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Photoassisted Access to New Polyheterocycles

Teresa M. Cowger

University of Denver

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Photoassisted Access to New Polyheterocycles

A Dissertation

Presented to

the Faculty of Natural Sciences and Mathematics

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In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

by

Teresa M. Cowger

March 2014

Advisor: Andrei G. Kutateladze
Abstract

Photoassisted diversity-oriented synthesis holds great promise in its ability to provide rapid access to complex and diverse molecular scaffolds. As it stands, while photochemical techniques have this potential, their implementation in the field of synthetic organic chemistry is very limited. The main goal of this project was to utilize photochemically assisted techniques in the synthesis of a variety of novel polyheterocycles.

Initially, we explored how the strain installed in these polycycles could be harnessed to trigger cationic rearrangements in the framework of the system. This was achieved via the high yield and rapid assembly of a highly strained system containing two oxetanes. This *bis* oxetane was derived from a compound containing carbonyl groups *endo-* to two respective bicyclic olefins which was assembled via a simple Diels-Alder step. The oxetanes were formed in a Paternò-Büchi reaction via excited-state chemistry. The protolytic ring-opening of this *bis*-oxetane compound afforded two highly unusual polycyclic products that both result from rather complex mechanisms which are proposed in this work. In addition, we were able to elaborate on this rapid Diels-Alder assembly motif by designing a double-tandem \([4+2][2+2][4+2][2+2]\) synthetic sequence which culminates in a complex scaffold containing an oxetane. When subjected to acidolysis, this oxetane affords a complex polycycle with rigidly held pendants rich in heteroatoms.
We then intended to study how a bicyclic olefin which also possessed endo-carbonyl groups would perform during irradiation when the length of the tether to the bicyclic system was lengthened. This lengthened tether allowed flexibility in the regiochemistry of the Paternò-Büchi cycloaddition. The regiochemistry was also able to be controlled by the introduction of a methyl group in the tether. The protolytic opening of the two different oxetanes gave polyheterocyclic products with completely different scaffolds that both demonstrate a great increase in complexity of structure relative to the quite simple starting materials.

In a departure from Paternò-Büchi, our next design strategies focused on the photo-generation of azaxylylenes via excited-state intramolecular proton transfer. We tethered these azaxylylenes to unsaturated pendants in the hopes that the short-lived intermediate would undergo cycloaddition with these pendants. In this endeavor, we were able to observe both [4+4] and [4+2] cycloadditions, depending on the type of pendant used. We were able to diversify this system by utilizing both carbonyls and imines as the proton abstraction agents, by using thiophene and furan as the unsaturated pendant, and by tethering the pendant to the carbonyl “half” and the aniline “half” of the photoprecursor—demonstrating the tolerance that this system has for a large range of modifications.

With the optimization of these methodologies, we aim to pave the way for the incorporation of photochemistry into the toolbox of synthetic chemists by demonstrating the molecular diversity that these techniques allow.
Acknowledgements

Most of all, I want to thank my advisor, Professor Andrei G. Kutateladze. He has a creative approach to chemical problems which has helped develop in me an “outside the box” view when it comes to synthetic challenges. His deep knowledge of his craft makes him an excellent teacher both in the classroom and in the lab. I have learned more from him than I could possibly contain in this thesis. I must also thank my committee members Dr. Gareth Eaton, Dr. Martin Margittai, Dr. Bryan Cowen, and Dr. Joe Angleson.

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Lastly, I would like to offer my appreciation and thanks to my family. My husband Doren, my son Brennan, and my parents, Joe and Annveig Arisco. Their support and love have been invaluable to me. For this and for countless other reasons, I am thankful for them.
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List of Abbreviations and Acronyms

Δ Temperature (heat)
Ac acetyl
aq. aqueous
Ar aryl
Bn benzyl
Bz benzoyl
cat. catalyst (or catalytic amount)
calcd calculated
DCM dichloromethane
DIEA (DIEA) N,N-diisopropylethylamine (Hünig's base)
DMAP 4-dimethylaminopyridine
DMF N,N-dimethylformamide
DMSO dimethyl sulfoxide
DOS Diversity-oriented synthesis
eq equivalent
ERG electron releasing (donating) group
ESI electrospray ionization
ESIPT excited-state intramolecular proton transfer
Et ethyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
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<tbody>
<tr>
<td>r.t.</td>
<td>room temperature</td>
</tr>
<tr>
<td>SAR</td>
<td>structure-activity relationship</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated</td>
</tr>
<tr>
<td>soln</td>
<td>Solution</td>
</tr>
<tr>
<td>TBDMS</td>
<td>Tert-butylmethysilyl</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>tetramethylsilane</td>
</tr>
<tr>
<td>p-Ts</td>
<td>\textit{para}-toluenesulfonyl (4-toluenesulfonyl)</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
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Chapter 1: Introduction

The utilization of photochemical techniques in synthetic organic chemistry can allow access to strained polycyclic structures whose framework would not easily be accessible via ground state chemistry. However, with very few exceptions, photochemical techniques are deeply underutilized in synthetic schemes, despite the concise pathways they can provide to complex targets and often privileged carbon scaffolds. Even rarer is the use of photochemistry in diversity-oriented synthesis.

Photoassisted Syntheses

Perhaps the most commonly applied photochemical step employed in syntheses is [2+2] cycloaddition, as it is the most convenient route to the formation of 4-membered rings. This pericyclic reaction is forbidden in the ground state, but is possible when one of the π-systems is excited. This relationship becomes clear when one considers the frontier molecular orbital theory, an approach first suggested by Kenichi Fukui in 1952. He posited that when trying to predict the reactivity of a π-system, one can assume that the electrons in the highest energy π-orbitals (i.e.; HOMO), which he dubbed frontier electrons, determine the overall electron density, and thus reactivity of the species. This concept was simultaneously developed by Robert B. Woodward and Roald Hoffmann* in their seminal publications Stereochemistry of Electrocyclic Reactions (1965) and Conservation of Orbital Symmetry (1968), the content of which outlines what we now

* Hoffmann and Fukui were both awarded the Nobel Prize for Chemistry in 1981 for their study in this area; Woodward received the prize in 1965 for his work in total synthesis.
call the Woodward-Hoffmann rules. These rules predict the reactivity in pericyclic reactions based on the orbital symmetry in the $\pi$-systems in either the ground or excited states.

Regarding [2+2] cycloaddition, Figure 1.1 demonstrates the application of these rules. In this frontier molecular orbital approach, one must consider the symmetry of the HOMO of one molecule with the LUMO of the other. If the orbital symmetry is conducive to bonding interactions, the reaction is allowed. In the example in Figure 1.1, the ground state chemistry of a [2+2] reaction gives an antibonding interaction upon the approach of the orbitals. In the excited state, however, the HOMO and LUMO give only bonding interactions; thus this reaction is allowed in the excited state.

![Figure 1.1: FMO Approach to [2+2] cycloaddition](image)

In a $\pi$-system, a cycloaddition reaction may only take place when the orbital symmetry of the HOMO and LUMO are conducive to a bonding interaction at the terminal orbitals of each molecule. This approach applied to a [2+2] cycloaddition
elucidates why it proceeds in photochemical conditions, as the barrier is too high in the ground state.†

A notable example of an elegant [2+2] reaction by Winkler et. al. in 2002 is in the first reported total synthesis of ingenol,\textsuperscript{4a} a lead compound related to a anticancerous terpenoid drug approved by the FDA called Picato®, or ingenol mebutate. Currently, the major source for ingenol mebutate is through direct extraction from \textit{Euphorbia peplus} (aka milkweed) which yields 1.1 mg of ingenol mebutate from every kilogram of \textit{E. peplus}.\textsuperscript{4b,c} In some cases, it is synthesized from ingenol, which can be extracted in a yield of 275 mg/kg of raw plant material (the dried seeds of \textit{E. lathryis}).\textsuperscript{4d} In comparison, the natural product artemisinin is the most commonly prescribed antimalarial on the market and is currently sourced by direct extract from raw plant material (\textit{Artemisia annua}) at 5 g/kg of dry leaves.\textsuperscript{4e} Thus, it follows that a better path to the synthesis of ingenol would be valuable tool for the pharmaceutical industry.

In Winkler’s synthetic sequence, a [2+2] cycloaddition is employed in order to install the skeletal framework necessary in 2, which sets it up for the further transformation into the [4.4.1] bicyclic framework in the final product, ingenol. While this synthesis was groundbreaking in that it was the first total synthesis, it was over 43 steps with an overall yield of less than 0.01%. However, as Winkler points out, the photoaddition and fragmentation approach establishes the unique \textit{trans}-bridgehead stereochemistry in the [4.4.1] skeleton, a challenging feat. It is also worth mentioning that while a higher-yielding non-photochemical total synthesis of ingenol has since been

\textsuperscript{†} It must be noted that this generalization is true for suprafacial approaches only. The opposite holds for antarafacial interactions, like in the cycloadditions of alkenes to ketenes.
reported, the photochemical step shown in Scheme 1.1 installs a tricyclo[6.2.0.0^{2,6}]decane core, a motif present in a variety of terpenoid natural products, which supports the potential for synthetic utility of this method.

![Scheme 1.1: Photochemical [2+2] in Ingenol synthesis](image)

Another example of a [2+2] step was reported in 2006 by Srikrishna and Ramasatry in their enantioselective total synthesis of a variety of phytoalexins, a family
of powerful antibacterial compounds derived from an isolate of tobacco leaves.\textsuperscript{5a} This sequence began from the derivatization of \((R)-(-)-\text{carvone}\) (\textbf{Scheme 1.2}), a relatively inexpensive commercially available starting material. After performing the cycloaddition to give 3, the photoproduct was then derivatized to form 4, (+)-\text{solanascone} and 5, (+)-dehydrosolanascone. With the success of this approach, they went on to synthesize a variety of further derivatives, including the natural product (+)-2\text{\textdegree}-\text{hydroxysolanascone}, 6.\textsuperscript{5b}

Cyclobutanes can also be installed via the DeMayo reaction, in which the enol tautomer of a 1,3-dicarbonyl is captured by a [2+2] cycloaddition. The subsequent retro-aldol fragmentation functionally serves to insert the alkene (now unsaturated) between the two carbonyls. \textbf{Scheme 1.3} shows a creative example of such a reaction employed by Minter and Winslow in 2004 in the synthesis of a galanthane skeleton which is contained in (-)-lycorine,\textsuperscript{6} a potent toxin found in daffodil bulbs. The synthesis of this framework is achieved via the intramolecular [2+2] cycloaddition of the enol tautomer to the isoquinolinone in 7 to form 8, which rapidly rearranges to 9. Treating 9 to basic piperidine conditions gives 10, a lead toward the synthesis of (-)-lycorine. This toxic compound and its relatives have proven to have anticancer activity in a thorough structure-activity relationship (SAR) study and holds promise as a lead compound against a variety of metastatic cancers,\textsuperscript{7} which further emphasizes the practicality of a high-yielding approach to this scaffold.
In the discussion of [2+2] cycloaddition, one would be remiss to neglect the Paternò-Büchi reaction—the cycloaddition of a carbonyl to an olefin to form an oxetane, a 4-membered cyclic ether. Notable in the Paternò-Büchi reaction scheme is the potential for intersystem crossing (ISC) of the singlet $n\rightarrow\pi^*$ excited state to form the triplet [the notation for these excited states are $^1(n,\pi^*)$ and $^3(n,\pi^*)$ respectively]. Howard Zimmerman first proposed a non-concerted mechanism for this reaction in which a 1,4-diradical is formed, with the stability of the diradical generally governing the major product. When the diradical intermediate proceeds in the triplet manifold, the final closure into the oxetane ring is forbidden and must first undergo ISC into the singlet state with the assistance of spin-orbit coupling, which also contributes to the stereochemical control.

**Scheme 1.3:** DeMayo reaction in galanthane synthesis

(-)-Lycorine
Greaney et. al. utilized the Paternò-Büchi reaction in a synthesis of the core structure of Merrilactone A (see Scheme 1.4), which is a natural product reported to act as a neurotropic agent.\textsuperscript{10} While this particular research group had the natural target in mind, one can’t help but marvel at the dramatic growth in molecular complexity in this single step from 11 to 12: from one stereocenter to four with perfect diastereoselectivity, the dramatic change in the polycyclic framework, and the possibility for the utilization of diversity inputs to explore the SAR of its natural product analog are all exciting features available with the assistance of this single photochemical step.

Scheme 1.4: Photochemical route to the Merrilactone A framework\textsuperscript{10}

Excited-state electrocyclic ring-closures are also an important way in which photochemistry is utilized to access difficult scaffolds. Similar to cycloadditions, photocyclizations in the singlet state are governed by the Woodward-Hoffmann rules. However, rather than considering the HOMO and LUMO frontier orbitals of two separate molecules, one examines the symmetry of the terminal orbitals in the HOMO of a π-system. The orbitals rotate in such a way that they form a bonding (rather than antibonding) interaction—and the molecular orbitals reveal if this proceeds via a conrotatory or disrotatory process, as demonstrated in Figure 1.2.
The generalization of this rule is that if there is an even number of electron pairs involved in the pericyclic reaction, the cyclization will proceed in a conrotatory fashion under thermal conditions. All other conditions (odd number of electron pairs, disrotatory, or photochemical conditions) can be inferred from this statement. The direction of rotation allowed in the given conditions determines the stereochemical configuration of the product (when applicable).
**Figure 1.3** shows a series of examples in which a $6\pi$ photocyclization is employed to assemble natural products. The arrows in the figure indicate the sigma bond which is formed in the cyclization step. Note that because this is an odd number of electron pairs and the conditions are photochemical, the reaction proceeds in a conrotatory fashion. However, because these examples are all subsequently oxidized from the cyclohexadiene intermediate to the aromatic final product, this nuance is not obvious.

![Figure 1.3: 6\(\pi\) photocyclization products of dictyodendrin B (13), \(^{11a}\) (+)-rebeccamycin (14), \(^{11b}\) the algycon of staurosporine (15), \(^{11c}\) ellipticine (16), \(^{11d}\) and methoxatin (17)\(^{11c}\)](image)

This type of photocyclization is not limited to olefinic scaffolds. The $6\pi$ photocyclization of enamides affords isoquinoline alkaloids. One such example is outlined in **Scheme 1.5** which was implemented by Rigby et. al. in the total syntheses of (+)- narciclasine and (+)-pancrastatin.\(^{12a}\) This cyclization is thought to proceed via the zwitterionic tautomer (19) of the amide (18). The photocyclization followed by a
suprafacial [1,5] hydride shift to give 21. The bulky stereogenic center adjacent to the π-system affords diastereoselective control in the formation of 20, which is crucial to the synthesis. Unique in this scheme is the utilization of the photoproduction as a common precursor for both natural products. (+)-Pancreatistatin is of particular interest due to its antineoplastic activity against ovarian sarcoma and lymphocytic leukemia.\(^{12b}\) It is also suggested that (+)-narciclasine warrants further investigation of activity as it is thought to act by disrupting protein biosynthesis in eukaryotes, though the mechanism is currently unclear.\(^{12c,d}\)

**Scheme 1.5:** 6π photocyclization of an enamide in natural product synthesis\(^{12}\)

While photochemical cycloaddition and cyclization reactions serve to install (or fragment in the case of retro-reactions) a target framework, photochemical
rearrangements often serve to “scramble” an existing scaffold. Arguably, this contributes to the idea that photochemistry is exotic. One such reaction is the di-π-methane rearrangement. This is a reaction in which two π-systems insulated by an sp³ carbon are excited to form a diradical which can rearrange, as in Scheme 1.6. When one of the π-systems is a carbonyl, this is called an oxa-di-π-methane rearrangement.

Scheme 1.6: Oxa-di-π-methane rearrangement

Demuth and Hinsken employed such a rearrangement in their synthesis of (−)-silphiperfol-6-en-5-one (22; see Scheme 1.7) in a rather congested system with reasonably good yield.¹³

Scheme 1.7: Photoassisted synthesis of (−)-silphiperfol-6-en-5-one¹³

In addition to using light as a reagent in photochemical transformations, irradiation conditions also provide the opportunity to generate singlet oxygen, which can complex with alkenes to form an exciplex and participate in an ene reaction (see Scheme 1.8). The stepwise mechanism for such an interaction, its rates, and steric control were
studied thoroughly by Clennan. The addition of oxygen in this reaction is often facially selective depending on the steric environment of the starting alkene. It is appealing to be able to use light and atmospheric oxygen as a means to selectively introduce heteroatoms into a compound which might be sensitive to harsher oxidation conditions.

![Scheme 1.8: Photo-oxidation of alkenes](image)

While this is not a comprehensive list of the photochemical reactions utilized in syntheses, exploration of the literature makes it clear that we have barely scratched the surface of the potential that excited state chemistry holds as a tool in synthesis for both the transformation and assembly of unique scaffolds.

**Diversity-Oriented Synthesis**

Targeted synthesis is deeply rooted in the history of organic chemistry. Commonly, the “targets” are natural compounds which present the researcher with a problem-solving puzzle of trying to synthesize a complex target from simpler starting materials. This process is called retrosynthetic analysis and has proven to be immensely useful at chipping away at the synthesis of many targets of value in medicinal chemistry. In the previous section, there were several examples of the utilization of a
photochemical step in the synthetic sequences of (or toward) the synthesis of many such natural compounds and targets.

While targeted synthesis is a “laser-focused” approach to compounds, diversity-oriented synthesis (DOS) can comparatively be considered a “shotgun approach.” The goal is aimed at collecting a large number of molecules that have a broad range of structural diversity and complexity. This ideology has the potential to work symbiotically with the characterization of the human genome. Hopkins and Groom discuss this topic and use the term “druggable genome” to emphasize that half of the proteins expressed by the human genome are not functionally classified—and how vast the “market” for drug leads really is.\textsuperscript{17} The National Cancer Institute has programs focused on collecting genomic information on such uncharacterized proteins and making it widely available. With the collective efforts of small molecule chemists as well as the information made available by the characterization of these proteins, Hopkins and Groom posit that these “druggable” domains should be the focus for those in the market for new drugs.

However, as Schreiber and Strausberg point out,\textsuperscript{18} there is still a large gap between having this genomic information and knowing what to do with it. They suggest that small molecule probes are the key to narrowing the gaps in these uncharacterized proteins—their function, binding pockets, native binding targets, etc.—and that the fastest way to achieving libraries of these probes is via a DOS approach.\textsuperscript{18} High-throughput screening combined with a diversity-oriented approach to drug targets could saturate the pharmaceutical industry with “hits” for druggable targets (i.e., proteins whose function can be modulated with drugs). In addition to rapidly identifying these hits, a
DOS approach could allow for a more rapid assessment of structure-activity relationships and elucidating the functionality of these uncharacterized proteins. For example, if a member of a library of molecules, let us call it \textbf{Mol-A}, is found to be an inhibitor of a kinase, \textbf{Kin-A}, one could screen the activity changes that result in \textbf{Kin-A} from any number of other members from the same library in order to see how the diversity inputs generated from the DOS approach modulate the protein function differently. Rather than exploring knockout genes or synthesizing analogs of \textbf{Mol-A} one-by-one, the DOS-approach provides rapid access to iterations of this lead compound. Not only could these small molecule probes serve as drug leads, but their function in these library screenings could serve to provide a deeper understanding of cell circuitry or disease biology by simply modulating a biological system in any way—if not activating or deactivating the mechanisms involved in diseases.

Because of this broad horizon in the context of high-throughput screening, DOS is a “fertile ground for chemists” in which the goal of new drug discovery holds great promise for connections to biology and medicine.\textsuperscript{19} Even in the spectrum of proteins with known function and characterized binding targets, the potential that high-throughput screening can offer for revealing new binding sites holds great promise. It is for this reason that there is a call to arms for small drug-like molecules—the structures of which can only be limited by our imagination.

Combinatorial techniques introduced in the 1990s began to address these demands in the synthesis of vast libraries of non-peptide organic compounds. Efficient drug discovery, lead optimization, and structure-activity studies were major contributions
provided by combinatorial chemistry. But even with this approach, Oh and Park posit that combinatorial chemistry “has not led to a notable increase in the number of new chemical entities…approved by the United States Food and Drug Administration.” As such, they argue that conventional combinatorial techniques tend to be iterative upon a small number of core skeletons and are unable to populate the chemical space which is relevant to applications in chemical biology. According to their line of thinking, proliferating libraries of compounds should not be iterative for its own sake, but rather focused on privileged core frameworks which have the greatest potential for biological impact. It is hoped that this focus will give rise to compounds rich in structural diversity but still having “drug-like” properties.

These are among the reasons that the field of DOS is rapidly growing. There is not only a need for the synthesis of a large number of valuable molecules, but for the development and optimization of methodologies which tolerate a variety of diversity inputs and provide a rapid growth in complexity. It is the hope that with such methodologies developed, libraries of compounds can be achieved rapidly, efficiently, and then screened for activity against any number of vectors.

**Polyheterocycles**

With the emerging focus on the characterization of gene and protein functions since the characterization of the human genome, biomedical research groups have begun to turn their focus to the utilization of small-molecule modulators in the control/manipulation of gene products. This growing field of chemical biology has the
core aims of identifying these small molecules which can perturb biological systems and use these agents to study the activation or deactivation of gene products by their direct or indirect interactions. This culminates in a growing demand for the synthesis of small, drug-like compounds which cover a broad range of molecular diversity.

Traditionally, medicinal chemists have turned to natural products as they certainly qualify for their molecular diversity. Natural products and their analogs have been widely successful as therapeutic agents, with 60% of anticancer and 75% of antibiotic agents in the pharmaceutical market being natural extracts or derived from such.\textsuperscript{21} A common theme among the family of natural targets as drug leads is that they are “anti”—anticancerous, antiviral, antitumor, antihelmintic, antifungal. This is because the function these natural products serve to their original hosts is in the protection from pathogens. Often, they do their job too well and kill everything—including an unreasonable amount of healthy human cells—making them unviable as drug leads. However, in disease states whose treatment is less interdependent on cytotoxicity (such as diabetes, depression, osteoporosis, etc.), natural products tend to be far less effective.\textsuperscript{21} Natural products also have significant hurdles in the endeavor to scale-up their production for either direct use or structural modification.

Waldmann et. al. claim that a wholly unbiased DOS approach to complex small molecules is not as important as an approach which has biologically validated molecular frameworks that are either derivatives of natural products or which contain motifs present in natural products.\textsuperscript{22} From this idea, it is argued that a diversity-oriented sequence aimed at rigid, polyheterocyclic substructures has a greater potential for identifying novel therapeutic agents and modulators.\textsuperscript{21} While this focus on these privileged structures is not
quite in keeping with the true intent of unbiased DOS, it is important to address the
demand for maximizing molecular diversity while still keeping within the framework of
what will more likely be relevant in biological and pharmacological applications. To this
end, the research within this work attempts to combine these concepts—the utilization of
photochemical techniques to access privileged polycyclic and polyheterocyclic structures
which are diverse, structurally complex, and via methodologies that can be augmented
with diversity inputs.
Chapter 2: Installing and Harnessing Strain in Oxetanes

Rearrangement of a bis-Oxetane

Introduction

In the attempt to access frameworks for biologically active natural products, Rawal employed the Paternò–Büchi reaction in endo-acylnorbornenes which are readily accessed from Diels-Alder reactions of cyclic dienes with vinyl ketones (Scheme 2.1). The oxetane product (and its transformations) shows remarkable growth in molecular complexity from such simple starting materials and is demonstrative of the appeal for such a synthetic sequence. The subsequent ring opening, oxidation, and radical fragmentation of these photoproducts resulted in the synthesis of di- and triquinanes, a motif that frequently occurs in natural products.

Scheme 2.1: Rawal’s approach to diquinanes

In 1973, Jones observed that oxetanes can be converted pyrolytically via cycloreversion to an alternative pair of an alkene and an aldehyde, constituting a carbonyl-olefin metathesis (Scheme 2.2). Griesbeck proposed an electron transfer
mechanism for a similar reaction in 2006. While these pyrolytic transformations have great synthetic potential, the harsh conditions under which they occur preclude their application to more delicate compounds.

\[
\text{O} + \text{MeO}_2\text{C} = \text{CO}_2\text{Me} \xrightarrow{\text{hv}} \text{MeO}_2\text{C} - \text{CO}_2\text{Me} \xrightarrow{\Delta} \text{MeO}_2\text{C} = \text{H} + \text{HCO}_2\text{Me}
\]

**Scheme 2.2:** Carbonyl-olefin metathesis

Sauers’ research on *endo*-norbornenyl systems combines these two concepts of an intramolecular Paternò–Büchi reaction to install an oxetane followed by carbonyl-olefin metathesis (henceforth *oxametathesis*) in 5-norbornenylacetone and 5-norbornenylacetaldehyde and the subsequent acid-catalyzed cleavage of the installed oxetane ring, shown in **Scheme 2.3**. This intramolecular transformation results in a polycycle with a completely new topology relative to the starting material.

\[
\text{O} \xrightarrow{\text{hv}} \text{O} \xrightarrow{\text{H}^+} \text{O} \
\]

**Scheme 2.3:** Sauers’ oxametathesis

Following his extensive research on these systems, Sauers’ attempt to apply this method to more strained polycycles came to a dead end when the *endo*-carbonyl was part of a cyclic ketone. This fused norbornene derivative containing a tricyclo[5.2.1.0\(^2,6\)] core (**Scheme 2.4**) was incapable of undergoing the Paternò-Büchi cycloaddition that had been
observed in so many other analogs. Rather, tricyclo[5.2.1.0^4,9]undecan-5-one was produced instead of the expected oxetane.\(^{26c}\)

It appears that in such a highly strained and rigid tricycle, the \(\pi\)-orbital of the carbonyl group simply cannot reach the double bond to complete the Paternò-Büchi cycloaddition. Instead, the excited carbonyl performs an electron transfer to the double bond (I), followed by alpha-H abstraction by the double bond (II). Tautomerization of the enol radical (III), and subsequent collapse of the 1,5-diradical (IV) results in the isolated product.

Due to this failure in the formation of the desired oxetane photoproduct, there were no subsequent fruitful studies in these fused \textit{endo}-carbonyl polycycles until in 1977 when Paddon-Row found a competing Paternò-Büchi side reaction in the attempts to
research an all-carbon [2+2] photocyclization in a hemicyclone-benzoquinone adduct.\textsuperscript{27a} This finding was later confirmed by Coxon.\textsuperscript{27b}

Roman A. Valiulin studied the photoreactivity of these fused ring systems, finding both computationally and experimentally that increasing the ring size of either “half” of the fused ring system (i.e., the ketone half or the bicyclo half), the photoreactivity could be restored. Density Functional Theory (DFT) calculations at the B3LYP/6-311+G(d,p) level confirmed that the target oxetane relaxes by as much as 11 kcal/mol when its cyclopentyl moiety is expanded by a single methylene group, suggesting that the Diels-Alder adducts of six membered and larger cycloalkenones can be Paternò-Büchi photoreactive.\textsuperscript{27}

In collaboration with Roman A. Valiulin, a system was designed which was capable of performing two intramolecular Paternò-Büchi cycloaddition reactions. The Diels-Alder adducts of benzoquinone with two molecules of cyclopentadiene and cyclohexadiene were known,\textsuperscript{29} but their photochemistry had not been studied.

![Scheme 2.6: bis-Diels Alder adducts of benzoquinone](image)

While the irradiation of the bis-adduct with cyclopentadiene (1a) was not photoreactive, the cyclohexadiene analog (2a) proved to be a promising lead. Upon irradiation, it formed a bis-oxetane polycycle (95% by NMR) via the mono-oxetane
intermediate (3a) observed during the irradiation (see Scheme 2.7). The structure of the bis-oxetane (4a) was proved by Roman A. Valiulin via X-ray crystallography.

It then became our goal to explore the oxemetathetic transformations capable in such a highly strained polycyclic structure.

![Scheme 2.7: Irradiation of 2a](image)

**Results and Discussion**

For this *bis*-oxetane, the interest for my research was supremely in the deep cationic rearrangement upon its protolytic ring opening in the presence of HCl. These rearrangements are only possible due to the high amount of strain installed in the photochemical Paternò-Büchi step. This strain is installed, then harnessed in order to produce complex polycyclic scaffolds. The minor products shown in Scheme 2.8 (5a and 6a; both less than 5% in yield) gave a unique insight into the mechanistic capabilities of this highly strained rigid polycycle.
Our proposed mechanism for the formation of 5a (see Scheme 2.9) begins with protolytic ring opening of one oxetane ring, which furnishes carbocation A1 that rearranges via 1,2-alkyl migration to form A2. The resulting electrophilic center is captured by chloride to form A3. Acid promoted ring opening of the second oxetane gives A4, which then is deprotonated in order to cyclize into the key intermediate, A5—containing a cyclopropyl ring. In Dr. Andrei Kutateladze’s force field estimate, the cyclopropyl intermediate A5 is about 20 kcal/mol lower in energy than its oxetane precursor, A3 (deprotonated). The subsequent acid-catalyzed Grob fragmentation gives the cis-fused alkene A6, which equilibrates via its enol intermediate into 5a, which has a trans configuration and is calculated to be 1.5 kcal/mol more stable than A6.\(^\text{\textsection}\)

\(^\text{\textsection}\)This research was done in collaboration with Roman A. Valiulin, who characterized 2a-1, 2a-2, and 2a-3 in Scheme 2.8

\(^\text{\textsection}\)See ref [28] and the SI therein for details regarding computational data.
The mechanism for the formation of 6a is far more complex. We propose that the rearrangement begins with an acid-catalyzed cycloreversion of an oxetane ring as shown in Scheme 2.10. This proposed cycloreversion is supported by the fact that one of the products recovered from the acidolysis is the starting alkene 2a. This is followed by a 1,2-hydride shift to form B2 via a retro-pinacol rearrangement. A second 1,2-hydride shift occurs (B3) followed by a Grob fragmentation to form B4. Protolytic ring opening then proceeds with the capture of the carbocation by the formyl group, which is then hydrolyzed into the hemiacetal B7. The subsequent intramolecular electrophilic conjugate addition to the alkene in the bicyclo[2.2.2]diene gives 6a.
The beauty of this system lies in its rapid assembly and clean photoreactivity, resulting in a remarkable increase in complexity from the very simple and inexpensive starting materials (benzoquinone and cyclohexadiene). The utilization of a photochemical step in this modular synthetic sequence can give access to a unique highly strained C2-symmetric structure. Harvesting the strain in this bis-oxetane allowed for cationic rearrangements upon its protolytic ring opening, resulting in novel carbocyclic scaffolds. These products are a spectacular example of how photochemistry combined with conventional synthetic techniques can give expeditious access to highly complex polycyclic scaffolds. While the syntheses of some of these interesting polyheterocycles is
not quite preparative due to the low yield in the acidolysis step, the scheme gives a good deal of insight into the deep skeletal rearrangements a strained scaffold can do.

Experimental Procedures and Data

Common solvents were purchased from Pharmco Aaper and used directly, except for THF—which was refluxed over and distilled from potassium benzophenone ketyl prior to use—and hexane—which was distilled over calcium hydride. Common reagents were purchased from Sigma Aldrich, Acros, or TCI America and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25°C on a Bruker Avance III 500 MHz or Varian Mercury 400 MHz instrument in CDCl₃ with TMS as an internal standard (unless noted otherwise). X-Ray structures were obtained with a Bruker APEX II instrument. High resolution mass spectra were obtained on the MDS SCIEX/Applied Biosystems API QSTAR™ Pulsar i Hybrid LC/MS/MS System mass spectrometer by Dr. Shuji Kato or Dr. Dan Gu from the University of Colorado at Boulder. For the synthetic details, ¹H, ¹³C, COSY NMR spectra see supporting information.²⁷

\[ \text{1SR, 2RS, 4RS, 5SR, 8RS, 9SR, 11SR, 12RS-pentacyclo[10.2.2.2^{5,8}.0^{2,11}.0^{4,9}] octadeca-6,13-diene-3,10-dione (2a): A solution of 4.00 g of 1,4-benzoquinone (37.0 mmol) and 8.90 g of 1,3-cyclohexadiene} \]
(111.0 mmol) in 20 mL of 1,2-dichlorobenzene was heated in a Pyrex screw-cap pressure tube at 135-150°C for 24 h. The solvent was removed on a high vacuum pump and the crude reaction mixture was then recrystallized from hot CH$_3$CN: 9.71 g (98%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 6.30 (m, 4H), 2.96 (m, 4H), 2.76 (m, 4H), 1.55-1.48 (m, 4H), 1.30-1.25 (m, 4H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ = 210.9, 134.0, 53.8, 32.6, 24.7.

(4a) A solution of 3.00 g of 2a (11.2 mmol) in 2 L of CH$_3$CN was irradiated in a quartz reaction vessel in a Rayonet reactor equipped with RPR-3000 UV lamps (a broadband 250-350 nm UV source with peak emission at 300 nm) for 60 hours. Irradiation resulted in nearly quantitative conversion to 4a (90% by NMR), which was used without further purification. For characterization, oxetanes partially survived flash chromatography on a silica gel column pre-treated with 2 mL of pyridine with an eluent of hexane – EtOAc, 20:1→5:1.: (> 95% by NMR). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 4.39 (m, 1H), 2.86 (dddd, $J$ = 5.5, 3.6, 1.8, 1.8 Hz, 1H), 2.43 (d, $J$ = 2.1 Hz, 1H), 2.38 (m, 1H), 2.17-2.14 (m, 1H) overlaps with 2.13 (dddd, $J$ = 7.8, 4.1, 2.0, 2.0 Hz, 1H), 1.84 (dddd, $J$ = 13.9, 10.1, 10.1, 2.3 Hz, 1H), 1.70 (ddd, $J$ = 3.7, 10.0, 13.7 Hz, 1H), 1.59 (ddd, $J$ = 13.3, 9.7, 4.0 Hz, 1H), 1.18 (dddd, $J$ = 13.1, 10.0, 10.0, 1.9 Hz, 1H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ = 99.7, 83.6, 54.8, 46.0, 44.5, 38.4, 34.8, 23.2, 17.8. **This characterization was completed by Roman A. Valiulin.**
**Acidolysis:** To a solution of 1.18 g (4.4 mmol) oxetane 4a in 100 mL acetonitrile, 4.4 mL 4M HCl (solution in dioxane) was added. This was allowed to stir for 10 min at ambient temperature before quenching with saturated sodium bicarbonate (2 x 20 mL), extracting with dichloromethane (2 x 20 mL). The organic layers were combined and dried over anhydrous sodium sulfate before concentrating to remove the solvent. The residue was purified on a silica gel column using hexane–ethyl acetate (10:1, then 5:1, then the column was washed with ethanol).

![Chemical structure](image)

(5a): 32 mg, 2.4% (pure recovery). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 5.98 (dd, $J = 5.8$, 2.7 Hz, 1H), 5.94 (dd, $J = 5.7$, 2.7 Hz, 1H), 3.59 (d, $J = 2.1$ Hz, 1H), 3.13 (ddd, $J = 5.3$, 2.5, 2.5 Hz, 1H), 2.85 (m, 1H), 2.80 (s, 1OH), 3.67 (m, 1H) overlaps with 2.66-2.61 (m, 1H), 2.32-2.29 (m, 2H), 2.15-2.06 (m, 2H), 2.02 (dddd, $J = 10.5$, 5.4, 5.4, 2.1 Hz, 1H), 1.91-1.85 (m, 2H), 1.82 (m, 1H), 1.63-1.55 (m, 3H), 1.29 (ddd, $J = 13.3$, 11.0, 2.3 Hz, 1H), 1.22 (d, $J = 10.3$ Hz, 1H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ = 213.7, 133.9, 132.5, 87.6, 66.6, 59.4, 59.4, 52.4, 49.3, 45.0, 44.9, 42.7, 42.6, 40.3, 38.5, 32.2, 30.3, 23.7. HRMS (ESI) calcd for C$_{18}$H$_{21}$ClNaO$_2$ (MNa$^+$) 327.1122, found 327.1112.
(6a): 20 mg, 1.1% (pure recovery). $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 6.39$ (ddd, $J = 8.0$, 6.6, 1.2 Hz, 1H), 6.25 (ddd, $J = 8.0$, 6.5, 1.4 Hz, 1H), 5.25 (d, $J = 4.9$ Hz, 1H), 3.73 (d, $J = 3.1$ Hz, 1H), 2.68 (m, 1H), 2.63 (m, 1H), 2.54 (d, $J = 5.4$ Hz, 1H), 2.46 (m, 1H) overlaps with 2.42 (dddd, $J = 6.3$, 2.1, 2.1, 2.1 Hz, 1H), 2.17 (ddddd, $J = 12.5$, 9.9, 4.5, 2.4 Hz, 1H) overlaps with 2.12 (d, $J = 2.4$ Hz, 1H), 2.04 (m, 1H), 1.96 (dd, $J = 13.7$, 1.8 Hz, 1H) overlaps with 1.94-1.91 (m, 1H), 1.65 (ddd, $J = 13.7$, 3.5, 3.5 Hz, 1H), 1.59-1.51 (m, 3H) overlaps with 1.51-1.38 (m, 2H), 1.17 (ddddd, $J = 11.9$, 11.9, 4.3, 2.9, 2.9 Hz, 1H), 1.03 (dddd, $J = 12.4$, 12.4, 3.8, 3.8 Hz, 1H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta = 134.5$, 132.6, 101.8, 99.2, 79.6, 78.9, 48.5, 48.2, 43.7, 40.0, 38.8, 37.2, 32.7, 30.4, 25.2, 22.8, 22.1, 18.4. HRMS (ESI) calcd for C$_{18}$H$_{22}$NaO$_3$ $^+$ (MNa$^+$) 309.1461, found 309.1459.
Double-Tandem Sequence of 1,4-Naphthoquinone

Introduction

Another way we endeavored to introduce diversity into our armory of photosynthetic sequences was to utilize 1,4-naphthoquinone in reaction with cyclic dienes. Filipescu and Kushner independently showed that the Diels-Alder adduct of cyclopentadiene with 1,4-naphthoquinone (7a) is known to undergo intramolecular alkene-arene [2+2] cycloaddition. The product of this reaction (8a) also contains a diene whose subsequent Diels-Alder reaction with a dienophile is known to be facially selective. Coxon, Marchand, and others studied the facial selectivity of Diels-Alder additions to 8a, showing that the attack of unsaturated dienophiles occurs on the face nearer to the carbonyl groups. The scaffold resulting from these reactions is shown in Scheme 2.11.

Scheme 2.11: Cycloaddition sequence

We employed this facially selective reaction to install an aroyl chromophore capable of undergoing a photochemical Paternò-Büchi reaction with the neighboring
olefin, furnishing an oxetane which can undergo further transformation via oxametathesis.

**Results and Discussion**

This high-yielding reaction sequence comprises a double-tandem approach which combines both ground state chemistry and two photochemical cycloadditions, culminating in a [4+2]@[2+2]@[4+2]@[2+2] scheme. As it was mentioned before, the Diels-Alder adduct of 1,4-naphthoquinone with cyclopentadiene is known to undergo the alkene-arene intramolecular [2+2] photocycloaddition. Our attempt to do the same with the cyclohexadiene analog did not undergo the desired “cage” reaction, but instead led to endo/exo isomerization, which is preceded.\(^\text{34}\) However, the adduct derived from cyclopentadiene (99%, 7a), provided the diene (8a) in good yield (Scheme 2.12). We then subjected this diene the second Diels-Alder reaction of this sequence by generating vinyl methyl ketone in situ as the dienophile, giving 9a, the structure of which is proven by X-ray. This facially selective step orients the aroyl group near to the olefin, making it a good candidate for the final step of the double-tandem sequence, a photochemical Paternò-Büchi cycloaddition to give 10a.
The final photochemical step, which furnishes oxetane 10a, allows for the capture of a large amount of strain in 10a. With inexpensive starting materials, and high yields throughout, this sequence exhibits rapid growth in molecular complexity and expeditious access to a strained scaffold rich in stereocenters. This oxetane was then treated with HCl to promote protolytic alkene-carbonyl oxametathesis as shown in Scheme 2.1. When a catalytic amount of $\text{H}^+$ was present, the product of this oxametathesis step was an aldehyde which is easily epimerized and difficult to separate (11a and 11a'). When this reaction was performed in the presence of excess HCl (> 5 equiv) and excess ethylene glycol, a single epimer of the acetal (presumably the first epimer formed in the oxametathesis prior to isomerization) was captured and able to be purified. Surprisingly,
in addition to the protection of the formyl group, the “cage” ketone distal to the formyl group was also protected to form the ketal, 12a.

In fact, after the optimization of this process, it was found that the entire transformation from 10a to 12a could be performed in a one-pot fashion. This one-pot irradiation reaction was performed on NMR scale in CD$_2$Cl$_2$ by irradiating the sample in solution along with ethylene glycol and a catalytic amount of HCl, giving 12a as the sole product.

Through this study, which was performed in tandem with Roman A. Valiulin (he was employing chromones rather than 1,4-naphthoquinone as the initial dienophile$^{33}$), it
was found that in the presence of *excess* HCl or BF$_3$-Et$_2$O, a secondary electrophilic addition of a proton to the styrene takes place, generating a benzylic cation which is intramolecularly intercepted by the local enol tautomer of the formyl group initially formed in the oxametathetic step (Scheme 2.14), furnishing the shown product containing a formylcyclopropane structure (13a). This process is halted by the acetal protection of the formyl in the presence of ethylene glycol, supporting the proposed mechanism in which the aldehyde (11a and 11a’) is an intermediate. Additionally, an epimeric mixture of the aldehyde products treated with an excess of acid, the mixture was entirely converted into 13a, functionally “purifying” the epimers into a single product.

**Scheme 2.14:** Mechanism for formylcyclopropane formation

During the study of this reaction series, there was a fortuitous discovery—extended irradiation in samples which were not properly degassed resulted in an oxidized product which contained an oxirane ring. We were able to accelerate and optimize this
reaction by performing the irradiation after bubbling the samples with O$_2$. The concentration of oxygen under 1 atm of O$_2$ gas in benzene is 10 mM.$^{35}$ While the photoepoxidation of olefins in the presence of organic sensitizers or transition metal complexes are well known,$^{36}$ the direct, nonsensitized photoreactions between vinyl arenes and molecular oxygen are very rare. Only one study was found which proposed a charge-transfer pair mechanism of such in 1-arylcyclohexenes, and the reported yield was poor.$^{37}$

The chromophore for the photoepoxidation reaction is the styrene (the olefin in 13a). While ordinarily this excitation is rapidly dissipated via rotation, these rigid polycyclic networks prevent such relaxation and improve the efficiency of the epoxide formation, likely via the interaction with singlet oxygen. In addition to assisting in the oxirane formation, the rigid and congested scaffold directs the stereochemistry resulting in complete facial selectivity of the reaction.

![Scheme 2.15: Photoepoxidation](image)

These scaffolds are another example of highly unique structures achieved with a modular approach employing high-yielding conventional and photosynthetic techniques.
The double-tandem \([4+2] \cdot [2+2] \cdot [4+2] \cdot [2+2]\) sequence employs two photochemical steps which assist in the construction of the topologically diverse products.

**Experimental Procedures and Data**

Common solvents were purchased from Pharmco Aaper and used directly, except for THF—which was refluxed over and distilled from potassium benzophenone ketyl prior to use—and hexane—which was distilled over calcium hydride. Common reagents were purchased from Sigma Aldrich, Acros, or TCI America and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25°C on a Bruker Avance III 500 MHz or Varian Mercury 400 MHz instrument in CDCl₃ with TMS as an internal standard (unless noted otherwise). X-Ray structures were obtained with a Bruker APEX II instrument. High resolution mass spectra were obtained on the MDS SCIEX/Applied Biosystems API QSTAR™ Pulsar i Hybrid LC/MS/MS System mass spectrometer by Dr. Shuji Kato or Dr. Dan Gu from the University of Colorado at Boulder. For the synthetic details, \(^1\)H, \(^{13}\)C, COSY NMR spectra see the supporting information document in ref 27.

**endo-4-(Cyclohex-2-enyl)-1,2-naphthoquinone (7a’):** 1.0 g of 1,4-naphthoquinone (6.3 mmol) and 0.97 g of 1,3-cyclohexadiene (12.1 mmol) in 20 mL of 1,2-dichlorobenzene at 150 °C (hexane/EtOAc 25:1 f 10:1): 0.75 g (50%). \(^1\)H NMR (400 MHz, CDCl₃): δ 8.15 (dd, \(J = 7.6, 1.5\) Hz, 1H), 7.69-7.61 (m, 2H), 7.50 (ddd, \(J = 7.4, 7.4,\)
1.4 Hz, 1H), 6.43 (s, 1H), 6.04 (dddd, J = 9.9, 3.8, 3.8, 2.1 Hz, 1H), 5.60 (dddd, J = 10.1, 3.1, 2.3, 2.3 Hz, 1H), 3.72 (m, 1H), 2.10 (m, 3H), 1.67 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 181.1, 180.1, 160.6, 135.7, 134.8, 132.0, 131.3, 130.72 overlaps with 130.71, 127.0, 126.6, 126.0, 37.2, 29.0, 25.1, 20.2. HRMS(ESI): calcd for C$_{16}$H$_{14}$NaO$_2^+$ (MNa$^+$) 261.0886, found 261.0896.

**endo-4,5-Benzotricyclo[6.2.1.0$^{2,7}$]undec-9-ene-3,6-dione (7a):** A solution of 5.70 g of 1,4- naphthoquinone (36.0 mmol) and 4.76 mL of freshly distilled 1,3-cyclopentadiene (72.2 mmol) was stirred in dichloromethane at ambient temperature for 1 h. Removal of the dichloromethane and excess 1,3-cyclopentadiene by high vacuum gave 7.21 g (99%). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.00 (m, 2H), 7.67 (m, 2H), 5.95 (t, J = 1.8 Hz, 2H), 3.64 (m, 2H), 3.43 (dd, J = 2.5, 1.5Hz, 2H), 1.56-1.49 (m, 2H).

**Hexacyclo[5.4.4.0$^{2,6}$,03,13.05,14]pentadeca-8,10-diene-12,15-dione (8a):** A solution of 1.35 g of 7a (6.0 mmol) in 1.0 L of DCM was irradiated in a Pyrex reaction vessel in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with a peak emission at 350 nm) for 24 h. Removal of the solvent via distillation gave 1.30 g (96%). $^1$H NMR (500 MHz, CDCl$_3$): δ 5.99 (m, 2H), 5.40 (m, 2H), 3.36 (m, 2H), 3.01 (m, 2H), 2.82 (m, 2H), 2.01 (d, J = 11.4 Hz, 1H), 1.78 (d, J = 11.4 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 210.5, 124.9, 120.0, 54.8, 51.8, 50.4, 44.4, 39.2.
Benzoylheptacyclo-[9.2.2.1^{2,5}.1^{7,10}.0^{2,4,8,0^{16,17}}]heptadec-12-ene-3,9-dione (9a): A solution of 1.30 g of 8a (5.8 mmol) and 0.98 g of 3-chloropropiophenone (5.8 mmol) was heated in a screw-cap pressure flask at 140°C for 12 h. After the reaction was cooled to room temperature, the solvent was removed on a high vacuum pump. The crude reaction mixture was purified on a silica gel flash column using hexane/EtOAc gradient 10:1 → 1:1 as the eluent: 1.94 g (94%). $^1$H NMR (400 MHz, CDCl$_3$): δ 8.07 (d, $J = 7.1$ Hz, 2H), 7.51 (t, $J = 7.3$ Hz, 1H), 7.44 (t, $J = 7.5$ Hz, 2H), 6.45 (ddd, $J = 8.2$, 6.9, 1.1 Hz, 1H), 6.24 (ddd, $J = 8.1$, 6.7, 1.3Hz, 1H), 4.10 (ddd, $J = 10.0$, 5.5, 1.9 Hz, 1H), 3.06 (ddd, $J = 6.6$, 1.9, 1.3Hz, 1H), 2.86 (m, 2H), 2.81 (ddddd, $J = 6.8$, 2.8, 2.8, 1.3Hz, 1H), 2.74, (d, $J = 2.1$ Hz, 2H), 2.62 (m, 2H), 2.26, (ddd, $J = 12.8$, 10.0, 2.6 Hz, 1H), 1.95 (d, $J = 11.2$ Hz, 1H), 1.78 (d, $J = 11.3$ Hz, 1H), 1.71 (ddd, $J = 13.0$, 5.5, 3.1 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 213.4, 212.8, 201.0, 136.2, 134.5, 133.1, 131.2, 129.1, 128.8, 56.3, 56.2, 54.6, 54.4, 43.9, 43.7, 42.2, 42.0, 41.1, 39.8, 34.3, 31.2, 23.4. HRMS (ESI): calcd for C$_{24}$H$_{21}$O$_3$ $^+$ (MH$^+$) 357.1485, found 357.1479.
**14-Phenyl-13-oxanonacyclo[9.4.2.1\(^{2,5}\)\(^{17,10}\)\(^{0}\)\(^{12,15}\)\(^{0}\)\(^{14,17}\)\(^{0}\)\(^{18,19}\)]nonadecane-3,9-dione (10a):** 0.74 g of 9a (2.1 mmol) was dissolved in 0.5 L of benzene and irradiated in a Pyrex reaction vessel in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with a peak emission at 350 nm) for 72 h. Removal of the solvent gave via distillation gave 0.68 g (92%). \(^1\)H NMR(500MHz,CDCl\(_3\)): δ 7.37-7.31 (m, 5H), 4.90 (ddd, \(J = 3.7, 1.9, 0.8\)Hz, 1H), 3.46 (ddddd, \(J = 5.5, 3.5, 1.7, 1.7\)Hz, 1H), 3.03 (dd, \(J = 8.1, 6.3\)Hz, 1H), 2.99-2.94 (m, 2H), 2.91 (m, 1H), 2.75 (m, 1H) overlaps with 2.74 (m, 1H), 2.68 (dd, \(J = 6.6, 1.8, 1.8\)Hz, 1H), 2.13 (ddd, \(J = 7.0, 5.8, 1.3\)Hz, 1H), 2.04 (d, \(J = 11.4\) Hz, 1H), 1.91 (ddd, \(J = 13.4, 7.1, 2.0\) Hz, 1H) overlaps with 1.87 (d, \(J = 11.5\) Hz, 1H), 1.55 (m, 1H) overlaps with HOD, 1.44 (dd, \(J = 13.4, 1.9\) Hz, 1H). \(^1\)HNMR (500MHz, C\(_6\)D\(_6\)): δ 7.32 (m, 2H), 7.15-7.12 (m, 2H), 7.08 (m, 1H), 4.54 (ddd, \(J = 3.6, 1.9, 0.9\)Hz, 1H), 3.14 (m, 1H), 2.74 (d, \(J = 6.7\) Hz, 1H), 2.64 (ddd, \(J = 6.6, 1.7, 1.7\) Hz, 1H), 2.27 (m, 2H), 2.14-2.04 (m, 4H), 1.95-1.89 (m, 2H), 1.74 (d, \(J = 11.3\) Hz, 1H), 1.19 (d, \(J = 11.0\) Hz, 1H), 1.08 (d, \(J = 11.0\) Hz, 1H).

**1SR, 2RS, 5RS, 6RS, 7SR-13,16-Dioxo-4-phenylheptacyclo[5.5.4.1\(^{2,5}\)\(^{0}\)\(^{17}\)\(^{8,12}\)\(^{0}\)\(^{9,15}\)\(^{0}\)\(^{11,14}\)]heptadec-3-ene-6-carboxaldehyde (11a):** To a solution of 100 mg (0.28 mmol) of 4d in 5 mL dichloromethane, 0.09 mL of HCl (4.0 M in dioxane, 0.34
mmol) was added and stirred for 12 h at ambient temperature. It was then washed with a 5% solution of NaOH (2 x 5 mL), and water (1 x 5 mL). The crude aldehyde was purified on a silica gel column with hexane/EtOH 10:1 as the eluent. This gave an inseparable mixture of 11a and 11a’ (2:3). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta\) 9.17 (s, 1H), 7.20 (d, \(J = 7.8\) Hz, 2H), 7.11 (t, \(J = 7.4\) Hz, 2H), 7.09-7.03 (m, 1H), 5.93 (d, \(J = 3.1\) Hz, 1H), 3.12 (d, \(J = 4.1\) Hz, 1H), 3.09 (dd, \(J = 5.7, 4.4\) Hz, 1H), 2.82 (dd, \(J = 9.1, 5.4\) Hz, 1H), 2.69 (dd, \(J = 5.0, 3.3\) Hz, 1H), 2.52-2.49 (m, 2H), 2.33 (ddd, \(J = 10.3, 4.1, 2.1\) Hz, 1H), 2.14 (ddd, \(J = 9.0, 5.8, 1.8\) Hz, 1H), 2.11-2.05 (m, 2H), 1.49 (d, \(J = 11.1\) Hz, 1H), 1.28-1.23 (m, 2H).

1SR, 2RS, 3SR, 6RS, 7SR-13,16-Dioxo-4-phenyloctacyclo[5.5.4.1\(^{3,6}\).0\(^{1,7}\).0\(^{2,4}\).0\(^{8,12}\).0\(^{9,15}\).0\(^{11,14}\)]heptadecane-2-carboxaldehyde (12a): To a solution of 170 mg (0.48 mmol) of 10a in 10 mL dichloromethane, 0.30 mL of BF\(_3\)-Et\(_2\)O (48%, 2.38 mmol) was added and allowed to stir at 12 h at ambient temperature. This reaction mixture was then washed with a 5% solution of NaOH (2 x 5 mL), and water (1 x 5 mL). The crude aldehyde was purified on a silica gel column with hexane/EtOH gradient 20:1\(\rightarrow\)10:1 as the eluent. 80 mg (47%); OR To a solution of 100 mg (0.28 mmol) of 11a and 11a’ in 5 mL dichloromethane, 0.14 mL of HCl (4.0 M in dioxane, 0.56 mmol) was added and allowed to stir for 12 h at ambient temperature. This reaction mixture was then washed with a 5% solution of NaOH (2 x 5 mL), and water (1 x 5 mL). The crude mixture was purified on a silica gel column with hexane/EtOH gradient 20:1\(\rightarrow\)10:1 as the eluent: 61 mg (61%). \(^1\)HNMR(500 MHz,CDCl\(_3\)): \(\delta\) 8.85 (s, 1H), 7.31 (d, \(J = 4.3\) Hz, 4H), 7.27-7.23 (m, 1H) overlaps with CDCl\(_3\), 3.27 (m, 1H) overlaps with 3.26-3.22 (ddd,
$J = 8.2, 5.7, 1.7 \text{ Hz, 1H}$, 3.01 (ddd, $J = 7.8, 6.0, 1.6 \text{ Hz, 1H}$), 2.86 (m, 1H) overlaps with 2.86-2.83 (ddd, $J = 10.4, 4.0, 1.8\text{ Hz, 1H}$), 2.76-2.73 (ddd, $J = 10.3, 4.1, 1.6 \text{ Hz, 1H}$) overlaps 2.75 (m, 1H), 2.52 (d, $J = 13.1 \text{ Hz, 1H}$), 2.22-2.17 (m, 2H), 2.10 (dd, $J = 13.1, 5.5 \text{ Hz, 1H}$), 2.06 (d, $J = 11.3\text{ Hz, 1H}$), 2.00 (d, $J = 12.5\text{ Hz, 1H}$), 1.93 (d, $J = 11.3 \text{ Hz, 1H}$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 212.3, 210.7, 199.3, 138.1, 129.2, 129.0, 127.8, 56.5, 55.4, 54.1, 48.5, 44.9, 44.5, 43.9, 42.6, 41.8, 41.0, 38.9, 38.4, 30.5, 29.8, 28.9. HRMS(ESI): calcd for C$_{24}$H$_{21}$O$_3^+$ (MH$^+$) 357.1485, found 357.1477.

13-Ethylene Glycol Monoacetel of 1SR, 2RS, 5RS, 6RS, 7SR-6-(1,3-dioxolan-2-yl)-4-phenylheptacyclo[5.5.4.1$^{2,5}.0^{1,7,0^{8,12,0^{9,15,0^{11,14}}}}$]heptadec-3-en-16-one (13a): To a solution of 360 mg (1.01 mmol) of 10a in an ethylene glycol/THF mixture (10:3; 10 mL), 1.26 mL of HCl (4.0 M in dioxane, 5.05 mmol) was added. This reaction mixture was then washed with a 5% solution of NaOH (2 x 5 mL), and water (1 x 5 mL). The crude aldehyde was purified on a silica gel column (treated with 2mL pyridine) with hexane/EtOH gradient 10:1 $\rightarrow$ 5:1 as the eluent. 229 mg (51%).

$^1$HNMR(500MHz,CDCl$_3$): $\delta$ 7.62 (d, $J = 7.2\text{ Hz, 2H}$), 7.30 (t, $J = 7.6\text{ Hz, 2H}$), 7.20 (t, $J = 7.3\text{ Hz, 1H}$), 6.54 (d, $J = 3.6 \text{ Hz, 1H}$), 4.53 (d, $J = 9.0 \text{ Hz, 1H}$), 3.96-3.88 (m, 5H), 3.71-3.62 (m, 2H), 3.53-3.49 (m, 1H), 3.31 (dd, $J = 5.6, 4.6\text{ Hz, 1H}$), 2.81 (dd, $J = 5.0, 3.6 \text{ Hz, 1H}$), 2.62 (m, 1H), 2.59-2.48 (m, 6H), 2.10 (ddd, $J = 10.8, 5.5, 5.5\text{ Hz, 1H}$), 1.80 (d, $J = 10.9 \text{ Hz, 1H}$), 1.62 (d, $J = 10.5 \text{ Hz, 1H}$), 1.54 (d, $J = 10.9 \text{ Hz, 1H}$).

$^{13}$CNMR(125MHz,CDCl$_3$): $\delta$ 215.8, 147.3, 136.4, 130.7, 128.5, 127.5, 126.2, 114.6,
104.2, 66.3, 65.5, 64.7, 64.3, 54.3, 51.5, 50.6, 47.5, 44.2, 44.2, 42.7, 40.0, 39.2, 39.0, 38.8, 38.1, 37.1. HRMS (ESI): calcd for C_{28}H_{28}NaO_5^+ (MNa^+) 467.1829, found 467.1822.

13-Ethylene Glycol Monoacetal of 1SR, 2RS, 5RS, 6RS, 7SR-6-(1,3-dioxolan-2-yl)-4-phenylheptacyclo[5.5.4.1^{2,5}.0^{1,7},0^{8,12},0^{9,15},0^{11,14}]heptadec-3-en-16-one (13a): from 9a (NMR experiment). To 5 mg (14 μmol) of 3d dissolved in 0.6 mL of CD_2Cl_2 in a Pyrex NMR tube were added 4 μL (71 μmol) of ethylene glycol and 17 μL of 4 M HCl/dioxane. The solution was irradiated with RPR-3500 lamps (λ_{max}=350 nm) until the starting material was consumed (ca. 3-4 h). At the end of the experiment NMR of the reaction mixture contained only peaks of 13a, described in the preceding experiment.

13-Ethylene Glycol Monoacetal of 1S(R), 2S(R), 3S(R), 5S(R), 6R(S), 7S(R)-7-(1,3-Sioxolan-2-yl)-5-phenyl-4-oxaoctacyclo-
[6.5.4.1^{2,6}.0^{1,8},0^{3,5},0^{9,13},0^{10,16},0^{12,15}]octadecane-14,17-dione (14a): 180 mg of 13a (0.40 mmol) dissolved in 100 mL of benzene (4 mM) irradiated for 48 h, solvent was evaporated, and the crude product was purified by column chromatography on silica gel
(gradient hexane [0→100% EtOAc]): 150 mg (82%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.55 (d, $J = 6.8$ Hz, 2H), 7.40-7.32 (m, 3H), 4.12 (s, 1H), 4.09 (d, $J = 9.2$ Hz, 1H), 3.99-3.84 (m, 5H), 3.96-3.88 (m, 5H), 3.62 (ddd, $J = 12.0$, 6.3, 6.3Hz, 1H), 3.48-3.39 (m, 2H), 3.18 (ddd, $J = 9.2$, 5.6, 1.6 Hz, 1H), 3.05 (dd, $J = 5.3$, 5.3 Hz, 1H), 2.76 (m, 1H), 2.66 (ddd, $J = 9.0$, 4.7, 2.2 Hz, 1H), 2.61-2.51 (m, 5H), 1.89 (d, $J = 10.8$ Hz, 1H), 1.81 (ddd, $J = 11.2$, 5.6, 5.6Hz, 1H), 1.67 (d, $J = 10.8$Hz, 1H), 1.08 (d, $J = 11.2$Hz,1H). $^{13}$C NMR (125MHz, CDCl$_3$): $\delta$ 214.1, 136.3, 128.9, 128.6, 114.5, 102.2, 66.21, 66.17, 65.4, 64.4, 63.9, 59.6, 55.0, 53.5, 50.2, 46.8, 44.8, 42.4, 41.7, 40.3, 39.3, 38.9, 36.1, 32.6, 28.2. HRMS (ESI): calcd for C$_{28}$H$_{28}$NaO$_6$\(^+\) (MNa\(^+\)) 483.1778, found 483.1786.
Chapter 3: Tethered γ- and δ-oxetanes.

Introduction

In the previous chapters, oxetanes were formed and transformed via oxametathesis from fused polycyclic scaffolds. Our success with the oxetane-cage adducts led to the consideration of additional Paternò-Büchi competent structures. Prior studies showed that endo-carbonyl and endo-aroyl photoprecursors in which the bicycle is directly attached to the carbonyl yield only one type of oxetane, shown in Scheme 3.1. Also shown is the resulting scaffold from the protolytic oxametathesis reaction.

![Scheme 3.1: Oxetane formation, bicyclic structure with endo-carbonyls attached](image)

However, when a scaffold is tethered to a benzoyl chromophore via a methylene group (see Scheme 3.2), this more flexible linker can allow the resulting oxetane to have a different regiochemistry, which we have termed γ- and δ-oxetanes, with α- being the attachment point of the phenacyl pendant to the bicyclic core.

Our aim was to develop a modular design of the photoprecursors and evaluate the viability of this design as a diversity-oriented synthetic scheme. As such, we explored
how variations in the diversity inputs changed the photoreactivity of the Paternò-Büchi step and how these variations manifested in the regio- and stereochemistry of the subsequent oxametathesis transformation.

Scheme 3.2: Longer tether; two photoproducts

Results and Discussion

The Diels-Alder reaction of cyclohexadiene with methyl propiolate is an efficient coupling step which gives 1b, a product that is a good target for Michael addition. In this case, the nucleophile is an aroyl enolate, shown in Scheme 3.3. This furnishes a benzoyl-containing chromophore which can be irradiated to undergo a Paternò-Büchi reaction with the olefin in the bicyclo[2.2.2] scaffold. Of the diastereomers produced in the Michael reaction, we were primarily interested in the endo-phenacyl isomers, which were isolable. This reaction is equally successful when the initial diene is cyclopentadiene, but the greater steric crowding provided by the 2-carbon bridge from the cycloaddition to cyclohexadiene provides a greater amount of endo- bias during the Michael addition of the enolate to the Diels-Alder adduct.
Scheme 3.3: Michael addition (only endo phenacyl shown)

**Acetophenone-derivatives**

Scheme 3.4 shows 2b, a bicyclo[2.2.2]octane system resulting from the addition of acetophenone to 1b in which the methoxycarbonyl is exo-trans to the photoreactive phenacyl pendant which is situated on the endo-face of the molecule (37%). We propose that the regiochemistry of the [2+2] photocycloaddition reflects some intrinsic properties of the system. In this case, upon the irradiation of 2b, oxetanes 3b and 4b form in nearly 1:1 ratio, indicating that with this tether there is no immediately obvious bias for cyclization. Because of subsequent examples in which hydrogen abstraction reactions are observed—successfully competing with the Paternò-Büchi channel, it is most likely that this photochemistry arises from the triplet state of the aroyl pendants. Thus, we propose that this reaction proceeds via intersystem crossing to the triplet state, forming diradical intermediate, as is typically the case of aroyl chromophores. The 1,4-diradical isomers leading to the oxetane products can be classified as exo-trig (e.g. 2b-1) and endo-trig (e.g. 2b-2)—the exo-trig resulting in the γ products and the endo-trig the δ products.
Scheme 3.4: 1,4-diradicals in endo- and exo-trig conformations

In general, these oxetanes are not stable on silica gel during purification and only the δ-oxetane 4b was able to be purified and fully characterized, including via X-ray crystallographic analysis. In fact, the γ-oxetane was so fragile that during irradiation, it is only observed by NMR when the irradiation is carried out at 0°C—otherwise, the oxetane undergoes oxametathesis in situ. Although the γ-oxetane was observed in these low temperature conditions, it rapidly underwent oxametathesis during any attempts at purification. Unsurprisingly, the ratio of δ-oxetane to γ-oxetane was quite different at 0°C than at ambient temperature, 1:2 and 1:1 respectively (as measured by ¹H NMR integration). When the sample was irradiated at ambient temperature, we could only indirectly measure the ratio of δ-oxetane to γ-oxetane from the mass balance of the recovered products after oxametathesis. Figure 3.1 shows the characteristic oxetane peaks which were observed in the ¹H NMR spectrum. The assignment of the δ-oxetane vs γ-oxetane “fingerprint” peaks is supported by predicted spectra calculated at the B3LYP/6-311+G(d,p) level of theory.
Figure 3.1: δ- and γ- “fingerprint” $^1$H NMR peaks; 0°C irradiation

Figure 3.2: Calculated γ (above) and δ (below) oxetane peaks

Also observed during irradiation was an undesired Norrish II side reaction. In this reaction, the excited chromophore (likely in the triplet state) abstracts the γ-hydrogen
which is $\alpha$ to the ester group. The resulting 1,4-diradical then fragments into the starting materials, shown in Scheme 3.5. For the photoprecursor 2b, these Norrish II byproducts were formed in a 1:2 ratio with the desired oxetanes at ambient temperature.

Scheme 3.5: Norrish type II fragmentation

Scheme 3.6: Oxemetathesis; aldehyde products
Under the conditions of protolytic oxametathesis (or uncatalyzed fragmentation in the case of 3b), these δ- and γ-oxetanes form the aldehydes \((5b' \text{ and } 6b')\) shown in Scheme 3.6. Since these aldehydes are easily epimerized in the acidic reaction conditions, the preferred reaction procedure for the oxametathesis step involved trapping the aldehydes in cyclic acetals, 1,3-dioxolanes 5b and 6b by performing the cycloreversion in the presence of ethylene glycol in a one-pot fashion; Scheme 3.7. These structures were not directly proven with X-ray analysis, but were able to be assigned by both analogy to proven structures and by careful analysis of the coupling constants by NMR.

![Scheme 3.7: One-pot Paternò-Büchi and oxametathesis](image)

During the one-pot procedure, only a small amount of the γ-product 5b isolated with reasonable purity. We found that this was due to a surprising side-reaction which occurs during the irradiation. We do not at this time propose a formal mechanism, but it believed to proceed with the assistance of dissolved O₂. Three separate products formed which were oxidized in the allylic position.
The addition of singlet oxygen (generated in photochemical conditions with the assistance of a sensitizer such as acenaphthenequinone or tetraphenylporphine) to an olefin via an ene-type mechanism is precedent.\textsuperscript{14,41} While product in the examples referenced are all peroxides, it is conceivable that in our examples, singlet oxygen added in a similar fashion, but decomposed to give the alcohol rather than the peroxide (see Scheme 1.8). While these reaction conditions did not contain a sensitizer to assist the generation of singlet oxygen, many reaction schemes employ aroyl compounds as sensitizers—and it happens that our initial chromophore for the Paternò-Büchi reaction is indeed an aroyl species and could be acting as a sensitizer.

In all, this tethered system derived from acetophenone provides the conformational flexibility necessary for the formation of both δ- and γ-oxetanes whose photoprotolytic transformation provides rapid access to diverse polycycles decorated with a variety of rigidly held functional groups.
**Propiophenone Derivatives**

When the enolate of propiophenone is used in the Michael addition, several diastereomers are formed, and only those which possess an *endo*-aroyl group should be Paternò-Büchi competent. We were able to isolate several of the isomers, with the *trans*-diastereomer possessing *endo*-phenacyl and *exo*-methoxycarbonyl groups being the major product (10b).

![Scheme 3.9: endo-phenacyl isomers of propiophenone addition](image)

When subjected to Paternò-Büchi conditions followed by oxametathesis, 10b showed high regioselectivity. The irradiation reaction exclusively produced the δ-oxetane 14b (>95% by $^1$H NMR) which was able to be purified and isolated in 65% yield—the reduction in yield is due to the precedent fragility of oxetanes on silica gel. Since the length of the tether in 10b is identical 2b, the *initial* conformational bias is likely due to the lower energy ground state conformation in which the benzoyl and methyl group are “out” (i.e., the hydrogen is “in,” see Newman projection in **Scheme 3.10**). Thus we posit that the formation of the oxetane proceeds with the least motion of the excited chromophore relative to the olefin in the bicyclic core, when the lowest energy ground state conformation is considered (i.e., the hydrogen is under the bicyclic framework).
The protolytic ring opening of 14b required that the temperature be elevated to 70°C due to an elimination reaction at ambient temperature. The structure of 16b was unambiguously proven via X-ray crystallographic analysis. The structure of 15b was determined via careful analysis of NMR constants, mechanistic interpretation, and analogy to the acetophenone-derived analog, 6b. As expected, only the fused ring product is formed from 14b.

The “least motion” hypothesis for the formation of solely the δ-oxetane from 10b is supported by an NMR experiment. The first example is the irradiation of 11b, which is
diasteromeric to 10b with respect to the position of the methyl group. Additionally, a sample of 12b was irradiated, which has the same tether stereochemistry (i.e., “methyl-in”) as 11b but has the ester cis- to the endo-aroyl group. The irradiation of these adducts resulted in the γ-oxetane in both cases. 12b to 18b was able to be observed directly and the spectrum contained the characteristic “gamma” peak (referenced in Figure 3.1). Similarly, 11b was irradiated (albeit, in a mixture with another compound), and the gamma product was observed in the mixture (17b). Thus it is our hypothesis that the lowest energy configuration of the starting material introduces sufficient steric constraint to control which oxetane is formed.

**Scheme 3.12**: Isomers which form γ-oxetanes

**Calculations**

In the aforementioned acetophenone system in which the δ- and γ-oxetanes are produced in 1:1 ratio (at ambient temperature), calculations showed that the δ-oxetane 4b is approximately 11 kcal/mol more stable than the γ-oxetane 3b (B3LYP/6-311+G(d,p), Gaussian 09, A.02). When the stability of the diradicals 2b-1 and 2b-2 is considered, the γ-diradical is 6.6 kcal/mol more stable than the δ-diradical. Their 1:1 ratio implies that while the γ-diradical may be forming to a greater extent, it less often closes into the 4-

**See SI from [42] for full reference and computational details; Calculations were run by Dr. Andrei Kutateladze.**
membered ring due to the greater strain associated with the γ-oxetane. Because of the unfavorable energetics for the formation of the γ-oxetane, we propose that the γ-diradicals partition into the back reaction to form the starting material more frequently than do the δ-diradicals, which more readily collapse into the oxetane. Because of this partitioning of the γ-diradicals, the two trends of the more stable γ-diradical vs. the more stable δ-oxetane cancel each other out. This is perhaps why a 1:1 ratio is observed. The 0°C experiment in which there was a 1:2 ratio of δ-oxetane to supports this hypothesis. At lower temperature, it follows that the kinetically favored γ-oxetane would form more frequently than the thermodynamically favored δ-oxetane.

Figure 3.3: NMR spectra; (bottom) 12b in C₆D₆, no irradiation; (top) irradiated 10 min, 18b
However, when the methyl group is introduced on the tether via the addition of propiophenone in 10b, the diastereomeric changes introduced into the tether alter the stability of the radical intermediates. The calculations show that the energy difference for the δ- vs γ-diradicals formed from 10 is only 2.8 kcal/mole in favor of the γ-diradical 10b-1 (δ-diradical is 10b-2), but the δ-oxetane is still ~11 kcal/mole more stable than the γ-oxetane (calculations not shown on table). With the smaller energy gap in the stability of the diradicals, the bias is not likely due to the divergent population of the δ- vs γ-intermediates. We must then assume that the methyl group reduces rotational freedom of the tethered endo-phenacyl group, and it is this rotational constraint that gives bias to the productive formation of 14b and the likely decay of the γ-diradical back to the ground state without the formation of a product.

Scheme 3.13: Least motion hypothesis; γ-diradical does not give the oxetane

In addition, for the photochemical reaction of 11b and 12b, which formed exclusively the γ-oxetanes, the γ- vs- δ-diradical stability changes yet again, with γ-being more stable in both cases; 7.8 kcal/mol and 7.3 kcal/mol respectively. The δ-oxetane is again the thermodynamically favored product in both cases, but the rotational barrier due to the methyl group combined with the slightly increased energy penalty of the δ-
diradical seems to create enough system bias that $\gamma$-oxetanes 17b and 18b are the only products of irradiation.

![Diagram](image)

**Table 3.1:** B3LYP/6-311+G(d,p), Gaussian 09, evision A.02, from [33]

This modular reaction scheme gave a great deal of insight into how perturbations in the tether of these endo-phenacyl compounds alters the regiochemistry of the products in the photochemical step. Additionally, this is another example in which the simple, inexpensive starting materials are transformed into much more highly complex polyheterocyclic scaffolds which have a variety of functional groups rigidly held about the framework. While the introduction of the methyl group in the tether complicated the isolation yield of the photoprecursors, the tether itself allowed the system to demonstrate complete regioselectivity in the product.
Experimental Procedures and Data

Common solvents were purchased from Pharmco Aaper and used directly, except for THF—which was refluxed over and distilled from potassium benzophenone ketyl prior to use—and hexane—which was distilled over calcium hydride. Common reagents were purchased from Sigma Aldrich, Acros, or TCI America and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25°C on a Bruker Avance III 500 MHz or Varian Mercury 400 MHz instrument in CDCl₃ with TMS as an internal standard (unless noted otherwise). X-Ray structures were obtained with a Bruker APEX II instrument. High resolution mass spectra were obtained on the MDS SCIEX/Applied Biosystems API QSTAR™ Pulsar i Hybrid LC/MS/MS System mass spectrometer by Dr. Shuji Kato or Dr. Dan Gu from the University of Colorado at Boulder. For the ¹H, ¹³C, COSY NMR spectra which are not included in Appendix A, see supporting information from ref. [42].

Methyl bicyclo[2.2.2]octa-2,5-diene-2-carboxylate (1b): A solution of propiolic acid methyl ester (3.0 mL of propiolic acid methyl ester, 33.6 mmol) and 1,3-cyclohexadiene (7.5 mL of 1,3-cyclohexadiene 78.7 mmol) in 10 mL of 1,2-dichlorobenzene was heated in a screw-cap pressure vessel at 70–75°C overnight. After the reaction was cooled to room temperature, the solvent was removed on a high vacuum pump. The crude reaction mixture was purified on a silica gel column using a mixture of hexane and EtOAc as an eluent.: 5.17 g (88%). ¹H NMR (500 MHz, CDCl₃) δ = 7.29 (dd, J = 6.4, 1.9 Hz, 1H), 6.38 (ddd, J = 7.4, 6.1, 1.5 Hz, 1H), 6.27 (ddd, J = 7.3, 5.9, 1.5 Hz, 1H), 4.20 (m, 1H), 3.76 (m, 1H), 3.73 (s, 3H), 1.38–1.29 (m, 4H).
Michael Addition

General Procedure: Fresh LDA (1.8 M solution, 1.3 equiv) was added under nitrogen atmosphere to the solution of an aroyl compound (1.0 equiv; acetophenone or propiophenone) in THF at 0 °C. After the anion was generated (in 20–30 min), the Diels–Alder adduct (1–6) was added (1.0 equiv) and the solution was allowed to warm to ambient temperature. The resulting mixture was stirred for 10–20 h. After the reaction was completed DCM was added, and the resulting mixture was quenched with NH₄Cl and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄ and removed under a vacuum. The crude mixture was purified on a silica gel column using a mixture of hexane and EtOAc as an eluent. In some cases, LDA was prepared via diisopropylamine (1.4 eq) dissolved in THF at -10°C, then n-BuLi was added (1.6 M solution in hexanes, 1.2 eq) and stirred for 20 min, then the aroyl compound was added to this mixture). The same procedure outlined above was followed after this point.

Methyl endo-5-phenacylbicyclo[2.2.2]oct-2-ene-exo-6-carboxylate (2b): From 10.7 mL of LDA (1.8 M solution, 19.18 mmol), 1.75 mL of acetophenone (15.06 mmol) and 2.25 g of 1b (13.70 mmol) (hexane/EtOAc gradient 50:1 → 10:1): 1.40 g (37%). ¹H NMR (500 MHz, CDCl₃) δ = 7.95 (d, J = 8.1 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 6.40 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H), 6.25 (t, J = 7.1 Hz, 1H), 3.74 (s, 3H), 2.91 (dd, J = 16.3, 7.6 Hz, 1H), 2.86–2.80 (m, 2H), 2.77 (dddd, J = 12.7, 5.4, 1.8, 1.8 Hz, 1H), 2.54 (m, 1H), 2.07 (dt, J = 5.4, 2.3 Hz, 1H), 1.73–1.62 (m, 2H), 1.34–1.27 (m, 1H), 1.17–1.10 (m, 1H). ¹³C NMR (500 MHz, CDCl₃) δ = 198.4,
175.0, 137.0, 134.3, 133.0, 132.9, 128.5, 128.1, 51.8, 50.1, 46.0, 36.8, 34.3, 33.0, 25.2, 20.1. HRMS (ESI/TOF) calcd for C_{19}H_{20}NaO_{3}^{+} (MNa^+) 307.1310, found 307.1292.

**Methyl (2RS, 4SR, 5SR, 6RS, 9SR)-endo-5-(1-methylphenacyl)bicyclo[2.2.2]oct-2-ene-exo-6-carboxylate (10b).** From 0.53 mL of diisopropylamine (3.78 mmol), 2.0 mL of n-BuLi (3.24 mmol), 0.40 mL of propiophenone (3.01 mmol) and 0.49 g of 2b (3.01 mmol). (hexane/ EtOAc gradient 30:1 → 10:1): 0.24 g (29%). ^1^H NMR (500 MHz, CDCl₃) δ = 7.92 (d, J = 7.6 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 6.34 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 6.24 (t, J = 7.3 Hz, 1H), 3.73 (s, 3H), 3.26 (dt, J = 15.3, 7.1 Hz, 1H), 2.75–2.71 (m, 1H), 2.61 (ddd, J = 8.3, 5.7, 1.7 Hz, 1H), 2.01–1.99 (m, 1H), 1.67–1.61 (m, 2H), 1.35–1.27 (m, 1H), 1.17 (d J = 7.0 Hz, 3H), 1.14–1.06 (m, 1H). ^13^C NMR (500 MHz, CDCl₃) δ = 204.0, 175.1, 137.0, 133.75, 133.0, 132.8, 128.6, 128.3, 51.7, 49.4, 46.1, 43.2, 33.4, 31.3, 25.3, 20.5, 15.8. HRMS (ESI/TOF) calcd for C_{19}H_{23}NaO_{3}^{+} (MNa^+) 299.1642, found 299.1649.

**Methyl (2RS, 4SR, 5SR, 6RS, 9RS)-endo-5-(1-methylphenacyl)bicyclo[2.2.2]oct-2-ene-exo-6-carboxylate (11b):** From 0.53 mL of diisopropylamine (3.78 mmol), 2.0 mL of n-BuLi (3.24 mmol), 0.40 mL of propiophenone (3.01 mmol) and 0.49 g of 2b (3.01 mmol) (hexane/ EtOAc gradient 30:1 → 10:1): 0.12 g (10%). (NMR extracted from a mixture). ^1^H NMR (500 MHz, CDCl₃) δ = 7.96 (d, J = 8.3 Hz, 2H), 7.59 (t, J = 7.8 Hz, 1H), 7.49 (t, J = 7.9 Hz, 2H), 6.28 (d, J =
7.6Hz, 1H), 6.08 (t, \( J = 7.2 \) Hz, 1H), 3.74 (s, 3H), 3.14 (dddd, \( J = 10.3, 7.0, 7.0, 7.0, 1H \)), 2.87 (m, 1H), 2.81-2.75 (m, 1H), 2.72-2.67 (m, 1H), 2.35 (m, 1H), 2.17 (ddd, \( J = 5.7, 2.6, 2.0 \) Hz, 1H), 1.67-1.57 (m, 4H).

Methyl (2RS, 4SR, 5SR, 6SR, 9RS)-endo-5-(1-methylphenacyl)bicyclo [2.2.2]oct-2-en-6-carboxylate (12b) From 0.53 mL of diisopropylamine (3.78 mmol), 2.0 mL of n-BuLi (3.24 mmol), 0.40 mL of propiophenone (3.01 mmol) and 0.49 g of 2b (3.01 mmol) (hexane/ EtOAc gradient 30:1 → 10:1): 0.07 g (6%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta = 8.03 \) (d, \( J = 7.8 \) Hz, 2H), 7.61 (t, \( J = 7.6 \) Hz, 1H), 7.51 (t, \( J = 7.8 \) Hz, 2H), 6.28 (t, \( J = 7.4 \) Hz, 1H), 6.06 (t, \( J = 7.8 \) Hz, 1H), 3.87 (ddd, \( J = 17.5, 6.7, 6.7 \) Hz, 1H), 3.69 (s, 3H), 3.02 (dd, \( J = 9.9, 1.9 \) Hz, 1H), 2.76 (m, 1H), 2.46 (ddd, \( J = 11.1, 9.8, 1.7 \) Hz, 1H), 2.36 (m, 1H), 1.34-1.10 (m, 4H). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \( \delta = 8.14 \) (d, \( J = 7.8 \) Hz, 2H), 7.10 (t, \( J = 7.4 \) Hz, 1H), 7.05 (t, \( J = 7.8 \) Hz, 2H), 6.26 (t, \( J = 7.4 \) Hz, 1H), 6.00 (t, \( J = 7.6 \) Hz, 1H), 4.12 (ddd, \( J = 17.6, 6.6, 6.6 \) Hz, 1H), 3.31 (s, 3H), 2.83 (dd, \( J = 9.8, 1.9 \) Hz, 1H), 2.54-2.44 (m, 3H), 1.31 (m, 1H), 1.19 (m, 1H), 1.01 (m, 1H), 0.95 (m, 1H).

Methyl (2RS, 4SR, 5SR, 6SR, 9SR)-endo-5-(1-methylphenacyl)bicyclo [2.2.2]oct-2-en-6-carboxylate (13b): From 0.53 mL of diisopropylamine (3.78 mmol), 2.0 mL of n-BuLi (3.24 mmol), 0.40 mL of propiophenone (3.01 mmol) and 0.49 g of 2b (3.01 mmol) (hexane/ EtOAc gradient 30:1
→ 10:1): 0.11 g (10%). (NMR extracted from a mixture). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 7.93 (d, $J = 8.7$ Hz, 2H), 7.53 (t, $J = 8.2$ Hz, 1H), 7.45 (t, $J = 8.5$ Hz, 2H), 6.42-6.35 (m, 2H), 3.61 (ddd, $J = 17.4$, 7.4, 7.4, 1H), 3.01 (s, 3H), 2.81-2.74 (m, 2H), 2.70 (m, 1H), 1.68-1.59 (m, 3H), 1.39 (ddd, $J = 12.3$, 9.0, 3.7, 1H), 1.33-1.27 (m, 1H).

**Methyl (1RS, 3SR, 4RS, 5RS, 6SR, 9RS, 10SR)-11-oxa-3-phenyltetracyclo[4.3.1.1$^{3,5}$.0$^{4,9}$]undecane-10-carboxylate (4b).** A solution of 0.18 g of 2b (0.63 mmol) in 120 mL benzene was irradiated for 20 h in a Pyrex reaction vessel in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm). The crude reaction mixture was purified on a silica gel column using hexane/EtOAc gradient 30:1 → 5:1 as the eluent: 79 mg (44%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 4.67 (dd, $J = 8.0$, 5.1 Hz, 1H), 3.78 (s, 3H), 3.33 (d, $J = 4.5$ Hz, 1H), 3.12 (dd, $J = 6.4$, 5.1 Hz, 1H), 3.05-3.01 (m, 1H), 2.52 (q, $J = 9.4$, 4.7 Hz, 1H), 2.22-2.18 (m, 1H), 2.16-2.02 (m, 1H), 1.91-1.83 (m, 1H), 1.65-1.58 (m, 1H), 1.56-1.50 (m, 1H), 1.14-1.06 (m, 1H). $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ = 176.6, 142.4, 128.2, 126.9, 124.0, 96.0, 51.7, 47.4, 44.1, 44.1, 36.2, 32.6, 17.2, 17.0. HRMS (ESI/TOF) calcd for C$_{18}$H$_{20}$NaO$_3^+$ (MNa$^+$) 307.1310, found 307.1317. See [42] for X-ray data.
Methyl (1SR, 2SR, 3SR, 4RS, 5RS, 6SR, 9RS, 10SR)-1-methyl-11-oxa-3-phenyltetracyclo[4.3.1.1\(^{3,5}\).0\(^{1,9}\)]undecane-10-carboxylate (14b). A solution of 0.55 g of 10b (0.18 mmol) in 120 mL benzene was irradiated for 20 h in a Pyrex reaction vessel in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm). The crude reaction mixture was purified on a silica gel column using hexane/EtOAc gradient 30:1 → 5:1 as the eluent: 36 mg (65%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta =\)
- 7.38 (t, \(J = 7.6\) Hz, 2H),
- 7.30 (d, \(J = 8.5\) Hz, 2H),
- 7.27 (t, \(J = 7.2\) Hz, 1H),
- 4.66 (dd, \(J = 7.9, 5.1\) Hz, 1H),
- 3.78 (s, 3H),
- 3.42 (d, \(J = 4.7\) Hz, 1H),
- 3.07 (ddd, \(J = 7.8, 4.9, 1.3\) Hz, 1H),
- 2.85 (t, \(J = 5.1\) Hz, 1H),
- 2.50 (q, \(J = 9.4, 4.7\) Hz, 1H),
- 2.27–2.18 (m, 2H),
- 1.91–1.82 (m, 1H),
- 1.67–1.60 (m, 1H),
- 1.54–1.47 (m, 1H),
- 1.13–1.05 (m, 1H),
- 0.92, (d, \(J = 6.9\) Hz, 3H).

\(^{13}\)C NMR (500 MHz, CDCl\(_3\)) \(\delta =\)
- 176.9, 143.9, 128.0, 126.6, 126.0, 124.0, 96.1, 51.7, 48.1, 47.8, 42.8, 37.6, 35.1, 32.5, 14.7, 17.1, 6.4. HRMS (ESI/TOF) calcd for C\(_{19}\)H\(_{22}\)NaO\(_3\)\(^+\) (MNa\(^+\)) 321.1467, found 321.1450.

Methyl (1SR, 2RS, 3RS, 5SR, 6SR, 7SR, 10RS, 11SR)-2-methyl-4-oxa-3-phenyltetracyclo[5.3.1.0\(^{2,5}\).0\(^{3,8}\)]undecane-10-carboxylate (18b): 5 mg of 12b was dissolved in C\(_6\)D\(_6\) in an NMR tube and then irradiated in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with a peak emission at 350 nm); 100% conversion. \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta =\)
- 7.78 (d, \(J = 7.4\) Hz, 2H),
7.28 (t, $J = 7.7$ Hz, 2H), 7.08 (t, $J = 7.4$ Hz, 1H), 4.02 (ddd, $J = 6.9$, 1.6, 1.6 1H), 3.32 (s, 3H), 3.09, (t, $J = 6.6$ Hz, 1H), 2.43 (d, $J = 6.2$ Hz, 1H), 2.33 (m, 1H), 2.25 (t, $J = 6.2$ Hz, 1H), 2.07 (m, 1H), 1.95 (q, $J = 13.5$, 6.7 Hz, 1H), 1.03-0.95 (m, 4H).

Methyl endo-3-(1,3-dioxalan-2-yl)-8-phenylbicyclo[4.3.0]non-7-ene-exo-2-carboxylate (6b). A solution of 0.18 g of 7a (0.63 mmol), 0.22 mL of HCl solution (4 M in dioxane, 0.89 mmol) and 0.08 g ethylene glycol (1.26 mmol) was prepared in dichloromethane (130 mL) in a Pyrex reaction vessel. This solution was irradiated for 29 h. The crude reaction mixture was purified on a silica gel column using a mixture of hexane and EtOAc as an eluent. The reaction mixture was then concentrated in vacuo to a volume of 20 mL and washed with saturated sodium bicarbonate solution (2 × 15 mL), and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed in vacuo to give a crude yellow oil. The crude mixture was purified on a silica gel column using hexane and ethyl acetate as the eluent (hexane/EtOAc gradient 30:1 → 5:1), 63 mg (30%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.44$ (d, $J = 7.9$ Hz, 2H), 7.34 (t, $J = 7.4$ Hz, 2H), 7.25 (t, $J = 7.4$ Hz, 1H), 6.01 (t, $J = 2.2$ Hz, 1H), 4.71 (d, $J = 3.9$ Hz, 1H), 3.94–3.77 (m, 4H), 3.72 (s, 1H), 3.11 (s, 1H), 2.80 (dddd, $J = 15.4$, 6.2, 3.7, 2.6 Hz, 1H), 2.59 (dt, $J = 12.8$, 6.5 Hz, 1H), 2.53 (d, $J = 15.4$ Hz, 1H), 2.32 (t, $J = 11.2$ Hz, 1H), 2.05–2.96 (m, 2H), 1.77–1.67 (m, 2H), 1.35–1.24 (m, 2H). $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta = 176.9$, 142.0, 136.6, 129.6, 128.3, 127.1, 125.5, 106.1, 65.0, 64.9, 51.5, 45.2, 45.0,
Methyl 6-(1,3-dioxalan-2-yl)-3-phenylbicyclo[3.3.1]non-2-ene-syn-9-carboxylate (5b). A solution of 0.18 g of 2b (0.63 mmol), 0.22 mL of HCl solution (4 M in dioxane, 0.89 mmol) and 0.08 g ethylene glycol (1.26 mmol) was prepared in dichloromethane (130 mL) in a Pyrex reaction vessel. This solution was irradiated for 29 h. The crude reaction mixture was purified on a silica gel column using a mixture of hexane and EtOAc as an eluent. The reaction mixture was then concentrated in vacuo to a volume of 20 mL and washed with saturated sodium bicarbonate solution (2 × 15 mL), and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed in vacuo to give a crude yellow oil. The crude mixture was purified on a silica gel column using hexane and ethyl acetate as the eluent (hexane/EtOAc gradient 30:1 → 5:1), epimeric mixture, 38 mg (18%). HRMS (ESI/TOF) calcd for C_{20}H_{24}NaO_{4}^+ (MNa^+) 351.1572, found 351.1558.

(1RS,4RS, 5SR, 8RS, 9SR)-Methyl 8-(1,3-dioxalan-2-yl)-4-hydroxy-3-phenylbicyclo[3.3.1]non-2-ene-9-carboxylate (7b): See procedure for 5b: 12 mg (5%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta = 7.54\) (d, \(J = 7.6\) Hz, 2H), 7.40 (t, \(J = 7.5\) Hz, 2H), 7.33 (t, \(J = 7.0\) Hz, 1H), 6.26 (d, \(J = 6.6\) Hz, 1H), 4.63m (dd, \(J = 3.7, 1.2\) Hz,
1H), 4.55 (d, J = 6.7 Hz, 1H), 4.02-3.93 (m, 2H), 3.88-3.81 (m, 2H), 3.78 (s, 3H), 3.22 (dt, J = 6.0, 2.8 Hz, 1H), 3.00 (s, 1H), 2.63 (s, 1H), 1.94-1.87 (m, 1H), 1.87-1.79 (m, 1H), 1.95-1.71 (m, 2H), 1.56-1.49 (m, 1H). 13C NMR (500 MHz, CDCl₃) δ = 173.8, 141.9, 138.8, 128.8, 127.8, 126.4, 1106.1, 71.6, 64.9, 64.7, 51.7, 40.6, 30.9, 37.2, 33.3, 24.9, 19.2.

(1RS,2RS, 5SR, 6RS, 9SR)-2-(2-hydroxyethyl-9-methyl-6-exo-hydroxy-7-phenylbicyclo[3.3.1]non-7-ene-2,9-dicarboxylate (8b): See procedure for 5b: 8 mg (3%). ¹H NMR (500 MHz, CDCl₃) δ = 7.50 (d, J = 8.1 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 6.22 (d, J = 6.5 Hz, 1H), 4.61 (dd, J = 3.4, 1.2 Hz, 1H), 4.25-4.14 (m, 2H), 3.81 (q, J = 9.9, 4.9, 2H), 3.78 (s, 3H), 3.39 (dt, J = 9.5, 3.1 Hz, 1H), 3.05 (t, J = 2.8 Hz, 1H), 2.85 (dt, J = 12.8, 3.5 Hz, 1H), 2.62 (s, 1H), 1.87 (t, J = 5.9 Hz), 1.77-1.69 (m, 4H). 13C NMR (500 MHz, CDCl₃) δ = 174.2, 173.8, 142.8, 138.5, 128.8, 128.0, 127.6, 126.4, 71.3, 66.1, 51.9, 40.4, 36.9, 33.8, 25.1, 20.2.

2-exo-Hydroxy-3-phenyl-11-oxatricyclo[4.3.2.0₂₉]dodec-3-ene-10-one (9b): See procedure for 5b: 5 mg (2%). ¹H NMR (500 MHz, CDCl₃) δ = 7.55 (d, J = 8.0 Hz, 2H), 7.44-7.32 (m, 3H), 6.16 (d, J = 5.7 Hz, 1H), 4.81 (t, J = 5.0 Hz, 1H), 4.55 (q, J = 4.6, 2.4 Hz, 1H), 4.32 (dt, J = 11.9, 6.0, 1H), 2.95 (t, J = 4.7 Hz, 1H), 2.54 (m, 1H), 2.11-1.98 (m, 1H), 1.82 (d, J = 4.6, 1H)
Methyl endo-3-(1,3-dioxalan-2-yl)-endo-10-methyl-8-phenylbicyclo[4.3.0]non-7-ene-exo-2-carboxylate (15b). A solution of 0.21 g of 14b (0.70 mmol), 0.25 mL of HCl solution (4 M in dioxane, 0.99 mmol) and 0.09 g ethylene glycol (1.40 mmol) was prepared in chloroform (10 mL) and then heated to 70 °C while stirring for 4 h. The reaction mixture was then concentrated in vacuo to remove chloroform, diluted with dichloromethane (10 mL), and washed with saturated sodium bicarbonate solution (2 × 15 mL), and the aqueous layer extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, and the solvent removed in vacuo to give a crude yellow oil. The crude mixture was purified on a silica gel column using hexane and ethyl acetate as the eluent (hexane/EtOAc gradient 30:1 → 5:1), 0.17 g (71%). ¹H NMR (500 MHz, CDCl₃) δ = 7.35–7.31 (m, 4H), 7.25 (t, J = 7.2 Hz, 1H), 5.87 (t, J = 2.1 Hz, 1H), 4.79 (d, J = 3.7 Hz, 1H), 4.01–3.85 (m, 3H), 3.71 (s, 3H), 3.31 (tt, J = 7.7, 1.7 Hz, 1H), 2.95–2.82 (m, 2H), 2.68 (t, J = 11.5 Hz, 1H), 2.08–2.00 (m, 2H), 1.78–1.71 (m, 2H), 1.56–1.48 (m, 2H), 1.08 (d, J = 7.4 Hz, 3H).

Methyl endo-5-hydroxy-2-methyl-3-phenyl tricyclo[4.3.1.0⁴⁻⁹]dec-2-ene-exo-10-carboxylate (16b). A solution of 0.11 g of
**14b** (0.37 mmol) and 0.13 mL of HCl solution (4 M in dioxane, 0.51 mmol) was prepared in chloroform (10 mL) and stirred at ambient temperature for 4 h. The reaction mixture was then concentrated in vacuo to remove chloroform, diluted with dichloromethane (10 mL), and washed with saturated sodium bicarbonate solution (2 × 15 mL), and the aqueous layer extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, and the solvent removed in vacuo to give a crude yellow oil. The crude mixture was purified on a silica gel column using hexane and ethyl acetate as the eluent (hexane/EtOAc gradient 30:1 → 5:1), 80 mg (73%). The structure is characterized by X-ray (see Supporting Information). $^1$H NMR (500 MHz, CDCl$_3$) $\delta =$ 7.45 (d, $J = 8.4$ Hz, 2H), 7.37 (t, $J = 7.7$ Hz, 2H), 7.24 (t, $J = 7.4$ Hz, 1H), 4.03 (dt, $J = 8.5$, 2.2 Hz, 1H), 3.75 (s, 3H), 3.15 (dd, $J = 8.7$, 4.3 Hz, 1H), 2.88 (d, $J = 4.5$ Hz, 1H), 2.76–2.74 (m, 1H), 2.54–2.50 (m, 1H), 2.32–2.28 (m, 1H), 2.03 (s, 3H), 1.80–1.59 (m, 4H). $^{13}$C NMR (500 MHz, CDCl$_3$) = 175.9, 145.5, 137.7, 137.3, 128.2, 128.1, 126.5, 69.3, 51.8, 51.4, 48.2, 42.3, 38.3, 38.1, 21.9, 18.1, 14.6. HRMS (ESI/TOF) calcd for C$_{19}$H$_{22}$LiO$_3$\(^+\) (MLi\(^+\)) 305.1728, found 305.1729.
Chapter 4: Azaxylylenes

Introduction

In a departure from oxetanes, let us consider other photochemically assisted syntheses which employ modular design toward novel polyheterocycles, and in some cases further reactions of the photoproducts. o-Azaxylylenes have been known for half a century\(^{43}\) but have remained in relative synthetic obscurity until a decade ago. Corey reported their first preparation under simple mild conditions via base-induced elimination of hydrogen chloride from derivatives of o-chloromethylaniline, noting that “Surprisingly, simplest method possible for o-azaxylylene production [...] has never been reported.”\(^{44}\)

![Scheme 4.1: Parent structures of Corey’s azaxylylene formation\(^{44}\)](image)

Since the synthetic utility of o-xylylenes (i.e. all-carbon o-quinodimethanes) is well-reported,\(^{45}\) and the photophysics of their generation via intramolecular photoinduced hydrogen abstraction in aromatic o-alkyl ketones is also studied,\(^{46}\) it was surprising for us to realize that the equally simple photogeneration of \(o\text{-}a\text{za}\text{x}\text{a}y\text{ly}l\text{y}l\text{en}e\text{s}\) from \(o\text{-}a\text{mi}n\text{ok}e\text{to}n\text{e}n\)es via excited state intramolecular proton transfer\(^{47}\) has never been utilized as
a synthetic tool. Indeed, such utilization may have been attempted but was unsuccessful due to the rapid reversibility of the initial proton transfer which could compete with a desired reaction (in our case, cycloaddition). Intramolecular proton transfers from one heteroatom to another (and back) are fast: a classic example is the much studied photophysics of salicylaldehyde or \( o \)-hydroxyacetophenone, although the transient tautomer is not impossible to characterize.\(^{48}\) We, however, found that the cycloaddition reactions of \( o \)-azaxylylenes photogenerated via excited state intramolecular proton transfer (ESIPT) can successfully compete with the back proton transfer when an unsaturated dienophile is tethered to the photoprecursor, resulting in an intramolecular cycloaddition.\(^{49}\) Additionally, this modular system allowed for the unique photochemical participation of imines and thiophenes—likely achievable due to the tethered pendant design. Shown in **Scheme 4.2** is a sample reaction scheme in which an azaxylylene is generated by the proton abstraction by a carbonyl from an amide which bears a thiophene pendant.

\[
\text{Scheme 4.2: Cycloaddition to azaxylylenes}
\]

**Carbonyl-type Azaxylylenes**

**Results and Discussion**

Thiophene propionic acid chloride (3c) was successfully coupled to TMS-protected \( o \)-aminobenzyl alcohol (1c), \( o \)-aminoacetophenone, and \( o \)-aminotetralone (2c);
Scheme 4.3. In the case of the \( o \)-aminobenzyl alcohol, the product was deprotected and subsequently oxidized to give the aldehyde (the ketones were able to be used directly). A similar photoprecursor was synthesized in which thiophene was tethered to \( o \)-aminoinadanone, but it was not photochemically reactive. Olga A, Mukhina found that this indanone derivative was indeed able to undergo the desired cycloaddition, albeit slowly, when the tethered pendant was furan—which is far more reactive than thiophene. When indanone was tethered to thiophene, the prohibitively slow reaction time resulted in the degradation of the starting material rather than in the formation of the desired cycloaddition product.

These \( o \)-acylamido precursors have broad UV absorption with a maximum at 340-350 nm. Irradiations were carried out with a Rayonet broadband 300-400 nm UV source (which has a maximum emission at 350 nm). The thiophenes were able to undergo diastereoselective [4+2] cycloaddition to give dihydrothiophenes (Scheme 4.4), giving only a single configuration for the ketones in which the OH group was \textit{anti} relative to the heteroatom in the annelated ring. For the reaction in which the carbonyl was an aldehyde, a minor amount of the \textit{syn} product was observed. Pendants other than thiophene (e.g. furan) are able to participate in [4+4] cycloaddition in these conditions, but thiophene tethers gave only the single [4+2] cycloaddition products. Shown in Figure 4.1 are the
configurations which we have designated “syn” and “anti.” There are only a few published examples in which thiophene participates in such a cycloaddition making this new reaction an exciting development.\textsuperscript{50} We are happy to report three such cycloaddition products (7c, 8c, and 9c) formed from the cycloaddition of a tethered thiophene to an azaxylylene photogenerated via ESIPT.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.1.png}
\caption{Cycloaddition products and stereochemistry}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme4.4.png}
\caption{Scheme 4.4: [4+2] cycloadditions of thiophene to azaxylylenes}
\end{figure}
The assembly of these photoprecursors is efficient (all yields > 85% yield), and with the potential for a large variety of diversity inputs, this photoassisted scheme provides ready access to polycycles rich in heteroatoms held in rigid spatial conformations. It is our further goal to submit these compounds to screening for their potential as drug leads.

We intended to explore a variety of methods for further transforming the dihydrothiophene including Povarov conditions. However, the only successful transformation so far proved to have a surprising result. During irradiation (and under acidic conditions), 7c undergoes a rearrangement in which the formed vinylic thiol recombines with the resulting alkene to form 10c (see Scheme 4.5). Surprisingly, treating 8c and 9c with acid was unsuccessful in generating the same rearranged product.

Scheme 4.5: Rearranged product

Scheme 4.6: “Butter-up” synthesis
After these successes with azaxylylenes, we were incited to explore alternatively tethered photoprecursors in which the unsaturated dienophile is tethered to the o-acyl moiety rather than to the amine. We affectionately call these carbonyl-precursors “butter-up” (as in: the butter-up side of toast; see Scheme 4.6) This was achieved by coupling 2-nitro-2’-bromoacetophenone to 2-furymethanethiol. The nitro group was then reduced to the aniline via treatment with tin (II) chloride to give 12c.

In irradiation reactions of “conventionally” tethered azaxylylene precursors, furan pendants typically react in both a [4+4] and [4+2] fashion, often giving both syn- and anti- products in various ratios. However, in the 12c, only the [4+4] cycloaddition takes place (Scheme 4.7), forming the intermediate product 13c. Even more interesting, this [4+4] was not isolated—and rather only a rearranged [3.3.1] product (14c) is isolable.

Scheme 4.7: “Butter-up” irradiation

The assignment of this structure is based on a similar rearrangement previously observed by Olga A. Mukhina, allowing for a structural determination of 14c by the analysis of the 1H NMR constants. Typically such a rearrangement is either a minor
product in irradiation or is implemented via acid catalysis—but in this case, it is the single product formed immediately during the irradiation. In most of the examples of the [4+4] cycloaddition with furan, the diastereoselectivity of the product is such that the OH group is syn to the heteroatom bridge. In acidic conditions, it is thought that the syn OH group is able to displace the distal end of the (likely protonated, if the conditions are acidic) O-bridge, resulting in the rearranged product. This mechanism is depicted in Scheme 4.8.

![Scheme 4.8: Rearrangement to [3.3.1]](image)

Mechanistic studies performed by Dmitri Kuznetsov support this mechanism.†† His studies show that when the anti isomer of the shown [4+4] photoproduct is isolated, its treatment with acid does NOT give the [3.3.1] rearranged product. Thus, for the rearrangement to occur, the hydroxyl group in the [4+4] cycloaddition product must be syn to the bridge oxygen.

Attempts to proliferate this reaction scheme (using furfurylamine, acylating or trifluoroacetylating the aniline, ester or thioester tethered furyl groups, or oxidizing the sulfur tether to the sulfone) were all unsuccessful (either unable to be synthesized in the

†† These studies are not yet published.
case of furfurylamine or photoinactive in the other cases mentioned). We did, however, note an interesting side reaction when attempting to synthesize a cyclic imine from 2-bromo-2'-nitroacetophenone with 2-aminoethanethiol. Rather than forming the desired imine, the major product 15c was formed via the proposed mechanism shown in Scheme 4.9. The structure of 15c is unambiguously proven via X-ray. We propose that after the nucleophilic sulfur displaces the bromide, the compound cyclizes to form the imine C1. The enamine tautomer of this compound (C2) is then able to undergo thermal 6π electrocyclization to form C3. In the basic conditions of the reaction, a proton is eliminated to form the thioester C4. The tautomerization to the imine (driven by rearomatization) and protonation gives the hydroxylamine (C5) which is oxidized to form C6. We have not yet identified the oxidant in this reaction mixture, but it is possible that there is a species which is reduced by C5 in the mixture as there are several species yet unidentified due to the difficulty in separation. Finally, the intramolecular nucleophilic attack by the imine on the nitroso group forms the delightfully unexpected 15c.

![Scheme 4.9: Unusual product and mechanism](image-url)
Experimental Procedures and Data

Common solvents were purchased from Pharmco Aaper and used directly, except for THF—which was refluxed over and distilled from potassium benzophenone ketyl prior to use—and hexane—which was distilled over calcium hydride. Common reagents were purchased from Sigma Aldrich, Acros, or TCI America and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25°C on a Bruker Avance III 500 MHz or Varian Mercury 400 MHz instrument in CDCl₃ with TMS as an internal standard (unless noted otherwise). X-Ray structures were obtained with a Bruker APEX II instrument. High resolution mass spectra were obtained on the MDS SCIEX/Applied Biosystems API QSTAR™ Pulsar i Hybrid LC/MS/MS System mass spectrometer by Dr. Shuji Kato or Dr. Dan Gu from the University of Colorado at Boulder. For the ¹H, ¹³C, COSY NMR spectra which are not included in Appendix B, see supporting information in ref. [49].

2-((Trimethylsilyloxy)methyl)aniline (1c): A solution of trimethylsilyl chloride (2.66 g, 24.3 mmol) in dichloromethane (25 mL) was added to a stirred solution of 2-aminobenzylmethanol (3.00 g, 24.3 mol) and triethylamine (2 eq, 4.92 g, 48.6 mmol) in dichloromethane (25 mL). The reaction mixture was stirred at 20°C for 24 h. After that, the mixture was quenched with saturated ammonium chloride solution (20 mL). The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic fractions were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by rotary evaporation. The product (4.30 g, 90%) was used
without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.14 (td, $J = 7.7$, 1.5, 1H), 7.10-7.06 (m, 1H), 6.74 (td, $J = 7.4$, 1.1, 1H), 6.71 (d, $J = 8.6$, 1H), 4.69 (s, 2H), 4.19 (s, 2H), 0.16 (s, 9H).

Amino-1-tetralone (2c): 5,6,7,8-Tetrahydro-1-naphthylamine (3.0 g, 21.6 mmol) in ethanol (10 mL, anhydrous) was added dropwise to a solution of acetic anhydride (4.1 mL, 43.2 mmol) in ethanol (40 mL) at 0°C. The mixture was stirred for 8 h at 20°C. The solvent was removed under vacuum on a rotary evaporator to yield 8-acetamidotetralin as a white solid (3.9 g) that was used without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.50 (d, $J = 7.7$, 1H), 7.15 (br s, 1H), 7.11 (t, $J = 7.7$, 1H), 6.93 (d, $J = 7.6$, 1H), 2.78 (t, $J = 6.1$, 2H), 2.59 (t, $J = 6.2$, 2H), 2.05 (s, 3H), 1.86-1.73 (m, 4H). 8-Azetamidotetralin (0.50 g, 2.7 mmol) in acetone (15 mL) and 15% aqueous magnesium sulfate (0.40 g in 2.5 mL of water) at 20°C was treated with potassium permanganate (1.15 g, 7.3 mmol). The mixture was allowed to stir at 20°C for 6 h. The mixture was filtered through celite and the solids were washed with chloroform and water. The organic layer was separated and the aqueous layer was extracted several times with chloroform. The combined organic fractions were washed with brine and dried over anhydrous magnesium sulfate, filtered and evaporated to give 8-acetamidotetralone (0.47 g, 88%) which was used without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 12.18 (s, 1H), 8.62 (d, $J = 8.4$, 1H), 7.54-7.41 (m, 1H), 7.01-6.89 (m, 1H), 3.00 (m, 2H), 2.71 (m, 2H), 2.29 (s, 3H), 2.10 (m, 2H). 8-Azetamidotetralone (0.47 g, 2.3 mmol) in 6N HCl (10 mL) was heated at 90°C for 3 h. The mixture was cooled to 20°C and evaporated
to dryness under vacuum. Ice was added to the mixture followed by addition of 2 M NaOH until the mixture was at pH 8. The aqueous layer was extracted with EtOAc and the organic fractions were combined, washed with brine, dried, filtered and concentrated to give 0.28 g (75%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.18 (dd, $J = 8.2, 7.3, 1$H), 6.65-6.36 (m, 4H), 2.92 (t, $J = 6.1, 2$H), 2.69 (t, $J = 6.1, 2$H), 2.07 (m, 2H).

3-(2-Thienyl)-propanoic acid chloride (3c): To a stirred solution of 0.45 g (2.6 mmol) of 3-(2-thienyl)-propanoic acid in 5 mL of dichloromethane, 0.34 g (2.9 mmol) of thionyl chloride was added and refluxed for 3 h. 0.42 g (93%) of yellow-brown oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.20 (dd, $J = 5.1, 1.2, 1$H), 6.96 (dd, $J = 5.1, 3.5, 1$H), 6.88 (m, 1H), 3.28 (m, 4H).

\[
\begin{align*}
\text{Cl} & \quad \text{S} \\
\text{O} & \quad \text{NH} \\
\text{OH} & \quad \text{S}
\end{align*}
\]

3-(Thien-2-yl)-N-(2-(hydroxymethyl)phenyl)propanamide (4c-1): A solution of 0.56 g 3c (3.2 mmol) in dry THF (25 mL) was slowly added to a stirred solution of 0.57 g 1c (2.9 mmol) and 0.25 g dry pyridine (3.2 mmol) in THF (50 mL) at 0°C. After stirring for 10 min the mixture was allowed to warm to 20°C, at which it was maintained overnight. It was then diluted with water (50 mL), extracted with EtOAc (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. Upon concentration, the crude product was purified by flash chromatography. 0.67 g (71%) yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.56 (br s, 1H), 7.94 (d, $J = 8.2, 1$H), 7.29 (td, $J = 7.8, 1.5, 1$H), 7.16-7.11 (m, 2H), 7.06 (t, $J = 7.4, 1$H), 6.91 (dd, $J = 5.1, 3.5, 1$H), 6.84 (d, $J = 3.0, 1$H), 4.54 (s, 2H), 3.23 (t, $J =
7.4, 2H), 2.81-2.73 (br s,1H), 2.70 (t, J = 7.4, 2H). 13C NMR (126 MHz, CDCl₃) δ 195.5, 171.9, 141.0, 136.2, 136.0, 133.6, 131.7, 122.8, 121.6, 119.9, 44.7, 42.5, 31.9, 29.7.

N-(2-Acetylphenyl)-3-(thien-2-yl)propanamide (5c): A solution of 0.11 g 3c (0.62 mmol) in dry THF (5 mL) was slowly added to a stirred solution of 0.08 g 2-aminoacetophenone (0.60 mmol) and 0.05 g dry pyridine (0.62 mmol) in THF (50 mL) at 0°C. After stirring for 10 min the mixture was allowed to warm to 20°C, at which it was maintained overnight. It was then diluted with water (50 mL), extracted with EtOAc (3 x 50 mL) and dried over anhydrous Na₂SO₄. Upon concentration, the crude product was purified by flash chromatography. 0.14 g (88%). H NMR (500 MHz, CDCl₃) δ 11.66 (s, 1H), 8.66 (d, J = 8.5, 1H), 7.77 (dd, J = 8.0, 1.5, 1H), 7.44 (ddd, J = 8.7, 7.2, 1.5, 1H), 7.03-6.98 (m, 2H), 6.80 (dd, J = 5.0, 3.5, 1H), 6.78-6.76 (m, 1H), 3.18 (t, J = 7.6, 2H), 2.71 (t, J = 7.6, 2H), 2.54 (s, 3H). 13C NMR (126 MHz, CDCl₃) δ 202.9, 171.0, 143.2, 140.9, 135.2, 131.7, 126.9, 124.8, 123.5, 122.4, 121.8, 120.8, 40.2, 28.6, 25.5. HRMS (ESI) calcd for C₁₅H₁₅NNaO₂S⁺ (MNa⁺) 296.0716, found 296.0706.

3-(Thien-2-yl)-N-(2-formylphenyl)propanamide (4c): To a well-stirred solution of 0.27 g 4c-1 (1.1 mmol) in dichloromethane (25 mL) at ambient temperature, a suspension of pyridinium chlorochromate (0.34 g, 1.6 mmol) in dichloromethane (10 mL) was added. The reaction mixture was left stirring overnight and
then filtered through a layer of silica gel affording the pure product. 0.31 g (91%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.17 (s, 1H), 9.90 (s, 1H), 8.76 (d, $J = 8.3$, 1H), 7.66 (dd, $J = 7.7$, 1.6, 1H), 7.61 (ddd, $J = 8.7$, 7.1, 1.6, 1H), 7.23 (td, $J = 7.5$, 0.9, 1H), 7.13 (dd, $J = 5.2$, 1.1, 1H), 6.91 (dd, $J = 5.1$, 3.5, 1H), 6.89-6.86 (m, 1H), 3.30 (t, $J = 7.6$, 2H), 2.84 (t, $J = 7.6$, 2H). 13C NMR (126 MHz, CDCl$_3$) $\delta$ 195.6, 171.1, 143.0, 140.8, 136.3, 136.1, 126.9, 124.8, 123.6, 123.0, 121.6, 120.0, 40.0, 25.4. HRMS (ESI) calcd for C$_{14}$H$_{13}$NNaO$_2$S$^+$ (MNa$^+$) 282.0559, found 282.0562.

$N$-(8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)-3-(thiophen-2-yl)propanamide (6c): A solution of 0.50 g 3c (2.9 mmol) in dry THF (5 mL) was slowly added to a stirred solution of 0.46 g 2c (2.9 mmol) and 0.45 g dry pyridine (5.7 mmol) in THF (50 mL) at 0°C. After stirring for 10 min the mixture was allowed to warm to 20°C, at which it was maintained overnight. It was then diluted with water (50 mL), extracted with EtOAc (3 x 50 mL) and dried over anhydrous Na$_2$SO$_4$. Upon concentration, the crude product was purified by flash chromatography. 0.74 g, 87%. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 12.25 (s, 1H), 8.65 (d, $J = 8.5$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 1H), 7.14 (dd, $J = 5.1$, 1.2 Hz, 1H), 6.96 (dd, $J = 7.6$, 1.0 Hz, 1H), 6.93 ($J = 5.1$, 3.5 Hz, 1H), 6.89 (ddd, $J = 3.3$, 1.0, 1.0, 1H), 3.32 (t, $J = 7.4$ Hz, 2H), 2.99 (t, $J = 6.1$ Hz, 2H), 2.85 (t, $J = 8.1$ Hz, 2H), 2.71 (t, $J = 6.2$ Hz, 2H), 2.11 (ddd, $J = 12.7$, 6.4, 6.4 Hz, 2H).
1-Aza-2,3-benzo-4-hydroxy-4-methyl-8-thia-
tricyclo[7.3.0.0^{5,9}]dodeca-2,6-dien-12-one (8c): 0.10 g (0.37 mmol) of 5c was dissolved in 50 mL toluene, heated to reflux and irradiated in a Pyrex reaction vessel in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm) until the reaction was complete. Upon flash chromatography 0.06 g (60%) of the product was obtained. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.72 (dd, $J = 7.9, 1.1, 1$H), 7.40 (td, $J = 8.0, 1.4, 1$H), 7.36 (dd, $J = 7.7, 1.4, 1$H), 7.21 (td, $J = 7.7, 1.3, 1$H), 6.11 (dd, $J = 6.7, 2.7, 1$H), 5.09 (dd, $J = 6.7, 2.5, 1$H), 3.91 (t, $J = 2.6, 1$H), 2.89-2.80 (m, 2H), 2.76-2.67 (m, 1H), 2.58-2.52 (m, 1H), 1.84 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.8, 134.9, 134.6, 129.2, 127.2, 125.8, 124.6, 124.5, 118.5, 84.5, 71.8, 68.8, 40.2, 31.3, 26.2. HRMS (ESI) calcd for C$_{15}$H$_{15}$NNaO$_2$S$^+$ (MNa$^+$) 296.0716, found 296.0713.

1-Aza 2,3-benzo-4-hydroxy-8-thia-tricyclo[7.3.0.0^{5,9}]dodeca-2,6-dien-12-one (7c): 0.21 g (0.81 mmol) of 4c was dissolved in 120 mL acetonitrile and irradiated in a Pyrex reaction vessel in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm) until the reaction was complete. Upon flash chromatography 0.13 g (64%) of the product was obtained. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.81 (d, $J = 8.1, 1.1, 1$H), 7.42 (dt, $J = 7.7, 1.7,$
1H), 7.24 (dd, J = 7.4, 1.6, 1H), 7.19 (dt, J = 7.5, 1.2, 1H), 6.12 (dd, J = 6.6, 2.7, 1H), 5.11 (dd, J = 6.6, 2.5, 1H), 4.92 (br s, 1H), 4.05 (q, J = 2.6, 1H), 2.88-2.52 (m, 5H).

13C NMR (126 MHz, CDCl3) δ 171.9, 134.7, 132.1, 129.7, 128.4, 127.1, 126.0, 124.1, 119.1, 84.2, 70.7, 63.7, 40.1, 31.4. HRMS (ESI) calcd for C14H13LiNO2S+ (MLi+) 266.0822, found 266.0832.

(31SR,13aSR,13bSR)-13a-hydroxy-4,5,11,12,13,13a-hexahydrobenzo[a]pyrrolo[1,2-a]thieno[2,3-b]quinolin-6(13bH)-one (9c): 0.12 g (0.40 mmol) of 6c was dissolved in 50 mL aqueous methanol (5% H2O by volume) and irradiated in a Pyrex reaction vessel in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm) for 6 h. Upon flash chromatography 75 mg (64%) of the product was obtained. 

1H NMR (500 MHz, CDCl3) δ 7.56 (d, J = 7.6, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.01 (d, J = 7.8Hz), 6.16 (dd, J = 6.7, 2.7 Hz, 1H), 5.21 (dd, J = 6.6, 2.6 Hz, 1H), 3.93 (t, J = 2.7 Hz, 1H), 2.91-2.83 (m, 2H), 2.93-2.69 (m, 3H), 2.57 (ddd, J = 16.8, 7.5, 2.2 Hz, 1H), 2.19 (s, 1H), 2.13 (m, 1H), 2.04 (dt, J = 15.8, 3.8, 1H), 1.95-1.83 (m, 2H). 

13C NMR (126 MHz, CDCl3) δ 172.0, 137.9, 134.3, 129.9, 128.4, 126.8, 126.5, 121.9, 118.9, 84.7, 70.3, 67.0, 40.3, 36.3, 31.3, 29.6, 19.0.

[6.3.1.04,12]dodeca-6,10-dien-2-one (10c): 0.21 g (0.81 mmol) of 4c was dissolved in
120 mL acetonitrile and irradiated in a Pyrex reaction vessel in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm) for 6 h. Upon flash chromatography 80 mg (28%) of the product was obtained. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.89 (d, $J = 8.5$ Hz, 1H), 7.43-7.86 (m, 2H), 7.14 (t, $J = 6.6$ Hz, 1H), 6.24 (dd, $J = 9.9$, 3.1 Hz, 1H), 5.31 (dd, $J = 9.9$, 2.8 Hz, 1H), 4.85-4.82 (m, 2H), 3.00 (t, $J = 6.2$ Hz, 1H), 3.54 (br s. 1H), 3.17 (dd, $J = 17.0$, 6.6 Hz, 1H), 2.87 (dt, $J = 6.2$, 2.8. 2.8 Hz, 1H), 2.65 (d, $J = 17$ Hz, 1H), 1.95 (d, $J = 2.8$ Hz). 13C NMR (126 MHz, CDCl$_3$) $\delta$ 172.1, 135.9, 130.2, 130.1, 124.5, 123.8, 123.6, 118.6, 117.9, 70.6, 54.6, 43.1, 36.5, 35.2. HRMS (ESI) calcd for C$_{14}$H$_{13}$LiNO$_2$S$^+$ (MLi$^+$) 266.0822, found 266.0832.

1-(2-Aminophenyl)-2-(furan-2-ylmethylthio)ethanone (12c):

2.24 g of 2-bromo-2’nitroacetophenone (9.2 mmol) was dissolved in 30 mL dichloromethane along with 1.08 g 2-furylmercaptan (9.2 mmol) and 1.48 g dry pyridine (18.4 mmol) for 1h before quenching the reaction with 5% HCl solution (10 mL), extracting the aqueous layer with dichloromethane (2 x 20 mL), combining the organic layers and drying them over anhydrous sodium sulfate. The organic layer was then decanted and concentrated to give the pure product (11c). 2.50 g (98%). This was then dissolved in 100 mL ethanol along with 5.23 g tin (II) chloride (27.0 mmol) and heated to 70°C under nitrogen atmosphere for 2h. Saturated sodium bicarbonate solution was added slowly until the pH of the mixture was 8, giving a thick milky white emulsion. This was filtered through celite and the filtrate was extracted with EtOAc (3 x 100 mL). The
organic phase was washed with brine (2 x 50 mL) and the organic layer was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography. 1.76 g (78%) yield. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.67 (dd, \(J = 8.2\), 1.0 Hz, 1H), 7.40 (d, \(J = 1.8\), 0.7 Hz, 1H) 7.30 (dt \(J = 8.4\), 1.3 Hz 1H), 6.69 (d, \(J = 8.4\) Hz, 1H), 6.15 (dt \(J = 8.2\), 1.0, 1H) 6.37-6.26 (m, 4H), 3.85 (s, 2H), 3.83 (s, 2H). \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 196.7, 151.1, 150.7, 142.4, 134.8, 131.4, 117.5, 116.3, 115.8, 110.4, 108.4, 37.6, 28.5. HRMS (ESI) calcd for C\(_{13}\)H\(_{14}\)NO\(_2\)S\(^+\) (MH\(^+\)) 248.0740, found 248.0743.

9-Aza-10,11-Benzohydroxy-2-oxa-3-thia-tricyclo[6.3.1.0\(^4,12\)]dodeca-6,10-diene (14c) 0.31 g of 12c was dissolved in 50 mL wet acetonitrile (5% H\(_2\)O by volume) and irradiated in a Pyrex reaction vessel in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm) for 2h. The irradiation solution was concentrated under reduced pressure and purified via flash chromatography. 0.28 g (89%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.32 (dd, \(J = 8.1\), 1.3 Hz, 1H), 7.24, (dt, \(J = 8.1\), 1.5 Hz, 1H), 6.97 (dt, \(J = 8.1\), 1.3 Hz, 1H), 6.76, (dd, \(J = 8.0\), 1.2 Hz, 1H), 6.31 (d, \(J = 9.8\) Hz, 1H), 5.63 (dd, \(J = 9.8\), 3.2 Hz, 1H), 5.50 (ddd, \(J = 5.0\), 3.4, 0.6 Hz, 1H), 4.60-4.55 (m, 1H), 3.38 (d, \(J = 9.8\) Hz), 3.07 (m, 2H), 2.91 (d, \(J = 9.8\) Hz, 1H), 2.85 (t, \(J = 1.4\) Hz, 1H). \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 196.7, 151.1, 150.7, 142.4, 134.8, 131.4, 117.5, 116.3, 115.8, 110.4, 108.4, 37.6, 28.5. HRMS (ESI) calcd for C\(_{13}\)H\(_{14}\)NO\(_2\)S (MH\(^+\)) 248.0740, found 248.0739.
1-oxo-3,4-dihydro-[1,4]thiazino[4,3-b]indazol-5-ium-6(1H)-olate (15c): 0.2 g 2-bromo-2'-nitroacetophenone (0.8 mmol) was stirred in 10 mL THF along with 2-aminoethanethiol (0.06 g, 0.05 mL, 0.8 mmol) and 0.12 g (1.23 mmol) triethylamine at ambient temperature for 12 h. The reaction mixture was concentrated under reduced pressure to remove THF, diluted with 10 mL EtOAc, and washed with saturated sodium bicarbonate solution (3 x 5 mL) and water (3 x 5 mL). The organic layer was then dried over anhydrous sodium sulfate and purified via flash chromatography. 0.11 g (61%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.25 (dt, \(J = 8.4, 1.0, 1.0\) Hz, 1H), 7.85 (dt, \(J = 8.7, 1.0, 1.0\) Hz, 1H), 7.50 (ddd, \(J = 8.4, 7.0, 1.0\) Hz, 1H), 7.45 (ddd, \(J = 8.4, 7.0, 1.0\) Hz, 1H), 4.86 (ddd, \(J = 5.8, 3.7, 2.2\) Hz, 2H), 3.64 (ddd, \(J = 5.8, 3.7, 2.2\) Hz, 2H). HRMS (ESI) calcd for C\(_{10}\)H\(_8\)N\(_2\)O\(_2\)SNa (M\(^+\)) 243.0199, found 243.0200.
Imine-Type Azaxylelenes

Results and Discussion

An additional diversity input considered for this excited-state intramolecular proton transfer (ESIPT) azaxylylene system was to vary the moiety which abstracts the proton from the ortho nitrogen. This thought led us to consider imines. Currently, there are no published examples of imines participating in ESIPT reactions. We discovered that while imines reacted more slowly than aldehydes or ketones, they did indeed react to generate an azaxylylene and were successfully able to participate in both [4+4] and [4+2] cycloaddition reactions. The products of these reactions were secondary amines which could potentially be used in subsequent post-photochemical modifications.

Several approaches were attempted in the effort to utilize an imine as the proton acceptor in the ESIPT manifold. Initially it was hoped that we could achieve this by simply converting our first-generation azaxylylene scaffolds (Scheme 4.10). Unfortunately, all imines of this type were inert in photochemical conditions. We posit that while it is likely that the imine is being promoted to the excited state, the free rotation of the R group assists in dissipating the energy, preventing any ESIPT from happening. In fact, in some cases, the imine was hydrolyzed back into the aldehyde, giving a nice photoproduct, but one which had already been thoroughly studied and characterized by my colleague, Olga A. Mukhina (see ref. 49).
Our next approach was to design an imine which would be unable to rotate in such a fashion. For this approach, we employed the synthesis scheme of Kuo and Wu\textsuperscript{51} which gave 16c (Scheme 4.11). While this imine was synthesized and coupled to furyl and norbornyl pendants, photoprecursors of this type had a handicap from the start. Olga Mukhina’s study in the irradiation of benzophenone-type photoprecursors coupled to furan tethers in this fashion were extraordinarily slow—nearly prohibitively so.\textsuperscript{49} Attempts to improve the reactivity for the imines of a similar structure by changing the conditions (differing solvents, HMPA addition, heat, long irradiation times), did not prove fruitful. In fact, some of the precursors degraded completely during irradiation with no evidence of the desired product formed.

\textbf{Scheme 4.11: Benzophenone-type imines}
Since the imine in this azaxylylene precursor could neither be freely rotating nor tethered to an “extra” aromatic ring, we endeavored to design aliphatic cyclic imines which could be coupled to unsaturated pendants. In this effort, we were successful. The first cyclic imine was synthesized via an ortho-directed Friedel-Crafts acylation of aniline with 4-chlorobutyronitrile. The nucleophilic displacement of the chloride with azide provided a good setup for an aza-Wittig reaction, furnishing the desired imine (Scheme 4.12).²

![Scheme 4.12: Cyclic aliphatic imine synthesis](image)

This imine was tethered to the unsaturated pendant that the Kutateladze group’s research⁴⁹ has shown to be the most reactive: 3-(2-furyl)-propanoic acid chloride (17c). Successful coupling and optimization of irradiation conditions furnished the [4+4] and [4+2] cycloaddition products (19c and 20c, respectively) in approximately 1:1 ratio (Scheme 4.13).

![Scheme 4.13: Synthesis and irradiation of cyclic imine 18c](image)
Unfortunately, the irradiation of a similar cyclic imine with a 6-membered ring was unsuccessful. Instead, we tethered the derivatives of 5-chlorovaleronitrile (the precursor for the 6-membered imine) to bromoacetyl bromide, displaced the resulting bromide with benzylamine, then furoylated the secondary amine to get the photoprecursor as either the azide or the chloride. The design of this type of pendant arm was first established by the Kutateladze group member Bhuvan Nandipati.\textsuperscript{49} When the ESIPT agent is a carbonyl, the furoyl pendants predominately added to the photogenerated azaxylylenes in a [4+4] fashion. In the case of the chloride 24c and azide 25c, the exclusive photoproducts are 26c and 27c respectively (Scheme 4.14). Their structures were proven via X-ray crystallographic analysis. These “linker” type compounds have the potential for diversification via either nucleophilic displacement of the chloride or via click chemistry in the azide. Cyclizing the azide via the aza-Wittig into the 6-membered cyclic imine was successful, but the compound was not photochemically active. While this pathway did not prove fruitful for the application of imines in the ESIPT photogeneration of azaxylylenes, it is our hope that the high-yielding synthesis of this scaffold be useful as a tether—perhaps in the attempt to immobilize this scaffold for solid-state syntheses.
Diversions aside, our next endeavor was in the synthesis of a cyclic imine derived from isatin. In this reaction, isatin both opened to form the aniline and cyclized to form the desired imine (28c) upon treatment with N-methylethylenediamine and anhydrous magnesium sulfate. This was coupled to 17c to furnish 29c. Its irradiation gave the desired [4+4] and [4+2] cycloaddition products in approximately 1:1 ratio (30c and 31c respectively; Scheme 4.15).
Scheme 4.15: Photoproducts of the cyclic imine derived from isatin

It is evident that the application of cyclic imines as the proton abstracting component in the ESIPT azaxylylene generation and cycloadditions is in its infancy. The use of cyclic imines in this sequence serves to increase the structural diversity of the polyheterocyclic scaffolds in both heteroatom saturation and skeletal structures available from the photoassisted generation of azaxylylenes in their intramolecular cycloadditions.

Experimental Procedures and Data

Common solvents were purchased from Pharmco Aaper and used directly, except for THF—which was refluxed over and distilled from potassium benzophenone ketyl prior to use—and hexane—which was distilled over calcium hydride. Common reagents were purchased from Sigma Aldrich, Acros, or TCI America and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25°C on a Bruker Avance III 500 MHz or Varian Mercury 400 MHz instrument in CDCl₃ with TMS as an
internal standard (unless noted otherwise). X-Ray structures were obtained with a Bruker APEX II instrument. High resolution mass spectra were obtained on the MDS SCIEX/Applied Biosystems API QSTAR™ Pulsar i Hybrid LC/MS/MS System mass spectrometer by Dr. Shuji Kato or Dr. Dan Gu from the University of Colorado at Boulder. For the $^1$H, $^{13}$C, COSY NMR spectra which are not included in Appendix B, see supporting information in ref. [49].

3-(2-Furyl)-propanoic acid chloride (17c): To a stirred solution of 0.73 g (4.6 mmol) of 3-(2-furyl)-propanoic acid in 10 mL of dichloromethane, 0.60 g (5.1 mmol) of thionyl chloride was added and refluxed for 3 h. 0.65 g (89%) of yellow-brown oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.35 (br s, 1H), 6.32 (br s, 1H), 6.10 (br s, 1H), 3.27 (t, $J$ = 7.1, 2H), 3.06 (t, $J$ = 7.1, 2H).

$N$-(2-(3,4-dihydro-2H-pyrrol-5-yl)phenyl)-3-(furan-2-yl)propanamide (18c): 0.30g of the 18c-1 (1.87 mmol), 0.30 g of 17c (1.87 mmol), and 0.25 g triethylamine (2.43 mmol, 1.3 equiv) were stirred at ambient temperature in freshly distilled THF for 2 h. The solvent was then removed, the residue dissolved in ethyl acetate (25 mL), and washed with saturated sodium bicarbonate (2 x 15 mL) and brine (1 x 15 mL). The organic layers were combined and dried over anhydrous sodium sulfate, concentrated, and purified via silica gel chromatography to give 0.43 g of
the product (82%). $^1$H NMR (500 MHz, CDCl$_3$) δ 13.31 (br. s, 1H), 8.80 (dd, $J$ = 8.3, 1.0, 1H), 7.55 (dd, $J$ = 7.9, 1.5, 1H), 7.43 (dt, $J$ = 7.9, 7.9, 1.5, 1H), 7.34 (dd, $J$ = 1.8, 0.7, 1H), 7.10 (dt, $J$ = 7.7, 7.7, 1.2, 1H), 6.30 (dd, $J$ = 3.2, 1.9, 1H), 6.11-6.09 (m, 1H), 4.17 (tt, $J$ = 9.2, 7.2, 1.8, 2H), 3.12 (t, $J$ = 7.6, 2H), 3.10-3.05 (m, 2H), 2.81-2.77 (m, 2H), 2.05-1.97 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.4, 171.1, 154.8, 141.1, 140.1, 131.4, 130.3, 122.2, 120.0, 119.4, 110.2, 105.2, 61.4, 36.7, 36.4, 23.9, 21.3.

5-Aza-6,7-benzo-12-oxa-9-spiropyrrolidino-tricyclo[7.2.1.0$^{1,5}$]dodeca-6,11-dien-4-one (19c): 0.11 g of 18c (0.39 mmol) was dissolved in aqueous methanol (5% water by volume), and irradiated in the RPR-3500 for 48 h. Two major products were observed in 1:1 ratio by NMR integration. After flash chromatography purification on silica gel using a gradient of 0%-100% ethyl acetate in hexanes, 37 mg (34%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.44 (dd, $J$ = 8.1, 1.6, 1H), 7.41 (dd, $J$ = 8.1, 1.4, 1H), 7.37 (td, $J$ = 7.3, 1.5, 1H), 6.35 (dd, $J$ = 5.8, 1.6, 1H), 5.84 (dd, $J$ = 5.8, 1.4, 1H), 4.66 (t, $J$ = 1.4, 1H), 4.15-4.09 (m, 1H), 3.39-3.32 (m, 1H), 2.98-2.89 (m, 1H), 2.75-2.65 (m, 2H), 2.60-2.51 (m, 1H), 2.45 (ddd, $J$ = 13.8, 9.4, 1.7, 1H), 2.22-2.15 (m, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.9, 162.4, 134.2, 130.8, 128.8, 128.7, 128.4, 127.1, 103.3, 87.4, 72.0, 44.0, 38.4, 30.0, 29.7, 28.3, 23.9.
(2’SR)-2,3-dihydrospiro[furo[2,3-b]pyrrolo[1,2-a]quinoline-7,2’-pyrrolidin]-1(6aH)-one (20c): 0.11 g of 18c (0.39 mmol) was dissolved in aqueous methanol (5% water by volume), and irradiated in the RPR-3500 for 48 h. Two major products were observed in 1:1 ratio by NMR integration. After flash chromatography purification on silica gel using a gradient of 0%-100% ethyl acetate in hexanes, 44 mg (40%). ¹H NMR (500 MHz, CDCl₃) δ 7.85 (d, J = 8.0, 1H), 7.34 (ddd, J = 7.8, 6.5, 2.5, 1H), 7.21-7.15 (m, 2H), 6.23 (t, J = 2.8, 1H), 4.63 (dd, J = 2.9, 2.3, 1H), 3.63 (t, J = 2.3, 1H), 2.99 (ddd, J = 10.2, 7.9, 5.0, 1H), 2.87 (ddd, J = 16.7, 10.5, 8.6, 1H), 2.80 (ddd, J = 10.2, 8.6, 6.5, 1H), 2.60-2.43 (m, 4H), 2.10-1.82 (m, 5H).

1-(2-aminophenyl)-5-chloropentan-1-one (21c): Boron trichloride (1 M in dichloromethane, 15 mL, 15 mmol) was diluted with dichloroethane (50 mL) and cooled to 0°C. Aniline (2.50 g, 26.8 mmol) was added dropwise and the solution was allowed to stir at 0°C for 10 min. 5-Chlorovaleronitrile (3.20 g, 27.2 mmol) was added, followed by aluminum chloride (4.00 g, 30.0 mmol) and the solution was allowed to warm to ambient temperature. After 10 minutes, the reaction mixture was heated at reflux for 3 h. The solution was allowed to cool to ambient temperature, 2 M HCl (15 mL) was added, and the reaction mixture was heated at reflux for 30 min. The reaction mixture was then diluted with water (20 mL) extracted with dichloromethane (3
x 20 mL), the combined organic layers washed with brine (25 mL) and dried over anhydrous sodium sulfate. Concentrating the organic layers then purifying via flash chromatography on silica gel using a gradient of 0%-100% ethyl acetate in hexanes, the pure product was recovered. 3.35 g (55%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.76 (dd, $J = 8.6, 1.6, 1$H), 7.29 (dt, $J = 8.3, 1.6, 1$H), 6.70-6.65 (m, 2H), 6.35-6.25 (br. s, 2H), 3.64-3.60 (m, 2H), 3.03-2.99 (m, 2H), 1.94-1.88 (m, 4H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 202.0, 150.4, 134.3, 131.1, 117.8, 117.4, 115.8, 44.8, 38.2, 32.2, 22.0.

1-(2-aminophenyl)-5-azidopentan-1-one (21c-1): 2.81 g of the 21c (13.3 mmol) was dissolved in 150 mL DMF along with 1.20 g sodium azide (18.5 mmol) and a catalytic amount of sodium iodide. This was heated to 100°C and kept at that temperature for 8h before it was filtered and concentrated. After flash chromatography purification on silica gel using a gradient of 0%-100% ethyl acetate in hexanes, the pure product was recovered. 2.26 g (78%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.76 (dd, $J = 8.7, 1.6, 1$H), 7.31-7.27 (m, 1H), 6.72-6.65 (m, 2H), 6.34-6.27 (br. s, 2H), 3.36 (t, $J = 7.0, 2$H), 3.01 (t, $J = 7.0, 2$H), 1.88-1.79 (m, 2H), 1.75-1.68 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 201.9, 150.4, 134.3, 131.1, 117.8, 117.4, 115.8, 51.4, 38.4, 28.6, 21.8.

2-(3,4,5,6-tetrahydropyridin-2-yl)aniline (21c-2): 2.48 g of the 21c-1 (11.4 mmol) was dissolved in 100 mL DMF along with 3.27 g triphenylphosphine (12.5
mmol). This was heated to 100°C and kept at that temperature for 2 h before it was cooled to ambient temperature and concentrated. After flash chromatography purification on silica gel using a gradient of 0%-100% ethyl acetate in hexanes, the pure product was recovered. 1.75 g (88%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.49 (dd, $J = 7.9, 1.4, 1$H), 7.12 (dt, $J = 8.4, 1.6, 1$H), 6.69-6.64 (m, 2H), 6.61-6.52 (br. s, 2H), 3.88 (tt, $J = 7.6, 5.9, 1.8, 2$H), 2.68 (tt, $J = 8.5, 6.6, 1.8, 2$H), 1.88-1.82 (m, 2H), 1.71-1.65 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.0, 148.2, 129.5, 128.1, 120.6, 116.9, 115.8, 49.0, 27.6, 21.8, 20.1.

3-(furan-2-yl)-N-(2-(3,4,5,6-tetrahydropyridin-2-yl)phenyl) propanamide (21c-3): 0.31 g of the 21c-2 (1.78mmol), 0.28 g of 17c (1.78mmol), and 0.23 g triethylamine (2.31 mmol, 1.3eq) were stirred at ambient temperature in freshly distilled THF for 2 h. The solvent was then removed, the residue dissolved in ethyl acetate (25 mL), and washed with saturated sodium bicarbonate (2 x 15 mL) and brine (1 x 15 mL). The organic layers were combined and dried over anhydrous sodium sulfate, concentrated, and purified via silica gel chromatography to give 0.44 g of the product (84%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.72 (dd, $J = 8.4, 1.2, 1$H), 7.62 (dd, $J = 7.9, 1.6, 1$H), 7.37 (td, $J = 8.4, 1.4, 1$H), 7.34 (dd, $J = 1.8, 0.8, 1$H), 6.30 (dd, $J = 3.1, 2.0, 1$H), 6.10-6.08 (m, 1H), 3.91 (ddd, $J = 7.8, 5.8, 2.0, 2$H), 3.11 (t, $J = 7.1, 2$H), 2.76-2.69 (m, 4H), 1.91-1.85 (m, 2H), 1.75-1.69 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.7, 168.9, 154.8, 141.1, 139.6, 130.6, 127.5, 123.4, 122.1, 120.6, 110.2, 105.3, 48.8, 36.9, 27.8, 24.0, 21.4, 19.8.
2-bromo-N-(2-(5-chloropentanoyl)phenyl)acetamide (22c): 0.59 g of 21c (2.8 mmol) was stirred in 25 mL dichloromethane along with 0.56 g bromoacetyl bromide (2.8 mmol) in the presence of 0.28 g dry pyridine (3.6 mmol). This was allowed to stir at ambient temperature for 20 min before it was washed with saturated sodium bicarbonate (2 x 10 mL) and the organic layer dried over anhydrous sodium sulfate then concentrated. Purification via flash chromatography gave the pure product. 0.88 g (94%). ¹H NMR (500 MHz, CDCl₃) δ 12.33 (s, 1H), 8.74 (dd, J = 8.5, 1.0 Hz, 1H), 7.98 (dd, J = 8.0, 1.5 Hz, 1H), 7.62 (dt, J = 7.4, 7.4, 1.4 Hz, 1H), 7.22 (dt, J = 7.4, 7.4, 1.2 Hz, 1H), 4.05 (s, 2H), 3.63 (t, 6.2 Hz, 2H), 3.12 (t, J = 6.7 Hz, 2H), 1.99-1.87 (m, 4H). ¹³C NMR (126 MHz, CDCl₃) δ 203.9, 165.4, 140.0, 135.0, 130.6, 122.4, 122.3, 121.1, 44.6, 39.0, 29.6, 21.8.

N-benzyl-N-(2-(2-(5-chloropentanoyl)phenylamino)-2-oxoethyl)furan-2-carboxamide (24c): 0.38 g of 22c (1.1 mmol) was dissolved in anhydrous dichloromethane (25 mL) along with 0.16 g benzylamine (1.4 mmol) and 0.32 g DIPEA (2.5 mmol). This was allowed to stir at ambient temperature for 8 h, then it was washed with saturated sodium bicarbonate (2 x 10 mL), and the organic layer was dried over anhydrous sodium sulfate to give 23c. The organic layer was decanted from the sodium sulfate and then 0.17 g 2-furoyl chloride (1.8 mmol) was added along with 0.24 g
DIPEA (1.9 mmol). This was stirred at ambient temperature for 8 h then washed with saturated sodium bicarbonate (2 x 10 mL) and the organic layer dried over anhydrous sodium sulfate then concentrated. Purification via flash chromatography gave the pure product. 0.38 g (77%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 12.22 (s, 1H), 8.78 (dd, $J = 8.5$, 1.0 Hz, 1H), 7.93 (d, $J = 8.0$, 1H), 7.58 (t, $J = 7.7$ Hz, 1H), 7.51 (s, 1H), 7.43-7.30 (m, 5H), 7.22 (s, 1H), 7.17 (t, $J = 7.3$ Hz, 1H), 6.52 (s, 1H), 5.07 (br s, 2H), 4.30 (br s, 2H), 3.57 (ddd, $J = 6.6$, 3.2, 3.2 Hz, 2H), 3.06 (ddd, $J = 6.7$, 3.6, 3.6, 2H), 1.90-1.78 (m, 4H).

$N$-(2-((2-(5-azidopentanoyl)phenylamino)-2-oxoethyl)-$N$-benzylfuran-2-carboxamide (25c): 2.08 g of 24c (4.6 mmol) was stirred in 20 mL DMF along with 0.30 g sodium azide (4.6 mmol) and then heated to 100°C for 6 h. The reaction mixture was concentrated under vacuum and then purified via flash chromatography to furnish the pure product. 1.92 g (91%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 12.20 (s, 1H), 8.79 (d, $J = 8.5$ Hz, 1H), 7.93 (d, $J = 7.8$, 1H), 7.59 (t, $J = 7.3$ Hz, 1H), 7.51 (s, 1H), 7.43-7.30 (m, 5H), 7.21 (s, 1H), 7.17 (t, $J = 7.5$ Hz, 1H), 6.52 (s, 1H), 5.07 (br s, 2H), 4.30 (br s, 2H), 3.32 (D, $J = 6.8$ Hz, 2H), 3.06 (d, $J = 7.0$, 2H), 1.77 (p, $J = 7.2$ Hz, 2H), 1.77 (p, $J = 7.2$ Hz, 2H).
syn-9-Hydroxy-9-(4-chlorobutyl)-3-N-benzyl-7,8-benzo-13-oxa-3,6-diazatricyclo[8.2.1.01,6] trideca-7,11-diene-2,5-dione (26c): 0.24 g of 24c (0.53 mmol) was dissolved in 20 mL aqueous methanol (5% H₂O by volume) and irradiated for 4 h. The mixture was then concentrated and purified via flash chromatography. 0.21 g (89%). ¹H NMR (500 MHz, CDCl₃) δ 7.45-7.31 (m, 8H), 7.16-7.12 (m, 1H), 6.25 (dd, J = 6.0, 1.8 Hz, 1H), 5.95 (dd, J = 6.0, 0.7 Hz, 1H), 5.07 (dd, J = 1.8, 0.7 Hz, 1H), 4.97 (d, J = 14.7 Hz, 1H), 4.55 (d, J = 14.5 Hz, 1H), 4.34 (d, J = 18.2 Hz, 1H), 4.09 (d, J = 18.2 Hz, 1H), 3.66 (ddd, J = 21.1, 10.9, 6.4 Hz, 2H), 3.15 (br. s, 1H), 2.20 (ddd, J = 14.0, 12.0, 4.9 Hz, 2H), 2.08 (ddd, J = 13.9, 11.8, 4.7 Hz, 2H), 2.02-1.93 (m, 2H), 1.82-1.77 (m, 1H).

syn-9-Hydroxy-9-(4-azido)-3-N-benzyl-7,8-benzo-13-oxa-3,6-diazatricyclo[8.2.1.01,6] trideca-7,11-diene-2,5-dione (27c): 0.31 g of 25c (0.67 mmol) was dissolved in 20 mL aqueous methanol (5% H₂O by volume) and irradiated for 4 h. The mixture was then concentrated and purified via flash chromatography. 0.25 g (81%). ¹H NMR (500 MHz, CDCl₃) δ 7.45-7.30 (m, 8H), 7.16-7.12 (m, 1H), 6.23 (dd, J = 6.1, 1.8 Hz, 1H), 5.95 (d, J = 6.0, Hz, 1H), 5.05 (dd, J = 1.6,
Hz, 1H), 4.97 (d, J = 14.5 Hz, 1H), 4.54 (d, J = 14.5 Hz, 1H), 4.34 (d, J = 18.4 Hz, 1H), 4.09 (d, J = 18.4 Hz, 1H), 3.41 (dd, J = 24.4, 12.4, 6.0 Hz, 2H), 2.11-2.03 (m, 1H), 1.85-1.69 (m, 4H), 1.62-1.52 (m, 1H).

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\text{3-(2-aminophenyl)-1-methyl-5,6-dihydropyrazin-2(1H)-one (28c): 0.34 g isatin (2.31 mmol), 0.17 g N-methylethylenediamine (2.31 mmol), and a large excess of anhydrous magnesium sulfate (2.78 g, 10 equiv) were stirred in freshly distilled THF at ambient temperature for 1 h. The solution was filtered to remove magnesium sulfate, concentrated, and purified on silica gel via flash chromatography to give 0.11 g of the pure product (24%).} 
\]

\[
1^H\text{ NMR (500 MHz, CDCl}_3\text{) }\delta \text{ 7.76 (dd, } J = 8.3, 1.5, \text{ 1H), 7.17 (dt, } J = 7.5, 7.5, 1.5, \text{ 1H), 6.75-6.67 (m, 2H), 5.78 (br. s, 2H), 3.94 (t, } J = 6.3, \text{ 2H), 3.52 (t, } J = 6.3, \text{ 2H), 3.17 (s, 3H).} 
\]

\[
13^C\text{ NMR (126 MHz, CDCl}_3\text{) }\delta \text{ 163.8, 157.2, 148.2, 132.4, 131.0, 117.0, 116.7, 116.2, 47.0, 46.3, 34.9.} 
\]

\[
\text{3-(furan-2-yl)-N-(2-(4-methyl-3-oxo-3,4,5,6-tetrahydropyrazin-2-yl)phenyl)propanamide (29c): 0.12 g of the 28c (0.59 mmol), 0.11 g of 17c (0.69 mmol, 1.2 eq), and 0.08 g triethylamine (0.83 mmol, 1.4 eq) were stirred at ambient temperature in freshly distilled THF (20 mL) for 2 h. The solvent was then removed, the residue dissolved in ethyl acetate (25 mL), and washed with saturated sodium bicarbonate} 
\]
(2 x 15 mL) and brine (1 x 15 mL). The organic layers were combined and dried over anhydrous sodium sulfate, concentrated, and purified via silica gel chromatography to give 0.14 g of the product (78%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.34 (br. s, 1H), 8.48 (d=, $J$ = 7.7, 1H), 7.76 (d, $J$ = 8.0, 1H), 7.43 (dt, $J$ = 7.6, 7.6, 1.5, 1H), 7.33 (d, $J$ = 2.0, 1H), 7.12 (t, $J$ = 7.6, 1H), 6.30 (dd, $J$ = 3.1, 2.0, 1H), 6.08 (d, $J$ = 3.1, 1H), 3.98 (t, $J$ = 6.1, 2H), 3.56 (t, $J$ = 6.1, 2H), 3.19 (s, 3H), 3.09 (t, $J$ = 7.4, 2H), 2.70 (t, $J$ = 7.4, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 170.8, 170.1, 164.0, 156.6, 154.5, 151.1, 138.5, 131.9, 131.3, 122.5, 121.6, 110.3, 105.4, 47.1, 46.1, 36.6, 35.0, 23.9.

(2'RS,3'SR,6aSR)-1'-methyl-2,3,4',5'-tetrahydro-1'H-spiro[furo[2,3-b]pyrrolo[1,2-a]quinoline-7,2'-pyrimidine]-1,6'(3'H,6aH)-dione (30c): 0.12 g of 29c (0.37 mmol) was dissolved in aqueous methanol (5% water by volume), and irradiated in a Pyrex reaction vessel in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm) for 36 h. After flash chromatography purification on silica gel using a gradient of 0%-100% ethyl acetate in hexanes, the pure product was recovered. 41 mg (35%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.84 (dd, $J$ = 8.0, 1.1, 1H), 7.38 (dt, $J$ = 8.0, 1.3, 1H), 7.18 (dt, $J$ = 7.7, 1.1, 1H), 7.12 (dd, $J$ = 7.7, 1.3, 1H), 6.20 (t, $J$ = 2.8, 1H), 5.43 (dd, $J$ = 2.8, 2.3, 1H), 3.91 (t, $J$ = 2.8, 1H), 3.54 (dd, $J$ = 12.0, 8.8, 4.9, 1H), 3.31 (dt, $J$ = 12.0, 4.5, 1H), 3.14 (s, 3H), 2.97-2.87 (m, 2H), 2.81 (ddd, $J$ = 13.3, 8.8, 4.4, 1H), 2.67 (dd, $J$ = 9.1, 1H), 2.64-2.51 (m, 2H), 2.44-
2.36 (m, 1H). \[^{13}\text{C}\] NMR (126 MHz, CDCl\(_3\)) \(\delta\) 167.8, 144.7, 133.3, 131.6, 128.6, 128.0, 125.4, 123.5, 101.8, 100.8, 64.4, 58.5, 50.8, 38.5, 35.6, 35.3, 29.8.

(2\(^{RS}\),3\(^{aSR},Z\))-1\(^{\prime}\)-methyl-3\(^{a}\),6-oxa-3\(^{a}\),4\(^{\prime}\),5\(^{\prime}\)-tetrahydro-1\(^{H}\),1\(^{\prime}\)-H-spiro[benzo[g]pyrrolo[1,2-a]azocine-7,2\(^{\prime}\)-pyrimidine]-1,6\(^{\prime}\)(2\(^{H}\),3\(^{\prime}H,6H\))-dione (31c): 0.12 g of 29c (0.37 mmol) was dissolved in aqueous methanol (5% water by volume), and irradiated in a Pyrex reaction vessel in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300-400 nm UV source with peak emission at 350 nm) for 36 h. After flash chromatography purification on silica gel using a gradient of 0%-100% ethyl acetate in hexanes, the pure product was recovered. 47 mg (39%). \(^{1}\text{H}\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.44 (dd, \(J = 8.0, 1.4, 1H\)), 7.33 (dt, \(J = 7.7, 1.5, 1H\)), 7.17 (dt, \(J = 8.0, 1.5, 1H\)), 6.97 (dd, \(J = 7.7, 1.4, 1H\)), 6.83 (dd, \(J = 5.7, 2.0, 1H\)), 5.67 (dd, \(J = 5.7, 1.0, 1H\)), 4.82 (dd, \(J = 1.9, 1.0, 1H\)), 3.61 (ddd, \(J = 11.4, 11.4, 5.6\) 1H), 3.22 (dd, \(J = 11.4, 4.2, 1.2, 1H\)), 3.13 (s, 3H), 2.97 (dt, \(J = 17.6, 9.5, 1H\)), 2.85 (ddd, \(J = 12.5, 5.4, 1.2, 1H\)), 2.77 (ddd, \(J = 12.1, 12.1, 4.2, 1H\)), 2.72-2.67 (m, 2H), 2.59-2.42 (m, 2H). \[^{13}\text{C}\] NMR (126 MHz, CDCl\(_3\)) \(\delta\) 173.1, 169.2, 168.2, 139.4, 133.6, 130.4, 128.8, 128.0, 127.8, 125.6, 103.7, 86.0, 73.1, 50.2, 37.9, 34.7, 30.4, 28.8.
Chapter 5: Conclusions and Summary

With the techniques and methodologies described in this research, we have been able to demonstrate the rapid growth in molecular complexity that excited state chemistry offers by providing expeditious access to a topologically diverse range of diverse polycyclic structures, many of which are decorated with rigidly held functional groups. Such small, drug-like molecules are thought by many to be desirable in their function as molecular probes for exploring unknown binding pockets in proteins, and are on point with Schreiber’s assertion that diversity-oriented syntheses and targets with a high level of molecular complexity are highly desirable for the exploration of biological and medicinal applications. With these heretofore underutilized techniques in the “synthetic toolbox” and the potential for various diversity inputs at many of the steps, it is our hope that these compounds and methods have a broader impact on medicinal chemistry and drug discovery.

To this end, we have probed the potential of how strain installed via a photochemical step can exact surprising rearrangements to give novel scaffolds. We also showed how adjusting the flexibility of a starting material can change the regiochemistry of a photochemical step as well as the topology of the products resulting from oxametathesis. We have also developed a modular assembly of compounds which can give rise to azaxyxlenes via ESIPT and which can undergo cycloaddition with tethered
unsaturated pendants. This assembly scheme is rich in potential for a variety of diversity inputs, a few of which are explored in this research.

Since our goal is the synthesis of polyheterocyclic drug-like scaffolds, several of the compounds listed in this work have been subjected to quick screening via OSIRIS Property Explorer, a program that has a proprietary algorithm for assessing a variety of characteristics of a given structure. This program estimates a molecule’s LogP or the partition coefficient for \( \log(c_{\text{octanol}}/c_{\text{water}}) \). This calculated LogP, or cLogP provides insight into how hydrophilic a compound is. Compounds with a high LogP are thought to have poor absorption/permeation as drugs. According to Lipinski’s rule of 5, this value should be less than 5. Tangential to this absorption calculation is the LogS value which is a second assessment of solubility. It is desirable to have a value greater than -4 in this category. Another value given is its druglikeness. This is assessed by comparing topological fragments within a given molecule to a database of common “fingerprint” fragments within existing drugs. Ideally, this value should be positive. Lastly is drug-score—a parameter that combines these and other features of a given compound (including Lipinski’s rule that molecular weight should be less than 500 g/mol). This value ranges from 0-1.0, with 1.0 being the better potential drug lead.
The focus on this research was in the methods—the implementation of various synthetic schemes which include photochemical techniques and furnishing unique, privileged polycyclic and polyheterocyclic scaffolds. It is promising that the products themselves hold the potential to be drug leads. With the methods described herein, we hope to have advanced the practical application of photoassisted syntheses in the DOS-approach to novel drug-like polyheterocycles.
References


Appendix A: NMR spectra for Chapter 3
5:1 mixture with $11b$

10:9 mixture with $13b$
Appendix B: NMR Spectra for Chapter 4
Appendix C: Published Works


Note: Teresa M. Arisco is a pseudonym (maiden name) of Teresa M. Cowger.