerry went on to study chemistry at Purdue University Calumet (since renamed Purdue University Northwest). Here, he conducted research in science education with Dr. Alan K. Szeto and research in organic chemistry with Dr. Harold W. Pinnick. After graduating with a B.S. in Chemistry received with highest distinction in May 2010, Jerry went to work for Avery Dennison Corp. However, he soon joined the graduate school at Duke University to continue his education in chemistry. Once there, he affiliated with a recent faculty hire, Dr. Qiu Wang, and has subsequently conducted his dissertation research while in her lab. So far he has authored three journal articles: “Direct and Cost-efficient Hyperpolarization of Long-lived Nuclear Spin States on Universal $^{15}$N Molecular Tags” *Sci. Adv.* 2016; “One-Pot Synthesis of 3-Azido- and 3-Aminopiperidines by Intramolecular Cyclization of Unsaturated Amines” *J. Org. Chem.* 2014; and “An Efficient Synthesis of Fluorinated Azaheterocycles by Aminocyclization of Alkenes” *Org. Lett.* 2013. He has received the Burroughs Wellcome, C. R. Hauser, and the Dean’s Fellowships during his time at Duke.