Synthesis and Applications of Strained Heterocycles

by

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Doctoral Committee:

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Professor Alison R. H. Narayan
Professor Melanie S. Sanford
Professor Corey R. J. Stephenson
Dedication

To Marc, Laura, Megan, and Brett
Acknowledgements

My journey at the University of Michigan has been deeply influential in my academic career, my personal growth, and my relationships with friends and family. I vividly remember stepping foot onto campus in the summer of 2017, nervous about working in a large research group with graduate students. That apprehension melted away as I was welcomed by a group of people that were eager to teach and support me. Completing a REU fellowship in the Schindler group between my junior and senior year of college was a life-altering experience that showed me a glimpse of my future and left me awe-inspired about organic chemistry research. During this experience, I had the opportunity to work along-side Dr. Jacob Ludwig and Dr. Marc Becker who are two of the most accomplished and talented scientists I have had the fortune of working with. I am infinitely appreciative of Professor Corinna Schindler taking a chance on me then and continuing to support me over the last six years. I would also like to thank Professor Brian Coppola, participating in the REU experience and obtaining a graduate research fellowship would not have been possible without his support.

Returning to the University of Michigan as a graduate student in Corinna’s group, I was nervous to begin taking on projects completely on my own, but Corinna has always been relentlessly supportive and optimistic. I am grateful for the freedom and space she provided me with to explore new projects and grow as a researcher. This growth was a product of Corinna’s drive to build a research group not just of exceptional scientists, but with thoughtful people who are always willing to help. Her attention to mentorship and ensuring every member has what they need to succeed through building a culture of teamwork and positivity has been a vital component
to my success. I have witnessed the first class of graduate students depart from the group and I have now worked with students who will be defending in years to come. A steadfast component of the Schindler group over the years is Corinna’s work-etic, enthusiasm, and commitment to her students. I would like to thank Corinna for continually building me up and instilling a confidence in me that I will carry forward.

I would like to thank my entire dissertation committee: Professor Corey Stephenson, Professor Alison Narayan, and Professor Melanie Sanford. In the Schindler and Stephenson labs, we are all the lucky recipients of Corey’s hospitality at the various co-group gatherings throughout the year. I have fond memories of Corey at early morning football tailgates, always grilling up something special for summer barbeques, and graciously welcoming everyone for holiday parties. I would like to thank Professor Alison Narayan for allowing me the opportunity to rotate in her group during my first year, this opportunity taught me invaluable research skills. I would like to thank Professor Melanie Sanford for giving me the opportunity to pursue research in her group the summer before graduate school, her entire group provided me with support to ask questions and find my footing as a graduate student. Thank you all for your time and input over the course of my PhD.

In the Schindler group, I have been able to work with a diverse group of people with unique interests and skills, and from each one of them I have learned something. Dr. Ahlam Armaly taught me an abundant amount of information that I am deeply thankful for. There was never a time that Ahlam wouldn’t drop everything to help a coworker, her commitment to mentorship and kindness in lending her time to others inspired me to carry that forward. Her legacy and the lessons she passed along have been instrumental in the success of the Schindler group. I would also like to thank Dr. Rebecca Watson for helping me set-up my very first reaction in graduate school and still
being someone who I can reach out to for advice. Rebecca’s openness to discussing career options and helping me prepare for my future career was a valuable resource that contributed to my success. I would also like to thank Dr. Lara Cala Alvarez and Dr. Paul Riehl for being incredible teachers when it came to my research. I always knew I could count on them to provide creative and thoughtful solutions and I cannot imagine not having their input in my early days. Dr. Alistair Richardson has also been an incredible coworker and friend in the group. I am lucky to have gotten to know Alistair, Nikki, and Granger and our time spent outside of the lab are some of my fondest Ann Arbor memories. I would also like to thank Dr. James Collins for always being available to help and offering guidance throughout my PhD.

There is an endless list of things that I must acknowledge Emily Wearing for, especially her sincere and genuine friendship over the past four years. Being there to celebrate each other’s successes and lift each other up in the tougher moments, is everything you could ask for in a friendship. Our countless coffee breaks, weekend baking projects, travelling together to conferences, and many other moments will always stand out when I reflect on my graduate school experience. While we never directly worked together, I attribute a lot of my success to her friendship and support throughout graduate school.

One of the greatest experiences a graduate student can partake in is mentoring another student. I have been lucky enough to directly mentor three gifted students. I feel very fortunate to have gotten to mentor Manasi Anantpur, I could not have asked for a more capable and willing student to embark on a brand-new project with. Additionally, getting to work with Grace Sánchez-Santiago last summer reminded me of my own summer internship in the Schindler group. I would especially like to thank Grace for her willingness to dive in and tackle challenges with poise and a desire to learn. I would like to thank Elvis McFee who jumped into a very challenging project as
a first-year graduate student. Elvis’s tenacity to push forward and see success has been inspiring to witness and I look forward to the work that he will continue to do.

The Schindler laboratory is a stimulating and collaborative space that would not be the same without every individual member. I would like to thank previous and current lab members that I have directly worked with: Dr. Jacob Ludwig, Dr. Marc Becker, Dr. Emilia Groso, Dr. Hannah Vonesh, Dr. Alistair Richardson, Mario Gaviria, Troy Zehnder, Manasi Anantpur, Grace Sánchez-Santiago and Elvis McFee. The entire lab has been critical to my journey and I would like to thank all past members: Dr. Lara Cala Alvarez, Dr. J. Lizeth Gomez Lopez, Dr. Dan Nasrallah, Dr. Zhu Xu, Dr. Haley Albright, Dr. Ahlam Armaly, Dr. Paul Riehl, Dr. Jacob Ludwig, Dr. Rebecca Watson, Dr. Alex Golonka, Dr. Yvonne DePorre, Dr. James Annand, Dr. Christopher McAtee, Dr. Ashlee Davis, and Dr. Jonathon Ryan. I would like to thank all my current lab members, especially Mario Gaviria and Troy Zehnder for going through all the milestones together over the past five years. I would like to thank current members: Dr. Dan Steigerwald, Dr. Saswata Gupta, Dr. Yu-Cheng Yeh, Dr. Ben Niu, Scott Kim, Emily Wearing, Trenton Vogel, Dominique Blackmun, Cody Ng, Elvis McFee, Emily Traficante, Mike Gatazk, Stephen Chamness, Tim McClure, Evan Ferry, and Lilly Chiu.

Working with undergraduate students and participating in recruiting events, I was often asked about advice for incoming graduate students. After five years I can say the best advice is to be willing and open to new opportunities. This openness has led to some of my fondest research experiences, through unique and exciting collaborations. I owe a lot of gratitude to Dr. Jesse Sabatini of the U.S. Army Research Laboratory. I have learned a vast amount of science from Jesse and his colleagues. I would like to thank Jesse for always taking time to thoughtfully answer my (many) questions, persevere through difficult chemistry, and being a mentor to me. Jesse’s input
and advice on my journey throughout graduate school and my post-graduation plans provided me with the confidence to make big decisions. Working with Jesse showed me how important it is to be kind, supportive, and an advocate for those you work with as Jesse embodies all these attributes. I would like to thank Professor Jolene Reid at the University of British Columbia for her invaluable contributions to one of my first projects in graduate school. I would also like to thank Professor Stephen Craig and Jafer Vakil at Duke University for embarking on an exciting new collaboration. I have also had the pleasure of working with Professor Javier Read de Alaniz and Thi Tran at the University of California Santa Barbara.

The possibility to even attend graduate school wouldn’t have happened without the education and mentorship I received at Seattle University. As an incoming undergraduate student, I had no intention of pursuing a PhD or organic chemistry as my professional career. I am immensely appreciative of Professor Joe Langenhan for his guidance over the years. Working in Joe’s group ignited my interest in chemistry and Joe fostered that interest into a passion by giving me opportunities to continue learning both in his research group, in the classroom, and by pushing me to pursue opportunities I didn’t know existed. Joe and Sophie have continued to inspire me throughout my graduate career and I always look forward to our conversations about chemistry and life. I would also like to Professor PJ Alaimo who was instrumental in my pursuit of a summer internship and fellowship applications. PJ’s willingness to always chat about chemistry, cooking, and anything else has been a bright and lasting memory of my time at Seattle University. Additionally, I would like to acknowledge Professor Jenny Loertscher and Professor Doug Latch both of which were extremely supportive of my academic journey.

While I have travelled from Seattle to Michigan, my home has always been Alaska and my family there is the single most important consideration in my success and the completion of this
thesis. First and foremost, I would like to thank my mom, Laura, for being my biggest supporter, always believing in me, and cheering me on. I am the product of strong female role models and no one exhibits this better than my mom who has worked relentlessly for her daughters happiness and success. I am fortunate to have an older sister, Megan, who has helped me every step of the way. I have and always will continue to look up to Megan for her work-ethic and thoughtfulness. I would also like to thank my brother-in-law, Brett, for always bringing a smile to my face and cheering me on. Getting to spend time together with Megan and Brett in Seattle, Alaska, or Michigan is always a good time and these visits together motivated me to push through difficult times. I would also like to thank my entire family that has served as a constant source of inspiration especially my grandma, grandpa, Aunt Kathy, Uncle Dave, Uncle Chris, Ryan, Taylor, Marla, and Doug. Finally, I have been fortunate to journey through graduate school with an incredibly supportive partner. I would like to thank Marc for his constant and unwavering support. His composure, caring disposition, and willingness to help in any situation are just a few of the many wonderful qualities that I want to thank him for. Every accomplishment along the way has been a product of his love and support and getting to share those moments together have been invaluable.
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMMO</td>
<td>3-azidomethyl-3-methyl oxetane</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>BAMO</td>
<td>3,3-bis(azidomethyl) oxetane</td>
</tr>
<tr>
<td>BBB</td>
<td>blood brain barrier</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butylloxycarbonyl</td>
</tr>
<tr>
<td>bpz</td>
<td>2,2′-bipyrazine</td>
</tr>
<tr>
<td>bpy</td>
<td>2,2′-bipyridine</td>
</tr>
<tr>
<td>BTTN</td>
<td>butane-1,2,4-triolnitrate</td>
</tr>
<tr>
<td>CAM</td>
<td>cerium ammonium molybdate</td>
</tr>
<tr>
<td>CFL</td>
<td>compact fluorescent lamp</td>
</tr>
<tr>
<td>CNS MPO</td>
<td>central Nervous System Multiparameter Optimization Desirability</td>
</tr>
<tr>
<td>Cp*</td>
<td>pentamethycyclopentadiene</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadiene</td>
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<td>CPA</td>
<td>chiral phosphoric acid</td>
</tr>
<tr>
<td>4′-CF3-ppy</td>
<td>2-(4-(trifluoromethyl)phenyl)pyridine</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N′-Dicyclohexylcarbodiimide</td>
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<tr>
<td>DCE</td>
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<td>d.r.</td>
<td>diastereomer ratio</td>
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<td>DIBAL-H</td>
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<tr>
<td>DIPEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
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<td>Abbreviation</td>
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<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMPU</td>
<td>N,N’-dimethylpropyleneurea</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DSC</td>
<td>differential scanning calorimetry</td>
</tr>
<tr>
<td>dtbbpy</td>
<td>4,4'-di-tert-butyl-2,2'-bipyridine</td>
</tr>
<tr>
<td>EDC</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>E</td>
<td>electrophile</td>
</tr>
<tr>
<td>EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>half maximal effective concentration</td>
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<td>EDO</td>
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<td>electrostatic discharge sensitivity</td>
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<td>electron-withdrawing group</td>
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<td>FTs</td>
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<td>GP</td>
<td>general procedure</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HAT</td>
<td>hydrogen atom abstraction</td>
</tr>
<tr>
<td>HATU</td>
<td>1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate</td>
</tr>
<tr>
<td>HBD</td>
<td>hydrogen bonding</td>
</tr>
<tr>
<td>hCL&lt;sub&gt;int&lt;/sub&gt;</td>
<td>human liver microsomes intrinsic clearance</td>
</tr>
<tr>
<td>HFIP</td>
<td>hexafluorisopropanol</td>
</tr>
<tr>
<td>HG-II</td>
<td>Hoveyda-Grubbs 2nd generation catalyst</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HMX</td>
<td>high melting explosive (cyclotetramethylenetetranitramine)</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>I</td>
<td>intensity</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>half maximal inhibitory concentration</td>
</tr>
<tr>
<td>INT</td>
<td>intermediate</td>
</tr>
<tr>
<td>IS</td>
<td>impact sensitivity</td>
</tr>
<tr>
<td>I&lt;sub&gt;sp&lt;/sub&gt;</td>
<td>specific impulse</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>ISC</td>
<td>intersystem crossing</td>
</tr>
<tr>
<td>LA</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LED</td>
<td>light-emitting diode</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LLE</td>
<td>LipE; ligand lipophilic efficiency</td>
</tr>
<tr>
<td>M</td>
<td>metal</td>
</tr>
<tr>
<td>MAO-B</td>
<td>monoamine oxidase B</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>MDPD&lt;sup&gt;+&lt;/sup&gt;</td>
<td>1-methyl-4-phenyl-2,3-dihydropyridinium</td>
</tr>
<tr>
<td>MDR1/MDCK</td>
<td>Multidrug Resistance 1/Madin Darby Canine Kidney cells</td>
</tr>
<tr>
<td>MPP&lt;sup&gt;+&lt;/sup&gt;</td>
<td>1-methyl-4-phenylpyridinium</td>
</tr>
<tr>
<td>MPTP</td>
<td>1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>MW</td>
<td>molecular weight</td>
</tr>
<tr>
<td>NADPH</td>
<td>nicotinamide adenine dinucleotide phosphate</td>
</tr>
<tr>
<td>NENA</td>
<td>alkylnitrotoethylnitramine</td>
</tr>
<tr>
<td>NIMMO</td>
<td>3-nitratomethyl-3-methyloxetane</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>NMM</td>
<td>N-methylmorpholine</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
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<tr>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>P_{app}</td>
<td>apparent permeability</td>
</tr>
<tr>
<td>P_{cj}</td>
<td>Detonation pressure</td>
</tr>
<tr>
<td>PETN</td>
<td>pentaerythritol tetranitrate</td>
</tr>
<tr>
<td>p-TsCl</td>
<td>para-toluenesulfonyl chloride</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>Pd(OH)_2−C</td>
<td>palladium hydroxide on carbon</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on carbon</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>phen</td>
<td>1,10-phenanthroline</td>
</tr>
<tr>
<td>ppy</td>
<td>2-phenylpyridine</td>
</tr>
<tr>
<td>RDX</td>
<td>hexogen (1,3,5-trinitro-1,3,5-triazine)</td>
</tr>
<tr>
<td>r.r.</td>
<td>regioisomer ratio</td>
</tr>
<tr>
<td>RRCK</td>
<td>Ralph Russ canine kidney cells</td>
</tr>
<tr>
<td>ρ</td>
<td>density</td>
</tr>
<tr>
<td>S_0</td>
<td>singlet ground state</td>
</tr>
<tr>
<td>S_1</td>
<td>first excited singlet state</td>
</tr>
<tr>
<td>SAR</td>
<td>structure–activity relationship</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated</td>
</tr>
<tr>
<td>SCE</td>
<td>saturated calomel electrode</td>
</tr>
<tr>
<td>SFC</td>
<td>supercritical fluid chromatography</td>
</tr>
<tr>
<td>S</td>
<td>substrate</td>
</tr>
<tr>
<td>T_1</td>
<td>first triplet excited state</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>T_{dec}</td>
<td>decomposition temperature (onset)</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>T_{freeze}</td>
<td>freezing temperature (onset)</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>TLC</td>
<td>thin-layer chromatography</td>
</tr>
<tr>
<td>$T_m$</td>
<td>melting temperature (onset)</td>
</tr>
<tr>
<td>TMETN</td>
<td>metrioltrinitrate</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilane</td>
</tr>
<tr>
<td>TNCTB</td>
<td>1,1,3,3-tetranitrocyclobutane</td>
</tr>
<tr>
<td>TNAZ</td>
<td>1,3,3-trinitroazetidine</td>
</tr>
<tr>
<td>TNT</td>
<td>2,4,6-trinitrotoluene</td>
</tr>
<tr>
<td>TPSA</td>
<td>topological polar surface area</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl</td>
</tr>
<tr>
<td>TS</td>
<td>transition state</td>
</tr>
<tr>
<td>U.S.</td>
<td>United States</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>$V_{\text{det}}$</td>
<td>detonation velocity</td>
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<tr>
<td>vs.</td>
<td>versus</td>
</tr>
<tr>
<td>WA</td>
<td>Weinreb amide</td>
</tr>
<tr>
<td>$\Omega_{\text{CO}}$</td>
<td>CO oxygen balance</td>
</tr>
<tr>
<td>$\Omega_{\text{CO}_2}$</td>
<td>CO$_2$ oxygen balance</td>
</tr>
<tr>
<td>2CzPN</td>
<td>4,5-di (9H-carbazol-9-yl) phthalonitrile</td>
</tr>
<tr>
<td>5-HT2AR</td>
<td>5-HT2A receptor</td>
</tr>
<tr>
<td>$\Delta H^\circ$</td>
<td>molar enthalpy of formation</td>
</tr>
<tr>
<td>$\sigma_p$</td>
<td>Hammet sigma constant</td>
</tr>
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</table>
Abstract

Heterocyclic compounds account for greater than 50% of all known compounds including a majority of FDA approved drugs, nucleic acids, and energy sources.\textsuperscript{1} The introduction of a heteroatom in lieu of a carbon atom alters the structural properties and therefore the activity of the compound. Of these substitutions, oxygen and nitrogen atoms have been widely incorporated into valuable compounds across multiple industries: pharmaceuticals, agrichemicals, electronics, and energetic materials. This wide use of oxygen and nitrogen heterocycles stems from their ability to participate in hydrogen bonding, alter the pKa, influence geometry and function as Lewis or Brønsted bases. More specifically, small, strained rings offer unique properties and can influence binding, store energy to be later released, and modulate physicochemical properties (solubility, lipophilicity, etc.). Accessing heterocycles, especially four-membered heterocycles is therefore of importance to the aforementioned industries. While the high ring strain makes them advantageous, this also poses a significant synthetic challenge. This dissertation discusses synthetic strategies towards accessing tetrahydropyridines from amino acids as well as employing visible-light-photocatalysis to access four-membered heterocycles, oxetanes and azetidines, and investigations into applications as energetic materials.

The first chapter of this dissertation studies the reactivity of carbonyls and olefins to cyclize, generating six-membered tetrahydropyridine products. Herein, it is demonstrated that a simple Lewis acid, FeCl\textsubscript{3}, can catalyze the transformation of amino-acid-derived substrates. Furthermore, the inclusion of a strongly electron-withdrawing protecting group on the nitrogen atom attenuates the Lewis-basicity to avoid undesired Lewis-acid/base interactions.
The second chapter of this dissertation studies the use of visible light to promote a Paternò-Büchi reaction to generate oxetane products. This strategy is advantageous as it results in densely substituted oxetanes in one-step from commercially available starting materials without any pre-functionalization required. Triplet energy transfer from an iridium-based photocatalyst allows for the use of blue LEDs instead of UV light which has been traditionally used.

The third chapter of this dissertation studies the applications of azetidines as energetic materials. This work was done in collaboration with scientists at the U.S. Army Research Laboratory. Synthetic routes are evaluated to synthesize highly-substituted azetidines that function as nitration precursors. Systematic variation of the regio- and stereochemistry results in nitroazetidine analogs that exhibit varying energetic properties. Scalable and robust inter- and intramolecular *aza* Paternò-Büchi reactions ultimately facilitate the synthesis of various azetidine products in an efficient manner. Evaluation of the synthesized azetidines resulted in superior materials to state-of-the-art compounds. This work greatly expands our knowledge of azetidine-based energetic materials and offers synthetic strategies to access unique products of interest to a variety of fields.
Chapter 1 Synthesis of Chiral Tetrahydropyridines via Lewis Acid Catalysis


1.1 Introduction

1.1.1 Six-Membered Nitrogen Heterocycles in Pharmaceuticals

![Diagram of nitrogen heterocycles in FDA approved drugs.](image)

Figure 1.1: Overview of nitrogen heterocycles in FDA approved drugs.

Nitrogen heterocycles are a key building block in the design of pharmaceuticals. A study from Njardson and coworkers found that 59% of all small-molecule drugs approved by the FDA contained at least one nitrogen heterocycle.² More specifically, six-membered rings are the most prevalent ring size, accounting for approximately 43% of nitrogen rings in nitrogen-heterocycle-containing drugs (Figure 1.1). The structural variability of these six-membered rings can fluctuate
widely from multiple heteroatom-containing rings (morpholine), aromatic rings (pyridine), carbonyl-containing (quinolinone), fused ring systems (phenothiazine) to the simplest of ring structures, piperidine. This variety in steric, electronic and the plethora of synthetic methods for six-membered nitrogen rings explains the dominance of this structural motif in drug design (Figure 1.1).

Figure 1.2: Structural overview of pyridine, piperidine, structural isomers of tetrahydropyridine, and functionalization.

Piperidine is the most prevalent nitrogen heterocycle in FDA approved drugs. The saturated ring can be densely functionalized and is the core of many commonly used antihistamines. Heterocycles with an additional unit of unsaturation are referred to as tetrahydropyridines, for which three possible isomers exist: 1,2,3,6-tetrahydropyridine, 1,2,3,4-tetrahydropyridine, and 2,3,4,5-tetrahydropyridines. These heterocycles hold the potential to balance many of the benefits (potency, metabolic stability, solubility, cell permeability) of the completely saturated piperidine and the aromatic pyridine, two of the most commonly used heterocycles (Figure 1.2). Tetrahydropyridines can be incorporated to be later functionalized at the alkene to generate piperidine analogs for structure-activity relationship studies. Despite its similarity to piperidine, tetrahydropyridines are much less represented in drug molecules which is often attributed to their underrepresentation in early small-molecule screening libraries, due to their challenging synthesis.
Biological functions and pharmaceutical applications of tetrahydropyridines are primarily focused on neurological activity.\textsuperscript{5} A very simple tetrahydropyridine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, 1.1), was first synthesized in 1947 as a potential analgesic, but resulted in Parkinson-like symptoms.\textsuperscript{6} Upon the discovery of its parkinsonogenic effects, researchers studied its mechanism of action determining that in the brain MPTP is transformed by monoamine oxidase B (MAO-B) to the neurotoxin 1-methyl-4-phenylpyridinium (MPP\textsuperscript{+}, 1.3) (Figure 1.3).\textsuperscript{7} Due to MPTP’s ability to cross the blood-brain barrier, analogs of this compound have been studied for neurodegenerative diseases and other neurological disorders.\textsuperscript{5}

![Conversion of MPTP to MPP\textsuperscript{+} and aryl tetrahydropyridine containing pharmaceutical compounds.](image1.png)

Figure 1.3: Conversion of MPTP to MPP\textsuperscript{+} and aryl tetrahydropyridine containing pharmaceutical compounds.

Many tetrahydropyridine-based neuro-targeting drugs maintain the 1,4-disubstition and have aryl substitution off the alkene.\textsuperscript{5} Roxindole (1.5), a drug produced by Merck was originally developed for Schizophrenia, but had unexpectedly exhibited anxiolytic effects and functions as an antidepressant.\textsuperscript{8,9} There are non-central nervous system targeting tetrahydropyridines including antibacterial agents such as 1.4 developed by Pharmacia which is active against gram-positive pathogens.\textsuperscript{10} Tetrahydropyridines also have been explored for anti-tumor properties including the anti-tumor agent 1.6 developed by Abbott which inhibits farnesyltransferase (Figure 1.3).\textsuperscript{11}
Despite these promising compounds, the overall mechanism of action for tetrahydropyridine-containing drugs is often not well understood and the structure-activity relationships are continuing to be studied to design better drugs. A key study that progressed the discovery of tetrahydropyridine drugs was the generation of a bespoke library of tetrahydropyridine compounds by Roth and Ellman in 2022. A virtual docking study was completed with 75 million tetrahydropyridines and a model of the serotonin 5-HT2A receptor (5-HT2AR). Hits across the virtual screening platform led the researchers to synthesize seventeen distinct compounds in the laboratory and ultimately identified chiral tetrahydropyridines (1.7–1.9) that exhibited high potency as 5-HT2AR agonists without any psychedelic activities (Figure 1.4). This study showed the promise of tetrahydropyridines and the benefit of using a defined structure-based library.

Figure 1.4: Workflow of virtual tetrahydropyridine screening library and synthesized hit compounds 1.7–1.9.

While six-membered rings dominate the chemical space of nitrogen heterocycles in pharmaceuticals, tetrahydropyridines have yet to break through as a prominent scaffold. The structural similarity to piperidine and pyridine holds promise in the design of subsequent drugs (Figure 1.2). The permeability across the blood-brain barrier and targeting of key receptors for neurological conditions such as Parkinson’s disease, Alzheimer’s, and depression holds promise for the incorporation of more tetrahydropyridines. The advent of new synthetic methods allows for
easier access and better representation in small-molecule libraries and therefore identification in early-stage campaigns.

1.1.2 Traditional Methods for the Synthesis of Tetrahydropyridines

Figure 1.5 A Overview of olefin-olefin metathesis and carbonyl-olefin metathesis. B Stereoselective Cu-catalyzed substitution to form chiral tetrahydropyridine products (1.12).

The ability to efficiently access tetrahydropyridines is key to their incorporation in pharmaceutical compounds. While the more commonly used piperidine can be synthesized by nucleophilic substitution and reductive amination, the alkene of the tetrahydropyridine provides an alternative disconnection. Olefin-olefin metathesis is a powerful methodology for synthesizing six-membered, olefin-containing rings.\textsuperscript{12} The first example of nitrogen-heterocycles being accessed by olefin-olefin metathesis came from Grubbs and Fu in 1992 with the first-generation Grubbs catalyst and Schrock’s catalyst.\textsuperscript{13} While this methodology unlocked an efficient way of accessing nitrogen heterocycles, the presence of a nitrogen can be challenging due to its ability to coordinate metal catalysts and therefore inhibit the reaction (Figure 1.5A). Carbamate, sulfonamide, and benzyl groups are commonly used as $N$-protecting groups to increase the steric bulk around the nitrogen as well as lowering its Lewis basicity, which has allowed for several olefin-olefin metathesis methodologies to emerge over previous decades (Figure 1.5A).
Additionally, the in situ deactivation of the amine product can be achieved with the addition of Brønsted or Lewis acids.\textsuperscript{14} Chiral tetrahydropyridines (1.12) have been investigated via the development of an asymmetric Cu-catalyzed substitution of allylic bromides (1.10) and subsequent olefin-olefin metathesis (1.11) (Figure 1.5B).\textsuperscript{15}

\[ \text{Subset of examples:} \]

\[ \text{MeO} \equiv \text{CO}_2R + 2 \text{O} + 2 \text{H}_2\text{N} \rightarrow \text{CPA}^* \text{ (cat.)} \rightarrow \text{RO}_2\text{C} + \text{HN}^2 \]

Figure 1.6: Example of multi-component reaction with chiral phosphoric acid catalyst.

Multicomponent reactions are another common route to access densely substituted tetrahydropyridine products. These protocols involve three or more components reacting in a specific manor, assembling a complex scaffold efficiently. Commonly, the three components used are β-keto esters (1.13), aromatic aldehydes (1.14), and amines (1.15) (Figure 1.6). Simple catalysts such as Lewis acids (InCl\textsubscript{3}, BF\textsubscript{3}•Et\textsubscript{2}O), Brønsted acids (acetic acid, tartaric acid), iodine, and ionic compounds (tetrabutylammonium bromide, triethylammonium acetate) have been shown to be competent in these reactions.\textsuperscript{16} To date, a limited amount of stereo-controlled synthetic procedures have been developed, such as the use of a chiral phosphoric acid catalyst by Xufeng to access products in up to >99% ee (Figure 1.6).\textsuperscript{17} Overall, the operational simplicity of multi-component reactions have made them an attractive approach towards tetrahydropyridine scaffolds.
Olefin-containing six-membered rings are often associated with Diels-Alder reactions. The incorporation of a nitrogen results in an aza Diels-Alder reaction. The diene-imine [4+2]-cycloaddition is a direct method for assembling tetrahydropyridines (Figure 1.7A). Often this intermolecular reaction relies on a Lewis acid catalyst, such as BF$_3$•Et$_2$O, which activates the imine that can subsequently react with a plethora of diene partners.$^{18}$ Intramolecular variants have also been well-established, especially in alkaloid total synthesis.$^{19}$ Additionally, the use of chiral imines derived from amino acids results in diastereoselective aza Diels-Alder reactions.$^{20,21}$ Less developed is the use of asymmetric catalysts in aza Diels-Alder reactions, this is due to the challenge of competing Lewis acid-base pairing between the imine or amine product and the chiral Lewis acid catalyst. Additionally, the $E/Z$ isomerization of imines complicates the catalyst binding. Primarily, chiral ligands in combination with Lewis acid catalysts such as boron, zirconium, and copper-based reagents have been exploited in asymmetric approaches (Figure 1.7B).$^{18}$ Conversely, in work from Tong and coworkers a chiral amine (1.18) is used as a chiral auxiliary for the aza Diels-Alder reaction.
annulation to access tetrahydropyridine products (1.20) in good yield and enantioselectivity via an intermediate dienamine (1.19) (Figure 1.7C).\textsuperscript{22}

Figure 1.8: \textbf{A} Potential pyridine reduction products. \textbf{B} Activation of pyridine 1.21 to pyridinium 1.22 and reduction with NaBH\textsubscript{4}. \textbf{C} Chiral rhodium complex reduction of pyridine 1.25 to tetrahydropyridine 1.26 and over-reduction to piperidine 1.27. \textbf{D} Hydrosilylation reaction of pyridine to silylated tetrahydropyridine 1.29.

In some cases, tetrahydropyridines are synthesized from an existing ring such as pyridines. Partial reduction of pyridines has obvious challenges in the selectivity and ability of the product to be over-reduced (Figure 1.8A).\textsuperscript{23} The conversion of pyridine (1.21) to a pyridinium salt (1.22) often precedes the partial reduction to a tetrahydropyridine (1.24) with stoichiometric reductants such as NaBH\textsubscript{4} (Figure 1.8B).\textsuperscript{24} Some catalytic alternatives have been developed, such as the Rh-catalyzed reduction from Xiao, but suffers from strict substrate requirements as the same conditions that give rise to tetrahydropyridine 1.26 also result in overreduction to piperidine 1.27 when substitution is removed from the four-position (Figure 1.8C).\textsuperscript{25} Additionally, pyridines have
been used as substrates in hydrosilylation reactions, most often giving rise to dihydropyridines, but limited examples for tetrahydropyridine products (1.29) do exist (Figure 1.8D).  

1.1.3 Carbonyl-Olefin Metathesis

![Carbonyl-Olefin Metathesis Diagram](image)

Figure 1.9: Overview of traditional carbonyl and olefin reactivity and examples of carbonyl-olefin metathesis.

Traditional reactivity between carbonyls and olefins activated with a Lewis acid typically falls into Prins and carbonyl-ene reactivity. Alternatively, our group has used Lewis acid activation of carbonyls to engage in a metathesis reaction with an alkene, namely carbonyl-olefin metathesis (Figure 1.9). In this reaction, activation of the carbonyl via a Lewis acid catalyst occurs first which prompts a [2+2]-cycloaddition to generate an intermediate oxetane product that subsequently fragments to generate a new olefin-containing product (often cyclic) and a new carbonyl product. This type of reactivity has been applied to multiple synthetic transformations including ring-closing metathesis for five- and six-membered carbocycles, ring-opening metathesis, intermolecular cross-metathesis, polycyclic aromatic hydrocarbon synthesis, and transannular carbonyl-olefin metathesis (Figure 1.9).

Recently, carbonyl-olefin metathesis was applied to amine-containing substrates to generate five-membered 3-aryl-2,5-dihydropyrrole products. The Li group in 2016 applied the FeCl₃ carbonyl-olefin metathesis methodology to a variety of substrates, including tosyl- and
mesyl-protected prenyl amines. Ultimately, they determined super-stoichiometric amounts of allyl trimethylsilane were necessary to achieve product formation (Figure 1.10A).  

![Figure 1.10: Examples of amine-containing carbonyl-olefin metathesis with different catalyst systems to generate 3-aryl-2,5-dihydropyrrole products: A FeCl₃ catalyst and allyl TMS additive. B FeCl₃ catalyst. C AuCl₃ catalyst. D HCl catalyst in supramolecular host. E Iodine catalyst. F p-TsOH catalyst with solvent (HFIP) activation.]

In 2018, our group synthesized a series of chiral allyl amine substrates derived from amino acids to generate chiral 3-aryl-2,5-dihydropyrrole products. We anticipated the use of a Lewis acid catalyst with a Lewis basic nitrogen present could lead to unproductive binding. This work identified that the electronics of the nitrogen protecting group were crucial for productive catalysis. By using an electron-withdrawing sulfonamide protecting group (Ts) the electron density is altered, lessening its Lewis basicity, and allowing the Lewis acid catalyst to interact with the aryl ketone (Figure 1.10B). Optimization landed on FeCl₃ as the ideal Lewis acid catalyst. Notably, Brønsted acids such as para-toluenesulfonic acid and hydrochloric acid resulted in no conversion. Additionally, in our studies we found that additives like allyl trimethylsilane were not required for productive conversion. The substrate scope was elaborated to thirty-four examples showing variability at the aryl ketone portion, olefin portion, and stereogenic center. This work provided
key insights for our group and other groups in the role of the protecting groups and engaging nitrogen-containing substrates.

Other groups have investigated alternative catalyst species, substrates, and performed mechanistic investigations. While most work has focused on carbocycle formation there have been significant advances in engaging amine-containing substrates to generate nitrogen-containing heterocyclic products.\textsuperscript{28} Notably, other Lewis acid catalysts have been studied, the work of Li and Lin showed \( \text{AuCl}_3 \) could function similarly to \( \text{FeCl}_3 \), but in this case with lower catalyst loadings (Figure 1.10C).\textsuperscript{31}

Using Brønsted acids as catalysts has been investigated by the groups of Tiefenbacher and Nguyen. Tiefenbacher and coworkers in 2022 formed 3-aryl-2,5-dihydropyrroles by using HCl in combination with a supramolecular capsule (Figure 1.10D).\textsuperscript{32} This report also demonstrated multiple successful examples of a mesyl-protected nitrogen, a protecting group that is significantly more Lewis-basic than previous reports. Also in 2022, the Nguyen group broadly expanded the use of Brønsted acids by using more ubiquitous catalysts such as \( \text{para}-\text{toluenesulfonic acid} \) and triflic acid. In their initial investigations they discovered that hexafluoroisopropanol acts as a hydrogen bond donor to increase the efficiency of the Brønsted acid catalyst (Figure 1.10F).\textsuperscript{33} Later in 2022, the Nguyen group found that nitromethane is a suitable solvent for both Lewis acid and Brønsted acid catalysts for carbonyl-olefin metathesis.\textsuperscript{34}

In addition to their work in Brønsted acid catalysis, the Nguyen group studied iodonium promoted carbonyl-olefin metathesis. In 2019, they determined both \( \text{N}-\text{iodosuccinimide} \) and iodine could operate as catalysts for nitrogen-containing carbonyl-olefin metathesis (Figure 1.10E).\textsuperscript{35} These studies applied iodonium catalysis to tosyl-protected allyl amines to form 3-aryl-2,5-
dihydropyrroles and carbon backbones to form cyclopentenes, with later work investigating the mechanism.\textsuperscript{36}

![Figure 1.11: Examples of carbonyl-olefin metathesis to form six-membered nitrogen containing rings.](image)

While five-membered ring closure to form 3-aryl-2,5-dihydropyrrole products was proven successful, there are limited examples of six-membered nitrogen-containing rings being formed via carbonyl-olefin metathesis. Even for completely carbon-based ring-systems, the increase in ring size, from five to six, is a known challenge in carbonyl-olefin metathesis, likely due to the added flexibility of the substrates. Regarding tetrahydropyridines, there are examples in works from Lambert and Li. The Lambert group applied their hydrazine catalyst to form quinoline products in up to 93% yield (Figure 1.11).\textsuperscript{37} In 2016, Li demonstrated that stoichiometric loadings of FeCl\textsubscript{3} resulted in a low yield of a tetrahydropyridine product, demonstrating the distinct challenge in forming tetrahydropyridines under established carbonyl-olefin metathesis conditions (Figure 1.11).\textsuperscript{29}

1.2 Reaction Design and Optimization

Strategies like olefin-olefin metathesis, cycloadditions, annulations, multi-component reactions, and pyridine reductions provide differentially substituted tetrahydropyridines, but often require precious metal catalysts, expensive chiral ligands, and extended reaction times or have a limited substrate scope. A strategy using chiral pool reagents and an earth-abundant catalyst would be an advantage over existing methodologies.
The general challenges with engaging nitrogen-containing substrates in carbonyl-olefin metathesis is the potential for Lewis acid-base pairing between the catalyst and nitrogen. Previous work from our group showed that electron-withdrawing sulfonamide protecting groups can overcome this challenge. Another challenge in the synthesis of tetrahydropyridines is the larger ring size. Most carbonyl-olefin metathesis methodologies are only competent for five-membered ring formation and going from cyclopentene products to cyclohexene products required a distinct catalyst system. We anticipated new conditions would be required for tetrahydropyridines compared to the previously accessible 3-aryl-2,5-dihydropyrroles. A guiding design principle in this project was to take advantage of amino acids as chiral pool reagents in our synthesis of the metathesis substrates. The desired substrates could be successfully accessed via a 4-step protocol: protection of the \( N \)-terminus with a sulfonyl protecting group (1.31), then converting the \( C \)-terminus to the corresponding Weinreb amide (1.32), alkylation of the nitrogen with homoprenyl iodide (1.33), and Grignard addition into the Weinreb amide to generate aryl ketone products (1.34) (Figure 1.12).

![Figure 1.12: General route to access carbonyl-olefin metathesis substrates (1.34).](image)

The reaction conditions were evaluated by screening a small library of potential Lewis acid catalysts at elevated temperatures (Table 1.1). We first evaluated strong Lewis acids like AlCl\(_3\) and TiCl\(_4\) which gave poor yields of the desired tetrahydropyridine product 1.36 (entries 1–2). Conversely, SnCl\(_4\) and BCl\(_3\) both provided modest yields of tetrahydropyridine 1.36 in 43 and 48%
yields, respectively (entries 3–4). A continued increase in performance was observed with Lewis acids GaCl₃ and BF₃•OEt₂ with 58 and 52% yields, respectively (entries 5–6). We next evaluated iron (III) based Lewis acids, which have been successful in a wide variety of carbonyl-olefin metathesis reactions. There was a clear benefit of using FeCl₃ with 88% yield (entry 10). We moved to alter the conditions with FeCl₃ and investigated the reaction at ambient temperature, which lowered the yield to 68% yield (entry 8). We had anticipated the elevated temperatures could help overcome the larger ring size barrier. Next, lower catalyst loadings were tested with 30 mol% performing equally to 50 mol%, and 10 mol% performing considerably worse providing only 6% yield (entries 10–12). Finally, metal triflate salts Fe(OTf)₃ and Sc(OTf)₃ were evaluated resulting in 30 and 37% yields, respectively (entries 14–15).

Table 1.1: Screening of Lewis acid catalysts for conversion of 1.35 to tetrahydropyridine 1.36.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>mol %</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>AlCl₃</td>
<td>50</td>
<td>24</td>
<td>7</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>TiCl₄</td>
<td>50</td>
<td>24</td>
<td>&lt;5</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>SnCl₄</td>
<td>50</td>
<td>24</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>BCl₃</td>
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<td>24</td>
<td>48</td>
<td>49</td>
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<tr>
<td>5</td>
<td>GaCl₃</td>
<td>50</td>
<td>24</td>
<td>58</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>BF₃•OEt₂</td>
<td>50</td>
<td>24</td>
<td>52</td>
<td>95</td>
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<td>9</td>
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<td>10</td>
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<td>88</td>
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<tr>
<td>11</td>
<td>FeCl₃</td>
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<td>24</td>
<td>89</td>
<td>99</td>
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<tr>
<td>12</td>
<td>FeCl₃</td>
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<td>6</td>
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</tr>
<tr>
<td>13</td>
<td>FeCl₃</td>
<td>10</td>
<td>72</td>
<td>39</td>
<td>40</td>
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<tr>
<td>14</td>
<td>Fe(OTf)₃</td>
<td>50</td>
<td>24</td>
<td>30</td>
<td>91</td>
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<tr>
<td>15</td>
<td>Sc(OTf)₃</td>
<td>50</td>
<td>24</td>
<td>37</td>
<td>97</td>
</tr>
</tbody>
</table>

* Lewis acid added at 0 °C and allowed to warm to room temperature.

We were interested in the electronics of the sulfonamide motif and its potential effects on yield (Table 1.2). A series of glycine-derived substrates were synthesized with different protecting groups. An increase in yield was observed with the increase in the electron-withdrawing effect of the protecting group. The para-trifluoromethyl substrate 1.37 resulted in 84% yield where the
*para*-chloro substrate 1.38 had a slightly lower yield of 80% and the unsubstituted aryl sulfonamide substrate 1.39 provided 78% yield (entries 1–3). Accordingly, increasing the electron-donating capability hindered the reaction. *Para*-methyl substrate 1.40 reacted in 72% yield and *para*-methoxy substrate 1.41 only provided 47% yield (entries 4–5). Stirring the reaction of 1.41 twice as long did result in 78% yield, indicating the reaction is still viable with electron-donating groups, albeit slower (entry 6). This result contrasted with our previous work on 3-aryl-2,5-dihydropyrroles which required the electron-withdrawing group. Concluding the optimization, we determined the ideal conditions to be 30 mol% FeCl₃ in DCE at reflux for 24 h. The electron-withdrawing groups on the sulfonamide helped to accelerate the reaction, but were not necessary for productive reactivity.

Table 1.2: Effects of varying electronics of the sulfonamide protection group.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R</th>
<th>time (h)</th>
<th>σᵣ</th>
<th>yield (%)</th>
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<td>CF₃</td>
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<td>0.54</td>
<td>84</td>
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<tr>
<td>2</td>
<td>1.38</td>
<td>Cl</td>
<td>24</td>
<td>0.37</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>1.39</td>
<td>H</td>
<td>24</td>
<td>0.0</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>1.40</td>
<td>Me</td>
<td>24</td>
<td>−0.17</td>
<td>72</td>
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<tr>
<td>5</td>
<td>1.41</td>
<td>OMe</td>
<td>24</td>
<td>−0.27</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>1.41</td>
<td>OMe</td>
<td>48</td>
<td>−0.27</td>
<td>78</td>
</tr>
</tbody>
</table>
1.3 Reaction Scope and Synthetic Modifications

Table 1.3: Evaluation of alkene substitution in carbonyl-olefin metathesis reaction.

Next, we moved to study the scope of the metathesis reaction first evaluating the olefin portion (Table 1.3). A series of phenylalanine-derived substrates were synthesized and evaluated under the optimal conditions. In previous carbonyl-olefin metathesis reactions, including the work on 3-aryl-2,5-dihydropyrroles, both prenyl- and styrenyl-derived olefins were shown to be competent olefin partners.\(^\text{30}\) For the synthesis of tetrahydropyridines, the prenyl-derived olefins were superior (entry 1) and little to no reactivity was observed with styrenyl-substrates (entries 2 and 4, Table 1.3).
Next, we evaluated the aryl ketone portion and altered substitution at the alpha carbon. Alanine-derived substrates performed well with both para-chloro and para-CF$_3$ sulfonamide groups generating tetrahydropyridine products 1.50 and 1.51 in 80 and 99% yields, respectively. Substitution on the aromatic portion was well tolerated, para-substitution was successful for electron-donating and electron-withdrawing groups. Namely, the para-fluoro aryl ketone substrate resulted in 75% yield of tetrahydropyridine 1.56. Additionally, the para-methoxy substrate resulted in 56% yields of 1.57. Meta- and ortho-substitution were less tolerated with meta-methyl substrate providing 50% yield of 1.53. The ortho-methoxy substrate 1.58 was subjected and ultimately stoichiometric amounts of Lewis acid were required to provide 22% yield of 1.58. The thiophene aryl ketone could also be converted to product 1.61 in 57% yield. Unnatural amino-acid-
derived substrates were successful in the carbonyl-olefin metathesis reaction resulting in 60–71% yields for products \(1.59\), \(1.60\), and \(1.62\) (Figure 1.13).

To highlight the synthetic utility of this methodology we set out to demonstrate the deprotection of the sulfonamide to the free amine. Subjecting sulfonamide \(1.51\) to SmI\(_2\) deprotection conditions generated the free amine product \(1.63\). Due to its instability, it was immediately reacted with Boc\(_2\)O to form carbamate product \(1.64\) (Figure 1.14). This sequence demonstrated that the electron-withdrawing sulfonamide protecting group (F\(\text{Ts}\)) was not synthetically hindering, and that the free amine can be engaged in subsequent transformations.

1.4 Conclusion

In summary, a carbonyl-olefin metathesis reaction was developed that proceeds with FeCl\(_3\) as the optimal Lewis acid catalyst and electron-withdrawing sulfonamide protecting groups aiding the reactivity. A series of tetrahydropyridines were synthesized being derived from both natural and unnatural amino acids. This work builds upon our labs foundational work in carbonyl-olefin metathesis and overcomes previous limitations such as generating six-membered rings, reacting nitrogen-containing substrates, and using electron-donating groups on the sulfonamide protecting group. Overall, this work provides a unique platform for chiral tetrahydropyridines that relies on a cheap earth-abundant catalyst and chiral pool reagents. The reaction is operationally simple and efficiently assembles complex nitrogen-heterocycle products.
1.5 Experimental Section

1.5.1 General Information

General Laboratory Procedures. All moisture-sensitive reactions were performed under an atmosphere of nitrogen in flame-dried round bottom flasks, glass vials fitted with rubber septa and/or septa equipped screw caps, or sealed microwave vials. Stainless steel syringes were used to transfer air or moisture sensitive liquids. Flash chromatography was performed using silica gel Silia Flash® 40–63 micron (230–400 mesh) from Silicycle.

Materials and Instrumentation. All chemicals were purchased from Sigma-Aldrich, VWR, Oakwood or Acros and were used as received unless otherwise stated. Tetrahydrofuran, ether, toluene, and N,N-dimethylformamide were dried by being passed through columns of activated alumina. Proton Nuclear Magnetic Resonance NMR (¹H NMR) spectra and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Varian Unity Plus 400, Varian MR400, Varian vnmrs 500, Varian Inova 500, Varian Mercury 500, and Varian vnmrs 700 spectrometers. Chemical shifts for protons are reported in parts per million and are references to the NMR solvent peak (CDCl₃: δ 7.26 ppm, DMSO-d₆: δ 2.50 ppm, or CD₂Cl₂: δ 5.32 ppm). Chemical shifts for carbons are reported in parts per million and are referenced to the carbon resonances of the NMR solvent (CDCl₃: δ 77.16 ppm, DMSO-d₆: δ 39.52, or CD₂Cl₂: δ 53.84 ppm). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), and coupling constants in Hertz (Hz). Mass spectroscopic (MS) data was recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent Q-TOF HPLC-MS with ESI high resolution mass spectrometer. Infrared (IR) spectra were obtained using either an Avatar 360 FT-IR or Perkin Elmer Spectrum BX FT-IR spectrometer. IR data are represented as frequency of
absorption (cm\(^{-1}\)) and all compounds were collected neat. Supercritical fluid chromatography (SFC) was performed on a Waters SFC instrument with a Waters Investigator SFC System with a Chiralpack AD-H column (4.6 x 250 mm). Optical rotations were measured at room temperature in chloroform (c = 0.1), unless denoted otherwise, on a JASCO P-2000 digital polarimeter at 589 nm (D-line).

1.5.2 Experimental Procedures

General Procedure for Protected, Homoprenylated Secondary Amines (GP-1.1)

A round bottom flask equipped with a magnetic stir bar was charged with the para-substituted benzenesulfonyl chloride. The solid was suspended in a 30% ammonium hydroxide solution (0.1 M) and allowed to stir at room temperature for 16 hours. The reaction mixture was diluted with EtOAc, and aqueous hydrochloric acid (1 M) was added until the pH was less than 9, then the resultant layers were partitioned. The organic layer was collected, and the aqueous phase was extracted with EtOAc (3x). The organic layers were then combined, washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), and concentrated under reduced pressure which was carried forward without purification.

A round bottom flask equipped with a magnetic stir bar was charged with the sulfonamide and sealed under nitrogen and anhydrous DMF (0.4 M) was added via syringe. The reaction was cooled to 0 °C and sodium hydride (1.0 equiv.) was added and the reaction was left to stir at 0 °C for 30 minutes and then homoprenyl iodide was added and reaction was left to warm to room temperature for 16 hours. The reaction was quenched with deionized water, diluted with EtOAc, and the resultant layers were partitioned. The organic layer was collected, and the aqueous phase was
extracted with EtOAc (3x). The organic layers were then combined, washed with brine (3x), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography afforded the desired intermediate.

**N-(4-methylpent-3-en-1-yl)-4-(trifluoromethyl)benzenesulfonamide (1.37 INT):** Prepared according to GP-1.1 using 4-(trifluoromethyl)benzenesulfonyl chloride (1.0 g, 4.09 mmol, 1.0 equiv.), 30 wt% NH₄OH (40 mL, 0.1 M) with a reaction time of 16 h. Crude benzenesulfonamide obtained as white solid (920 mg, 99%). Then using benzenesulfonamide (920 mg, 4.09 mmol, 1.0 equiv.), sodium hydride (157 mg, 4.09 mmol, 1.0 equiv., 60% dispersion in mineral oil), homoprenyl iodide (858 g, 4.09 mmol, 1.0 equiv.) and DMF (10 mL) with a reaction time of 16 h. Purification by flash column chromatography (5–55% EtOAc/hexanes) afforded the pure compound as clear, faint yellow oil (507 mg, 40%). Spectral data was found to be in accordance with literature data.³⁰

![Structural formula for N-(4-methylpent-3-en-1-yl)-4-(trifluoromethyl)benzenesulfonamide](attachment:image)

**4-chloro-N-(4-methylpent-3-en-1-yl)benzenesulfonamide (1.38 INT):** Prepared according to GP-1.1 using 4- chlorobenzenesulfonyl chloride (2.01 g, 9.51 mmol, 1.00 equiv.), 30 wt% NH₄OH (95 mL, 0.1 M) with a reaction time of 16 h. Crude 4-chlorobenzenesulfonamide obtained as white solid (1.7976 g, 98%). Then using 4-chlorobenzenesulfonamide (1.76 g, 9.17 mmol, 1.00 equiv.), sodium hydride (369.7 mg, 9.65 mmol, 1.0 equiv., 60% dispersion in mineral oil), homoprenyl iodide (1.94 g, 9.25 mmol, 1.0 equiv.) and DMF (30 mL) with a reaction time of 16 h. Purification by flash column chromatography (3–50% EtOAc/hexanes) afforded the pure compound as white solid (901 mg, 34%). ¹H NMR (700 MHz, CDCl₃) δ 7.79 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 4.92 (t, J = 7.2 Hz, 1H), 4.39 (s, 1H), 2.97 (q, J = 6.5 Hz, 2H), 2.16 (q, J = 6.8 Hz, 2H), 1.68 (s, 3H), 1.57 (s, 3H); ¹³C NMR (176 MHz, CDCl₃) δ 139.2,
138.7, 136.2, 129.5, 128.7, 119.6, 77.3, 77.0, 43.1, 28.3, 25.9, 18.0; \textbf{IR} (cm$^{-1}$): 2970, 2915, 1585, 1475, 1450, 1338, 1276, 1199, 1156, 1091, 1013, 955, 916, 872, 826; \textbf{HRMS}: \textit{m/z} calculated for C$_{12}$H$_{16}$ClNO$_2$SNa$^+$ [M+Na]$^+$: 296.0482; found: 296.0481.

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

\textbf{N-(4-methylpent-3-en-1-yl)benzenesulfonamide (1.39 INT)}: Prepared according to GP-1.1 using benzenesulfonyl chloride (1.45 mL, 11.32 mmol, 1.00 equiv.), 30 wt\% NH$_4$OH (113 mL, 0.1 M) with a reaction time of 16 h. Crude benzenesulfonamide obtained as white solid (1.96 g, 99%). Then using benzenesulfonamide (1.94 g, 12.32 mmol, 1.00 equiv.), sodium hydride (411.4 mg, 10.73 mmol, 1.0 equiv., 60\% dispersion in mineral oil), homoprenyl iodide (2.13 g, 10.15 mmol, 1.0 equiv.) and DMF (30 mL) with a reaction time of 16 h. Purification by flash column chromatography (5–55\% EtOAc/hexanes) afforded the pure compound as clear, colorless oil (973 mg, 36\%). \textbf{1H NMR} (700 MHz, CDCl$_3$) \textit{δ} 7.86 (d, J = 7.8 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 4.92 (t, J = 7.3 Hz, 1H), 4.34 (s, 1H), 2.98 (q, J = 6.5 Hz, 2H), 2.15 (q, J = 6.9 Hz, 2H), 1.67 (s, 3H), 1.56 (s, 3H); \textbf{13C NMR} (176 MHz, CDCl$_3$) \textit{δ} 140.2, 136.0, 132.7, 129.2, 127.2, 119.8, 77.3, 77.2, 77.0, 43.1, 28.3, 25.9, 18.0; \textbf{IR} (cm$^{-1}$): 3346, 3251, 1553, 1447, 1331, 1311, 1180, 1158, 1091, 1071, 1025, 997, 904, 755; \textbf{HRMS}: \textit{m/z} calculated for C$_{12}$H$_{17}$NO$_2$SH$^+$ [M+H]$^+$: 240.1053; found: 240.1050.

\begin{center}
\includegraphics[width=0.2\textwidth]{image2}
\end{center}

\textbf{4-methyl-N-(4-methylpent-3-en-1-yl)benzenesulfonamide (1.40 INT)}: Prepared according to GP-1.1 using 4- methylbenzenesulfonyl chloride (2.00 g, 10.50 mmol, 1.00 equiv.), 30 wt\% NH$_4$OH (105 mL, 0.1 M) with a reaction time of 16 h. Crude 4-methylbenzenesulfonamide obtained as white solid (1.76 g, 98\%). Then using 4-methylbenzenesulfonamide (1.75 g, 10.22 mmol, 1.00 equiv.), sodium hydride (412.5 mg, 10.76 mmol, 1.0 equiv., 60\% dispersion in mineral oil), homoprenyl iodide (2.15 g, 10.22 mmol, 1.0 equiv.)
and DMF (30.0 mL) with a reaction time of 16 h. Purification by flash column chromatography (5–55% EtOAc/hexanes) afforded the pure compound as clear, colorless oil (956.9 mg, 36%). $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.74 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 4.91 (t, J = 7.2 Hz, 1H), 4.29 (t, J = 5.4 Hz, 1H), 2.95 (q, J = 6.6 Hz, 2H), 2.43 (s, 3H), 2.15 (q, J = 6.9 Hz, 2H), 1.67 (s, 3H), 1.56 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 143.5, 137.2, 135.9, 129.8, 127.3, 119.8, 77.3, 77.0, 43.1, 28.3, 25.9, 21.7, 18.0; IR (cm$^{-1}$): 3277, 2929, 1596, 1579, 1497, 1440, 1377, 1321, 1300, 1257, 1179, 1148, 1111, 1094, 1023, 935, 885, 832, 803; HRMS: m/z calculated for C$_{13}$H$_{19}$NO$_3$SNa$^+$ [M+Na]$^+$: 276.1029; found: 276.1025.

4-methoxy-N-(4-methylpent-3-en-1-yl)benzenesulfonamide (1.41 INT): Prepared according to GP-1.1 using 4-methoxybenzenesulfonyl chloride (1.0 g, 4.84 mmol, 1.0 equiv.), 30 wt% NH$_4$OH (47 mL, 0.1 M) with a reaction time of 16 h. Crude benzenesulfonamide obtained as white solid (800 mg, 88%). Then using benzenesulfonamide (800 mg, 4.27 mmol, 1.0 equiv.), sodium hydride (164 mg, 4.27 mmol, 1.0 equiv., 60% dispersion in mineral oil), homoprenyl iodide (898 g, 4.27 mmol, 1.0 equiv.) and DMF (11 mL) with a reaction time of 16 h. Purification by flash column chromatography (5–55% EtOAc/hexanes) afforded the pure compound as clear, faint yellow oil (507 mg, 40%). $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.79 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.92 (t, J = 7.2 Hz, 1H), 4.68 (t, J = 6.1 Hz, 1H), 3.86 (s, 3H), 2.91 (q, J = 6.7 Hz, 2H), 2.13 (q, J = 7.1 Hz, 2H), 1.65 (s, 3H), 1.54 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 162.7, 135.4, 131.5, 129.1, 119.7, 114.1, 55.5, 42.9, 28.1, 25.7, 17.8; IR (cm$^{-1}$): 3277, 2929, 1596, 1579, 1497, 1440, 1377, 1321, 1300, 1257, 1179, 1148, 1111, 1094, 1023, 935, 885, 832, 803; HRMS: m/z calculated for C$_{13}$H$_{19}$NO$_3$SNa$^+$ [M+Na]$^+$: 292.0978; found: 292.0963.
General Procedure for Alkylation of Secondary Amines (GP-1.2)

A round bottom flask equipped with a magnetic stir bar was charged with starting material INT and K₂CO₃ (2 equiv.). The flask was sealed under nitrogen, and anhydrous DMF (0.2 M) was added via syringe. To the stirring solution was added 2-bromoacetophenone (1.1 equiv.) suspended in anhydrous DMF (0.2 M) via syringe. The reaction was allowed to stir for 3 hours or until complete by TLC analysis, at which point it was quenched with deionized water and diluted with EtOAc, and the resultant layers were partitioned. The organic layer was collected, and the aqueous phase was extracted with EtOAc (3x). The organic layers were then combined, washed with brine (1x), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure.

\[
\text{N-(4-methylpent-3-en-1-yl)-N-(2-oxo-2-phenylethyl)-4-(trifluoromethyl)benzenesulfonamide (1.37):}
\]
Prepared according to GP-1.2 using protected homoprenyl amine \textbf{1.37 INT} (500 mg, 1.63 mmol, 1 equiv.), 2-bromoacetophenone (356 mg, 1.79 mmol, 1.1 equiv.), K₂CO₃ (450 mg, 3.25 mmol, 2 equiv.), and DMF (17 mL) with a reaction time of 16 h. Purification by flash column chromatography (3–6% EtOAc/hexanes) afforded the pure compound as pale yellow oil (237 mg, 34%). Spectral data was found to be in accordance with literature data.³⁰

\[
\text{4-chloro-N-(4-methylpent-3-en-1-yl)-N-(2-oxo-2-phenylethyl)benzenesulfonamide (1.38):}
\]
Prepared according to GP-1.2 using protected homoprenyl amine \textbf{1.38 INT} (500 mg, 1.83 mmol, 1 equiv.), 2-bromoacetophenone (400 mg, 2.01 mmol, 1.1 equiv.), K₂CO₃ (505 mg, 3.65 mmol, 2 equiv.), and DMF
(19 mL) with a reaction time of 16 h. Purification by flash column chromatography (3–6% EtOAc/hexanes) afforded the pure compound as pale yellow oil (268 mg, 37%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.91 (d, $J =$ 7.1 Hz, 2H), 7.81 (d, $J =$ 8.6 Hz, 2H), 7.61 (t, $J =$ 7.4 Hz, 1H), 7.48 (dd, $J =$ 9.4, 7.0 Hz, 4H), 4.96 (t, $J =$ 7.1 Hz, 1H), 4.83 (s, 2H), 3.30–3.23 (m, 2H), 2.22 (q, $J =$ 7.3 Hz, 2H), 1.61 (s, 3H), 1.55 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 193.7, 138.9, 138.5, 134.7, 133.8, 129.0, 128.9, 127.9, 127.9, 119.8, 52.8, 47.9, 27.1, 25.6, 17.7; IR (cm$^{-1}$): 2914, 2361, 1700, 1597, 1584, 1476, 1337, 1224, 1156, 1093, 1013, 970, 942, 912, 827; HRMS: m/z calculated for C$_{20}$H$_{22}$ClNO$_3$S$^+\text{[M+Na]}^+$: 414.0901; found: 414.0896.

$N$-(4-methylpent-3-en-1-yl)-$N$-(2-oxo-2-phenylethyl)benzenesulfonamide (1.39): Prepared according to GP-1.2 using protected homoprenyl amine 1.39 INT (894.4 mg, 3.74 mmol, 1.00 equiv.), 2-bromoacetophenone (893 mg, 4.48 mmol, 1.1 equiv.), K$_2$CO$_3$ (1.05 g, 7.57 mmol, 2.0 equiv.), and DMF (37.4 mL) with a reaction time of 16 h. Purification by flash column chromatography (3–6% EtOAc/hexanes) afforded the pure compound as a viscous clear, yellow oil (494.7 mg, 37%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.94 (d, $J =$ 7.6 Hz, 2H), 7.88 (d, $J =$ 7.5 Hz, 2H), 7.60 (dt, $J =$ 12.5, 7.3 Hz, 2H), 7.55–7.46 (m, 4H), 4.95 (t, $J =$ 7.1 Hz, 1H), 4.80 (s, 2H), 3.31–3.24 (m, 2H), 2.21 (q, $J =$ 7.6 Hz, 2H), 1.61 (s, 3H), 1.54 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 193.9, 139.9, 139.9, 134.9, 134.6, 133.8, 132.6, 128.9, 128.8, 128.0, 127.4, 119.9, 53.0, 48.0, 27.1, 25.6, 17.7; IR (cm$^{-1}$): 2929, 1702, 1598, 1450, 1405, 1322, 1226, 1161, 1132, 1094, 1108, 1062, 1016, 1001, 973, 913, 844, 788; HRMS: m/z calculated for C$_{20}$H$_{23}$NO$_3$SNa$^+\text{[M+Na]}^+$: 380.1291; found: 380.1294.
**4-methyl-N-(4-methylpent-3-en-1-yl)-N-(2-oxo-2-phenylethyl)benzenesulfonamide (1.40):** Prepared according to GP-1.2 using protected homoprenyl amine **1.40 INT (879.1 mg, 3.47 mmol, 1.00 equiv.),** 2-bromoacetophenone (829 mg, 4.16 mmol, 1.1 equiv.), K$_2$CO$_3$ (959 mg, 6.94 mmol, 2.00 equiv.), and DMF (34.7 mL) with a reaction time of 16 h. Purification by flash column chromatography (4–7% EtOAc/hexanes) afforded the pure compound as a viscous yellow oil (483.37 mg, 37%). **$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.95 (d, $J = 8.5$ Hz, 2H), 7.75 (d, $J = 8.3$ Hz, 2H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 2H), 7.30 (d, $J = 8.3$ Hz, 2H), 4.95 (tdt, $J = 7.4$, 3.0, 1.5 Hz, 1H), 4.77 (s, 2H), 3.24 (dd, $J = 8.6$, 6.7 Hz, 2H), 2.43 (s, 3H), 2.20 (q, $J = 7.5$ Hz, 2H), 1.60 (s, 3H), 1.53 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 194.0, 143.2, 136.8, 134.9, 134.5, 133.7, 129.5, 128.8, 128.0, 127.5, 120.0, 53.1, 48.0, 27.1, 25.6, 17.7.; IR (cm$^{-1}$): 2919, 1700, 1597, 1448, 1333, 1289, 1183, 1153, 1091, 1001, 969, 942, 912, 813; HRMS: $m/z$ calculated for C$_{21}$H$_{25}$NO$_3$SNa$^+$ [M+Na$^+$]: 394.1447; found: 394.1450.

![4-methyl-N-(4-methylpent-3-en-1-yl)-N-(2-oxo-2-phenylethyl)benzenesulfonamide](image)

**4-methoxy-N-(4-methylpent-3-en-1-yl)-N-(2-oxo-2-phenylethyl)benzenesulfonamide (1.41):** Prepared according to GP-1.2 using protected homoprenyl amine **1.41 INT (500 mg, 1.86 mmol, 1 equiv.),** 2-bromoacetophenone (406 mg, 2.04 mmol, 1.1 equiv.), K$_2$CO$_3$ (513 mg, 3.71 mmol, 2 equiv.), and anhydrous DMF (20 mL) with a reaction time of 16 h. Purification by flash column chromatography (3–6% EtOAc/hexanes) afforded the pure compound as pale yellow oil (256 mg, 36%). **$^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.79 (d, $J = 8.8$ Hz, 2H), 6.97 (d, $J = 8.8$ Hz, 2H), 4.92 (t, $J = 7.2$ Hz, 1H), 4.68 (t, $J = 5.9$ Hz, 1H), 3.86 (s, 3H), 2.91 (q, $J = 6.7$ Hz, 2H), 2.13 (q, $J = 6.9$ Hz, 2H), 1.65 (s, 3H), 1.54 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 194.2, 162.8, 134.9, 134.5, 133.7, 131.5, 129.6, 128.8, 128.0, 120.0, 114.0, 55.5, 53.1, 48.0, 27.1, 25.6, 17.7; IR (cm$^{-1}$): 2916, 1700, 1596, 1579, 1498, 1449, 1413, 1334, 1302, 1259, 1302, 1259,
4-chloro-N-(4-methylpent-3-en-1-yl)-N-(2-oxo-2-(p-tolyl)ethyl)benzenesulfonamide (1.49 S):
Prepared according to GP-1.2 using protected homoprenyl amine 1.38 INT (500 mg, 1.83 mmol, 1 equiv.), 2-bromo-1-(p-tolyl)ethanone (428 mg, 2.01 mmol, 1.1 equiv.), K2CO3 (505 mg, 3.65 mmol, 2 equiv.), and anhydrous DMF (19 mL) with a reaction time of 16 h. Purification by flash column chromatography (3–6% EtOAc/hexanes) afforded the pure compound as pale yellow oil (314 mg, 42%). 1H NMR (400 MHz, CDCl3) δ 7.80 (dd, J = 8.4, 2.7 Hz, 4H), 7.46 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 4.95 (t, J = 6.4 Hz, 1H), 4.80 (s, 2H), 3.29–3.19 (m, 2H), 2.42 (s, 3H), 2.21 (dd, J = 13.9, 6.8 Hz, 2H), 1.61 (s, 3H), 1.55 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 193.3, 144.9, 138.9, 138.5, 134.8, 132.3, 129.6, 129.1, 129.0, 128.0, 119.8, 52.7, 47.9, 27.1, 25.6, 21.8, 17.8; IR (cm⁻¹): 2917, 2361, 2337, 1700, 1695, 1684, 1652, 1576, 1559, 1539, 1506, 1456, 1336, 1229, 1155, 1092, 1012, 924, 826, 808, 786; HRMS: m/z calculated for C21H25ClNO4SNa⁺ [M+Na]⁺: 428.1058; found: 428.1056.

General Procedure for N-Protection and Weinreb Amidation (GP-1.3)
A round bottom flask equipped with a magnetic stir bar was charged with the appropriate amino acid. The amino acid was dissolved in deionized water (0.4 M), and NaOH (2.5 equiv.) was added. The mixture was stirred until the solid was fully dissolved. To the resulting mixture was added a solution of the aryl sulfonyl chloride (1.2 equiv.) in diethyl ether (0.4 M). The reaction stirred for 12 hours, or until judged complete by TLC analysis. Aqueous hydrochloric acid (1 M) was added until the reaction mixture had a pH = 1, and the
layers were partitioned. The organic layer was collected, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure to give the desired protected amino acid, which was carried forward without purification.$^{38}$

A round bottom flask equipped with a magnetic stir bar was charged with the protected amino acid and N,O-dimethylhydroxylamine hydrochloride (1.1 equiv.). The flask was sealed under a nitrogen atmosphere, and anhydrous CH$_2$Cl$_2$ (0.3 M) followed by NMM (1.4 equiv.) were subsequently added via syringe. The stirring mixture was cooled to 0 °C, and DCC (1.1 equiv.) was added in one portion. The reaction was allowed to warm to room temperature over 4–6 hours based on TLC analysis. The reaction was then filtered over a pad of celite, eluted with multiple CH$_2$Cl$_2$ washes, and the combined organic eluent was washed with saturated aqueous NaHCO$_3$ (2x). The organic layer was washed with brine (1x), dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography eluting with (5–60% EtOAc/hexanes) provided the desired Weinreb amide.

(S)-N-methoxy-N-methyl-3-phenyl-2-((4-(trifluoromethyl)phenyl)sulfonamido)propenamide  (1.35 WA): Prepared according to GP-1.3 using L-phenylalanine (3.00 g, 18.2 mmol, 1 equiv.), water (0.4 M), NaOH (1.82 g, 45.4 mmol, 2.5 equiv.), 4-(trifluoromethyl)benzenesulfonyl chloride (5.33 g, 21.8 mmol, 1.2 equiv.), ether (0.4 M) with a reaction time of 12 h. Crude protected amine was then used with N,O-dimethylhydroxylamine hydrochloride (1.95 g, 20.0 mmol, 1.1 equiv.), CH$_2$Cl$_2$ (0.3 M), NMM (2.57 g, 25.4 mmol, 1.4 equiv.), and DCC (4.12 g, 20.0 mmol, 1.1 equiv.) with a reaction time of 48 h. Purification by flash column chromatography (5–60% EtOAc/hexanes) afforded the pure compound as a white solid (4.04 g, 53%). Spectral data was in accordance with literature data.$^{30}$
(S)-2-((4-chlorophenyl)sulfonamido)-N-methoxy-N-methylpropanamide (1.50 WA): Prepared according to GP-1.3 using L-alanine (1.00 g, 11.2 mmol, 1 equiv.), water (0.4 M), NaOH (1.12 g, 28.1 mmol, 2.5 equiv.), 4-chlorobenzenesulfonyl chloride (2.84 g, 13.5 mmol, 1.2 equiv.), ether (0.4 M) with a reaction time of 12 h. Crude protected amine was then used with N,O-dimethylhydroxylamine hydrochloride (936 mg, 9.6 mmol, 1.1 equiv.), CH₂Cl₂ (0.3 M), NMM (1.24 g, 12.2 mmol, 1.4 equiv.), and DCC (1.98 g, 9.6 mmol, 1.1 equiv.), with a reaction time of 12 h. Purification by flash column chromatography (5–60% EtOAc/hexanes) afforded the pure compound as a colorless oil (760 mg, 22%).

¹H NMR (700 MHz, CDCl₃) δ 7.79 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 5.54 (d, J = 9.4 Hz, 1H), 4.37 (p, J = 6.7, 6.1 Hz, 1H), 3.60 (s, 3H), 3.01 (s, 3H), 1.33 (d, J = 7.0 Hz, 3H); ¹³C NMR (176 MHz, CDCl₃) δ 172.1, 139.1, 138.6, 129.2, 128.7, 61.5, 49.0, 32.2, 20.0.; IR (cm⁻¹): 2929, 2939, 1651, 1585, 1476, 1437, 1387, 1334, 1277, 1163, 1083, 1052, 1013, 1052, 1013, 985, 911, 871, 829; HRMS: m/z calculated for C₁₁H₁₅ClN₂O₄SNa⁺ [M+Na⁺]: 329.0333; found: 329.0332; [α]D = + 36.2.

(5)-N-methoxy-N-methyl-2-((4-(trifluoromethyl)phenyl)sulfonamido)propanamide (1.51 WA): Prepared according to GP-1.3 using L-alanine (1.50 g, 16.8 mmol, 1 equiv.), water (0.4 M), NaOH (1.68 g, 42.1 mmol, 2.5 equiv.), 4-(trifluoromethyl)benzenesulfonyl chloride (4.94 g, 20.2 mmol, 1.2 equiv.), ether (0.4 M) with a reaction time of 12 h. Crude protected amine was then used with N,O-dimethylhydroxylamine hydrochloride (1.30 mg, 13.3 mmol, 1.1 equiv.), CH₂Cl₂ (0.3 M), NMM (1.71 g, 16.9 mmol, 1.4 equiv.), and DCC (2.74 g, 13.3 mmol, 1.1 equiv.), with a reaction time of 36 h. Crude material was then used with Purification by flash column chromatography (5–60% EtOAc/hexanes) afforded the pure compound as a white solid (1.99 g, 35%). ¹H NMR (700 MHz, CDCl₃) δ 7.99 (d, J = 8.1
Hz, 2H), 7.77 (d, J = 8.1 Hz, 2H), 5.62 (d, J = 9.3 Hz, 1H), 4.41 (p, J = 6.9 Hz, 1H), 3.60 (s, 3H), 2.98 (s, 3H), 1.34 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 171.9, 143.7, 134.3 (q, J = 33.0 Hz), 127.8, 126.0 (q, J = 3.7 Hz), 123.2 (q, J = 27.2 Hz), 61.5, 49.0, 32.2, 19.9.; IR (cm$^{-1}$): 2940, 1721, 1654, 1404, 1384, 1320, 1267, 1167, 1129, 1107, 1093, 1061, 1017, 989, 911, 874, 842; HRMS: m/z calculated for C$_{12}$H$_{15}$F$_{3}$N$_{2}$O$_{4}$SH$^+$ [M+H]$^+$: 341.0777; found: 341.0780; $^{[a]}$$\Delta$D = +39.7.

3-(4-bromophenyl)-N-methoxy-N-methyl-2-((4-(trifluoromethyl)phenyl)sulfonamido)propenamide (1.59 WA): Prepared according to GP-1.3 using p-bromo-DL-phenylalanine (5.00 g, 20.5 mmol, 1 equiv.), triethylamine (6.22 g, 61.5 mmol, 3 equiv.), 4-(trifluoromethyl)benzenesulfonyl chloride (5.01 g, 20.5 mmol, 1.2 equiv.), THF:water (1:2, 0.2 M) with a reaction time of 12 h. Crude protected amine was then used with N$_2$O- dimethylhydroxylamine hydrochloride (2.10 g, 21.5 mmol, 1.1 equiv.), CH$_2$Cl$_2$ (0.3 M), NMM (2.77 g, 27.4 mmol, 1.4 equiv.), and DCC (4.44 g, 21.5 mmol, 1.1 equiv.) with a reaction time of 36 h. Crude material was then used with Purification by flash column chromatography (5–60% EtOAc/hexanes) afforded the pure compound as an off-white solid (1.99 g, 21%). $^1$H NMR (700 MHz, CDCl$_3$) δ 7.76 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 6.95 (d, J = 7.9 Hz, 2H), 5.59 (d, J = 9.8 Hz, 1H), 4.52 (q, J = 9.0 Hz, 1H), 3.59 (s, 3H), 3.04 (s, 3H), 2.96 (dd, J = 13.8, 5.1 Hz, 1H), 2.75 (dd, J = 13.8, 8.3 Hz, 1H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 170.7, 143.5, 134.8, 134.2 (q, J = 34.0 Hz), 131.5, 131.1, 127.5, 125.9 (d, J = 3.9 Hz), 123.2 (d, J = 273.5 Hz), 121.1, 61.5, 54.5, 38.7, 32.1; IR (cm$^{-1}$): 2944, 1721, 1647, 1488, 1436, 1405, 1324, 1163, 1126, 1106, 1096, 1061, 1011, 989, 964, 865, 843, 806; HRMS: m/z calculated for C$_{18}$H$_{18}$BrF$_3$N$_2$O$_4$SNa$^+$ [M+Na]$^+$: 517.0015; found: 517.0012.
N-methoxy-N-methyl-3-(thiophen-2-yl)-2

((4(trifluoromethyl)phenyl)sulfonylamo)propenamide (1.60 WA): Prepared according to GP-1.3 using 3-(2-thienyl)-DL-alanine (2.00 g, 11.7 mmol, 1 equiv.), water (0.4 M), NaOH (1.17 g, 29.2 mmol, 2.5 equiv.), 4-(trifluoromethyl)benzenesulfonyl chloride (3.43 g, 14.0 mmol, 1.2 equiv.), ether (0.4 M) with a reaction time of 15 h. Crude protected amine (2.20 g) was then used with N,O-dimethylhydroxylamine hydrochloride (622 mg, 6.4 mmol, 1.1 equiv.), CH$_2$Cl$_2$ (0.3 M), NMM (821 mg, 0.893 mL, 8.1 mmol, 1.4 equiv.), and DCC (1.32 g, 6.4 mmol, 1.1 equiv.) with a reaction time of 12 h. Purification by flash column chromatography (5–50% EtOAc/hexanes) afforded the pure compound as a white foam (469 mg, 9%). Spectral data was in accordance with literature data.$^{30}$

(S)-3-(4-(benzyloxy)phenyl)-N-methoxy-N-methyl-2-

((4(trifluoromethyl)phenyl)sulfonylamo) propanamide (1.62 WA): Prepared according to GP-1.3 using ortho-benzyl-L-tyrosine (2.5 g, 9.2 mmol, 1 equiv.), water (0.4 M), NaOH (921 mg, 23.0 mmol, 2.5 equiv.), 4 (trifluoromethyl)benzenesulfonyl chloride (2.70 g, 11.1 mmol, 1.2 equiv.), ether (0.4 M) with a reaction time of 15 h. Crude protected amine (3.75 g) was then used with N,O-dimethylhydroxylamine hydrochloride (839 mg, 8.6 mmol, 1.1 equiv.), CH$_2$Cl$_2$ (0.3 M), NMM (1.11 g, 1.20 mL, 10.9 mmol, 1.4 equiv.), and DCC (1.78 g, 8.6 mmol, 1.1 equiv.) with a reaction time of 12 h. Purification by flash column chromatography (5–60% EtOAc/hexanes) afforded the pure compound as a white solid (1.25 g, 26%). $^{1}$H NMR (700 MHz, CDCl$_3$) δ 7.78 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 7.3 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 6.98 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 5.46 (br, 1H), 5.01 (s, 3H), 4.56–4.49 (m,
1H), 3.48 (s, 3H), 2.97 (s, 3H), 2.94 (dd, J = 13.9, 5.6 Hz, 1H), 2.76 (dd, J = 13.8, 7.8 Hz, 1H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 171.1, 157.9, 143.8, 136.9, 133.9 (q, J = 33.0 Hz), 130.6, 128.6, 128.1, 127.7, 127.6, 125.9-125.8 (m), 123.4 (q, J = 272.9 Hz), 114.9, 69.9, 61.5, 54.7, 38.6, 32.0; IR (cm$^{-1}$): 2950, 1670, 1605, 1511, 1452, 1441, 1419, 1401, 1383, 1362, 1334, 1255, 1206, 1163, 1142, 1078, 1062, 1032, 844; HRMS: m/z calculated for C$_{25}$H$_{25}$F$_3$N$_2$O$_5$SNH$^+$ [M+NH$_4$]$^+$: 540.1775; found: 540.1773; $[\alpha]$D = −37.4.

**General Procedure for N-Alkylation and Grignard Addition (GP-1.4)**

A round bottom flask equipped with a magnetic stir bar was charged with Weinreb amide WA and sealed under a nitrogen atmosphere. Anhydrous DMF (0.1 M) was added via syringe, and the reaction mixture was cooled to 0 °C. Sodium hydride (2 equiv., 60% dispersion in mineral oil) was added in one portion, and the reaction was allowed to stir at 0 °C for 30 minutes before homoprenyl iodide (1.2 equiv.) was added via syringe. The mixture was then warmed to room temperature over 3 hours, or until judged complete by TLC analysis. The reaction was quenched with deionized water, diluted with EtOAc, and the resultant layers were partitioned. The organic layer was collected, and the aqueous phase was extracted with EtOAc (3x). The organic layers were then combined, washed with brine (3x), dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. Purification by flash column chromatography eluting with EtOAc/hexanes (1:4) afforded the desired intermediate (INT).

A round bottom flask equipped with a magnetic stir bar was charged with acid-washed magnesium turnings (3 equiv.) and a crystal of iodine then sealed under a nitrogen atmosphere. Anhydrous THF (0.2 M) was added via syringe, followed by the desired aryl bromide (3 equiv.). The solution
was allowed to stir (heating via heating mantle as necessary) until all magnesium turnings had dissolved. The mixture was then cooled to 0 °C and added to a cooled solution (0 °C) of intermediate (INT) suspended in anhydrous THF (0.2 M) dropwise via cannula. The reaction was allowed to warm to room temperature over 12 hours, or until judged complete by TLC analysis, at which point it was quenched with 1 M HCl. The reaction mixture was diluted with EtOAc, the layers were partitioned, and the organic layer was collected. The aqueous phase was extracted with EtOAc (3x), and the combined organic layers were washed with brine (1x), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography eluting with EtOAc/hexanes (1:9) afforded the desired substrate.

(S)-2-((4-chloro-N-(4-methylpent-3-en-1-yl)phenyl)sulfonamido)-N-methoxy-N-methylpropanamide (1.50 INT): Prepared according to GP-1.4 using Weinreb amide 1.50 WA (335 mg, 1.1 mmol, 1 equiv.), sodium hydride (83.7 mg, 2.2 mmol, 60% dispersion in mineral oil, 2 equiv.), homoprenyl iodide (275 mg, 1.3 mmol, 1.2 equiv.), DMF (0.1 M) with a reaction time of 3 h. Purification by flash column chromatography eluting with EtOAc/hexanes (1:4) afforded the pure Weinreb amide as a white solid (202 mg, 47%). ¹H NMR (700 MHz, CDCl₃) δ 7.76 (d, J = 6.5 Hz, 2H), 7.46 (d, J = 6.5 Hz, 2H), 5.11 (s, 1H), 5.05 (t, J = 6.8 Hz, 1H), 3.77 (s, 3H), 3.33 (q, J = 10.9, 5.7 Hz, 1H), 3.24 (q, J = 11.9, 11.2 Hz, 1H), 3.08 (s, 3H), 2.40 (tt, J = 12.8, 6.0 Hz, 1H), 2.31 (dp, J = 13.2, 6.4 Hz, 1H), 1.68 (s, 3H), 1.64 (s, 3H), 1.30 (d, J = 7.1 Hz, 3H).; ¹³C NMR (176 MHz, CDCl₃) δ 171.9, 138.9, 138.5, 134.4, 129.1, 128.7, 120.1, 61.7, 51.1, 44.8, 32.0, 30.6, 25.6, 17.8, 15.9.; IR (cm−1): 2970, 2915, 1585, 1475, 1450, 1338, 1276, 1157, 1091, 1013, 955,
916, 872; **HRMS**: m/z calculated for C$_{17}$H$_{25}$ClN$_{2}$O$_{4}$Na$^+$ [M+Na]$^+$: 411.1116; found: 411.1113; [$\alpha$]D = +2.6.

(S)-4-chloro-N-(4-methylpent-3-en-1-yl)-N-(1-oxo-1-phenylpropan-2-yl)benzenesulfonamide (1.50 S): Prepared according to GP-1.4 using Weinreb amide 1.50 INT (250 mg, 0.62 mmol, 1 equiv.) with Mg turnings (46.9 mg, 1.93 mmol, 3 equiv.), bromobenzene (303 mg, 1.93 mmol, 3 equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a reaction time of 12 h. Purification by flash column chromatography eluting with EtOAc/hexanes (1:4) afforded the pure compound as a colorless oil (231 mg, 89%). **$^1$H NMR** (700 MHz, CDCl$_3$) $\delta$ 8.04 (d, J = 7.7 Hz, 2H), 7.72 (d, J = 7.3 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.42 (d, J = 7.3 Hz, 2H), 5.61 (q, J = 7.0 Hz, 1H), 4.93 (t, J = 7.6 Hz, 1H), 3.15 (ddd, J = 16.0, 10.9, 5.6 Hz, 1H), 3.06 (ddd, J = 15.4, 10.9, 5.7 Hz, 1H), 2.16 (ddq, J = 24.2, 12.9, 12.5, 5.9 Hz, 2H), 1.61 (s, 3H), 1.55 (s, 3H), 1.28 (d, J = 7.0 Hz, 3H); **$^{13}$C NMR** (176 MHz, CDCl$_3$) $\delta$ 197.6, 139.2, 138.3, 135.2, 134.7, 133.6, 129.3, 128.9, 128.8, 128.7, 119.8, 55.8, 44.8, 30.0, 29.7, 25.6, 17.7, 14.4.; **IR** (cm$^{-1}$): 2738, 1687, 1583, 1448, 1342, 1220, 1159, 1093, 1014, 953, 823; **HRMS**: m/z calculated for C$_{21}$H$_{24}$ClNO$_3$SNH$^+$ [M+NH$_4$]$^+$: 423.1504; found: 423.1502; [$\alpha$]D = +8.0.

(S)-N-methoxy-N-methyl-2-((N-(4-methylpent-3-en-1-yl)-4-(trifluoromethyl)phenyl)sulfonamido) propanamide (1.51 INT): Prepared according to GP-1.4
using Weinreb amide 1.51 WA (530 mg, 1.95 mmol, 1 equiv.), sodium hydride (150 mg, 3.91 mmol, 60% dispersion in mineral oil, 2 equiv.), homoprenyl iodide (492 mg, 2.34 mmol, 1.2 equiv.), DMF (0.1 M) with a reaction time of 12 h. Purification by flash column chromatography eluting with EtOAc/hexanes (1:4) afforded the pure Weinreb amide as a white solid (395 mg, 48%). $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.95 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H), 5.13 (d, J = 8.2 Hz, 1H), 5.05 (t, J = 7.5 Hz, 1H), 3.78 (s, 3H), 3.36 (ddd, J = 16.7, 11.2, 5.4 Hz, 1H), 3.27 (ddd, J = 15.9, 11.6, 5.4 Hz, 1H), 3.06 (s, 3H), 2.42 (dq, J = 12.6, 6.6 Hz, 1H), 2.32 (tt, J = 13.1, 6.7 Hz, 1H), 1.69 (s, 3H), 1.64 (s, 3H), 1.33 (d, J = 7.1 Hz, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 171.7, 143.5, 134.5, 134.2 (q, J = 33.1 Hz), 127.8, 125.9 (q, J = 3.7 Hz), 123.2 (q, J = 272.8 Hz), 120.0, 61.7, 51.2, 45.0, 32.0, 30.6, 25.6, 17.8, 16.0; IR (cm$^{-1}$): 2945, 1593, 1465, 1342, 1321, 1257, 1116, 1083, 1015, 977, 832; HRMS: m/z calculated for C$_{18}$H$_{25}$F$_3$N$_2$O$_4$SNa$^+$ [M+Na]$^+$: 445.1379; found: 445.1377; $[\alpha]_D$ = $^{-2.0}$.

(S)-N-(4-methylpent-3-en-1-yl)-N-(1-oxo-1-phenylpropan-2-yl)-4-(trifluoromethyl)benzenesulfonamide (1.51S): Prepared according to GP-1.4 using Weinreb amide 1.51 INT (250 mg, 0.59 mmol, 1 equiv.) with Mg turnings (43.2 mg, 1.78 mmol, 3 equiv.), bromobenzene (279 mg, 1.78 mmol, 3 equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a reaction time of 12 h. Purification by flash column chromatography eluting with EtOAc/hexanes (1:4) afforded the pure compound as a colorless oil (109 mg, 42%). $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 8.01 (d, J = 6.8 Hz, 2H), 7.90 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 5.64 (q, J = 7.0 Hz, 1H), 4.94 (tt, J = 7.4, 1.6 Hz, 1H), 3.19 (ddd, J = 15.0, 10.3, 6.3 Hz, 1H), 3.13 (ddd, J = 15.0, 10.2, 6.3 Hz, 1H), 2.21 (ddt, J = 17.3, 13.0, 6.6 Hz,
2H), 1.62 (s, 3H), 1.56 (s, 3H), 1.32 (d, J = 7.1 Hz, 3H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 197.5, 143.3, 135.1, 134.8, 134.3 (q, J = 33.1 Hz), 133.7, 128.9, 128.6, 127.9, 126.1 (q, J = 3.7 Hz), 123.2 (q, J = 273.0 Hz), 119.7, 55.9, 45.0, 30.1, 25.6, 17.7, 14.8; IR (cm\(^{-1}\)): 2932, 1688, 1597, 1449, 1403, 1342, 1322, 1229, 1167, 1134, 1108, 1091, 1062, 1017, 991, 963, 920, 844, 787; HRMS: m/z calculated for C\(_{22}\)H\(_{24}\)F\(_3\)NO\(_3\)SNa\(^+\) [M+Na\(^+\)]: 462.1321; found: 462.1323; \([\alpha]D = \) –2.36.

(S)-N-(4-methylpent-3-en-1-yl)-N-(1-oxo-1-(p-tolyl)propan-2-yl)-4-(trifluoromethyl)benzenesulfonamide (1.52 S): Prepared according to GP-1.4 using Weinreb amide 1.51 INT (250 mg, 0.59 mmol, 1 equiv.) with Mg turnings (43.2 mg, 1.78 mmol, 3 equiv.), 4-bromotoluene (304 mg, 1.78 mmol, 3 equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a reaction time of 12 h. Purification by flash column chromatography eluting with EtOAc/hexanes (1:4) afforded the pure compound as a white solid (195 mg, 73%). \(^{1}\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.91 (d, J = 7.9 Hz, 4H), 7.70 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 7.6 Hz, 2H), 5.62 (q, J = 7.0 Hz, 1H), 4.96 (t, J = 7.5 Hz, 1H), 3.20 (ddd, J = 16.3, 10.5, 6.2 Hz, 1H), 3.13 (ddd, J = 15.5, 10.3, 6.2 Hz, 1H), 2.43 (s, 3H), 2.22 (qt, J = 14.7, 6.8 Hz, 2H), 1.63 (s, 3H), 1.57 (s, 3H), 1.31 (d, J = 7.0 Hz, 3H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 197.0, 144.7, 143.4, 143.7, 134.2 (q, J =33.0 Hz), 132.5, 129.5, 128.7, 127.9, 126.0 (q, J = 3.7 Hz), 123.2 (q, J = 272.9 Hz), 119.7, 55.7, 45.0, 30.2, 25.5, 21.6, 17.7, 14.9; IR (cm\(^{-1}\)): 2925, 1686, 1607, 1404, 1323, 1167, 1135, 1100, 1062, 1017, 924, 843; HRMS: m/z calculated for C\(_{23}\)H\(_{26}\)F\(_3\)NO\(_3\)SNa\(^+\) [M+Na\(^+\)]: 476.1478; found: 476.1474; \([\alpha]D = +14.9\).
(S)-N-(4-methylpent-3-en-1-yl)-N-(1-oxo-1-(m-tolyl)propan-2-yl)-4-(trifluoromethyl)benzenesulfonamide (1.53 S): Prepared according to GP-1.4 using Weinreb amide 1.51 INT (250 mg, 0.59 mmol, 1 equiv.) with Mg turnings (43.2 mg, 1.78 mmol, 3 equiv.), 3-bromotoluene (304 mg, 1.78 mmol, 3 equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a reaction time of 12 h. Purification by flash column chromatography eluting with EtOAc/hexanes (1:4) afforded the pure compound as a colorless oil (93 mg, 35%). 

\[ \text{\^H NMR (700 MHz, CDCl}_3) \delta 7.89 (d, J = 8.1 Hz, 2H), 7.81–7.77 (m, 2H), 7.69 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 7.5 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 5.63 (q, J = 7.1 Hz, 1H), 4.96 (t, J = 7.4 Hz, 1H), 3.24–3.11 (m, 2H), 2.42 (s, 3H), 2.23 (q, J = 8.0 Hz, 2H), 1.63 (s, 3H), 1.57 (s, 3H), 1.33 (d, J = 7.1 Hz, 3H); \]

\[ \text{\^C NMR (176 MHz, CDCl}_3) \delta 197.8, 143.4, 138.7, 135.2, 134.7, 134.5, 134.3 (q, J = 32.9 Hz), 129.1, 128.7, 127.9, 126.1 (q, J = 3.7 Hz), 125.8, 123.2 (d, J = 272.8 Hz), 119.8, 56.0, 45.1, 30.2, 25.6, 21.3, 17.7, 15.1; \]

\[ \text{IR (cm}^{-1}): 2760, 1688, 1403, 1323, 1253, 1167, 1135, 1108, 1062, 1018, 844; \]

\[ \text{HRMS: } m/z \text{ calculated for } C_{23}H_{26}F_3NOSNa}^+ [M+Na]^+: 476.1478; \text{ found: 476.1481; } [\alpha]D = -3.0. \]

(S)-N-(1-((1,1'-biphenyl)-4-yl)-1-oxopropan-2-yl)-N-(4-methylpent-3-en-1-yl)-4-(trifluoromethyl)benzenesulfonamide (1.54 S): Prepared according to GP-1.4 using Weinreb amide 1.51 INT (250 mg, 0.59 mmol, 1 equiv.) with Mg turnings (43.2 mg, 1.78 mmol, 3 equiv.), 4-bromobiphenyl (414 mg, 1.78 mmol, 3 equiv.), a crystal of iodine and anhydrous THF (0.2 M)
with a reaction time of 12 h. Purification by flash column chromatography eluting with EtOAc/hexanes (1:4) afforded the pure compound as a colorless oil (114 mg, 37%). $^1$H NMR (700 MHz, CDCl$_3$) δ 8.12 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 8.1 Hz, 2H), 7.73 (dd, J = 8.4, 3.2 Hz, 4H), 7.66 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.4 Hz, 1H), 5.68 (q, J = 7.0 Hz, 1H), 4.97 (t, J = 7.5 Hz, 1H), 3.22 (ddd, J = 16.1, 10.6, 6.0 Hz, 1H), 3.14 (ddd, J = 15.5, 10.6, 6.0 Hz, 1H), 2.24 (tq, J = 10.8, 7.0 Hz, 2H), 1.63 (s, 3H), 1.58 (s, 3H), 1.33 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 196.9, 146.4, 143.4, 134.8, 134.3 (q, J = 33.1 Hz), 133.7, 129.3, 129.0, 128.4, 127.9, 127.4, 127.2, 126.1 (q, J = 3.7 Hz), 123.2 (q, J = 272.9 Hz), 119.7, 55.9, 45.0, 30.1, 25.6, 17.7, 14.7; IR (cm$^{-1}$): 2925, 1684, 1603, 1404, 1322, 1230, 1167, 1135, 1107, 1062, 1017, 922, 847; HRMS: m/z calculated for C$_{28}$H$_{28}$F$_3$NO$_3$SNa$^+$ [M+Na$^+$]: 538.1634; found: 538.1631; [$\alpha$]D= +36.8.

(S)-N-(1-(4-chlorophenyl)-1-oxopropan-2-yl)-N-(4-methylpent-3-en-1-yl)-4-(trifluoromethyl)benzenesulfonamide (1.55 S): Prepared according to GP-1.4 using Weinreb amide 1.51 INT (330 mg, 0.78 mmol, 1 equiv.) with Mg turnings (57.0 mg, 2.34 mmol, 3 equiv.), 1-bromo-4-chlorobenzene (449 mg, 2.34 mmol, 3 equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a reaction time of 12 h. Purification by flash column chromatography eluting with EtOAc/hexanes (1:4) afforded the pure compound as a colorless oil (320 mg, 86%). $^1$H NMR (700 MHz, CDCl$_3$) δ 8.03 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 5.58 (q, J = 7.0 Hz, 1H), 4.91 (dt, J = 7.6, 4.6 Hz, 1H), 3.14 (ddd, J = 16.1, 11.1, 5.4 Hz, 1H), 3.04 (ddd, J = 15.4, 11.1, 5.5 Hz, 1H), 2.19 (tt, J = 12.5, 6.2 Hz, 1H), 2.10 (tt, J = 13.0, 6.3 Hz, 1H), 1.61 (s, 3H), 1.54 (s, 3H), 1.24 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (176 MHz,
CDCl₃ δ 196.1, 135.0, 134.5 (q, J = 33.3 Hz), 133.3, 130.2, 129.2, 127.9, 126.2 (q, J = 3.6 Hz),
123.1 (q, J = 273.0 Hz), 119.5, 55.9, 44.8, 29.9, 25.6, 17.7, 14.0; IR (cm⁻¹): 2932, 1685, 1588,
1388, 1321, 1226, 1161, 1133, 1090, 1061; HRMS: m/z calculated for C₂₂H₂₃ClF₃NO₃SH⁺ [M+H]⁺: 474.1118; found: 474.1108; [α]D = +13.6.

(S)-3-(4-(benzyloxy)phenyl)-N-methoxy-N-methyl-2-((N-(4-methylpent-3-en-1-yl)-4-
(trifluoromethyl)phenyl)sulfonamido)propanamide (1.62 INT): Prepared according to GP-1.4
using Weinreb amide 1.62 WA (1.10 g, 2.1 mmol, 1 equiv.), sodium hydride (161 mg, 4.2 mmol,
60% dispersion in mineral oil, 2 equiv.), homoprenyl iodide (531 mg, 2.5 mmol, 1.2 equiv.), DMF
(0.1 M) with a reaction time of 5 h. Purification by flash column chromatography eluting with
EtOAc/hexanes (1:4) afforded the pure Weinreb amide as a clear, colorless oil (580 mg, 46%).
¹H NMR (500 MHz, CDCl₃) δ 7.89 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.42-7.36 (m, 4H),
7.32 (t, J = 7.1 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.22 (dd, J = 8.7, 5.6
Hz, 1H), 5.06–5.03 (s, 3H), 3.51–3.44 (m, 1H), 3.35–3.26 (m, 4H), 3.20 (dd, J = 13.3, 9.7 Hz, 1H),
2.97 (s, 3H), 2.74 (dd, J = 13.3, 5.1 Hz, 1H), 2.40-2.28 (m, 2H), 1.68 (s, 3H), 1.63 (s, 3H); ¹³C
NMR (176 MHz, CDCl₃) δ 170.1, 157.8, 144.0, 137.0, 134.7, 134.1 (q, J = 33.0 Hz), 130.5, 128.9,
128.7, 128.1, 128.0, 127.6, 126.2–125.8 (m), 123.4 (q, J = 273.0 Hz) 120.1, 70.1, 61.6, 56.2, 45.1,
35.9, 31.9, 30.2, 25.8, 18.0; IR (cm⁻¹): 2951, 1590, 1472, 1344, 1325, 1310 1246, 1172, 1128,
1073, 1027, 950, 834; HRMS: m/z calculated for C₃₁H₃₅F₃N₂O₅SH⁺ [M+H]⁺: 605.2292; found:
605.2295; [α]D = –4.3.
(S)-N-(3-(4-(benzyloxy)phenyl)-1-oxo-1-phenylpropan-2-yl)-N-(4-methylpent-3-en-1-yl)-4-(trifluoromethyl)benzenesulfonamide (1.62S): Prepared according to GP-1.4 using Weinreb amide 1.62 INT (500 mg, 0.827 mmol, 1 equiv.) with Mg turnings (60 mg, 2.48 mmol, 3 equiv.), bromobenzene (389 mg, 0.265 mL, 2.48 mmol, 3 equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a reaction time of 7 h. Purification by flash column chromatography eluting with EtOAc/hexanes (1:4) afforded the pure compound as a clear, yellow oil (348 mg, 68%). $^1$H NMR (500 MHz, CD$_2$Cl$_2$) δ 7.84 (dd, J = 13.3, 7.9 Hz, 4H), 7.67 (d, J = 8.3 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46–7.34 (m, 5H), 7.31 (t, J = 7.0 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 5.67 (dd, J = 9.3, 5.2 Hz, 1H), 4.99-4.96 (m, 3H), 3.34 (dd, J = 13.8, 9.3 Hz, 1H), 3.30–3.18 (m, 2H), 2.64 (dd, J = 13.8, 5.1 Hz, 1H), 2.24–2.11 (m, 2H), 1.64 (s, 3H), 1.58 (s, 3H); $^{13}$C NMR (176 MHz, CD$_2$Cl$_2$) δ 197.1, 158.3, 144.1, 137.7, 136.4, 135.4, 134.6 (q, J = 33.0 Hz), 134.2, 130.8, 129.4, 129.3, 129.1, 129.0, 128.5, 128.4, 128.1, 127.0–126.5 (m), 123.9 (q, J = 272.8 Hz), 120.2, 115.5, 70.4, 61.2, 45.6, 34.5, 30.3, 25.9, 18.0; IR (cm$^{-1}$): 2925, 1686, 1610, 1582, 1512, 1449, 1494, 1322, 1244, 1164, 1134, 1108, 1092, 1062, 1016, 942, 844, 822; HRMS: m/z calculated for C$_{35}$H$_{34}$F$_3$NO$_4$SNa$^+$ [M+Na]$^+$: 644.2053; found: 644.2058; [α]D = −41.6.
General Procedure for Grignard Addition followed by N-Alkylation (GP-1.5)

A round bottom flask equipped with a magnetic stir bar was charged with acid-washed magnesium turnings (3 equiv.) and a crystal of iodine then sealed under a nitrogen atmosphere. Anhydrous THF (0.2 M) was added via syringe, followed by the desired aryl bromide (3 equiv.). The solution was allowed to stir (heating via heating mantle as necessary) until all magnesium turnings had dissolved, and was then cooled to 0 °C. To the mixture was added Weinreb amide WA suspended in anhydrous THF (0.2 M) dropwise via cannula. The reaction was allowed to warm to room temperature over 12 hours, or until judged complete by TLC analysis, at which point it was quenched with a saturated ammonium chloride solution. The reaction mixture was diluted with EtOAc, the layers were partitioned, and the organic layer was collected. The aqueous phase was extracted with EtOAc (3x), and the combined organic layers were washed with brine (1x), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography afforded the desired intermediate INT.

A round bottom flask equipped with a magnetic stir bar was charged with intermediate INT and sealed under a nitrogen atmosphere. Anhydrous DMF (0.1 M) was added via syringe, and the reaction mixture was cooled to 0 °C. Potassium carbonate (2 equiv.) was added in one portion, and the reaction was allowed to stir at 0 °C for 30 minutes before homoprenyl iodide (1.2 equiv.) was added via syringe. The mixture was allowed to warm to room temperature over 3 hours, or until judged complete by TLC analysis. The reaction was quenched with deionized water, diluted with EtOAc, and the resultant layers were partitioned. The organic layer was collected, and the aqueous phase was extracted with EtOAc (3x). The organic layers were then combined, washed with an aqueous 5% LiCl solution (3x), brine (1x), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography afforded the desired substrate.
(S)-N-(1-oxo-1,3-diphenylpropan-2-yl)-4-\((\text{trifluoromethyl})\text{benzenesulfonamide (1.35 INT):}\)
Prepared according to GP-1.5 using Weinreb amide 1.35 WA (500 mg, 1.2 mmol, 1 equiv.) with Mg turnings (87.6 mg, 3.61 mmol, 3 equiv.), bromobenzene (566 mg, 3.61 mmol, 3 equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a reaction time of 12 h. Purification by flash column chromatography (1-10% EtOAc/hexanes) afforded the pure compound as a white solid (364 mg, 70%). Spectral data was found to be in accordance with literature data.\(^\text{30}\)

(S)-N-(4-methylpent-3-en-1-yl)-N-(1-oxo-1,3-diphenylpropan-2-yl)-4-(\text{trifluoromethyl})\text{benzenesulfonamide (1.35):}\) Prepared according to GP-1.5 using aryl ketone 1.35 INT (400 mg, 0.92 mmol, 1 equiv.), K\(_2\)CO\(_3\) (255 mg, 1.85 mmol, 2 equiv.), homoprenyl iodide (233 mg, 1.1 mmol, 1.2 equiv.), anhydrous DMF (0.1 M) with a reaction time of 24 h. Purification by flash column chromatography (0-15% EtOAc/hexanes) afforded the pure tertiary amine as a colorless oil (229 mg, 48%). Spectral data was found to be in accordance with literature data.\(^\text{30}\)

(S)-N-(1-(4-fluorophenyl)-1-oxo-3-phenylpropan-2-yl)-4-(\text{trifluoromethyl})\text{benzenesulfonamidebenzenesulfonamide (1.56 INT):}\) Prepared according to GP-1.5 using Weinreb amide 1.35 WA (1.0 g, 2.4 mmol, 1 equiv.) with Mg turnings (175 mg, 7.2 mmol, 3 equiv.), 4-bromofluorobenzene (1.3 g, 7.4 mmol, 3 equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a reaction time of 12 h. Purification by flash column chromatography
(1–12% for CV and then 12% isocratic EtOAc/hexanes) afforded the pure compound as a white solid (810 mg, 74%). $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.79 (dd, $J = 8.7$, 5.3 Hz, 3H), 7.77 (d, $J = 8.2$ Hz, 3H), 7.21–7.15 (m, 3H), 7.13 (t, $J = 8.5$ Hz, 2H), 6.98 (dd, $J = 7.4$, 1.9 Hz, 2H), 5.67 (d, $J = 9.1$ Hz, 1H), 5.13 (ddd, $J = 9.1$, 6.7, 5.5 Hz, 1H), 3.14 (dd, $J = 14.1$, 5.6 Hz, 1H), 2.93 (dd, $J = 14.1$, 6.9 Hz, 1H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 195.7, 166.3 (d, $J = 257.8$ Hz), 143.5, 134.8, 134.1 (q, $J = 33.1$ Hz), 131.2 (d, $J = 9.5$ Hz), 130.4 (d, $J = 2.4$ Hz), 129.4, 128.6, 127.4, 127.3, 126.0 (q, $J = 3.7$ Hz), 123.1 (q, $J = 272.9$ Hz), 116.2 (d, $J = 22.1$ Hz), 58.5, 40.1; IR (cm$^{-1}$): 3273, 3066, 1685, 1597, 1506, 1457, 1430, 1407, 1324, 1263, 1229, 1166, 1155, 1127, 1093, 1109, 1063, 1016, 983, 950, 838; HRMS: m/z calculated for C$_{22}$H$_{17}$F$_4$NO$_3$SNa$^+$ [M+Na]$^+$: 474.0757; found: 474.0751; $[\alpha]_D$ = +63.5.

(S)-N-(1-(4-fluorophenyl)-1-oxo-3-phenylpropan-2-yl)-N-(4-methylpent-3-en-1-yl)-4-(trifluoromethyl)-benzenesulfonamide (1.56 S): Prepared according to GP-1.5 using aryl ketone 1.56 INT (400 mg, 0.8 mmol, 1 equiv.), K$_2$CO$_3$ (245 mg, 1.7 mmol, 2 equiv.), homoprenyl iodide (223 mg, 1.1 mmol, 1.2 equiv.), anhydrous DMF (0.1 M) with a reaction time of 24 h. Purification by flash column chromatography (0–5% EtOAc/hexanes) afforded the pure tertiary amine as a yellow oil (162 mg, 34%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.99 (dd, $J = 8.8$, 5.4 Hz, 2H), 7.86 (d, $J = 8.2$ Hz, 2H), 7.70 (d, $J = 8.2$ Hz, 2H), 7.23 (t, $J = 7.2$ Hz, 2H), 7.20–7.16 (m, 1H), 7.14 (d, $J = 6.8$ Hz, 2H), 7.08 (t, $J = 8.5$ Hz, 2H), 5.73 (dd, $J = 9.6$, 4.7 Hz, 1H), 4.96 (t, $J = 7.4$ Hz, 1H), 3.39 (dd, $J = 13.6$, 9.6 Hz, 1H), 3.27 (ddd, $J = 15.0$, 11.1, 5.5 Hz, 1H), 3.19 (ddd, $J = 15.0$, 11.0, 5.7 Hz, 1H), 2.63 (dd, $J = 13.6$, 4.7 Hz, 1H), 2.24 (tt, $J = 12.5$, 6.2 Hz, 1H), 2.12 (dq, $J = 12.7$, 6.6 Hz, 1H), 1.64 (s, 3H), 1.58 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 194.6, 166.0 (d, $J = 259.0$ Hz), 143.3, 136.3, 135.0, 134.4 (d, $J = 36.0$ Hz), 132.0, 131.5 (d, $J = 9.6$ Hz), 129.1, 128.7, 127.8, 126.9, 126.20–126.14 (m), 123.1 (d, $J = 271.8$ Hz), 119.5, 115.9 (d, $J = 21.7$ Hz), 60.3, 45.0, 34.6, 29.6,
25.6, 17.7; IR (cm\(^{-1}\)) : 2931, 1692, 1608, 1454, 1405, 1321, 1164, 1128, 1093, 1063, 1017, 941, 844, 788; HRMS: m/z calculated for \(C_{28}H_{27}F_4NO_3SNa^+\) [M+Na]^+: 556.1540; found 556.1541; \([\alpha]D = -50.6.

\(\text{(S)}\)-N-(1-(4-methoxyphenyl)-1-oxo-3-phenylpropan-2-yl)-4-(trifluoromethyl)benzenesulfonamide (1.57 INT): Prepared according to GP-1.5 using Weinreb amide 1.35 WA (425 mg, 1.02 mmol, 1 equiv.) with Mg turnings (74.4 mg, 3.06 mmol, 3 equiv.), 4-bromoanisole (573 mg, 3.06 mmol, 3 equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a reaction time of 12 h. Purification by flash column chromatography (0–13% for 10 CV and then 13% isocratic EtOAc/hexanes) afforded the pure compound as a white solid (221 mg, 47%).

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 77.76 (dd, \(J = 14.6, 8.3\) Hz, 4H), 7.53 (d, \(J = 8.0\) Hz, 2H), 7.21–7.15 (m, 3H), 7.04–6.99 (m, 2H), 6.91 (d, \(J = 8.5\) Hz, 2H), 5.83 (d, \(J = 9.0\) Hz, 1H), 5.13 (q, \(J = 7.0\) Hz, 1H), 3.88 (s, 3H), 3.14 (dd, \(J = 14.1, 5.3\) Hz, 1H), 2.93 (d, \(J = 14.1, 7.0\) Hz, 1H); \(^{13}\text{C NMR}\) (176 MHz, CDCl\(_3\)) \(\delta\) 195.2, 164.4, 143.5, 135.0, 134.0 (q, \(J = 33.0\) Hz), 130.8, 129.5, 128.5, 127.4, 127.2, 126.7, 125.9 (q, \(J = 3.7\) Hz), 123.1 (q, \(J = 273.1\) Hz), 114.2, 58.2, 55.6, 40.4; IR (cm\(^{-1}\)) : 3255, 1676, 1596, 1457, 1327, 1259, 1164, 1090, 1063, 1017; HRMS: m/z calculated for \(C_{23}H_{20}F_3NO_SNa^+\) [M+Na]^+: 486.0957; found: 486.0962; [\(\alpha]D = +109.8.

\(\text{(S)}\)-N-(1-(4-methoxyphenyl)-1-oxo-3-phenylpropan-2-yl)-N-(4-methylpent-3-en-1-yl)-4-(trifluoromethyl)benzenesulfonamide (1.57 S): Prepared according to GP-1.5 using aryl ketone using aryl ketone 1.57 INT (100 mg, 0.22 mmol, 1 equiv.), K\(_2\)CO\(_3\) (59.6 mg, 0.43 mmol, 2 equiv.), homoprenyl iodide (54.4 mg, 0.26 mmol, 1.2 equiv.), anhydrous DMF (0.1 M) with a reaction time of 24 h. Purification by flash column chromatography (0–15% EtOAc/hexanes) afforded the pure
tertiary amine as a colorless oil (55 mg, 47%). \textsuperscript{1}H NMR (700 MHz, CDCl\textsubscript{3}) \(\delta\) 7.91 (d, \(J = 8.8\) Hz, 2H), 7.85 (d, \(J = 7.4\) Hz, 2H), 7.67 (d, \(J = 8.5\) Hz, 2H), 7.25–7.19 (m, 2H), 7.16 (t, \(J = 4.0\) Hz, 3H), 6.87 (d, \(J = 8.9\) Hz, 2H), 5.73 (dd, \(J = 9.5, 4.9\) Hz, 1H), 4.96 (d, \(J = 7.3\) Hz, 1H), 3.85 (s, 3H), 3.41 (ddd, \(J = 12.3, 9.5, 2.4\) Hz, 1H), 3.29 (dddd, \(J = 14.1, 11.6, 5.7, 2.4\) Hz, 1H), 3.25–3.15 (m, 1H), 2.67 (dd, \(J = 13.6, 4.5\) Hz, 1H), 2.23 (dp, \(J = 12.1, 6.0\) Hz, 1H), 2.14 (dq, \(J = 20.1, 12.7, 9.5\) Hz, 1H), 1.64 (s, 3H), 1.58 (s, 3H); \textsuperscript{13}C NMR (176 MHz, CDCl\textsubscript{3}) \(\delta\) 194.5, 163.8, 143.5, 136.6, 134.8, 134.3 (d, \(J = 32.8\) Hz), 131.1, 129.2, 128.7, 128.6, 127.9, 126.8, 126.1 (q, \(J = 3.4\) Hz), 123.2 (d, \(J = 274.8\) Hz), 119.7, 114.0, 59.8, 55.5, 45.0, 34.9, 29.8, 25.6, 17.7; IR (cm\textsuperscript{-1}): 2930, 1674, 1598, 1403, 1320, 1239, 1161, 1130, 1061, 936; HRMS: \(m/z\) calculated for C\textsubscript{29}H\textsubscript{30}F\textsubscript{3}NO\textsubscript{4}SNa\textsuperscript{+} [M+Na]\textsuperscript{+}: 568.1740; found: 568.1736; [\(\alpha\)]D = –15.5.

\(\text{(S)-N-(1-(2-methoxyphenyl)-1-oxo-3-phenylpropan-2-yl)-4-}
\text{(trifluoromethyl)benzenesulfonylamide (1.58 INT): Prepared according to GP-1.5 using Weinreb}
\text{amide 1.35 WA (1 g, 2.4 mmol, 1 equiv.) with Mg turnings (175 mg, 7.2 mmol, 3 equiv.), 2-
\text{bromoanisole (1.3 g, 7.4 mmol, 3 equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a}
\text{reaction time of 12 h. Purification by flash column chromatography (0–13% for 10 column}
\text{volumes and then 13% isocratic EtOAc/hexanes) afforded the pure compound as a white solid}
\text{(808 mg, 72%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.79 (d, \(J = 8.2\) Hz, 2H), 7.60–7.52 (m, 4H), 7.19–7.16 (m, 3H), 7.05–6.95(m, 4H), 5.73 (d, \(J = 9.1\) Hz, 1H), 5.42 (ddd, \(J = 9.1, 7.2, 4.9\) Hz, 1H), 3.94 (s, 3H), 3.17 (dd, \(J = 14.2, 4.9\) Hz, 1H), 2.79 (dd, \(J = 14.2, 7.2\) Hz, 1H); \textsuperscript{13}C NMR (176 MHz, CDCl\textsubscript{3}) \(\delta\) 198.2, 159.0, 144.0, 136.1, 135.6, 134.1 (q, \(J = 32.9\) Hz), 131.9, 129.8,128.6, 127.8, 127.2, 126.1 (q, \(J = 3.6\) Hz), 124.5, 121.6, 112.0, 62.8, 56.0, 39.2; IR (cm\textsuperscript{-1}): 2950, 1672,
(S)-N-(2-methoxypent-3-en-1-yl)-N-(1-oxo-1-(o-tolyl)propan-2-yl)-4-
(trifluoromethyl)benzenesulfonamide (1.58 S): Prepared according to GP-1.5 using aryl ketone 
1.58 INT using aryl ketone (400 mg, 0.9 mmol, 1 equiv.), K₂CO₃ (239 mg, 1.7 mmol, 2 equiv.), 
homoprenyl iodide (218 mg, 1.0 mmol, 1.2 equiv.), anhydrous DMF (0.1 M) with a reaction time 
of 24 h. Purification by flash column chromatography (0–15% EtOAc/hexanes) afforded the pure 
tertiary amine as a pale yellow oil (223 mg, 47%). ^1H NMR (700 MHz, CDCl₃) δ 7.79 (d, J = 8.2 
Hz, 2H), 7.60–7.52 (m, 4H), 7.20–7.17 (m, 3H), 7.04–6.99 (m, 3H), 6.97 (d, J = 8.4 Hz, 1H), 5.73 
(d, J = 9.2 Hz, 1H), 5.42 (ddd, J = 9.0, 7.1, 4.8 Hz, 1H), 3.94 (s, 3H), 3.17 (dd, J = 14.1, 4.8 Hz, 
1H), 2.79 (dd, J = 14.1, 7.1 Hz, 1H); ^13C NMR (176 MHz, CDCl₃) δ 197.8, 158.6, 143.6, 135.7, 
135.2, 133.8 (q, J = 32.8 Hz), 131.5, 129.4, 128.2, 127.4, 126.8, 125.8 (q, J = 3.7 Hz), 123.1 (q, J 
= 272.8 Hz), 121.2, 111.7, 62.5, 55.7, 38.8; IR (cm⁻¹): 2827, 1685, 1598, 1485, 1455, 1437, 1404, 
1321, 1287, 1245, 1161, 1130, 1097, 1093, 1062, 1017, 943, 869, 842; HRMS: m/z calculated for 
C₂₉H₃₀F₃NO₄SNa⁺ [M+Na]⁺: 568.1740; found: 568.1732; [α]D = +31.5.

N-(3-(4-bromophenyl)-1-oxo-1-phenylpropan-2-yl)-4-(trifluoromethyl)benzenesulfonamide 
(1.59 INT): Prepared according to GP-1.5 using Weinreb amide 1.59 WA (1.30 g, 2.62 mmol, 1 
equiv.) with Mg turnings (192 mg, 7.88 mmol, 3 equiv.), bromobenzene (1.24 mg, 7.88 mmol, 3 
equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a reaction time of 12 h. Purification 
by flash column chromatography (1–12% EtOAc/hexanes) afforded the pure compound as a white
solid (500 mg, 37%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.78 (dd, $J = 19.6$, 7.9 Hz, 4H), 7.65 (t, $J = 7.5$ Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 2H), 7.49 (t, $J = 7.7$ Hz, 2H), 7.31(d, $J = 7.9$ Hz, 2H), 6.87 (d, $J = 7.8$ Hz, 2H), 5.72 (d, $J = 8.6$ Hz, 1H), 5.16 (q, $J = 6.8$ Hz, 1H), 3.15 (dd, $J = 14.3$, 5.2 Hz, 1H), 2.89 (dd, $J = 14.2$, 6.7 Hz, 1H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 196.5, 143.3, 134.5, 134.3 (d, $J = 33.4$ Hz), 133.7, 133.5, 131.6, 131.2, 129.1, 128.4, 127.4, 126.1 (q, $J = 3.5$ Hz), 123.0 (d, $J = 273.0$ Hz), 121.4, 58.2, 39.5.; IR (cm$^{-1}$): 2930, 1684, 1596, 1506, 1457, 1430, 1407, 1324, 1297, 1263, 1228, 1166, 1154, 1126, 1093, 1109, 1063, 1016, 982, 950, 915, 875, 837; HRMS: m/z calculated for C$^{22}$H$_{17}$BrF$_3$NO$_3$SNa$^+$ [M+Na]$^+$: 533.9957; found: 533.9952.

$N$-(3-(4-bromophenyl)-1-oxo-1-phenylpropan-2-yl)-$N$-(4-methylpent-3-en-1-yl)-4-(trifluoromethyl)benzenesulfonamide (1.59 S): Prepared according to GP-1.5 using aryl ketone 1.59 INT (500 mg, 0.98 mmol, 1 equiv.), K$_2$CO$_3$ (270 mg, 1.95 mmol, 2 equiv.), homoprenyl iodide (246 mg, 1.17 mmol, 1.2 equiv.), anhydrous DMF (0.1 M) with a reaction time of 3 h. Purification by flash column chromatography (0–15% EtOAc/hexanes) afforded the pure tertiary amine as a yellow oil (203 mg, 35%). $^1$H NMR (700 MHz, CDCl$_3$) δ 7.87 (d, $J = 7.8$ Hz, 2H), 7.83 (d, $J = 8.1$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 2H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.40 (t, $J = 7.7$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.07 (d, $J = 8.0$ Hz, 2H), 5.70 (dd, $J = 9.6$, 4.7 Hz, 1H), 4.94 (t, $J = 7.5$ Hz, 1H), 3.41 (dd, $J = 13.7$, 9.6 Hz, 1H), 3.25 (ddd, $J = 16.1$, 11.1, 5.3 Hz, 1H), 3.18 (ddd, $J = 15.5$, 11.1, 5.6 Hz, 1H), 2.68 (dd, $J = 13.7$, 4.7 Hz, 1H), 2.19 (dp, $J = 12.5$, 6.2 Hz, 1H), 2.11 (tt, $J = 13.0$, 6.4 Hz, 1H), 1.63 (s, 3H), 1.56 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 195.9, 143.3, 135.5, 135.1, 134.4 (q, $J = 33.5$ Hz), 133.9, 131.8, 130.9, 128.8, 128.6, 127.8, 126.2 (q, $J = 3.7$ Hz), 123.1 (q, $J = 271.9$, 270.9 Hz), 120.9, 119.4, 60.1, 45.0, 34.3, 29.5, 25.6, 17.7; IR (cm$^{-1}$): 2929, 1686, 1596, 1489, 1449, 1320, 1161, 1132, 1107, 1092, 1012, 932, 908, 871, 843; HRMS: m/z calculated for C$^{28}$H$_{27}$BrF$_3$NO$_3$SH$^+$ [M+H]$^+$: 594.0920; found: 594.0918.
**N-(1-oxo-1-phenyl-3-(thiophen-2-yl)propan-2-yl)-4-(trifluoromethyl)benzenesulfonamide (1.60 INT):** Prepared according to GP-1.5 using Weinreb amide 1.60 WA (469 mg, 1.11 mmol, 1 equiv.) with Mg turnings (81.0 mg, 3.33 mmol, 3 equiv.), bromobenzene (0.356 mL, 3.33 mmol, 3 equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a reaction time of 4 h. Purification by flash column chromatography (5–30% EtOAc/hexanes) afforded the pure compound as a clear, colorless oil (470 mg, 96%). Spectral data was in accordance with literature data.  

**N-(4-methylpent-3-en-1-yl)-N-(1-oxo-1-phenyl-3-(thiophen-2-yl)propan-2-yl)-4-(trifluoromethyl)- benzenesulfonamide (1.60 S):** Prepared according to GP-1.5 using aryl ketone 1.60 INT (470 mg, 1.07 mmol, 1 equiv.), K₂CO₃ (296 mg, 2.14 mmol, 2 equiv.), homoprenyl iodide (270 mg, 1.28 mmol, 1.2 equiv.), anhydrous DMF (0.1 M) with a reaction time of 4 h. Purification by flash column chromatography (2–15% EtOAc/hexanes) afforded the pure tertiary amine as a clear, yellow oil (272 mg, 49%). \(^1\)H NMR (500 MHz, CDCl₃) δ 7.98 (d, J = 7.3 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.12–7.08 (m, 1H), 6.85 (dd, J = 5.1, 3.5 Hz, 1H), 6.77 (d, J = 3.2 Hz, 1H), 5.70 (dd, J = 9.5, 4.3 Hz, 1H), 4.93 (t, J = 7.4 Hz, 1H), 3.68 (dd, J = 14.5, 9.5 Hz, 1H), 3.27–3.20 (m, 1H), 3.18–3.08 (m, 1H), 2.73 (dd, J = 14.5, 4.3 Hz, 1H), 2.26–2.18 (m, 1H), 2.15–2.07 (m, 1H), 1.61 (s, 3H), 1.56 (s, 3H); \(^13\)C NMR (176 MHz, CDCl₃) δ 195.9, 143.5, 134.2, 134.6 (q, J = 33.1 Hz), 134.0, 129.0, 128.1, 127.3, 126.7, 126.5 (q, J = 3.6 Hz), 124.7, 123.3 (q, J = 272.8 Hz), 119.6, 60.9, 45.2, 29.8, 28.9, 25.8, 17.8; IR (cm⁻¹): 2929, 1685, 1597, 1448, 1404, 1347, 1322, 1229, 1162, 1134, 1107, 1092, 1062, 1014, 908, 844, 743, 712; HRMS: m/z calculated for C₂₆H₂₆F₃NO₃S₂Na⁺ [M+Na]⁺: 544.1198; found: 544.1199.
(S)-N-(1-oxo-3-phenyl-1-(thiophen-2-yl)propan-2-yl)-4-
(trifluoromethyl)benzenesulfonamide (1.61 INT): Prepared according to GP-1.5 using Weinreb amide 1.35 WA (1.00 g, 2.40 mmol, 1 equiv.) with Mg turnings (175 mg, 7.20 mmol, 3 equiv.), 2-bromothiophene (1.21 g, 7.44 mmol, 3.1 equiv.), a crystal of iodine and anhydrous THF (0.2 M) with a reaction time of 12 h. Purification by flash column chromatography (1–12% EtOAc/hexanes) afforded the pure compound as a white solid (700 mg, 66%). Spectral data was in accordance with literature data.30

(S)-N-(3-methylbut-2-en-1-yl)-N-(1-oxo-1-phenyl-3-(thiophen-2-yl)propan-2-yl)-4-
(trifluoromethyl)benzenesulfonamide (1.61 S): Prepared according to GP-1.5 using aryl ketone 1.61 INT (400 mg, 0.9 mmol, 1 equiv.), K$_2$CO$_3$ (252 mg, 1.8 mmol, 2 equiv.), homoprenyl iodide (229 mg, 1.1 mmol, 1.2 equiv.), anhydrous DMF (0.1 M) with a reaction time of 24 h. Purification by flash column chromatography (0–15% EtOAc/hexanes) afforded the pure tertiary amine as a yellow oil (179 mg, 37%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.91–7.84 (m, 3H), 7.67 (dd, J = 17.1, 6.5 Hz, 3H), 7.23 (t, J = 7.2 Hz, 2H), 7.19 (d, J = 6.9 Hz, 1H), 7.17–7.13 (m, 2H), 7.07 (t, J = 4.5 Hz, 1H), 5.61 (dd, J = 9.6, 5.0 Hz, 1H), 5.01 (t, J = 7.5 Hz, 1H), 3.43–3.31 (m, 2H), 3.24 (ddd, J = 15.4, 11.1, 5.6 Hz, 1H), 2.68 (dd, J = 13.6, 5.0 Hz, 1H), 2.27 (dtq, J = 31.6, 13.2, 6.3 Hz, 2H), 1.67 (s, 3H), 1.61 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 188.9, 143.4, 142.8, 136.2, 135.4, 134.9, 134.3 (q, J = 33.2 Hz), 133.9, 129.2, 128.7, 128.5, 127.8, 126.9, 126.2 (q, J = 3.6 Hz), 123.1 (q, J = 272.9 Hz), 119.6, 61.4, 45.1, 34.8, 29.8, 25.6, 17.7; IR (cm$^{-1}$): 2732, 1662, 1413, 1404, 1341, 1248, 1163, 1138, 1132, 1249, 1163, 1138, 1108, 1062, 1017, 847, 737; HRMS: m/z calculated for C$_{26}$H$_{26}$F$_3$NO$_3$S$_2$Na$^+$ [M+Na]$^+$: 544.1198; found: 544.1207; [$\alpha$]D = –35.0.
General Procedure for Mitsunobu Reaction (GP-1.6)

A round bottom flask equipped with a magnetic stir bar was charged with a solution of the secondary amine (1.0 equiv.), alcohol (2.2 equiv.) and PPh\textsubscript{3} (3.0 equiv.). The flask was sealed under nitrogen, and anhydrous CH\textsubscript{2}Cl\textsubscript{2} (0.1 M) was added via syringe. To the stirring solution was added DEAD (3.0 equiv., 40% solution in toluene) dropwise at 0 °C. The mixture was warmed to room temperature and stirred under a nitrogen atmosphere for 24 h, at which point the reaction mixture was quenched with deionized water and diluted with EtOAc. The resultant layers were partitioned, and the organic phase was collected. The aqueous phase was extracted with EtOAc (3x). The organic layers were then combined, washed with brine (2x), and dried over Na\textsubscript{2}SO\textsubscript{4}. Purification by chromatography on silica gel gave the desired product.

(S,E)-N-(1-oxo-1,3-diphenylpropan-2-yl)-N-(4-phenylbut-3-en-1-yl)-4 (trifluoromethyl)benzenesulfonamide (1.47): Prepared according to GP-1.6 using secondary amine 1.35 INT (200 mg, 0.46 mmol, 1 equiv.), alcohol (150.4 mg, 1.02 mmol, 2.2 equiv.), PPh\textsubscript{3} (363 mg, 1.38 mmol, 3.0 equiv.), DEAD (602.7 mg, 1.38 mmol, 3.0 equiv., 40% solution in toluene), and CH\textsubscript{2}Cl\textsubscript{2} (0.1 M) with a reaction time of 24 h. Purification by flash column chromatography (0–25% EtOAc/hexanes) afforded the pure tertiary amine as a colorless oil (242...
mg, 93%). \textbf{\textsuperscript{1}H NMR} (700 MHz, CDCl\textsubscript{3}) $\delta$ 7.85 (t, $J = 7.0$ Hz, 4H), 7.63 (d, $J = 8.2$ Hz, 2H), 7.54 (t, $J = 7.5$ Hz, 1H), 7.37 (t, $J = 7.7$ Hz, 2H), 7.28 (t, $J = 9.3$ Hz, 4H), 7.24 (q, $J = 6.4$, 5.1 Hz, 3H), 7.18 (dd, $J = 7.7$, 3.2 Hz, 3H), 6.33 (d, $J = 15.9$ Hz, 1H), 6.03 (dt, $J = 15.2$, 7.2 Hz, 1H), 5.79 (dt, $J = 6.7$, 3.1 Hz, 1H), 3.53 (ddd, $J = 15.3$, 9.4, 5.9 Hz, 1H), 3.47 (td, $J = 14.6$, 13.0, 7.6 Hz, 2H), 2.77 (dd, $J = 13.7$, 5.4 Hz, 1H), 2.46 (t, $J = 16.7$ Hz, 2H); \textbf{\textsuperscript{13}C NMR} (176 MHz, CDCl\textsubscript{3}) $\delta$ 196.5, 143.3, 137.1, 136.3, 135.6, 134.4 (q, $J = 32.7$ Hz), 133.75, 132.5, 129.1, 128.8, 128.7, 128.6, 128.5, 127.9, 127.3, 127.0, 126.2 (q, $J = 3.5$ Hz), 126.1, 125.8, 123.1 (d, $J = 273.8$ Hz), 60.3, 45.1, 35.0, 34.3; \textbf{IR} (cm$^{-1}$): 2934, 1685, 1597, 1582, 1495, 1448, 1404, 1347, 1320, 1233, 1162, 1130, 1107, 1090, 1062, 1015, 935, 943, 909, 842; \textbf{HRMS}: \textit{m/z} calculated for C\textsubscript{32}H\textsubscript{28}F\textsubscript{3}NO\textsubscript{3}SH$^+$ [M+H]$^+$: 564.1815; found: 564.1815.

(\textit{S,E})-N-(4-(4-chlorophenyl)but-3-en-1-yl)-N-(1-oxo-1,3-diphenylpropan-2-yl)-4-(trifluoromethyl)benzenesulfonamide (1.46): Prepared according to GP-1.6 using secondary amine 1.35 INT (177.6 mg, 0.41 mmol, 1 equiv.), alcohol (150.4 mg, 0.82 mmol, 2.0 equiv.), PPh\textsubscript{3} (322.5 mg, 1.23 mmol, 3.0 equiv.), DEAD (535.3 mg, 1.23 mmol, 3.0 equiv., 40% solution in toluene), and CH\textsubscript{2}Cl\textsubscript{2} (0.1 M) with a reaction time of 24 h. Purification by flash column chromatography (0–25% EtOAc/hexanes) afforded the pure tertiary amine as a colorless oil (140 mg, 28%). \textbf{\textsuperscript{1}H NMR} (700 MHz, CDCl\textsubscript{3}) $\delta$ 7.85 (d, $J = 7.9$ Hz, 4H), 7.64 (d, $J = 8.2$ Hz, 2H), 7.53 (t, $J = 7.4$ Hz, 1H), 7.37 (t, $J = 7.4$ Hz, 2H), 7.26–7.22 (m, 4H), 7.20–7.15 (m, 5H), 6.27 (d, $J = 15.9$ Hz, 1H), 6.00 (ddd, $J = 15.4$, 7.9, 6.5 Hz, 1H), 5.79 (dd, $J = 9.6$, 4.9 Hz, 1H), 3.52 (ddd, $J = 15.3$, 9.2, 6.8 Hz, 1H), 3.45 (ddd, $J = 22.9$, 14.5, 8.1 Hz, 2H), 2.73 (dd, $J = 13.8$, 5.1 Hz, 1H), 2.47
(hept, J = 7.2 Hz, 2H); \textsuperscript{13}C NMR (176 MHz, CDCl\textsubscript{3}) \(\delta\) 196.5, 143.2, 136.2, 135.6, 134.5 (d, J = 33.1 Hz), 133.8, 132.9, 131.3, 129.1, 128.8, 128.6, 128.6, 127.9, 127.3, 127.0, 126.8 (d, J = 344.1 Hz), 126.20 (q, J = 3.5 Hz), 60.3, 44.9, 34.9, 34.3; IR (cm\textsuperscript{-1}): 2729, 1685, 1596, 1491, 1449, 1322, 1234, 1164, 1133, 1091, 1062, 1013, 968, 945, 844; HRMS: m/z calculated for C\textsubscript{32}H\textsubscript{27}ClF\textsubscript{3}NO\textsubscript{3}S\textsuperscript{H\textsuperscript{+}}[M+H\textsuperscript{+}]: 598.1431; found: 598.1420.

(\textit{S,E})-N-(1-oxo-1,3-diphenylpropan-2-yl)-N-(4-(p-tolyl)but-3-en-1-yl)-4-(trifluoromethyl)benzenesulfonamide (1.44): Prepared according to GP-1.6 using secondary amine 1.35 INT (50.5 mg, 0.12 mmol, 1 equiv.), alcohol (38.0 mg, 0.23 mmol, 2.0 equiv.), PPh\textsubscript{3} (91.7 mg, 0.35 mmol, 3.0 equiv.), DEAD (15.2 mg, 0.35 mmol, 3.0 equiv., 40% solution in toluene), and CH\textsubscript{2}Cl\textsubscript{2} (0.1 M) with a reaction time of 24 h. Purification by flash column chromatography (0–25% EtOAc/hexanes) afforded the desired substrate as an inseparable mixture of \textit{E:Z} isomers (4:1 ratio) (110 mg, 81%). \textsuperscript{1}H NMR (700 MHz, CDCl\textsubscript{3}) \(\delta\) 7.86–7.81 (m, 4H), 7.62 (q, J = 10.0, 9.5 Hz, 3H), 7.37 (t, J = 7.3 Hz, 2H), 7.23 (q, J = 10.2, 8.7 Hz, 2H), 7.20–7.16 (m, 5H), 7.10 (d, J = 7.7 Hz, 2H), 6.29 (d, J = 15.8 Hz, 1H), 5.97 (dt, J = 15.0, 7.1 Hz, 1H), 5.78 (dd, J = 9.0, 5.1 Hz, 1H), 3.54–3.47 (m, 1H), 3.45 (td, J = 11.5, 10.5, 4.9 Hz, 2H), 2.77 (dd, J = 13.8, 5.1 Hz, 1H), 2.43 (ddt, J = 24.2, 17.5, 7.0 Hz, 2H), 2.34 (s, 3H); \textsuperscript{13}C NMR (176 MHz, CDCl\textsubscript{3}) \(\delta\) 196.6, 143.3, 137.4, 137.1, 136.6, 136.3, 135.7, 134.5, 134.3, 134.3, 133.7, 133.4, 132.6, 132.4, 129.3, 129.2, 129.1, 128.8, 128.77, 128.75, 128.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.0, 126.8, 126.2 (q, J = 3.5 Hz), 126.0, 125.8 (d, J = 3.5 Hz), 124.7, 123.1 (d, J = 272.8 Hz), 60.7, 60.3, 49.0, 45.2, 35.6, 35.0, 34.3, 21.2, 21.0; IR (cm\textsuperscript{-1}): 3027, 1686, 1595, 1581, 1513, 1495, 1448, 1430,
1348, 1321, 1233, 1132, 1107, 1062, 1015, 968, 943, 842, 787; **HRMS**: \( m/z \) calculated for C\(_{33}\)H\(_{30}\)F\(_3\)NO\(_5\)SH\(^+\) [M+H]\(^+\): 578.1971; found: 578.1970.

\[(S,E)-N-(4-(4-methoxyphenyl)but-3-en-1-yl)-N-(1-oxo-1,3-diphenylpropan-2-yl)-4-(trifluoromethyl) benzenesulfonamide (1.45):\] Prepared according to GP-1.6 using secondary amine 1.35 INT (20.0 mg, 0.046 mmol, 1 equiv.), alcohol (42 mg, 0.24 mmol, 5.0 equiv.), PPh\(_3\) (92.3 mg, 0.35 mmol, 7.5 equiv.), DEAD (153.2 mg, 0.35 mmol, 7.5 equiv., 40% solution in toluene), and CH\(_2\)Cl\(_2\) (0.1 M) with a reaction time of 24 h. Purification by flash column chromatography (0–25% EtOAc/hexanes) afforded the pure tertiary amine as a colorless oil (36 mg, 26%). Purification by flash column chromatography over silica eluting with EtOAc/hexanes (1:4) afforded the desired substrate as an inseparable mixture of E:Z isomers (1.5:1 ratio). **\(^1\)H NMR** (700 MHz, CDCl\(_3\)) \( \delta \) 7.84 (t, \( J = 8.4 \) Hz, 3H), 7.63 (t, \( J = 8.2 \) Hz, 3H), 7.53 (t, \( J = 7.5 \) Hz, 2H), 7.37 (d, \( J = 8.0 \) Hz, 2H), 7.34–7.30 (m, 1H), 7.26–7.14 (m, 9H), 6.83 (d, \( J = 8.6 \) Hz, 2H), 6.27 (d, \( J = 15.8 \) Hz, 1H), 5.87 (dt, \( J = 15.5, 7.2 \) Hz, 1H), 5.78 (dd, \( J = 9.3, 5.1 \) Hz, 1H), 3.82 (s, 3H), 3.47 (dtd, \( J = 29.0, 9.1, 3.7 \) Hz, 3H), 2.77 (dd, \( J = 13.6, 4.9 \) Hz, 1H), 2.43 (ddq, \( J = 23.8, 16.3, 7.2 \) Hz, 2H); **\(^{13}\)C NMR** (176 MHz, CDCl\(_3\)) \( \delta \) 196.6, 196.5, 159.2, 159.0, 143.3, 136.7, 136.3, 136.0, 135.7, 134.4 (d, \( J = 33.0 \) Hz), 133.7, 133.4, 131.9, 130.3, 129.9, 129.8, 129.3, 129.2, 129.1, 128.76, 128.75, 128.72, 128.61, 128.59, 128.53, 128.5, 128.3, 128.2, 127.9, 127.8, 127.5, 127.2, 127.0, 126.8, 126.2 (q, \( J = 3.5 \) Hz), 125.8 (d, \( J = 3 \) Hz), 123.1 (d, \( J = 273.0 \) Hz) 114.3, 113.9, 113.7, 113.5, 60.7, 60.5, 60.3, 55.3, 55.2, 48.7, 45.2, 35.4, 35.0, 34.3; **IR (cm\(^{-1}\))**: 2919, 1686, 1607, 1512, 1448,
HRMS: m/z calculated for C$_{33}$H$_{30}$F$_{3}$NO$_{4}$SH$^+$ [M+H]$^+$: 594.1920; found: 594.1920.

General Procedure for N-Alkylation to obtain Olefin Substrates (GP-1.7)

A round bottom flask equipped with a magnetic stir bar was charged with KI (0.8 equiv.) and K$_2$CO$_3$ (2.0 equiv.). The flask was sealed under nitrogen, and anhydrous DMF (0.1 M) was added via syringe. To the stirring solution was added a solution of secondary amine (1 equiv.) in DMF (0.1 M). To the stirring solution was added the corresponding bromide (2 equiv.). The mixture was warmed to 55 °C via heating mantle and stirred under a nitrogen atmosphere for 24 h, at which point the reaction mixture was quenched with deionized water and diluted with Et$_2$O. The resultant layers were partitioned, and the organic phase was collected. The aqueous phase was extracted with Et$_2$O (3x). The organic layers were then combined, washed with an aqueous 5% LiCl solution (3x), brine (1x), dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. Purification by flash column chromatography eluting with EtOAc/hexanes (0–25%) afforded the desired substrate.

(S,E)-N-(1-oxo-1,3-diphenylpropan-2-yl)-N-(4-phenylpent-3-en-1-yl)-4-(trifluoromethyl)benzenesulfonamide (1.42): Prepared using GP-1.7, secondary amine 1.35 INT (53 mg, 0.12 mmol, 1 equiv.), (5-bromopent-2-en-2-yl)benzene (55.1 mg, 0.24 mmol, 2.0 equiv.), K$_2$CO$_3$ (33.9 mg, 0.24 mmol, 2.0 equiv.), and KI (16.2 mg, 0.09 mmol, 0.8 equiv.) in anhydrous
DMF (0.05 M) with a reaction time of 24 h. Purification by flash column chromatography (0–25% EtOAc/hexanes) afforded the desired product as a clear, colorless oil (30 mg, 43%). \textbf{\textit{\textsuperscript{1}H NMR}} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.84 (dd, \(J = 13.0, 7.9\) Hz, 4H), 7.62 (d, \(J = 8.3\) Hz, 2H), 7.53 (t, \(J = 7.4\) Hz, 1H), 7.37 (t, \(J = 7.8\) Hz, 2H), 7.30 (q, \(J = 7.8\) Hz, 4H), 7.26–7.19 (m, 3H), 7.17 (d, \(J = 7.2\) Hz, 3H), 5.79 (dd, \(J = 9.3, 5.1\) Hz, 1H), 5.60 (t, \(J = 7.0\) Hz, 1H), 3.40 (dt, \(J = 29.6, 15.1, 14.5, 7.7\) Hz, 3H), 2.76 (dd, \(J = 13.7, 5.0\) Hz, 1H), 2.43 (ddh, \(J = 20.9, 14.0, 6.9\) Hz, 2H), 1.99 (s, 3H); \textbf{\textit{\textsuperscript{13}C NMR}} (100 MHz, CDCl\textsubscript{3}) \(\delta\) 196.5, 143.3, 143.2, 137.7, 136.3, 134.4 (d, \(J = 33.0\) Hz), 133.8, 129.2, 128.8, 128.7, 128.6, 128.2, 127.8, 126.9, 126.8, 126.2 (q, \(J = 4.3, 3.5\) Hz), 125.6, 124.6 (d, \(J = 267.2\) Hz), 123.0, 60.3, 44.7, 35.0, 30.4, 15.8; \textbf{IR} (cm\textsuperscript{-1}): 2923, 1685, 1596, 1581, 1495, 1448, 1404, 1321, 1266, 1163, 1131, 1108, 1091, 1028, 1016, 944, 843, 787; \textbf{HRMS} m/z calculated for C\textsubscript{33}H\textsubscript{30}F\textsubscript{3}NO\textsubscript{3}SK\textsuperscript{+} [M+K]: 616.1530; found: 616.1531.

\textbf{(S)-N-(4-methylpent-4-en-1-yl)-N-(1-oxo-1,3-diphenylpropan-2-yl)-4-(trifluoromethyl)benzenesulfonamide} (1.43): Prepared using GP-1.7, secondary amine 1.35 INT (50 mg, 0.12 mmol, 1 equiv.), 4-iodo-2-methyl-but-1-ene (22.6 mg, 0.12 mmol, 1.0 equiv.), K\textsubscript{2}CO\textsubscript{3} (31.9 mg, 0.23 mmol, 2.0 equiv.) in anhydrous DMF (0.05 M) with a reaction time of 24 h. Purification by flash column chromatography (0–25% EtOAc/hexanes) afforded the product as a clear, colorless oil (17.3 mg, 29%). \textbf{\textit{\textsuperscript{1}HNMR}} (700 MHz, CDCl\textsubscript{3}) \(\delta\) 7.86 (d, \(J = 7.4\) Hz, 2H), 7.81 (d, \(J = 8.2\) Hz, 2H), 7.64 (d, \(J = 8.3\) Hz, 2H), 7.55 (t, \(J = 7.4\) Hz, 1H), 7.40 (t, \(J = 7.8\) Hz, 2H), 7.26–7.22 (m, 2H), 7.18 (d, \(J = 6.7\) Hz, 3H), 5.78 (dd, \(J = 9.4, 5.0\) Hz, 1H), 4.73 (s, 1H), 4.63 (s, 1H), 3.43 (dd, \(J = 13.7, 9.4\) Hz, 1H), 3.35 (dd, \(J = 15.0, 11.1, 5.3\) Hz, 1H), 3.27 (ddd, \(J = 15.0, 11.0, 5.3\) Hz, 1H), 2.73 (dd, \(J = 13.7, 5.0\) Hz, 1H), 1.93 (t, \(J = 7.5\) Hz, 2H), 1.73–1.68 (m, 1H), 1.67 (s,
3H), 1.63 (ddt, J = 11.2, 7.4, 3.8 Hz, 1H); \(^{13}\text{C NMR}\) (176 MHz, CDCl\(_3\)) \(\delta\) 196.6, 144.3, 143.4, 136.4, 135.7, 134.3 (q, J = 33.1 Hz), 133.7, 129.1, 128.8, 128.7, 128.6, 127.8, 126.9, 126.1 (q, J = 3.7 Hz), 123.1 (q, J = 272.9 Hz), 110.6, 60.3, 45.1, 35.02, 34.98, 28.1, 22.1; \(^{\text{IR}}\) (cm\(^{-1}\)): 2926, 1687, 1597, 1496, 1404, 1349, 1233, 1233, 1164, 1134, 1108, 1063, 1016, 945, 890, 844, 787;

**HRMS:** \(m/z\) calculated for C\(_{28}\)H\(_{28}\)F\(_3\)NO\(_3\)SNa\(^+\) [M+Na]\(^+\): 538.1634; found: 538.1724.

**General Procedure for Carbonyl-Olefin Metathesis (GP-1.8)**

A Schlenk flask or microwave vial is charged with a stir bar and FeCl\(_3\) (30 mol%) and placed under a nitrogen atmosphere. To the reaction vessel is added a 0.01 M solution of substrate (0.1 mmol) in anhydrous DCE via syringe. The vessel is then sealed, and the reaction mixture is heated to 84 °C via oil bath and allowed to stir for 24 h. The reaction is then cooled to room temperature and flushed through a small silica plug rinsing with CH\(_2\)Cl\(_2\). The resultant organic mixture is then concentrated under reduced pressure to give the crude product. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/Hexanes) provided the desired tetrahydropyridine product.

\[\text{(S)-6-benzyl-5-phenyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.36): Prepar} \]

Prepared according to GP-1.8 using substrate \(1.35\) (51.6 mg, 0.1 mmol, 1 equiv.), FeCl\(_3\) (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M) with a reaction time of 24 h at 84 °C.

Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided \(1.36\) as a white solid (40.8 mg, 89%). The reaction was also run on a
1.0 mmol scale using substrate 1.35 (516.0 mg, 1.0 mmol, 1 equiv.), FeCl₃ (48.7 mg, 0.3 mmol, 30 mol%), anhydrous DCE (0.01 M) with a reaction time of 24 h at 84 °C (heated via oil bath). The reaction is then cooled to room temperature and flushed through a small silica plug with CH₂Cl₂. The resultant organic mixture is then concentrated under reduced pressure to give the crude product. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided the product as a white solid (401.2 mg, 88%). Furthermore, the reaction could be run on a 0.02 mmol scale with 0.3 equiv. FeCl₃ in toluene (0.01 M) at 84 °C for 24 h and resulted in 75% yield of the metathesis product. Spectral data was found to be in accordance with literature data.³⁰¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 4.3 Hz, 4H), 7.34 (h, J = 4.3 Hz, 1H), 7.17 (dd, J = 7.9, 3.3 Hz, 3H), 7.01 (dd, J = 6.8, 2.7 Hz, 2H), 5.92 (t, J = 3.9 Hz, 2H), 5.21 (d, J = 8.5 Hz, 1H), 3.77 (dd, J = 14.6, 6.8 Hz, 1H), 3.15 (ddd, J = 15.2, 12.0, 4.8 Hz, 1H), 2.88 (dd, J = 14.3, 3.8 Hz, 1H), 2.73 (dd, J = 14.3, 9.4 Hz, 1H), 2.29 (ddd, J = 18.9, 12.8, 5.6 Hz, 1H), 2.04 (dt, J = 18.4, 5.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 144.32, 139.48, 139.24, 137.73, 133.61 (q, J = 35.1 Hz), 129.31, 128.85, 128.33, 128.03, 127.82, 127.32, 126.56, 126.23, 125.84 (q, J = 3.7 Hz), 123.92, 122.54 (q, J = 255.1 Hz), 56.74, 39.01, 37.66, 24.37; ee: 98%.

1-((4-chlorophenyl)sulfonyl)-5-phenyl-1,2,3,6-tetrahydropyridine (1.38 PDT): Prepared according to GP-1.8 using substrate 1.38 (39.2 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.38 PDT as a clear, colorless oil (26.6 mg, 80%). ¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, J = 8.5 Hz,
5-phenyl-1-(phenylsulfonyl)-1,2,3,6-tetrahydropyridine (1.39 PDT): Prepared according to GP-1.8 using substrate 1.39 (35.7 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.39 PDT as a clear, colorless oil (23.5 mg, 78%). ¹H NMR (700 MHz, CDCl₃) δ 7.85 (d, J = 7.4 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 7.35–7.31 (m, 2H), 7.31–7.28 (m, 3H), 6.08 (tt, J = 4.1, 1.9 Hz, 1H), 3.98 (d, J = 2.4 Hz, 2H), 3.28 (t, J = 5.8 Hz, 2H), 2.40 (dh, J = 5.9, 2.8 Hz, 2H). ¹³C NMR (176 MHz, CDCl₃) δ 138.7, 136.5, 133.4, 132.8, 129.1, 128.5, 127.7, 127.6, 125.2, 122.2, 46.4, 42.4, 25.6. IR (cm⁻¹) 2921, 1495, 1446, 1342, 1169, 1098, 1011, 969, 899, 854, 744; HRMS m/z calculated for C₁₁H₁₂NO₂SNa⁺ [M+Na⁺]: 322.0872; found: 322.0869.

5-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine (1.40 PDT): Prepared according to GP-1.8 using substrate 1.40 (37.1 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous
DCE (0.01 M, 10 mL) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.40 PDT as a clear, colorless oil (22.3 mg, 72%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.73 (d, J = 8.2 Hz, 2H), 7.36–7.27 (m, 7H), 6.08 (tt, J = 4.1, 1.9 Hz, 1H), 3.95 (q, J = 2.4 Hz, 2H), 3.25 (t, J = 5.8 Hz, 2H), 2.44 (s, 3H), 2.39 (dq, J = 7.5, 3.2, 2.6 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.6, 138.7, 133.5, 133.4, 129.7, 128.5, 127.7, 125.2, 122.2, 46.4, 42.3, 25.6, 21.5; IR (cm$^{-1}$) 2920, 1597, 1493, 1446, 1341, 1305, 1267, 1240, 1164, 1097, 1010, 979, 853, 816, 757; HRMS calculated for C$_{18}$H$_{19}$NO$_2$SNa$^+$ [M+Na$^+$]: 336.1029; found: 336.1026.

1-((4-methoxyphenyl)sulfonyl)-5-phenyl-1,2,3,6-tetrahydropyridine (1.41 PDT): Prepared according to GP-1.8 using substrate 1.41 (38.7 mg, 0.1 mmol, 1 equiv.), FeCl$_3$ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.41 PDT as a clear, colorless oil (15.4 mg, 47%). The reaction was also run for 48 h at otherwise identical conditions to provide 78% of the desired product. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.77 (d, J = 8.6 Hz, 2H), 7.32 (t, J = 7.5 Hz, 3H), 7.31–7.26 (m, 4H), 6.99 (d, J = 8.5 Hz, 2H), 6.07 (tt, J = 4.0, 2.0 Hz, 1H), 3.94 (s, 2H), 3.86 (s, 4H), 3.24 (t, J = 5.6 Hz, 2H), 2.39 (s, 2H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 163.0, 138.7, 133.5, 129.8, 128.5, 128.1, 127.7, 125.2, 122.2, 114.2, 55.6, 46.4, 42.3, 25.6; IR (cm$^{-1}$) 2921, 2814, 1596, 1577, 1460, 1446, 1340, 1306, 1260, 1179, 1098, 1013, 1025, 969, 900, 835, 805, 757; HRMS m/z calculated for C$_{18}$H$_{19}$NO$_3$SNa$^+$ [M+Na$^+$]: 352.0978; found: 352.0976.
5-phenyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.48): Prepared according to GP-1.8 using substrate 1.37 (42.5 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.48 as a clear, colorless oil (32.5 mg, 89%). Spectral data was found to be in accordance with literature data.³⁰ ¹H NMR (700 MHz, CDCl₃) δ 7.96 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.33 (t, J = 7.4 Hz, 2H), 7.28 (t, J = 8.9 Hz, 3H), 6.12–6.05 (m, 1H), 4.00 (s, 2H), 3.31 (t, J = 5.8 Hz, 2H), 2.39 (qd, J = 6.1, 2.6 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 140.6, 138.6, 134.7 (q, J = 33.1 Hz), 133.4, 128.8, 128.2, 128.0, 126.4 (q, J = 3.7 Hz), 125.3, 122.3, 46.5, 42.5, 25.6.

1-((4-chlorophenyl)sulfonyl)-5-(p-tolyl)-1,2,3,6-tetrahydropyridine (1.49): Prepared according to GP-1.8 using substrate 1.49 S (39.2 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.49 as a clear, colorless oil (17.6 mg, 53%). ¹H NMR (500 MHz, CDCl₃) δ 7.77 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.15 (dd, J = 20.8, 8.1 Hz, 4H), 6.03 (s, 1H), 3.95 (d, J = 2.0 Hz, 2H), 3.27 (t, J = 5.8 Hz, 2H), 2.37 (d, J = 3.4 Hz, 2H), 2.34 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 139.3, 137.7, 135.2, 133.1, 129.4, 129.2, 129.0, 125.0, 121.3, 46.4, 42.3, 25.4, 21.1; IR (cm⁻¹) 2921, 1586,
1513, 1475, 1460, 1394, 1278, 1242, 1166, 1087, 1020, 972, 900, 812, 762; **HRMS**
m/z calculated for C_{18}H_{18}ClNO_{2}SNa^+ [M+Na]^+: 370.0639; found: 370.0635.

(S)-1-((4-chlorophenyl)sulfonyl)-6-methyl-5-phenyl-1,2,3,6-tetrahydropyridine (1.50):
Prepared according to GP-1.8 using substrate **1.50 S** (40.6 mg, 0.1 mmol, 1 equiv.), FeCl$_3$ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided **1.50** as a clear, colorless oil (27.7 mg, 80%). **$^1$H NMR** (700 MHz, CDCl$_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.1 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 5.78 (d, J = 5.5 Hz, 1H), 5.02 (q, J = 6.9 Hz, 1H), 3.92 (dd, J = 14.3, 6.6 Hz, 1H), 3.27 (td, J = 14.5, 4.7 Hz, 1H), 2.17–2.09 (m, 1H), 2.04 (dt, J = 18.4, 5.2 Hz, 1H), 1.22 (d, J = 6.8 Hz, 3H); **$^{13}$C NMR** (176 MHz, CDCl$_3$) δ 140.4, 140.0, 139.3, 138.8, 129.3, 128.7, 128.2, 127.7, 126.2, 122.5, 50.9, 37.1, 24.5, 19.4; **IR** (cm$^{-1}$) 2932, 1688, 1584, 1475, 1446, 1393, 1338, 1276, 1207, 1154, 1089, 1012, 1000, 953, 907, 868, 829, 755; **HRMS** m/z calculated for C$_{18}$H$_{18}$ClNO$_2$SNa$^+$ [M+Na]$^+$: 370.0639; found: 370.0643; [α]$_D$ = +175.54.

(S)-6-methyl-5-phenyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.51): Prepared according to GP-1.8 using substrate **1.51 S** (43.9 mg, 0.1 mmol, 1 equiv.), FeCl$_3$ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 24 h at
84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.51 as a clear, colorless oil (38.0 mg, 99%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.01 (d, \(J = 8.1\) Hz, 2H), 7.74 (d, \(J = 8.1\) Hz, 2H), 7.35 (d, \(J = 7.3\) Hz, 2H), 7.31 (d, \(J = 6.5\) Hz, 1H), 7.28 (d, \(J = 5.6\) Hz, 2H), 5.79 (d, \(J = 4.7\) Hz, 1H), 5.06 (q, \(J = 6.6\) Hz, 1H), 3.95 (dd, \(J = 14.3, 6.1\) Hz, 1H), 3.30 (dd, \(J = 14.9, 11.3, 5.2\) Hz, 1H), 2.19–2.01 (m, 2H), 1.23 (d, \(J = 6.7\) Hz, 3H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 145.1, 140.4, 139.1, 134.1 (q, \(J = 32.9\) Hz), 128.7, 127.8, 127.2, 126.3–126.0 (m), 124.8 (d, \(J = 272.9\) Hz), 122.4, 51.1, 37.2, 24.6, 19.4; IR (cm\(^{-1}\)) 3028, 2927, 1607, 1495, 1454, 1403, 1321, 1162, 1130, 1107, 1096, 1062, 1016, 973, 957, 911, 880, 845; HRMS \(m/z\) calculated for C\(_{19}\)H\(_{18}\)F\(_3\)NO\(_2\)SNa\(^+\) [M+Na]\(^+\): 404.0903; found: 404.1003; \([\alpha]\)_D = +147.64.

(S)-6-methyl-5-(p-tolyl)-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.52): Prepared according to GP-1.8 using substrate 1.52 S (45.4 mg, 0.1 mmol, 1 equiv.), FeCl\(_3\) (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.52 as a clear, colorless oil (35.1 mg, 85%). \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 8.00 (d, \(J = 8.0\) Hz, 2H), 7.73 (d, \(J = 7.9\) Hz, 2H), 7.17 (s, 4H), 5.75 (d, \(J = 5.9\) Hz, 1H), 5.04 (t, \(J = 7.1\) Hz, 1H), 3.94 (dd, \(J = 14.5, 6.5\) Hz, 1H), 3.29 (td, \(J = 12.9, 11.4, 4.0\) Hz, 1H), 2.36 (s, 3H), 2.12 (dt, \(J = 17.8, 7.4\) Hz, 1H), 2.08–2.01 (m, 1H), 1.23 (d, \(J = 4.8\) Hz, 3H); \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 145.1, 140.1, 137.6, 136.2, 134.0 (q, \(J = 33.0\) Hz), 129.4, 127.2, 126.1 (q, \(J = 3.8\) Hz), 125.96, 123.2 (d, \(J = 272.9\) Hz), 121.7, 51.1, 37.2, 24.5, 21.1, 19.4; IR (cm\(^{-1}\)) 2927,
1607, 1457, 1403, 1320, 1214, 1164, 1130, 1107, 1061, 1017, 1004, 966, 880, 843, 785; HRMS m/z calculated for C_{20}H_{20}F_{3}NO_{2}SH^{+} [M+H]^+: 396.1240; found: 396.1238; [α]D = +329.98.

(S)-6-methyl-5-(m-tolyl)-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.53): Prepared according to GP-1.8 using substrate 1.53 S (45.4 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.53 as a clear, colorless oil (19.7 mg, 50%). ¹H NMR (700 MHz, CDCl₃) δ 8.01 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.24 (t, J = 7.7 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 7.2 Hz, 2H), 5.77 (d, J = 3.2 Hz, 1H), 5.05 (q, J = 6.9 Hz, 1H), 3.94 (dd, J = 14.2, 6.5 Hz, 1H), 3.29 (ddd, J = 14.3, 11.7, 4.9 Hz, 1H), 2.37 (s, 3H), 2.16–2.08 (m, 1H), 2.05 (dt, J = 18.1, 5.2 Hz, 1H), 1.23 (d, J = 6.8 Hz, 3H); ¹³C NMR (176 MHz, CDCl₃) δ 145.1, 140.5, 139.1, 138.3, 134.1 (q, J = 32.8 Hz), 128.5 (d, J = 3.3 Hz), 127.2, 126.9, 126.2 (q, J = 3.7 Hz), 123.3, 123.2 (d, J = 272.8 Hz), 122.2, 51.1, 37.2, 24.6, 21.5, 19.4; IR (cm⁻¹) 2933, 1607, 1403, 1322, 1165, 1134, 1107, 1062, 1016, 843, 785; HRMS m/z calculated for C_{20}H_{20}F_{3}NO_{2}SH^{+} [M+H]^+: 396.1240; found: 396.1235; [α]D = +313.8.
(S)-5-([1,1'-biphenyl]-4-yl)-6-methyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.54): Prepared according to GP-1.8 using substrate 1.54 S (51.6 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.54 as a white solid (29.7 mg, 65%). ¹H NMR (700 MHz, CDCl₃) δ 8.02 (d, J = 6.5 Hz, 2H), 7.75 (d, J = 6.5 Hz, 2H), 7.60 (p, J = 5.8 Hz, 4H), 7.46 (q, J = 6.8 Hz, 2H), 7.36 (q, J = 8.1, 6.6 Hz, 3H), 5.87 (d, J = 5.3 Hz, 1H), 5.12 (q, J = 6.5 Hz, 1H), 5.96 (dt, J = 12.9, 5.8 Hz, 1H), 3.32 (td, J = 13.8, 12.3, 5.4 Hz, 1H), 2.21–2.12 (m, 1H), 2.09 (dt, J = 18.5, 5.3 Hz, 1H), 1.28 (d, J = 5.9 Hz, 3H); ¹³C NMR (176 MHz, CDCl₃) δ 145.1, 140.7, 140.4, 139.9, 137.9, 134.1 (d, J = 32.5 Hz), 128.8, 127.5, 127.4, 127.3, 127.0, 126.5, 126.2 (d, J = 4.0 Hz), 124.8 (d, J = 272.8 Hz), 122.5, 51.0, 37.2, 24.7, 19.5; IR (cm⁻¹) 2927, 1608, 1488, 1448, 1403, 1340, 122, 1168, 1130, 1107, 1062, 1017, 1000, 956, 909, 871, 843, 827, 789; HRMS m/z calculated for C₂₅H₂₂F₃NO₂SH⁺ [M+H⁺]: 458.1396; found: 458.1395; [α]D = +253.76.

(S)-5-(4-chlorophenyl)-6-methyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.55): Prepared according to GP-1.8 using substrate 1.55 S (47.4 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.55 as a clear, colorless oil (35.0 mg, 84%). ¹H NMR (700 MHz, CDCl₃) δ 7.99 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 5.80 (dd, J = 5.4, 2.2 Hz, 1H), 5.00 (q, J = 7.2 Hz, 1H), 3.94 (dd, J = 14.2, 6.6
Hz, 1H), 3.27 (ddd, J = 13.9, 11.8, 4.7 Hz, 1H), 2.21–2.12 (m, 1H), 2.07 (dt, J = 18.4, 5.2 Hz, 1H), 1.20 (d, J = 6.7 Hz, 3H); ¹³C NMR (176 MHz, CDCl₃) δ 145.0, 139.4, 137.5, 134.2 (d, J = 33.2 Hz), 133.7, 128.9, 127.4, 127.2, 126.2 (q, J = 3.7 Hz), 124.7 (d, J = 272.0 Hz), 123.1, 50.9, 37.1, 24.7, 19.2; IR (cm⁻¹) 2922, 2361, 2337, 1700, 1506, 1490, 1319, 1157, 1061, 871; HRMS m/z calculated for C₁₉H₁₇ClF₃NO₂SNa⁺ [M+Na]⁺: 438.0513; found: 438.0509; [α]D = +181.92.

(S)-6-benzyl-5-(4-fluorophenyl)-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.56): Prepared according to GP-1.8 using substrate 1.56 S (45.0 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.56 as a clear, colorless oil (30.0 mg, 75%). ¹H NMR (700 MHz, CDCl₃) δ 7.57–7.51 (m, 4H), 7.40–7.35 (m, 2H), 7.20–7.14 (m, 3H), 7.10 (td, J = 8.5, 1.3 Hz, 2H), 6.99 (d, J = 7.1 Hz, 2H), 5.89 (d, J = 7.4 Hz, 1H), 5.15 (q, J = 3.5 Hz, 1H), 3.77 (dd, J = 14.6, 6.8 Hz, 1H), 3.17 (ddd, J = 15.3, 12.0, 4.8 Hz, 1H), 2.85 (dd, J = 14.5, 4.0 Hz, 1H), 2.72 (dd, J = 14.4, 9.5 Hz, 1H), 2.36 (dt, J = 19.1, 9.0 Hz, 1H), 2.07 (dt, J = 18.4, 5.2 Hz, 1H); ¹³C NMR (176 MHz, CDCl₃) δ 162.4 (d, J = 247.5 Hz), 144.2, 138.5, 137.6, 135.7, 133.7 (d, J = 33.0 Hz), 129.3, 128.4, 127.9 (d, J = 7.9 Hz), 127.3, 126.7, 125.9 (q, J = 3.6 Hz), 124.1, 120.7 (d, J = 631.0 Hz), 115.7 (d, J = 21.4 Hz), 56.9, 39.0, 37.6, 24.5; IR (cm⁻¹) 2927, 1685, 1602, 1508, 1454, 1403, 1322, 1262, 1232, 1160, 1131, 1107, 1062, 1017, 974, 958, 829, 786; HRMS m/z calculated for C₂₅H₂₁F₄NO₂SNa⁺ [M+Na]⁺: 498.1121; found: 498.1127; [α]D = +148.30 (c = 0.02).
(S)-6-benzyl-5-(4-methoxyphenyl)-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.57): Prepared according to GP-1.8 using substrate 1.57 S (54.5 mg, 0.1 mmol, 1 equiv.), FeCl₃ (16.2 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 48 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.57 as a clear, colorless oil (27.3 mg, 56%). ¹H NMR (700 MHz, CDCl₃) δ 7.58 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 7.20–7.16 (m, 3H), 7.05–7.00 (m, 2H), 6.95 (d, J = 8.7 Hz, 2H), 5.84 (s, 1H), 5.17 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H), 3.76 (dd, J = 14.6, 6.7 Hz, 1H), 3.14 (ddd, J = 14.7, 12.0, 4.8 Hz, 1H), 2.89 (dd, J = 14.4, 3.8 Hz, 1H), 2.74 (dd, J = 14.4, 9.4 Hz, 1H), 2.32–2.23 (m, 1H), 2.02 (dt, J = 18.3, 5.1 Hz, 1H); ¹³C NMR (176 MHz, CDCl₃) δ 159.3, 144.4, 133.6 (q, J = 33.0 Hz), 132.0 129.3, 128.3, 127.3 (d, J = 1.6 Hz), 126.6, 125.8 (q, J = 3.8 Hz), 123.2 (d, J = 273.1 Hz), 122.5, 114.2, 56.9, 55.3, 39.0, 37.7, 24.3; IR (cm⁻¹) 3029, 2935, 2837, 1607, 1511, 1403, 1320, 1291, 1061, 749; HRMS m/z calculated for C₂₆H₂₄F₃NO₃SH⁺ [M+H⁺]: 488.1502; found: 488.1504; [α]D = +121.26.

(5S)-6-benzyl-5-(2-methoxyphenyl)-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.58): Prepared according to GP-1.8 using substrate 1.58 S (54.5 mg, 0.1 mmol, 1 equiv.), FeCl₃ (16.2 mg, 0.1 mmol), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 48 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes
(3–5% EtOAc/hexanes) provided 1.58 as a clear, colorless oil (10.5 mg, 22%). \(^1\)H NMR (700 MHz, CDCl₃) δ 7.67 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.40 (t, J = 7.8 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.26 (q, J = 8.1 Hz, 4H), 7.21 (t, J = 6.7 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 5.95 (t, J = 7.2 Hz, 1H), 5.04 (ddt, J = 8.8, 7.2, 1.5 Hz, 1H), 3.69 (s, 3H), 3.41 (dd, J = 14.3, 7.2 Hz, 1H), 3.35 (dd, J = 14.7, 11.6, 5.3 Hz, 1H), 3.24 (dd, J = 14.8, 11.5, 5.2 Hz, 1H), 2.95 (dd, J = 14.3, 7.2 Hz, 1H), 2.34 (tt, J = 12.5, 6.2 Hz, 1H), 2.24 (tt, J = 12.7, 6.2 Hz, 1H); \(^{13}\)C NMR (176 MHz, CDCl₃) δ 199.1, 157.7, 143.7, 137.2, 134.6, 133.9, 133.7 (q, J = 33.0 Hz), 130.4, 129.1, 128.4, 127.6, 127.0, 126.6, 125.6 (q, J = 3.6 Hz), 123.2 (d, J = 272.9 Hz), 120.9, 120.0, 111.4, 64.7, 55.4, 45.5, 35.6, 29.7, 25.6, 17.8; IR (cm⁻¹) 2925, 1598, 1488, 1455, 1436, 1404, 1321, 1233, 1160, 1129, 1107, 1096, 1062, 1018, 978, 958, 910, 881, 842; HRMS: m/z calculated for C₂₆H₂₄F₃NO₃SH⁺ [M+H]⁺: 488.1502; found: 488.1493; [α]D = +27.0 (c = 0.03).

6-(4-bromobenzyl)-5-phenyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.59): Prepared according to GP-1.8 using substrate 1.59 S (59.4 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.59 as a clear, colorless oil (38 mg, 71%). \(^1\)H NMR (700 MHz, CDCl₃) δ 7.99 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 5.80 (d, J = 3.3 Hz, 1H), 5.01 (q, J = 7.1 Hz, 1H), 3.94 (dd, J = 14.2, 6.6 Hz, 1H), 3.27 (ddd, J = 14.0, 11.9, 4.7 Hz, 1H), 2.16 (dddt, J = 14.2, 11.5, 5.8, 2.7 Hz, 1H), 2.07 (dt, J = 18.4, 5.1 Hz, 1H), 1.20 (d, J = 6.7 Hz, 3H); \(^{13}\)C NMR (176 MHz, CDCl₃) δ 144.9,
139.4, 137.5, 134.1 (q, J = 33.1 Hz), 133.6, 128.9, 127.4, 127.2, 126.2 (q, J = 3.7 Hz), 123.2 (d, J = 272.9 Hz), 123.1, 50.9, 37.1, 24.7, 19.2; IR (cm⁻¹) 2937, 1688, 1488, 1446, 1403, 1322, 1163, 1132, 1107, 1062, 1012, 959, 843, 809, 760; HRMS m/z calculated for C₂₅H₂₁BrF₃NO₂SH⁺ [M+H]⁺: 536.0501; found: 536.0502.

5-phenyl-6-(thiophen-2-ylmethyl)-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.60): Prepared according to GP-1.8 using substrate 1.60 S (52.2 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.60 as a clear, colorless oil (29.7 mg, 64%).

¹H NMR (700 MHz, CDCl₃) δ 7.76 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.44–7.38 (m, 4H), 7.35 (t, J = 7.0 Hz, 1H), 7.10 (d, J = 5.1 Hz, 1H), 6.85 (t, J = 4.2 Hz, 1H), 6.70 (d, J = 3.4 Hz, 1H), 5.93 (d, J = 4.1 Hz, 1H), 5.21 (d, J = 8.2 Hz, 1H), 3.81 (dd, J = 14.6, 6.8 Hz, 1H), 3.11 (dd, J = 15.4, 4.0 Hz, 1H), 3.04 (ddd, J = 14.7, 12.1, 4.8 Hz, 1H), 2.99 (dd, J = 15.4, 8.4 Hz, 1H), 2.21 (td, J = 15.7, 12.7, 6.1 Hz, 1H), 2.02 (dt, J = 18.2, 5.4 Hz, 1H); ¹³C NMR (176 MHz, CDCl₃) δ 144.6, 139.3, 139.2, 138.4, 133.9 (d, J = 32.9 Hz), 128.9, 128.0, 127.4, 126.9, 126.4, 126.3, 126.0 (q, J = 3.7 Hz), 124.5, 124.4, 123.2 (d, J = 251.6 Hz), 56.5, 37.9, 33.3, 24.3; IR (cm⁻¹) 2919, 1403, 1322, 1163, 1130, 1107, 1062, 1015, 842, 711; HRMS m/z calculated for C₂₅H₂₁BrF₃NO₂S₂H⁺ [M+H]⁺: 464.0960; found: 464.0955.
(S)-6-benzyl-5-(thiophen-2-yl)-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.61): Prepared according to GP-1.8 using substrate 1.61 S (52.2 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with EtOAc/hexanes (3–5% EtOAc/hexanes) provided 1.61 as a white solid (26.2 mg, 57%). $^1$H NMR (500 MHz, CDCl₃) δ 7.55 (q, J = 8.4 Hz, 4H), 7.26–7.19 (m, 4H), 7.14–7.09 (m, 3H), 7.06 (dd, J = 5.1, 3.7 Hz, 1H), 6.05 (dd, J = 5.2, 2.9 Hz, 1H), 5.09 (d, J = 9.6 Hz, 1H), 3.78 (dd, J = 14.7, 7.0 Hz, 1H), 3.24 (ddd, J = 14.7, 11.8, 5.0 Hz, 1H), 3.14 (dd, J = 14.5, 3.6 Hz, 1H), 2.87 (dd, J = 14.5, 9.8 Hz, 1H), 2.31 (dddd, J = 18.6, 11.6, 8.4, 3.7 Hz, 1H), 2.04 (dt, J = 18.7, 5.1 Hz, 1H); $^{13}$C NMR (176 MHz, CDCl₃) δ 144.1, 142.9, 137.7, 133.7 (d, J = 33.0 Hz), 132.9, 129.3, 128.5, 127.6, 127.4, 126.7, 125.8 (q, J = 3.7 Hz), 124.2, 123.2 (d, J = 273.0 Hz) 122.9, 122.6, 57.1, 39.3, 37.6, 24.0; IR (cm$^{-1}$) 2921, 1404, 1323, 1165, 1132, 1107, 1094, 1062, 1016, 851, 764; HRMS m/z calculated for C$_{23}$H$_{20}$F$_3$NO$_2$S$_2$H$^+$ [M+H]$^+$: 464.0960; found: 464.0961; [$\alpha$]D = +31.92.

(S)-6-(4-(benzyloxy)benzyl)-5-phenyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,6-tetrahydropyridine (1.62): Prepared according to GP-1.8 using substrate 1.62 S (62.2 mg, 0.1 mmol, 1 equiv.), FeCl₃ (4.87 mg, 0.03 mmol, 30 mol%), anhydrous DCE (0.01 M, 10 mL) with a reaction time of 24 h at 84 °C. Purification by flash column chromatography eluting with
EtOAc/hexanes (3–5% EtOAc/hexanes) provided **1.62** as a clear, colorless oil (34.0 mg, 60%). **1H NMR** (700 MHz, CDCl$_3$) $\delta$ 7.66 (d, $J = 8.1$ Hz, 2H), 7.58 (d, $J = 8.2$ Hz, 2H), 7.45 (d, $J = 7.6$ Hz, 2H), 7.43–7.37 (m, 5H), 7.34 (t, $J = 7.4$ Hz, 2H), 6.94 (d, $J = 8.1$ Hz, 2H), 6.81 (d, $J = 8.1$ Hz, 2H), 5.90 (s, 1H), 5.19 (d, $J = 8.4$ Hz, 1H), 5.03 (s, 2H), 3.77 (dd, $J = 14.6, 6.8$ Hz, 1H), 3.11 (ddd, $J = 15.9, 12.1, 4.7$ Hz, 1H), 2.84 (dd, $J = 14.6, 4.0$ Hz, 1H), 2.71 (dd, $J = 14.5, 8.9$ Hz, 1H), 2.29–2.21 (m, 1H), 2.02 (dt, $J = 18.3, 5.1$ Hz, 1H); **13C NMR** (176 MHz, CDCl$_3$) $\delta$ 157.6, 144.5, 139.5, 139.2, 137.0, 133.7 (d, $J = 32.8$ Hz), 130.4, 130.0, 128.9, 128.6, 128.0, 127.8, 127.5, 127.4, 126.3, 125.8 (q, $J = 3.4$ Hz), 123.9, 123.3 (d, $J = 273.1$ Hz), 114.7, 70.0, 56.7, 38.3, 37.7, 24.3; **IR** (cm$^{-1}$) 3029, 2925, 1685, 1609, 1511, 1495, 1453, 1403, 1322, 1262, 1163, 1133, 1107, 1062, 1016, 984, 843, 758; **HRMS** m/z calculated for C$_{32}$H$_{28}$F$_3$NO$_3$SH$^+$ [M+H]$^+$: 564.1815; found: 564.1813; $[\alpha]_D^{20} = +134.6$.

**Deprotection of the Carbonyl-Olefin Metathesis Product with SmI$_2$**

A 0.13 M solution of SmI$_2$ is prepared with samarium metal and diiodoethane according to previously reported procedures.$^{39}$ The carbonyl-olefin metathesis product (0.1 mmol) is added to a flame-dried round-bottom flask equipped with a stir bar and placed under a nitrogen atmosphere. The SmI$_2$ solution (6.0 equiv.) is then added to the flask while stirring. Next, a degassed solution of water (12.0 equiv.) is added to the reaction mixture, which immediately turns red. The reaction is allowed to stir for 3 min, at which point triethylamine (18.0 equiv.) is added. After an additional 3 minutes, the reaction mixture is filtered under nitrogen over a celite plug. The crude product is collected into a flask charged with a stir bar and Boc$_2$O (2.5 equiv.). The mixture is then heated to 50 °C via heating mantle and allowed to stir for 12 h. Once the reaction is complete, the mixture
is concentrated under reduced pressure give the crude product. Purification by flash column chromatography eluting with EtOAc/hexanes (1:10) provided the desired carbamate.

**tert-butyl (S)-6-methyl-5-phenyl-3,6-dihydropyridine-1(2H)-carboxylate (1.64):** Prepared using tetrahydropyridine 1.51 (20 mg, 0.05 mmol, 1 equiv.), SmI$_2$ (0.3 mmol, 3 equiv.), Boc anhydride (28.6 mg, 0.13 mmol, 2.5 equiv.), triethylamine (95.5 mg, 0.94 mmol, 18 equiv.), and water (11.32 mg, 0.63 mmol, 12 equiv.). Purification by flash column chromatography eluting with EtOAc/hexanes (1:10) provided 1.64 as a mixture of rotamers (13.2 mg, 92% yield).

**1H NMR** (700 MHz, CDCl$_3$) δ 7.33 (d, J = 16.3 Hz, 4H), 7.27 (d, J = 5.7 Hz, 1H), 5.95 (s, 1H), 5.19 (s, 1H), 4.99 (s, 1H), 4.26–4.13 (m, 1H), 4.13–4.00 (m, 1H), 3.02 (s, 1H), 2.94 (s, 1H), 2.41 (s, 1H), 2.14 (s, 1H), 1.53 (d, J = 4.7 Hz, 10H), 1.13 (d, J = 6.7 Hz, 3H); **13C NMR** (176 MHz, DMSO-d$_6$) δ 154.4, 141.1, 140.8, 140.2, 135.9, 129.6, 128.3, 126.9, 124.4, 124.1, 79.8, 49.6, 48.5, 36.9, 35.4, 29.0, 28.6, 27.8, 26.4, 26.2, 18.7, 18.4; **IR** (cm$^{-1}$) 2975, 2827, 1689, 1494, 1453, 1417, 1390, 1364, 1311, 1245, 1212, 1167, 1116, 1077, 1031, 1011, 862, 749; **HRMS** calculated for C$_{17}$H$_{23}$NONa$^+$ [M+Na]$^+$: 296.1621; found: 296.1616.
1.5.3 SFC Analysis for Tetrahydropyridine 1.36

Racemic phenylalanine metathesis product 1.36: Chiralpack AD-H, 30% $i$-PrOH, 8 min run, 3.5 mL/min.
Enantioenriched phenylalanine metathesis product **1.36**: Chiralpack AD-H, 30% $i$-PrOH, 8 min run, 3.5 mL/min.
Chapter 2 Development of a Visible-Light-Mediated Paternò-Büchi Reaction for the Synthesis of Functionalized Oxetanes

Portions of this chapter have been published in Rykaczewski, K. A.; Schindler, C. S. Visible-Light-Enabled Paternò-Büchi Reaction via Triplet Energy Transfer for the Synthesis of Oxetanes Org. Lett. 2020, 22, 6516–6519.

2.1 Introduction

2.1.1 Oxetane Structural Properties

Figure 2.1: A Ring strain of oxygen heterocycles. B Bond angles and ring puckering of oxetanes. C Hydrogen bonding of carbonyl groups and oxetane.
Oxetanes are strained cyclic ethers that are found in natural products and constitute an interesting medicinal chemistry motif, due to the small and polar nature. Work in the 1960’s determined the ring strain of oxetane to be 106 kJ mol\(^{-1}\). Oxetanes are significantly more strained than the five-membered tetrahydrofuran (25 kJ mol\(^{-1}\)), but similarly strained to the three-membered epoxide (112 kJ mol\(^{-1}\)) (Figure 2.1A).\(^{40,41}\) X-ray crystal structures of the unsubstituted oxetane ring from Buschmann in 1984 showed an essentially planar structure with minor ring puckering (7°), especially compared to cyclobutanes (30°).\(^{42}\) Later work showed that increased substitution about the oxetane ring, increases the unfavorable eclipsing interactions, therefore increasing the puckering, such as in insecticide EDO with a puckering angle of 16° (Figure 2.1B).\(^{43}\)

The presence of the oxygen embedded in the ring affects the bond angles of the 4-membered ring with a \(\text{C–O–C}\) bond angle of approximately 91° determined by X-ray crystallography.\(^{42,44}\) The strained nature exposes the oxygen lone electron pairs, making it an excellent hydrogen bond acceptor. The hydrogen bonding capabilities of oxetanes make them highly advantageous structural units and allow them to serve as bioisosteres for carbonyl groups. When compared to other cyclic ethers, oxetanes are significantly better hydrogen bond acceptors.\(^{44,45}\) Moreover, oxetanes compete as hydrogen bond acceptors with most carbonyl functionalities such as aldehydes, esters, and ketones\(^{46,47}\) with only amides outcompeting oxetanes in hydrogen-bonding capabilities (Figure 2.1C).\(^{48}\)

2.1.2 Oxetane Natural Products

Despite its strain, the oxetane does appear in a selection of natural products. While not many, these products have been shown to display important biochemical properties. The most well-known oxetane natural product is paclitaxel (Taxol) which was isolated from the stem bark of a Pacific Yew tree in 1971.\(^{49}\) Structure-activity studies have indicated the possibilities of the
oxetane rigidifying the structure or functioning as a hydrogen bond acceptor. While the biosynthesis is not definitively known, studies have hypothesized multiple mechanistic routes involving an epoxy ester/oxetane ester rearrangement (Figure 2.2B).

![Figure 2.2: A Structure of Paclitaxel, Docetaxel, and Cabazitaxel. B Potential biosynthetic mechanisms for oxetane formation.](image)

Since its discovery Taxol has been widely used in chemotherapy regimens for breast, lung, and ovarian cancer. Due to the incredibly complex structure a plant cell fermentation method was developed by Phyton Catalytic that is still used to date. Since then, derivatives of Taxol, such as Docetaxel and Cabazitaxel, have been developed and commercialized to improve some of the drawbacks of Taxol such as water solubility and toxicity (Figure 2.2A). While Taxol can be mass-produced through plant cell fermentation, the incredibly complex target has also been well explored in the total synthesis community.

![Figure 2.3: A Structure of Merrilactone A and oxetane formation in total synthesis efforts. B Structure and IC₅₀ values of oxetane-containing Maoyecrystal I and non-oxetane analog Rubescensin W.](image)

Merrilactone A, a sesquiterpene dilactone, was first isolated in 2000 from Illicium merrillianum (Figure 2.3A). The initial isolation publication also explored biological activity and discovered neurotrophic activity observed in fetal rat cortical neuron cultures. Multiple synthetic strategies have been applied towards the caged pentacyclic architecture of Merrilactone A, the first
total synthesis coming from Professor Danishefsky’s group in 2002. Since then, all total synthesis efforts have followed the initial report and installed the oxetane motif in the final step via an epoxide opening (Figure 2.3A). Maoyecrystal I, an ent-Kauranoid diterpenoid was first isolated from *Isodon japonicus* in 2004. Bioassay studies from Sub and coworkers showed toxicity against human chronic myelogenous leukemia cells (K562) with a comparable inhibitory effect (IC$_{50}$ = 7.30 µg mL$^{-1}$) to cisplatinum (IC$_{50}$ = 1.14 µg mL$^{-1}$). These initial studies indicated that the oxetane motif was potentially the bioactive moiety as the related structure (rubescensin W), lacking the oxetane, showed a diminished inhibitory effect (Figure 2.3B). While Maoyecrystal I is related to the popular synthetic target Maoecrystal V, there have not been any reported total syntheses.

**Figure 2.4: Synthetic strategies towards oxetin.**

Oxetanocin A, a novel nucleoside, contains a trisubstituted monocyclic oxetane which was first isolated in 1986 from soil bacteria *Bacillus megaterium*. Importantly, Oxetanocin A was found to inhibit the in vitro replication of human immunodeficiency virus (HIV). The promising biological activity has led to multiple synthetic efforts. One of the simplest oxetane natural products isolated to date is oxetin, which was isolated from *Streptomyces* sp. OM-2317, a soil
isolate. This β-amino acid showed herbicidal and antibacterial effects. The simple structure has been synthesized a variety of ways including from glucose via a late-stage cyclization, lactone reduction, and [2+2]-cycloaddition approaches (Figure 2.4).

### 2.1.3 Oxetanes in Medicinal Chemistry

![Comparison of gem-dimethyl groups and oxetanes.](image)

In 2006, Carreira and coworkers published a highly influential report on oxetanes as a unique medicinal chemistry structural motif which has since sparked decades of research. The Carreira group demonstrated the use of 3,3-disubstituted oxetanes as bioisosteres for gem-dimethyl groups, which led to an increased metabolic stability by lowering lipophilicity. The origin of using gem-dimethyl groups in pharmaceutical compounds arose from the need to block metabolically labile methylene sites. The non-polar nature of methyl groups increases the lipophilicity, which has adverse effects on the pharmacokinetics. Interestingly oxetanes have a similar molar volume to gem-dimethyl groups, but are significantly more polar, striking an ideal balance between steric and electronic effects (Figure 2.5).

![Amphiphilic test compound (2.1) to study effects of oxetane incorporation.](image)
To study the potential effects of oxetanes, a model compound (2.1) was selected that was highly amphiphilic with both a large non-polar end and a basic polar amine, making it insoluble in water in its neutral form (Figure 2.6). 73 Each saturated position was replaced with an oxetane and pharmacokinetic properties were measured including: solubility, intrinsic clearance (hCLint), lipophilicity (logD and logP), and pKa (Table 2.1). Overall, solubility was improved among all oxetane analogs compared to the parent compound (2.1). Analogs that situated the polar amine and polar oxetane groups away from each other (entries 2–6) resulted in the greatest improvement in solubility. In line with this, the compounds with greater solubility also were more stable and resulted in improved intrinsic clearances in both mouse and human microsomal cells (entries 2–6). The measured lipophilicity also followed this trend where compounds now with two distinctly polar sites were significantly less lipophilic, especially compounds in which the lipophilic tert-butyl group was replaced (entries 2–4). Conversely, compounds with the oxetane closely neighboring the basic amine did not demonstrate improved pharmacokinetic properties, but the authors observed a pronounced change in the pKa of the amine (entries 7–8). This work was profound in setting up the principle that oxetanes are metabolically stable and can improve solubility and lipophilicity of amphiphilic compounds.
Following their initial disclosure of oxetanes as gem-dimethyl replacements, Carreira and coworkers also studied the possibility of oxetanes to replace carbonyl groups. This was of considerable interest due to the hydrogen-bonding role carbonyls plays in drug binding, but the propensity to undergo enzymatic attack and epimerization of neighboring carbons limits their use in certain situations (Figure 2.7B). Oxetanes have the potential to limit these pathways while still offering a similar dipole moment and hydrogen bonding. Although the oxetane is almost twice the length of a carbonyl group, this can result in increased binding efficiency (Figure 2.7A). Carreira and coworkers synthesized a series of spirocyclic oxetane compounds and evaluated their biochemical properties compared to both the gem-dimethyl and carbonyl analogs. Pyrrolidine and piperidine (entries 3–4) exhibit considerably better metabolic stability as their oxetane analogs (2.5 and 2.8) compared to the carbonyl compounds (2.6 and 2.9) (Table 2.2). Additionally, this work made an azetidine-oxetane spirocycle (2.3) to mimic the effects of morpholine, a heterocycle often

Table 2.1: Solubility, intrinsic clearance, lipophilicity, and pKa of parent compound and oxetane analogs.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>solubility (pH 9.9)</th>
<th>hClint (min⁻¹ mg⁻¹ mL⁻¹)</th>
<th>logD (pH 7.4)</th>
<th>pKa (in H₂O)</th>
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<td>&lt; 1</td>
<td>16</td>
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<td>6</td>
<td>1.7</td>
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<td>13</td>
<td>3.3</td>
<td>7.2</td>
</tr>
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</table>

Following their initial disclosure of oxetanes as gem-dimethyl replacements, Carreira and coworkers also studied the possibility of oxetanes to replace carbonyl groups. This was of considerable interest due to the hydrogen-bonding role carbonyls plays in drug binding, but the propensity to undergo enzymatic attack and epimerization of neighboring carbons limits their use in certain situations (Figure 2.7B). Oxetanes have the potential to limit these pathways while still offering a similar dipole moment and hydrogen bonding. Although the oxetane is almost twice the length of a carbonyl group, this can result in increased binding efficiency (Figure 2.7A). Carreira and coworkers synthesized a series of spirocyclic oxetane compounds and evaluated their biochemical properties compared to both the gem-dimethyl and carbonyl analogs. Pyrrolidine and piperidine (entries 3–4) exhibit considerably better metabolic stability as their oxetane analogs (2.5 and 2.8) compared to the carbonyl compounds (2.6 and 2.9) (Table 2.2). Additionally, this work made an azetidine-oxetane spirocycle (2.3) to mimic the effects of morpholine, a heterocycle often
incorporated to increase solubility, but often is the target of oxidative metabolism. The oxetane-azetidine spirocycle 2.2 (entry 2) had remarkably better solubility and metabolic stability compared to morpholine (entry 1) (Table 2.2). Concerns about oxetane stability under acidic conditions were addressed in this work, in which a variety of oxetanes were incubated in aqueous solutions buffered at pH 1–10 for two hours in which most oxetanes studied had good recovery.

Figure 2.7: A Structural comparison of oxetane and carbonyl groups. B Potential issues of incorporating carbonyls into drug molecules.
Table 2.2: Lipophilicity, solubility, intrinsic clearance, and pKa of morpholine, spirocyclic oxetanes, and gem-dimethyl and carbonyl analogs.

<table>
<thead>
<tr>
<th>entry</th>
<th>compound</th>
<th>substituent</th>
<th>logD (pH 7.4)</th>
<th>solubility (pH 9.9)</th>
<th>hCLint (min⁻¹ mg⁻¹ µL)</th>
<th>pKa (in H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>morpholine</td>
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<td>1.5</td>
<td>36000</td>
<td>9</td>
<td>7.0</td>
</tr>
<tr>
<td>2</td>
<td>gem-Me₂ (2.2)</td>
<td>0.8</td>
<td>1300</td>
<td>0</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
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<td>oxetane (2.3)</td>
<td>0.5</td>
<td>100000</td>
<td>3</td>
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</tr>
<tr>
<td>3</td>
<td>gem-Me₂ (2.4)</td>
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<td>10</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>oxetane (2.5)</td>
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<td>0.7</td>
<td>2</td>
<td>8.1</td>
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</tr>
<tr>
<td></td>
<td>carbonyl (2.6)</td>
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<tr>
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<td>gem-Me₂ (2.7)</td>
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<td>2.3</td>
<td>31</td>
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<tr>
<td></td>
<td>oxetane (2.8)</td>
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<td>1.7</td>
<td>16</td>
<td>7.9</td>
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<tr>
<td></td>
<td>carbonyl (2.9)</td>
<td>0.1</td>
<td>0.1</td>
<td>120</td>
<td>7.6</td>
<td></td>
</tr>
</tbody>
</table>

In 2013, Carreira and coworkers studied the effects of oxetanes on known, albeit notorious, bioactive molecules, thalidomide (2.10) and lenalidomide (2.12). The R-isomer of thalidomide is an anti-emetic, whereas the S-isomer is a teratogen. Unfortunately, racemization occurs under physiological conditions. Lenalidomide is still a commonly used drug today for multiple myeloma, but the patient population is extremely controlled due to the risk of birth defects in offspring. Carreira and coworkers reasoned that the introduction of an oxetane to replace the carbonyl would eliminate the racemization. The oxetane analogs 2.11 and 2.13 were found to be more stable in human blood plasma over the course of five hours compared to parent compounds 2.10 and 2.12 (Figure 2.8). This study involving an actual drug scaffold solidified the concept of oxetanes as a bioisostere for carbonyl groups.
The work from Carreira and many others in the early 2000’s focused mainly on 3-substituted oxetanes, but relatively little was known regarding substitution about the oxetane and the structure-activity relationships of structural isomers. A study from scientists at Pfizer in 2011 addressed this topic through the evaluation of a series of γ-secretase inhibitors, which were considered important targets for tackling Alzheimer’s disease. In the early 2000’s a number of γ-secretase inhibitors (2.14–2.15) that had minimal impact of Notch processing, an important function in the brain, were reported and entered into clinical trials (Figure 2.9).82–84

heterocycles were evaluated. More specifically, nine oxetanes were synthesized and evaluated for their potency (IC₅₀), Notch selectivity, metabolic stability (CL_int,app), lipophilicity (ElogD), absorptive permeability (RRCK P_app), and central nervous system permeability (MDR1/MDCK) (Table 2.3). One noteworthy example was entry 7 where the desired potency was maintained, but dramatic improvement in the metabolic stability was observed. It is important to distinguish that the diastereomer of this specific oxetane maintained the stability but lacked potency (entry 6).

Table 2.3: Potency, intrinsic clearance, lipophilicity, absorptive permeability, and central nervous system permeability of parent compound and oxetane analogs.

<table>
<thead>
<tr>
<th>entry</th>
<th>compound</th>
<th>IC₅₀ (nM)</th>
<th>hCL_int (mL min⁻¹ kg⁻¹)</th>
<th>ElogD (pH 7.4)</th>
<th>RRCK (10⁻⁶ cm s⁻¹)</th>
<th>MDR1/MDCK</th>
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</thead>
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<td>5.60</td>
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<td></td>
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<td>62.1</td>
<td>2.60</td>
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</tr>
<tr>
<td>3</td>
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<td>16.9</td>
<td>28.6</td>
<td>2.50</td>
<td>25.4</td>
<td>1.99</td>
</tr>
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<td>10.8</td>
<td>167</td>
<td>3.40</td>
<td>21.8</td>
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<td></td>
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<td>78.9</td>
<td>3.40</td>
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<td></td>
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<td>29.0</td>
<td>3.80</td>
<td>18.1</td>
<td>1.32</td>
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<tr>
<td>7</td>
<td></td>
<td>16.5</td>
<td>25.9</td>
<td>3.80</td>
<td>14.9</td>
<td>1.04</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>49.0</td>
<td>&gt; 293</td>
<td>3.90</td>
<td>22.3</td>
<td>1.78</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>49.5</td>
<td>262</td>
<td>3.90</td>
<td>26.4</td>
<td>1.51</td>
</tr>
</tbody>
</table>

Studies that determined the sites of oxidative metabolism were completed for eleven of the compounds, providing an important insight into substitution and stability (Figure 2.10). For example, the mono-substituted oxetane 2.17 was found to predominantly undergo ring scission to the diol (2.18) and hydroxy acid metabolites (2.19), with N-dealkylation (2.20) also observed as a minor metabolite (Figure 2.10). Overall, this work found that oxetanes can outperform the parent cyclohexane compound by improving the polar surface area, lipophilic efficiency, and central
nervous system multiparameter optimization (CNS-MPO) desirability score. The depth to which this study looked at degree and placement of substitution of the oxetane further solidified the idea that oxetanes can be used to increase the drug-likeness of a molecule but more so, they discovered that the distinct substitution of an oxetane can play an important role in key parameters.

![Figure 2.10: Overview of increasing metabolic stability with oxetane analogs and characterized metabolites of compound 2.17.](image)

**2.1.4 Synthesis of Oxetanes**

Oxetanes are structurally unique, present in complex natural products, and have found use as a motif for improving drug properties. The synthesis of oxetanes has been a challenging field continually innovating and improving on the types of oxetanes accessible (Figure 2.11A). The inherent ring strain associated with oxetanes and the unfavorable kinetics for ring closure for four-membered rings in comparison to smaller and larger rings has been one of the largest barriers. Intramolecular etherification is still one of the most common disconnections for oxetane synthesis in which a base-mediated nucleophilic substitution occurs between an alcohol and a carbon pre-functionalized with a leaving group.\(^{52}\) While straight-forward, the unfavorable eclipsed conformation required, diminishes the reaction efficiency and yields of the desired product are
often variable with competing Grob fragmentation commonly observed, resulting in aldehyde and alkene byproducts (Figure 2.11B). \textsuperscript{85,86}

![Diagram](image)

Figure 2.11: A Common synthetic strategies for oxetane synthesis. B Challenges in intramolecular substitution. C Stereoselective reduction of carbonyl and subsequent cyclization to chiral oxetanes.

Stereo-controlled oxetane synthesis via etherification is often done by stereoselective reduction of a carbonyl compound resulting in a chiral 1,3-halo alcohol and cyclization results in specific oxetane stereoisomers (Figure 2.11C). \textsuperscript{87,88} A leaving group can also be installed in situ by reacting 1,3-diols with tosyl chloride under basic conditions (Figure 2.11D). \textsuperscript{89} Intramolecular etherification is the most common method when synthesizing complex oxetane-containing natural products including the first synthesis of oxetin stereoisomers from Ōmura\textsuperscript{69}, the synthesis of Oxetanocin from Yamamura\textsuperscript{90}, and the synthesis of Taxol from Nicolaou.\textsuperscript{91} Despite new synthetic strategies for these complex natural products, most routes today still rely on late-stage intramolecular etherification for installing the oxetane moiety. \textsuperscript{52}
Three-membered oxygen rings, epoxides, can be easier to form and ultimately be leveraged to access oxetanes through a ring-expansion strategy. Most commonly, sulfur ylides are employed as nucleophiles for the ring opening, forming the oxetane product after loss of dimethyl sulfoxide (Figure 2.12). Epoxides can be an attractive starting material for the synthesis of chiral oxetanes due to the variety of methods for generating epoxides enantioselectively. For example, an expansion of chiral epoxide (2.21) was performed by Fokin and coworkers by using dimethylsulfoxonium methyldide to form oxetane products (2.22) with >98% ee (Figure 2.12).

![Figure 2.12: Ring expansion of chiral epoxide 2.21 to chiral oxetane 2.22 and ring contraction of lactone 2.23 to substituted oxetane 2.24.]

Analogously, five-membered rings can be leveraged to access oxetanes via a ring contraction. Saccharides are commonly used for these reactions and can be transformed into α-hydroxy-γ-lactones (2.23) which spontaneously contract under basic conditions (Figure 2.12). Highly substituted saccharides lead to highly substituted oxetanes which can be synthetically manipulated to introduce new functionality such as azides, fluorine, thiols, and nucleobases.

### 2.1.5 Paternò-Büchi Reaction

The photochemical [2+2]-cycloaddition between an excited state carbonyl and olefin is referred to as the Paternò-Büchi reaction. In 1909 Emanuele Paternò, an Italian scientist, observed the [2+2]-cycloaddition adduct between benzaldehyde and 2-methyl-2-butene from irradiation with sunlight for 2–3 months, albeit unsure of which isomer was formed (Figure 2.13A). It wasn’t until forty-five years later that George Büchi reproduced the results from Paternò and confirmed the oxetane product by studying the acid-promoted cleavage products.
Since 1954, there have been several reports regarding the mechanism of this photochemical transformation. It is often hypothesized that the cycloaddition proceeds through n,π* excitation of the carbonyl. While there have been in-depth kinetic studies performed on the Paternò-Büchi reaction\(^\text{101}\) it is well accepted that both singlet and triplet [2+2]-cycloadditions can proceed (Figure 2.13B). In cases where a singlet mechanism is proposed (often alkene concentration is high) the alkene conformation is retained due to a concerted process or rapid ring closure from the short-lived singlet biradical. In singlet excited state mechanisms, the reaction can be run without inhibition in the presence of triplet quenchers such as 1,3-pentadiene and naphthalene.\(^\text{101}\) Whereas in a triplet state mechanism, the [2+2]-cycloaddition is stepwise, after the C–O bond formation, the intermediate triplet biradical undergoes intersystem crossing prior to C–C bond formation. The longer-lived triplet biradical intermediate can undergo bond rotation which typically results in a mixture of diastereomeric products.

The reaction can also proceed through π,π* transitions when the internal conversion between the triplet states is low, such as with naphthaldehydes. The triplet state is also able to
undergo single electron transfer with the alkene resulting in radical-ion pairs. Overall, either type of excitation ($\pi,\pi^*$ or $n,\pi^*$) and singlet or triplet excited states can result in a biradical intermediate that can ultimately form the oxetane (Figure 2.13C). Because the reaction converts $\pi$ bonds to $\sigma$ bonds, the reverse reaction cannot be performed with the same wavelength of light.

The regioselectivity of the Paternò-Büchi reaction is usually dependent on the relative stabilities of the biradical intermediates whereas the diastereoselectivity is often guided by steric influences.

In triplet state mechanisms, the intermediate triplet biradical is long-lived enough to undergo free bond rotation to the more sterically accessible conformation before undergoing intersystem crossing and ring closure. The singlet mechanisms are often concerted or have a very short-lived biradical, therefore the alkene geometry is often retained in the products.

Figure 2.14: Norrish type I and type II reactivity of excited state carbonyls.

Despite the simplicity and the prevalence of oxetanes in natural products and pharmaceutical candidates, very few are synthesized through a $[2+2]$-cycloaddition. There are many challenges in these reactions including the use of UV light for carbonyl excitation. Multiple functional groups on a molecule can be excited by UV light, such as thiols, halides, and activated alkenes, leading to undesired reactivity. Excited state carbonyls can also participate in several other reactions besides $[2+2]$-cycloadditions, such as Norrish type I reactivity which involves $C-$
C bond cleavage and Norrish type II reactivity that proceeds via hydrogen atom transfer (HAT) (Figure 2.14). Due to these pathways and other substrate limitations like poor orbital overlap, one of the biggest constraints remaining for generating oxetanes via a [2+2]-cycloaddition is the reliance on UV light. In contrast, utilizing visible-light methods would hold many opportunities, such as reducing the cost of energy sources, eliminating the need for specialized reactors and quartz reaction vessels, and improving chemoselectivity.

2.1.6 Visible-Light [2+2]-Cycloadditions and Triplet Energy Transfer

Figure 2.15: Examples of common catalysts for photoredox catalysis including ruthenium, iridium, and organic catalysts.

The early 2000’s emerged with seminal works in the area of photoredox catalysis and the use of visible light to catalyze the formation of new bonds. Along with this, visible-light-photocatalysis was recognized as a powerful synthetic strategy for [2+2]-cycloadditions. In 2009, work from Yoon and coworkers formed radical ions of alkenes via single electron transfer to forge cyclobutane products. Three years later they disclosed the ability to apply similar visible-light-absorbing metal catalysts used previously for single electron transfer, but now for triplet energy transfer to alkenes to also generate cyclobutanes via a [2+2]-cycloaddition (Figure 2.16). The use of energy transfer negated the need for photo-induced electron transfer which had previously greatly limited the scope. These results, in addition to reports from Yamazaki and Castellano opened an avenue of research in which historically UV light promoted C–C bond forming reactions could now be catalyzed by visible-light-absorbing photocatalysts and triplet energy transfer sensitization.
Figure 2.16: Seminal works from Yoon in visible-light-mediated photoredox catalysis and triplet energy transfer for intra- and intermolecular cyclobutane formation

Triplet energy transfer is a distinct process from single electron transfer, despite the use of similar catalysts (Figure 2.15). Single electron transfer operates by the excited state photocatalyst either reducing or oxidizing a substrate with the substrate remaining in its ground state. The reactions can be overall oxidative, reductive, or neutral, but the photocatalyst will change oxidation states over the course of the catalytic cycle. Triplet energy transfer also uses the excited state of the photocatalyst, but in this case the triplet state is transferred from the photocatalyst to the substrate so that the substrate achieves its triplet excited state (Figure 2.17). This triplet excited state is equivalent to the triplet state that could be achieved through direct excitation with UV light. This process proceeds by absorption of a photon via irradiation and excitation to the singlet excited state ($S_1$). The singlet excited state is typically short lived and can forego two different paths, either decay back to the ground state ($S_0$) via fluorescence or intersystem crossing to the triplet excited state ($T_1$) which is a longer-lived excited state (Figure 2.17A). Triplet energy transfer occurs through a double electron transfer process in which an electron from the excited state of the photosensitizer is exchanged with an electron from the ground state of the substrate, referred to as Dexter triplet energy transfer (Figure 2.17B). This process must be energetically favorable with the triplet energy of the photosensitizer being greater than the substrate. Triplet energies ($E_T$) are defined as the energy gap between the singlet ground state ($S_0$) and the triplet excited state ($T_1$).
These values are typically determined through emission spectroscopy (phosphorescence), quenching experiments with a range of sensitizers of known $E_T$ values, or through computational methods.

![Figure 2.17: A Simplified Jablonski diagram for excitation from singlet state, intersystem crossing (ISC) to the triplet state, and relaxation modes. B Double electron transfer process of Dexter triplet energy transfer between an excited state photosensitizer and a ground state substrate.](image)

The seminal work from Yoon in 2012 that applied triplet energy transfer to sensitize a styrene to its triplet excited state which then intramolecularly reacted with an unactivated alkene to form cyclobutane products spurred years of innovation in organic synthesis (Figure 2.16).\(^\text{106}\) Since then, steady growth in the field of visible-light-mediated triplet energy transfer [2+2]-cycloadditions has been observed.\(^\text{109}\) Asymmetric reactions have been developed, for example Bach in 2014 designed a visible-light-absorbing chiral organic photosensitizer. Due to the close proximity required for energy transfer to occur, the chirality of the photosensitizer influenced the cycloaddition and resulted in cyclobutanes in up to 94% ee (Figure 2.18A).\(^\text{110}\) Yoon in 2016 expanded the scope of photocatalysts that could sensitize activated alkenes by lowering the triplet energy of the alkene through Lewis acid binding. This reaction allowed a photosensitizer with a low triplet energy (46.9 kcal mol\(^{-1}\)) to sensitize an alkene with typically a much higher triplet energy (54 kcal mol\(^{-1}\)).\(^\text{111}\) Because the binding of a Lewis acid was necessary for the reaction to proceed, this also allowed them to include a chiral ligand which could impart chirality to the reactive species, generating cyclobutanes in 83–98% ee (Figure 2.18B).
Foundational work for visible-light triplet-energy-transfer-mediated [2+2]-cycloadditions focused on cyclobutane formation. The application of triplet energy transfer to form heterocycles also held the potential to impact the field. Work from our group applied these reaction principles to heterocyclic systems. In 2019 we reported one of the first *aza* Paternò-Büchi reactions promoted by visible-light irradiation (Figure 2.19A). This work relied on styrenes, which from the excited state could react intramolecularly with an oxime or hydrazone to generate azetidine products (Figure 2.19A).\textsuperscript{112} Our group further expanded the generality of visible-light *aza* Paternò-Büchi reactions by developing an intermolecular reaction relying on triplet energy transfer to 2-isoxazoline-3-carboxylates (Figure 2.19B).\textsuperscript{113}
An example of using triplet energy transfer to activated alkenes for a [2+2]-cycloaddition with a carbonyl was developed by the Sivaguru group in 2017, referred to as a “transposed Paternò-Büchi” (Figure 2.19C). Unlike the use of excited state alkenes to generate cyclobutanes (Figure 2.16) and azetidines (Figure 2.19A), this example for oxetanes still relied on UV light and acetone as the photosensitizer. Beyond the work of cyclobutanes and azetidines, there was relatively minimal innovation for the classic Paternò-Büchi reaction in visible-light photocatalysis. This sparked our work in developing a visible-light-mediated Paternò-Büchi reaction using triplet energy transfer from an iridium (III) photosensitizer to an aryl glyoxylate carbonyl, discussed in section 2.2.
Since our work in this area, others have contributed to visible-light-mediated Paternò-Büchi reactions. Yoon and coworkers also studied this visible-light-mediated Paternò-Büchi reaction with aryl glyoxylates in congruence with our studies. Beyond synthesizing oxetanes they also discovered a divergent reactivity profile with the addition of a Lewis acid (Figure 2.20). Differing from their earlier reports in the role of the Lewis acid to lower the triplet energy (Figure 2.18B), they found in this case that they could switch to a photoredox pathway to generate tertiary alcohol products (Figure 2.20).\(^{115}\)

Other groups have used these aryl glyoxylates to generate oxetanes including work from Zhu who paired the activated carbonyls with activated alkenes and white CFL light and no photosensitizer (Figure 2.21).\(^{116}\) Dell’Amico and coworkers have extensively explored the mechanism of aryl glyoxylates and their reactivity with conjugated alkenes such as indoles, where they synthesized dearomatized indole-oxetane products.\(^{117}\) They found that different wavelengths can initiate different excitation complexes, with visible light an EDA complex is generated, whereas with UV light a \(n,\pi^*\) exciplex is formed (Figure 2.22).\(^{118}\) The Dell’Amico group has also explored microfluidic platforms for Paternò-Büchi reactions of benzophenone and enol ethers.\(^{119}\)
Figure 2.22: Mechanistic studies of activated carbonyls and activated alkenes at 370 nm and 456 nm irradiation and the corresponding effects on diastereoselectivity of the resulting oxetane products.

2.2 Reaction Design and Optimization

At the outset of this work, we were inspired to consider how the traditional Paternò-Büchi reaction could be accomplished with visible light without necessarily relying on substrates that can absorb visible light. We envisioned triplet energy transfer could be a suitable sensitization platform where only the photocatalyst would need to absorb visible light. This could remove the requirement for UV light and in general provide a new pathway to excited state carbonyls. The constraint of using triplet energy transfer is that there needs to be orbital overlap between the photosensitizer and substrate. We surveyed the literature for known triplet energies of carbonyls, which ultimately motivated us to consider dicarbonyl compounds as a potential suitable substrate due to their low triplet energies.\textsuperscript{120} Additionally, Neckers previously explored the photochemistry of dicarbonyl compounds and demonstrated their propensity to engage in Paternò-Büchi reactions under UV light irradiation.\textsuperscript{103,121}
We evaluated a variety of dicarbonyl substrates, most of which were unsuccessful (Figure 2.23A). In fact, many of the carbonyl substrates when irradiated with a blue LED lamp (456 nm) in the absence of photosensitizer or alkene present resulted in decomposition, which we attributed to Norrish type I and II cleavage (Figure 2.23B). We continued evaluation and found that methyl ester 2.26 resulted in a productive [2+2]-cycloaddition with alkene 2.27 to generate oxetane 2.28 in 3:1 r.r and >20:1 d.r (Table 2.4). We evaluated different visible-light-absorbing photosensitizers with a range of triplet energies ($E_T$). Unsurprisingly, those with high triplet energies were successful (entries 1–3) while those with lower triplet energies resulted in lower conversion (entries 4–6). These observations were consistent with a triplet energy transfer mechanism.

Table 2.4: Photocatalyst evaluation in Paternò–Büchi reaction between aryl glyoxylate 2.26 and alkene 2.27.

<table>
<thead>
<tr>
<th>entry</th>
<th>photocatalyst</th>
<th>$E_T$ (kcal mol$^{-1}$)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Ir(dF(Me)ppy)$_2$(dtbbpy)]PF$_6$</td>
<td>60.2</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (2.25)</td>
<td>60.1</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>[Ir(dFppy)$_2$(dtbbpy)]PF$_6$</td>
<td>57.1</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>[IrFppy)$_2$(dtbbpy)]PF$_6$</td>
<td>53.3</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>[Ir(ppy)$_2$(dtbbpy)]PF$_6$</td>
<td>49.2</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>[Ru(bpy)$_3$]PF$_6$$_2$</td>
<td>46.9</td>
<td>0</td>
</tr>
</tbody>
</table>

Subsequent efforts focused on additional reaction optimization, including varying the solvent, catalyst loading, and alkene equivalents (Table 2.5). The reaction was determined to
proceed in good yields of up to 75% relying on 1,2-dichloroethane, methylene chloride, acetone, toluene, ethyl acetate, methanol, and acetonitrile as the reaction solvent (entries 1–7). Catalyst loadings as low as 0.5 mol % and equimolar amounts of alkene 2.27 proved to be sufficient in forming oxetane 2.28 (entries 8–13).

Table 2.5: Optimization of solvent, alkene (2.27) equivalents, and catalyst (2.25) loading.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>equiv. alkene</th>
<th>cat. loading</th>
<th>yield (%)</th>
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</thead>
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<td>1</td>
<td>MeCN</td>
<td>10</td>
<td>2.5 mol%</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>10</td>
<td>2.5 mol%</td>
<td>74</td>
</tr>
<tr>
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<tr>
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<td>acetone</td>
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<td>72</td>
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<td>1</td>
<td>2.5 mol%</td>
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<tr>
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<td>MeCN</td>
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<td>13</td>
<td>MeCN</td>
<td>10</td>
<td>2.5 mol%</td>
<td>73</td>
</tr>
</tbody>
</table>

2.3 Substrate Scope

We were interested in investigating the substitution about the oxetane and set out to study the variations to the aryl glyoxylate and alkene components (Figure 2.24). We first altered the alkyl ester portion and reacted the aryl glyoxylates with 2-methyl propene. Methyl, ethyl, adamantyl, and tert-butyl ester all provided the desired products (2.29–2.32) in good yields. While we had originally found that the ethyl ester was unstable upon irradiation (Figure 2.23A), the use of a large excess of a gaseous alkene allowed the desired [2+2]-cycloaddition to outcompete the other decomposition pathways.
Both electron-withdrawing and electron-donating groups on the aromatic portion of the aryl glyoxylate were tolerated. The anisole derivative 2.34 was obtained in 72% yield. The electron-withdrawing para-nitrile generated oxetane 2.33 in 66% yield. Using a para-methyl ester on the aromatic ring was also tolerated providing oxetane 2.35 in 91% yield. Para-bromo oxetane 2.37 was isolated in 77% yield.

After determining a broad generality in reactivity of the aryl glyoxylate portion we increased the substitution about the oxetane by reacting methyl ester 2.26 with di-, tri-, and tetra-substituted alkenes to generate oxetanes 2.28, 2.29, and 2.38 in yields from 68–83%. Bicyclic oxetanes (2.39–2.41) could be synthesized by using cyclic alkenes like cyclohexene, furan, and benzofuran. Finally, ethyl vinyl ether was used a reaction partner to access oxetane 2.42 in 68%
yield. While we did observe good reactivity with these alkenes it is worth noting that activated alkenes, like styrenes, were not suitable. Additionally, terminal unactivated alkenes like hexene and octene were also not successful in the reaction.

2.4 Mechanistic Studies

To confirm our mechanistic hypothesis, we performed studies to rule out other mechanistic possibilities. Namely we were interested in seeing if direct excitation could be responsible, or if a photoredox mechanism could be operative instead of the hypothesized triplet energy transfer. To detect if direct excitation of the carbonyl was occurring, we ran the reaction without any photocatalyst present at 456 nm for the allotted reaction time (0.5 h) which showed trace amounts of oxetane 2.28 (< 5% yield). Leaving the reaction for extended time (16 hours) more product was generated (25% yield). Using a higher energy light source (365 nm) after 0.5 hour 25 % of oxetane 2.28 was observed by quantitative $^1$H NMR (Figure 2.25A). These control experiments showed that the aryl glyoxylate can be directly excited with either UV light or blue LED’s, but the reaction is less efficient and prolonged reaction times still only gave low yields of the desired product. Importantly, running the reaction under thermal conditions with either no photocatalyst or in the absence of light while heating to 50 °C, did not result in product formation. These results suggested that our reaction required both visible light (456 nm) and photocatalyst.
We still wanted to determine that a photoredox mechanism was not operative. We knew the reduction and oxidation potentials of the optimal catalyst (2.25) and could compare those values to the reduction potential of aryl glyoxylate 2.26 (Figure 2.25B). We postulated that a photoredox process was unlikely under the optimized reaction conditions, as the excited state redox potentials of 2.25 (Ir$^{III*}/II$ = +1.21 V versus SCE; Ir$^{IV/III*}$ = −0.89 V versus SCE) were not expected to be sufficient for an effective oxidation or reduction of glyoxylate 2.26 (E$_{red}$ = −1.16 V versus SCE; E$_{red}$ = −1.75 V versus SCE). Finally, we performed Stern-Volmer quenching experiments to determine which component of the reaction was interacting with the photocatalyst. We observed that the aryl glyoxylate 2.26 quenched the photocatalyst, whereas cyclohexene demonstrated no quenching (Figure 2.25C). With the aforementioned studies performed we postulate the mechanism is as follows: triplet energy transfer from the excited state iridium photocatalyst to 2.26 which then forms the C−O bond to form biradical 2.44 and then C−C bond formation generates the oxetane product 2.28 (Figure 2.26).
2.5 Conclusion

This work added to years of research in performing traditionally challenging reactions, but with mild visible light photochemical conditions. Oxetanes have a rich history as targets in complex natural products (Section 2.1.2) and as structural motifs relevant for medicinal chemistry (Section 2.1.3). The lack of new synthetic methods for oxetane synthesis and the advent of visible-light-mediated triplet energy transfer for cyclobutane and azetidine synthesis inspired this work. The Paternò-Büchi reaction has been studied for over a century, but breaking free of the use of high energy UV light has been a long-standing challenge. This method identified aryl glyoxylates as suitable substrates for triplet energy transfer sensitization to access triplet state carbonyls from carbonyls that do not absorb visible light efficiently.

2.6 Experimental Section

2.6.1 General Information

General Laboratory Procedures. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an atmosphere of nitrogen. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates using UV light (254 or 366 nm), KMnO₄ or CAM stain for visualization. Flash chromatography was performed using silica gel Silia Flash® 40–63 micron (230–400 mesh) from Silicycle unless noted. The alumina plugs were performed with: Aluminum Oxide for chromatography, neutral, Brockmann I, 50–200 μm, 60 Angstrom CAS# 1344-28-1 (purchased from Acros Organics).

Materials and Instrumentation. All chemicals were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Oakwood, TCI America, Frontier Scientific, Matrix Scientific, Ark Pharm, and Chem Impex International, and were used as received unless otherwise stated. THF, CH₂Cl₂, Et₂O,
MeOH, MeCN and DMF were dried by being passed through a column of activated alumina under argon using a JC-Meyer Solvent Systems. Methyl benzoylformate was purchased from Acros Organics and 2-methyl-2-butene was purchased from Sigma-Aldrich and both were used as received. Photocatalysts: [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$, [Ir(dFppy)$_2$(dtbbpy)]PF$_6$, and [Ir(Fppy)$_2$(dtbbpy)]PF$_6$ were prepared according to a literature procedure.$^{123}$ All other photocatalysts were purchased from Sigma-Aldrich and used as received. Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on Varian MR400, Varian vnmrs 500, Varian Inova 500, and Varian vnmrs 700 spectrometers and are referenced to residual protic NMR solvent (CDCl$_3$: $\delta$ 7.26 ppm). Data for $^1$H NMR are reported as follows: chemical shift ($\delta$ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (Hz), integration. Carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on Varian vnmrs 500 and Varian vnmrs 700 spectrometers and are referenced to the carbon resonances of the NMR solvent (CDCl$_3$: $\delta$ 77.16 ppm). High-resolution mass spectrometry (MS) data was recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent 6230 TOF HPLC-MS (ESI) or Micromass AutoSpec Ultima Magnetic Sector mass spectrometer (ESI, EI). Infrared (IR) spectra were obtained using a PerkinElmer Frontier MIR spectrometer. IR data are represented as frequency of absorption ($\text{cm}^{-1}$).

**Photochemical Setup.** Visible light-mediated reactions were carried out using one 40 W PR160-456 Kessil light (100% intensity) that was placed on one side of the reaction vessel at a distance of approximately 6 cm. The ambient reaction temperature was maintained by cooling with a fan positioned behind the reaction.
**Stereo- and Regiochemistry of Oxetane Products.** Diastereomer and regioisomer ratios of the developed intermolecular Paternò-Büchi reaction were determined by $^1$H NMR analysis of the crude reaction mixture. In general, the transformation displays diastereoselectivities between 5:1 to >20:1. The regio- and stereochemical assignments for oxetane products were based on 1D NMR ($^1$H, $^{13}$C), 2D NMR (gCOSY, gHMBCAD, gHSQCAD) and $^1$H NMR NOE analysis. Specifically, the regiochemistry was typically assigned according to the $^{13}$C NMR shift of the carbon signals adjacent to the oxetane oxygen. The stereochemistry of the oxetane products was assigned based on NOE correlations of characteristic $^1$H NMR signals. When a mixture was isolated, the major diastereomer is drawn in Section 2.6.3.

**2.6.2 Mechanistic Investigations**

**Cyclic Voltammetry.** Cyclic voltammetry was performed on a CHI620E electrochemical analyzer (CH instruments) using a 3-mL five-neck electrochemical cell equipped with a glassy carbon working electrode, a platinum counter or auxiliary electrode and an Ag/AgCl (3 M KCl) reference electrode. The experimental setup was calibrated using ferrocene (Fc$^+/$/Fc) prior to each experiment. Samples were prepared with 0.03 mmol substrate in 3 mL $n$-Bu$_4$NP$F_6$ electrolyte (0.1 M in MeCN) and degassed prior to use by sparging with argon gas for 10 min. Data acquisition was performed at a scan rate of 100 mV/s and the potential ($E_{p/2}$) determined according to literature procedures. All potentials are reported versus the saturated calomel electrode (SCE). The cyclic voltammogram for glyoxylate 2.26 shows two irreversible reduction process at $E_{p/2} = −1.16$ V (vs. SCE) and $E_{p/2} = −1.75$ V (vs. SCE). A weak oxidation process was observed at approximately $E = 1.17$ V (Figure 2.27). This peak is due to an artifact present in the electrochemical set up and not the substrate. Cyclic voltammetry was also performed on a buffered solution and the same oxidation peak was observed, without any substrate present. The excited state redox potentials of
the photocatalyst [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (2.25) used in this study are not sufficient to reduce glyoxylate 2.26, indicating that a single-electron transfer mechanism is unlikely.

Figure 2.27: Cyclic voltammogram of glyoxylate 2.26.

**Stern-Volmer Quenching Studies.** Samples for the quenching study were prepared using stock solutions of 2.26 (4.87 mM), cyclohexene (4.93 mM) and [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (0.20 mM) in anhydrous MeCN. To a 4-mL volumetric flask was added [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (496 µL) and the respective amount of quencher (for 2.26: 0 µL, 102 µL, 205 µL, 523 µL; for alkene: 0 µL; 101 µL, 203 µL, 507 µL) and the volume adjusted to 4 mL with anhydrous MeCN. The solution was transferred to a 1-cm quartz cuvette, which was sealed with a septum-equipped cap and degassed by sparging with nitrogen gas for 10 min. Emission spectra were recorded using a PTI quantaMaster fluorimeter (Horiba) with an excitation wavelength of 420 nm. Emission was observed at 474 nm and the ratio of I₀/I plotted as a function of the quencher concentration (I₀: emission intensity without quencher; I: emission intensity with quencher), (Figure 2.28). Analysis was attempted at a higher wavelength (456 nm) to avoid potential inner-filter effects, but due to the lowered fluorescence of 2.25 at higher wavelengths a non-linear quenching was observed.
2.6.3 Experimental Procedures

General Procedure for Synthesis of Alkyl Esters (GP-2.1)

To a solution of 2-oxo-2-phenylacetic acid in anhydrous CH₂Cl₂ (1.0 M) were added oxalyl dichloride (1.2 equiv.) and a few drops of DMF at 0 °C, and the reaction mixture was warmed up to room temperature. After stirring for 4 h, CH₂Cl₂ and oxalyl dichloride were removed in vacuo. CH₂Cl₂ (0.5 M), pyridine (1.1 equiv.), and alcohol (2.5–10.0 equiv.) were added to the residue at 0 °C and the reaction mixture was warmed up to room temperature. After stirring for 16 h, the reaction mixture was quenched with NaHCO₃ (aq., sat.) and CH₂Cl₂ was removed in vacuo. The crude reaction mixture was brought up in EtOAc and the organic and aqueous layers were separated. The organic extracts were washed with NaHCO₃ (aq., sat.) (x3). The combined organic extracts were washed with NaCl (aq., sat.), dried over Na₂SO₄, filtered over cotton, and concentrated in vacuo. The crude residue was purified by silica gel flash column chromatography (gradient from 0–20% EtOAc/n-hexane) to give corresponding the α-keto ester.

adamantyl 2-oxo-2-phenylacetate (2.31-sub): Prepared according to GP-2.1 (adapted from literature procedure). To a solution of 2-oxo-2-phenylacetic acid (1 g, 6.7 mmol, 1 equiv.) in...
anhydrous CH₂Cl₂ (6.0 mL, 1.0 M) were added oxalyl dichloride (0.67 mL, 7.9 mmol, 1.2 equiv.) and a few drops of DMF at 0 °C, and the reaction mixture was warmed up to room temperature. After stirring for 4 h, CH₂Cl₂ and oxalyl dichloride were removed in vacuo.

Following this, CH₂Cl₂ (12 mL, 0.5 M), pyridine (0.59 mL, 7.3 mmol, 1.1 equiv.), and 1-adamantanol (2.54 g, 16.7 mmol, 2.5 equiv.) were added to the residue at 0 °C and the reaction mixture was warmed up to room temperature. After stirring for 16 h, the reaction mixture was quenched with NaHCO₃ (aq., sat.) and CH₂Cl₂ was removed in vacuo. The crude reaction mixture was brought up in EtOAc and the aqueous and organic layers were separated. The organic extracts were washed with NaHCO₃ (sat., aq.) (x3). The organic extracts were washed with NaCl (aq., sat.), dried over Na₂SO₄, filtered over cotton, and the solvent was removed in vacuo. The crude residue was purified by silica gel flash column chromatography (gradient from 0–20% EtOAc/n-hexane) to give corresponding the α-keto ester (2.31-sub) as a white solid (1.142 g, 60% yield). Spectroscopic data was consistent with that reported in the literature.¹²⁵ ¹H NMR (400 MHz, CDCl₃): δ 8.03–7.91 (d, J = 7.2 Hz, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 2.29 (d, J = 2.9 Hz, 6H), 2.27–2.23 (m, 3H), 1.77–1.67 (m, 6H).

**tert-buty 2-oxo-2-phenylacetate (2.32-sub):** Prepared according to GP-2.1 (adapted from literature procedure). To a solution of 2-oxo-2-phenylacetic acid (1 g, 6.7 mmol, 1 equiv.) in anhydrous CH₂Cl₂ (6.0 mL, 1.0 M) were added oxalyl dichloride (0.67 mL, 7.9 mmol, 1.2 equiv.) and a few drops of DMF at 0 °C, and the reaction mixture was warmed up to room temperature. After stirring for 7 h, CH₂Cl₂ and oxalyl dichloride were removed in vacuo.

Following this, CH₂Cl₂ (12 mL, 0.5 M), pyridine (0.59 mL, 7.3 mmol, 1.1 equiv.), and tert-butanol (6.37 mL, 66.6 mmol, 10.0 equiv.) were added to the residue at 0 °C and the reaction mixture was
warmed up to room temperature. After stirring for 16 h, the reaction mixture was quenched with NaHCO$_3$ (aq., sat.) and CH$_2$Cl$_2$ was removed in vacuo. The crude reaction mixture was brought up in EtOAc and the aqueous and organic layers were separated. The organic extracts were washed with NaHCO$_3$ (sat., aq.) (x3). The organic extracts were washed with NaCl (aq., sat.), dried over Na$_2$SO$_4$, filtered over cotton, and the solvent was removed in vacuo. The crude residue was purified by silica gel flash column chromatography (gradient from 0–20% EtOAc/n-hexane) to give 2.32-sub (1.245 g, 90% yield) as a light brown oil. Spectroscopic data was consistent with that reported in the literature.$^{125}$

**Synthesis of Anisole-Derived Glyoxylate**

methyl 2-(4-methoxyphenyl)-2-oxoacetate (2.34-sub): In a 25 mL round-bottom flask AlCl$_3$ (733 mg, 5.5 mmol, 2.2 equiv.) was suspended in CH$_2$Cl$_2$ (5.0 mL, 0.43 M) at 0 °C. To this mixture methyl 2-chloro-2-oxoacetate (0.51 mL, 5.5 mmol, 2.2 eq.) was added dropwise. At 0 °C, anisole (0.27 mL, 2.5 mmol, 1 equiv.) was added dropwise. Then the solution was stirred at r.t. for 2 h. After completion of the reaction, as determined by TLC, the mixture was cooled and carefully added 20 g crushed ice and 20 mL of conc. HCl. Extraction was performed with CH$_2$Cl$_2$ (x3), the combined organic extracts were collected and washed with 1 M NaOH (aq., sat.) (x1) and NaCl (aq., sat.) (x1). The organic extracts were dried over Na$_2$SO$_4$, filtered over cotton, and the solvent was removed in vacuo and the crude glyoxylate product was purified by silica gel flash column chromatography (gradient from 10–30% EtOAc/n-hexane, eluting at 20% EtOAc/n-hexane) to give 2.34-sub (260 mg, 54% yield) as a white solid. Spectroscopic data was consistent with that
reported in the literature.\textsuperscript{126} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 8.01 (dd, \(J = 9.0, 1.0\) Hz, 2H), 6.97 (d, \(J = 8.9\) Hz, 2H), 3.96 (s, 3H), 3.89 (s, 3H).

**Synthesis of Ester Glyoxylate**

![Molecular structure of the ester glyoxylate](image)

**methyl 4-(2-methoxy-2-oxoacetyl)benzoate (2.35-sub):** In a 10 mL round-bottom flask, to a solution of NaOH (98 mg, 2.5 mmol, 5 equiv.) in water (2 mL, 0.2 M) and methanol (4.9 mmol, 0.2 mL, 10 equiv.) was added ethyl 2-(4-cyanophenyl)-2-oxoacetate (100 mg, 0.49 mmol, 1 equiv.). The reaction mixture was heated to reflux for 14 h. The mixture was cooled to room temperature and diluted with 5 mL H\textsubscript{2}O, and then extracted with CH\textsubscript{2}Cl\textsubscript{2} (x2). The aqueous extracts were acidified with addition of 1 N HCl (aq.) and extracted with EtOAc (x2). The combined organic extracts were washed with NaCl (aq., sat.) and dried over Na\textsubscript{2}SO\textsubscript{4} (aq., sat.), filtered over cotton, and the solvent was removed in vacuo.

The crude carboxylic acid was brought up in methanol (4 mL, 0.1 M) and 3 drops of conc. H\textsubscript{2}SO\textsubscript{4} was added, and the reaction was heated to reflux for 14 h. The mixture was cooled to room temperature and was neutralized with NaHCO\textsubscript{3} (aq., sat.) and diluted with EtOAc and the aqueous and organic layers were separated. The aqueous layer was extracted with EtOAc (x3) and the combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4} (aq., sat.), filtered over cotton, and the solvent was removed in vacuo. Purified by silica gel flash column chromatography (gradient from 5–40% EtOAc/n-hexane, product eluting at 18% EtOAc/n-hexane) to give 3.5-sub (79 mg, 72% yield) as a white solid. \textsuperscript{1}H NMR (700 MHz, CDCl\textsubscript{3}): \(\delta\) 8.17 (d, \(J = 8.4\) Hz, 2H), 8.10 (d, \(J = 8.4\) Hz, 2H), 4.00 (s, 3H), 3.97 (s, 3H); \textsuperscript{13}C NMR (176 MHz, CDCl\textsubscript{3}): \(\delta\) 185.3, 166.0, 163.5, 135.7, 130.1, 53.0;
IR (cm\(^{-1}\)): 1966, 1718, 1687, 1429, 1277, 1106, 1003, 752, 697. HRMS: \(m/z\) calculated for 
\(\text{C}_{11}\text{H}_{10}\text{O}_{5}\text{H}^+\) [M+H\(^+\)]: 223.0601; found 223.0603.

**Synthesis of para-bromo Glyoxylate**

![Synthesis of para-bromo Glyoxylate](image)

*methyl 2-(4-bromophenyl)-2-oxoacetate (2.37-sub)*: In a 25 mL round-bottom flask to a solution of 1-(4-bromophenyl)ethan-1-one (1.0 g, 5.0 mmol, 1 equiv.) in pyridine (5.0 mL, 1.0 M) was added selenium dioxide (1.11 g, 10.0 mmol, 2.0 equiv.) at room temperature and the mixture was heated to 110 °C via heating mantle for 17 h. Upon cooling to room temperature, the crude reaction mixture was filtered over a small bed of celite, rinsing the celite plug with CH\(_2\)Cl\(_2\). The solvent was removed from the filtrate *in vacuo*. The resulting residue was used for the next reaction without further purification.

In a 25 mL round-bottom flask, to a solution of the crude oxidation product in DMF (7 mL, 0.6 M) at 0 °C was added K\(_2\)CO\(_3\) (2.08 g, 15.0 mmol, 3.0 equiv.) and iodomethane (0.94 mL, 15 mmol, 3.0 equiv.) and the mixture was stirred at room temperature for 2 h. After quenching with 1 N HCl (aq.), the crude solution was extracted with Et\(_2\)O (x3). The combined organic extracts were washed with NaHCO\(_3\) (aq., sat.) (x1), then washed with Na\(_2\)S\(_2\)O\(_3\) (aq., sat.) (x2) and then washed with NaCl (aq. sat.) (x1), then dried over Na\(_2\)SO\(_4\), filtered over cotton, and the solvent was removed *in vacuo*. The resulting residue was purified by silica gel flash column chromatography (gradient from 0–20% EtOAc/n-hexane, eluting at 11% EtOAc/n-hexane) to give the corresponding \(\alpha\)-keto methyl ester (70 mg, 6% yield) as an off-white solid. Spectroscopic data was consistent with that reported in the literature.\(^{127}\) \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.92 (d, \(J = 8.2\) Hz, 2H), 7.67 (d, \(J = 8.3\) Hz, 2H), 3.98 (s, 3H).
General Procedure for [2+2]-Cycloaddition (GP-2.2)

A 1-dram vial equipped with a magnetic stir bar was charged with carbonyl (0.1 mmol, 1.0 equiv.), alkene (if solid/liquid 1.5 equiv., if gaseous, sparged for 3–5 min.), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (2.25) (1 mol %) and MeCN (1.0 mL). The vial was sealed with a septum-equipped cap and the reaction mixture degassed by sparging with nitrogen gas for 3 min. Then, alkene (if solid/liquid, 1.5 equiv.) was added and the reaction mixture was stirred at ambient temperature (fan cooling) under irradiation with one blue LED light (456 nm, Kessil PR–160). After disappearance of glyoxylate starting material, determined by TLC, 0.5–1 h the solvent (and excess alkene if volatile) was removed in vacuo. The crude mixture was then purified by passing through a short plug of alumina: after concentration, the crude material was brought up in a very small amount of CH₂Cl₂ and loaded onto a short plug of basic alumina. The product was eluted off the alumina with a 10% EtOAc/n-hexane mixture. The purified oxetane was concentrated in vacuo and analyzed by ¹H NMR (major regioisomer/diastereomer is drawn).

Note: Oxetanes 2.39–2.42 were purified by silica gel flash column chromatography (gradient from 0–20% EtOAc/n-hexane, eluting between 4–8% EtOAc/n-hexane).

methyl 3,3,4-trimethyl-2-phenyloxetane-2-carboxylate (2.28): Prepared according to GP-2.2 using methyl benzoylformate (purchased from Acros Organics and used as is) (14 mL, 0.1 mmol, 1.0 equiv.), 2-methyl-2-butene (purchased from Sigma Aldrich and used as is) (15 µL, 0.15 mmol, 1.5 equiv.), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 0.5 h. ¹H NMR analysis of the crude reaction mixture revealed a
regioisomer ratio of 3:1 and a diastereomer ratio of >20:1. Purification by alumina plug (10% EtOAc/n-hexane) afforded the pure title compound as a clear colorless oil which crystallized to a white solid upon cooling (20 mg, 83% combined yield; >20:1 d.r, 3:1 r.r.).

This experiment was also completed on a 1.0 mmol scale with a lower catalyst loading and higher concentration: Prepared according to GP-2.2 using methyl benzoylformate (0.142 mL, 1.0 mmol, 1.0 equiv.), 2-methyl-2-butene (0.15 mL, 1.5 mmol, 1.5 equiv.), [Ir(dF(CF3)ppy)2(dtbbpy)]PF6 (2.8 mg, 0.0025 mmol, 0.25 mol %) and MeCN (5.0 mL, 0.2 M) with a reaction time of 0.5 h. Purification was completed the same way for the 0.1 mmol scale, passage through an alumina plug (eluting with 10% EtOAc/hexanes) afforded the pure title compound as a clear colorless oil which crystallized to a white solid upon cooling (195 mg, 83% combined yield; >20:1 d.r, 3:1 r.r.).

\[^{1}\text{H}\] NMR (700 MHz, CDCl\(_3\)): \(\delta\) 7.57 (d, \(J = 7.7\) Hz, 2H), 7.32 (t, \(J = 7.5\) Hz, 2H), 7.27 (d, \(J = 7.4\) Hz, 1H), 4.66 (q, \(J = 6.4\) Hz, 1H), 3.76 (s, 3H), 1.27 (s, 3H), 1.21 (d, \(J = 6.2\) Hz, 3H), 0.76 (s, 3H);

\[^{13}\text{C}\] NMR (176 MHz, CDCl\(_3\)): \(\delta\) 173.0, 138.8, 127.8, 127.6, 126.0, 90.4, 83.8, 52.4, 46.2, 25.6, 19.8, 17.3; \[^{\text{IR}}\text{(cm}^{-1}\text{)}\): 2965, 1747, 1730, 1448, 1267, 1229, 1033, 748, 699; HRMS: \(m/z\) calculated for C\(_{14}\)H\(_{18}\)O\(_3\)Na\(^+\) [M+Na]\(^+\): 257.1148; found 257.1143.

methyl 3,3-dimethyl-2-phenyloxetane-2-carboxylate (2.29): Prepared according to GP-2.2 using methyl benzoylformate (14 mL, 0.1 mmol, 1.0 equiv.), 2-methyl-prop-1-ene (sparged for 3 min), [Ir(dF(CF3)ppy)2(dtbbpy)]PF6 (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 0.5 h. \[^{1}\text{H}\] NMR analysis of the crude reaction mixture revealed a regioisomer ratio of 4:1. Purification by alumina plug (10% EtOAc/n-hexane) afforded the mixture of regioisomers as a clear colorless oil which crystallized to a white solid upon cooling (15 mg, 68% combined yield; 19:1 r.r.). \[^{1}\text{H}\] NMR (700 MHz, CDCl\(_3\)): \(\delta\) 7.61 (d, \(J = 7.4\) Hz, 2H), 7.38 (t,
J = 7.7 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 4.37 (d, J = 5.2 Hz, 1H), 4.23 (d, J = 5.2 Hz, 1H), 3.79 (s, 3H), 1.39 (s, 3H), 0.90 (s, 3H); 13C NMR (176 MHz, CDCl3): δ 172.3, 137.9, 128.1, 127.9, 125.8, 92.5, 79.5, 52.4, 44.4, 25.0, 24.4; IR (cm⁻¹): 2961, 2876, 1731, 1274, 1239, 1060, 979, 754, 701; HRMS: m/z calculated for C₁₃H₁₆O₃Na⁺ [M+Na]⁺: 243.0992; found 243.0987.

ethyl 3,3-dimethyl-2-phenyloxetane-2-carboxylate (2.30): Prepared according to GP-2.2 using ethyl benzyloformate (16 mL, 0.1 mmol, 1.0 equiv.), 2-methyl-prop-1-ene (sparged for 3 min), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 0.5 h. ¹H NMR analysis of the crude reaction mixture revealed a regioisomer ratio of 3:1. Purification by alumina plug (10% EtOAc/n-hexane) afforded the mixture of regioisomers as a clear colorless oil which crystallized to a white solid upon cooling (13 mg, 56% combined yield; 5:1 r.r.). ¹H NMR (700 MHz, CDCl3): δ 7.62 (d, J = 7.7 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 4.36 (d, J = 5.2 Hz, 1H), 4.25 (dd, J = 13.2, 7.0 Hz, 2H), 4.22 (d, J = 5.2 Hz, 1H), 1.40 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 0.89 (s, 3H); ¹³C NMR (176 MHz, CDCl3): δ 171.8, 138.1, 128.0, 127.8, 125.9, 92.2, 79.4, 61.4, 44.3, 25.0, 24.4, 14.4; IR (cm⁻¹): 2792, 2875, 1745, 1726, 1447, 1236, 1089, 1059, 857, 170; HRMS: m/z calculated for C₁₄H₁₈O₃Na⁺ [M+Na]⁺: 257.1148; found 257.1144.

(3S,5S,7S)-adamantan-1-yl-3,3-dimethyl-2-phenyloxetane-2-carboxylate (2.31): Prepared according to GP-2.2 using 2.31-sub (28 mg, 0.1 mmol, 1.0 equiv.), 2-methyl-prop-1-ene (sparged for 3 min), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 1 h. ¹H NMR analysis of the crude reaction mixture revealed a
regioisomer ratio of 4:1. Purification by alumina plug (10% EtOAc/n-hexane) afforded the mixture of regioisomers as a pale yellow oil (34 mg, 99% combined yield; 3:1 r.r.). \textit{\textbf{1H NMR}} (700 MHz, CDCl$_3$): $\delta$ 7.59 (d, $J = 7.8$ Hz, 2H), 7.35 (t, $J = 7.6$ Hz, 2H), 7.28 (t, $J = 7.2$ Hz, 1H), 4.32 (d, $J = 5.1$ Hz, 1H), 4.16 (d, $J = 5.2$ Hz, 1H), 2.16–2.13 (m, $J = 8.6$ Hz, 9H), 1.68–1.65 (m, $J = 8.3$ Hz, 6H), 1.43 (s, 3H), 0.87 (s, 3H); \textit{\textbf{13C NMR}} (176 MHz, CDCl$_3$): $\delta$ 170.3, 138.6, 127.8, 127.5, 126.0, 91.9, 82.4, 79.1, 44.0, 41.5, 36.2, 31.0, 24.8; \textit{\textbf{IR}} (cm$^{-1}$): 2912, 2845, 1722, 1457, 1235, 1053, 967, 756, 729; \textit{\textbf{HRMS}}: $m/z$ calculated for C$_{22}$H$_{28}$O$_3$Na$^+$ [M+Na]$^+$: 363.1931; found 363.1934.

tert-butyl 3,3-dimethyl-2-phenyloxetane-2-carboxylate (2.32): Prepared according to GP-2.2 using 2.32-sub (21 mg, 0.1 mmol, 1.0 equiv.), 2-methyl-prop-1-ene (sparged for 3 min), [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1.1 mg, 0.001 mmol, 1 mol%) and MeCN (1.0 mL, 0.1 M) with a reaction time of 0.5 h. \textit{\textbf{1H NMR}} analysis of the crude reaction mixture revealed a regioisomer ratio of 3:1. Purification by alumina plug (10% EtOAc/n-hexane) afforded the mixture of regioisomers as a yellow oil (19.0 mg, 72% combined yield; 3:1 r.r.). \textit{\textbf{1H NMR}} (700 MHz, CDCl$_3$): $\delta$ 7.59 (d, $J = 7.8$ Hz, 2H), 7.35 (t, $J = 7.5$ Hz, 2H), 7.28 (t, $J = 7.4$ Hz, 1H), 4.32 (d, $J = 5.1$ Hz, 1H), 4.18 (d, $J = 5.1$ Hz, 1H), 1.48 (s, 9H), 1.43 (s, 3H), 0.87 (s, 3H); \textit{\textbf{13C NMR}} (176 MHz, CDCl$_3$): $\delta$ 170.6, 138.5, 127.9, 127.6, 126.0, 92.0, 82.3, 79.1, 44.11, 28.2, 25.1, 24.5; \textit{\textbf{IR}} (cm$^{-1}$): 2974, 1742, 1721, 1448, 1369, 1250, 1158, 844, 700; \textit{\textbf{HRMS}}: $m/z$ calculated for C$_{16}$H$_{22}$O$_3$Na$^+$ [M+Na]$^+$: 285.1461; found 285.1470.

ethyl 2-(4-cyanophenyl)-3,3-dimethyloxetane-2-carboxylate (2.33): Prepared according to GP-2 using ethyl 4-cyanobenzoyleformate (17 mL, 0.1 mmol, 1.0 equiv.), 2-methyl-prop-1-ene
(sparged for 3 min), [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 0.5 h. $^1$H NMR analysis of the crude reaction mixture revealed a regioisomer ratio of 5:1. Purification by alumina plug (10% EtOAc/n-hexane) afforded the mixture of regioisomers as a clear colorless oil (17.0 mg, 66% combined yield; 5:1 r.r.).

$^1$H NMR (700 MHz, CDCl$_3$): $\delta$ 7.74 (d, $J = 8.5$ Hz, 2H), 7.67 (d, $J = 8.6$ Hz, 2H), 4.41 (d, $J = 5.3$ Hz, 1H), 4.27 (dd, $J = 14.9$, 7.2 Hz, 2H), 4.21 (d, $J = 5.4$ Hz, 1H), 1.39 (s, 3H), 1.31 (t, $J = 7.1$ Hz, 3H), 0.88 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ 170.9, 143.4, 131.8, 126.8, 118.9, 111.8, 91.9, 79.6, 62.0, 44.8, 24.7, 24.6, 14.4; IR (cm$^{-1}$): 2972, 2229, 1745, 1726, 1465, 1273, 1238, 1067, 974; HRMS: calculated for C$_{15}$H$_{17}$NO$_3$Na$^+$ [M+Na]$^+$: 282.1101; found 282.1100.

methyl 2-(4-methoxyphenyl)-3,3-dimethyloxetane-2-carboxylate (2.34): Prepared according to GP-2.2 using 2.34-sub (19 mg, 0.1 mmol, 1.0 equiv.), 2-methyl-prop-1-ene (sparged for 3 min), [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 0.5 h. $^1$H NMR analysis of the crude reaction mixture revealed a regioisomer ratio of 6:1. Purification by alumina plug (10% EtOAc/n-hexane) afforded the mixture of regioisomers as a clear colorless oil (18 mg, 72% combined yield; 7:1 r.r.). $^1$H NMR (700 MHz, CDCl$_3$): $\delta$ 7.52 (d, $J = 8.7$ Hz, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 4.33 (d, $J = 5.2$ Hz, 1H), 4.21 (d, $J = 5.2$ Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 1.36 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ 172.5, 159.3, 130.0, 127.1, 113.5, 92.3, 79.5, 55.36, 52.2, 44.2, 25.0, 24.3; IR (cm$^{-1}$): 2958, 2876, 2251, 1730, 1609, 1509, 1244, 1174, 730; HRMS: $m$/z calculated for C$_{14}$H$_{18}$O$_4$Na$^+$ [M+Na]$^+$: 273.1097; found 273.1096.
methyl 2-(4-(methoxycarbonyl)phenyl)-3,3-dimethyloxetane-2-carboxylate (2.35): Prepared according to GP-2.2 using 2.35-sub (22 mg, 0.1 mmol, 1.0 equiv.), 2-methyl-prop-1-ene (sparged for 3 min), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 0.5 h. ¹H NMR analysis of the crude reaction mixture revealed a regioisomer ratio of 4:1. Purification by alumina plug (10% EtOAc/n-hexane) afforded the mixture of regioisomers as a clear colorless oil which crystallized to a white solid upon cooling (25 mg, 91% combined yield; 5:1 r.r.). ¹H NMR (700 MHz, CDCl₃): δ 8.04 (d, J = 7.9 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 4.40 (d, J = 4.9 Hz, 1H), 4.23 (d, J = 4.9 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 1.39 (s, 3H), 0.89 (s, 3H); ¹³C NMR (176 MHz, CDCl₃): δ 171.8, 167.0, 143.0, 129.8, 129.4, 126.0, 92.5, 79.6, 52.6, 52.3, 44.8, 24.9, 24.5; IR (cm⁻¹): 2956, 2879, 1721, 1609, 1436, 1274, 1107, 1067, 764; HRMS: calculated for m/z C₁₅H₁₈O₅Na⁺ [M+Na]⁺: 301.1046; found 301.1045.

methyl 2-(4-bromophenyl)-3,3-dimethyloxetane-2-carboxylate (2.37): Prepared according to GP-2.2 using 2.37-sub (24 mg, 0.100 mmol, 1.0 equiv.), 2-methyl-prop-1-ene (sparged for 3 min), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 0.5 h. ¹H NMR analysis of the crude reaction mixture revealed a regioisomer ratio of 4:1. Purification by alumina plug (10% EtOAc/n-hexane) afforded the mixture of regioisomers as a clear colorless oil which crystallized to a white solid upon cooling (23 mg, 77% combined yield; 7:1 r.r.). ¹H NMR (700 MHz, CDCl₃): δ 7.48 (s, 4H), 4.36 (d, J = 5.3 Hz, 1H), 4.20 (d, J = 5.3 Hz, 1H), 3.77 (s, 3H), 1.35 (s, 3H), 0.88 (s, 3H); ¹³C NMR (176 MHz, CDCl₃): δ 171.9, 137.0,
methyl 3,3,4,4-tetramethyl-2-phenyloxetane-2-carboxylate (2.38): Prepared according to GP-2.2 using methyl benzoyleformate (14 mL, 0.10 mmol, 1.0 equiv.), 2,3-dimethylbut-2-ene (18 mL, 0.15 mmol, 1.5 equiv.), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 0.5 h. Purification by alumina plug (10% EtOAc/ n-hexane) afforded the product as a clear colorless oil (18 mg, 73% yield). ^1H NMR (700 MHz, CDCl₃): δ 7.63 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.28 (t, J = 7.3 Hz, 1H), 3.74 (s, 3H), 1.43 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 0.85 (s, 3H); ^13C NMR (176 MHz, CDCl₃): δ 173.5, 139.4, 127.8, 127.6, 126.3, 88.7, 85.4, 52.3, 47.3, 25.8, 25.6, 22.7, 22.4; IR (cm⁻¹): 2965, 2925, 1748, 1728, 1447, 1374, 1374, 1242, 1050, 702; HRMS: calculated for C₁₃H₁₅BrO₃Na⁺ [M+Na]⁺: 321.0097; found 321.0093.

methyl 8-phenyl-7-oxabicyclo[4.2.0]octane-8-carboxylate (2.39): Prepared according to GP-2.2 using methyl benzoyleformate (14 mL, 0.10 mmol, 1.0 equiv.), cyclohexene (15 mL, 0.15 mmol, 1.5 equiv.), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 1 h. ^1H NMR analysis of the crude reaction mixture revealed a diastereomer ratio of 6:1. Purification silica gel flash column chromatography (gradient from 0–10% EtOAc/ n-hexane, eluting at 4% EtOAc/ n-hexane) afforded the product as a clear colorless oil
(16 mg, 65% yield, >20:1 d.r.). $^1$H NMR (700 MHz, CDCl$_3$): δ 7.45 (d, $J = 7.6$ Hz, 2H), 7.36 (t, $J = 7.7$ Hz, 2H), 7.29 (t, $J = 7.4$ Hz, 1H), 5.01 (q, $J = 5.5$ Hz, 1H), 3.76 (s, 3H), 3.35 (q, $J = 7.9$ Hz, 1H), 1.91–1.88 (m, 1H), 1.61–1.55 (m, 2H), 1.46–1.43 (m, 1H), 1.41–1.35 (m, 2H), 1.29–1.25 (m, 1H), 1.06–1.01 (m, 1H); $^{13}$C NMR (176 MHz, CDCl$_3$): δ 174.8, 137.7, 128.1, 127.7, 125.3, 87.7, 75.5, 52.7, 40.7, 28.1, 22.1, 20.3, 19.1; IR (cm$^{-1}$): 2934, 2869, 1749, 1728, 1449, 1257, 1232, 731, 699; HRMS: m/z calculated for C$_{15}$H$_{18}$O$_3$Na$^+$ [M+Na]$^+$: 269.1148; found 269.1142.

methyl 2-phenyl-2a,7a-dihydro-2H-oxeto[2,3-b]benzofuran-2-carboxylate (2.40): Prepared according to GP-2.2 using methyl benzoylformate (14 mL, 0.10 mmol, 1.0 equiv.), benzofuran (17 mL, 0.15 mmol, 1.5 equiv.), [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 1 h. $^1$H NMR analysis of the crude reaction mixture revealed a diastereomer ratio of 5:1. Purification silica gel flash column chromatography (gradient from 0–10% EtOAc/n-hexane, eluting at 4% EtOAc/n-hexane) afforded the mixture of diastereomers as a clear colorless oil which crystallized to a white solid upon cooling (18 mg, 64% yield, 5:1 d.r., >20:1 r.r.). $^1$H NMR (700 MHz, CDCl$_3$): δ 7.29–7.24 (m, 3H), 7.18 (t, $J = 7.5$ Hz, 2H), 7.04 (t, $J = 7.4$ Hz, 1H), 6.87 (d, $J = 8.1$ Hz, 1H), 6.74 (d, $J = 7.4$ Hz, 1H), 6.64 (t, $J = 7.5$ Hz, 1H), 6.62 (d, $J = 4.0$ Hz, 1H), 5.02 (d, $J = 3.9$ Hz, 1H), 3.87 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$): δ 172.3, 160.6, 135.8, 129.4, 128.1, 128.0, 126.6, 124.6, 123.5, 121.7, 110.6, 106.2, 90.7, 54.2, 53.2; IR (cm$^{-1}$): 2954, 2925, 1754, 1734, 1596, 1463, 1242, 961, 943; HRMS: m/z calculated for C$_{17}$H$_{14}$O$_4$Na$^+$ [M+Na]$^+$: 305.0784; found 305.0778.
methyl 6-phenyl-2,7-dioxabicyclo[3.2.0]hept-3-ene-6-carboxylate (2.41): Prepared according to GP-2.2 using methyl benzoylformate (14 mL, 0.10 mmol, 1.0 equiv.), furan (11 mL, 0.15 mmol, 1.5 equiv.), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 1 h. ¹H NMR analysis of the crude reaction mixture revealed a diastereomer ratio of 5:1. Purification silica gel flash column chromatography (gradient from 0–10% EtOAc/n-hexane, eluting at 4% EtOAc/n-hexane) afforded the mixture of diastereomers as a pale brown oil (11 mg, 46% yield, 6:1 d.r., >20:1 r.r.). ¹H NMR (700 MHz, CDCl₃): δ 7.40 (d, J = 7.1 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.31 (t, J = 7.1 Hz, 1H), 6.42 (d, J = 4.3 Hz, 1H), 6.40 (d, J = 2.5 Hz, 1H), 4.82 (t, J = 2.9 Hz, 1H), 4.49 (t, J = 3.4 Hz, 1H), 3.80 (s, 3H); ¹³C NMR (176 MHz, CDCl₃): δ 172.7, 148.7, 136.7, 128.7, 128.2, 125.4, 105.6, 101.5, 92.2, 54.5, 53.2; IR (cm⁻¹): 2955, 1732, 1607, 1449, 1237, 1134, 1052, 1011, 930, 729; HRMS: m/z calculated for C₁₃H₁₂O₄Na⁺ [M+Na]⁺: 255.0628; found 255.0624.

methyl 3-ethoxy-2-phenyloxetane-2-carboxylate (2.42): Prepared according to GP-2.2 using methyl benzoylformate (14 mL, 0.10 mmol, 1.0 equiv.), ethyl vinyl ether (14 mL, 0.15 mmol, 1.5 equiv.), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1.1 mg, 0.001 mmol, 1 mol %) and MeCN (1.0 mL, 0.1 M) with a reaction time of 0.5 h. ¹H NMR analysis of the crude reaction mixture revealed a regioisomer ratio of 5:1 and a diastereomer ratio of 5:1. Purification silica gel flash column chromatography (gradient from 0–10% EtOAc/n-hexane, eluting at 8% EtOAc/n-hexane) afforded 7 mg of a mixture of diastereomers (2:1 d.r., >20:1 r.r.) as a clear colorless oil and 9 mg of pure major diastereomer (>20:1 r.r., >20:1 r.r.) as a clear colorless oil (combined yield of 16 mg, 68%). ¹H NMR’s of both the mixture of diastereomers and the pure major diastereomer are provided. ¹H NMR (700 MHz, CDCl₃): δ 7.55 (d, J = 7.9 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.35 (t, J = 7.4
Hz, 1H), 4.86 (t, \(J = 6.6\) Hz, 1H), 4.74 (t, \(J = 7.1\) Hz, 1H), 4.45 (t, \(J = 6.5\) Hz, 1H), 3.81 (s, 3H), 3.55–3.52 (m, 1H), 3.49–3.44 (m, 1H), 0.96 (t, \(J = 7.0\) Hz, 3H) \(^{13}\text{C NMR}\) (176 MHz, CDCl₃): \(\delta\) 172.7, 134.8, 128.5, 128.4, 126.0, 93.6, 81.1, 74.2, 65.9, 52.9, 15.0; \(\text{IR}\) (cm\(^{-1}\)): 2976, 2886, 1729, 1436, 1377, 1244, 1088, 964, 734; \(\text{HRMS}\): \(m/z\) calculated for \(\text{C}_{13}\text{H}_{16}\text{O}_4\text{Na}^+\) [M+Na]: 259.0941; found 259.0936.
Chapter 3 Synthesis of Azetidine-Based Energetic Materials


3.1 Introduction

3.1.1 Energetic Materials - History of Nitroglycerin

*While the remainder of this chapter is focused of the synthesis of nitrogen-containing energetic materials and their applications as melt-castable explosives and propellant plasticizers, it is important to understand how energetic materials research can have profound impacts on humanity, not only in their commonly assumed application.* Energetic materials have a long history dating back as early as 6th century Chinese texts. While the entirety of energetic materials history is too vast to be covered, the discovery and commercialization of dynamite, which is a mixture of nitroglycerin and celite, has a unique history bridging warfare, pharmacology, and civil engineering. Nitroglycerin was first synthesized by Ascanio Sobrero in 1847 when combining glycerol with nitric and sulfuric acid. Even these early studies noted violent headache symptoms upon ingestions of nitroglycerin. In 1863, Imanuel Nobel and his son Alfred commercialized the synthesis of nitroglycerin outside of Stockholm. Efficient cooling and stirring of the highly exothermic reaction, especially on large scales, was critical to the safety of the process. This was especially evident after an explosion in 1864 at the Nobel factory that killed Imanuel’s youngest
son, Emil. So, while nitroglycerin proved to be very reactive it was important to attenuate the sensitivity which was done by solidifying nitroglycerin via addition of mineral powder. This solid material was later referred to as dynamite, an energetic material that is commonplace in today’s world. While dynamite brings forwards thoughts of coal mining and demolition, the key ingredient of dynamite, nitroglycerin, has a much more nuanced story.

During the mid-19th century scientists in Britain began using amyl nitrite as a vasodilator, which are medications that open the blood vessels and reduce blood pressure. In 1867, Lauder Brunton, a prominent figure in the history of pharmacology, used amyl nitrite to relieve chest pain from reduced blood flow to the heart (angina), but was interested in identifying a compound that would have a longer-lasting effect. While nitroglycerin had only been previously used in homeopathic medicine, it was not until the late 1870’s when physicians in London began using it therapeutically for angina. Dr. William Murrell was the first to use nitroglycerin for angina and noted the dramatic difference in the duration of relief where amyl nitrite lasted seconds, nitroglycerin provided hours of relief. By the end of the 19th-century nitroglycerin was hailed as a first line treatment for the relief of chest pain.

Interestingly, some key studies in the tolerance of nitroglycerin came about from factory workers in the production of dynamite, where many experienced severe headaches upon first exposure, but then built-up tolerance after the first few days of handling nitroglycerin. The tolerance was short-lived as workers over the weekend would recover and then by Monday experience the same symptoms which was referred to as “Monday disease”. This experience was frustrating to the point that workers would bring home nitroglycerin and rub it on their skin to prevent the headaches from returning to work Monday. This situation became even more dire as
some workers experienced nitrate withdrawal over the weekend leading to severe arterial spasms and in rare cases sudden death, which became referred to as “Sunday heart attack”.

The mechanism of action of nitroglycerin became known almost a century later in 1977 when Ferid Murad discovered the release of nitric oxide from nitroglycerin and its effect on vascular smooth muscle. Independently, the two pharmacologists Furchgott and Zawadazki proposed that there was an unstable substance that led to vasodilation that they named “endothelial-derived relaxing factor”. Ultimately a third group, led by Louis Ignarro, recognized this unstable substance to be nitric oxide. All three scientists, Murad, Furchgott, and Ignarro were awarded the Nobel prize in physiology or medicine in 1998 and the role of nitric oxide is still widely studied today.

In summary, dynamite today is rarely used in warfare and has been an essential component to mining and construction. The medical impacts of nitroglycerin have been fundamental to treating chest pain and developing modern medicines widely used today, such as beta-blockers. The establishment of the “Nobel prize” from Alfred Nobel in 1901 and ultimately awarding of the Nobel Prize in 1998 to the discovery of nitric oxide as a signaling molecule in the cardiovascular system rounds out a colorful history of a seemingly small molecule.

3.1.2 Melt-Castable Materials

Melt-casting is an old technical process used in energetic materials formulation in which the solid material is melted and re-solidified in a metal cast. An ideal melt-castable explosive will have a melting point between 70–120 °C so that steam-heating can be used to efficiently melt the material. Too low of a melting point will result in a difficult to handle material at ambient temperatures. The vapor pressure should also be low, as molten material with a high vapor pressure can result in a significant inhalation toxicity risk and the evaporated explosive can deposit
in other places creating a hazardous work environment. Additionally, a sufficient charge separation between melting and detonation temperatures is required out of concern for safety and to avoid premature detonation. Ideally, the material will have a high density and improved explosive properties compared to the state-of-the-art benchmark. More technically speaking there should be no cracking or shrinking upon cooling which can lead to separation from the shell or casing. Not all these factors will be “ideal” for all new materials developed, as it is commonly observed that those with better performance also are usually prone to more cracking and those with better thermal stability also usually have poorer detonation properties.

Today, melt-castable explosives are commonly compared to 2,4,6-trinitrotoluene (TNT). TNT was first synthesized in 1863 by Joseph Wilbrand by nitrating toluene with a mixture of nitric and sulfuric acid usually sequentially over 2–3 steps. TNT isn’t regarded as a high-performance explosive, but its ability to be melt-casted and it’s insensitivity make it a highly used explosive. In fact, it was originally used as a yellow dye and its explosive properties took decades to be recognized due to the challenging detonation of TNT. In modern applications like mining and building, TNT has since replaced nitroglycerin. Compounds like hexogen (RDX) and octogen (HMX) are better performing explosives, but the melt-casting properties of TNT continues to make it widely used and is commonly used in explosive mixtures like torpex (42% RDX, 40% TNT, 18% aluminum). The toxicity and environmental pollution have prompted studies to replace TNT through the development of other melt-castable explosives. Still an unmet area is understanding structure-performance relationships, especially influences on melting points, densities, detonation properties, thermal stabilities, and sensitivities.
3.1.3 Propellant Plasticizers

Plasticizers are usually incorporated into energetic compositions to improve the workability, flexibility, or distensibility.\textsuperscript{145} The handling of energetic mixtures in extremely low temperatures is critical for the success of the system and is almost always achieved through the addition of a plasticizer. Typically, one of the most important considerations for a plasticizer is a low glass transition temperature, less than $-50$ °C. Beyond this, compatibility with the other components is important, some of which include: a binder, stabilizers, and primary and secondary explosives.\textsuperscript{128} One disadvantage of traditional plasticizers, such as acetyl triethyl citrate, diethyl adipate, diethyl sebacate and dioctyl adipate, is that they lessen the performance of the material as they can make up a significant portion of the energetic composition, but do not contribute to the explosive properties (Figure 3.1).\textsuperscript{146}

To overcome this, energetic plasticizers have been developed where the primary role is to modify the mechanical properties including softening and improving flexibility of the polymer matrix and secondary concerns being altering viscosity to aid in the processing, improving overall oxygen balance, and altering the burn rate of propellants.\textsuperscript{146} The important characteristics for an energetic plasticizer include 1) positive influence on safety and performance, 2) improved mechanical properties, 3) compatibility with all ingredients 4) stability and low toxicity, 5) low volatility, 6) environmental impacts, and 7) cost of production.\textsuperscript{146}

Figure 3.1: A Examples of non-energetic plasticizers. B Nitrate-based state-of-the-art energetic plasticizers.
An early example of using an energetic material as a plasticizer was the addition of nitroglycerin to nitrocellulose which resulted in the gelation of the mixture. There are obvious downsides to handling nitroglycerin (Section 3.1.1) and therefore modern energetic plasticizers have been developed, many of which are still nitrate-based including: alkylNitritoethylNitramine (NENA), ethylene glycol dinitrate (EGDN), metrioltrinitrate (MTN or TMETN), and butane-1,2,4-triolnitratre (BTTN) (Figure 3.1). One of the biggest challenges in the incorporation of plasticizers, especially small molecule plasticizers, is exudation, migration of the compound from the surface of the formulation. Because of this, low-weight polymers, often derived from oxetanes, have become popular to increase miscibility with the energetic polymer support network.

3.1.4 Four-Membered Ring Energetic Materials

The ring strain of four-membered rings can further increase the performance of energetic materials by raising the heat of formation of the system. Two examples of high-energy materials based on four-membered rings are tetranitrocyclobutane (TNCB, 3.1) and trinitroazetidine (TNAZ, 3.2), the latter of which will be discussed in Section 3.1.5. Tetranitrocyclobutane was first synthesized by Thomas Archibald (Fluorochem Inc.) in 1989 from bis-amine 3.3 via oxidation to di-nitro cyclobutane 3.4 followed by a second nitration step with sodium nitrate and silver nitrate to access TNCB (Figure 3.2). TNCB has a very powerful energetic profile with an explosive power greater than HMX, but unfortunately a low decomposition temperature of 165 °C which precludes its use.

![Diagram of four-membered energetic materials and Synthesis of TNCB](image-url)
A series of cyclobutane-based energetic materials were evaluated by the Baran group in collaboration with the U.S. Army Research Laboratory, specifically Dr. Jesse Sabatini. Six different poly-nitric ester cyclobutane materials were synthesized with a variety of methods including: [2+2]-cycloaddition, intramolecular substitution, and electrochemical conditions (Figure 3.3). There was special consideration to evaluate the effects of stereo- and regiochemistry in their design of the substrates. An important conclusion to come from this work was the significant role that stereo- and regiochemistry play in the energetic properties. This is particularly impactful because theoretical calculations for energetic properties typically only consider the molecular formula of a compound, thus ignoring stereo- and regiochemistry, which in practice can lead to vastly different observations. The Baran group in collaboration with the U.S. Army Research Laboratory generated new potential melt-castable materials (3.5–3.7) in addition to a potential plasticizer for propellants (3.8) (Figure 3.3). This work, which demonstrated the tunability provided by altering the stereo- and regiochemistry, will likely impact all future energetic material designs of chiral compounds. Following this report, the Baran Lab continued the collaboration and developed a continuous flow electrochemical reaction to synthesize cyclobutane 3.7 on a greater than 100-gram scale.150
Azetidines and derivatives of trinitroazetidine (3.2) have been appended to other nitrogen-rich compounds to increase the energetic performance. Dinitroazetidine has been used in nucleophilic addition reactions with other electron-deficient reagents like chlorinated tetrazines and triazines (Figure 3.4).[151] In 2023, Li and Pang used difluorinated azetidines with similar nitrogen-rich triazolyl polycyclic compounds to form new energetic materials. The fluorinated compounds have improved stability and density compared to the nitroazetidine materials previously synthesized (Figure 3.4).[152]

Oxetane monomers have also been studied as building blocks for energetic materials. Typically, energetic oxetanes are used as the corresponding polymer for energetic binders, with
the most popular ones being derived from 3,3-bis(azidomethyl) oxetane (BAMO), 3-azidomethyl 3-methyl oxetane (AMMO), and 3-nitratomethyl-3-methyloxetane (NIMMO). That being said, new research in monomer design is needed to enable advances in small molecule energetics and energetic polymers. Recently in 2022, Klapötke and coworkers performed an aza Michael addition between nitroalkene 3.9 and tetrazole 3.10 to generate regio- and diastereomeric products (3.11–3.12) (Figure 3.5). Spirocyclic oxetane energetics have also been synthesized and evaluated by the Klapötke group starting from oxetanone (3.13) and condensation with a hydrazine and subsequent hydrazinolysis to generate spirocyclic tetrahydrotetrazine derivatives (3.15) (Figure 3.5). While powerful, the compounds all suffered from low decomposition points, but this work laid a path forward to considering substituted oxetane monomers as standalone energetic materials.

Figure 3.5: Synthetic strategies towards monomeric oxetane energetic materials.

3.1.5 Trinitroazetidine (TNAZ)

The only prominent azetidine-based energetic material to be developed to date is trinitroazetidine, referred to as TNAZ (3.2). It was originally considered to be a potential replacement for TNT with the biggest benefits being that TNAZ was steam melt-castable with improved impact sensitivity to already manufactured secondary explosives, like composition B.
Importantly, TNAZ had an energetic profile much greater than the most powerful HMX-based formulations in use at the time. The ability to continue to be melt-castable, like TNT, but with greater energetic performance, was extremely attractive.

The first synthesis of TNAZ was completed in 1983 from Kurt Baum and Thomas Archibald of Fluorochem Inc. In the following years the X-ray crystal structure was determined by Richard Gilardi of the Naval Research Laboratory. In their published synthetic route chloro-epoxide 3.16 was reacted with a primary amine to access hydroxy azetidine 3.17. Mesylation of the secondary alcohol (3.18) and nitration with sodium nitrate provided the mono-nitrated azetidine 3.19. Following this, the C–H bond could be converted to a nitro-group (3.20) and finally nitration of the amine with nitric acid and acetic anhydride to form TNAZ (3.2) in overall five steps from epoxide 3.16 (Figure 3.6).\(^\text{157}\) Since then, multiple other groups and national agencies have investigated the synthesis of TNAZ in order to improve the cost and efficiency.\(^\text{158–160}\)

Despite lengthy synthetic routes and cost of production, the biggest downside and ultimate demise of TNAZ is the high volatility. The rapid rate of evaporation of TNAZ in the molten phase is problematic when it comes to safely processing the material. A sample of TNAZ held at 150 °C will completely evaporate over the course of only twenty-eight minutes.\(^\text{156}\) Because the sample would need to be heated above the melting point (101 °C) for melt-casting, there is no way to overlook the significant safety risk and toxicity risk of those working in the production area.
The synthesis, characterization, and evaluation of TNAZ from the 1990’s to early 2000’s did provide us with information on the potential for nitroazetidine materials to serve as excellent energetic materials. While TNAZ did not replace TNT, there is the potential for alternative azetidine structures to fulfill the promise of high-energy materials, with low sensitivity and safe processing. The ability to access azetidines efficiently is a remaining challenge in addressing this question.

3.1.6 Azetidine Synthetic Strategies

The most common method for synthesizing azetidines is the intramolecular substitution approach with an amine nucleophile (Figure 3.7). The reactive conformation for the intramolecular ring-closing is the disfavored eclipsed conformation, explaining why the rate of ring closure is significantly slower when compared to both larger (pyrrolidine) and smaller rings (aziridine). One example comes from De Kimpe and coworkers where in situ reduction of the imine cyclizes under ambient conditions to form the azetidine. Stepwise reduction to the amine and then

Figure 3.7: Challenges in 4-membered ring intramolecular substitution for azetidine synthesis. Example of in situ imine reduction and subsequent cyclization vs. stepwise reduction and cyclization.

The first chapter of this dissertation covered the prevalence and importance of six-membered nitrogen-containing heterocycles (Section 1.1.1). A nitrogen heterocycle much less studied is the four-membered ring, the azetidine. Similar to oxetanes discussed in the second chapter (Section 2.1.1), the azetidine is considerably strained leading to challenges in the synthesis.

The most common method for synthesizing azetidines is the intramolecular substitution approach with an amine nucleophile (Figure 3.7). The reactive conformation for the intramolecular ring-closing is the disfavored eclipsed conformation, explaining why the rate of ring closure is significantly slower when compared to both larger (pyrrolidine) and smaller rings (aziridine). One example comes from De Kimpe and coworkers where in situ reduction of the imine cyclizes under ambient conditions to form the azetidine. Stepwise reduction to the amine and then
cyclization with excess base results in a cyclopropane product, due to the presence of an acidic proton \( \alpha \) to the ester (Figure 3.7).\textsuperscript{162}

\[ \text{A Reduction of } \beta\text{-lactam [Alcaide, 2000]} \]

\[ \begin{array}{c}
\text{3.21} \\
\text{AlCl}_3, \text{LiAlH}_4 \\
\text{Et}_2\text{O, 81\%}
\end{array} \]

\[ \text{3.22} \]

\[ \text{B Synthesis and functionalization of azabicyclobutane} \]

\[ \begin{array}{c}
\text{3.23} \\
\text{NH}_2 \\
\text{Br}_2 \\
\text{Br} \\
\text{3.24} \\
\text{PhLi} \\
\text{3.25}
\end{array} \]

\[ \text{3.26} \]

\[ \text{examples of Nu\textendash}E \text{ reagents} \]

\[ \begin{array}{ll}
\text{Cl\textendash}Cl & \text{R\textendash}MX \\
\text{Ts\textendash}Cl & \text{Ts\textendash}N_3 \\
\text{N\textendash}Cl & \text{R}_2\text{N\textendash}Boc
\end{array} \]

Figure 3.8: \textbf{A} Example of \( \beta \)-lactam (3.21) reduction with chloroallane. \textbf{B} Synthesis of azabicyclobutane (3.25) and examples of reagents for di-functionalization via strain release.

The second strategy often applied in the synthesis of azetidines is the reduction of \( \beta \)-lactams. Besides being the structural base unit of many antibiotics, \( \beta \)-lactams are easily synthesized and can be reduced to the azetidine core. Typically, reagents such as LiAlH\(_4\), chloroallanes, DIBAL-H, and Raney Nickel are known to selectively reduce the lactam. One example of the efficiency of this reaction is the reduction of lactam 3.21 to azetidine 3.22 with chloroallane formed in situ from AlCl\(_3\) and LiAlH\(_4\) by Alcaide and coworkers (Figure 3.8A).\textsuperscript{163}

A contemporary synthetic route for azetidine synthesis has been the strain release of azabicyclobutanes (Figure 3.8B). While this type of reactivity was initially reported in 1969 by Funke\textsuperscript{164,165}, it has experienced a resurgence of popularity by groups like the Baran group.\textsuperscript{166–168} The starting material 3.25 can be synthesized from the bromination of allylamine (3.23) and subsequent cyclization with phenyllithium. The azabicyclobutane (3.25) is generated in situ at cryogenic temperatures where an exogenous nucleophile is added to functionalize at the 3-position (Figure 3.8B).\textsuperscript{166}
The [2+2]-cycloaddition to generate azetidines is the most efficient way to access the four-membered ring. Some thermal reactions have been developed with fine tuning of the electronics, such as pairing electron-deficient imines with electron-rich vinyl ethers (Figure 3.9A). A more general method for the [2+2]-cycloaddition is the photochemical variant, referred to as the aza Paternò-Büchi reaction. This reaction was first reported by Tsuge in 1986 and shares many parallels with the Paternò-Büchi reaction, in that many of the pathways from the excited state of the C=N double bond are similar, such as fragmentation and rearrangement (Figure 3.9C). Additionally, the reaction can proceed from either singlet or triplet excited states. These excited states can be accessed from direct irradiation with UV light or from a photosensitizer through triplet energy transfer (Section 2.1.6). A unique aspect to the use of excited state C=N double bonds compared to C=O double bonds is the unproductive non-radiative relaxation to the ground state via E/Z isomerization (Figure 3.9B). While this is challenging, the addition of a substituent on the nitrogen can aid the reaction through the tuning of sterics and electronics. It is also worth noting
that despite the potential importance of azetidines in pharmaceutical applications, the *aza* Paternò-Büchi reaction is significantly less developed than the Paternò-Büchi reaction.

![Diagram of azetidine formation](image)

**Figure 3.10:** Selected examples of triplet energy transfer [2+2]-cycloadditions for azetidine formation: **A** Intramolecular *aza* Paternò-Büchi via activated alkene sensitization. **B** Intermolecular *aza* Paternò-Büchi via \(C=\text{N}\) bond sensitization with unactivated alkenes. **C** Intramolecular *aza* Paternò-Büchi reaction via \(C\equiv\text{N}\) bond sensitization with unactivated alkenes.

Our group has spent the past few years developing visible-light-enabled *aza* Paternò-Büchi reactions both intra- and intermolecularly via triplet energy transfer. In 2019 we used activated alkenes like styrenes and dienes to react intramolecularly with oximes and hydrazones to access bicyclic azetidines (Figure 3.10A). Following this work, an intermolecular approach was pursued where excited state 2-isoxazoline-3-carboxylates were reacted with unactivated alkenes, which ultimately resulted in a very general approach to access highly substituted azetidines (Figure 3.10B). Finally, we expanded the use of triplet excited state 2-isoxazoline-3-carboxylates to react intramolecularly with unactivated alkenes to generate tricyclic ring systems (Figure 3.10C).
3.2 Reaction Design and Optimizations-Collaboration with U.S. Army Research Laboratory

3.2.1 Reaction Design

While TNAZ showed initial promise as a TNT alternative and other azetidines have been appended onto nitrogen-rich rings\(^{151,152}\), the study of monocyclic polynitric ester azetidines as energetic materials has not received much improvement over the past three decades. We felt as if innovation in designing new nitroazetidine materials had the potential to dramatically broaden the scope of azetidine-based materials, especially with the advent of new photocatalyzed methods for azetidine synthesis. Similar to the history of nitroglycerin (Section 3.1.1) we anticipated that overcoming limitations in azetidine-based energetic materials could further enable the use of azetidines in a variety of other fields such as pharmaceuticals, agrichemicals, and non-energetic materials. Namely, we were interested in modifying the azetidine structure by providing 1) access to non-symmetric azetidines, 2) enabling substitution in the alpha-position to the azetidine nitrogen, 3) introduction of multiple substituents including stereocenters and 4) including

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Figure 3.11: A Design principles in developing new azetidine-based energetic materials. B Targeted substitution patterns for azetidine products.
additional nitrogen and oxygen atoms (Figure 3.11A). We planned to systematically vary the substitution and stereochemistry about the azetidine ring as we anticipated from the work of Baran and Sabatini that these could potentially play a large role in the energetic properties that would not be predicted by theoretical calculations (Figure 3.11B).149

3.2.2 Intramolecular Cyclization

![Figure 3.12: Initial calculations for density, detonation pressure and detonation velocity for proposed symmetric nitroazetidine 3.27 and comparison to state-of-the-art melt-castable material, TNT (3.28).](image)

Working with the U.S. Army Research Laboratory and specifically Dr. Jesse Sabatini our collaboration commenced with the proposal of the completely symmetric polynitric azetidine 3.27. Initial calculations predicted that the detonation velocity and pressure would exceed that of TNT (3.28), the state-of-the-art standard in melt-castable materials (Figure 3.12). With this information we began the synthesis by converting cis-diol 3.29 to epoxide 3.30 in 86% yield over two steps. The epoxide was then opened with benzylamine and alkylated to form amino alcohol 3.31. The secondary alcohol was chlorinated to form 3.32 in 96% yield (Figure 3.13A). The cyclization of amino chloride 3.32 was much more challenging than expected. Notable by-products in the reaction included elimination of the chloride to the 1,2-disubstituted alkene (3.37) and the Grob fragmentation product (3.38) (Figure 3.13B). The equivalents of base and solvent mixtures were evaluated under different reaction times, but little improvement was observed (Figure 3.13C). Nevertheless, we isolated the major diastereomer (3.34) in 28% yield and the minor diastereomer (3.33) in 5% yield. The major diastereomer was carried forward and reduced with LiAlH₄ and then debenzylated under hydrogenolysis conditions resulting in azetidine 3.35 in 89% yield over the two steps (Figure 3.13A).
Figure 3.13: A Synthetic route to nitroazetidine 3.36 and X-ray crystal structure. B Undesired byproducts of amino chloride cyclization. C Subset of optimization for amino chloride cyclization and resulting product distributions between desired product 3.34 and undesired products (3.37+3.38).

Due to the safety requirements of handling high-energy compounds, nitration studies were carried out at the U.S. Army Research Laboratory. It is important to note that these reactions should not be run unless safe practices can be ensured: working on small scales, behind a blast-shield, and Kevlar gloves and lab-coat as a minimum level of precaution. Compared to Dr. Sabatini’s previous work on cyclobutanes149 pure nitric acid was not feasible due to the presence of the amine functionality. Aprotic nitration conditions were applied in which acetic anhydride and nitric acid were pre-stirred to generate acetyl nitrate as the active nitration reagent. Under these conditions, nitroazetidine 3.36 was synthesized in 80% yield. The energetic evaluation of azetidine 3.36 was very promising, in-depth details on the energetic parameters evaluated are outlined in Section 3.2.4, but it is important to note that this material had characteristics suitable for a melt-castable material (Figure 3.13A). However, the synthetic route was not ideal moving forward and the scalability of the sequence was questionable, especially with the low-yielding cyclization step.
We had initially planned to vary the regio- and stereochemistry and it appeared that accessing other isomers through this route would incur similar challenges.

### 3.2.3 Aza Paternò-Büchi Reaction

**A** General scheme for intermolecular aza Paternò-Büchi to access azetidine energetics

![Scheme A](image)

**B** Intermolecular aza Paternò-Büchi to access azetidines 3.47 and 3.48

![Scheme B](image)

**C** Intermolecular aza Paternò-Büchi to access azetidine 3.53

![Scheme C](image)

*Figure 3.14: A Overview of intermolecular [2+2]-cycloaddition route. B Intermolecular aza Paternò-Büchi reaction of 2-isoaxazoline-3-carboxylate 3.39 and terminal alkene 3.49 and elaboration of diastereomeric products to nitroazetidines 3.47 and 3.48. C Intermolecular aza Paternò-Büchi reaction of 3.39 and disubstituted alkene 3.49, followed by reduction, hydrogenolysis, and unsuccessful nitration.*

We hypothesized that a more efficient route could be achieved by avoiding the intramolecular cyclization disconnection. Our group’s previous work in assembling azetidines via aza Paternò-Büchi reactions held the potential to be a much more efficient and scalable route. One structural constraint of the intermolecular aza Paternò-Büchi reaction we developed is the cyclic 2-isoaxazoline-3-carboxylates required. We envisioned that the cycloadducts would be converted...
to nitration precursors via reduction of the ester and then $N-O$ bond cleavage to result in monocyclic azetidines (Figure 3.14A). These azetidine compounds would be similar to the original product isolated (3.36), but would contain a quaternary center alpha to the nitrogen. However, we envisioned that these materials could provide an overall benefit in our energetic materials design in that the extra conformational flexibility could result in highly energetic liquid materials that could be applied as energetic plasticizers in propellant mixtures.

We set forth to test our synthetic route on a multi-gram scale as this type of *aza* Paternò-Büchi reactions had previously only been performed on sub-gram quantities. The first approach towards this method commenced with oxime 3.39 and alkene 3.40. A low catalyst loading (0.02 mol%) and a high concentration allowed for a conventional photochemical set-up to be applied on a multi-gram scale. The [2+2]-cycloaddition proceeded in 87% yield and produced the diastereomers (3.41–3.42) in a 1:1 mixture that could be easily separated by column chromatography. Having equal access to both diastereomers would provide us the opportunity to study the potential effects of stereochemistry on energetic properties. The pendant ester of each diastereomer could then be cleaved with Red-Al in 90% and 95% yields, respectively. Hydrogenolysis of the $N-O$ bonds and benzyl groups with Pd(OH)$_2$ on carbon was the final step towards accessing azetidine HCl salts 3.45 and 3.46. The nitration under aprotic conditions was successfully applied by Dr. Jesse Sabatini to form novel nitroazetidines 3.47 and 3.48 (Figure 3.14B). Both azetidines were liquids with very promising physical properties for a plasticizer, namely the low freezing points and high decomposition temperatures.
We next looked at changing the alkene portion in order to change the substitution pattern. The 1,1-disubstituted alkene 3.49 was applied in the [2+2]-cycloaddition to result in bicyclic azetidine 3.50 as a single regioisomer. Next, the ester was reduced with Red-Al to 3.51, then N–O bond cleavage, and HCl salt formation to result in 3.52 (Figure 3.14C). Our developed nitration conditions were attempted but ultimately only partial nitration could be achieved, likely due to the increased steric bulk. Unfortunately, moving to harsher conditions either resulted in incomplete nitration or rapid decomposition.

We were interested in incorporating substitution across from the nitrogen which could not be achieved via the intermolecular [2+2]-cycloaddition due to the inherent regioselectivity. By
tethering the oxime and alkene components together only one regioisomer is favorable to form and we suspected that we could generate just two diastereomers which would allow for facile separation (Figure 3.15A). The intramolecular substrate 3.54 was accessed in one step from the carboxylic acid and benzylated alcohol. The oxime carboxylic acid was the product of a simple hydrolysis of 3.39. The original conditions in our 2020 report\textsuperscript{113} used LiOH in a mixture of MeOH/H\textsubscript{2}O, but on large scale the liquid-liquid extraction was challenging to reproduce a high yield. Instead by using NaOH upon the addition of HCl, NaCl was formed and could be efficiently filtered off and then subjected to esterification with HATU and the corresponding alcohol. The [2+2]-cycloaddition had to be amended to account for the intramolecular reaction taking place, high concentration conditions resulted in low isolated yields of the desired product and significant amounts of intermolecular products. Substantially lowering the concentration proved beneficial, but became cumbersome when scaling the reaction. Ultimately, slow addition of substrate 3.54 to a solution of the photocatalyst allowed for a more reasonable reaction concentration and gram-scale reactions to be performed with a combined yield of 70% with a 1:1 mixture of diastereomers. Following separation of the diastereomers, azetidines 3.55 and 3.56 were reduced with Red-Al and then converted to HCl salts 3.59 and 3.60. Five nitro groups could then be installed in one step by Dr. Jesse Sabatini in 75% and 84% yields (3.61 and 3.62), respectively (Figure 3.15B). Diastereomer 3.62 immediately solidified and showed promising properties of a melt-castable material. Diastereomer 3.61 ultimately was determined to be a low-melting solid after taking months in the freezer to solidify. We had now generated three different types of materials all from azetidine scaffolds.

Our last foray into these compounds was arguably the most challenging as engaging terminal alkenes, especially intramolecularly, was not expected to be high yielding. Since we had
already established a slow-addition protocol to overcome deleterious side reactivity we were able to achieve 60% yield of the desired tricyclic azetidine 3.64. Lactone reduction proceeded in 68% yield and hydrogenolysis in quantitative yield to form 3.66. The acetyl nitrate conditions were successful in converting the HCl salt (3.66) to nitroazetidine 3.67, a low-melting solid (Figure 3.15C).

3.2.4 Energetic Properties

Our collaboration resulted in six novel polynitric ester azetidines that were evaluated for their energetic properties. We used TNT and TMETN as the state-of-the-art comparisons for melt-castable materials and energetic plasticizers, respectively (Table 3.1). A property that was important to initially determine was the physical state of the materials (solid vs. liquid). In the case of a solid material the melting point needed to be determined as to categorize it as a low-melting solid or as a potential melt-castable material, which would require a melting point between 70–120 °C. For a liquid material, the freezing point needed to be determined to consider its potential application as a plasticizer. Due to the role of a plasticizer modulating the glass transition temperature, low freezing temperatures are desirable.
Table 3.1: Combined physical properties and theoretical calculations for synthesized nitroazetidines products and comparison to state-of-the-art materials: TNT and TMETN.

<table>
<thead>
<tr>
<th>Data</th>
<th>TNT</th>
<th>3.36</th>
<th>3.62</th>
<th>3.61</th>
<th>3.67</th>
<th>3.47</th>
<th>3.48</th>
<th>TMETN</th>
</tr>
</thead>
<tbody>
<tr>
<td>density (g/cc)</td>
<td>1.65 (X-ray)</td>
<td>1.71 (X-ray)</td>
<td>1.71 (X-ray)</td>
<td>1.67 (X-ray)</td>
<td>1.68 (X-ray)</td>
<td>1.58 (liquid)</td>
<td>1.58 (liquid)</td>
<td>1.47 (liquid)</td>
</tr>
<tr>
<td>T&lt;sub&gt;m&lt;/sub&gt; or T&lt;sub&gt;froz&lt;/sub&gt; (°C)</td>
<td>80.4</td>
<td>74</td>
<td>89</td>
<td>56</td>
<td>65</td>
<td>&lt;−40</td>
<td>&lt;−40</td>
<td>−3</td>
</tr>
<tr>
<td>T&lt;sub&gt;dec&lt;/sub&gt; (°C)</td>
<td>295.0</td>
<td>193</td>
<td>185</td>
<td>182</td>
<td>187</td>
<td>184</td>
<td>176</td>
<td>182.0</td>
</tr>
<tr>
<td>Ω&lt;sub&gt;CO2&lt;/sub&gt; (%)</td>
<td>-74</td>
<td>−26.9</td>
<td>−30.8</td>
<td>−30.8</td>
<td>−39.9</td>
<td>−39.9</td>
<td>−39.9</td>
<td>−34.5</td>
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<td>Ω&lt;sub&gt;CO&lt;/sub&gt; (%)</td>
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<td>+2.45</td>
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<td>0</td>
<td>−7.03</td>
<td>−7.03</td>
<td>−7.03</td>
<td>−3.1</td>
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<tr>
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<td>27.4</td>
<td>27.2</td>
<td>27.0</td>
<td>24.6</td>
<td>24.7</td>
<td>24.9</td>
<td>23.7</td>
</tr>
<tr>
<td>V&lt;sub&gt;det&lt;/sub&gt;</td>
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<td>7986</td>
<td>7884</td>
<td>7744</td>
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<td>I&lt;sub&gt;p&lt;/sub&gt; (s)</td>
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<td>256</td>
<td>249</td>
<td>250</td>
<td>250</td>
<td>247.0</td>
</tr>
<tr>
<td>ΔH&lt;sup&gt;r&lt;/sup&gt; (kJ mol&lt;sup&gt;−1&lt;/sup&gt;)</td>
<td>-59.3</td>
<td>−308.5</td>
<td>−436.4</td>
<td>−434.3</td>
<td>−356.4</td>
<td>−355.6</td>
<td>−351.5</td>
<td>−425.0</td>
</tr>
<tr>
<td>IS (J)</td>
<td>15</td>
<td>4.3</td>
<td>5.6</td>
<td>4.3</td>
<td>5.2</td>
<td>5.6</td>
<td>6.2</td>
<td>0.20</td>
</tr>
<tr>
<td>FS (N)</td>
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<td>240</td>
<td>256</td>
<td>256</td>
<td>&gt;360</td>
<td>&gt;360</td>
<td>&gt;360</td>
<td>-</td>
</tr>
<tr>
<td>ESD (J)</td>
<td>0.25</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
<td>-</td>
</tr>
</tbody>
</table>

T<sub>m</sub> = onset temperature of melting or freezing; T<sub>dec</sub> = onset temperature of decomposition; Ω<sub>CO2</sub> = CO<sub>2</sub> oxygen balance; Ω<sub>CO</sub> = CO oxygen balance; P<sub>0</sub> = detonation pressure; V<sub>det</sub> = detonation velocity; I<sub>p</sub> = specific impulse; ΔH<sup>r</sup> = molar enthalpy of formation; IS = impact sensitivity; FS = friction sensitivity; ESD = electrostatic discharge sensitivity; SOTA = state-of-the-art.

Legend:
- standalone melt-castable materials
- improved detonation pressures & velocities
- low melting point solids
- improved impact & friction sensitivities
- low freezing point liquids

To determine the applicability of these materials as energetic compounds the onset temperature of decomposition needed to be measured. This was done by differential scanning calorimetry (DSC). This analytical technique measures the amount of heat required to increase the temperature of the sample and a reference. The temperature of the material and reference will remain the same, but when the material is going through a phase change, such as melting, it will absorb the heat being put into the system. Analogously, when the material begins to decompose and therefore release heat, a change will be observed in the amount of heat required to go into the system. For the solid materials, DSC was used to determine both the melting point and the decomposition point. Importantly for compounds 3.36 and 3.62 that had high-melting points it was
important to determine that there was significant charge separation between melting and decomposition which then allowed them to be classified as melt-castable materials (Table 3.1). For the liquid materials, DSC was used to determine the decomposition temperatures. For azetidines 3.47 and 3.48 the decomposition temperatures, 184 °C and 176 °C respectively, were suitable and on par with commonly handled energetic plasticizers such as TMETN (182 °C), in combination with their low freezing points (<−40 °C), both materials were considered to be suitable energetic plasticizers.

The CO₂ and CO oxygen balances were calculated for each product based off the molecular formula. In general, the oxygen balance describes the excess (positive value) or deficit (negative value) of oxygen to achieve a balanced ratio between the oxidizer and fuel component. An oxygen balance value of zero would mean that the substance can be converted entirely into oxidized products by heating in a closed vessel without any additional oxidizer, fuel, or external oxygen present. Furthermore, the oxygen balance can be described in terms of generating CO₂ (Ω₉₀₂%) or CO (Ω₉₀%). Both values are important because while fully oxidized carbon will generate CO₂, compounds that have a negative oxygen balance will have incomplete combustion and generate CO instead. Often, explosives with a negative oxygen balance, like TNT, will be mixed with a secondary component that has a positive oxygen balance so complete combustion can be achieved. All the azetidines synthesized had improved oxygen balances compared to state-of-the-art compounds and the corresponding polynitric ester cyclobutane materials.¹⁴⁹

The density of each material was experimentally determined, with all solid materials densities being determined via single X-ray crystal structures obtained by the U.S. Army Research Laboratory. Importantly, the experimental density values allowed for theoretical calculations to be performed. Obtaining experimental values for properties such as detonation velocity (Vₜₐₜ) and
pressure ($P_{cj}$), were outside the scope of this work and would require much more material than was practical to make at this time. The theoretical detonation velocities and pressures calculated of all azetidine materials surpassed the state-of-the-art materials TNT and TMETN. These two parameters are of key importance when determining the energetic activity.

The specific impulse ($I_{sp}$) is also an important consideration, especially in rocket propellant formulations as it considers the exhaust velocity of the combustion gases. In general, the specific impulse values of the polynitric ester azetidines were improved to commonly used energetic materials (Table 3.1). Having a highly energetic material is important, but it is more important to determine the safety of handling these materials. In order to determine this, the impulse sensitivity (IS), friction sensitivity (FS), and electrostatic discharge (ESD) were measured. All the polynitric ester azetidines displayed equal or lower friction sensitivity than TNT. The impact sensitivity was found to be between PETN and RDX, two commonly manufactured and used secondary explosives (Table 3.1).

### 3.2.5 Conclusion

Together with the U.S. Army Research Laboratory we developed six novel polynitric ester azetidine energetic materials. This collaboration resulted in the synthesis of two novel melt-castable reagents (3.36 and 3.62), two low-melting solid materials (3.61 and 3.67), and two liquid energetic plasticizers (3.47–3.48) (Table 3.1). Taking inspiration from the promise and the ultimate demise of TNAZ, we were excited to be able to generate new azetidine-based materials that surpassed state-of-the-art materials like TNT and TMETN in terms of energetic performance, but also generated materials safer than TNAZ.

The synthetic efforts to synthesize unique azetidine products we believe can be enabling for a wide array of industries. Energetics materials research has historically been linked to
advancements across engineering, space exploration, and even medicine. This collaboration opened our synthetic chemistry lab to the unique aspects and multi-parameter optimization done in the field of energetic materials, something often overlooked due to the end-use of these materials. Additionally, we have been able to share our synthetic methodologies and education on novel ways to forge four-membered heterocycles.

3.3 Experimental Section

3.3.1 General Information

General Laboratory Procedures. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an atmosphere of nitrogen. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates using UV light (254 or 366 nm), KMnO₄ or CAM stain for visualization. Flash chromatography was performed using silica gel Silia Flash® 40–63 micron (230–400 mesh) from Silicycle unless noted.

Materials and Instrumentation. All chemicals were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Oakwood, TCI America, Frontier Scientific, Matrix Scientific, Ark Pharm, and Chem Impex International, and were used as received unless otherwise stated. THF, CH₂Cl₂, Et₂O, MeOH, MeCN, toluene, and DMF were dried by being passed through a column of activated alumina under argon using a JC-Meyer Solvent Systems. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporating using a temperature-controlled water bath. Cis-2-butene-1,4-diol (3.29) was purchased from Acros Organics and fac-[Ir(dFppy)₃] was purchased from Sigma-Aldrich and both were used as received. 2-Isoxazoline-3-carboxylate (3.39) was prepared following a literature preparation.¹¹³ 98% HNO₃ and Ac₂O were used as received from Fisher Scientific. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on Varian MR400, Varian vnmrs 600, and Varian vnmrs 700 spectrometers and are referenced to
residual protic NMR solvent (CDCl$_3$: $\delta$ 7.26 ppm, CD$_3$OD: $\delta$ 3.31 ppm, d$_6$-DMSO: $\delta$ 2.50 ppm, d$_6$-acetone: $\delta$ 2.05 ppm). Data for $^1$H NMR are reported as follows: chemical shift ($\delta$ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet,qd = quartet of doublets, dq = doublet of quartets, quint = quintet, m = multiplet (denotes complex pattern), dd = doublet of doublets, ddd = doublet of doublets of doublets, dddd = doublet of doublets of doublets of doublets, dt = doublet of triplets, td = triplet of doublets, br = broad signal), coupling constant (Hz), integration. Carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on Varian vnmrs 500, and Varian vnmrs 700 spectrometers and are referenced to the carbon resonances of the NMR solvent (CDCl$_3$: $\delta$ 77.16 ppm, CD$_3$OD: $\delta$ 49.00 ppm; d$_6$-acetone: $\delta$ 206.26 ppm). $^1$H and $^{13}$C NMR spectra of 3.36, 3.47, 3.48, 3.61, 3.62, and 3.67 were recorded using a Bruker 400 MHz and 101 MHz instrument, respectively. High-resolution mass spectrometry (MS) data was recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent 6230 TOF HPLC-MS (ESI) or Micromass AutoSpec Ultima Magnetic Sector mass spectrometer (ESI, EI). Infrared (IR) spectra were obtained using a PerkinElmer Frontier MIR spectrometer. Infrared spectra of 3.36, 3.47, 3.48, 3.61, 3.62, and 3.67 were measured with a Bruker Alpha-P FTIR instrument. IR data are represented as frequency of absorption (cm$^{-1}$). Melting and decomposition temperatures were measured at a heating rate of 10 °C/min using a TA Instruments Q10 DSC instrument. Single-crystal X-ray diffraction (XRD) studies were performed with a SuperNova Dualflex diffractometer containing an EosS2 charge-coupled device detector and a molybdenum Mo_ Ka ($\lambda$ = 0.71073 Å) radiation source.

**Handling High Energy Materials.** **Caution!** Although we did not experience any problems handling the compounds described in this report, proper laboratory precautions should be taken. Laboratories and personnel should be properly grounded, and safety equipment such as heavy
Kevlar/steel gloves, reinforced Kevlar coat, ballistic face shield, ear plugs, and blast shields are necessary for all energetic transformations, and in handling any material that is determined to be energetic.

**Photochemical Set-Up 1.** Visible light-mediated intermolecular aza Paternò-Büchi reactions were carried out using two 40 W PR160-427 Kessil light (100% intensity) that were placed on either side of the reaction vessel at a distance of approximately 3 cm. The ambient reaction temperature was maintained by cooling with a fan positioned behind the reaction. An orange tinted shield was placed in-front of the reaction for eye protection.

**Photochemical Set-Up 2.** Visible light-mediated intramolecular aza Paternò-Büchi reactions were carried out using two 40 W PR160-427 Kessil light (100% intensity) that were placed on either side of the reaction vessel at a distance of approximately 3 cm. The ambient reaction temperature was maintained by cooling with a fan positioned behind the reaction. A syringe pump was positioned elevated and in-front of the reaction vessel. A long, wide gauge needle was used with an appropriately sized syringe and the connection between the syringe and needle was sealed with Teflon tape. The reaction was fitted with a nitrogen line as to not build up pressure over the course of the addition. An orange tinted shield was placed in-front of the reaction for eye protection.

**Stereo- and Regiochemistry of Azetidine Products.** The regio- and stereochemical assignments for the azetidine products were based on 1D NMR ($^1$H, $^{13}$C), 2D NMR (gCOSY, gHMBCAD, gHSQCAD) and $^1$H NMR NOE analysis. Specifically, the regiochemistry was typically assigned according to the shift of the protons directly appended to the azetidine ring. The stereochemistry of the azetidine products was assigned based on NOE correlations of characteristic $^1$H NMR signals.
3.3.2 Experimental Procedures

cis-2,3-bis((benzylloxy)methyl)oxirane (3.30): A 2-L 3-neck flask equipped with a magnetic stir bar, a 125-mL addition funnel, nitrogen inlet and a septum with inserted temperature probe was charged with NaH (60% dispersion in mineral oil; 18.25 g, 456 mmol, 2.5 equiv.). The flask was evacuated and refilled with nitrogen before adding DMF (400 mL) and cooling the mixture in an ice bath. Then, a solution of (Z)-but-2-ene-1,4-diol (3.29) (16.08 g, 183 mmol, 1.0 equiv.) in DMF (15 mL) was added dropwise over 30 min via the addition funnel maintaining an internal temperature below 10 °C. After completion of addition, the addition funnel was rinsed with DMF (5 mL) and the reaction mixture was stirred for 1 h, before adding benzyl bromide (78.04 g, 456 mmol, 2.5 equiv.) dropwise via the addition funnel maintaining an internal temperature below 10 °C. The ice bath was removed and the reaction mixture stirred at ambient temperature for 19 h, at which point analysis by TLC indicated full consumption of the starting material. The reaction mixture was cooled in an ice bath, before adding aq., sat. NH₄Cl solution (100 mL) and water (100 mL) carefully and stirring the resulting mixture for 15 min. The reaction mixture was transferred to a 2-L separation funnel containing water (1 L). The resulting mixture was extracted with Et₂O (3x 400 mL), and the combined organic extracts were washed with a 5% aq. LiCl solution (2x 400 mL) and brine (1x 400 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude product was dried using high vac at 45 °C affording the crude, alkylated diol as a yellow oil (65.31 g).

The crude, alkylated diol was transferred to a 2-L round bottom flask equipped with a magnetic stir bar and dissolved in CH₂Cl₂ (750 mL). The resulting solution was cooled in an ice bath, before adding mCPBA (70wt%; 89.99 g, 365 mmol, 2.0 equiv.) slowly. The reaction mixture was stirred
for 0.5 h, before removing the ice bath and stirring for 23 h at ambient temperature, at which point TLC analysis indicated full consumption of the starting material. The reaction mixture was cooled to 0 °C and solids were removed by filtration. To the filtrate was added an aq., sat. Na₂CO₃ solution (400 mL), which resulted in the precipitation of solids that were removed by filtration. Then, the filtrate was washed with 10% aq. Na₂CO₃ solution (2x 400 mL), brine (1x 400 mL), before concentrating in vacuo. The crude product was purified by flash column chromatography (2% to 5% to 10% to 20% EtOAc/hexanes) to afford the pure title compound as a pale-yellow oil (44.78 g, 86% over 2 steps). Spectroscopic data were found consistent with those reported in the literature.¹⁷³

¹H NMR (400 MHz, CDCl₃): δ 7.40–7.28 (m, 10H), 4.63 (d, J = 11.9 Hz, 2H), 4.53 (d, J = 11.9 Hz, 2H), 3.71 (dd, J = 11.4, 3.3 Hz, 2H), 3.55 (dd, J = 10.5, 5.7 Hz, 2H), 3.32–3.24 (m, 2H).

tert-butyl N-benzyl-N-(1,4-bis(benzzyloxy)-3-hydroxybutan-2-yl)glycinate (3.31): A 200-mL round bottom flask equipped with a magnetic stir bar was charged with 3.30 (44.75 g, 157 mmol, 1.0 equiv.). Then, benzylamine (20.24 g, 189 mmol, 1.2 equiv.) and Zn(ClO₄)₂•6 H₂O (11.72 g, 31 mmol, 0.2 equiv.) were added sequentially and the flask sealed with a rubber septum. The reaction vessel was evacuated and refilled with nitrogen three times, before heating the reaction at 80 °C (heating mantle) for 22 h, at which point TLC analysis indicated full consumption of the starting material. After cooling to ambient temperature, CH₂Cl₂ (100 mL) was added, and the mixture transferred to a 1-L Erlenmeyer flask. CH₂Cl₂ (200 mL) and 0.1 M aq. NaOH solution (500 mL) was added, the mixture stirred vigorously for 5 min, before removing the precipitated solids by filtration over celite. The filter cake was washed three times with CH₂Cl₂ (3x 200 mL). The filtrate was transferred to a 2-L separation funnel and the organic layer separated. The aqueous
layer was extracted with \( \text{CH}_2\text{Cl}_2 \) (3x 350 mL) and the combined organic extracts dried over MgSO\(_4\), filtered, and concentrated \textit{in vacuo}, then dried using high vac to obtain the crude amino alcohol as an orange solid (62.34 g).

The crude amino alcohol was transferred to a 2-L round bottom flask equipped with a magnetic stir bar and dissolved in DMF (400 mL). Next, \( \text{K}_2\text{CO}_3 \) (65.25 g, 472 mmol, 3.0 equiv.) and tert-butyl bromoacetate (46.05 g, 236 mmol, 1.5 equiv.) were added sequentially and the resulting mixture stirred at ambient temperature for 18 h, at which point TLC analysis indicated full consumption of the starting material. The reaction mixture was diluted with water (800 mL), transferred to a 2-L separation funnel, and extracted with Et\(_2\)O (3x 500 mL). The combined extracts were washed with a 5% aq. lithium chloride solution (2x 300 mL) and brine (1x 300 mL) and concentrated \textit{in vacuo}. Purification by flash column chromatography (5% to 7.5% to 10% to 15% to 20% EtOAc/hexanes) afforded the pure title compound as a pale-yellow oil (61.22 g, 77% over 2 steps). \(^1\)H NMR (700 MHz, CDCl\(_3\)): \( \delta \) 7.38–7.21 (m, 15H), 4.69 (s, 1H), 4.56 (d, \( J = 12.0 \) Hz, 1H), 4.48 (d, \( J = 12.0 \) Hz, 1H), 4.46 (d, \( J = 12.1 \) Hz, 1H), 4.41 (d, \( J = 12.0 \) Hz, 1H), 3.96 (d, \( J = 13.3 \) Hz, 1H), 3.75–3.71 (m, 2H), 3.66 (dd, \( J = 10.3, 3.6 \) Hz, 1H), 3.61 (dd, \( J = 10.5, 3.4 \) Hz, 1H), 3.57 (dd, \( J = 10.3, 7.3 \) Hz, 1H), 3.48 (dd, \( J = 10.5, 4.2 \) Hz, 1H), 3.44 (d, \( J = 17.2 \) Hz, 1H), 3.35 (d, \( J = 17.2 \) Hz, 1H), 3.07–3.03 (m, 1H), 1.36 (s, 9H). \(^{13}\)C NMR (176 MHz, CDCl\(_3\)): \( \delta \) 172.0, 138.8, 138.5, 138.2, 129.4, 128.5, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 127.4, 81.4, 73.6, 73.5, 71.6, 68.4, 68.0, 63.0, 56.4, 54.1, 28.1. IR (cm\(^{-1}\)): 3426, 3030, 2979, 2862, 1729, 1495, 1454, 1367, 1222, 1151, 1097, 1028, 909, 729, 697. HRMS: \( m/z \) calculated for C\(_{31}\)H\(_{40}\)NO\(_5\) \([\text{M+H}]^+\): 506.2901; found: 506.2899.
**tert-butyl N-benzyl-N-(1,4-bis(benzyloxy)-3-chlorobutan-2-yl)glycinate (3.32):** A 2-L three-neck flask equipped with a magnetic stir bar, a 125-mL addition funnel, a reflux condenser and a septum with a temperature probe and nitrogen inlet, was charged with 3.31 (61.00 g, 121 mmol, 1.0 equiv.) and CH$_2$Cl$_2$ (380 mL). The solution was cooled in an ice bath, before slowly adding a solution of thionyl chloride (18.0 mL, 247 mmol, 2.05 equiv.) in CH$_2$Cl$_2$ (20 mL) via the addition funnel at a rate that maintained the internal temperature of the reaction at 5–7 °C. After complete addition, the reaction was heated at reflux for 1 h, at which point TLC analysis indicated complete consumption of the starting material. Next, the solution was cooled in an ice bath, before slowly adding an aq., sat. NaHCO$_3$ solution (400 mL). The pH of the aqueous layer was carefully adjusted to pH 7–8 via the addition of solid Na$_2$CO$_3$. The resulting biphasic mixture was stirred for 20 min, and subsequently diluted with CH$_2$Cl$_2$ (100 mL) and transferred to a 2-L separation funnel. The organic layer was separated and the aqueous layer extracted with CH$_2$Cl$_2$ (2x 500 mL). The combined organic extracts were washed with brine (1x 300 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1% to 2% to 5% EtOAc/hexanes) afforded the pure title compound as a pale-yellow oil (60.90 g, 96%).

**$^1$H NMR** (700 MHz, CDCl$_3$): δ 7.38–7.24 (m, 14H), 7.21 (t, $J = 7.3$ Hz, 1H), 4.55–4.46 (m, 4H), 4.40 (q, $J = 5.4$ Hz, 1H), 4.08 (d, $J = 13.4$ Hz, 1H), 3.91 (dd, $J = 9.4$, 5.3 Hz, 1H), 3.87 (d, $J = 13.5$ Hz, 1H), 3.84–3.73 (m, 3H), 3.48 (d, $J = 17.3$ Hz, 1H), 3.36 (q, $J = 5.2$ Hz, 1H), 3.33 (d, $J = 17.3$ Hz, 1H), 1.40 (s, 9H).

**$^{13}$C NMR** (176 MHz, CDCl$_3$): δ 171.6, 139.5, 138.3, 138.1, 129.2, 128.47, 128.46, 128.3, 127.8, 127.8, 127.74, 127.72, 127.2, 80.6, 73.4, 73.3, 72.2, 68.5, 62.2, 60.9, 56.6, 54.2, 28.2. **IR** (cm$^{-1}$): 3065, 2978, 2864, 1733, 1496, 1454, 1392, 1367, 1251, 1218, 1148, 1097, 1076, 1028, 1000, 908, 849, 729, 696. **HRMS:** $m/z$ calculated for C$_{31}$H$_{39}$ClNO$_4^+$ [M+H]$^+$: 524.2562; found: 524.2565.
all-cis tert-butyl 1-benzyl-3,4-bis((benzyloxy)methyl)azetidine-2-carboxylate (3.34): A 5-L three-neck flask, which is equipped with a magnetic stir bar, a 400-mL addition funnel and a septum with a thermometer and nitrogen inlet, is charged with 3.32 (60.30 g, 115 mmol, 1.0 equiv.) and anhydrous THF (2.3 L) under a nitrogen atmosphere. The solution was cooled to an internal temperature of –75 °C with a anhydrous ice/acetone bath. Then, a 1 M LiHMDS solution in anhydrous THF (255 mL) was added dropwise via the addition funnel at a rate that kept the internal temperature below –70 °C. The solution was stirred for 0.5 h, before removing the cooling bath. After 1.5 h, at which point the reaction mixture had reached an internal temperature of –20 °C, the flask was partially submerged in ambient temperature water, which brought the internal temperature of the reaction to ambient temperature after 0.5 h. After stirring at ambient temperature for 2 h, TLC analysis indicated full consumption of the starting material. The reaction was cooled in an ice bath and an aq., sat. NH₄Cl solution (250 mL) and water (250 mL) were added. The resulting mixture was concentrated in vacuo to a remaining volume of approximately 1.5-L and transferred to a 2-L separation funnel. The organic layer was separated and the aqueous layer extracted with EtOAc (3x 300 mL). The combined organic extracts were washed with brine (1x 500 mL), dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography (2% to 5% to 7.5% to 10% to 15% EtOAc/hexanes) afforded the pure title compound as a yellow oil (15.48 g, 28%). ¹H NMR (400 MHz, CDCl₃): δ 7.35–7.21 (m, 15H), 4.42 (qd, J = 12.0, 3.2 Hz, 4H), 3.90 (d, J = 12.7 Hz, 1H), 3.74 (dt, J = 22.0, 8.8 Hz, 2H), 3.66–3.54 (m, 3H), 3.49–3.38 (m, 2H), 2.89 (quint, J = 7.4 Hz, 1H), 1.27 (s, 9H). ¹³C NMR (126 MHz, CDCl₃): δ 170.0, 138.5, 138.3, 137.0, 130.1, 128.4, 128.4, 128.2, 127.9, 127.8, 127.64, 127.61,
127.3, 80.7, 73.5, 73.3, 71.1, 66.9, 63.0, 62.2, 61.1, 36.4, 28.0. IR (cm⁻¹): 3030, 2976, 2858, 1737, 1496, 1476, 1454, 1392, 1366, 1300, 1254, 1211, 1151, 1091, 1075, 1028, 948, 909, 843, 820, 733, 696. HRMS: m/z calculated for C₃₁H₃₈NO₄⁺ [M+H]⁺: 488.2795; found: 488.2785.

**all-cis 1-benzyl-3,4-bis((benzyloxy)methyl)azetidin-2-yl)methanol (3.35-INT):** A 2-L three-neck flask, which was equipped with a stir bar, a nitrogen inlet, a 125-mL addition funnel and a septum, was charged with LiAlH₄ (2.78 g, 73 mmol, 2.5 equiv.) and THF (300 mL) under a nitrogen atmosphere. The suspension was cooled in an ice bath, before adding a solution of 3.34 (14.27 g, 29 mmol, 1.0 equiv.) in THF (50 mL) dropwise via the addition funnel. After complete addition, the reaction mixture was stirred for 2 h at 0 °C, at which point TLC analysis indicated full consumption of the starting material. Water (10 mL) was added carefully, before diluting the reaction mixture with Et₂O (300 mL). The ice bath was removed and an aq., sat. Rochelle salt solution (600 mL) was added. The biphasic mixture was vigorously stirred at ambient temperature until the layers were clear (approx. 1 h). The reaction mixture was transferred to a 2-L separation funnel and the organic layer separated. The aqueous layer was extracted with Et₂O (2x 300 mL) and the combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography (30% to 35% to 40% to 45% EtOAc/hexanes) afforded the pure title compound 3.35 as a pale-yellow oil (10.99 g, 90%). ¹H NMR (500 MHz, CDCl₃): δ 7.39–7.18 (m, 15H), 4.48 (s, 2H), 4.44–4.35 (m, 2H), 3.99 (t, J = 10.0 Hz, 1H), 3.78 (d, J = 12.7 Hz, 1H), 3.66 (dd, J = 9.3, 5.3 Hz, 1H), 3.56 (d, J = 12.7 Hz, 1H), 3.47 (dt, J = 8.2, 6.2 Hz, 1H), 3.41–3.32 (m, 3H), 3.25 (dd, J = 9.7, 5.8 Hz, 1H), 3.17 (d, J = 9.0 Hz, 1H), 2.99 (s, 1H), 2.91–2.80 (m, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 138.5, 138.2, 137.6, 129.3, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.7, 127.4, 73.8, 73.4, 70.3, 67.3, 65.2, 62.7, 61.8, 61.1, 34.9. IR
(cm⁻¹): 3481, 3063, 3039, 2923, 2862, 1604, 1496, 1454, 1413, 1366, 1330, 1207, 1177, 1156, 1088, 1072, 1033, 1028, 945, 911, 847, 821, 735, 696. **HRMS**: m/z calculated for C_{27}H_{32}NO_{3}^{+} [M+H]^+: 418.2377; found: 418.2380.

**all-cis 2,3,4-tris(hydroxymethyl)azetidine hydrochloride (3.35):** A 100-mL round bottom flask equipped with a magnetic stir bar was charged with 3.35-INT (5.03 g, 12 mmol, 1.0 equiv.) and Pd(OH)₂ on carbon (20wt%; 1.69 g, 2.4 mmol, 0.2 equiv.). The flask was sealed with a rubber septum and evacuated and refilled with nitrogen gas three times. Then, MeOH (30 mL) and trifluoroacetic acid (9.2 mL) were added via syringe and the reaction mixture sparged with hydrogen gas from a balloon. The reaction mixture was subsequently stirred at 40 °C under an hydrogen atmosphere from a balloon for 22 h, at which point TLC analysis indicated full consumption of the starting material. The reaction mixture was passed through celite and the filter cake washed with MeOH. The filtrate was collected and concentrated in vacuo, then dried using high vac. The crude residue was dissolved in MeOH (75 mL) and the solution cooled in an ice bath. Next, a 4 M HCl solution in 1,4-dioxane (30 mL) was added slowly, the ice bath removed, and the solution stirred at ambient temperature at 10 min. The solution was subsequently concentrated in vacuo, then dried using high vac to obtain the pure title compound as an off-white solid (2.38 g, quant.). **¹H NMR** (700 MHz, CD₃OD): δ 4.54–4.48 (m, 2H), 4.02 (dd, J = 12.2, 8.0 Hz, 2H), 3.93 (d, J = 6.8 Hz, 2H), 3.89 (dd, J = 12.3, 4.4 Hz, 2H), 3.07 (quint, J = 7.8 Hz, 1H). **¹H NMR** (400 MHz, DMSO-d₆): δ 9.25 (s, 1H), 8.80 (s, 1H), 4.90 (br, 3H), 4.35–4.20 (m, 2H), 3.88–3.60 (m, 6H), 2.85 (quint, J = 8.2 Hz, 1H). **¹³C NMR** (176 MHz, CD₃OD): δ 61.6, 59.1, 57.5, 40.0. **IR** (cm⁻¹): 3682, 3338, 3271, 3171, 2982, 2938, 2876, 2845, 1566, 1471, 1362, 1348, 1311,
1268, 1153, 1118, 1094, 1033, 1012, 991, 929, 899, 877, 835, 799, 723, 685. **HRMS:** m/z calculated for C₆H₁₄NO₃⁺ [M+H]⁺: 148.0968; found: 148.0967.

*Caution!* Although we did not experience any problems handling the compounds described in this report, proper laboratory precautions should be taken. Laboratories and personnel should be properly grounded, and safety equipment such as heavy Kevlar/steel gloves, reinforced Kevlar coat, ballistic face shield, ear plugs, and blast shields are necessary for all energetic transformations, and in handling any material that is determined to be energetic.

(1-nitro-3-((nitrooxy)methyl)azetidine-2,4-diyl)bis(methylene) dinitrate (3.36): To a 100 mL round-bottom flask equipped with a stir bar, was added 20.6 mL of Ac₂O (22.2 g, 0.218 mol, 20.0 equiv.). The flask was immersed into an ice-water bath, and the Ac₂O was cooled to 0–5 °C. Next, 9.10 mL of 98% HNO₃ (13.7 g, 0.218 mol, 20.0 equiv.) was added over 1 h at such a rate that the internal temperature did not rise above 10 °C. The reaction mixture was stirred for 15 min, during which time the reaction mixture re-cooled to 0–5 °C. Azetidine 3.35 (2.00 g, 10.9 mmol, 1.00 equiv.) was added portion wise over 1 h at such a rate that the reaction mixture did not rise above 15 °C. When addition of the alcohol (3.35) was complete, the reaction mixture was stirred overnight for 15 h, during which time the ice-water bath melted, and the temperature of the reaction mixture warmed to ambient temperature. The reaction mixture was quenched when poured onto a stirring mixture of 100 g of crushed ice and 100 mL of distilled water. The quenched reaction mixture was stirred for 4 h, during which time the ice melted, and a solid appeared. The light-yellow solid was collected by Büchner filtration, and was recrystallized from 100 mL of hot isopropanol to afford 2.85 g (80%) of nitroazetidine 3.36 as white, crystalline solid. **¹H NMR** (400 MHz, acetone-d₆): δ 5.36–5.30 (m, 2H), 5.20–5.13 (m, 4H), 5.05 (dd, J = 12.0, 8.0 Hz, 2H),
3.74–3.66 (qu, J = 8.0 Hz, 1H). $^{13}$C NMR (101 MHz, acetone-d$_6$): δ 71.0, 69.5, 65.9, 31.3. IR (cm$^{-1}$): 1632, 1542, 1261, 1214. T$_{\text{melt}}$ = 74.1 °C (onset); 75.3 °C (peak). T$_{\text{dec}}$ = 193.0 °C (onset); 223.5 °C (peak)

**allyl benzyl ether (3.49):** A 500-mL round bottom flask equipped with a magnetic stir bar was charged with NaH (60% dispersion in mineral oil; 5.55 g, 139 mmol, 1.5 equiv.) and DMF (175 mL) and the suspension cooled in an ice bath. Next, a solution of benzyl alcohol (10.00 g, 92 mmol, 1.0 equiv.) in DMF (25 mL) was added dropwise. After complete addition, the resulting mixture was stirred for 0.5 h, before adding allyl bromide (10.0 mL, 116 mmol 1.25 equiv.). The ice bath was subsequently removed, and the reaction mixture stirred at ambient temperature for 18 h. Next, the reaction mixture was cooled in an ice bath and an aq. NH$_4$Cl solution (sat.) and water were added sequentially, before extracting the mixture with Et$_2$O (3x). The combined organic extracts were washed with an aq. 5% LiCl solution (2x), brine, dried over MgSO$_4$, filtered, and concentrated in vacuo. The crude product was purified by vacuum distillation (2.4 torr) and the fraction distilling at 60 ºC was collected to afford the pure title compound as a colorless oil (10.45 g, 76%). Spectroscopic data were consistent with those reported in the literature.$^{174}$

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.39–7.27 (m, 5H), 6.04–5.89 (m, 1H), 5.32 (dd, J = 17.3, 2.0 Hz, 1H), 5.21 (d, J = 10.4 Hz, 1H), 4.53 (s, 2H), 4.04 (d, J = 5.3 Hz, 2H).

**ethyl 7-((benzyloxy)methyl)-2-oxa-1-azabicyclo[3.2.0]heptane-5-carboxylate (3.41 and 3.42):** A 130-mL round bottom flask equipped with a magnetic stir bar was charged with ethyl 4,5-dihydroisoxazole-3-carboxylate (3.39) (6.00 g, 41.9 mmol, 1.0 equiv.), allyl benzyl ether (6.96 g,
46.9 mmol, 1.1 equiv.), fac-[Ir(dFppy)₃] (8.0 mg, 11 µmol, 0.00025 equiv.) and MeCN (85 mL). The flask was sealed with a rubber septum and the solution degassed by sparging with nitrogen gas for 20 min. The reaction mixture was subsequently stirred under blue LED irradiation (427 nm) at ambient temperature (fan cooling) for 23 h. Next, the reaction mixture was concentrated in vacuo, and the crude reaction mixture purified by flash column chromatography (5–40% EtOAc/CH₂Cl₂) to afford 3.41 as a yellow oil (5.54 g, 45%) and 3.42 as a yellow oil (5.09 g, 42%).

**trans Diastereomer (3.41):**

**¹H NMR** (700 MHz, CDCl₃): δ 7.37–7.27 (m, 5H), 4.58–4.52 (m, 2H), 4.32–4.21 (m, 4H), 4.21–4.14 (m, 1H), 3.81 (dd, J = 10.9, 6.3 Hz, 1H), 3.63 (dd, J = 10.8, 5.2 Hz, 1H), 2.92 (dd, J = 12.3, 8.7 Hz, 1H), 2.56 (dt, J = 12.3, 7.8 Hz, 1H), 2.34 (ddd, J = 12.3, 6.3, 4.1 Hz, 1H), 2.28 (dd, J = 12.3, 8.6 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H).

**¹³C NMR** (176 MHz, CDCl₃): δ 172.6, 138.2, 128.5, 127.8 (2C), 73.4, 73.3, 71.0, 67.9, 61.9, 61.1, 39.9, 30.6, 14.3. **IR** (cm⁻¹): 2981, 2939, 1728, 1497, 1452, 1368, 1318, 1272, 1179, 1140, 1027, 911, 863, 737, 698. **HRMS**: m/z calculated for C₁₆H₂₁NNaO₄⁺ [M+Na]⁺: 314.1363; found: 314.1354.

**cis Diastereomer (3.42):**

**¹H NMR** (700 MHz, CDCl₃): δ 7.33 (d, J = 4.3 Hz, 4H), 7.29–7.26 (m, 1H), 4.61–4.55 (m, 2H), 4.34–4.28 (m, 2H), 4.28–4.22 (m, 1H), 4.22–4.17 (m, 1H), 3.68 (dd, J = 9.6, 5.6 Hz, 1H), 3.67–3.62 (m, 1H), 3.59 (dd, J = 9.6, 5.5 Hz, 1H), 2.59 (dt, J = 12.6, 9.0 Hz, 1H), 2.49 (dd, J = 12.1, 7.5 Hz, 1H), 2.38 (dd, J = 12.7, 6.3, 2.9 Hz, 1H), 2.28 (dd, J = 12.2, 9.3 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H). **¹³C NMR** (176 MHz, CDCl₃): δ 172.9, 138.3, 128.5, 127.9, 127.7, 73.6, 72.3, 72.2, 67.8, 61.7, 60.6, 39.0, 27.2, 14.2. **IR** (cm⁻¹): 2958, 2863, 1728, 1497, 1453, 1368, 1316, 1270, 1178, 1144, 1097, 1028, 998, 902, 860, 737, 698. **HRMS**: m/z calculated for C₁₆H₂₁NNaO₄⁺ [M+Na]⁺: 314.1363; found: 314.1365.
trans (7-((benzylxy)methyl)-2-oxa-1-azabicyclo[3.2.0]heptan-5-yl)methanol (3.43): A 1-L round bottom flask equipped with a magnetic stir bar was charged with Red-Al (≥60wt.% in toluene) (16 mL, 49 mmol, 2.1 equiv.) and toluene (75 mL), and the flask submerged in an ice/water bath. Next, a solution of 3.41 (6.93 g, 24 mmol, 1.0 equiv.) in toluene (12 mL) was added dropwise over 30 min using a syringe pump. After complete addition the syringe and cannula were rinsed with toluene (5 mL) and the rinse added to the reaction mixture. After stirring the reaction for 1 h at 0 ºC, water (5 mL) was added carefully, before diluting the mixture with a sat., aq. Rochelle salt solution (150 mL) and Et₂O (150 mL). The ice bath was removed, and the biphasic mixture stirred vigorously for 2 h at ambient temperature. Next, the mixture was diluted with water (100 mL), before separating the organic layer and extracting the aqueous layer with Et₂O (3x 250 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo, then dried using high-vac to obtain the title compound 3.43 as a yellow oil (5.34 g, 90%).

**¹H NMR** (700 MHz, CDCl₃): δ 7.37–7.33 (m, 4H), 7.31–7.27 (m, 1H), 4.61–4.52 (m, 2H), 4.22 (td, J = 8.6, 6.3 Hz, 1H), 4.16–4.09 (m, 2H), 3.85 (dd, J = 10.7, 6.9 Hz, 1H), 3.74 (d, J = 11.8 Hz, 1H), 3.62 (d, J = 11.8 Hz, 1H), 3.58 (dd, J = 10.7, 5.2 Hz, 1H), 2.57 (s, 1H), 2.47 (dd, J = 12.0, 8.6 Hz, 1H), 2.20–2.13 (m, 1H), 2.11–2.03 (m, 2H). **¹³C NMR** (176 MHz, CDCl₃): δ 138.3, 128.5, 127.8, 127.7, 74.2, 73.2, 70.8, 68.2, 65.7, 60.2, 37.9, 29.3. **IR (cm⁻¹):** 3199, 2926, 2859, 1497, 1453, 1367, 1202, 1096, 1061, 1028, 998, 941, 882, 736, 697. **HRMS: m/z** calculated for C₁₄H₂₀NO₃⁺ [M+H]^+: 250.1438; found: 250.1433.

![cis](image)

cis (7-((benzylxy)methyl)-2-oxa-1-azabicyclo[3.2.0]heptan-5-yl)methanol (3.44): A 1-L round bottom flask equipped with a magnetic stir bar was charged with Red-Al (≥60wt.% in toluene) (17 mL, 52 mmol, 2.1 equiv.) and toluene (85 mL), and the flask submerged in an
ice/water bath. Next, a solution of 3.42 (7.41 g, 25 mmol, 1.0 equiv.) in toluene (12 mL) was added dropwise over 30 min using a syringe pump. After complete addition the syringe and cannula were rinsed with toluene (5 mL) and the rinse added to the reaction mixture. After stirring the reaction for 1 h at 0°C, water (5 mL) was added carefully, before diluting the mixture with a sat., aq. Rochelle salt solution (150 mL) and Et₂O (150 mL). The ice bath was removed, and the biphasic mixture stirred vigorously for 2 h at ambient temperature. Next, the mixture was diluted with water (100 mL), before separating the organic layer and extracting the aqueous layer with Et₂O (3x 250 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo, then dried using high-vac to obtain the title compound 3.42 as a pale-yellow oil (6.05 g, 95%).

**¹H NMR** (700 MHz, CDCl₃): δ 7.38–7.33 (m, 4H), 7.31–7.27 (m, 1H), 4.63–4.57 (m, 2H), 4.31 (td, J = 9.7, 6.5 Hz, 1H), 4.20 (t, J = 8.6 Hz, 1H), 3.65–3.53 (m, 4H), 3.50 (dd, J = 11.9, 3.7 Hz, 1H), 2.59 (s, 1H), 2.39 (dd, J = 11.9, 7.0 Hz, 1H), 2.15 (ddd, J = 12.6, 6.5, 2.1 Hz, 1H), 2.07 (dd, J = 11.8, 9.4 Hz, 1H), 2.02 (q, J = 10.4 Hz, 1H).

**¹³C NMR** (176 MHz, CDCl₃): δ 138.1, 128.5, 127.9, 127.8, 73.6, 73.1, 72.0, 67.5, 66.6, 59.9, 37.4, 24.2. **IR** (cm⁻¹): 3400, 3030, 2945, 2859, 1497, 1453, 1366, 1311, 1206, 1161, 1064, 991, 851, 814, 737, 698. **HRMS**: m/z calculated for C₁₄H₂₀NO₃⁺ [M+H]⁺: 250.1438; found: 250.1436.

**trans 2-(2-hydroxyethyl)-2,4-bis(hydroxymethyl)azetidine hydrochloride (3.45):** A 250-mL round bottom flask equipped with a magnetic stir bar was charged with 3.43 (5.14 g, 21 mmol, 1.0 equiv.), Pd(OH)₂ on carbon (20wt%; 2.90 g, 4.1 mmol, 0.2 equiv.), MeOH (50 mL) and trifluoroacetic acid (16 mL). The flask was sealed with a rubber septum and the flask purged with
nitrogen gas. Then, the reaction mixture was sparged with hydrogen gas from a balloon for 20 min, before stirring the reaction at ambient temperature under a hydrogen atmosphere. After 24 h the reaction mixture was passed through a celite plug, and the filter was washed with MeOH. The filtrate was collected and concentrated \textit{in vacuo}, then dried using high vac to remove any excess trifluoroacetic acid. Next, the residue was dissolved in MeOH (100 mL), a 4 M HCl solution in dioxane (50 mL) was added at 0 °C, and the reaction stirred at ambient temperature for 15 min. The solution was subsequently concentrated \textit{in vacuo}, then dried using high vac to afford the title compound \textbf{3.45} as a yellow wax (4.14 g, quant.). \textbf{1H NMR} (700 MHz, CD$_3$OD): $\delta$ 4.40–4.34 (m, 1H), 3.85–3.80 (m, 3H), 3.79–3.72 (m, 3H), 2.50 (dd, $J = 12.2, 8.4$ Hz, 1H), 2.41 (dd, $J = 12.2, 9.2$ Hz, 1H), 2.11 (ddd, $J = 14.7, 7.5, 4.9$ Hz, 1H), 2.04 (ddd, $J = 14.7, 6.5, 4.7$ Hz, 1H). \textbf{1H NMR} (700 MHz, $d_6$-DMSO): $\delta$ 8.98 (s, 1H), 8.60 (s, 1H), 5.57 (t, $J = 5.7$ Hz, 1H), 5.40 (t, $J = 5.8$ Hz, 1H), 4.80 (s, 1H), 4.21–4.13 (m, 1H), 3.73–3.56 (m, 4H), 3.55–3.46 (m, 2H), 2.30–2.20 (m, 2H), 2.05–1.92 (m, 2H). \textbf{13C NMR} (176 MHz, CD$_3$OD): $\delta$ 69.6, 65.0, 61.5, 57.9, 57.4, 36.9, 28.2. \textbf{IR} (cm$^{-1}$): 3306, 2939, 1579, 1448, 1380, 1315, 1049, 1019, 896. \textbf{HRMS}: $m/z$ calculated for C$_7$H$_{16}$NO$_3$ $\text{[M+H]}^{+}$: 162.1125; found: 162.1131.

\textit{cis} 2-(2-hydroxyethyl)-2,4-bis(hydroxymethyl)azetidine hydrochloride (\textbf{3.46}): A 250-mL round bottom flask equipped with a magnetic stir bar was charged with \textbf{3.44} (5.83 g, 23 mmol, 1.0 equiv.), Pd(OH)$_2$ on carbon (20 wt%; 3.28 g, 4.7 mmol, 0.2 equiv.), MeOH (60 mL) and trifluoroacetic acid (18 mL). The flask was sealed with a rubber septum and the flask purged with nitrogen gas. Then, the reaction mixture was sparged with hydrogen gas from a balloon for 20 min, before stirring the reaction at ambient temperature under a hydrogen atmosphere. After 24 h the
reaction mixture was passed through a celite plug, and the filter was washed with MeOH. The filtrate was collected and concentrated in vacuo, then dried using high vac to remove any excess trifluoroacetic acid. Next, the residue was dissolved in MeOH (100 mL), a 4 M HCl solution in 1,4-dioxane (50 mL) was added at 0 °C, and the reaction stirred at ambient temperature for 15 min. The solution was subsequently concentrated in vacuo, then dried using high vac to afford the title compound 3.44 as an off-white solid (4.57 g, 99%). ¹H NMR (700 MHz, CD₃OD): δ 4.45–4.39 (m, 1H), 3.90–3.80 (m, 3H), 3.80–3.75 (m, 2H), 3.72 (d, J = 12.1 Hz, 1H), 2.47 (dd, J = 12.3, 8.3 Hz, 1H), 2.36 (dd, J = 12.3, 9.3 Hz, 1H), 2.22–2.11 (m, 2H). ¹H NMR (700 MHz, d₆-DMSO): δ 8.77 (s, 1H), 8.53 (s, 1H), 4.99 (br, 3H), 4.28–4.19 (m, 1H), 3.68 (dd, J = 12.3, 6.8 Hz, 1H), 3.65–3.52 (m, 5H), 2.22 (d, J = 8.8 Hz, 2H), 2.04 (t, J = 6.3 Hz, 2H). ¹³C NMR (176 MHz, CD₃OD): δ 69.7, 64.6, 61.5, 58.2, 56.5, 36.6, 27.8. IR (cm⁻¹): 3297, 2932, 1572, 1307, 1048, 895, 845. HRMS: m/z calculated for C₇H₁₆NO₅⁺ [M+H]⁺: 162.1125; found: 162.1128.

**Caution!** Although we did not experience any problems handling the compounds described in this report, proper laboratory precautions should be taken. Laboratories and personnel should be properly grounded, and safety equipment such as heavy Kevlar/steel gloves, reinforced Kevlar coat, ballistic face shield, ear plugs, and blast shields are necessary for all energetic transformations, and in handling any material that is determined to be energetic.

**trans** (1-nitro-4-(2-(nitrooxy)ethyl)-4-((nitrooxy)methyl)azetidin-2-yl)methyl nitrate (3.47):
To a 100 mL round-bottom flask equipped with a stir bar, was added 19.1 mL of Ac₂O (20.7 g, 0.203 mol, 20.0 equiv.). The flask was immersed into an ice-water bath, and the Ac₂O was cooled to 0-5 °C. Next, 8.45 mL of 98% HNO₃ (12.8 g, 0.203 mol, 20.0 equiv.) was added over 1 h at such a rate that the internal temperature did not rise above 10 °C. The reaction mixture was stirred for 15 min, during which time the reaction mixture re-cooled to 0–5 °C. Azetidine 3.45 (2.00 g,
10.1 mmol, 1.00 equiv.) was added portion wise over 1 h at such a rate that the reaction mixture did not rise above 15 °C. When addition of the alcohol (3.45) was complete, the reaction mixture was stirred overnight for 15 h, during which time the ice-water bath melted, and the temperature of the reaction mixture warmed to ambient temperature. The reaction mixture was quenched when poured onto a stirring mixture of 100 g of crushed ice and 100 mL of distilled water. The quenched reaction mixture was stirred for 4 h, during which time the ice melted. 100 mL of CH₂Cl₂ was added to the quenched reaction mixture, and was stirred for 15 min. The quenched reaction mixture was transferred to a separatory funnel and was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic extracts were washed with a saturated NaHCO₃ solution (2 x 100 mL), dried over MgSO₄, and filtered into a 600 mL beaker. Evaporation of the solvent overnight in a well-ventilated fume hood afforded a green oil, which was purified by flash chromatography on silica gel (elution with 10-15% EtOAc/hexanes) to afford 2.62 g (72 %) of nitroazetidine 3.47 as a colorless oil, which failed to solidify after 4 months in the freezer (-12 °C). ¹H NMR (400 MHz, acetone-d₆): δ 5.24–4.96 (m, 4H), 4.92–4.74 (m, 3H), 2.71 (ABq, J_AB = 8.0 Hz, 1H), 2.56–2.43 (m, 3H). ¹³C NMR (101 MHz, acetone-d₆): δ 72.8, 72.2, 71.7, 69.3, 62.9, 32.9, 25.3. IR (cm⁻¹): 1625, 1532, 1272.

T_freeze = <-40 °C. T_dec = 184.2 °C (onset); 210.7 °C (peak)

**Caution!** Although we did not experience any problems handling the compounds described in this report, proper laboratory precautions should be taken. Laboratories and personnel should be properly grounded, and safety equipment such as heavy Kevlar/steel gloves, reinforced Kevlar coat, ballistic face shield, ear plugs, and blast shields are necessary for all energetic transformations, and in handling any material that is determined to be energetic.

**cis (1-nitro-4-(2-(nitrooxy)ethyl)-4-((nitrooxy)methyl)azetidin-2-yl)methyl nitrate (3.48):** To a 100 mL round-bottom flask equipped with a stir bar, was added 19.1 mL of Ac₂O (20.7 g, 0.203
The flask was immersed into an ice-water bath, and the Ac₂O was cooled to 0-5 °C. Then, 8.45 mL of 98% HNO₃ (12.8 g, 0.203 mol, 20.0 equiv.) was added over 1 h at such a rate that the internal temperature did not rise above 10 °C. The reaction mixture was stirred for 15 min, during which time the reaction mixture re-cooled to 0–5 °C. Azetidine 3.46 (2.00 g, 10.1 mmol, 1.00 equiv.) was added portion wise over 1 h at such a rate that the reaction mixture did not rise above 15 °C. When addition of the alcohol (3.46) was complete, the reaction mixture was stirred overnight for 15 h, during which time the ice-water bath melted, and the temperature of the reaction mixture warmed to ambient temperature. The reaction mixture was quenched when poured onto a stirring mixture of 100 g of crushed ice and 100 mL of distilled water. The quenched reaction mixture was stirred for 4 h, during which time the ice melted. Then 100 mL of CH₂Cl₂ was added to the quenched reaction mixture, and was stirred for 15 min. The quenched reaction mixture was transferred to a separatory funnel and was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic extracts were washed with a saturated NaHCO₃ solution (2 x 100 mL), dried over MgSO₄, and filtered into a 600 mL beaker. Evaporation of the solvent overnight in a well-ventilated fume hood afforded a green oil, which was purified by flash chromatography on silica gel (elution with 10–15% EtOAc/hexanes) to afford 2.69 g (78 %) of nitroazetidine 3.48 as a colorless oil, which failed to solidify after 4 months in the freezer (−12 °C). ¹H NMR (400 MHz, acetone-d₆): δ 5.11–4.87 (m, 4H), 4.87–4.78 (m, 3H), 2.73–2.58 (m, 3H), 2.45 (AB, JAB = 8.0 Hz, 1H). ¹³C NMR (176 MHz, CDCl₃): δ 74.1, 73.9, 72.3, 69.2, 62.0, 28.2, 23.9. IR (cm⁻¹): 1624, 1534, 1273. Tfreeze = −40 °C. Tdec = 175.7 °C (onset); 204.9 °C (peak)

Procedure adopted from a published procedure¹⁷⁵: A 250-mL round bottom flask equipped with a magnetic stir bar
was charged with NaH (60% dispersion in mineral oil; 3.52 g, 88 mmol, 2.2 equiv.) and 3-chloro-2-(chloromethyl)prop-1-ene (5.00 g, 40.0 mmol, 1 equiv.) in anhydrous THF (60 mL). The suspension cooled in an ice bath. Next, a solution of benzyl alcohol (9.52 g, 9.15 mL, 88 mmol, 2.2 equiv.) in THF (18 mL) was added dropwise. After complete addition, the ice bath was removed and the resulting mixture was brought up to ambient temperature, equipped with a reflux condenser, and heated to 65 °C (via heating mantle). The reaction mixture stirred at 65 °C temperature for 15 h. Next, the reaction mixture was cooled to ambient temperature and distilled H2O was added before extracting the mixture with Et2O (2x). The combined organic extracts were washed with brine, dried over MgSO4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (0–15% EtOAc/hexanes) to afford 3.49 as a clear pale-yellow oil (7.37 g, 68%). Spectroscopic data were consistent with those reported in the literature.175 1H NMR (400 MHz, CDCl3): δ 7.41–7.27 (m, 10H), 5.31–5.25 (m, 2H), 4.53 (s, 4H), 4.09 (s, 4H).

ethyl 7,7-bis((benzyl oxy)methyl)-2-oxa-1-azabicyclo[3.2.0]heptane-5-carboxylate (3.50): A 100-mL round bottom flask equipped with a magnetic stir bar was charged with ethyl 4,5-dihydroisoxazole-3-carboxylate (2.00 g, 14.0 mmol, 1.0 equiv.), fac-[Ir(dFppy)3] (2.1 mg, 2.8 µmol, 0.0002 equiv.) and MeCN (46 mL). The flask was sealed with a rubber septum and the solution degassed by sparging with nitrogen gas for 40 min. Then alkene 3.49 (4.50 g, 16.8 mmol, 1.2 equiv.) was added through the septum. The flask was subsequently sealed with electrical tape. The reaction mixture was subsequently stirred under blue LED irradiation (427 nm) at ambient
temperature (fan cooling) for 22 h. Next, the reaction mixture was concentrated in vacuo, and the crude reaction mixture purified by flash column chromatography (5–50% EtOAc/hexanes) to afford 3.50 as a yellow oil (4.98 g, 87%). \textit{^1H NMR} (600 MHz, CDCl$_3$): $\delta$ 7.35–7.25 (m, 10H), 4.60–4.50 (m, 4H), 4.29 (dt, $J$ = 8.1, 6.8 Hz, 1H), 4.18 (dq, $J$ = 10.7, 7.1 Hz, 1H), 4.15–4.07 (m, 2H), 3.68 (d, $J$ = 1.7 Hz, 2H), 3.64–3.58 (m, 2H), 2.71 (d, $J$ = 12.3 Hz, 1H), 2.51 (dt, $J$ = 12.2, 7.0 Hz, 1H), 2.45–2.41 (m, 1H), 2.40 (d, $J$ = 12.4 Hz, 1H), 1.24 (t, $J$ = 7.1 Hz, 3H). \textit{^13C NMR} (151 MHz, CDCl$_3$): $\delta$ 173.2, 138.4, 138.3, 128.4, 128.3, 127.8, 127.71, 127.68, 127.6, 73.7, 73.6, 73.5, 71.1, 70.8, 68.0, 66.8, 61.6, 40.4, 31.7, 14.2. \textit{IR (cm$^{-1}$)}: 3031, 2938, 1730, 1496, 1453, 1366, 1319, 1275, 1203, 1158, 1093, 1027, 909, 727, 696. \textit{HRMS} : $m/z$ calculated for C$_{24}$H$_{29}$NNaO$_5$ $^[\text{M+Na}]^{+}$: 434.1938; found: 434.1939.

(7,7-bis((benzyloxy)methyl)-2-oxa-1-azabicyclo[3.2.0]heptan-5-yl)methanol (3.51): A 100 mL round bottom flask equipped with a magnetic stir bar was charged with Red-Al ($\geq$60wt.% in toluene) (3.32 mL, 10.2 mmol, 2.1 equiv.) and toluene (16 mL), and the flask submerged in an ice/water bath. Next, a solution of 3.50 (2.00 g, 4.9 mmol, 1.0 equiv.) in toluene (2 mL) was added dropwise using a syringe pump (0.3 mL/min). After complete addition, the syringe and cannula were rinsed with toluene (5 mL) and the rinse added to the reaction mixture. After stirring the reaction for 0.5 h at 0°C, the reaction solution was diluted with Et$_2$O. Then distilled H$_2$O (0.41 mL) was added carefully, followed by aq. 15% NaOH (0.41 mL) and then distilled H$_2$O (1.02 mL). The ice bath was removed, and the biphasic mixture stirred vigorously for 20 min at ambient temperature. Next, MgSO$_4$ was added to the vigorously stirring mixture and left to stir at ambient temperature for 20 min. The crude reaction mixture was filtered over a bed of celite, eluting with
Et₂O. Next, the reaction mixture was concentrated \textit{in vacuo}, and the crude reaction mixture purified by flash column chromatography (0–10\% MeOH/CH₂Cl₂) to afford \textbf{3.51} as a pale-yellow oil (1.68 g, 94\%). \textbf{¹H NMR} (700 MHz, CDCl₃): δ 7.36–7.27 (m, 10H), 4.58 (s, 2H), 4.56–4.51 (m, 2H), 4.23 (td, J = J = 8.0, 5.0 Hz, 1H), 3.87 (q, J = 7.6 Hz, 1H), 3.71-3.66 (m, 2H), 3.60 (d, J = 1.8 Hz, 2H), 3.57 (dd, J = 11.9, 7.7 Hz, 1H), 3.48 (dd, J = 11.7, 4.4 Hz, 1H), 3.07 (s, 1H), 2.35 (d, J = 12.0 Hz, 1H), 2.30 (dt, J = 12.2, 7.7 Hz, 1H), 2.17–2.11 (m, 2H). \textbf{¹³C NMR} (176 MHz, CDCl₃):

δ 138.3, 138.2, 128.45, 128.45, 127.9, 127.8, 127.73, 127.72, 73.8, 73.7, 73.6, 71.04, 71.03, 68.9, 66.9, 65.8, 39.3, 28.9. \textbf{IR} (cm⁻¹): 3064, 3031, 2861, 1496, 1453, 1364, 1275, 1091, 1075, 908, 728, 696. \textbf{HRMS}: m/z calculated for C₂₂H₂₈NO₄⁺ [M+H]⁺: 370.2013; found: 370.2010.

(4-(2-hydroxyethyl)azetidine-2,2,4-triyl)trimethanol hydrochloride (\textbf{3.52}): A 250-mL round bottom flask equipped with a magnetic stir bar was charged with \textbf{3.51} (1.64 g, 4.5 mmol, 1.0 equiv.), Pd(OH)₂ on carbon (20wt%; 625 mg, 0.9 mmol, 0.2 equiv.), MeOH (11 mL) and trifluoroacetic acid (3.4 mL). The flask was sealed with a rubber septum and the flask purged with nitrogen gas. Then, the reaction mixture was sparged with hydrogen gas from a balloon for 20 min, before stirring the reaction at ambient temperature under a hydrogen atmosphere. After 24 h the reaction mixture was passed through a celite plug, and the filter was washed with MeOH. The filtrate was collected and concentrated \textit{in vacuo}, then dried using high vac to remove any excess trifluoroacetic acid. Next, the residue was dissolved in MeOH (22 mL), a 4 M HCl solution in 1,4-dioxane (11 mL) was added at 0 °C, and the reaction stirred at ambient temperature for 15 min. The solution was subsequently concentrated \textit{in vacuo}, then dried using high vac to afford the title compound \textbf{3.52} (1.01 g, quant.) as a yellow sticky wax. \textbf{¹H NMR} (700 MHz, CD₃OD): δ 3.92
(dd, J = 15.3, 12.0, 5.5 Hz, 2H), 3.86–3.79 (m, 2H), 3.79–3.70 (m, 4H), 2.36 (s, 2H), 2.35–2.30 (m, 1H), 2.30–2.25 (m, 1H). \(^1\)\text{H NMR} (600 MHz, \(d_6\)-DMSO): \(\delta\) 8.53 (s, 2H), 5.53 (s, 1H), 5.34 (d, \(J = 37.6\) Hz, 2H), 4.75 (br, 1H), 3.73 (dd, \(J = 25.0, 12.1\) Hz, 2H), 3.67–3.56 (m, 4H), 3.49 (td, \(J = 6.5, 2.5\) Hz, 2H), 2.19 (d, \(J = 12.3\) Hz, 1H), 2.16–2.07 (m, 3H). \(^1\)\text{C NMR} (176 MHz, CD\textsubscript{3}OD): \(\delta\) 67.7, 66.8, 64.1, 63.2, 62.6, 58.0, 36.8, 31.1. \(\text{IR (cm}^{-1}\)): 3306, 2936, 1571, 1445, 1403, 1321, 1042, 873, 839. \(\text{HRMS: m/z}\) calculated for C\textsubscript{8}H\textsubscript{18}NO\textsubscript{4}\+[M+H]\+: 192.1230; found: 192.1229.

**(Z)-4-(benzyloxy)but-2-en-1-ol (3.54-A):** Procedure adopted from a published procedure\(^{176}\): A flame dried 250-mL round bottom flask equipped with a magnetic stir bar was charged with (Z)-but-2-ene-1,4-diol (13.22 g, 150 mmol, 12.3 mL, 1.5 equiv.) and anhydrous THF (120 mL) and the flask submerged in an ice/water bath. Next, the reaction was charged with NaH (60% dispersion in mineral oil; 4.20 g, 105 mmol, 1.05 equiv.). The flask was sealed with a rubber septum and the flask purged with nitrogen gas and left to stir at 0 °C for 15 minutes. The ice bath was subsequently removed, and the reaction mixture stirred at ambient temperature for 1 h. Benzyl bromide (17.10 g, 100 mmol, 11.9 mL, 1 equiv.) was added to the suspension. The reaction was equipped with a reflux condenser and the reaction was heated to reflux for 2 h. Next, the reaction mixture was cooled to 0 °C and acidified with 1 N HCl carefully and diluted with CH\textsubscript{2}Cl\textsubscript{2} and water. Separate the resulting two phases, before extracting the mixture with CH\textsubscript{2}Cl\textsubscript{2} (3x). The combined organic extracts were washed with brine, dried over MgSO\textsubscript{4}, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10–80% EtOAc/hexanes) to afford mono-benzylated alcohol 3.54-A as a pale-yellow clear oil (14.166 g, 80%). Spectroscopic data were consistent with those reported in the literature.\(^{176}\) \(^1\)\text{H NMR
(600 MHz, CDCl₃): δ 7.38–7.27 (m, 5H), 5.83–5.78 (m, 1H), 5.76-5.70 (m, 1H), 4.52 (s, 2H), 4.15 (t, J = 5.8 Hz, 2H), 4.09 (d, J = 6.3 Hz, 2H).

**4,5-dihydroisoxazole-3-carboxylic acid (3.54-B):** A 500-mL round bottom flask equipped with a magnetic stir bar was charged with 3.39 (10.09 g, 1.0 equiv., 70.5 mmol) and was brought up in MeOH (150 mL) and H₂O (50.0 mL) and the flask submerged in an ice/water bath. Then, NaOH (3.1 g, 1.10 equiv., 77.5 mmol) was added at 0 °C. The ice bath was subsequently removed, and the reaction mixture stirred at ambient temperature for 21 h. The crude reaction mixture was acidified with 2 N HCl to pH 1 and concentrated to dryness in vacuo. The white solid was brought up in acetone (100 mL) and filtered over a short plug of celite and rinsed with an additional 100 mL of acetone. The filtered solution was then concentrated in vacuo to afford carboxylic acid 3.54-B as an off-white solid (8.017 g, 99%). The product was used without any further purification.

**¹H NMR (700 MHz, CDCl₃):** δ 9.80 (br, 1H), 4.62 (t, J = 10.8 Hz, 2H), 3.23 (t, J = 10.8 Hz, 2H).

**¹³C NMR (176 MHz, CDCl₃) δ:** 164.1, 151.6, 72.5, 33.2. **IR (cm⁻¹):** 2864, 2576, 1688, 1583, 1428, 1268, 1141, 917, 845. **HRMS:** m/z calculated for C₄H₄NO₃ [M-H]: 114.0197; found: 114.0194.

**(Z)-4-(benzyloxy)but-2-en-1-yl 4,5-dihydroisoxazole-3-carboxylate (3.54):** A 100-mL round bottom flask equipped with a magnetic stir bar was charged with 3.54-B (5.424 g, 1.2 equiv., 47.1 mmol) and HATU (17.92 g, 1.2 equiv., 47.1 mmol) and sealed with a septa and evacuated and refilled with nitrogen. The solids were brought up in DMF (29.00 mL) and TEA (10.9 mL, 2 equiv., 78.6 mmol) was added and left to stir for 15 min. Next, 3.54-A (7.00 g, 1 equiv., 39.3 mmol) was added via syringe and the reaction mixture stirred at ambient temperature under
nitrogen for 21 h. The reaction was quenched with aq., sat. NH₄Cl (15 mL) and diluted with H₂O (50 mL) and ether (50 mL). Aqueous and organic layers were separated before being extracted with Et₂O (3 x 100 mL). Combined organic extracts were washed with 5% aq. LiCl (2 x 100 mL), then brine, and subsequently dried over MgSO₄ and filtered. Next, the reaction mixture was concentrated in vacuo, and the crude reaction mixture purified by flash column chromatography (0–5% EtOAc/CH₂Cl₂) to provide 3.54 as a yellow oil (10.504 g, 97%). ¹H NMR (700 MHz, CDCl₃): δ 7.34 (dt, J = 4.2, 2.3 Hz, 4H), 7.29 (q, J = 5.2, 4.6 Hz, 1H), 5.90–5.84 (m, 1H), 5.79–5.74 (m, 1H), 4.85 (d, J = 6.7 Hz, 2H), 4.54–4.48 (m, 4H), 4.16 (d, J = 6.5 Hz, 2H), 3.17 (t, J = 10.7 Hz, 2H). ¹³C NMR (176 MHz, CDCl₃): δ 160.4, 151.6, 138.0, 131.9, 128.5, 127.8, 127.8, 125.6, 72.54, 71.5, 65.8, 61.7, 33.7. IR (cm⁻¹): 3031, 2859, 1718, 1587, 1384, 1255, 1115, 914, 736, 698. HRMS: m/z calculated for C₁₅H₁₇NNaO₄⁺ [M+Na]⁺: 298.1050; found: 298.1046.

4-((benzylxy)methyl)tetrahydro-1H,3H-furo[3',4':2,3]azeto[1,2-b]isoxazol-1-one (3.55 and 3.56): A 1000-mL round bottom flask equipped with a magnetic stir bar was charged with fac-[Ir(dFppy)₃] (4.39 mg, 2.8 µmol, 0.00025 equiv.) and MeCN (425 mL). The flask was sealed with a rubber septum and the solution degassed by sparging with nitrogen gas for 30 min. Then 3.54 (6.34 g, 23.0 mmol, 1 equiv.) in MeCN (45 mL) was added via syringe pump* over the course of 9 h through the septum under nitrogen with blue irradiation (427 nm) at ambient temperature (fan cooling). After addition, the remaining solution in the needle was dispensed into the reaction mixture and the syringe was removed along with the nitrogen inlet and the septa was sealed with electrical tape. The reaction mixture was subsequently stirred under blue LED irradiation (427 nm) at ambient temperature (fan cooling) for 15 h (24 h total). Next, the reaction mixture was
concentrated in vacuo, and the crude reaction mixture purified by flash column chromatography (0–20% MeCN/CH$_2$Cl$_2$) to afford 3.55 as a white solid (2.40 g, 38%) and 3.56 as a yellow oil (solidifies upon storage at 0 °C) (1.99 g, 32%). *Note: Similar purity products can be obtained by running the reaction at 0.01 M in MeCN without the use of a syringe pump. With the scale of the reaction, a more concentrated reaction (0.05M) was desired, in which case slow addition of the substrate was required. **trans** Diastereomer (3.55): $^1$H NMR (700 MHz, CDCl$_3$): δ 7.37–7.33 (m, 2H), 7.32–7.28 (m, 3H), 4.54 (s, 2H), 4.42 (ddd, J = 9.1, 7.4, 1.4 Hz, 1H), 4.39–4.36 (m, 1H), 4.31–4.23 (m, 2H), 4.08 (qd, J = 5.9, 1.5 Hz, 1H), 3.83 (ddd, J = 10.8, 5.8, 1.5 Hz, 1H), 3.72 (ddd, J = 10.8, 5.9, 1.5 Hz, 1H), 3.18 (ddd, J = 7.7, 4.7, 1.8 Hz, 1H), 2.52 (ddddd, J = 12.7, 9.1, 7.5, 1.5 Hz, 1H), 2.40 (ddddd, J = 12.7, 5.7, 3.5, 1.3 Hz, 1H). $^{13}$C NMR (176 MHz, CDCl$_3$): δ 175.3, 137.7, 128.5, 128.0, 127.8, 73.5, 72.7, 72.0, 70.8, 68.9, 66.7, 38.6, 35.2. IR (cm$^{-1}$): 2921, 2877, 1772, 1453, 1378, 1241, 1178, 1133, 1101, 1076, 975, 864. HRMS: m/z calculated for C$_{15}$H$_{18}$NO$_4$+ [M+H]$^+$: 276.1230; found: 276.1228.

cis Diastereomer (3.56): $^1$H NMR (700 MHz, CDCl$_3$): δ 7.37–7.33 (m, 2H), 7.30 (td, J = 5.8, 5.3, 2.4 Hz, 3H), 4.61–4.44 (m, 3H), 4.41–4.29 (m, 3H), 3.95 (td, J = 8.6, 6.3 Hz, 1H), 3.74–3.68 (m, 2H), 3.17 (td, J = 9.0, 3.3 Hz, 1H), 2.53 (ddddd, J = 13.7, 11.0, 7.8, 2.4 Hz, 1H), 2.37 (ddddd, J = 13.0, 5.4, 1.1 Hz, 1H). $^{13}$C NMR (176 MHz, CDCl$_3$): δ 175.2, 137.5, 128.6, 128.1, 128.0, 73.7, 72.3, 68.7, 67.9, 66.0, 63.2, 34.3, 33.3. IR (cm$^{-1}$): 2865, 2252, 1771, 1494, 1441, 1379, 1245, 1180, 1094, 990, 908, 729, 698. HRMS: m/z calculated for C$_{15}$H$_{17}$NNaO$_4$+ [M+Na]$^+$: 298.1050; found: 298.1048.

(7-((benzyloxy)methyl)-2-oxa-1-azabicyclo[3.2.0]heptane-5,6-diyl)dimethanol (3.57): A 100 mL round bottom flask equipped with a magnetic stir bar was charged with 3.55 (2.70 g, 9.8 mmol,
1 equiv.) and toluene (33 mL). After dissolving all of 3.55, the flask was submerged in an ice/water bath (the crude solution will occasionally turn to a slurry at lower temperatures, due to the limited solubility). Next, Red-Al (≥60 wt.% in toluene) (3.32 mL, 10.2 mmol, 2.1 equiv.) was added dropwise at 0 °C, the reaction will turn from a slurry to a clear yellow solution. After stirring the reaction for 1 h at 0 °C, water (2.5 mL) was added carefully, before diluting the mixture with an aq., sat. Rochelle salt solution (60 mL), then water (40 mL) and CH₂Cl₂ (60 mL). The ice bath was removed, and the biphasic mixture stirred vigorously for 14 h at ambient temperature. Next, the mixture was diluted with additional CH₂Cl₂ and water, before separating the organic layer and extracting with CH₂Cl₂ (3x 100 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo, then dried using high-vac to obtain the title compound 3.57 as a white solid (2.27 g, 83%). No further purification was performed. ¹H NMR (700 MHz, CDCl₃): δ 7.35–7.26 (m, 5H), 4.55–4.47 (m, 2H), 4.26 (q, J = 8.4 Hz, 1H), 4.13 (ddd, J = 9.8, 6.8, 4.9 Hz, 1H), 3.90 (dd, J = 7.7, 5.4 Hz, 2H), 3.85–3.74 (m, 3H), 3.71–3.59 (m, 3H), 3.45 (dd, J = 11.4, 7.3 Hz, 1H), 2.73 (dt, J = 10.4, 7.8 Hz, 1H), 2.24 (dd, J = 7.6, 5.2 Hz, 2H). ¹³C NMR (176 MHz, CDCl₃): δ 137.5, 128.6, 128.00, 127.98, 74.6, 73.7, 68.8, 67.7, 64.5, 62.0, 59.0, 41.3, 40.1. IR (cm⁻¹): 3382, 2871, 1367, 1167, 1117, 1092, 1061, 1037, 997, 871, 831, 756, 699, 656. HRMS: m/z calculated for C₁₅H₂₂NO₄⁺ [M+H]⁺: 280.1543; found: 280.1540.

(7-((benzyloxy)methyl)-2-oxa-1-azabicyclo[3.2.0]heptane-5,6-diyldimethanol (3.58): A 100 mL round bottom flask equipped with a magnetic stir bar was charged with 3.56 (4.70 g, 17.1 mmol, 1 equiv.) and toluene (58 mL). The suspension was sonicated until any large chunks dissipated, note that 3.56 will not be fully soluble in toluene at room temperature or 0 °C. The flask submerged in an ice/water bath and Red-Al (≥60 wt.% in toluene) (11.7 mL, 35.9 mmol,
2.1 equiv.) was added dropwise at 0 °C, the reaction will turn from a suspension to a clear yellow solution over the course of the reaction. After stirring the reaction for 1 h at 0 °C, the reaction was complete by TLC. Then, water (3.0 mL) was added carefully, before diluting the mixture with an aq., sat. Rochelle salt solution (75 mL), then water (50 mL) and CH₂Cl₂ (75 mL). The ice bath was removed, and the biphasic mixture stirred vigorously for 14 h at ambient temperature. Next, the mixture was additional CH₂Cl₂ and water, before separating the organic layer and extracting the aqueous layer with CH₂Cl₂ (3 x 200 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo, and the crude reaction mixture purified by flash column chromatography (2–12% MeOH/CH₂Cl₂) to afford 3.58 as a yellow oil (solidifies upon storage at 0 °C) (4.08 g, 86%). ¹H NMR (700 MHz, CDCl₃): δ 7.34–7.30 (m, 4H), 7.27 (d, J = 6.7 Hz, 1H), 4.56–4.49 (m, 2H), 4.14 (td, J = 8.7, 6.3 Hz, 1H), 4.11–4.06 (m, 1H), 3.94–3.88 (m, 2H), 3.83–3.76 (m, 2H), 3.73 (ddd, J = 11.7, 5.2, 3.0 Hz, 1H), 3.65 (dd, J = 11.8, 2.5 Hz, 1H), 3.56 (ddd, J = 10.5, 5.5, 2.0 Hz, 1H), 2.63 (td, J = 8.7, 5.3 Hz, 1H), 2.16 (ddd, J = 12.3, 6.1, 3.3 Hz, 1H), 2.10 (ddd, J = 12.3, 9.1, 7.4 Hz, 1H). ¹³C NMR (176 MHz, CDCl₃): δ 138.0, 128.5, 127.8, 127.7, 75.7, 73.4, 70.5, 67.4, 63.8, 63.0, 60.6, 45.9, 40.1. IR (cm⁻¹): 3342, 2865, 2246, 1454, 1367, 1095, 1027, 909, 727, 697. HRMS: m/z calculated for C₁₅H₂₂NO₄⁺ [M+H]⁺: 280.1543; found: 280.1539.

**trans 2-(2-hydroxyethyl)azetidine-2,3,4-triyl)trimethanol hydrochloride (3.59):** A 100-mL round bottom flask equipped with a magnetic stir bar was charged with 3.57 (3.75 g, 13.4 mmol, 1.0 equiv.), Pd(OH)₂ on carbon (20 wt%; 1.89 g, 2.7 mmol, 0.2 equiv.), MeOH (35 mL) and trifluoroacetic acid (10 mL). The flask was sealed with a rubber septum and the flask purged with
nitrogen gas. Then, the reaction mixture was sparged with hydrogen gas from a balloon for 10 min, before stirring the reaction at ambient temperature under a hydrogen atmosphere. After 24 h the reaction mixture was passed through a celite plug, and the filter was washed with MeOH. The filtrate was collected and concentrated in vacuo, then dried using high vac to remove any excess trifluoroacetic acid. Next, the residue was dissolved in MeOH (22 mL), a 1 M HCl solution in diethyl ether* (54 mL) was added at 0 °C, and the reaction stirred at ambient temperature for 15 min. The solution was subsequently concentrated in vacuo, then dried using high vac to afford the title compound as a 3.59 (3.09 g, quant.) as a pale amber sticky wax. *4 M HCl in 1,4-dioxane is also suitable for the salt metathesis. The 1 M HCl in diethyl ether was used due to availability.

**1H NMR** (700 MHz, CD$_3$OD): δ 4.28 (dt, J = 8.7, 3.9 Hz, 1H), 4.09 (d, J = 12.0 Hz, 1H), 3.90–3.71 (m, 7H), 3.09 (dt, J = 9.3, 6.7 Hz, 1H), 2.15 (ddd, J = 13.4, 7.6, 5.2 Hz, 1H), 2.06 (dt, J = 14.5, 5.5 Hz, 1H). **1H NMR** (700 MHz, d$_6$-DMSO): δ 9.00 (t, J = 9.3 Hz, 1H), 8.69 (d, J = 10.6 Hz, 1H), 5.42 (s, 1H), 4.81 (s, 1H), 4.05 (dp, J = 10.6, 6.4 Hz, 1H), 3.93 (d, J = 12.4 Hz, 1H), 3.67 (d, J = 12.4 Hz, 1H), 3.65–3.44 (m, 6H), 2.80 (q, J = 7.6 Hz, 1H), 1.95–2.02 (m, 2H). **13C NMR** (176 MHz, CD$_3$OD): δ 71.3, 61.9, 61.2, 60.9, 59.4, 57.8, 44.1, 38.0. **IR** (cm$^{-1}$): 3293, 2936, 2890, 2633, 2484, 1575, 1393, 1317, 1044. **HRMS**: m/z calculated for C$_8$H$_{17}$NNaO$_4^{+}$ [M+Na]$^+$: 214.1050; found: 214.1044.

cis-2-(2-hydroxyethyl)azetidine-2,3,4-triyltrimethanol hydrochloride (3.60): A 100-mL round bottom flask equipped with a magnetic stir bar was charged with 3.58 (2.94 g, 10.5 mmol, 1.0 equiv.), Pd(OH)$_2$ on carbon (20wt%; 1.48 g, 2.1 mmol, 0.2 equiv.), MeOH (27 mL) and trifluoroacetic acid (8 mL). The flask was sealed with a rubber septum and the flask purged with
nitrogen gas. Then, the reaction mixture was sparged with hydrogen gas from a balloon for 10 min, before stirring the reaction at ambient temperature under a hydrogen atmosphere. After 24 h the reaction mixture was passed through a celite plug, and the filter was washed with MeOH. The filtrate was collected and concentrated in vacuo, then dried using high vac to remove any excess trifluoroacetic acid. Next, the residue was dissolved in MeOH (22 mL), a 4 M HCl solution in 1,4-dioxane (21 mL) was added at 0 °C, and the reaction stirred at ambient temperature for 15 min. The solution was subsequently concentrated in vacuo, then dried using high-vac to afford the title compound as a 3.60 (2.40 g, quant.) as a pale amber sticky wax. \(^1\text{H NMR}\) (700 MHz, CD\(_3\)OD): \(\delta\) 4.53–4.45 (m, 1H), 4.10–3.97 (m, 3H), 3.96–3.76 (m, 5H), 3.09 (q, \(J = 8.4\) Hz, 1H), 2.23 (t, \(J = 6.0\) Hz, 2H). \(^1\text{H NMR}\) (700 MHz, d\(_6\)-DMSO): \(\delta\) 9.09 (t, \(J = 8.7\) Hz, 1H), 8.67 (t, \(J = 8.2\) Hz, 1H), 5.45–4.56 (m, 4H), 4.27 (q, \(J = 7.0\), 6.6 Hz, 1H), 3.93–3.86 (m, 2H), 3.74–3.64 (m, 3H), 3.62 (d, \(J = 12.2\) Hz, 1H), 3.52 (t, \(J = 6.5\) Hz, 2H), 2.84 (q, \(J = 8.5\) Hz, 1H), 2.15–2.02 (m, 2H). \(^{13}\text{C NMR}\) (176 MHz, CD\(_3\)OD): \(\delta\) 71.6, 61.2, 58.9, 58.8, 58.0, 57.4, 44.8, 38.4. \(\text{IR}\) (cm\(^{-1}\)): 3294, 2938, 2891, 2645, 2481, 1583, 1425, 1308, 1040. \(\text{HRMS}\): \(m/z\) calculated for C\(_8\)H\(_{18}\)NO\(_4\)\(^+\) [M+H]\(^+\): 192.1230; found: 192.1231.

\begin{center}
\includegraphics[width=\textwidth]{image.png}
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**Caution!** Although we did not experience any problems handling the compounds described in this report, proper laboratory precautions should be taken. Laboratories and personnel should be properly grounded, and safety equipment such as heavy Kevlar/steel gloves, reinforced Kevlar coat, ballistic face shield, ear plugs, and blast shields are necessary for all energetic transformations, and in handling any material that is determined to be energetic.

**trans** (1-nitro-2,3,4-tris((nitrooxy)methyl)azetidin-2-yl)ethyl nitrate (3.61): To a 100 mL round-bottom flask equipped with a stir bar, was added 16.6 mL of Ac\(_2\)O (18.0 g, 0.176 mol, 20.0 equiv.). The flask was immersed into an ice-water bath, and the Ac\(_2\)O was cooled to 0–5 °C. 7.34 mL of 98% HNO\(_3\) (11.1 g, 0.176 mol, 20.0 equiv.) was then added over 1 h at such a rate that the
internal temperature did not rise above 10 °C. The reaction mixture was stirred for 15 min, during which time the reaction mixture re-cooled to 0–5 °C. Azetidine 3.59 (2.00 g, 8.79 mmol, 1.00 eq) was added portion wise over 1 h at such a rate that the reaction mixture did not rise above 15 °C. When addition of the alcohol (3.59) was complete, the reaction mixture was stirred overnight for 15 h, during which time the ice-water bath melted, and the temperature of the reaction mixture warmed to ambient temperature. The reaction mixture was quenched when poured onto a stirring mixture of 100 g of crushed ice and 100 mL of distilled water. The quenched reaction mixture was stirred for 4 h, during which time the ice melted. 100 mL of CH₂Cl₂ was added to the quenched reaction mixture, and was stirred for 15 min. The quenched reaction mixture was transferred to a separatory funnel and was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic extracts were washed with a saturated NaHCO₃ solution (2 x 100 mL), dried over MgSO₄, and filtered into a 600 mL beaker. Evaporation of the solvent overnight in a well-ventilated fume hood afforded a green oil, which was purified by flash chromatography on silica gel (elution with 10% EtOAc/hexanes) to afford a colorless oil. This colorless oil slowly crystallized over several weeks in the freezer (–12 °C) to give 2.75 g (75 %) of nitroazetidine 3.61 as a white powder. ¹H NMR (400 MHz, acetone-d₆): δ 5.30 (ABq, Jₓᵧ = 12.0 Hz, 2H), 5.14–5.10 (m, 1H), 5.03–4.88 (m, 6 H), 3.28 (q, J = 8.0, 1H), 2.59 (m, 2H). ¹³C NMR (101 MHz, acetone-d₆): δ 74.9, 71.0, 70.3, 70.1, 69.1, 66.1, 36.2, 34.0. IR (cm⁻¹): 1661, 1628, 1551, 1273. Tₘₑₜ = 55.7 °C (onset); 60.0 °C (peak). Tₜₐₜ = 182.1 °C (onset); 205.3 °C (peak).

**Caution!** Although we did not experience any problems handling the compounds described in this report, proper laboratory precautions should be taken. Laboratories and personnel should be properly grounded, and safety
equipment such as heavy Kevlar/steel gloves, reinforced Kevlar coat, ballistic face shield, ear plugs, and blast shields are necessary for all energetic transformations, and in handling any material that is determined to be energetic.

cis (1-nitro-2,3,4-tris((nitrooxy)methyl)azetidin-2-yl)ethyl nitrate (3.62): To a 100 mL round-bottom flask equipped with a stir bar, was added 16.6 mL of Ac₂O (18.0 g, 0.176 mol, 20.0 equiv.). The flask was immersed into an ice-water bath, and the Ac₂O was cooled to 0–5 °C. 7.34 mL of 98% HNO₃ (11.1 g, 0.176 mol, 20.0 equiv.) was then added over 1 h at such a rate that the internal temperature did not rise above 10 °C. The reaction mixture was stirred for 15 min, during which time the reaction mixture re-cooled to 0–5 °C. Azetidine 3.60 (2.00 g, 8.79 mmol, 1.00 eq) was added portion wise over 1 h at such a rate that the reaction mixture did not rise above 15 °C. When addition of the alcohol (3.60) was complete, the reaction mixture was stirred overnight for 15 h, during which time the ice-water bath melted, and the temperature of the reaction mixture warmed to ambient temperature. The reaction mixture was quenched when poured onto a stirring mixture of 100 g of crushed ice and 100 mL of distilled water. The quenched reaction mixture was stirred for 4 h, during which time the ice melted, and a solid appeared. The off-white solid was collected by Büchner filtration and was recrystallized from 100 mL of hot isopropanol to afford 3.07 g (84%) of nitroazetidine 3.62 as white, crystalline solid.

\[ \text{1H NMR (400 MHz, acetone-d₆):} \delta 5.38-5.33 (m, 1H), 5.27-5.11 (m, 5H), 5.06 (ABq, J = 8.0 Hz, 1H), 4.87 (t, J = 8.0 Hz, 2H), 3.62 (q, J = 8 Hz, 1H), 2.92-2.86 (m, 1H), 2.69-2.62 (m, 1H); 5.36 (dt, J = 8.0 Hz, 4.0 Hz, 1H), 5.27-5.11 (m, 5H), 5.06 (dd, J = 12.0, 8.0 Hz, 1H), 4.87 (t, J = 8.0 Hz, 2H), 3.69-3.54 (m, 1H), 2.89 (dt, J = 12.0, 8.0 Hz, 1H), 2.66 (dt, J = 12.0, 8.0 Hz, 1H).

\[ \text{13C NMR (400 MHz, acetone-d₆):} \delta 75.0, 72.2, 69.9, 68.9, 68.6, 62.9, 36.0, 29.6. \text{IR (cm}^{-1})\text{:} 1633, 1535, 1271. \text{T}_{\text{melt}} = 89.3 \text{ °C (onset);} 91.7 \text{ °C (peak).} \text{T}_{\text{dec}} = 184.6 \text{ °C (onset);} 208.9 \text{ °C (peak.}}\]
**allyl 4,5-dihydroisoxazole-3-carboxylate (3.63):** A 100-mL round bottom flask equipped with a magnetic stir bar was charged with 3.54-B (1.80 g, 1.1 equiv., 15.6 mmol) and HATU (5.94 g, 1.1 equiv., 15.6 mmol) and sealed with a septa and evacuated and refilled with nitrogen. The solids were brought up in DMF (10.0 mL) and TEA (2.9 mL, 1.5 equiv., 21.3 mmol) was added and left to stir for 15 min. Next, allyl alcohol (0.97 mL, 1 equiv., 14.2 mmol) was added via syringe and the reaction mixture stirred at ambient temperature under nitrogen for 21 h. The reaction was quenched with aq., sat. NH₄Cl (10 mL) and diluted with H₂O (30 mL) and ether (30 mL). Aqueous and organic layers were separated before being extracted with Et₂O (3 x 40 mL). Combined organic extracts were washed with 5% aq. LiCl (100 mL), then brine, and subsequently dried over MgSO₄ and filtered. Next, the reaction mixture was concentrated in vacuo, and the crude reaction mixture purified by flash column chromatography (5–40% EtOAc/hexanes) to 3.63 as a clear colorless oil (1.81 g, 82%).

**¹H NMR (700 MHz, CDCl₃):** δ 5.97-5.92 (m, 1H), 5.36 (d, J = 15.3 Hz, 1H), 5.27 (d, J = 10.4 Hz, 1H), 4.75 (d, J = 5.8 Hz, 2H), 4.51 (t, J = 10.7 Hz, 2H), 3.18 (t, J = 10.8 Hz, 2H).

**¹³C NMR (176 MHz, CDCl₃):** δ 160.4, 151.7, 131.2, 119.5, 71.5, 66.5, 33.8. **IR (cm⁻¹):** 2967, 1729, 1588, 1391, 1332, 1255, 1119, 911, 854, 748. **HRMS:** m/z calculated for C₇H₁₀NO₃⁺ [M+H]⁺: 156.0655; found: 156.0659.

tetrahydro-1H,3H-furo[3',4':2,3]azeto[1,2-b]isoxazol-1-one (3.64): A 500-mL round bottom flask equipped with a magnetic stir bar was charged with fac-[Ir(dFppy)₃] (2.4 mg, 3.2 µmol, 0.00025 equiv.) and MeCN (240 mL). The flask was sealed with a rubber septum and the solution degassed by sparging with nitrogen gas for 30 min. Then 3.63 (1.97 g, 12.7 mmol, 1 equiv.) in MeCN (20 mL) was added via syringe pump over the course of 9 h through the septum under
nitrogen with blue irradiation (427 nm) at ambient temperature (fan cooling). After addition, the remaining solution in the needle was dispensed into the reaction mixture and the syringe was removed along with the nitrogen inlet and the septa was sealed with electrical tape. The reaction mixture was subsequently stirred under blue LED irradiation (427 nm) at ambient temperature (fan cooling) for 15 h (24 h total). Next, the reaction mixture was concentrated \textit{in vacuo}, and the crude reaction mixture purified by flash column chromatography (2–50\% EtOAc/CH\textsubscript{2}Cl\textsubscript{2}, eluting at 20\% EtOAc) to afford \textbf{3.64} as a white solid (1.17 g, 60\%). \textbf{\textit{1H NMR}} (700 MHz, CDCl\textsubscript{3}): \(\delta\) 4.59 (dd, \(J = 9.9, 9.0\) Hz, 1H), 4.46 (dd, \(J = 10.0, 3.8\) Hz, 1H), 4.42–4.37 (m, 2H), 3.77 (dd, \(J = 11.6, 8.9\) Hz, 1H), 3.66 (dd, \(J = 11.5, 3.9\) Hz, 1H), 3.10 (tt, \(J = 8.9, 3.8\) Hz, 1H), 2.54 (dt, \(J = 13.0, 9.8\) Hz, 1H), 2.41–2.35 (m, 1H). \textbf{\textit{13C NMR}} (176 MHz, CDCl\textsubscript{3}): \(\delta\) 175.1, 75.6, 72.3, 68.2, 58.8, 33.6, 32.6. \textbf{IR} (cm\textsuperscript{-1}): 2987, 1755, 1383, 1231, 1182, 1147, 963, 720, 671. \textbf{HRMS:} \(m/z\) calculated for C\textsubscript{7}H\textsubscript{10}NO\textsubscript{3}\textsuperscript{+} [M+H]\textsuperscript{+}: 156.0655; found: 156.0657.

(2-oxa-1-azabicyclo[3.2.0]heptane-5,6-diyl)dimethanol (\textbf{3.65}): A 200 mL round bottom flask equipped with a magnetic stir bar was charged with \textbf{3.64} (1.99 g, 12.8 mmol, 1 equiv.) and toluene (28 mL). The suspension was sonicated until any large chunks dissipated, note that \textbf{3.64} will not be fully soluble in toluene at room temperature or 0 \(^\circ\)C. The flask submerged in an ice/water bath and Red-Al (\(\geq 60\text{wt.\% in toluene}\)) (8.8 mL, 26.9 mmol, 2.1 equiv.) was added dropwise at 0 \(^\circ\)C to the suspension. After stirring the reaction for 1 h at 0 \(^\circ\)C, the reaction was complete by TLC. The reaction was diluted with ether (50 mL) at 0 \(^\circ\)C. Next, Glaubers salt was added at 0 \(^\circ\)C until bubbling stopped. Next, the mixture was stirred at ambient temperature overnight then filtered over celite, rinsing with ether (about 500 mL) and MeOH (100 mL). The filtrate was concentrated \textit{in vacuo}, and the crude reaction mixture purified by flash column chromatography (20%
MeOH/CH₂Cl₂) to afford 3.65 as a clear colorless oil (1.39 g, 68%). **¹H NMR** (600 MHz, CDCl₃): δ 4.49 (br, 2H), 4.32 (td, J = 9.4, 6.7 Hz, 1H), 4.15 (tdd, J = 7.8, 2.8, 1.1 Hz, 1H), 3.94–3.83 (m, 2H), 3.78 (ddd, J = 11.6, 4.5, 1.8 Hz, 1H), 3.53 (dd, J = 11.9, 1.7 Hz, 1H), 3.48–3.39 (m, 2H), 2.66 (tdd, J = 9.4, 6.5, 4.6 Hz, 1H), 2.26 (ddd, J = 12.6, 6.6, 2.8 Hz, 1H), 2.18 (ddd, J = 12.7, 9.8, 7.9 Hz, 1H). **¹³C NMR** (176 MHz, CDCl₃): δ 77.7, 67.0, 64.5, 61.8, 52.7, 40.6, 39.6. **IR** (cm⁻¹): 3312, 2934, 2873, 1447, 1273, 1050, 1025, 917, 727. **HRMS**: m/z calculated for C₇H₁₄NO₃⁺ [M+H]⁺: 160.0968; found: 160.0973.

**(2-(2-hydroxyethyl)azetidine-2,3-diyl)dimethanol hydrochloride (3.66):** A 100-mL round bottom flask equipped with a magnetic stir bar was charged with 3.65 (1.27 g, 8.0 mmol, 1.0 equiv.), Pd(OH)₂ on carbon (20 wt%; 1.12 g, 1.6 mmol, 0.2 equiv.), MeOH (18 mL) and trifluoroacetic acid (6 mL). The flask was sealed with a rubber septum and the flask purged with nitrogen gas. Then, the reaction mixture was sparged with hydrogen gas from a balloon for 10 min, before stirring the reaction at ambient temperature under a hydrogen atmosphere. After 24 h the reaction mixture was passed through a celite plug, and the filter was washed with MeOH. The filtrate was collected and concentrated *in vacuo*, then dried using high vac to remove any excess trifluoroacetic acid. Next, the residue was dissolved in MeOH (36 mL) and cooled to 0 °C. Next, concentrated HCl (aq. 37%, 12 M) (2.6 mL, 4 equiv.) was added and the reaction stirred at ambient temperature for 15 min. The solution was subsequently concentrated *in vacuo*, then dried using high vac to afford the title compound 3.66 (1.56 g, quant.) as a yellow wax. **¹H NMR** (700 MHz, CD₃OD): δ 4.08 (dd, J = 12.1, 1.9 Hz, 1H), 3.95–3.76 (m, 7H), 3.10 (dddd, J = 15.0, 9.3, 7.4, 1.8 Hz, 1H), 2.13 (dd, J = 7.5, 4.3 Hz, 2H). **¹H NMR** (700 MHz, d₆-DMSO): δ 9.01 (s, 1H), 8.82 (s,
1H), 5.54–4.28 (m, 3H), 3.95 (d, J = 12.3 Hz, 1H), 3.74 (dt, J = 6.0, 3.1 Hz, 1H), 3.69 (d, J = 12.3 Hz, 1H), 3.64–3.95 (m, 2H), 3.58–3.50 (m, 3H), 2.88–2.81 (m, 1H), 2.05 (td, J = 6.5, 2.3 Hz, 2H).

$^{13}$C NMR (176 MHz, CD$_3$OD): δ 75.0, 61.7, 59.9, 58.0, 45.2, 43.1, 38.2. IR (cm$^{-1}$): 3296, 2936, 2889, 2630, 1587, 1417, 1315, 1041, 939. HRMS: m/z calculated for C$_7$H$_{16}$NO$_3^+$ [M+H]$^+$: 162.1125; found: 162.1129.

**Caution!** Although we did not experience any problems handling the compounds described in this report, proper laboratory precautions should be taken. Laboratories and personnel should be properly grounded, and safety equipment such as heavy Kevlar/steel gloves, reinforced Kevlar coat, ballistic face shield, ear plugs, and blast shields are necessary for all energetic transformations, and in handling any material that is determined to be energetic.

*(1-nitro-2,3-bis((nitrooxy)methyl)azetidin-2-yl)ethyl nitrate (3.67):* To a 100 mL round-bottom flask equipped with a stir bar, was added 19.1 mL of Ac$_2$O (20.7 g, 0.203 mol, 20.0 equiv.). The flask was immersed into an ice-water bath, and the Ac$_2$O was cooled to 0–5 °C. 8.45 mL of 98% HNO$_3$ (12.8 g, 0.203 mol, 20.0 equiv.) was then added over 1 h at such a rate that the internal temperature did not rise above 10 °C. The reaction mixture was stirred for 15 min, during which time the reaction mixture re-cooled to 0–5 °C. Azetidine 3.65 (2.00 g, 10.1 mmol, 1.00 eq) was added portion wise over 1 h at such a rate that the reaction mixture did not rise above 15 °C. When addition of the alcohol (3.65) was complete, the reaction mixture was stirred overnight for 15 h, during which time the ice-water bath melted, and the temperature of the reaction mixture warmed to ambient temperature. The reaction mixture was quenched when poured onto a stirring mixture of 100 g of crushed ice and 100 mL of distilled water. The quenched reaction mixture was stirred for 4 h, during which time the ice melted, and a solid appeared. The light-yellow solid was collected by Büchner filtration, and was recrystallized from 100 mL of hot isopropanol to afford...
2.83 g (82%) of nitroazetidine 3.66 as white, crystalline solid. \textbf{\textsuperscript{1}H NMR} (400 MHz, acetone-\textit{d}_6): \(\delta\) 5.27 (ABq, \(J_{\text{AB}}\) = 12.0 Hz, 2 H), 5.00–4.87 (m, 4H), 4.37 (ABs, \(J_{\text{AB}}\) = 8.0 Hz, 2H), (qu, 1H), 2.63 (m, 2H); \textbf{\textsuperscript{13}C NMR} (101 MHz, acetone-\textit{d}_6): \(\delta\) 77.2, 71.4, 71.2, 69.6, 56.7, 33.7, 33.3. \textbf{IR} (cm\(^{-1}\)): 1656, 1619, 1539, 1262. \(T_{\text{melt}}\) = 64.6 °C (onset); 67.0 °C (peak). \(T_{\text{dec}}\) = 186.7 °C (onset); 210.4 °C (peak).
3.3.3 DSC Information

Compound 3.36

![DSC graph for Compound 3.36]

Compound 3.47

![DSC graph for Compound 3.47]
Compound 3.48

Compound 3.61
Compound 3.62

![Graph of Compound 3.62](image)

Compound 3.67

![Graph of Compound 3.67](image)
3.3.4 X-ray Crystallographic Information

Compound 3.36 (CCDC: 2279065)

Bond precision:  C-C = 0.0024 Å

Wavelength=0.71073

Cell:  
\[ a = 7.6654(2) \quad b = 7.9513(2) \quad c = 20.7457(7) \]

\[ \alpha = 90 \quad \beta = 90.086(3) \quad \gamma = 90 \]

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Data completeness= 1.000  Theta(max)= 26.372

\[ R(\text{reflections}) = 0.0462(2215) \]

\[ wR2(\text{reflections}) = 0.1139(2583) \]

S = 1.080  Npar= 235
Compound 3.67 (CCDC: 2179082)

Bond precision:  C-C = 0.0020 Å  Wavelength=0.71073 Å

Cell:  
- a = 8.3417(2) Å  b = 12.8066(3) Å  c = 25.2292(5) Å
- alpha = 90°  beta = 90°  gamma = 90°

Temperature: 297 K

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Data completeness = 1.000  Theta(max) = 26.369

R(reflections) = 0.0369 (2196)  wR2(reflections) = 0.0867 (2753)
S = 1.066  Npar = 252
Compound 3.62 (CCDC: 2179072)

Bond precision: C-C = 0.0020 Å

Wavelength=0.71073 Å

Cell: a=7.9238(4)  b=8.5596(4)  c=12.8672(5)

alpha=77.708(4)  beta=74.962(4)  gamma=76.346(4)

Temperature: 296 K

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R(reflections)= 0.0433 (2888)  wr2(reflections)= 0.1068 (3302)
S = 1.065  Npar= 253
Compound 3.61 (CCDC: 2179080)

![Structure Image]

**Bond precision:**

\[
C-C = 0.0023 \text{ Å} \\
\text{Wavelength}=0.71073
\]

**Cell:**

\[
a=14.5227(6) \quad b=8.8001(2) \quad c=14.2408(6) \\
\alpha=90 \quad \beta=114.241(5) \quad \gamma=90
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**Temperature:** 296 K

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**Correction method:** # Reported T Limits: Tmin=0.797

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**Data completeness:** 1.000 \( \text{Theta(max)} = 26.363 \)

**R(reflections) = 0.0405 (2798) \text{ wR2(reflections)} = 0.0946 (3384) \)

**S = 1.039 \text{ Npar} = 301**
Chapter 4 General Remarks and Conclusion

Chapters 1–3 of this dissertation cover the development of new synthetic methodologies for the synthesis of heterocyclic compounds. Chapter 1 of this dissertation describes a carbonyl-olefin metathesis strategy for the synthesis of six-membered nitrogen-containing heterocycles, tetrahydropyridines. Six-membered nitrogen heterocycles are an established motif in FDA approved pharmaceutical compounds, albeit tetrahydropyridines are less represented due to limited synthetic strategies. Conversely, four-membered heterocycles are significantly less incorporated in FDA approved pharmaceuticals despite their potential to impart favorable characteristics. To address this, Chapter 2 describes a visible-light-mediated Paternò-Büchi reaction to access highly-substituted oxetanes under mild conditions. Chapter 3 also looks at the scalable synthesis of highly substituted four-membered rings, azetidines, using a visible light [2+2]-cycloaddition strategy and their application as energetic materials. The unifying theme of this dissertation is addressing gaps in the field of heterocycle synthesis, to enable their use and applications, for example the development of new pharmaceuticals, agrichemicals, and energetic materials. Looking into the future, it is envisioned that this work will not only enable industrial endeavors, but also serve as a starting point for new methodologies.
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