

Visible-Light Mediated Redox Processes: Strategies and Applications in Organic Synthesis

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**A thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
in partial fulfillment of the requirements for the
Doctorate in Philosophy degree in Chemistry**

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Abstract

Over the past decade, the field of photoredox catalysis has garnered increasing amounts of attention in the organic chemistry community due to its wide applicability in sustainable free radical-mediated processes. Several examples have demonstrated that under carefully optimized conditions, efficient and highly selective processes can be developed through excitation of a photosensitizer using inexpensive, readily available light sources. Furthermore, these reactions can generally be performed under milder conditions than thermal reactions, as all the energy required to overcome the reaction barrier is supplied by light.

Despite all these recent advancements in the field, many of these discoveries often lack in depth investigations into the excited state kinetics and underlying mechanisms. Furthermore, the vast majority of these transformations are photocatalyzed by ruthenium and iridium polypyridyl complexes. Not only are these precious metal catalysts extremely costly, but these metals are also known to be toxic, limiting their potential use in the development of pharmaceutical protocols. Herein, we present our solutions to these shortcomings, which involve a three-prong approach in the development of novel protocols, understanding the underlying mechanisms through detailed kinetic analysis, and by the development of new tools to facilitate mechanistic investigation for practitioners who may not possess specialized photochemical equipment.

In this work, we were the first to demonstrate that radicals derived from amines, commonly employed as “sacrificial” electron-donors, can also act as reducing agents in photoredox transformations. We also present examples in which Methylene Blue, an inexpensive, non-toxic organic dye, can be employed as a viable alternative to ruthenium complexes for photoredox transformations. By employing a photosensitizer with more favourable excited state kinetics for electron-transfer, we successfully demonstrated that Methylene Blue could be used to increase the efficiency of a previously developed photoredox transformation.

While employing organic dyes is an excellent strategy to lowering the cost of photoredox transformations, another viable strategy is to employ heterogeneous semiconductors. Titanium dioxide is an example of a semiconductor which is often employed in photocatalytic applications due to its low cost, desirable redox properties, and high chemical stability which allows for continued use. However, titanium dioxide has seen limited use in organic synthesis due to the requirement of UV irradiation for excitation. Herein, we present a process which led to the discovery of visible light photochemistry with titanium dioxide, generated through the adsorption of indole substrates creating a new, visible light absorbing complex. Employing this strategy, we were able to promote the photocatalytic Diels–Alder reaction of indoles with electron-rich dienes, giving access to valuable tetrahydrocarbazole scaffolds.

Finally, in order to facilitate the characterization of chain processes in photoredox catalysis, we have successfully developed a visible light actinometer based on the ubiquitous photocatalyst, $\text{Ru}(\text{bpy})_3\text{Cl}_2$. This actinometer offers many advantages compared to other visible light actinometers, such as completely eliminating the need for spectral matching, as the actinometer is also the photocatalyst. This technique should provide researchers with a mechanistic tool to properly characterize chain propagation in the transformation of interest.

Acknowledgements

I have to begin by thanking my Ph.D. supervisor, Dr. Tito Scaiano. I am extremely grateful to have been given the opportunity to move to Ottawa and study under his direction. Tito has been an incredible supervisor and mentor to me throughout my graduate studies, and his group provides a research environment that is second to none with the available equipment and expertise. Over the years, Tito has given me the freedom to explore my own ideas, and he also gave me the opportunity to write manuscript drafts. This hands-off approach has helped me grow as a researcher, giving me invaluable experience as I pursue my career in academia. I would also like to thank Tito and Elda for their wonderful hospitality when hosting the yearly group ski and camping trips at their cottage in Morin-Heights. These group outings are just another aspect of what makes the group such a great place to be for graduate studies.

Of course, I wouldn't be where I am today without the RISE program, and my Honours thesis supervisor Dr. Brian Wagner at UPEI. Brian introduced me to the RISE program during my third year of undergraduate studies, and during the annual RISE conference, I met Tito, who later agreed to take me on as a graduate student. For this, and all of Brian's support throughout the years, I am grateful.

During 2015, I had the opportunity to spend four months in the lab of Tehshik Yoon at the University of Wisconsin-Madison. I would like to thank Tehshik for agreeing to host me as a visiting graduate student, and I would like to thank NSERC for supplying the funding for this once in a lifetime opportunity. I learned a lot about organic chemistry, in particular, in regards to organic synthesis during that time. I would like to thank the entire Yoon group for being so welcoming to me, especially Elliot Farney and Kaz Skubi, who I've had countless chemistry discussions with. I've learned so much from you all, which has only strengthened me as a researcher, and I thank you all for this.

The Scaiano group was a wonderful environment for graduate studies, with graduate students and post-docs with expertise in a wide array of different backgrounds, from nanomaterials to physical organic chemistry to biomaterials. Most importantly, you are all great people who made coming to the lab everyday a great experience. Thank you Betty Yakimento for everything you do for our lab, and for ensuring everything runs smoothly. Thank you to Michel Grenier, our laser and LED technician, and our Mr. Fix It, for all your help in designing and setting up experimental apparatuses, and for your help in troubleshooting instrumentation problems. Without Michel, many of the experiments presented in this dissertation would not be possible. Thank you to Hossein Ismaili for teaching me everything you know about how to be an organic chemist. Thank you for your patience in training a new graduate student, and for all the daily discussions on photoredox catalysis. A huge thank you to Christopher McTiernan, who I had the pleasure of collaborating with on a number of projects throughout my graduate studies. I've learned so much from our daily chemistry discussions, and I wouldn't be where I am today without your help. Finally, I'd like to thank Greg Hodgson, Kevin Stamplecoskie and Matt Decan for all your chemistry discussions and good times in and out of the lab, and I wish all current and former Scaiano group members nothing but the best in your future endeavours.

One of the best aspects of doing chemistry at the University of Ottawa is the collaboration between groups throughout the department. I've had the pleasure to collaborate with Terry McCallum and Mathieu Morin from the Barriault group during the last couple of years, both who share common interests with me in photoredox catalysis. I've learned a lot from chemistry discussions with the Barriault group, and I find myself in their lab every day asking questions relating to organic chemistry and synthesis. Thank you all for this, and of course for the good times outside of the lab.

Finally, a huge thank you to all of my family and friends, especially to my parents, Paul and Nancy, and to my brother, Shawn. It's been a long road to this point, and you have supported me every step of the way in this adventure which has seen me move to Ottawa, and briefly to Madison, Wisconsin. I don't know where this road I'm on will continue to take me, but I know that wherever I end up, you'll be there to support me, and for this I thank you.

Contribution Statement

All of the projects presented in this dissertation were completed under the supervision and guidance of Dr. Tito Scaiano. Throughout my graduate studies, I have had the opportunity to collaborate with my fellow graduate students and postdoctoral fellows to combine our expertise on a variety of projects. Therefore, while the majority of the work presented in this dissertation is the result of independent research, due to the highly collaborative nature of the Scaiano group I wanted to highlight my direct contribution as well as contributions from my peers who collaborated with me on some of the projects presented.

While investigating the role of α -aminoalkyl radicals in photoredox catalysis, two independent systems were studied. The work presented employing Irgacure 379 was done by Hossein Ismaili, a former postdoctoral fellow in the Scaiano group, while I performed experiments employing the thioxanthone systems.

The work presented employing Methylene Blue as an inexpensive alternative for photoredox transformations was done in collaboration with Christopher McTiernan and Hossein Ismaili. The original idea of employing Methylene Blue for photoredox transformations was conceived by Hossein Ismaili and I. All of the bench scale photochemistry experiments described in both of these projects were performed by myself. Christopher performed the laser flash photolysis experiments presented in this work, while Hossein was also involved in many discussions throughout both projects.

The work presented on the library of organic dyes was done in collaboration with Christopher McTiernan. I, along with supervisor Tito Scaiano, conceived the idea of collecting these data, and compiling it into a useful appendix. Christopher performed the majority of the laser flash photolysis and steady-state fluorescence experiments, as well as all of the cyclic voltammetry experiments. I performed all of the bench scale photochemistry experiments, as well as some of the laser flash

photolysis experiments, including the determination of the triplet energies for a number of the organic dyes studied.

The work presenting the development of a visible light actinometer based on $\text{Ru}(\text{bpy})_3\text{Cl}_2$ was done in collaboration with Christopher McTiernan, and two RISE summer students, Wyatt Vine and Rebecca DiPuchio. It should be noted that this project was published alongside our modified intermittent illumination method, however that work, which was performed by Christopher McTiernan, was presented in Christopher's thesis. The idea to develop an actinometer based on $\text{Ru}(\text{bpy})_3\text{Cl}_2$ was conceived by Tito Scaiano. The system, employing $\text{Ru}(\text{bpy})_3\text{Cl}_2$ and 9,10-diphenylanthracene, was designed by myself. The work presented for this project was done in collaboration with Wyatt Vine, a summer student under my supervision. The laser flash photolysis data presented in this work was done by Christopher McTiernan.

Finally, the work presented on photocatalytic Diels–Alder reactions was done in collaboration with Dr. Tehshik Yoon, a project which started when I was a visiting graduate student in his lab. The idea of employing heterogeneous semiconductors to promote the Diels–Alder reaction of indoles was conceived by Tehshik Yoon and myself. All of the work presented for this project was done by myself under the supervision and guidance of both Tehshik Yoon and Tito Scaiano.

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List of Abbreviations

[]	Concentration
$^1\text{O}_2$	Singlet oxygen
A	Electron acceptor
AcCl	Acetyl chloride
Bpin	Bis(pinacolato)diborane
CB	Conduction Band
CdS	Cadmium sulfide
CF_3	Trifluoromethyl
CH_2Cl_2	Dichloromethane
Cp_2Fe	Ferrocene
CTC	Charge-transfer complex
D	Electron donor
DBU	1,8-diazobicyclo-[5.4.0]undec-7-ene
DFT	Density functional theory
DMF	Dimethylformamide
DPA	9,10-diphenylanthracene
DPBF	1,3-diphenylbenzoisofuran
e^-	Electron
$E_{1/2}$	Half wave Potential
EA	Electron affinity
E_{Ph}	Energy of a photon

eT	Electron-transfer
ET	Energy-transfer
EtOAc	Ethyl acetate
Exciplex	Excited state complex
f_{Δ}^T	Singlet oxygen generation efficiency
GC-MS	Gas chromatography mass spectrometry
H ⁺	Proton
h ⁺	Hole
h	Planck's constant
Hex	Hexanes
HOMO	Highest occupied molecular orbital
h ν	Light
Hz	Hertz
I-379	Irgacure 379
IC	Internal conversion
IP	Ionization potential
<i>i</i> Pr ₂ NEt	<i>N,N</i> -diisopropylethylamine
Ir(ppy) ₃	Tris[2-phenylpyridinato-C ² ,N]iridium(III)
ISC	Intersystem crossing
J	Joules or Coupling constant
k _q	Bimolecular rate constant
K _A	Association Constant

K _{SV}	Stern-Volmer constant
LFP	Laser flash photolysis
LUMO	Lowest unoccupied molecular orbital
MB	Methylene Blue
MeCN	Acetonitrile
MeNO ₂	Nitromethane
MeOH	Methanol
Mes-Acr ⁺	9-mesityl-10-methyl acridinium perchlorate
MLCT	Metal-to-ligand charge-transfer
NaHCO ₃	Sodium bicarbonate
NMe ₃	Trimethylamine
NEt ₃	Triethylamine
Ox	Oxidation
PC	Photocatalyst
PCeT	Proton-coupled electron-transfer
PhTHIQ	2-phenyl-1,2,3,4-tetrahydrosisoquinoline
pK _a	Acid dissociation constant
Red	Reduction
Ru(bpy) ₃ Cl ₂	Tris(2,2'-bipyridyl)ruthenium(II) chloride
S _x	Singlet state
SCE	Saturated calomel electrode
SeT	Single electron-transfer
SOMO	Singly occupied molecular orbital

T_x	Triplet state
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TiO_2	Titanium dioxide
TLC	Thin layer chromatography
TMEDA	<i>N, N, N', N'</i> -tetramethyl-ethylenediamine
TPPT	Triphenylpyrylium tetrafluoroborate
UV	Ultraviolet
VB	Valence band
ΔE_{BG}	Band gap energy
$\Delta E_{Coulombic}$	Coulombic energy
ΔG_{eT}	Gibbs free energy
ε	Molar absorptivity
δ	Chemical Shift
Φ	Quantum yield
Φ_{Ph}	Photon flux
λ	Wavelength
τ	Lifetime
ν	Rate
ζ_p	Photonic Efficiency

1. An Introduction to Organic Photochemistry and Photoredox Catalysis

1.1 Opening Remarks

The work presented in this dissertation is centered on the field of photoredox catalysis, which has become an emerging strategy in organic synthesis to promote clean and selective free-radical transformations. Despite the many synthetic advancements made using photoredox catalysis over the last twenty years, many of the transformations, typically catalyzed by expensive ruthenium and iridium complexes, are obtained in the absence of an understanding of the excited state kinetics and underlying mechanisms. The goals of this dissertation are threefold:

- 1) To develop inexpensive alternatives based off of organic dyes and heterogeneous semiconductor materials to catalyze these photoredox transformations.
- 2) To gain an understanding of the excited state kinetics and underlying mechanisms in order to rationalize and improve the overall reactivity of photoredox transformations.
- 3) To develop novel methods to facilitate mechanistic investigations for synthetic laboratories who may not possess the specialized equipment or expertise to perform such studies.

This chapter will focus on introducing the reader to the theory behind organic photochemistry and to photoredox catalysis, while also highlighting some of the recent advancements in the field. The importance of excited state kinetic analysis to gain a deeper understanding of the underlying photochemistry will also be discussed.

1.2 An Introduction to Organic Photochemistry

Organic photochemistry is a subfield of chemistry that is concerned with the structures and dynamic processes of organic molecules that result from the interaction with light.

Simply, organic photochemistry involves the overall process of $R + h\nu \rightarrow {}^*R \rightarrow P$, where R is an organic molecule which absorbs a photon (light, $h\nu$), whose frequency (ν) is appropriate for light absorption by R, ${}^*R$ is an electronically excited organic molecule, and P is the product of the light promoted reaction of R. This paradigm is summarized in Figure 1.1, which describes all of the physical and chemical steps that occur as the result of the absorption of light by an organic molecule (R) and the eventual formation of the product (P) or the possible regeneration of the starting material (R).¹

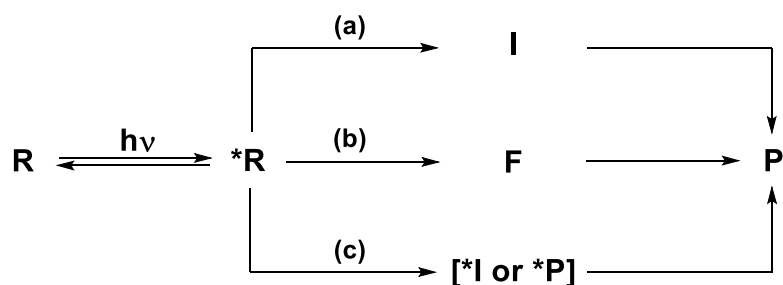


Figure 1.1. The paradigm of organic photochemical reactions, where R is an organic molecule, I is a reactive intermediate, and P is the product of the reaction. Adapted with permission from reference 1. Copyright 2010 University Science Publishers.

As demonstrated in Figure 1.1, there are three distinct pathways that can lead to the formation of an isolated product upon the generation of an electronically excited organic molecule (${}^*R$). The first, labeled pathway (a), involves the formation of a distinct reactive intermediate (I), which can generally be described as possessing the characteristics of a radical pair, a biradical, or a zwitterion. The second, labeled pathway (b), does not involve a discrete reactive intermediate (I) but instead proceeds via a "funnel" (F). This pathway can be described, in terms of energy surfaces, as a conical surface intersection or as a minimum produced by surface-avoided intersections. This pathway is less common, and will not be further discussed as it is outside the scope of this dissertation. The third and final pathway, labeled (c) in Figure 1.1, involves the formation of an electronically excited

intermediate (*I) or an electronically excited product (*P). Of these three pathways, the majority of organic photochemistry examples proceed through pathway (a), including the examples to be disclosed in this dissertation.

Since all three pathways are initiated by a ground state reactant (R) absorbing a photon ($h\nu$) to create an electronically excited molecule (*R), it is important to understand the nature of this process. Figure 1.2 displays a typical Jablonski diagram², which summarizes all the processes which can occur when an organic molecule (R) absorbs a photon. The diagram depicts the ground state of the molecule (S_0), the first and second singlet electronic excited states (S_1 and S_2 , respectively), and the lowest-energy triplet state (T_1). At each of these electronic energy levels, the molecule can exist in a number of vibrational energy levels, depicted as 0, 1, 2, etc. Processes such as quenching through energy- and electron-transfer are not included here and will be discussed in detail in Section 1.3.

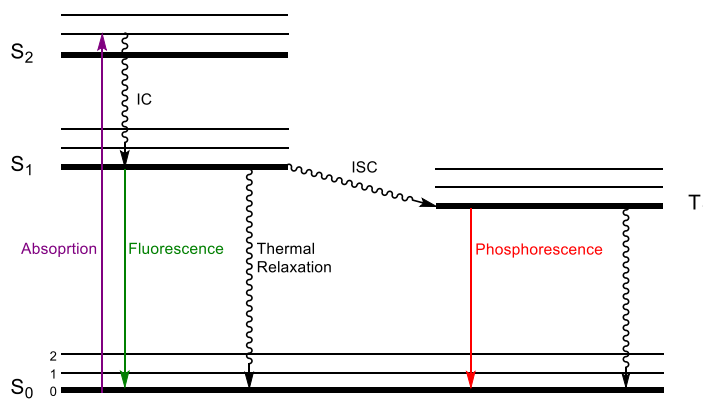


Figure 1.2. A Jablonski diagram, where the vertical axis relates to the energy, and the horizontal axis relates to the multiplicity.

The terms “singlet” and “triplet” states describe the nature of the spin of the electrons in the ground or excited state species. In the ground state, an organic molecule typically has an electronic configuration of $(HO)^2(LU)^0$, where HO refers to the highest occupied molecular orbital (HOMO) and LU refers to the lowest unoccupied molecular orbital

(LUMO). According to the Pauli Exclusion Principle, the spins of the two electrons in the same orbital must be paired (antiparallel spins), which corresponds to a singlet spin state (Figure 1.3).¹ The electronic nature of $^*R$, both which possess one electron in the HOMO and LUMO, are not required to be spin-paired by the Pauli Exclusion Principle, therefore they can either be paired (singlet state) or unpaired, corresponding to a triplet spin state. The terms “singlet” and “triplet” originate from the magnetic properties of electron spins.

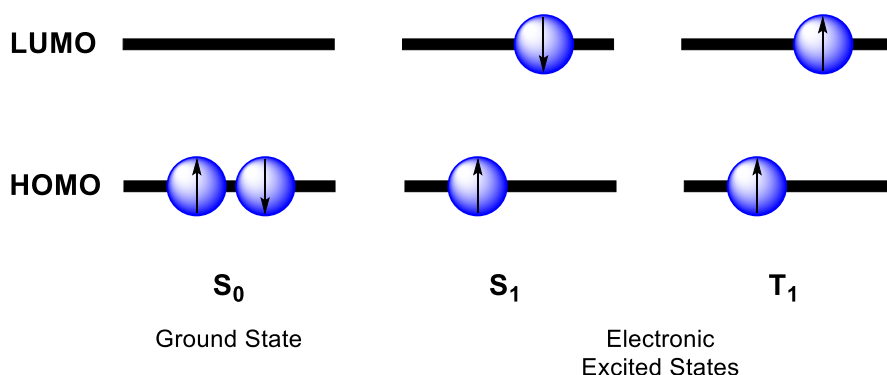


Figure 1.3. The spin configuration of singlet and triplet states.

Following the absorption of a photon by R , several processes can occur. The organic molecule is typically excited to some higher vibrational level of either S_1 or S_2 . With a few rare exceptions, these molecules typically rapidly relax to the lowest vibrational level of S_1 . This process is known as internal conversion (IC), and typically occurs in 10^{-12} s or less.² Since singlet state lifetimes are typically in the nanosecond regime, IC is complete prior to any other measurable process. This results in a thermally equilibrated excited state, that is, the lowest vibrational state of S_1 . This phenomenon is known as Kasha's rule.³

From the singlet excited state, several processes can occur. $^*R$ can return to the ground state through emission of light (fluorescence) or through thermal relaxation. $^*R$ can be quenched through energy- or electron-transfer to another molecule, resulting in the

formation of an intermediate (I), or finally $^*R$ can undergo a spin conversion to the first triplet state (T_1). This spin conversion process is known as intersystem crossing (ISC).² The T_1 state is lower in energy compared to the S_1 state, obeying Hund's rule, which states that the orbital with the greatest spin multiplicity has the lowest energy.⁴ Triplet states typically display longer excited state lifetimes compared to singlet states, due to the fact that transitions from the T_1 state to the ground state (S_0) are spin forbidden. Therefore, organic molecules which relax to the triplet state after light absorption, known as triplet photosensitizers, make excellent choices for photocatalysts to undergo either energy- or electron-transfer events with other molecules, due to their longer excited state lifetimes.^{5,6} The longer the excited state lifetime, the higher the probability that $^*R$ is quenched by other molecules of interest to form I (Figure 1.1). These properties have been heavily exploited throughout the literature and will be discussed further in the upcoming sections.

1.3 Excited State Energy- and Electron-Transfer Processes

This section will discuss electronic energy- and electron-transfer processes in organic photochemistry. In theory, two different types of energy- and electron-transfer processes can be at play in photochemical reactions.¹ The first involves an electronic interaction between $^*R$ and a second molecular species (M). The second type involves no electronic interaction between the orbitals of $^*R$ and M but instead occurs *through space*, a process referred as "trivial" energy- and electron-transfer. In trivial energy-transfer, $^*R$ emits a photon that is subsequently absorbed by M to produce $^*M$, whereas, in trivial electron-transfer, $^*R$ ejects an electron that is subsequently quenched by M to produce $M^{\bullet-}$. Further details into these trivial processes are outside the scope of this dissertation, and will not be discussed further.

In organic photochemistry, four cases of energy- and electron-transfer processes are generally considered. Energy-transfer may occur either by an electron exchange interaction that requires orbital overlap or by a dipole-dipole interaction that occurs through an oscillating electric field in space (Figure 1.4).¹ A critical difference between electron exchange and dipole-dipole interactions is that dipole-dipole interactions of two electric fields do not involve orbital overlap. Consequently, dipole-dipole interactions can occur through space, therefore the observed energy-transfer rate constants will depend on a variety of factors, including the distance separation and optical properties of $^*R$ and M , where $^*R$ is the energy donor, and M is the energy acceptor. However, the majority of examples in organic photochemistry, in particular, those relating to the field of photoredox catalysis, deal with electronic interactions between $^*R$ and M . Some recent examples of applying excited state energy-transfer to organic synthesis will be presented in Section 1.5.

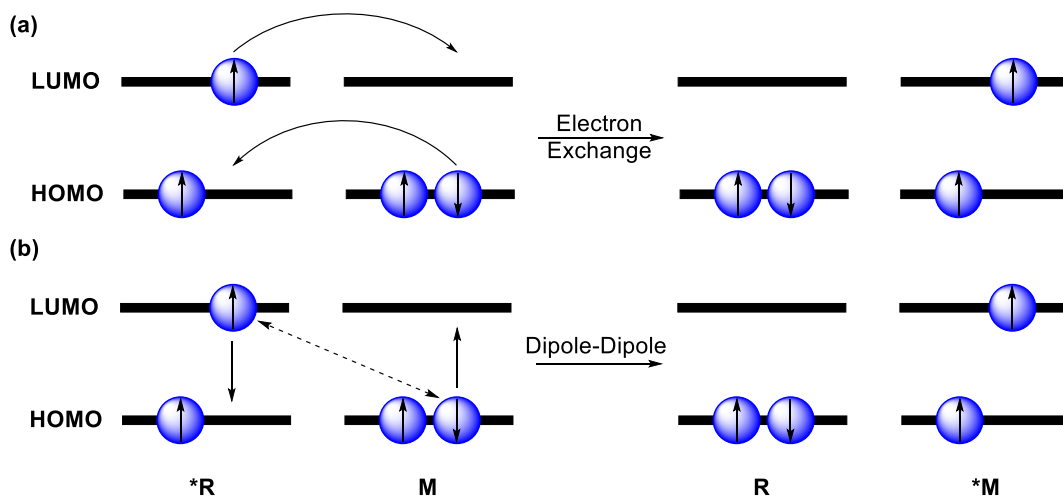


Figure 1.4. Orbital representations of (a) electronic energy-transfer and (b) energy-transfer through dipole-dipole interactions.

In comparison to energy-transfer, excited state electron-transfers occur only through electron exchange interactions and require orbital overlap.¹ In these processes, $^*R$ can be

either an electron donor (D) or an electron acceptor (A). For the case where $^*R$ is an electron donor, electron-transfer occurs from the LU of $^*R$ to the LU of M, whereas in the case where $^*R$ is an electron acceptor, electron-transfer occurs from the HO of M to the HO of $^*R$ (Figure 1.5). These electron-transfer events result in the formation of radical ion pairs, following the pathway (a) introduced in Figure 1.1. Excited state electron-transfer has become the basis of the vast majority of photoredox transformations, which take advantage of the ability of $^*R$ to act as both an electron donor and acceptor, depending on the nature of the substrate (M). This ability for diamagnetic molecules to act as both electron donors and acceptors in their excited state, and how these properties can be applied to organic photochemistry will be discussed in detail in Section 1.4.

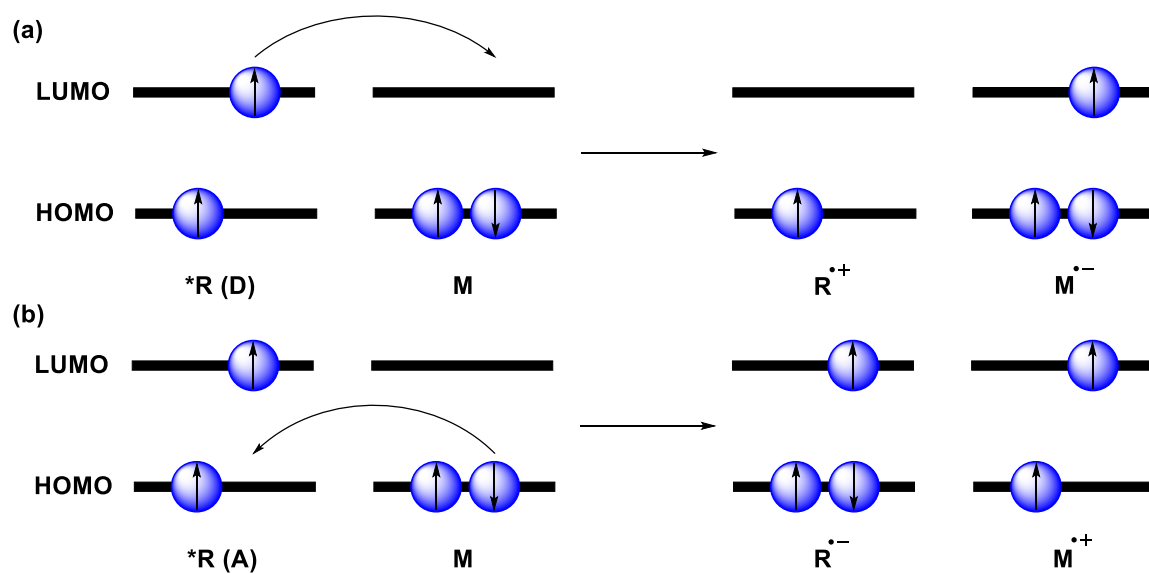


Figure 1.5. Orbital representations of excited state electron transfer **(a)** when $^*R$ acts as an electron donor (D) and **(b)** when $^*R$ acts as an electron acceptor (A).

One of the most important parameters for both energy- and electron-transfer processes in photochemical reactions is the rate constant of the primary photochemical process. The rate constants are dependent on a variety of factors, such as the distance separation between $^*R$ and M, the polarity of the solvent, the excited state energy of $^*R$, and perhaps

most relevant to photoredox transformations, the redox potentials of $^*R$ and M . For energy-transfer processes, the bimolecular rate constant (k) for the primary photochemical process of $^*R + M \rightarrow R + ^*M$ will strongly depend on whether the overall energy-transfer process is energetically downhill (exothermic) or uphill (endothermic) with respect to the thermodynamics of the overall energy-transfer process. In fluid solution, exothermic energy-transfer processes generally proceed at a rate that is close to the rate of diffusion of the solvent employed.⁷ In this case, $^*R$ possesses sufficient energy to electronically excite M , generating $^*M$ without the need for significant thermal activation, allowing for the process to occur at the rate at which $^*R$ and M diffuse together and interact in solution. In organic photochemistry, $^*R$ is referred to as the photosensitizer, sensitizing M to an electronically excited state $^*M$. This strategy can be employed when $^*M$ is not easily produced directly if $^*M$ is a necessary intermediate for a desired photochemical transformation.

Excited state electron-transfer processes correspond to the primary photochemical process $^*R \rightarrow I$, where I is a geminate radical ion pair.¹ These radical ion pairs will have the form of $(R^{\bullet+}, M^{\bullet-})$ or $(R^{\bullet-}, M^{\bullet+})$ if $^*R$ is an electron donor or an electron acceptor, respectively. The bimolecular rate constant (k) between $^*R$ and M will depend not only on the excited state energy of $^*R$ but more importantly on the thermodynamics of the electrochemical redox characteristics of the overall electron-transfer process. A discussion on how to determine the thermodynamic feasibility of the overall electron-transfer process between $^*R$ and M will be presented in Section 1.4.

1.4 Redox Properties of Excited States

Many of the chemical transformations that can be attained in the recent literature of photochemical redox reactions (termed photoredox) have previously been or can be

accomplished using reagents that are either strong single electron oxidants or reductants in the ground state. However, many of these reagents are inherently difficult to handle and use due to their high reactivity. One of the advantages of photochemical reactions over traditional oxidation and reduction reactions is that a relatively inert photocatalyst in the ground state can be employed, and the desired oxidizing or reducing agent can be generated *in situ* through excitation of the photocatalyst ($R + h\nu \rightarrow {}^*R$). This temporal control is one of the reasons that makes employing photoredox for organic transformations so alluring.

As previously discussed in Section 1.3, all closed-shell, diamagnetic molecules can act as both electron donors and acceptors in their electronic excited state. In fact, all diamagnetic molecules will become both better electron donors and acceptors in their excited state in respect to their ground state. This phenomenon can be explained by comparing the ionization potential and electron affinity of an excited state diamagnetic molecule (${}^*R$) with those of its corresponding ground state (R).¹ From Figure 1.6, it becomes evident that the electron affinity of ${}^*R$ is higher than that of R , while the ionization potential of R^* is lower than that of R . Looking at this from a thermodynamic perspective, the addition of an electron to a half-filled HOMO of ${}^*R$ is more exothermic than its addition to the LUMO of R . However, it is also apparent that removal of an electron from the LUMO of ${}^*R$ is less endothermic than removal of an electron from the HOMO of R . It is for these reasons that diamagnetic molecules become both better oxidizing and reducing agents in their excited states.

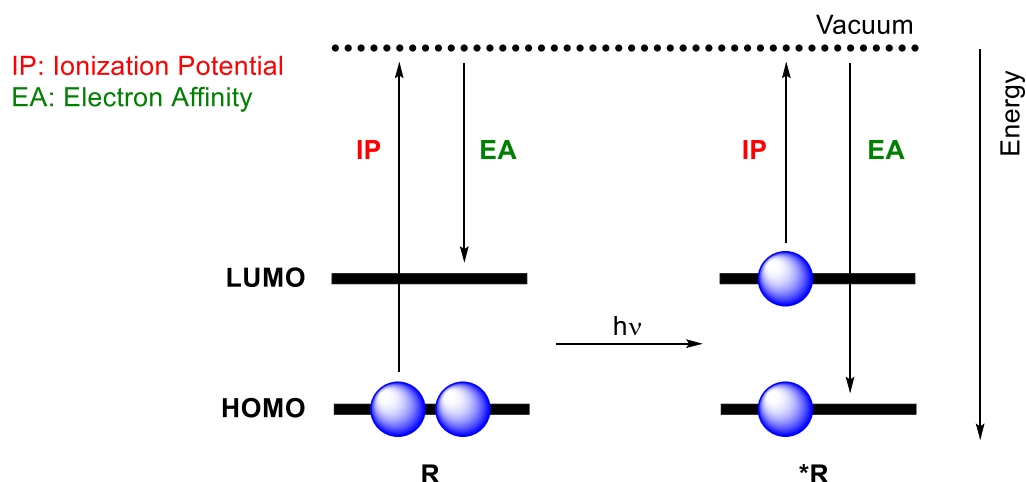


Figure 1.6. Orbital representations of the oxidation and reduction processes of ground state (R) and excited state (*R) diamagnetic molecules. Adapted with permission from reference 1. Copyright 2010 University Science Publishers.

While every diamagnetic molecule becomes a more potent oxidizing and reducing agent in their excited state, this does not imply that any organic molecule can act as a suitable photocatalyst for photoredox transformations. Therefore, what are the ideal characteristics for a photocatalyst? The best photocatalysts are sensitizers which form long-lived triplet excited states upon absorbing light. This signifies that the molecule undergoes ISC at a much higher rate than any other mode of deactivation. As previously mentioned, triplet excited states (μs - ms) are much longer lived than singlet excited states (ps-ns), resulting in a higher probability of being quenched by energy- or electron-transfer before deactivation back to the ground state. It is also beneficial to have a high triplet energy so that energy-transfer will be exothermic with a variety of acceptors. For electron-transfer reactions, high triplet energies will result in more oxidizing or reducing excited state, making quenching via electron-transfer more thermodynamically favourable with a wider range of substrates. Importantly, the photocatalyst should not absorb in the same region as the reactants and products of the desired reaction, as this will create unwanted side reactions and molecular decomposition. Care should also be taken to choose catalysts

with low chemical reactivity, in order to avoid unwanted side reactions which could result in the destruction of the active photocatalyst.

In photoredox catalysis, the first step of the catalytic cycle is the initial electron-transfer to or from the excited state photocatalyst, therefore it is important to determine the thermodynamic feasibility of these electron-transfer steps when designing a photoredox system. This can be accomplished by calculating the Gibbs free energy for the electron-transfer process (ΔG_{eT}). In the ground state, this can be calculated using the following equation:

$$\Delta G_{eT} = E_{1/2}^{ox}(D) - E_{1/2}^{red}(A) + \Delta E_{Coulombic} \quad (1)$$

where $E_{1/2}^{ox}(D)$ is the oxidation potential of the donor molecule, $E_{1/2}^{red}(A)$ is the reduction potential of the acceptor molecule, and $\Delta E_{Coulombic}$ is a measure of the interaction between charged ions in the dielectric constant of the solvent in which the reaction is performed. In order for a reaction to be thermodynamically favourable, the oxidation potential of the donor must be lower (or more negative) than the reduction potential of the acceptor.

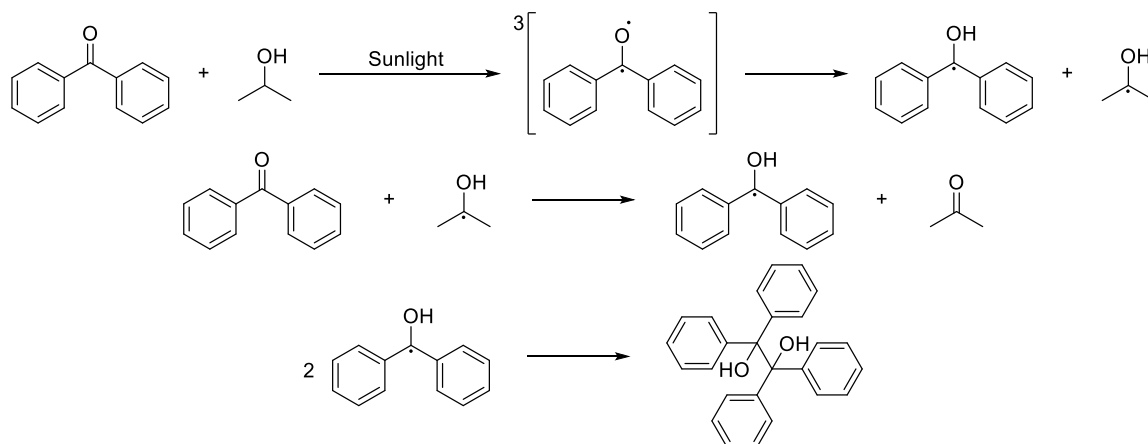
One of the underlying principles behind photochemically catalyzed reactions is that through the use of photosensitizers, low-energy photons can be used to achieve high energy processes. This implies that when the photocatalyst is in the ground state, electron-transfer to or from the photocatalyst is thermodynamically uphill. To account for the excited state energy of the photocatalyst, one can employ the Rehm-Weller equation^{8,9}:

$$\Delta G_{eT} = E_{1/2}^{ox}(D) - E_{1/2}^{red}(A) - E(^*R) + \Delta E_{Coulombic} \quad (2)$$

where $E(^*R)$ is the excited state energy (singlet or triplet) of the excited donor or acceptor molecule (photocatalyst). In many instances, the $\Delta E_{Coulombic}$ term is negligible and can be omitted because many of these transformations are in polar solvents, which have high dielectric constants that reduce the Coulombic attractions between the ions of opposite charge. From equation (2), it becomes evident that the higher the excited state energy of $^*R$, the more likely it is that the reaction will be thermodynamically favourable.

1.5 An Introduction to Photoredox Catalysis

While the use of photochemistry for applications in organic synthesis has seen a rejuvenation in interest in the last two decades, organic photochemistry can be dated back over a century to the laboratory of Giacomo Ciamician, who many consider the pioneer photochemistry. In his famous article “The photochemistry of the future”, Ciamician challenged scientists to imagine a chemical industry that could synthesize chemicals in the same manner as plants; by using light, particularly sunlight, as a safe, abundant, inexpensive, and renewable energy source.¹⁰ In his laboratory in Italy, Ciamician studied the effect of sunlight irradiation on a variety of organic molecules. One of his first examples involved the dimerization of benzophenone in the presence of isopropanol to form benzopinacol (Scheme 1.1).¹¹ Upon irradiation, benzophenone is excited to a diradical-like triplet state, where the O-centered radical can abstract a hydrogen atom from isopropanol to form the corresponding ketyl radicals. The newly formed ketyl radical, an excellent reducing agent, undergoes a proton-coupled electron-transfer (PCeT) with another molecule of benzophenone to form acetone and another ketyl radical. Finally, benzopinacol is formed by the radical-radical coupling of two ketyl radicals. This is considered one of the first examples of a photoredox system, dating back over a century to 1900.



Scheme 1.1. The photochemical synthesis of benzopinacol by Ciamician.

For many years, applying photochemistry to the synthesis of complex molecules remained a challenge for organic chemists. This largely stemmed from the fact that many organic molecules tend to absorb photons in the UV-region of the electromagnetic spectrum. This can be problematic due to the high-energy nature of UV-photons, which can cause unproductive decomposition or side reactions occurring on the molecules of interest. This problem can be alleviated by employing a photosensitizer as a catalyst to promote the transformation of interest, as a photocatalyst can be chosen which does not absorb in the same region as the reagents and products of the reaction. An analogy can be made to traditional organic synthesis, where enough energy, in the form of heat, must be supplied for the reaction to proceed yet not so much as to compromise the stability of the reaction products. As previously stated, since the vast majority of organic molecules absorb in the UV-region, photosensitizers can be chosen which absorb in the visible region of the electromagnetic spectrum (400-700 nm), thus avoiding issues of product decomposition and unwanted side reactions. It is also important to note that the thermodynamics of excited state energy- and electron-transfer also need to be taken into account when selecting an appropriate photosensitizer. It is this ability to promote high energy processes

with lower energy, visible light photons that has rejuvenated interests of organic chemists to employ photochemistry for synthetic problems.

A generalized photoredox catalytic cycle that summarizes the vast majority of photoredox transformations is presented in Figure 1.7.^{6,12,13} Upon absorption of a photon of sufficient energy to generate the singlet excited state, the photocatalyst (PC) undergoes ISC from the singlet to the longer lived triplet excited state. Do to the nature of diamagnetic molecules being better both oxidizing and reducing agents in their excited states (Section 1.4), the photocatalyst can follow two possible catalytic cycles, which are termed as a *reductive quenching cycle* or an *oxidative quenching cycle*. In a *reductive quenching cycle*, the ^3PC is quenched by an electron donor, such as an aliphatic amine, to generate the one-electron reduced form of the photocatalyst ($\text{PC}^{\bullet-}$).¹⁴ The neutral ground state of the PC is then regenerated upon quenching of $\text{PC}^{\bullet-}$ by an electron acceptor. Conversely, in an *oxidative quenching cycle*, the ^3PC is quenched by an electron acceptor, such as oxygen, viologens, or persulfates, to generate the one-electron oxidized form of the PC ($\text{PC}^{\bullet+}$).¹⁴ The neutral ground state of the PC is then regenerated upon quenching of $\text{PC}^{\bullet+}$ by an electron donor. Recent examples have also demonstrated redox reactions initiated by energy-transfer from ^3PC to an acceptor molecule to generate the appropriate reactive intermediates. One such example is the triplet sensitization of styrenes to initiate [2+2] intramolecular cyclizations reported by Yoon and coworkers, and this example will be discussed further *vide infra*.

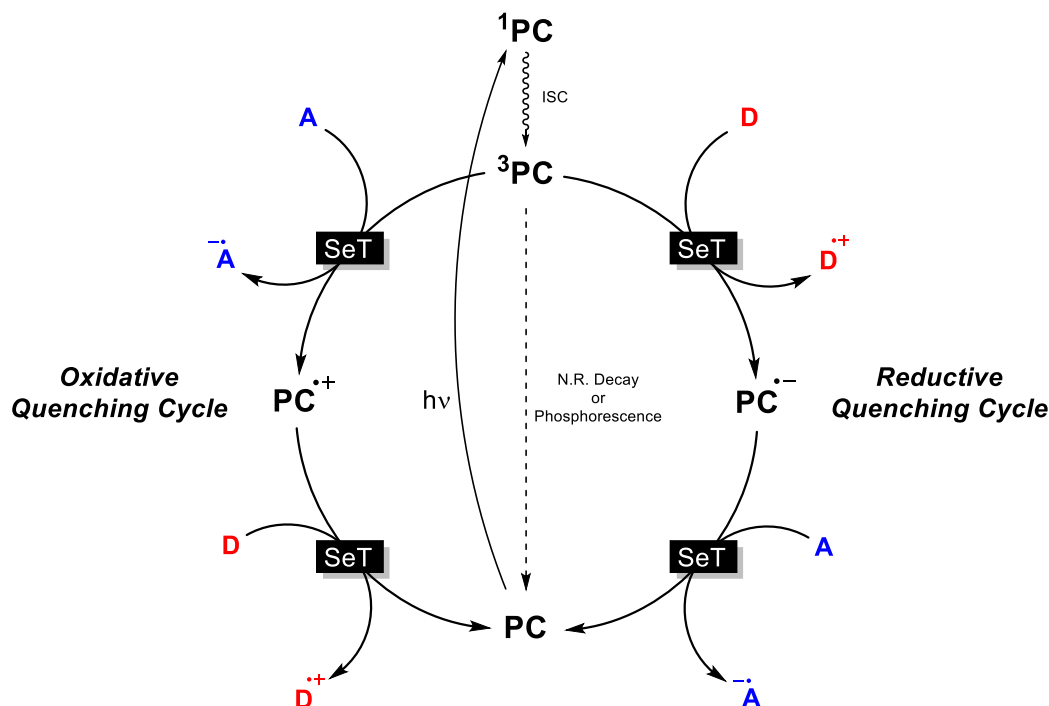
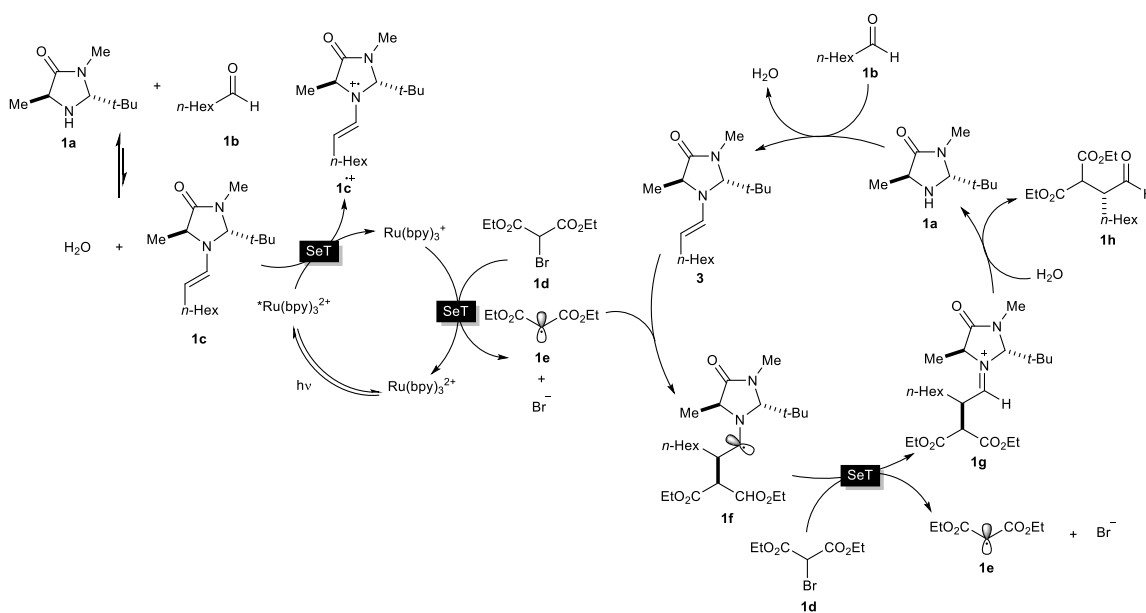


Figure 1.7. A generalized photoredox catalytic cycle, where PC = photocatalyst, A = electron acceptor, D = electron donor, and SeT = single electron-transfer.

While many groups around the world are now harnessing the unique reactivity available with photoredox systems, three groups are considered to be at the forefront for the rejuvenation of the field. Perhaps the leader in the field of photoredox catalysis in terms of innovation and methodology is the group of David MacMillan at Princeton University. Their first entry into the field involved merging photoredox catalysis and organocatalysis for the direct asymmetric alkylation of aldehydes using α -bromoketones in 2008.¹⁵ This work combined their innovation of SOMO (singly occupied molecular orbital) catalysis¹⁶ with photoredox catalysis, employing tris(2,2'-bipyridyl)ruthenium(II) chloride ($\text{Ru}(\text{bpy})_3\text{Cl}_2$) as their visible light absorbing photosensitizer. The proposed mechanism, updated by Tehshik Yoon and coworkers to include radical chain propagation, is presented in Scheme 1.2.¹⁷ Initially, the organocatalyst **1a** condenses with aldehyde **1b** to form enamine **1c**. A sacrificial amount of enamine **1c** is quenched by the excited state of $\text{Ru}(\text{bpy})_3^{2+}$ through a

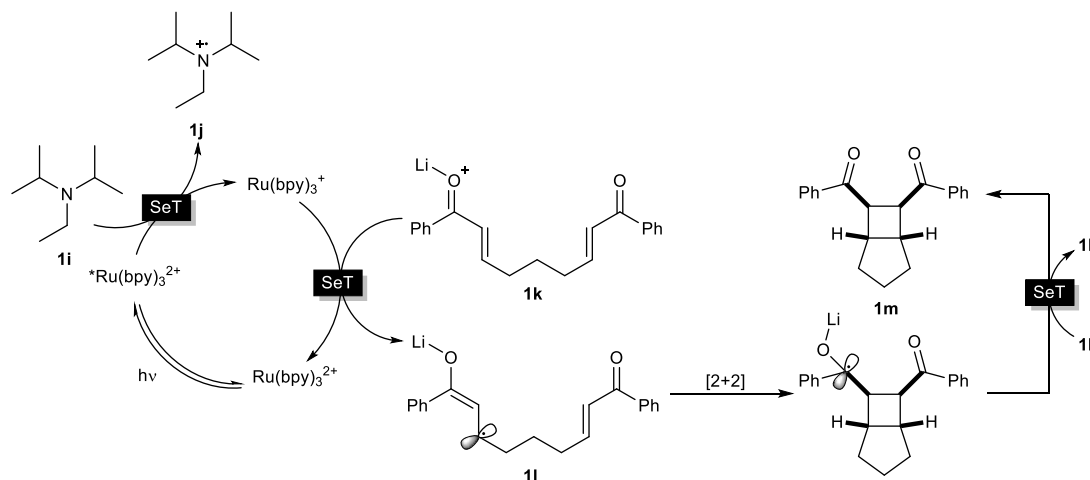
reductive quenching cycle forming **1c^{•+}** and $\text{Ru}(\text{bpy})_3^+$. $\text{Ru}(\text{bpy})_3^+$ can then be quenched by **1d** to regenerate the ground state, forming alkyl radical **1e**. Alkyl radical **1e** can be intercepted by enamine **1c**, forming α -amino radical **1f**. α -Amino radical **1f** can then reduce **1d**, inducing a radical chain propagation, generating iminium **1g**, which becomes hydrolyzed to release the final product **1h** in high enantioselectivities, and regenerate the organocatalyst **1a**. The MacMillan group was able to further expand on this technique of combining photoredox catalysis with organocatalysis by extending this method to accommodate electrophilic benzyl and trifluoromethyl radicals.^{18,19}



Scheme 1.2. Proposed mechanism for MacMillan's asymmetric alkylation of aldehydes, edited by Cismesia and Yoon to account for radical chain propagation.^{15,17}

Another group considered to be at the forefront of the field of photoredox catalysis is the group of Tehshik Yoon at the University of Wisconsin-Madison. Also in 2008, the Yoon group made their entry in the field through the development of a visible light catalyzed [2+2] cycloaddition reaction of bis(enones) catalyzed by $\text{Ru}(\text{bpy})_3\text{Cl}_2$.²⁰ Their proposed mechanism for the transformation is presented in Scheme 1.3. Upon excitation, the

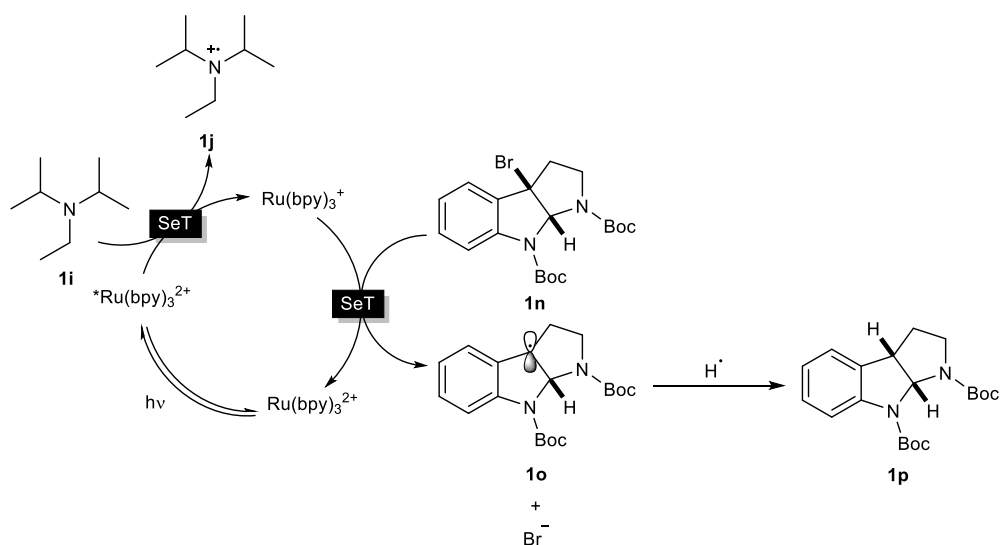
excited state of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ is quenched by a sacrificial electron donor, *N,N*-diisopropylethylamine (*i*Pr₂NEt) (**1i**), generating an amine radical-cation **1j** and the reduced form of the photocatalyst, $\text{Ru}(\text{bpy})_3^+$. The reduced form is then quenched through SeT by activated bis(enone) **1k**, resulting in radical intermediate **1l** and regeneration of the ground state of $\text{Ru}(\text{bpy})_3\text{Cl}_2$. Radical intermediate **1l** then undergoes a [2+2] cycloaddition yielding the desired cyclobutane product **1m** after the loss of an additional electron, either quenched by another activated bis(enone) **1l**, or possibly $^*\text{Ru}(\text{bpy})_3^{2+}$. While *i*Pr₂NEt was employed only as a sacrificial electron donor to generate the highly reducing $\text{Ru}(\text{bpy})_3^+$ species, the corresponding amine radical-cation can readily deprotonate to generate an α -aminoalkyl radical, which has been demonstrated to be an excellent single-electron reducing agent.²¹ Therefore, in many instances, the “sacrificial” electron donor may play a more significant role in the underlying reaction mechanism, which will be the focus of the work presented in Chapter 2.



Scheme 1.3. Proposed mechanism for Yoon's [2+2] cycloadditions of bis(enones).²⁰

The group of Corey Stephenson at the University of Michigan has also made many important contributions to the field. The Stephenson's group first entry into the field of photoredox came in 2009 with the development of a tin-free free radical dehalogenation

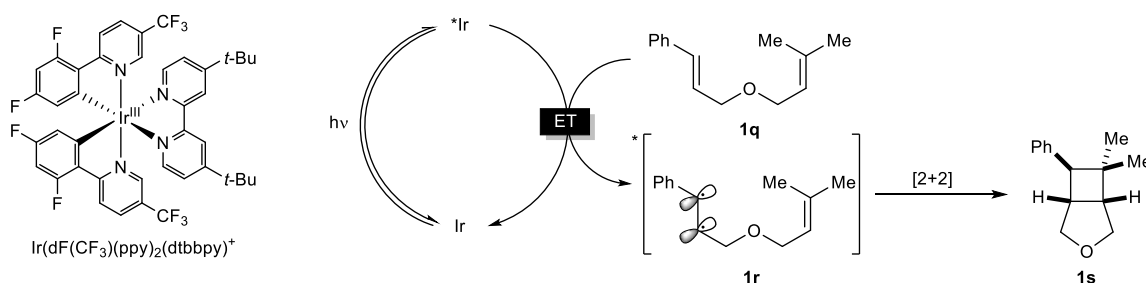
protocol employing $\text{Ru}(\text{bpy})_3\text{Cl}_2$ and visible light irradiation, eliminating the need of tributyltin hydride, a highly toxic ground state reducing agent.²² Their proposed mechanism for this transformation is presented in Scheme 1.4. Employing a reductive quenching cycle, the excited state of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ is quenched by a sacrificial electron donor, $i\text{Pr}_2\text{NEt}$ (**1i**) to generate the highly reducing $\text{Ru}(\text{bpy})_3^+$ species. This species is then quenched by **1n** through SeT, generating free radical **1o** and regenerating the neutral ground state of the photocatalyst. The desired product **1p** is then formed upon hydrogen atom abstraction from either $i\text{Pr}_2\text{NEt}$ or Hantzsch's ester. The Stephenson group has since developed protocols to tackle substrates which are considerably more difficult to reduce, such as unactivated aryl and alkyl iodides.²³



Scheme 1.4. Proposed mechanism for Stephenson's reductive dehalogenation protocol.²²

While many of the newly developed visible light mediated photoredox transformations proceed through either an oxidative or reductive quenching cycle, there have been reports in which the desired reactive intermediates are generated through a triplet-triplet energy-transfer from the visible light absorbing photosensitizer to the substrate. One such example, reported by Yoon and coworkers in 2012, is the intramolecular [2+2]

cycloaddition of styrenes employing an iridium polypyridyl complex ($\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})^+$) as the triplet photosensitizer.²⁴ In this example, presented in Scheme 1.5, the thermodynamics for electron-transfer were calculated to be uphill by over 12 kcal mol⁻¹, however $\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})^+$ was found to possess a sufficiently high triplet energy (61 kcal mol⁻¹) to sensitize styrenes (~60 kcal mol⁻¹). The proposed mechanism involves the quenching of $^*\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})^+$ by styrene **1q** by energy-transfer, generating the triplet diradical intermediate **1r**. Intermediate **1r** can then undergo an intramolecular [2+2] cycloaddition to yield the desired cyclobutane product **1s**.



Scheme 1.5. Proposed mechanism for Yoon's intramolecular [2+2] cycloadditions of styrenes. ET = energy-transfer.²⁴

1.6 Mechanistic Photochemistry and Kinetic Analysis

Many of the newly developed transformations in the field of visible light mediated photoredox catalysis are obtained in the absence of any new understanding of the excited state kinetics and mechanisms that underlie these new discoveries. Excited state kinetics is a powerful tool to predict, rationalize, and optimize photoredox systems. Although the initial excited state electron-transfer may be thermodynamically favourable, this does not necessarily indicate whether the reaction will occur. In other words, while thermodynamics describes if the reaction *can occur*, it is ultimately kinetics which dictates if the reaction *will occur*.

Through the use of techniques such as steady-state and time-resolved fluorescence spectroscopy and laser flash photolysis (LFP), the kinetics of both singlet and triplet states can be studied. Due to the short lifetimes of singlet excited states (ps-ns) compared to the relatively long lifetime of triplet excited states (μs -ms), one might expect the majority of the chemistry to occur from the triplet manifold. However, this ultimately depends on the rate at which different components of the reaction quench the excited state of the photocatalyst and on the concentrations of the reagents employed. It should be noted that in the equations *vide infra*, it is concentrations and not “equivalents” that are required. While equivalents are a useful tool in synthetic organic chemistry, they do not contain the information required for kinetic analysis.

A convenient method for studying singlet quenching is to perform steady-state fluorescence quenching studies. This is accomplished by monitoring the photocatalyst's fluorescence intensity as a function of quencher concentration ($[Q]$) (Figure 1.8a) and employing Stern-Volmer analysis²:

$$\frac{I_0}{I_{[Q]}} = 1 + K_{SV}[Q] \quad (3)$$

where I_0 and $I_{[Q]}$ are the fluorescence intensities in the absence and presence of quencher, respectively, and the K_{SV} is the Stern-Volmer constant. Ideally, a Stern-Volmer plot ($\frac{I_0}{I_{[Q]}}$ vs. $[Q]$) is linear and its slope corresponds to K_{SV} (Figure 1.8b). In the case of dynamic quenching, the bimolecular rate constant of quenching (k_q) is calculated using the following equation:

$$k_q = \frac{K_{SV}}{\tau_0} \quad (4)$$

where τ_0 is the excited state lifetime of the photocatalyst in the absence of any quencher. Occasionally, the resulting k_q is greater than the rate of diffusion of the employed solvent. This is due to static quenching, which arises from pre-association of the quencher and the photocatalyst in the ground state.^{1,2}

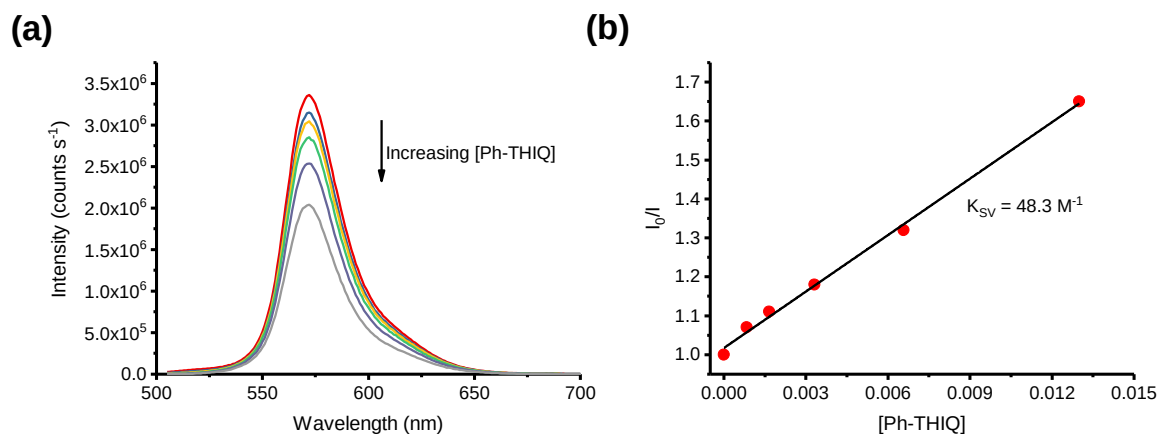


Figure 1.8. (a) Steady-state fluorescence spectra of Pyronin Y in the presence of increasing concentration of the quencher 2-phenyl-1,2,3,4-tetrahydroisoquinoline (Ph-THIQ). (b) Corresponding Stern-Volmer plot, the slope of which corresponds to the Stern-Volmer Constant (K_{SV}). This system used for this general example corresponds to data presented in Chapter 5.

The relatively long lifetimes of triplet excited state photosensitizers are attributed to the fact that their relaxation back to the singlet ground state is spin forbidden. While many of the popular ruthenium and iridium polypyridyl based photocatalysts have strongly emissive (phosphorescence) triplet states whose kinetics can be evaluated using the same steady-state techniques as previously described, there are many other triplet photosensitizers who have weakly or non-emissive excited states. In these instances, LFP can be employed to record triplet-triplet absorption kinetics. However, LFP can also be applied to record phosphorescence decay traces for photosensitizers with emissive excited states. Figure 1.9A depicts an example of phosphorescence decay traces of Ir(ppy)₃ obtained in the presence of increasing concentrations of quencher.

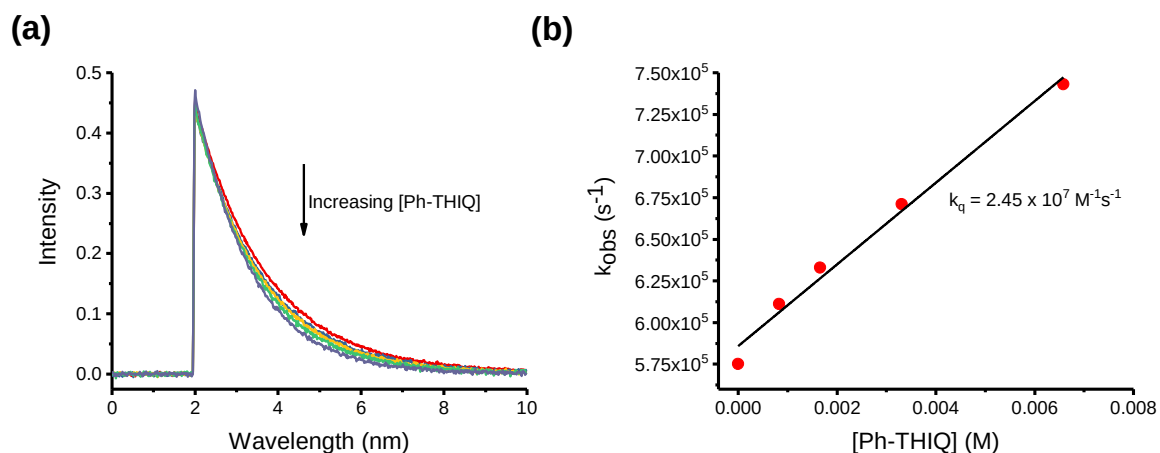


Figure 1.9. (a) Phosphorescence decay traces of Ir(ppy)₃ in the presence of increasing concentration of the quencher 2-phenyl-1,2,3,4-tetrahydrosisoquinoline (PhTHIQ). (b) Corresponding kinetic quenching plot, the slope of which corresponds to the bimolecular quenching constant (k_q). This system used for this general example corresponds to data presented in Chapter 5.

By monitoring the rate of triplet decay in the presence of increasing $[Q]$, it is possible to determine k_q for triplet quenching. When the triplet absorption decays with mono-exponential kinetics, one can employ the following equation to calculate k_q :

$$k_{obs} = \tau_0^{-1} + k_q[Q] \quad (5)$$

where k_{obs} (usually in s⁻¹) is the observed rate constant for triplet decay at a given $[Q]$, and τ_0^{-1} is the inverse of the photocatalyst's excited state lifetime in the absence of quencher.²⁵ On the basis of equation (5), a plot of k_{obs} vs. $[Q]$ (Figure 1.9b) can be used to calculate k_q , with k_q equal to the slope of this linear plot.

Using these techniques, the kinetics in which the different components of the system quench the excited state of the photocatalyst can be determined. Although the rate constants can indicate how efficient a particular quencher is, without accounting for the concentration of the quencher or the lifetime of the excited state it is difficult to draw conclusions about how the reaction is proceeding. A simple yet powerful way to exploit

the rate constant data is to calculate the probability that an excited state is intercepted by a particular quencher. This can be accomplished employing the following equation:

$$\% \text{ } ^*PC \text{ quenched by } Q_A = \frac{k_q^A [Q_A]}{\tau_0^{-1} + k_q^A [Q_A] + k_q^B [Q_B] + k_q^C [Q_C] + \dots} \times 100\% \quad (6)$$

where k_q^A is the bimolecular rate constant for the quencher of interest (usually in $\text{M}^{-1}\text{s}^{-1}$), and $[Q_A]$ is the corresponding quencher concentration (M). Generally, equation (6) is employed to calculate the probability of quenching under initial reaction conditions, however it can also be applied at any other point in the reaction provided that the required rate constants and concentrations for all components, including all possible reaction products, are known.

From equation (6), it becomes more evident that although excited state processes are thermodynamically favourable, it may not necessarily occur because of time constraints and competition from other reaction components. Nevertheless, these data can be employed to optimize the system by modifying reagent concentrations or eliminating possible quenchers. In practice, one of the simplest examples is the removal of O_2 from transformations mediated by triplet photosensitizers. Since O_2 is a potent quencher of triplet excited states, purging the reaction vessel of O_2 can lead to increased reaction efficiency. However, in the cases where O_2 plays a role in the overall reaction mechanism, this would not be feasible.

It is important to note that all experimentally determined k_q values incorporate all modes of deactivation of the excited state, therefore the calculated probability of an excited state quenched by an electron donor or acceptor gives only a rough estimate of the efficiency of electron-transfer, as not all quenching events lead to electron-transfer. In order to better understand the system, a method is required to distinguish between productive and non-

productive events. In some cases, following electron-transfer the oxidized or reduced substrate will give rise to a new absorption signal. An excellent example of this is the reduction of methyl viologen to its radical-cation, which has a strong absorption centered at around 600 nm.²⁶ In some cases, depending on the photosensitizer employed, the oxidized or reduced photocatalyst can be observed directly.²⁷ This added advantage also allows for the rate of catalyst turnover to be measured. By monitoring the decay of the intermediate in the presence of different electron donors or acceptors, it may be possible to further optimize the system at play.

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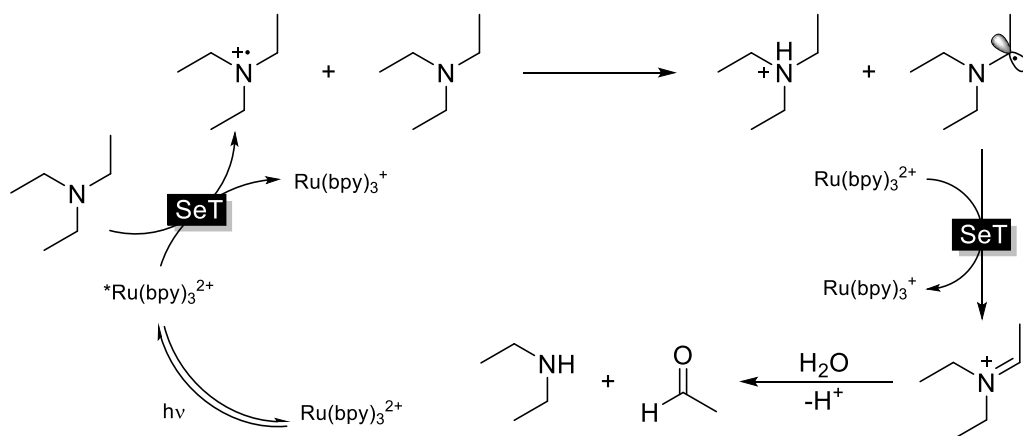
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2. The Role of α -Aminoalkyl Radicals in Photoredox Transformations

2.1 Introduction to α -Aminoalkyl Radicals

Throughout the last twenty years, the development of novel photoredox protocols for organic synthesis has grown exponentially.¹⁻³ In the first chapter, the general catalytic cycle for photoredox transformations was discussed. When the photocatalyst is promoted to its excited state, whether it be singlet or triplet, it becomes a better electron donor and acceptor compared to its ground state.⁴ The excited photocatalyst can then be quenched by a variety of electron donors or acceptors in solution. While this has been heavily exploited in the recent literature, this reactivity has been known since the pioneering work by Balzani and coworkers during the 1970s.⁵⁻⁷

In 1978, Whitten and coworkers examined light-induced electron-transfer reactions of $\text{Ru}(\text{bpy})_3^{2+}$ and its analogues.⁸ When examining the reductive quenching of $\text{Ru}(\text{bpy})_3^{2+}$, they discovered that the addition of triethylamine (NEt_3) produced spectral signatures of the reducing $\text{Ru}(\text{bpy})_3^+$ species and an amine radical-cation. Upon prolonged irradiation, they discovered the formation of acetaldehyde. This was the result of hydrolysis of the iminium formed from NEt_3 oxidation. Their proposed mechanism is presented in Scheme 2.1. Upon generation of the amine radical-cation through excited state quenching, the amine radical-cation is deprotonated by another molecule of NEt_3 to generate an α -aminoalkyl radical. The α -aminoalkyl radical then reduces another $\text{Ru}(\text{bpy})_3^{2+}$ complex, generating a second $\text{Ru}(\text{bpy})_3^+$ species. This would then result in the formation of an iminium, which upon hydrolysis would generate diethylamine and acetaldehyde.



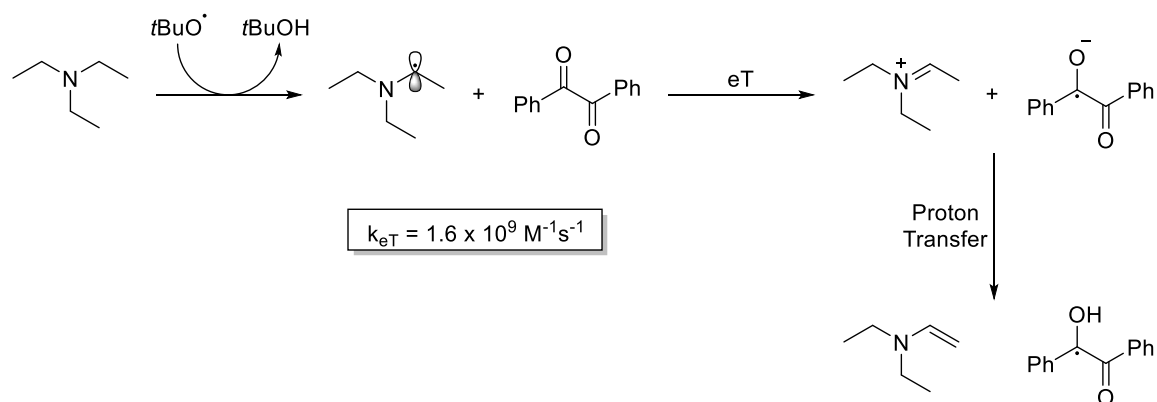
Scheme 2.1. Proposed mechanism for the reductive quenching of $\text{Ru}(\text{bpy})_3^{2+}$ analogues by triethylamine under aqueous conditions.

While this was one of the first examples of amines being employed for the photoreduction of $\text{Ru}(\text{bpy})_3^{2+}$, their use in photoreduction reactions, especially for the photoreduction of aromatic ketones, had been previously well documented.⁹ In agreement with Whitten's proposal, radicals derived from amine oxidation were reported to also be good electron donors, as shown by their capability to reduce ground state ketones. In order to gain a better understanding of radicals derived from amine oxidation, Das and von Sonntag examined the reactivity of radicals derived from trimethylamine (NMe_3).¹⁰ Using pulse radiolysis techniques, they were able to determine rate constants for the formation of α -aminoalkyl radicals from the NMe_3 radical-cation. Under basic pH, the NMe_3 radical-cation ($\text{pK}_a \approx 8$) deprotonates at a unimolecular rate constant of 35 s^{-1} or can be deprotonated by another molecule of NMe_3 at a rate constant of $7.3 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$. Therefore, upon amine oxidation, deprotonation will be heavily favoured under basic conditions, giving access to an α -aminoalkyl radical, which can also act as a reducing agent.

Given the precedence of α -aminoalkyl radicals acting as reducing agents, Wayner and coworkers set out to determine the reducing capabilities of these radicals.^{11,12} Using a modulated photolysis technique for the generation of radicals, and phase sensitive

voltammetry for their detection, they were able to calculate the oxidation potential of the α -aminoalkyl radical derived from NEt_3 to be -1.12 V versus saturated calomel electrode (SCE).^{11,12} When considering the oxidation potential of the highly reducing $\text{Ru}(\text{bpy})_3^+$ species generated upon photoreduction (-1.33 V vs. SCE)⁷, it is evident that α -aminoalkyl radicals can also act as potent reducing agents.

Knowing that α -aminoalkyl radicals were known to reduce ketones, Scaiano employed laser flash photolysis techniques to determine the bimolecular rate constant for the reduction of benzil by the α -aminoalkyl radical derived from NEt_3 .¹³ To generate the α -aminoalkyl radical, Scaiano photolyzed *tert*-butylhydroperoxide to form peroxy radicals that could then abstract a hydrogen from NEt_3 . The reaction between the α -aminoalkyl radical with benzil was analyzed by monitoring the growth of the benzil ketyl radical, produced upon one-electron reduction from the α -aminoalkyl radical, followed by a proton-transfer (Scheme 2.2). The rate for this bimolecular reaction was calculated to be $1.6 \times 10^9\text{ M}^{-1}\text{s}^{-1}$, not only demonstrating that α -aminoalkyl radicals can be employed for the reduction of ketones, but that it occurs at rates which are among the fastest for known radical-molecule reactions.¹³

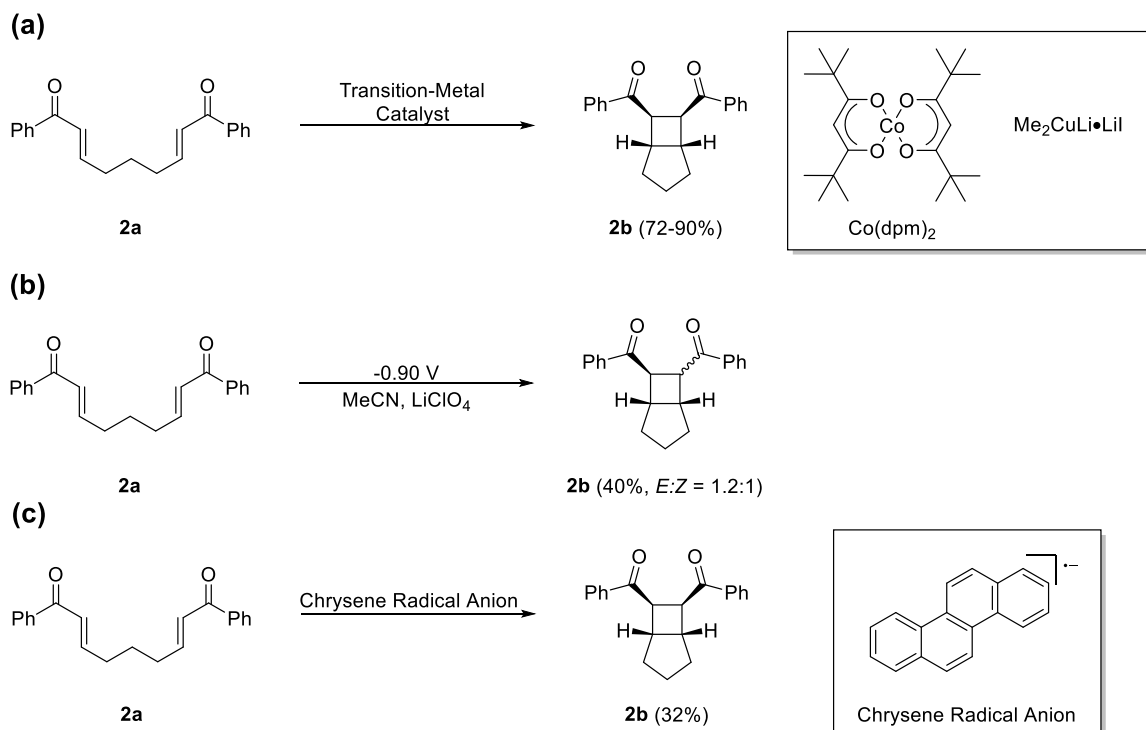


Scheme 2.2. Proposed mechanism for the reduction of benzil by α -aminoalkyl radicals as studied by Scaiano.

Based on the highly reducing nature of these radicals, and their ability to be generated upon deprotonation from the corresponding amine radical-cations, we wondered if these radicals were indeed playing a more significant role in many of the reductive quenching photoredox transformations which have been recently developed. In reductive quenching cycles, aliphatic amines are often employed as “sacrificial” electron donors to quench the excited state of the photocatalyst to generate a more reducing catalyst species and an amine radical-cation. Due to fast rates for deprotonation of amine radical-cations under basic conditions, and their highly reducing oxidation potentials, we decided to test the ability of amine-derived radicals to participate in photoredox transformations.

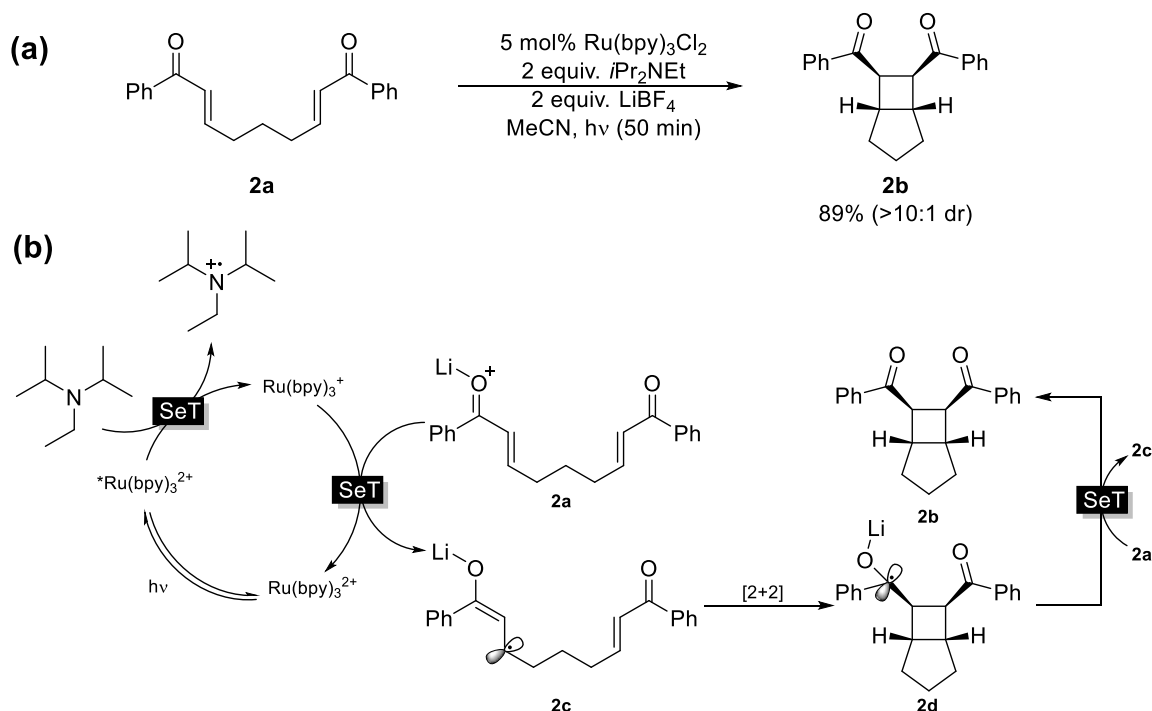
2.2 Reductive Cyclizations of Aryl (Bis)enones Mediated by Photoredox Catalysis

In order to examine the possible participation of amine-derived radicals in photoredox catalysis, we chose to study the reductive cyclization of aryl (bis)enones. The cyclization of (*E,E*)-1,7-dibenzoyl-1,6-heptadiene (**2a**) was first reported in a series of contributions by Krische and coworkers. In this seminal work, they demonstrated that both cobalt and copper could be employed to catalyze the intramolecular [2+2] cyclization of **2a** (Scheme 2.3a).¹⁴⁻¹⁶ In all cases, they obtained the bicyclo[3.2.0] product (**2b**) in good yields as a single diastereomer, along with small amounts of the Michael addition side-product. In their studies, they noted that at least one aromatic (bis)enone was required to promote the [2+2] cycloaddition, suggesting that the reactive intermediate may possess radical anion character. In accordance with this theory, they were able to demonstrate the [2+2] cyclization of **2a** in the presence of reducing electrochemical conditions (Scheme 2.3b)¹⁷ or a homogeneous one-electron reductant (Scheme 2.3c)¹⁸, albeit with a decrease in selectivity for the bicyclo[3.2.0] product. It should also be noted that under cathodic conditions, both the *cis* and *trans* isomers of **2b** were observed.



Scheme 2.3. Intramolecular [2+2] cycloadditions of (*E,E*)-1,7-dibenzoyl-1,6-heptadiene employing (a) transition-metal catalysis, (b) reducing electrochemical conditions, and (c) a homogeneous one-electron reductant.

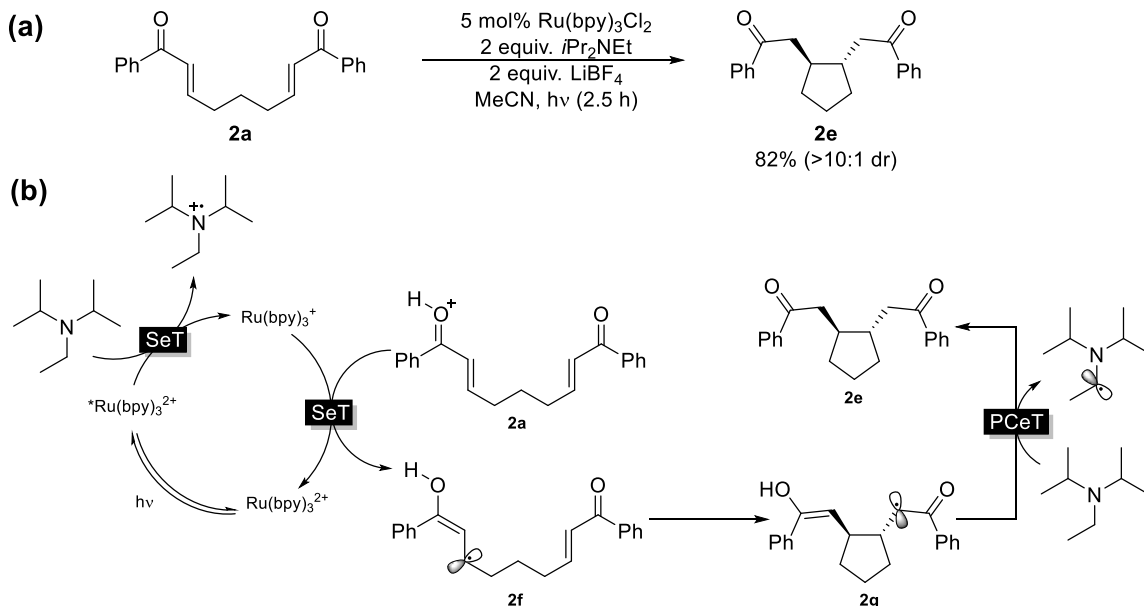
Based on the evidence provided by Krische and coworkers that the intramolecular [2+2] cycloaddition of **2a** proceeded through a radical anion intermediate, Yoon and coworkers envisioned a possible photoredox protocol, in which the photocatalyst provided the electron to access the radical anion intermediate, initiating the cyclization. In 2009, Yoon and coworkers reported that employing Ru(bpy)₃Cl₂ as the photoredox catalyst, these transformations could be accessed in high yields and diastereoselectivity (Scheme 2.4a).¹⁹ Importantly, unlike the previous examples reported by Krische and coworkers which displayed poor selectivity for **2b**, Yoon's protocol produced only the bicyclo[3.2.0] product.



Scheme 2.4. (a) Yoon and coworker's protocol for the intramolecular [2+2] cycloaddition of (*E,E*)-1,7-dibenzoyl-1,6-heptadiene and (b) the proposed mechanism for their transformation.

The proposed mechanism for Yoon's protocol is presented in Scheme 2.4b.¹⁹ Upon excitation of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ with visible light irradiation, the $^3\text{MLCT}$ excited state is formed. $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$ is then quenched by *N,N*-diisopropylethylamine ($i\text{Pr}_2\text{NEt}$) to generate the highly reducing $\text{Ru}(\text{bpy})_3^+$ species (-1.33 V vs. SCE), and an amine radical-cation. $\text{Ru}(\text{bpy})_3^+$ is then capable of reducing **2a**, which is coordinated to a lithium Lewis acid (LiBF_4) to activate **2a** towards one-electron reduction, generating the radical intermediate **2c**. Then **2c** undergoes a [2+2] radical cyclization, followed by loss of an electron to form **2b**. Subsequent studies revealed that chain propagation plays an important role in the observed efficiency of this transformation, as they were able to calculate a quantum yield (Φ) of 77 and a chain length of 135 for this transformation.²⁰ Therefore, it was proposed that following the [2+2] cycloaddition, the subsequent radical intermediate (**2d**) reduces another molecule of **2a**, initiating the chain reaction.

Depending on the nature of the activation, Yoon and coworkers were also able to control the nature of the cyclization. In 2011, they discovered that by employing a Bronsted acid instead of a Lewis acid, they could access the 5-*exo*-trig reductively cyclized product (**2e**) in excellent yield (Scheme 2.5a).²¹ They proposed that using Bronsted acid activation would result in the generation of a neutral radical intermediate (**2f**) that would display different reactivity compared to the radical anion intermediate (**2c**). The proposed mechanism for this transformation is presented in Scheme 2.5b.²¹ Similar to their previous work, $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$, formed upon excitation with visible light irradiation, is quenched by *i*Pr₂NEt to generate the highly reducing $\text{Ru}(\text{bpy})_3^+$ state and an amine radical-cation. $\text{Ru}(\text{bpy})_3^+$ then reduces Bronsted-activated **2a**, producing neutral radical **2f**. **2f** then undergoes a 5-*exo*-trig cyclization, yielding neutral α -keto radical intermediate **2g**. Yoon and coworkers propose that radical **2g** abstracts a hydrogen atom from the amine-radical cation to generate the final product. However, considering the low concentrations and the high reactivity of these respective radicals in solution, radical disproportionation seems unlikely. One possible pathway involves the oxidation of *i*Pr₂NEt by radical intermediate **2g**, followed by proton-transfer to give the desired product. This is supported by work presented by Steenken and Neta who demonstrated that α -keto radicals are excellent oxidizing agents for amines, with rates of electron-transfer approaching diffusion control.²²



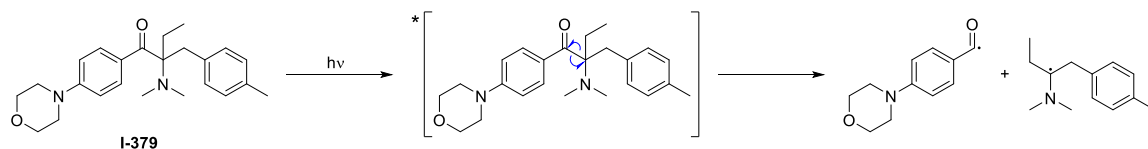
Scheme 2.5. (a) Yoon and coworker's protocol for the 5-exo-trig reductive cyclization of (*E,E*)-1,7-dibenzoyl-1,6-heptadiene and (b) the proposed mechanism for their transformation. PCeT = proton-coupled electron-transfer.

It is worth noting that in all these examples reported by the Yoon group, an aliphatic amine was employed as a “sacrificial” electron-donor to generate the highly reducing $\text{Ru}(\text{bpy})_3^+$ state. However, the fate of the amine radical-cations produced was never investigated. As previously stated, these amine radical-cations can be easily deprotonated to generate an α -aminoalkyl radical, which have been demonstrated to be potent reducing agents.¹⁰⁻¹² In light of the known reactivity for the reduction of aromatic ketones by α -aminalkyl radicals, some of the fastest radical-molecule reactions every reported¹³, we wondered if the α -aminoalkyl radicals produced from the oxidation of $i\text{Pr}_2\text{NEt}$ could be playing a role in the reduction of **2a**. In this chapter, evidence for the involvement of α -aminoalkyl radicals as a reducing agent in photoredox transformations is presented. α -Aminoalkyl radicals derived from amines commonly employed as “sacrificial” electron donors were demonstrated to promote the reductive cyclization of **2a**. It is possible that, as long as electron-transfer from the α -aminoalkyl radical is thermodynamically favourable, the

participation of these radicals in the underlying mechanisms of photoredox transformations could be more widespread than this test system.

2.3 Reductive Cyclizations Mediated by α -Aminoalkyl Radicals

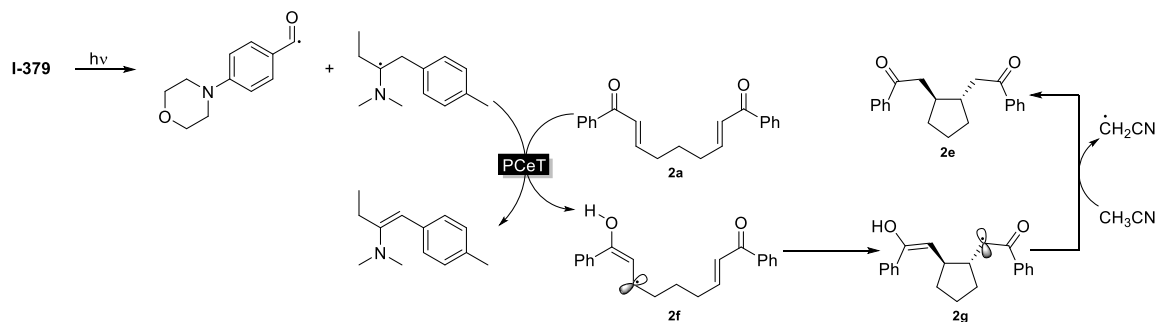
In order to examine the role of amine-derived radicals in the reductive cyclization of **2a**, we decided to employ the photoinitiator Irgacure 379 (**I-379**) as the α -aminoalkyl radical source (Scheme 2.6). Upon UVA excitation, the excited state of **I-379** undergoes a Norrish type I reaction⁴, resulting in homolysis and the formation of two free radicals. One of the free radicals produced is a tertiary α -aminoalkyl radical. Therefore, knowing that α -aminoalkyl radicals are known to reduce ketones at diffusion controlled rates¹³, we hypothesized that the α -aminoalkyl radicals generated from the photolysis of **I-379** could be employed to promote the reductive cyclization of **2a**.



Scheme 2.6. Formation of an α -aminoalkyl radical upon photolysis of Irgacure-379.

Gratifyingly, upon UVA irradiation of 20 mM **I-379** in the presence of 20 mM **2a** in MeCN, the reductive cyclized **2h** product was formed in 73% yield after 2 hours as a single *trans*-isomer (Scheme 2.7). We propose that upon UVA excitation, the excited state of **I-379** undergoes a Norrish type I cleavage, resulting in a carbonyl radical and a tertiary α -aminoalkyl radical. The carbonyl radical, under these reaction conditions, is proposed to dimerize to give a substituted benzil by-product. The α -aminoalkyl radical will then undergo a single-electron transfer to **2a**, followed by a proton transfer to protonate the radical anion, to give the corresponding enamine and radical intermediate **2f**. **2f** will then undergo a 5-*exo*-trig cyclization to give α -keto radical intermediate **2g**. Then **2g** abstracts

a hydrogen atom from the solvent to give the final 5-exo-trig cyclized product **2e**. While MeCN is a poor hydrogen donor, it has been demonstrated to undergo hydrogen-transfer reactions, albeit at relatively slow rates.²³ However, it is likely the dominant pathway in this system considering the absence of other viable hydrogen donors.



Scheme 2.7. Proposed mechanism for the reductive cyclization of (*E,E*)-1,7-dibenzoyl-1,6-heptadiene mediated by Irgacure-379 and UVA irradiation.

In order to demonstrate that the reaction indeed proceeds via single electron-transfer from the α -aminoalkyl radical to **2a**, the reaction was analyzed using gas chromatograph mass spectrometry (GC-MS) in order to detect the corresponding enamine that forms after the loss of an electron and proton from the α -aminoalkyl radical. This method was chosen to identify the formation of the enamine due to their isolation being difficult, as enamines are prone to hydrolysis. By taking an aliquot from the reaction, and subjecting it to GC-MS analysis, a peak corresponding to the molecular weight of the enamine was observed (Figure 2.1). This result supports the proposed mechanistic pathway, confirming the presence of the by-product formed by loss of an electron and proton from the α -aminoalkyl radical.

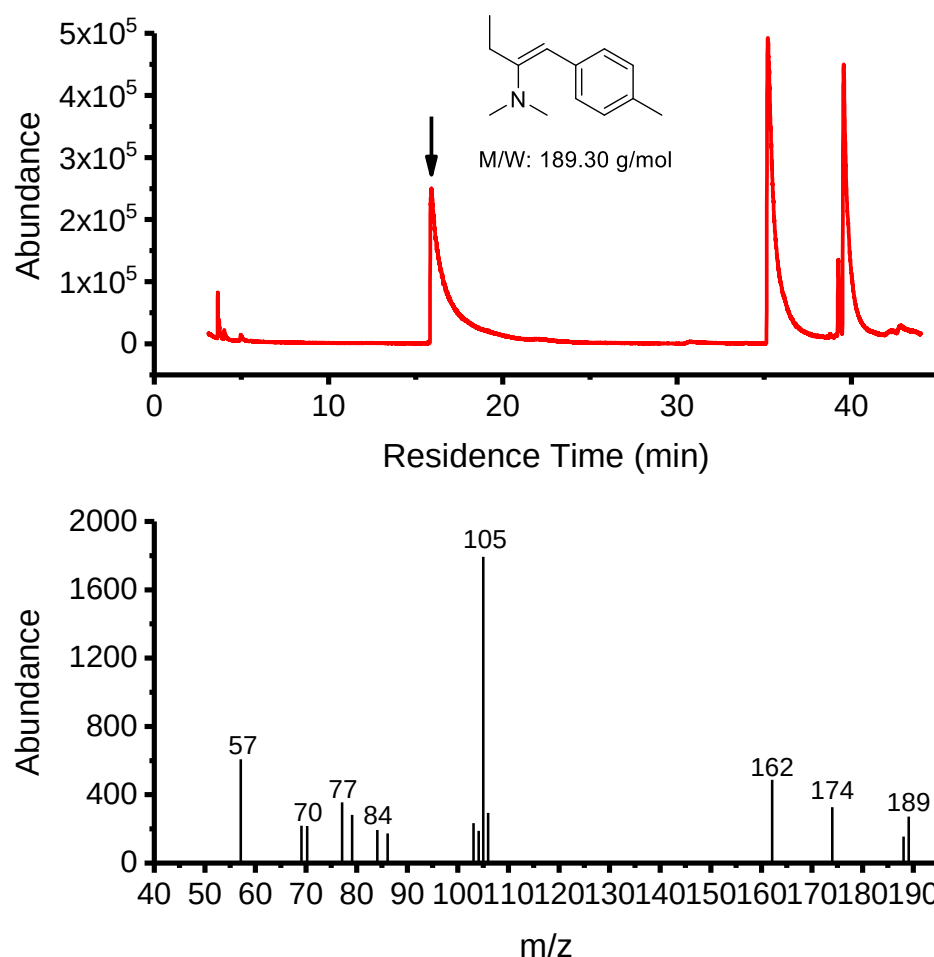
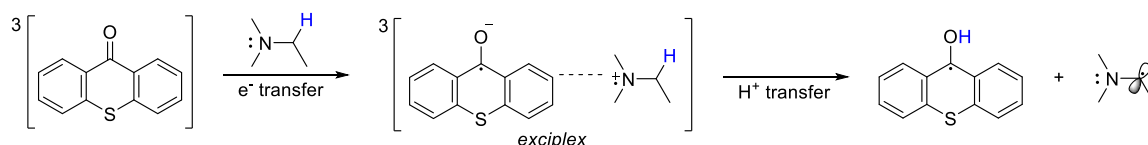


Figure 2.1. GC-MS data corresponding to an aliquot from the reaction involving the reductive cyclization of (*E,E*)-1,7-dibenzoyl-1,6-heptadiene mediated by Irgacure 379 and UVA irradiation, confirming the presence of the enamine by-product.

With these results in hand, the next step was to examine the involvement of the α -aminoalkyl radical derived from *i*Pr₂NEt, the same amine employed in the pioneering photoredox studies by the Yoon group.^{19,21} In order to generate an α -aminoalkyl radical from *i*Pr₂NEt independent of a photoredox catalyst, we proposed a protocol involving hydrogen atom abstraction by an excited aromatic ketone. Aromatic ketones have been known to react with amines via hydrogen atom abstraction since the landmark studies of Cohen in the 1970s.⁹ In fact, aromatic ketones and amines are often employed in tandem to initiate free-radical polymerizations and are known as type II photoinitiators.²⁴ In general,

hydrogen atom abstraction gives rise to the formation of two radicals, a ketyl radical and the corresponding α -aminoalkyl radical. These reactions have been reported to occur with near unity quantum yields.^{25,26} In solvents like MeCN, radical combination and disproportionation reactions will remove the ketyl radical, another potential reducing agent, from the system and the α -aminoalkyl radical can be utilized for reductive transformations. Therefore, we proposed that a system involving thioxanthone and its derivatives as the aromatic ketone and *i*Pr₂NEt as the amine could promote the reductive cyclization of **2a**. In agreement with this proposal, thioxanthone and aliphatic amine systems are often employed to promote free-radical polymerizations. In these systems, the triplet of thioxanthone is quenched by an aliphatic amine, generating an exciplex between the radical anion of thioxanthone and the radical cation from the amine (Scheme 2.8).²⁴ This is followed by a proton-transfer to generate the corresponding ketyl and α -aminoalkyl radicals. Importantly, the ketyl radical from thioxanthone has been reported to be unreactive in these systems, either terminating by recombination to yield the pinacol dimer, or disproportionation to return to the ground state of thioxanthone and form a thioxanthole species.²⁴ Based on these data, it is anticipated that the ketyl radical will not play role in the reduction of **2a**, however, this possibility ultimately cannot be ruled out.



Scheme 2.8. Photoreduction of triplet thioxanthone by aliphatic amines.

Upon subjecting 3 mM thioxanthone and 15 mM *i*Pr₂NEt to visible light irradiation in the presence of **2a**, the reductive cyclized product was observed in 82% yield as a single *trans*-isomer after 18 hours. In order to reduce the irradiation time of the experiment, a

derivative of thioxanthone, 2,4-diethylthioxanthone, was chosen as its absorption tailed more into the visible region (Figure 2.2). Employing this strategy, it was possible to achieve 55% yield of the desired 5-exo-trig product after only 5 hours of irradiation.

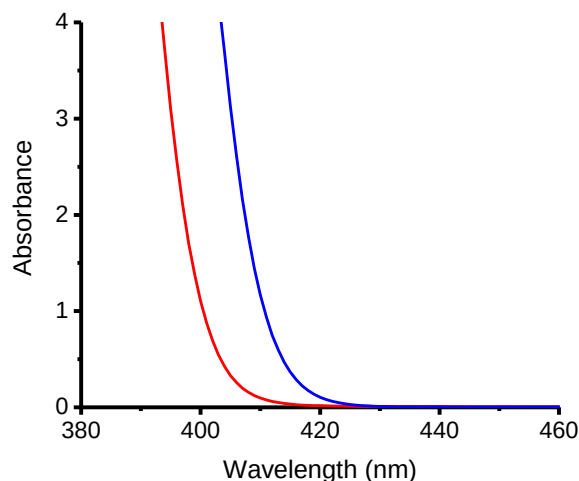
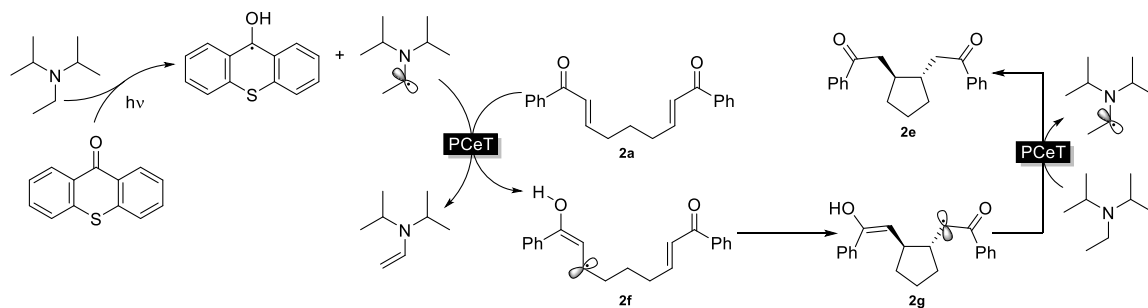


Figure 2.2. Absorption spectra of 3 mM thioxanthone (red) and 3 mM 2,4-diethylthioxanthone (blue) in MeCN. Spectra were recorded at 3 mM in order to reflect the concentrations employed under standard reaction conditions.

The proposed mechanism for the reductive cyclization of **2a** mediated by thioxanthone and *i*Pr₂NEt is presented in Scheme 2.9. Upon excitation of thioxanthone (or 2,4-diethylthioxanthone), the excited state abstracts a hydrogen atom from *i*Pr₂NEt, generating a ketyl radical and an α -aminoalkyl radical. It should be noted that the radical will be primarily centered at the least sterically hindered α -carbon, as it has been reported that the α -hydrogen is more acidic compared to the tertiary α -hydrogen, therefore having a lower BDE.²⁷ The α -aminoalkyl radical then undergoes a proton-coupled electron-transfer with **2a**, generating radical intermediate **2f** and the corresponding enamine. **2f** then undergoes a 5-exo-trig cyclization to yield radical intermediate **2g**. As previously mentioned, Steenken and Neta demonstrated that α -keto radicals are excellent oxidizing agents for amines, with rates of electron-transfer approaching diffusion control.²²

Therefore, it is proposed that radical intermediate **2g** oxidizes $i\text{Pr}_2\text{NEt}$, followed by proton-transfer to yield the desired product **2e** and another α -aminoalkyl radical.



Scheme 2.9. Proposed mechanism for the reductive cyclization of (E,E) -1,7-dibenzoyl-1,6-heptadiene mediated by thioxanthone and $i\text{Pr}_2\text{NEt}$.

2.4 Conclusion

In this chapter, examples for the participation of amine-derived radicals in a photoredox transformation were presented. Using **I-379**, which upon UVA irradiation photolyses to yield an α -aminoalkyl radical, the reductive cyclization of (E,E) -1,7-dibenzoyl-1,6-heptadiene (**2a**) proceeded in 73% yield after two hours of irradiation. When employing a type II photoinitiator system based on thioxanthone and $i\text{Pr}_2\text{NEt}$, the reductive cyclization of **2a** could be achieved in up to 83% yield with visible light irradiation. Similar to the seminal examples reported by Yoon and coworkers, the desired product was produced as a single *trans*-isomer.

Considering these examples, the possibility of the participation of amine-derived radicals in reductive quenching photoredox transformations should always be considered. Considering the oxidation potential of α -aminoalkyl radicals, their role in the underlying mechanism of photoredox transformations should not be excluded when electron-transfer is thermodynamically favourable. Methods, such as the experiments described in this chapter, could be employed to test the participation of α -aminoalkyl radicals.

The implication of the participation of these radicals in photoredox transformations is that many of the underlying mechanisms will possess a propagating chain component. Another way to test for the participation of these radicals is to confirm the presence of chain propagation in the transformation of interest. This can be achieved by determining the quantum yield of the reaction, or by analyzing the reaction employing intermittent illumination. These types of experiments will be discussed in further detail in chapter 6.

2.5. Experimental Details

2.5.1 General Information. All reagents were purchased from commercial suppliers and used without further purification. MeCN was freshly distilled over calcium hydride before use. The light source was a Luzchem photoreactor equipped with either UVA or visible light lamps. Typically, the photoreactor was operated with 12 lamps, corresponding to a power of 70-80 W/m². Product isolation was performed by preparative thin layer chromatography using 1000 μ m thick glass baked TLC plates from Silicycle. All ¹H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer. UV-vis spectra were recorded on a Varian Cary 50 spectrometer.

2.5.2 Synthesis of (*E,E*)-1,7-dibenzoyl-1,6-heptadiene. To a solution of stabilized ylide (benzoylmethylene)triphenylphosphorane (5.26 mmol, 2.0 g) in 25 mL of THF was added 50% glutaraldehyde (2.10 mmol, 420 μ L) and MgSO₄ (2 g). The mixture was stirred under reflux and progress was monitored by TLC. Upon completion, the precipitate was removed by filtration, and the solvent was removed by rotary evaporation. The crude was purified by column chromatography (10:1 Hex:EtOAc) to give the title compound as a colourless oil in 41% yield (262 mg).

2.5.3 Procedure for Reductive Cyclization of (*E,E*)-1,7-dibenzoyl-1,6-heptadiene using Irgacure-379. (*E,E*)-1,7-dibenzoyl-1,6-heptadiene (0.2 mmol, 61 mg) and Irgacure-

379 (0.2 mmol, 76 mg) were added to a 25 mL round bottom flask equipped with a magnetic stir bar. The flask was then purged with argon, followed by the addition of 10 mL of degassed MeCN. The reaction was then irradiated with UVA bulbs and stirred for 2 hours at room temperature. MeCN was removed by rotary evaporation, and the crude was purified by preparative thin layer chromatography (5:1 Hex:EtOAc) to give the desired cyclized product as a colourless oil in 73% yield (45 mg) as a single diastereomer.

2.5.4 Procedure for Reductive Cyclization of (*E,E*)-1,7-dibenzoyl-1,6-heptadiene using Thioxanthone and *i*Pr₂NEt. An appropriate amount of a stock solution of (*E,E*)-1,7-dibenzoyl-1,6-heptadiene in MeCN was concentrated by rotary evaporation in a 50 mL round bottom flask. To the 50 mL flask containing 1,7-dibenzoyl-1,6-heptadiene (0.06 mmol, 18 mg) was added thioxanthone (0.06 mmol, 13 mg). The flask was then purged with argon, followed by the addition of 20 mL of degassed MeCN and *i*Pr₂NEt (0.3 mmol, 51 μ L). The contents were transferred to previously degassed quartz test tubes using a cannula, and the reaction was irradiated with visible light bulbs for 18 hours at room temperature using a carousel. **Note:** Quartz tubes were only used for experimental convenience, and are not required for visible light irradiation. MeCN was removed by rotary evaporation, and the crude was purified by preparative thin layer chromatography (7:1 Hex:EtOAc) to give the desired cyclized product as a colourless oil in 83% yield (15 mg) as a single diastereomer.

2.5.5 Procedure for Reductive Cyclization of (*E,E*)-1,7-dibenzoyl-1,6-heptadiene using 2,4-Diethylthioxanthone and *i*Pr₂NEt. An appropriate amount of a stock solution of (*E,E*)-1,7-dibenzoyl-1,6-heptadiene in MeCN was concentrated by rotary evaporation in a 50 mL round bottom flask. To the 50 mL flask containing 1,7-dibenzoyl-1,6-heptadiene (0.07 mmol, 22 mg) was added 2,4-diethylthioxanthone (0.07 mmol, 19 mg). The flask

was then purged with argon, followed by the addition of 20 mL of degassed MeCN and *i*Pr₂NEt (0.36 mmol, 62 μ L). The contents were transferred to previously degassed quartz test tubes using a cannula, and the reaction was irradiated with visible light bulbs for 5 hours at room temperature using a carousel. **Note:** Quartz tubes were only used for experimental convenience, and are not required for visible light irradiation. MeCN was removed by rotary evaporation, and the crude was purified by preparative thin layer chromatography (7:1 Hex:EtOAc) to give the desired cyclized product as a colourless oil in 55% yield (12 mg) as a single diastereomer.

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3. Methylene Blue Photocatalysis: Oxidative Hydroxylation of Arylboronic Acids

3.1 An Introduction to Methylene Blue Photochemistry

During the last two decades, visible light photoredox transformations have become a well-established method for promoting important chemical reactivity under mild conditions.¹⁻³ Many of these transformations rely on $\text{Ru}(\text{bpy})_3\text{Cl}_2$, which is often employed in a reductive quenching catalytic cycle.¹ In reductive quenching cycles, the excited state of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ is quenched by an electron donor to form the highly reducing $\text{Ru}(\text{bpy})_3^+$ species (-1.33 V vs. SCE), which can then be employed to reduce a variety of organic substrates. In these transformations, it is common that aliphatic amines, such as triethylamine (NEt_3) or *N,N*-diisopropylethylamine ($i\text{Pr}_2\text{NEt}$) are employed as electron-donors.¹ While this reactivity has been heavily exploited in the recent literature, the quenching of triplet $\text{Ru}(\text{bpy})_3\text{Cl}_2$ by amines has been documented as early as the 1970s.⁴ In 1978, Whitten and coworkers reported that prolonged irradiation of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ analogues resulted in the formation of $\text{Ru}(\text{II})^+$, as evidenced by the bathochromic shift in the absorption spectrum of the photosensitizer.⁵ Also in 1978, Balzani and coworkers investigated this reactivity further by measuring the bimolecular rate constants (k_q) for the quenching of triplet $\text{Ru}(\text{bpy})_3\text{Cl}_2$ with a variety of electron-donors, many of which were aromatic and aliphatic amines.⁶ A summary of their data is presented in Table 3.1. Interestingly, a large portion of the table, largely corresponding to aliphatic amines, was left blank (highlighted in red). This was due to the fact that Balzani and coworkers did not observe any quenching of the luminescence of $^*\text{Ru}(\text{bpy})_3^{2+}$.⁶ Similarly, in 2001, Previtali and coworkers also reported that aliphatic amines do not quench the excited state of $\text{Ru}(\text{bpy})_3\text{Cl}_2$.⁷

Table 3.1. Bimolecular rate constants for the quenching of $\text{Ru}(\text{bpy})_3^{2+}$ as reported by Balzani and coworkers in 1978 (Ref. 6).

Quencher	$E_{1/2} (\text{D/D}^+)^a$	$\text{Ru}(\text{bpy})_3^{2+} k_q (\text{M}^{-1}\text{s}^{-1})$
4-Aminodiphenylamine	0.27 V	6.7×10^9
<i>N,N,N',N'</i> -Tetramethylbenzidine	0.32 V	7.4×10^9
<i>N,N</i> -Diphenyl- <i>p</i> -phenylenediamine	0.35 V	5.8×10^9
Benzidine	0.46 V	4.5×10^9
Phenothiazine	0.53 V	4.1×10^9
<i>N,N</i> -Dimethyl- <i>p</i> -toluidine	0.65 V	1.1×10^9
<i>N,N</i> -Diethylaniline	0.76 V	1.5×10^8
<i>N,N</i> -Dimethylaniline	0.78 V	6.5×10^7
Diphenylamine	0.83 V	-
Triphenylamine	0.86 V	-
Tributylamine	0.92 V	-
Triethylamine	0.96 V	-
<i>N,N</i> -dimethylbenzylamine	1.01 V	-
<i>N</i> -Methylaniline	1.03 V	-
Dicyclohexylamine	1.12 V	-
Dibutylamine	1.17 V	-
Dipropylamine	1.22 V	-
Aniline	1.28 V	-
Diethylamine	1.30 V	-
<i>tert</i> -Butylamine	1.45 V	-

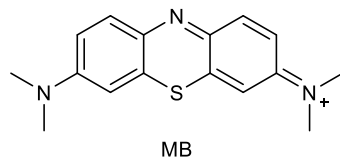
^aHalf-wave potentials reported versus saturated calomel electrode (SCE).

Despite the fact that luminescence quenching was not observed for aliphatic amines, the vast majority of photoredox transformations today employ aliphatic amines to quench the excited state of $\text{Ru}(\text{bpy})_3\text{Cl}_2$.¹ This seems strange, as literature precedence would suggest that these reactions should not occur, however, this is obviously not the case. Therefore, it is possible that the bimolecular rate constants for quenching between $^*\text{Ru}(\text{bpy})_3^{2+}$ and aliphatic amines occur at rates which are too slow to have been measured with previous technologies.

Understanding the slow nature of these rate constants, we wondered if we could find a photocatalytic system in which these quenching events are more favourable, leading to an increase in reaction efficiency for these photoredox transformations. We also identified other factors that may possibly affect the photocatalytic activity of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ that could be addressed. For example, the lifetime of the $\text{Ru}(\text{bpy})_3\text{Cl}_2$ excited state ($1.1 \mu\text{s}$ in MeCN)⁸

is relatively short when compared to other triplet photosensitizers, reducing the probability of excited state quenching before radiative relaxation.

An ideal candidate that fulfills these criteria is Methylene Blue (MB, Figure 3.1). MB is a member of the thiazine dye family, and has been employed widely in both biological and chemical applications, most notably for the generation of singlet oxygen.⁹⁻¹¹ These reactions occur by the way of a triplet state, where ^3MB and the substrate interact to form radicals or in the case of oxygen, singlet oxygen. The triplet state of MB forms with a quantum yield (Φ_T) of 0.52, and possesses a long lifetime of 32 μs (in MeCN).¹² MB also possesses a strong absorption in the visible region of the spectrum, with an extinction coefficient (ϵ) of 90,000 $\text{M}^{-1}\text{cm}^{-1}$ at 665 nm.⁸ Therefore, with a long excited state lifetime, and a strong absorption in the visible region, MB fulfills two out of three requirements in our criteria for an ideal photocatalyst.



Photochemical Properties

Absorption λ_{max} : 665 nm
 $\epsilon = 90,000 \text{ M}^{-1}\text{cm}^{-1}$
 Triplet Energy: 1.50 eV
 $\Phi_T = 0.52$
 Triplet τ_0 (MeCN): 32 μs
 Triplet Transient λ_{max} : 420 nm
 Triplet $\epsilon = 11,000 \text{ M}^{-1}\text{cm}^{-1}$

Redox Properties

$E_{1/2} (\text{MB}^+/\text{MB}^\bullet) = -0.47 \text{ V vs. SCE}$
 $E_{1/2} (^*\text{MB}^+/\text{MB}^\bullet) = 0.97 \text{ V vs. SCE}$

Figure 3.1. The photophysical and redox properties of Methylene Blue.

In 1976, Kayser and Young investigated the photoreduction of MB by amines. They determined that the triplet state of MB could be quenched by a variety of aromatic and aliphatic amines, producing the amine radical-cation, and the semi-reduced form of MB ($^*\text{MB}$).^{13,14} Importantly, they measured a series of bimolecular rate constants between ^3MB and aliphatic amines, which ranged between 10^7 and $10^8 \text{ M}^{-1}\text{s}^{-1}$.¹³ Through mechanistic

analysis, they were also able to determine the probability at which quenching events would undergo electron-transfer. For example, 40% of quenching events between ^3MB and NEt_3 led electron-transfer, forming $^{\bullet}\text{MB}$ and the NEt_3 radical-cation.¹³

Based on the ability for ^3MB to undergo reductive quenching with aliphatic amines, we wondered if MB would make an ideal candidate to catalyze reductive quenching photoredox transformations. We envisioned that MB could be employed in a photoredox cycle as depicted in Figure 3.2. Upon excitation, ^3MB could be quenched by an aliphatic amine to generate the amine radical-cation, and $^{\bullet}\text{MB}$. As discussed in chapter 2, the amine radical-cation will readily deprotonate to yield an α -aminoalkyl radical¹⁵, which can also be employed as a reducing agent in these transformations.¹⁶ The mildly reducing $^{\bullet}\text{MB}$ ($E_{1/2}^{\text{ox}} = -0.47 \text{ V vs. SCE}$)¹⁷ can then be employed as an electron-donor to regenerate the MB ground state. In good agreement, $^{\bullet}\text{MB}$ has been demonstrated to donate an electron to oxygen to yield superoxide at a rate of $10^5 \text{ M}^{-1}\text{s}^{-1}$.¹⁸

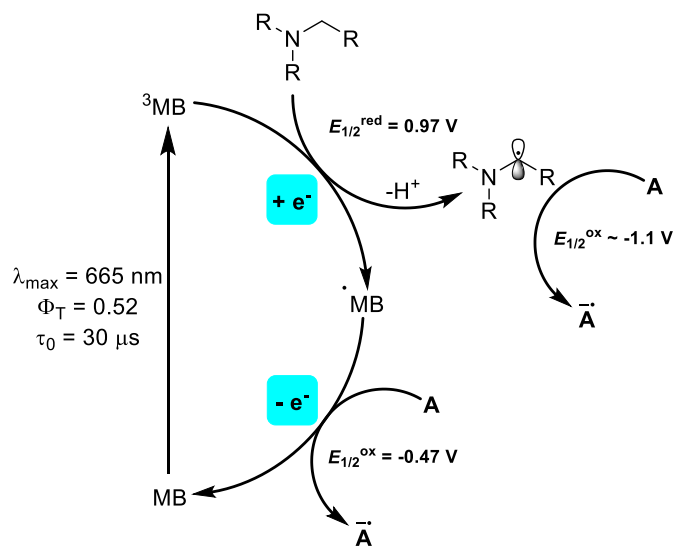


Figure 3.2. General reductive quenching cycle employing MB as a photoredox catalyst.

As an added benefit, MB could provide practitioners of photoredox catalysis with a more economically viable catalytic system, especially when comparing to currently employed

ruthenium and iridium polypyridyl complexes. Based on recent figures from Sigma Aldrich, $\text{Ru}(\text{bpy})_3\text{Cl}_2$ costs ~ \$140 (CAN) per gram, while in comparison 1 gram of MB costs only ~ \$3 (CAN). On a per mole basis, this difference in cost is even more pronounced, with $\text{Ru}(\text{bpy})_3\text{Cl}_2$ at ~ \$10,000 (CAN) per mole whereas MB only costs ~ \$100 (CAN) per mole. This has the potential to significantly reduce the cost of photoredox transformations, making scaling-up to industrially relevant scales more affordable. Finally, MB is also non-toxic, with many applications in clinical medicine, which could prove beneficial when applying photoredox catalysis in the synthesis of pharmaceutically relevant compounds.¹⁹ In fact, while MB has been demonstrated to be toxic to neural tissues, it does not show any local toxicity with other tissues.¹⁹ For example, when comparing MB to Ru and Ir, strict U.S. Food and Drug Administration (FDA) regulations exist on how much elemental impurities of these metals can be present in pharmaceuticals. For example, for orally administered drugs, the permitted concentration of Ru and Ir is 10 $\mu\text{g/g}$, whereas for inhaled drugs, the limit is only 0.1 $\mu\text{g/g}$.²⁰ In contrast, the FDA has already approved MB-based drugs such as ProvayBlue.²¹ Therefore, it is clear that the use of Ru and Ir catalysts for photoredox transformations must be limited so that the need for trace metal removal to meet FDA regulations is circumvented, and non-toxic dyes such as MB could act as viable replacements moving forward.

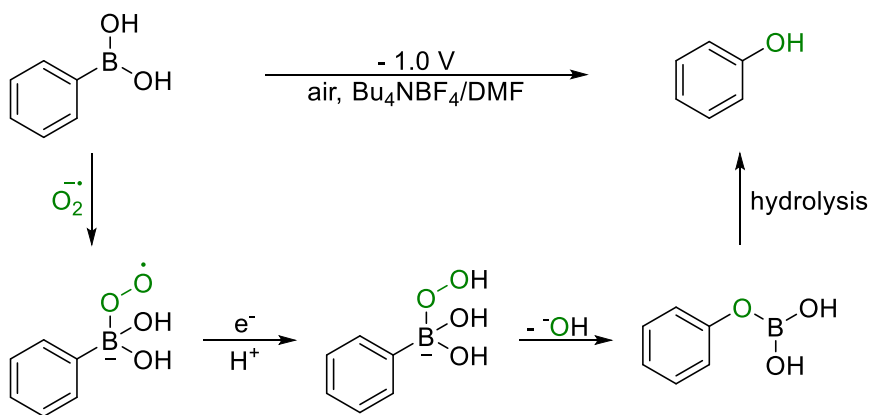
Despite the many foreseen advantages of employing organic dyes such as MB for these photoredox transformations, some of the drawbacks of these dyes should be discussed. Perhaps the most significant drawback is dye bleaching over the course of the reaction, whereas the transition-metal complexes generally employed can withstand long periods of irradiation. However, it was postulated that the more favourable excited state kinetics for these reductive quenching transformations would lead to decreased reaction times, thereby avoiding possible loss of reactivity due to bleaching.

3.2 Photoredox Catalyzed Oxidative Hydroxylation of Arylboronic Acids

The phenol motif is prevalent in a wide array of polymers, pharmaceuticals, and naturally occurring compounds.²² Moreover, it often serves as an important building block for the construction of more complex structures. Conventional methods for the synthesis of phenols include nucleophilic aromatic substitution, hydrolysis of arene diazonium salts, and benzyne protocols.²³⁻²⁷ These methods tend to suffer from low functional group compatibility, poor accessibility of the starting material, and harsh reaction conditions. As a result, establishing practical, general, and efficient catalytic methods for the synthesis of phenols remains an effort of intensive research among synthetic laboratories.

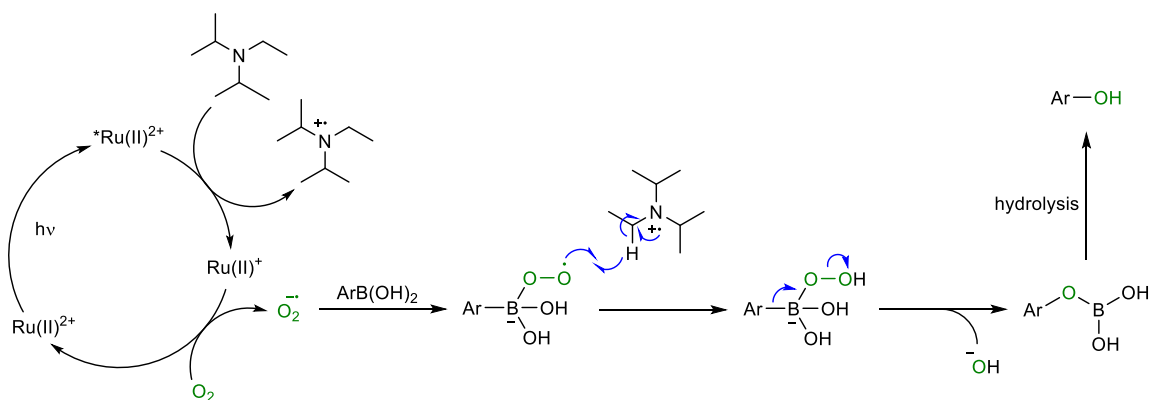
Photoredox catalysis has shown great promise for the development of practical, general, and efficient catalytic methods for organic synthesis due to the mild conditions employed, as all the energy required for the reaction is supplied by light. In 2012, Xiao and coworkers hypothesized that photoredox catalysis could be employed as a means to promote the synthesis of phenols through the oxidative hydroxylation of arylboronic acids.²⁸ Xiao and coworkers were inspired by their recent electrochemical studies, along with others, on the oxidative hydroxylation of arylboronic acids, which employed molecular oxygen as the oxidant (Scheme 3.1).^{29,30} In these studies, a cathodic current was employed to reduce molecular oxygen to the nucleophilic superoxide radical anion, which was then proposed to add to the boron center, creating a peroxy radical intermediate. The peroxy radical is then immediately reduced by either the cathodic conditions or another superoxide radical anion and protonated to give the boron peroxo species. To complete the reaction, it is proposed that the aryl group undergoes an irreversible migration to the peroxide system with subsequent hydrolysis to give the corresponding phenol. According to DFT calculations, the migration step was calculated to have an activation barrier of just 17.5 kcal mol⁻¹, which suggests that the reaction could readily occur at room temperature.²⁸

Based on these electromediated systems, Xiao and coworkers hypothesized that the superoxide radical anion could be generated employing visible light photoredox catalysis, which would then be employed for the oxidative hydroxylation of arylboronic acids.



Scheme 3.1. Proposed mechanism for the electromediated oxidative hydroxylation of arylboronic acids.^{29,30}

Employing 2 mol% of $\text{Ru}(\text{bpy})_3\text{Cl}_2$, 2 equivalents of $i\text{Pr}_2\text{NEt}$, DMF, and visible light irradiation, Xiao and coworkers were able to successfully promote the oxidative hydroxylation of a variety of arylboronic acids to their corresponding phenols.²⁸ As a model example, the oxidative hydroxylation of phenylboronic acid to phenol could be achieved in 81% yield after 28 hours of irradiation from a 36 W fluorescence lamp (Scheme 3.2). $^{18}\text{O}_2$ studies confirmed that the hydroxyl oxygen atom originates from atmospheric oxygen. They proposed that upon generation of the superoxide radical anion through a reductive quenching photoredox cycle, it adds to the boron center, creating a peroxyl radical intermediate, which abstracts a hydrogen atom from an amine radical-cation generated through reductive quenching (Scheme 3.2).²⁸ This is followed by aryl migration, and finally hydrolysis to generate the final phenol product.



Scheme 3.2. Proposed mechanism for the photoredox catalyzed oxidative hydroxylation of arylboronic acids developed by Xiao and coworkers.²⁸

One of the disadvantages of Xiao's system is the long irradiation times required to achieve synthetically useful yields. We hypothesized that these long irradiation times were an artifact of the slow excited state kinetics for the quenching of $*\text{Ru}(\text{bpy})_3\text{Cl}_2$ by $i\text{Pr}_2\text{NEt}$, a critical step in the formation of the active reducing species in this transformation. As mentioned in section 3.1, it has been reported that aliphatic amines do not quench the luminescence of $\text{Ru}(\text{bpy})_3\text{Cl}_2$.^{6,7} While this cannot be true, or examples such as the one reported by Xiao would not yield any reactivity, it is likely that these rate constants are so slow that, at the time, they could not be measured with the current technology available. We hypothesized that by employing a photosensitizer with more favourable excited state kinetics for electron-transfer with aliphatic amines, such as MB, the efficiency of the reaction could be dramatically improved.

On this basis, we decided that Xiao's system for the oxidative hydroxylation of arylboronic acids to the corresponding phenols would be an ideal example to test MB as the basis of an inexpensive, metal-free photocatalytic system. The system was chosen due to its analytical simplicity, making it ideal to perform in depth kinetic and mechanistic analyses. This chapter not only focuses on the ability of MB to photocatalyze this transformation but also focuses on comparative measurements with $\text{Ru}(\text{bpy})_3\text{Cl}_2$, the photocatalyst employed

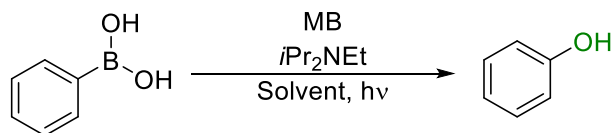
in the work initially reported by Xiao. This way, the reactivity of the two systems could be compared directly, and excited state kinetics could be employed to explain the observed differences in reactivity.

3.3 Methylene Blue Photocatalyzed Oxidative Hydroxylation of Arylboronic Acids

Optimization of the oxidative hydroxylation of arylboronic acids employing MB as the photocatalyst began by exposing phenylboronic acid to 0.5 mol% of MB, 2 equiv. of *i*Pr₂NEt, DMF, and visible light irradiation from two warm-white LEDs for 6 hours. Gratifyingly, 34% conversion of phenylboronic acid to the desired phenol product was observed (Table 3.2, Entry 1). Increasing the concentration of MB to 5 mol% was determined to have an adverse effect on the reaction, possibly due to the formation of MB dimers at higher concentrations, resulting in self-quenching (Entry 3).^{31,32} Increasing the concentration of *i*Pr₂NEt from 2 equiv. to 5 equiv. was found to provide a small increase in conversion (Entries 4 and 5). While this increase in yield was not significant, we chose to continue with higher concentrations of *i*Pr₂NEt to ensure higher probabilities of ³MB quenching by *i*Pr₂NEt. Increasing the concentration of MB to 2 mol% further increased the overall conversion (Entry 6). Hypothesizing that diffusion of O₂ from the atmosphere into solution was limiting the observed reaction rates, the reaction was performed under an O₂ atmosphere, yielding 98% conversion after 12 hours of irradiation (Entry 7). When performing a control reaction where *i*Pr₂NEt, the reductive quencher, was removed, the reaction still proceeded to 40% conversion after 12 hours of irradiation. It was hypothesized that the reaction still proceeded due to the presence of amine impurities (specifically, dimethylamine) in the DMF.³³ In order to test this hypothesis, a 4:1 mixture of MeCN:H₂O was chosen, as both MeCN and H₂O are considered inert solvents for free radical reactions³⁴, and the 4:1 mixture still provides a polar environment that allows MB

to be completely solubilized. Under these conditions, 2 mol% of MB was able to catalyze the complete conversion of phenylboronic acid to phenol (Entry 9).

Table 3.2. Optimization of reaction conditions and control reactions for the oxidative hydroxylation of phenylboronic acid to phenol.



Entry	MB	<i>i</i> Pr ₂ NEt	Solvent	Atm.	Time	Percent Conversion
1	0.5 mol%	2 equiv.	DMF	air	6 h	34%
2	1 mol%	2 equiv.	DMF	air	6 h	34%
3	5 mol%	2 equiv.	DMF	air	6 h	25%
4	1 mol%	2 equiv.	DMF	air	12 h	52%
5	1 mol%	5 equiv.	DMF	air	12 h	54%
6	2 mol%	5 equiv.	DMF	air	12 h	60%
7	2 mol%	5 equiv.	DMF	O ₂	12 h	98%
8	2 mol%	-	DMF	O ₂	12 h	40%
9	2 mol%	5 equiv.	MeCN:H ₂ O (4:1)	O ₂	12 h	100%
10	1 mol%	5 equiv.	MeCN:H ₂ O (4:1)	O ₂	7 h	100% (94%) ^a
11	1 mol%	-	MeCN:H ₂ O (4:1)	O ₂	7 h	No Reaction

Reaction Conditions: Phenylboronic acid (0.6 mmol), MB, *i*Pr₂NEt, and solvent (10 mL) was irradiated with two warm-white LEDs. Percent conversion was determined by ¹H NMR analysis. ^aIsolated yield.

In order to determine at what point in time full conversion was achieved, the reaction was performed in deuterated solvents and followed by ¹H NMR. It was determined that the reaction reached conversion within 7 hours of irradiation and that in fact, a catalytic loading of only 1 mol% of MB was sufficient to promote the reaction (Figure 3.3). The sigmoidal shape observed in the conversion versus time plot in Figure 3.3 will be discussed in greater detail *vide infra*. The reaction was then repeated in non-deuterated solvents, and after 7 hours of irradiation, complete conversion of phenylboronic acid and 94% isolated yield of phenol was observed (Table 3.2, Entry 10). Importantly, a control reaction with no *i*Pr₂NEt did not yield any conversion (Entry 11), indicating that the conversion previously observed with the control reaction in DMF most likely related to impurities already present in the solvent or generated throughout the course of the reaction.³³

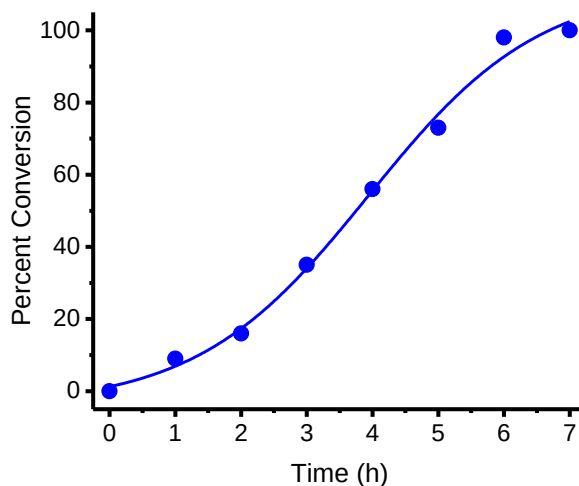
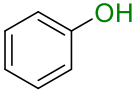
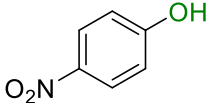
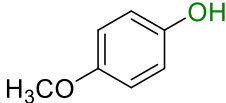
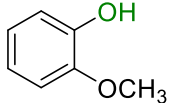
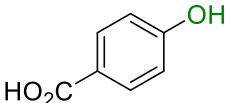
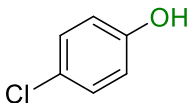
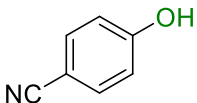
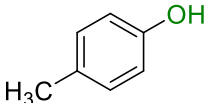
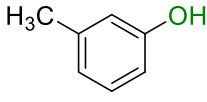
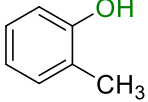
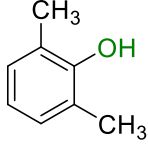


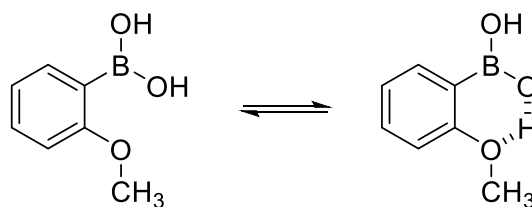
Figure 3.3. Conversion versus time plot for the oxidative hydroxylation of phenylboronic acid photocatalyzed by Methylene Blue.

With the optimized conditions in hand, the scope of the oxidative hydroxylation of arylboronic acids photocatalyzed by MB was examined (Table 3.3). In almost all cases, complete conversion to the corresponding phenol was achieved with only 7 hours of irradiation, with the exception of 2-methoxyphenylboronic acid, where only 75% conversion was achieved (**3e**). Since the reactivity of 4-methoxyphenylboronic acid (**3d**) was unaffected by *para*-methoxy substitution, it is unlikely that the low reactivity observed with **3e** is due to electron donation from the methoxy substituent. Alternatively, it is proposed that the decreased reactivity of **3e** is due to the formation of a six-membered chelate in 2-methoxyphenylboronic acid, which is illustrated in Figure 3.4.

Table 3.3. Reaction scope for the oxidative hydroxylation of arylboronic acids.

			
3b: 100% (94%)	3c: 100% (98%)	3d: 100% (96%)	3e: 75% (69%)
			
3f: 100%	3g: 100%	3h: 99%	3i: 100%
			
3j: 99%	3k: 100%	3l: 100%	

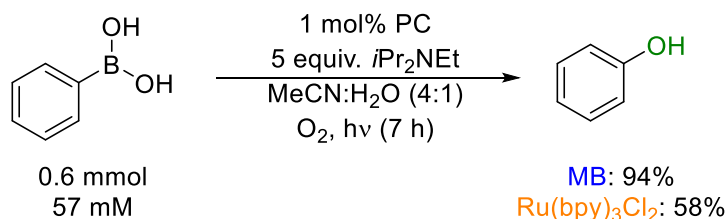
Percent conversion determined by ^1H NMR analysis. Isolated yields for select examples are indicated in brackets. For reaction conditions, see Section 3.7.2.

**Figure 3.4.** Formation of a six-membered chelate in 2-methoxyphenylboronic acid, resulting in decreased reactivity in the photocatalytic oxidative hydroxylation reaction.

3.4 Mechanistic and Kinetic Analysis

In order to accurately compare the efficiency of our newly developed MB photocatalytic system to that developed by Xiao and coworkers²⁸, a reaction was performed with the same concentration of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ in comparison to that of MB. Due to the high concentrations of the photosensitizers employed, and the broad emission of the warm-white LEDs, it was assumed that >99% of the incident photons at the respective absorption maxima of the photocatalyst were absorbed in both cases. When performing the reaction

with $\text{Ru}(\text{bpy})_3\text{Cl}_2$, only 58% isolated yield of phenol was observed after 7 hours of irradiation (Scheme 3.3). In this same period of irradiation, the reaction photocatalyzed by MB reaches complete conversion, with 94% isolated yield.



Scheme 3.3. Photocatalyst comparison for the visible light mediated oxidative hydroxylation of phenylboronic acid. Yields are reported as isolated yields.

While this increased efficiency when employing MB was exciting, it was important to determine what factors led to these observed differences in reactivity. It was hypothesized that the increase in reactivity of MB compared to $\text{Ru}(\text{bpy})_3\text{Cl}_2$ stemmed from the improved excited state quenching by $i\text{Pr}_2\text{NEt}$. In order to test this hypothesis, nanosecond laser flash photolysis (LFP) was employed.³⁵ In LFP, the photosensitizer is excited with a short laser pulse, generating the triplet state. Concurrently, the reaction is illuminated with a monitoring beam, typically from a Xenon lamp. The photogenerated triplet state is then excited to a higher energy triplet state, a process which is known as triplet-triplet absorption. The unimolecular decay rate of this triplet-triplet absorption can be monitored at different concentrations of the desired excited state quencher, and by employing a pseudo-first order kinetic analysis, the bimolecular rate constant can be determined. A typical set-up for a nanosecond LFP system is presented in Figure 3.5.³⁵

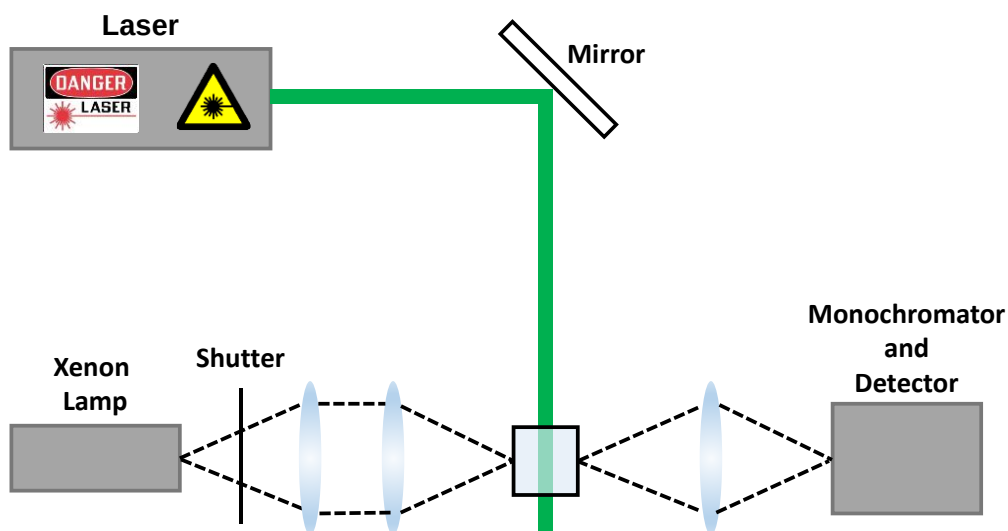


Figure 3.5. Schematic of a typical configuration of a laser flash photolysis system.

LFP is also a powerful tool for the study of other short-lived reactive intermediates. For example, methyl viologen is commonly employed as an electron-acceptor, and upon one-electron reduction, produces a strong absorption at 605 nm.³⁶ The growth of this absorption can be monitored along with the decay of the photosensitizer, providing evidence that the quenching event is proceeding through electron-transfer. Often, the one-electron reduced or oxidized photosensitizers also possess transient absorptions that can also be detected employing LFP techniques.

By employing nanosecond LFP, the ground state recovery of MB and the decay of $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$ were monitored in the presence of increasing concentration of all the reaction components (Table 3.4). Interestingly, despite numerous reports that quenching of the luminescence of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ could not be observed in the presence of aliphatic amines, it was observed that $i\text{Pr}_2\text{NEt}$ quenched $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$ at a rate of $6.21 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$. Therefore, it is likely that the advances in technology, resulting in improved signal-to-noise

ratios, allowed for this rate constant to be determined. For ^3MB , however, a rate constant of $2.44 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ was observed for quenching by $i\text{Pr}_2\text{NEt}$. Therefore, excited state quenching by $i\text{Pr}_2\text{NEt}$ occurs at rates two orders of magnitude faster for MB compared to $\text{Ru}(\text{bpy})_3\text{Cl}_2$ or was found to be 39 times more efficient (Figure 3.6). This improved excited state quenching efficiency, the crucial step in generating the active reducing species in this reaction, is most likely the primary reason for the improved yields observed employing MB.

Table 3.4. Rate constants for triplet quenching of Methylene Blue and $\text{Ru}(\text{bpy})_3\text{Cl}_2$ derived from laser flash photolysis studies.

Quencher	Triplet Quenching: $k_q \text{ (M}^{-1}\text{s}^{-1}\text{)}$	
	Methylene Blue	$\text{Ru}(\text{bpy})_3\text{Cl}_2$
$i\text{Pr}_2\text{NEt}$	$2.44 \pm 0.24 \times 10^8$	$6.21 \pm 0.30 \times 10^6$
Phenylboronic acid ^a	$1.34 \pm 0.13 \times 10^8$	$3.72 \pm 0.37 \times 10^6$
Phenol ^a	$5.81 \pm 0.58 \times 10^5$	$6.68 \pm 0.67 \times 10^5$
O_2	$2.46 \pm 0.25 \times 10^9$	$2.97 \pm 0.30 \times 10^9$

^aRate constants for $\text{Ru}(\text{bpy})_3\text{Cl}_2$ estimated from the plateau region of the corresponding kinetic quenching plots. See Figures 3.13 and 3.14 for more information.

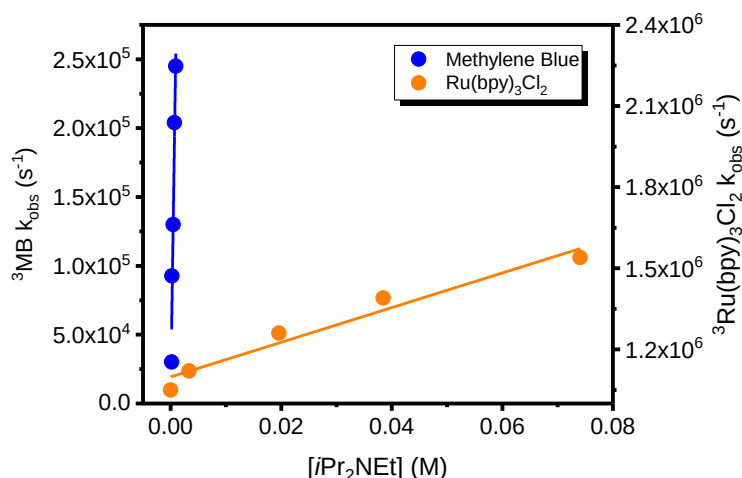


Figure 3.6. Rate of triplet quenching as a function of $[i\text{Pr}_2\text{NEt}]$ for Methylene Blue (blue) and $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (orange). Kinetic quenching plots correspond to data from Table 3.4.

While comparing the rate constants for excited state quenching by $i\text{Pr}_2\text{NEt}$ gives insight into the overall activity, it would be more accurate to take into consideration all of the possible pathways that can occur from the triplet excited state. These pathways include

relaxation (radiative or non-radiative) back to the ground state, or quenching by the other reaction components.³⁷ In order to take these alternate pathways into account, equation (1) can be employed to calculate the probability of triplet quenching by *i*Pr₂NEt at any point throughout the reaction:

% Triplet Quenching by *i*Pr₂NEt =

$$\frac{100 \% \times k_q^{iPr_2NEt}[iPr_2NEt]}{\tau_0^{-1} + k_q^{iPr_2NEt}[iPr_2NEt] + k_q^{PhB(OH)_2}[PhB(OH)_2] + k_q^{PhOH}[PhOH] + k_q^{O_2}[O_2]} \quad (1)$$

where τ_0^{-1} is the inverse of the excited state lifetime in the absence of quencher, $k_q^{iPr_2NEt}$ is the rate of triplet quenching by *i*Pr₂NEt, $k_q^{PhB(OH)_2}$ is the rate of triplet quenching by phenylboronic acid, k_q^{PhOH} is the rate of triplet quenching by phenol, and $k_q^{O_2}$ is the rate of triplet quenching by oxygen. The calculation can be further simplified by performing simulating initial reaction conditions, eliminating the phenol term to give:

% Triplet Quenching by *i*Pr₂NEt under initial reaction conditions =

$$\frac{100 \% \times k_q^{iPr_2NEt}[iPr_2NEt]}{\tau_0^{-1} + k_q^{iPr_2NEt}[iPr_2NEt] + k_q^{PhB(OH)_2}[PhB(OH)_2] + k_q^{O_2}[O_2]} \quad (2)$$

Employing the initial reaction concentrations, and all of the bimolecular rate constants listed in Table 3.4, the probability of excited state quenching, under initial reaction conditions as calculated using equation (2), was determined to be 85% for MB, and only 20% for Ru(bpy)₃Cl₂. The calculation was performed assuming a concentration of O₂ in solution of 2.1 mM.³⁸ Therefore, by accounting for all of the possible pathways for excited state deactivation, it can be seen that the reaction of ³MB with *i*Pr₂NEt is only 4.25 times more favourable than the corresponding reaction with ³Ru(bpy)₃Cl₂, which more accurately reflects the experimental observations.

While the excited state quenching is significantly more favourable with MB, the reaction performed with MB is only roughly twice as efficient compared to that with $\text{Ru}(\text{bpy})_3\text{Cl}_2$, and not 4 times more efficient as the excited state quenching data may suggest. A possible explanation is that the turnover step, the reduction of molecular oxygen to form the superoxide radical anion, proceeds more efficiently with $\text{Ru}(\text{bpy})_3\text{Cl}_2$. The reduction of oxygen by $\text{Ru}(\text{bpy})_3^+$ has been measured to proceed at a rate of $8.5 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, whereas the reduction of oxygen by ^1MB only proceeds at a rate of $5.0 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$.^{18,39} Therefore, despite the slow excited state kinetics of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ and the reduced probability of being quenched by $i\text{Pr}_2\text{NEt}$, catalytic turnover and generation of superoxide occurs at much higher rates compared to the MB system. These turnover rates could account for why the difference in reactivity is not as large as the excited state kinetics would suggest, demonstrating the benefit of understanding the kinetics of all the key steps in the reaction.

Excited state kinetics can also be employed to gain a further understanding of the underlying reactivity. For example, let's return to Figure 3.3, where an increase in the rate of the reaction is observed, beginning after two hours of irradiation, producing a sigmoidal conversion versus time plot. This type of behavior would not be expected if the reaction mechanism was following typical first order kinetics, where conversion versus time would follow a mono-exponential trajectory, with a plateau in reactivity occurring once higher conversion is reached. However, this reaction begins with what resembles as a period of induction before an increase in the reaction rate is observed, after which the reaction follows a more standard first order kinetics behavior. When examining the excited state kinetics for the quenching of MB by all of the reaction components, it was discovered that the starting material, phenylboronic acid, quenches MB at a rate two orders of magnitude larger compared to the final product, phenol. Any quenching by phenylboronic acid, or phenol, would inhibit the desired reaction, quenching by $i\text{Pr}_2\text{NEt}$, resulting in non-

productive quenching events. Therefore, we hypothesize that at initial concentrations, phenylboronic acid is partially inhibiting the desired ^3MB quenching by $i\text{Pr}_2\text{NEt}$, which is alleviated as the reaction progresses, due to the final product being a lesser quencher of ^3MB .

In order to quantify this change in reactivity, the probability for quenching by $i\text{Pr}_2\text{NEt}$ was calculated at different irradiation time intervals. Employing equation (2) at $t = 0$ hours, the probability of triplet quenching by $i\text{Pr}_2\text{NEt}$ is 85%, while the probability of ^3MB being quenched by phenylboronic acid is 9%. As phenylboronic acid is consumed, the overall rate of the reaction is observed to increase (Figure 3.3), due phenol being a lesser quencher of ^3MB . By employing equation (1) at $t = 4$ hours, and assuming that 1 equivalent of $i\text{Pr}_2\text{NEt}$ is consumed for each mole of phenylboronic acid consumed, the probability of triplet quenching by $i\text{Pr}_2\text{NEt}$ increases to 88%, while quenching by either phenylboronic acid or phenol only adds up to 5%. Interestingly, plotting the probability of triplet quenching by $i\text{Pr}_2\text{NEt}$ as a function of reaction progress (Figure 3.7), it is observed that the probability of triplet quenching by $i\text{Pr}_2\text{NEt}$ continually increases as the reaction proceeds towards completion, i.e. as phenylboronic acid is consumed. Therefore, it would be expected that as the reaction progresses, the overall reaction rate should increase, which is what is observed in Figure 3.3.

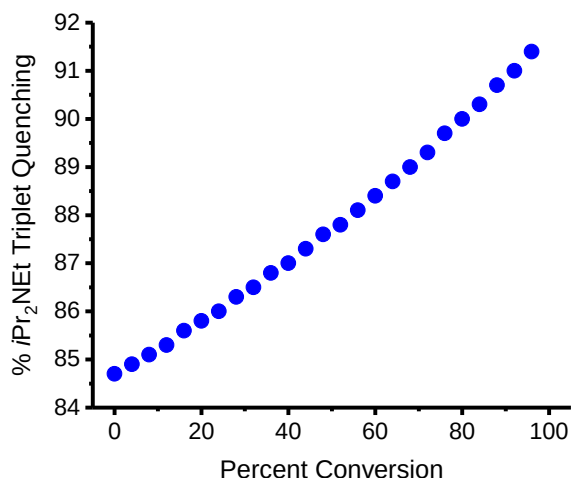


Figure 3.7. Probability of *iPr*₂NEt quenching ³MB as a function of reaction conversion for the oxidative hydroxylation of phenylboronic acid.

In order to gain a better understanding of the oxidative hydroxylation of phenylboronic acid catalyzed by Ru(bpy)₃Cl₂, the reaction was also performed in deuterated solvents, and progress was monitored by ¹H NMR (Figure 3.8a). Unlike the reaction performed with MB, the reaction photocatalyzed by Ru(bpy)₃Cl₂ displayed a relatively linear conversion versus time relationship. By employing equation (1) to determine the probability of triplet quenching by *iPr*₂NEt over the course of the reaction, it can be seen that the probability of *iPr*₂NEt quenching ³Ru(bpy)₃Cl₂ decreases slightly (~ 2%) over the course of the reaction as *iPr*₂NEt is consumed (Figure 3.8b). In this case, the effect of the concentration of *iPr*₂NEt is magnified, as higher concentrations of *iPr*₂NEt are required to intercept ³Ru(bpy)₃Cl₂ over oxygen, which quenches at 10⁹ M⁻¹s⁻¹. Therefore, because quenching by oxygen dominates in this system, and the probability of quenching by *iPr*₂NEt only changes by ~ 2% over the course of the reaction, the oxidative hydroxylation of phenylboronic acid proceeds slowly in a more linear fashion. However, a minor induction period is still observed, as phenylboronic acid does quench ³Ru(bpy)₃Cl₂ at a higher rate (3.72 x 10⁶ M⁻¹s⁻¹) compared to phenol (6.68 x 10⁵ M⁻¹s⁻¹).

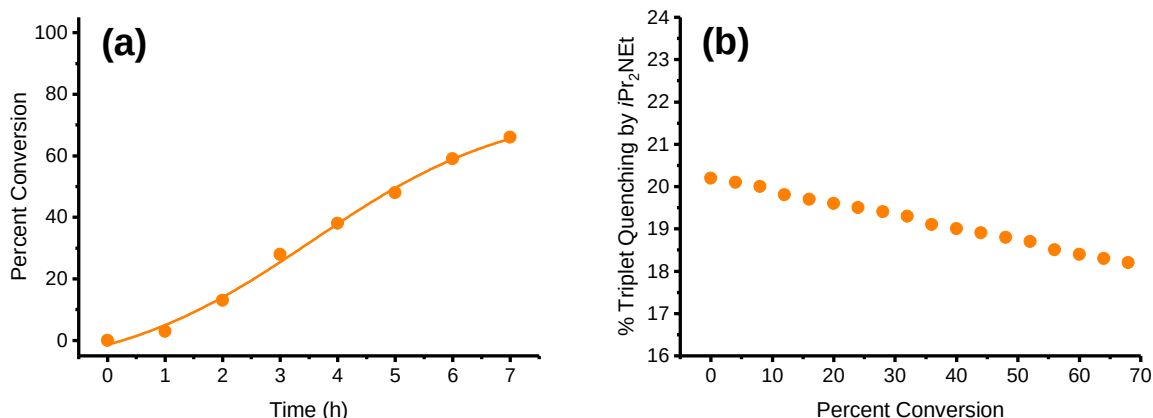


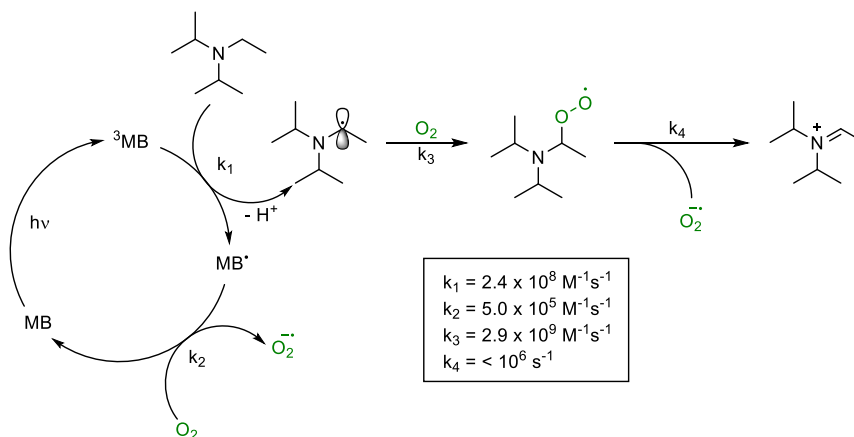
Figure 3.8. (a) Conversion versus time plot for the oxidative hydroxylation of phenylboronic acid photocatalyzed by $\text{Ru}(\text{bpy})_3\text{Cl}_2$. (b) Probability of $i\text{Pr}_2\text{NEt}$ quenching $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$ as a function of reaction conversion for the oxidative hydroxylation of phenylboronic acid.

It is important to note at this stage that without investigating the kinetics of the mechanistically key steps of the reaction, these detailed mechanistic interpretations to explain the underlying reactivity of these systems would not be possible. This highlights the importance of examining the excited state kinetics of the photocatalyst when developing new photoredox protocols.

3.5 Proposed Pathways for the Oxidative Hydroxylation of Arylboronic Acids

Previous mechanistic studies by Xiao and coworkers, who conducted the oxidative hydroxylation of 4-methoxyphenylboronic acid under an $^{18}\text{O}_2$ atmosphere, demonstrated that the hydroxyl oxygen atom comes from atmospheric oxygen.²⁸ Therefore, it is highly probable that the superoxide radical plays an integral role in the underlying mechanism. A proposed mechanism for the generation of superoxide is presented in Scheme 3.4. Upon excitation, ^3MB is quenched by $i\text{Pr}_2\text{NEt}$, generating $^{\bullet}\text{MB}$ and an amine radical-cation. The amine radical-cation will be quickly deprotonated to form an α -aminoalkyl radical, which is known to react with oxygen to generate an α -aminoperoxy radical.⁴⁰ This radical is too short-lived to be experimentally monitored and yields the Schiff-base and a

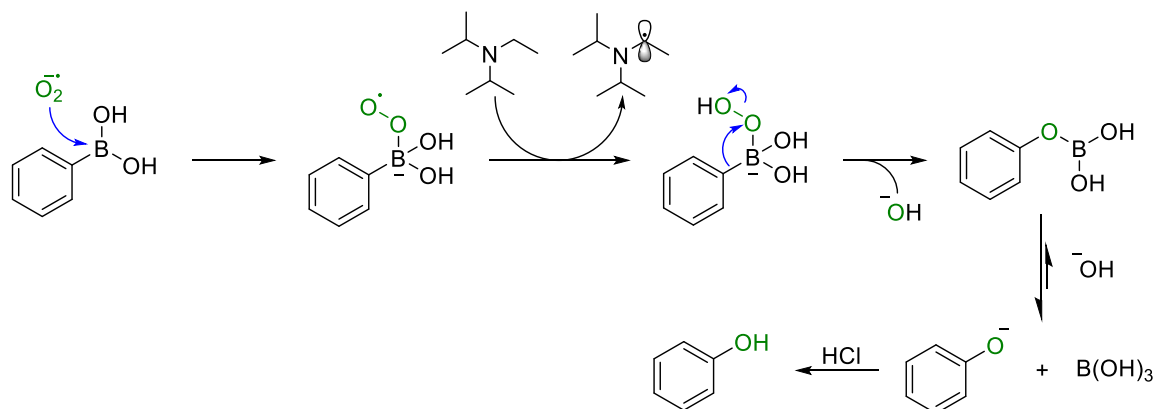
superoxide radical-anion. Another route to the formation of superoxide involves reduction of molecular oxygen by $\bullet\text{MB}$, which has been experimentally determined to occur at a rate of $10^5 \text{ M}^{-1}\text{s}^{-1}$.¹⁸ This step regenerates the ground state of MB, completing the catalytic cycle.



Scheme 3.4. Proposed catalytic cycle for the reduction of molecular oxygen to superoxide mediated by Methylene Blue.

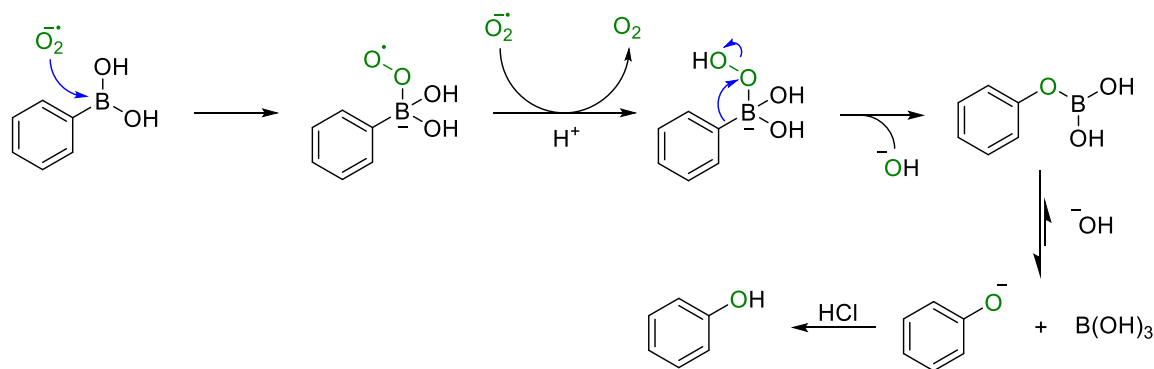
The mechanism in which the oxidative hydroxylation of arylboronic acids by superoxide proceeds is not well understood. Therefore, three possible pathways for the generation of phenol from phenylboronic acid will be presented. Pathways A and B involve the nucleophilic attack of a superoxide radical anion to the electrophilic boron center. Superoxide has been demonstrated to participate in a variety of nucleophilic substitution reactions^{41,42}, and the low pKa of phenylboronic acid (pKa 8.9) renders the boron center sufficiently electrophilic to stabilize the addition a superoxide radical anion.⁴³ In pathway A, the resulting peroxy radical is then proposed to abstract a hydrogen atom from $i\text{Pr}_2\text{NEt}$, which is present at a concentration of 300 mM in solution (Scheme 3.5). This step is followed by an aryl migration and the release of a hydroxide anion, a step which has been calculated to possess an activation barrier of 17 kcal mol^{-1} .²⁸ Therefore, this rearrangement could easily occur at room temperature. Since the presence of the

phenolate anion is clearly visible over the course of the reaction, characterized by its deep purple colour in solution, it is proposed that hydroxide adds to boron, resulting in the release of phenolate. Finally, the phenolate is protonated with an acid work-up after irradiation, yielding phenol.



Scheme 3.5. Proposed mechanism for the oxidative hydroxylation of phenylboronic acid involving hydrogen abstraction from $i\text{Pr}_2\text{NEt}$ (Pathway A).

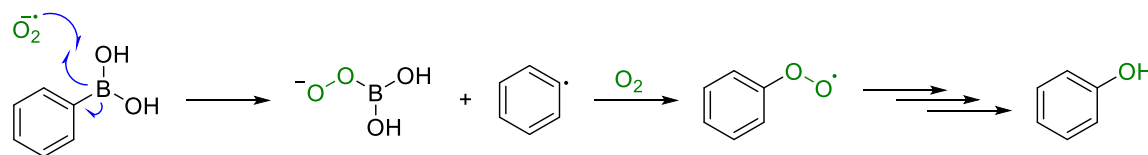
In pathway B, after nucleophilic addition of a superoxide radical anion to the boron center, the resulting peroxy radical is reduced by another superoxide radical anion⁴⁴, and the peroxide intermediate is generated upon protonation. From there, the mechanism to the final product remains the same as that presented for pathway A. In electrochemical studies of the oxidative hydroxylation of phenylboronic acid, it has also been proposed that the radical anion that results from reduction by superoxide adds to the boron center kicking out a hydroxide anion, yielding an intermediate in which both oxygen atoms are bonded to boron.²⁹ Aryl migration then occurs, and phenol forms upon hydrolysis. It should be noted that pathway B is likely only a very minor contributor to the overall transformation, as the proposed mechanism relies on the radical-radical reaction of two transient species in solution.



Scheme 3.6. Proposed mechanism for the oxidative hydroxylation of phenylboronic acid involving reduction by superoxide (Pathway B).

One can also not rule out a homolytic substitution pathway as part of the underlying mechanism (Pathway C). It has been demonstrated that peroxy radicals undergo homolytic substitution reactions with trialkyl- and triarylboranes, resulting in the formation of a highly stable boron-oxygen bond, and the release of an alkyl or phenyl radical.⁴⁵ Therefore, it is proposed that superoxide could undergo a homolytic substitution reaction with phenylboronic acid, resulting in the release of a highly reactive phenyl radical. Phenyl radicals are known to be highly reactive towards oxygen, resulting in the formation of a phenyl peroxy radical. The phenyl peroxy radical would then abstract a hydrogen atom to form the peroxide, which could eventually decompose to yield phenol.²² However, there are experimental observations throughout the course of the reaction that is inconsistent with this type of mechanism. For example, any attempts made to gain spectroscopic evidence for the formation of the phenylperoxy radical using transient spectroscopy were futile. Considering the high reactivity of phenyl radicals, and that *i*Pr₂NEt is present at a concentration of 300 mM at the beginning of the reaction, one would expect small amounts of a reduced side product, in this case, benzene, forming as a result from hydrogen-abstracting by the phenyl radical.⁴⁶ However, in all cases, complete conversion to the corresponding phenol is obtained, with no evidence for the formation of any reduced side

products. Despite this experimental evidence, however, the possibility of homolytic substitution cannot be completely ruled out.



Scheme 3.7. Proposed mechanism for the oxidative hydroxylation of phenylboronic acid involving a homolytic substitution reaction with superoxide (Pathway C).

Since ^3MB can also be quenched by oxygen to generate singlet oxygen ($^1\text{O}_2$), we decided to also investigate whether $^1\text{O}_2$ could play a role in the oxidation of phenylboronic acid. However, phenylboronic acid was found to be a poor quencher of $^1\text{O}_2$ ($1.23 \pm 0.35 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$), therefore any $^1\text{O}_2$ produced is likely to be quenched by $i\text{Pr}_2\text{NEt}$, which was found to be a potent quencher of $^1\text{O}_2$ ($2.25 \pm 0.16 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$).

3.6 Conclusion

In this chapter, the first example of employing MB, a cheap, non-toxic thiazine dye, as a photocatalyst for reductive quenching photoredox transformations was presented. MB was found to catalyze the oxidative hydroxylation of a variety of substituted arylboronic acids to the corresponding phenols in high yields after only 7 hours of visible light irradiation. Importantly, MB was also found to outperform $\text{Ru}(\text{bpy})_3\text{Cl}_2$ in a direct comparison study, demonstrating that MB could be an economically viable alternative for reductive quenching photoredox transformations.

In order to understand the increased reaction efficiency when employing MB as the photocatalyst, the excited state kinetics for both systems were studied in detail. It was determined that the desired reaction, the reductive quenching of the triplet photosensitizer by $i\text{Pr}_2\text{NEt}$, proceeded at a rate of $2.44 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for ^3MB , while the rate was found to

be only $6.21 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ for $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$. This resulted in the reaction being more efficient when MB was employed as the photosensitizer. This did not come as a surprise, however, as it has been well documented that aliphatic amines are inefficient quenchers of the excited state of $\text{Ru}(\text{bpy})_3\text{Cl}_2$.

In order to more accurately reflect the reaction conditions of the oxidative hydroxylation of phenylboronic acid, the bimolecular rate constants for the quenching of both triplet photosensitizers by all of the reaction components were measured. From these data, the probability at which each component quenches the excited state at various points throughout the reaction can be determined. Under initial reaction conditions, it was found that the probability of triplet quenching by $i\text{Pr}_2\text{NEt}$ was 85% and 20% for MB and $\text{Ru}(\text{bpy})_3\text{Cl}_2$, respectively. This difference is more representative of the experimentally observed results for the oxidative hydroxylation of phenylboronic acid, instead of directly comparing the rate constants for $i\text{Pr}_2\text{NEt}$ quenching. This highlights the importance of analyzing the excited state kinetics of all the reaction components to gain a better understanding of the underlying reactivity.

Excited state kinetics was also employed to gain an understanding of the overall reactivity over the course of the reaction. By analyzing the reaction by ^1H NMR, it was found that the reaction followed a sigmoidal shape, proceeding at higher rates as the reaction progressed. However, by examining the excited state kinetics of all the reaction components, it was determined that phenylboronic acid is also a potent quencher of ^3MB , while the final product, phenol, is not. Therefore, as the reaction progressed, a potent quencher was eliminated, and the desired quenching by $i\text{Pr}_2\text{NEt}$ proceeded more efficiently. This could also be seen by plotting the probability of triplet quenching by $i\text{Pr}_2\text{NEt}$ versus the progress of the reaction.

The goal of this work was not only to highlight that MB could be employed as a metal-free alternative to catalyze photoredox transformations, but also the importance of performing mechanistic analysis for photoredox transformations. While MB was found to be more efficient for this type of transformation, there may be reactions where the desired electron-transfer events with MB may be thermodynamically unfavourable compared to other photocatalysts, such as Ru(bpy)₃Cl₂. In these instances, quenching studies could be performed to find more efficient quenchers of the triplet photosensitizer to improve the overall rate of the reaction and facilitate the optimization of reaction conditions. An example of employing these types of studies to facilitate the development and optimization of a new photoredox protocol will be highlighted in the next chapter.

3.7 Experimental Details

3.7.1 General Information. Arylboronic acids, *N,N*-diisopropylethylamine (*i*Pr₂NEt), triethylamine, and solvents were purchased from chemical suppliers and used without further purification. The light source, unless otherwise noted, was two 90 W warm-white LEDs purchased from LedEngin. Product isolation was either performed by flash column chromatography using 230-400 mesh silica gel or by preparative thin layer chromatography using 60 Å glass baked TLC plates from Silicycle. All ¹H NMR spectra were recorded on a Bruker Avance 300 spectrometer (300 MHz) and a Bruker Avance 400 (400 MHz) spectrometer. UV-vis spectra were recorded on a Varian Cary 50 spectrometer.

3.7.2 General Procedure for the Oxidative Hydroxylation of Arylboronic Acids.

Arylboronic acid (0.6 mmol), *i*Pr₂NEt (3 mmol, 520 µL), MB (0.006 mmol, 2.2 mg), and MeCN:H₂O (4:1, 10 mL) were added to a 10 mL Schlenk tube equipped with a magnetic stir bar. The schlenk tube was then capped with a balloon, and back-filled with O₂. The

reaction mixture was then sonicated to ensure the contents were completely dissolved. The reaction was then irradiated and stirred for 7 hours. The reaction mixture was then cooled to 0 °C and quenched with roughly 5 mL of 10% HCl. The reaction mixture was then stirred for an additional 30 minutes, then extracted with diethyl ether (x3). The organic layer was washed with brine (x3), dried over MgSO₄, and concentrated by rotary evaporation. For examples with isolated yields, the crudes were purified by either flash column chromatography or by preparatory thin layer chromatography using 5:1 Hex:EtOAc as the eluent.

3.7.3 Procedure for Conversion vs. Time Experiments. Phenylboronic acid (1.2 mmol, 150 mg), *i*Pr₂NEt (6 mmol, 1 mL), MB or Ru(bpy)₃Cl₂ (0.012 mmol), and CD₃CN:D₂O (4:1, 15 mL) were added to a Schlenk tube equipped with a magnetic stir bar. The schlenk tube was then enclosed using a balloon, and back-filled with O₂. The reaction mixture was then sonicated to ensure all the contents were completely dissolved. The reaction was then irradiated and stirred for 7 hours. After each hour of irradiation, 500 µL of the reaction mixture was removed and placed in an NMR tube, and examined by ¹H NMR. This was also performed at t = 0 h.

3.8 Laser Flash Photolysis Data

3.8.1 Triplet Quenching of Methylene Blue. The triplet quenching experiments of MB were performed using a Surelite OPO Plus pumped with a Nd-YAG 355 nm (650 nm, 10 mJ/pulse) or an excimer laser (308 nm, 10 mJ/pulse) in a LFP-111 laser flash photolysis system (Luzchem Inc., Ottawa, CA). The samples were measured in 1 x 1 cm LFP-Luzchem cuvettes or 1 x 1 cm flow system. Samples of MB were prepared in a 4:1 solution of MeCN:H₂O with a total volume of 3 mL and an absorbance of ~0.1 at either 650 or 308 nm. The samples were purged with N₂ for 30 minutes prior to use. The solutions of

phenylboronic acid, *i*Pr₂NEt, and phenol used for the quenching studies were prepared in 4:1 MeCN:H₂O which was also degassed for the duration of the experiment.

Triplet quenching of MB by phenylboronic acid, phenol, and O₂ was measured employing laser excitation at 650 nm. However, due to the overlap of triplet MB (420 nm) and semi-reduced MB (430 nm) signals, it was necessary to monitor the recovery of the ground state (650 nm) to measure triplet quenching of MB by *i*Pr₂NEt. In this instance, laser excitation was performed at 308 nm in order to monitor the recovery of the ground state at 650 nm.

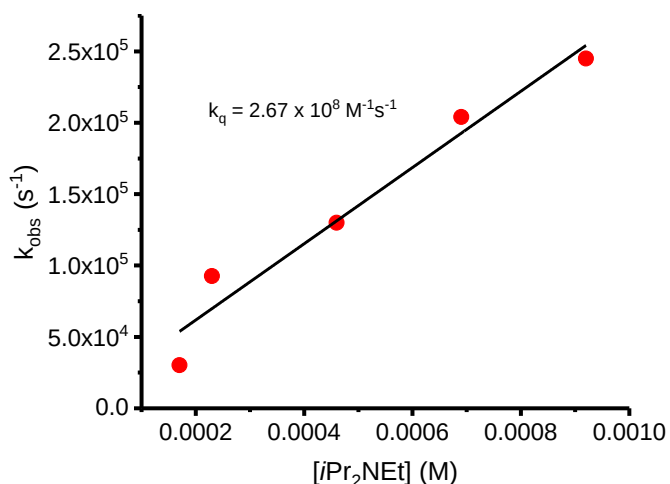


Figure 3.9. Representative kinetic plot for the quenching of ³MB by *i*Pr₂NEt in 4:1 MeCN:H₂O using 308 nm laser excitation.

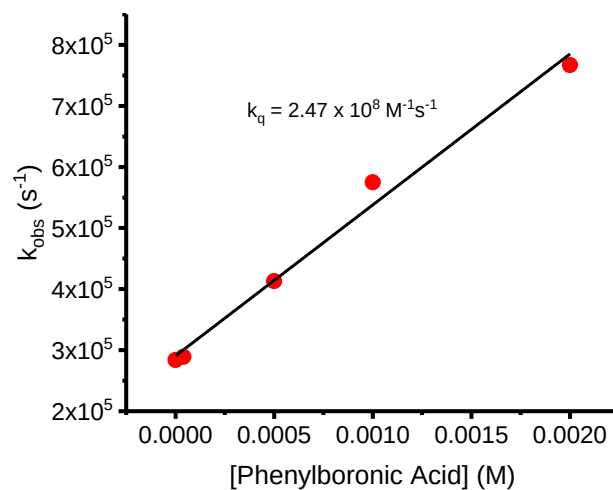


Figure 3.10. Representative kinetic plot for the quenching of ^3MB by phenylboronic acid in 4:1 MeCN:H₂O using 650 nm laser excitation.

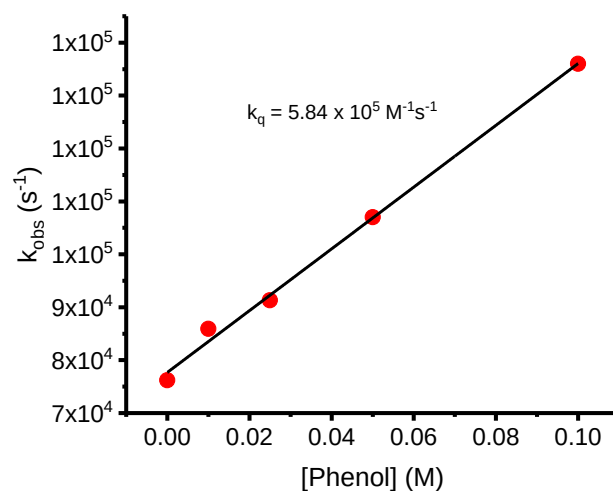


Figure 3.11. Representative kinetic plot for the quenching of ^3MB by phenol in 4:1 MeCN:H₂O using 650 nm laser excitation.

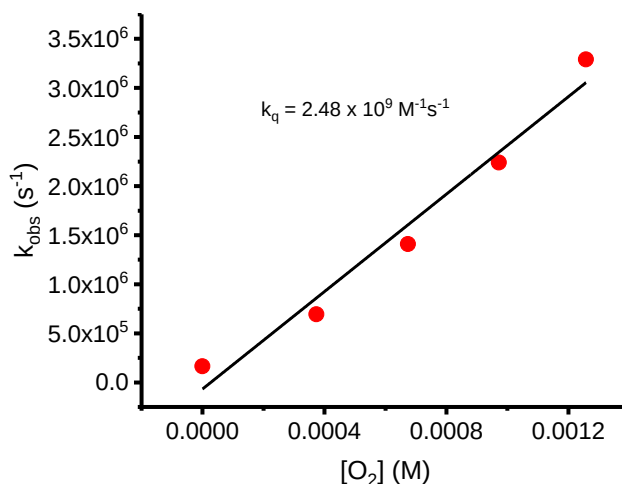


Figure 3.12. Representative kinetic plot for the quenching of ^3MB by O_2 in 4:1 MeCN:H $_2$ O using 650 nm laser excitation.

3.8.2 Triplet Quenching of $Ru(bpy)_3Cl_2$. The triplet quenching experiments of $Ru(bpy)_3Cl_2$ were performed using a Nd-YAG laser (355 nm, 10 mJ/pulse) in a LFP-111 laser flash photolysis system (LuzChem Inc., Ottawa, CA). The samples were measured in 1 x 1 cm LFP-Luzchem cuvettes. Samples of $Ru(bpy)_3Cl_2$ were prepared in 4:1 MeCN:H $_2$ O with a total volume of 3 mL and an absorbance of ~ 0.1 at 355 nm. The samples were purged with N_2 for 30 minutes prior to use. The solutions of phenylboronic acid, iPr_2NEt , and phenol used for the quenching studies were prepared in 4:1 MeCN:H $_2$ O which was also degassed for the duration of the experiment.

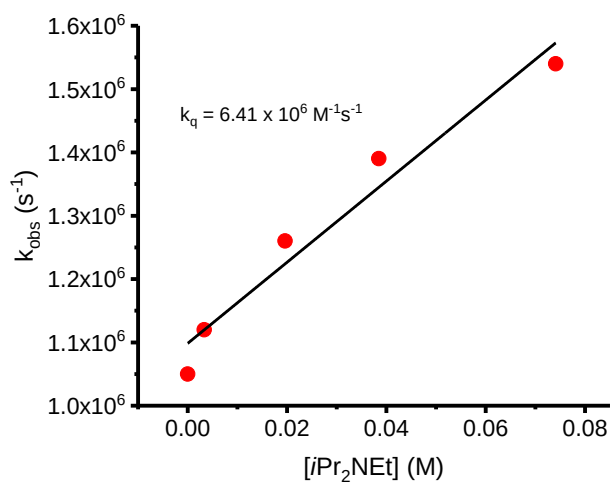


Figure 3.13. Representative kinetic plot for the quenching of $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$ by $i\text{Pr}_2\text{NEt}$ in 4:1 MeCN:H₂O using 355 nm laser excitation.

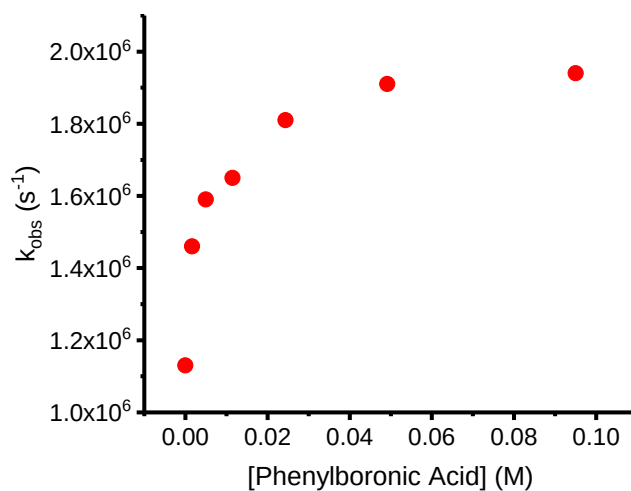


Figure 3.14. Representative kinetic plot for the quenching of $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$ by phenylboronic acid in 4:1 MeCN:H₂O using 355 nm laser excitation.

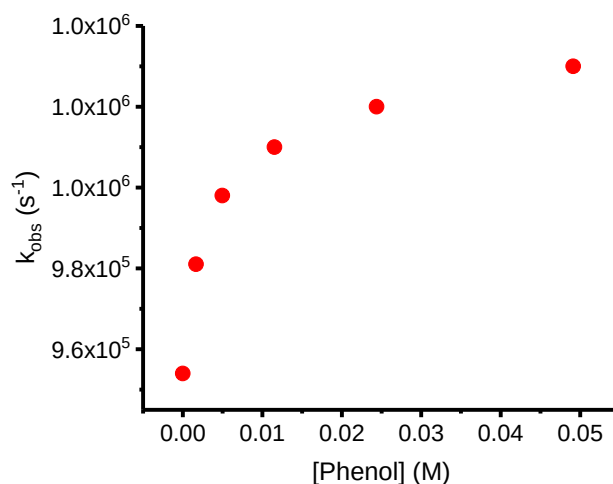


Figure 3.15. Representative kinetic plot for the quenching of $^3Ru(bpy)_3Cl_2$ by phenol in 4:1 MeCN:H₂O using 355 nm laser excitation.

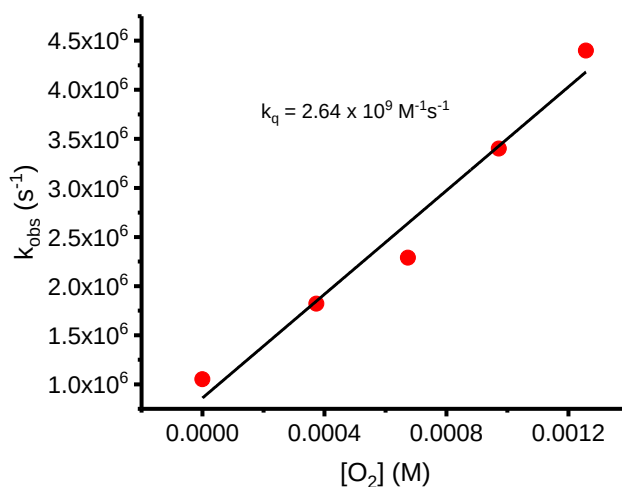


Figure 3.16. Representative kinetic plot for the quenching of $^3Ru(bpy)_3Cl_2$ by O₂ in 4:1 MeCN:H₂O using 355 nm laser excitation.

3.8.3 Quenching of Singlet Oxygen ($^1O_2$). The $^1O_2$ quenching experiments by phenylboronic acid and *i*Pr₂NEt were performed using a Nd-YAG laser (355 nm, 10 mJ/pulse) or an excimer laser (308 nm, 10 mJ/pulse) in a LFP-111 laser flash photolysis system (Luzchem Inc., Ottawa, CA). The samples were measured in 1 x 1 cm LFP-Luzchem cuvettes. The LFP system was fitted with a Hamamatsu NIR-PMT which monitored the phosphorescence of $^1O_2$ at 1270 nm. Excitation of Ru(bpy)₃Cl₂ in 4:1

MeCN:D₂O at 355 nm or excitation of MB in 4:1 MeCN:D₂O was used to sensitize the formation of ¹O₂. Solutions of 100 mM phenylboronic acid and *i*Pr₂NEt were prepared in 4:1 MeCN:D₂O were used as ¹O₂ quenchers.

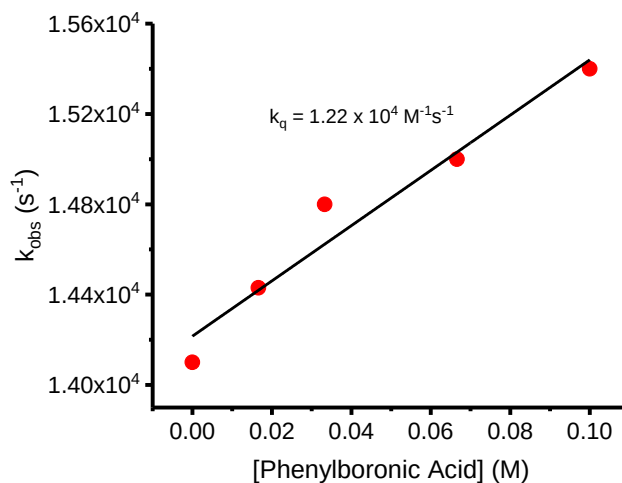


Figure 3.17. Representative kinetic plot for the quenching of ¹O₂ by phenylboronic acid in 4:1 MeCN:D₂O. ¹O₂ was sensitized by Ru(bpy)₃Cl₂ using 355 nm laser excitation.

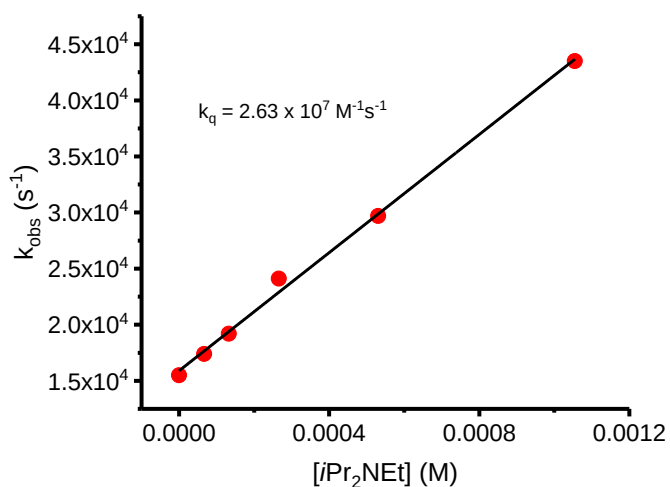


Figure 3.18. Representative kinetic plot for the quenching of ¹O₂ by *i*Pr₂NEt in 4:1 MeCN:D₂O. ¹O₂ was sensitized by Ru(bpy)₃Cl₂ using 355 nm laser excitation.

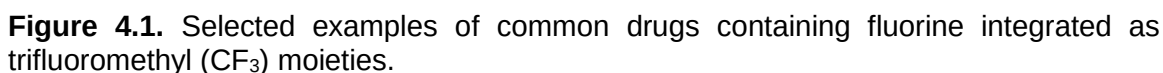
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Over the years, the impact of organofluorine compounds in the field of medicinal chemistry has grown exponentially. For example, many of the best-selling and newly approved drugs all contain fluorine atoms, which are normally present as arene substituents or trifluoromethyl (CF₃) moieties.^{1,2} A few selected examples of common drugs that benefit from the incorporation of CF₃ moieties are presented in Figure 4.1. Considering that organofluorine compounds are virtually absent in nature, it is interesting to question why many of the drugs in the pharmaceutical pipeline all contain fluorine atoms. Therefore, what effect does fluorine impart on the efficiency of these drugs? There are several key features that are vital to the efficiency of a drug. In the case of orally administered drugs, it must be able to withstand physiological pH of the stomach long enough to cross into the blood stream to be delivered to the desired target.² The drug then must perform its task efficiently and finally be metabolized at an appropriate rate into non-toxic by-products.² This section will discuss the role of how fluorine substituents, such as CF₃ moieties, aid in addressing these criteria.



The perturbation of pK_a caused by the inclusion of fluorine substituents can affect many properties of a drug, which includes changes in potency, selectivity, toxicity, and pharmacokinetic properties including absorption, distribution, metabolism, and excretion.³ Since fluorine is the most electronegative atom, its inclusion has a strong effect on the acidity or basicity of proximal functional groups. For example, a study on piperidinyl and piperazinyl indoles, drugs used to treat antipsychotic symptoms and migraines, found that fluorination decreased the basicity of the amine which resulted in an improvement in the bioavailability of the drugs.⁴

During drug delivery, the ability for a drug to pass through a cell membrane is most affected by two parameters: molecular size and lipophilicity.³ Lipophilicity is expressed as a partition coefficient ($\log P$) between octanol and water, where the most lipophilic compounds being partitioned in the octanol layer. When predicting good drug candidates, the Lipinski “rule-of-5” is often employed, which states that a $\log P > 5$ will likely lead to poor absorption of the drug candidate.⁵ Excess lipophilicity ($\log P > 5$) is a common cause of poor solubility, thereby leading to ineffective absorption of the drug. Fluorination is often employed to modulate the overall lipophilicity of a drug. For example, monofluorination or trifluoromethylation of saturated alkyl groups has a tendency to decrease lipophilicity due to the strong electron-withdrawing capabilities of fluorine.⁶ In contrast, aromatic fluorination, per/polyfluorination, and fluorination adjacent to π -bonds results in increased lipophilicity.⁶ In this case, it is the excellent overlap between the fluorine 2s and 2p orbitals with the corresponding orbitals on carbon that makes the C-F bond highly non-polarizable, thereby increasing lipophilicity.

Following administration of the drug, the physiological response of the body is to eliminate the drug. Drugs can be eliminated unchanged, however, it is more common that they are

metabolized prior to elimination.² The most important group of enzymes that metabolize drugs are Cytochrome P450 monooxygenases.² Low metabolic stability due to oxidation processes mediated by P450 enzymes is a common problem in drug discovery, however, it has been demonstrated that blocking metabolically labile sites with fluorine atoms can often circumvent P450 oxidation. For example, fluorine substitution has been employed to block metabolism of aromatic methoxy groups.⁷ In a recent study, it was demonstrated that replacing metabolically labile methoxy groups with a difluoromethoxy group increased the half-life of a series of second-generation cyclic nucleotide phosphodiesterase inhibitors, developed for the treatment of asthma.⁷

Considering the importance of organofluorine compounds in medicinal chemistry, and that they are virtually absent in nature, it is imperative that methods for the inclusion of fluorine substituents, such as CF₃ moieties, which are mild, efficient, and which display high functional group tolerability must be developed. One strategy for the inclusion of CF₃ moieties is through the generation of CF₃ radicals, which will be discussed in detail in the next section.

4.2 An Introduction to Radical Trifluoromethylation

A comprehensive review of the structure, reactivity, and properties of fluoroalkyl radicals was described by Dolbier in 1996.⁸ Since the fluorine atom is the most electronegative element, it exerts a strong σ -inductive effect on the carbon-centered radical.⁹ Concurrently, the fluorine atom is also a potentially strong π -donor to the carbon π -systems, because the lone pairs of the fluorine substituents demonstrate good orbital overlap with the SOMO of the carbon.⁹ These two opposing effects act in concert. In comparison to the planar $\bullet\text{CH}_3$ radical, the $\bullet\text{CF}_3$ radical is pyramidal, almost tetrahedral, implying that the $\bullet\text{CF}_3$ radical has more “s” character (Figure 4.2).¹⁰ The strong influence

of fluorine substitution on the geometry of the radical can be mainly attributed to the σ -inductive influence of fluorine on the thermodynamics of bonding. There is a thermodynamic advantage for the carbon orbitals used in bonding with fluorine to be high in p character.⁸ In this regard, the SOMO in a fluoromethyl radical would have increasing s character as the number of fluorine increases. The geometry of the $\bullet\text{CF}_3$ can also be explained from a simple MO perturbation perspective in that the pyramidalization of a radical $\bullet\text{CH}_{3-n}\text{X}_n$ occurs when it can lead to a mixing of the SOMO with the LUMO.^{8,11} The more electronegative the substituent X is, the lower the LUMO energy becomes, thereby lowering the SOMO-LUMO gap, resulting in more orbital mixing. Therefore, since fluorine is the most electronegative element, it will have the strongest influence on non-planarity.

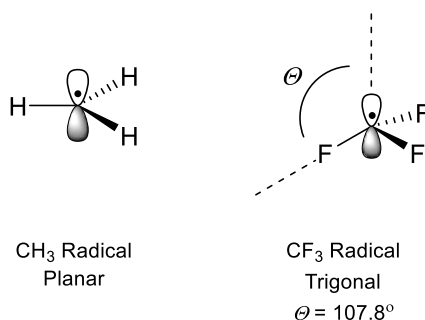
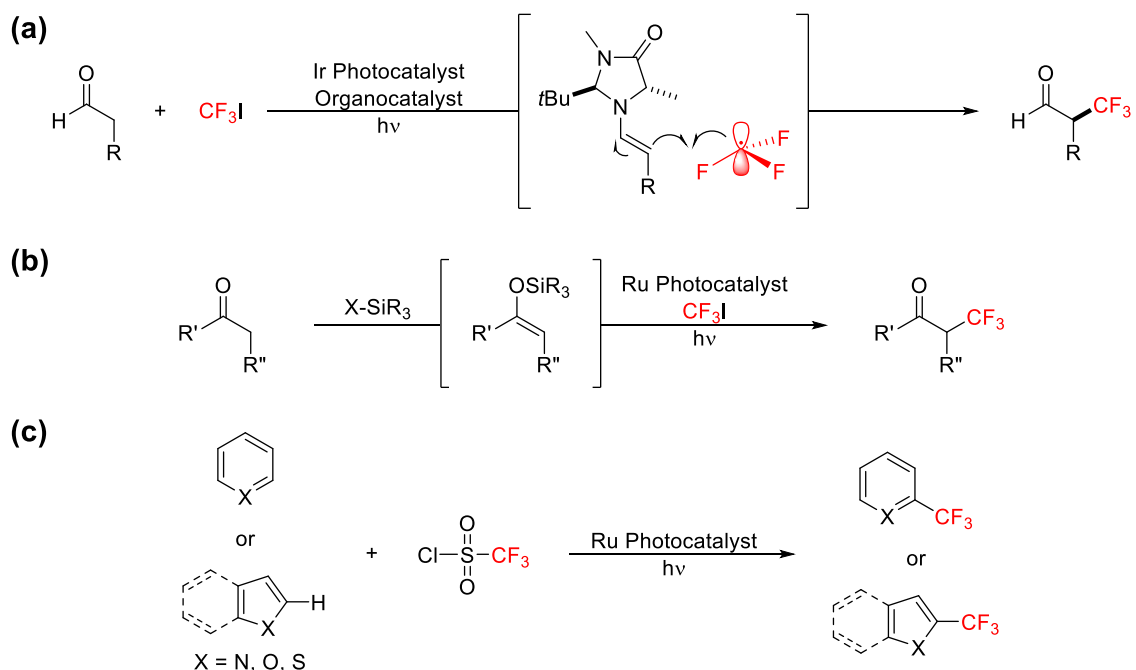


Figure 4.2. Structures of the $\bullet\text{CH}_3$ radical (left) and the $\bullet\text{CF}_3$ radical (right).⁹

In regards to stability, the $\bullet\text{CF}_3$ radical is less stable than the $\bullet\text{CH}_3$ radical, with a stabilization energy of $2.4 \text{ kcal mol}^{-1}$, which is strongly influenced by stereoelectronic effects.¹² There is a donor-acceptor interaction between the lone pairs of the fluorine atoms and the adjacent $\sigma^*(\text{C-F})$ orbitals.⁹ However, this same interaction is even more pronounced in the parent CF_3H . Therefore, the radical destabilization of the $\bullet\text{CF}_3$ radical is likely a result of the reduced stabilization caused by stereoelectronic effects going from the parent CF_3H to the $\bullet\text{CF}_3$ radical. This effect is absent in the $\bullet\text{CH}_3$ radical due to the lack of heteroatoms.

The $\bullet\text{CF}_3$ radical is an electrophilic radical with a low-lying SOMO, therefore radical addition reactions with electron-rich alkenes with high-lying HOMOs proceed efficiently.⁸ For example, the $\bullet\text{CF}_3$ radical is significantly more reactive than the $\bullet\text{CH}_3$ radical towards alkenes. When employing styrene as the radical acceptor, $\bullet\text{CF}_3$ radicals add to styrene 440 times faster compared to $\bullet\text{CH}_3$ radicals.¹³

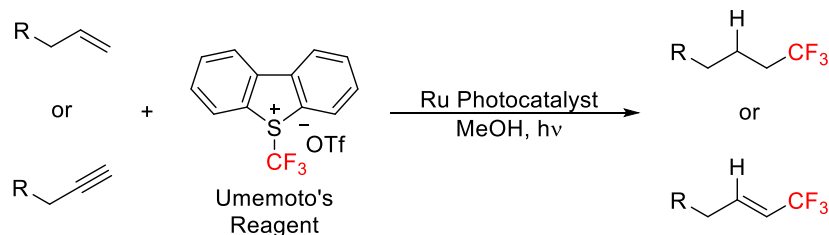
During the last decade, the development of methods for the direct replacement of C-H bonds with C- CF_3 bonds using free radical protocols has received a great deal of attention. In particular, many protocols have been developed employing photoredox-based techniques. For example, MacMillan and coworkers have developed a highly efficient photocatalytic technique for the trifluoromethylation of a variety of different substrates based on ruthenium and iridium polypyridyl catalysts using various $\bullet\text{CF}_3$ radical precursors (Scheme 4.1). Building on their previous studies of merging organocatalysis and photoredox catalysis, the MacMillan group was able to develop a novel method for the enantioselective α -trifluoromethylation of aldehydes (Scheme 4.1a).¹⁴ In order to access ketones, esters, and amides, the MacMillan group developed a new protocol where *in situ* or pre-generated enolates, or enolate equivalents, undergo $\bullet\text{CF}_3$ radical addition to generate α -trifluoromethyl carbonyl compounds (Scheme 4.1b).¹⁵ Finally, employing triflyl chloride as the $\bullet\text{CF}_3$ radical source, MacMillan and coworkers were able to employ an oxidative quenching photoredox cycle for the trifluoromethylation of a variety of arenes and heteroarenes (Scheme 4.1c).¹⁶ MacMillan has also developed a non-photocatalytic approach for the enantioselective α -trifluoromethylation of aldehydes employing iodonium salts developed by Togni and catalytic amounts of a Lewis acid.¹⁷



Scheme 4.1. Radical trifluoromethylation protocols developed by MacMillan and coworkers for (a) the enantioselective α -trifluoromethylation of aldehydes, (b) the α -trifluoro-methylation of ketones, esters, and amides, and (c) the trifluoromethylation of arenes and heteroarenes.

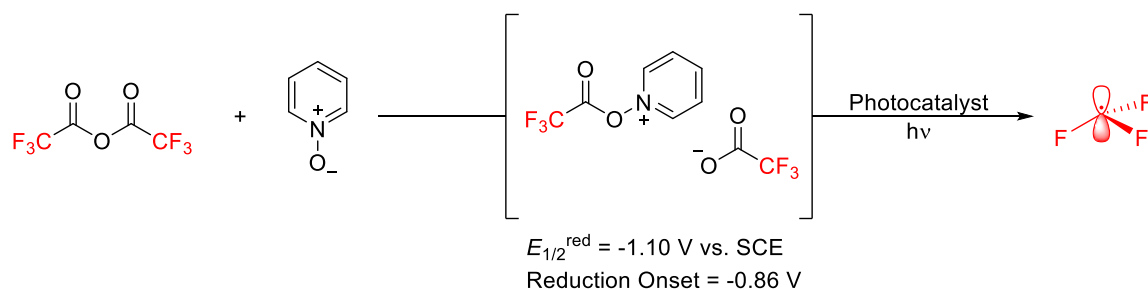
Cho and coworkers reported a protocol for the trifluoromethylation of heterocycles similar to the protocol developed by MacMillan (Figure 4.3c). In their system, Cho employed a reductive quenching photoredox cycle, using *N, N, N', N'*-tetramethyl-ethylenediamine (TMEDA) as the sacrificial electron donor, $\text{Ru}(\text{bpy})_3\text{Cl}_2$ as the photocatalyst, and CF_3I as the source of $\cdot\text{CF}_3$ radicals.¹⁸

Employing photoredox techniques has also provided a facile route to access hydrotrifluoromethylated products. Gouverneur and coworkers were the first to demonstrate that photoredox catalysis could be employed to promote these transformations (Scheme 4.2).¹⁹ In their system, Gouverneur employed an oxidative quenching photoredox cycle, using $\text{Ru}(\text{bpy})_3\text{Cl}_2$ as the photocatalyst, Umemoto's reagent as the $\cdot\text{CF}_3$ radical source, and MeOH as the hydrogen donor.



Scheme 4.2. Hydrotrifluoromethylation of terminal alkenes and alkynes developed by Gouverneur and coworkers.

One drawback of many of the trifluoromethylation protocols developed in the literature is that they require expensive $\bullet\text{CF}_3$ radical precursors. To help lower the cost of these important transformations, the Stephenson group developed a radical trifluoromethylation protocol where they successfully employed trifluoroacetic acid as the $\bullet\text{CF}_3$ radical precursor (Scheme 4.2).²⁰ Upon oxidation of the trifluoroacetate anion, CO_2 is expelled, resulting in the formation of a $\bullet\text{CF}_3$ radical. However, due to the exceedingly high oxidation potential of the trifluoroacetate anion (+2.4 V vs. SCE for $\text{F}_3\text{CCO}_2\text{Na}$)²¹, implementation of trifluoroacetic acid as a $\bullet\text{CF}_3$ radical precursor is impractical, as the potentials required are strong enough to oxidize many common organic solvents. To address this challenge, Stephenson and coworkers employed pyridine *N*-oxide to form a reducible trifluoroacetate adduct (Scheme 4.3). This adduct forms *in situ*, and possesses a mild reduction potential of -1.10 V vs. SCE, with an onset potential as low as -0.86 V.²⁰ These mild potentials can be accessed by a wide array of photoredox catalysts, such as $\text{Ru}(\text{bpy})_3\text{Cl}_2$ employed in this work. Upon single-electron reduction, the pyridine-trifluoroacetate adduct cleaves, releasing CO_2 , pyridine, and a $\bullet\text{CF}_3$ radical. Importantly, the low cost of both pyridine *N*-oxide and trifluoroacetic anhydride makes this a highly desirable method for $\bullet\text{CF}_3$ radical generation.



Scheme 4.3. Stephenson's $\bullet\text{CF}_3$ radical precursor based on a pyridine *N*-oxide and trifluoroacetic anhydride adduct.

While many photoredox transformations have been developed to promote radical trifluoromethylation reactions, thermal transition-metal catalyzed protocols have also been developed to access $\bullet\text{CF}_3$ radicals. In 2011, Buchwald and Wang independently developed trifluoromethylation protocols for unactivated alkenes catalyzed by copper (I) salts, using hypervalent iodine reagents developed by Togni as the CF_3 source.^{22,23} In each report, evidence was provided to support a free radical mechanism as one of the primary reaction pathways. Buchwald also reported an iron (II) catalyzed trifluoromethylation protocol in 2012, however, this transformation requires the use of vinyltrifluoroborates instead of simple, unactivated alkenes.²⁴

While transition-metal catalysis has provided many solutions to performing radical trifluoromethylation reactions, they present several drawbacks. For the photoredox transformations described, they all rely on precious metal ruthenium and iridium complexes as photocatalysts. Not only are these complexes expensive, but heavy metals such as ruthenium and iridium possess potentially carcinogenic effects²⁵, limiting their use in both the pharmaceutical and agrochemical industries. For the thermal examples, while they take advantage of cheap, first-row transition-metals such as iron and copper, they require higher catalytic loadings due to the lower catalytic activity. In light of these disadvantages, there has been a recent push to develop novel, transition-metal-free

photocatalytic systems to promote these transformations.²⁶⁻²⁹ However, the use of these systems still remains rather underdeveloped, and many of the current examples suffer from undesirably long reaction times. In Chapter 3, we demonstrated that Methylene Blue (MB), a cheap, non-toxic, organic dye from the thiazine family, could be employed as a photosensitizer for the oxidative hydroxylation of arylboronic acids. In this work, MB demonstrated similar reaction scope compared to a ruthenium catalyzed-based protocol and saw increased reaction efficiencies due to more favourable excited state kinetics. Therefore, MB could make an ideal candidate to promote radical trifluoromethylation reactions.

In order to demonstrate the viability of MB as a photosensitizer for radical trifluoromethylation reactions, it must fulfill a variety of requirements. Firstly, the scope of radical trifluoromethylation reactions accessible by transition-metal catalysts must also be accessible with MB. Secondly, the issues of high catalyst loading and long reaction times must be overcome.

In this chapter, the first use of MB as a photocatalyst, coupled with Togni's reagent as the source of $\bullet\text{CF}_3$ radicals, for the trifluoromethylation of electron-rich heterocycles and for the hydrotrifluoromethylation of terminal alkenes and alkynes is disseminated. In this work, considerable emphasis was placed on understanding the kinetics of the mechanistically relevant steps using laser flash photolysis techniques to more efficiently optimize the reaction conditions. Rate constants for these steps will also be presented, as well as the proposed mechanism of these transformations based on these obtained data.

4.3 Reaction Optimization through Kinetic Analysis

Due to the electrophilic nature of the $\bullet\text{CF}_3$ radical, the electron-rich heterocycle 3-methylindole was chosen as a model substrate. Indole alkaloids also represent an

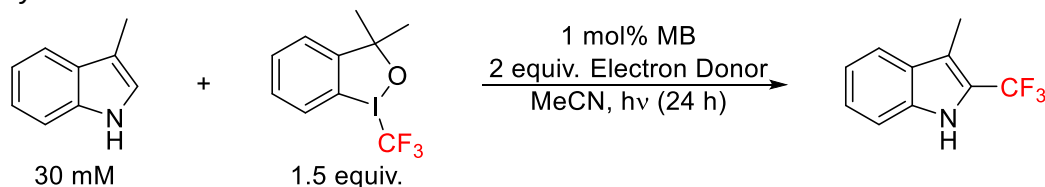
important class of natural products³⁰, therefore mild and efficient protocols for their functionalization is also of importance to the medicinal community. Recently, Cho and coworkers reported the trifluoromethylation of 3-methylindole employing $\text{Ru}(\text{bpy})_3\text{Cl}_2$ as the photoredox catalyst and CF_3I as the $\bullet\text{CF}_3$ radical source.¹⁸ One limitation to this method, however, is the use of CF_3I , which is a gas at standard temperature and pressure. This makes it difficult to know the exact concentration of CF_3I present in solution, making optimization of the kinetics of key reaction steps problematic. With this in mind, electrophilic CF_3 reagents were chosen for these studies, such as hypervalent iodine reagents developed by Togni³¹, and Umemoto's reagent³² (see Table 4.2 for structures).

As demonstrated in Chapter 3, MB can be employed for reductive quenching photoredox transformations. This means that in order to access the semi-reduced form of MB ($\bullet\text{MB}$), an electron-donor such as an aliphatic amine must be employed. Upon quenching of triplet MB (^3MB) by electron-transfer, $\bullet\text{MB}$ is generated along with an α -aminoalkyl radical (upon deprotonation of the amine radical-cation), both of which could be employed for the reduction of electrophilic CF_3 reagents.

To begin optimizing the radical trifluoromethylation of 3-methylindole with MB, the role of the electron donor was first examined. In a typical reaction, 3-methylindole (0.3 mmol, 30 mM) was reacted with Togni's reagent (II) (1.5 equiv.) and 2 equiv. of an aliphatic amine as the electron donor in MeCN (Table 4.1). In this case, triethylamine (NEt_3), *N,N*-diisopropylethylamine (*iPr*₂NEt), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) were employed. In all cases, the desired trifluoromethylated product, 3-methyl-2-(trifluoromethyl)indole, was observed. The highest yield was obtained when TMEDA was employed as the electron donor (Table 4.1, Entry 3). This came to no surprise, however,

as it was previously determined that TMEDA possessed the highest rate constant for the quenching of ^3MB of the three amines employed.

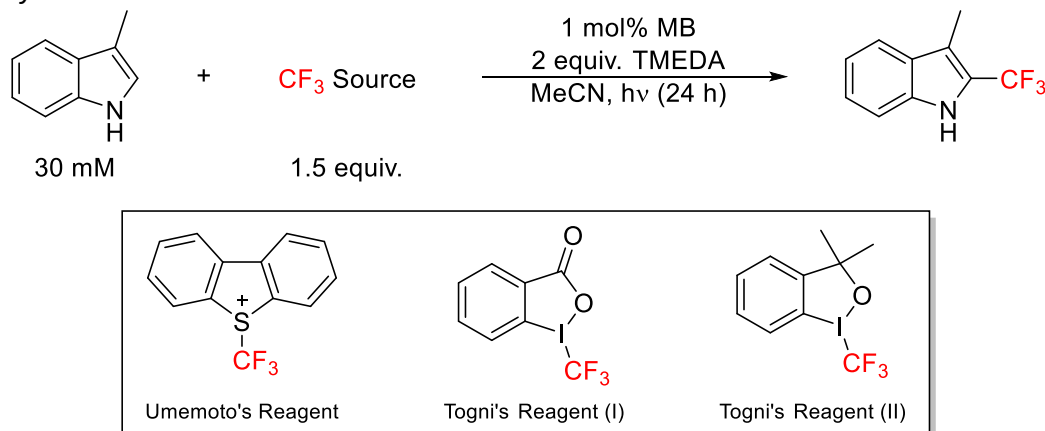
Table 4.1. Screening of the electron donor for the radical trifluoromethylation of 3-methylindole.



Entry	Electron Donor	$^3\text{MB } k_q \text{ (M}^{-1}\text{s}^{-1}\text{)}$	Isolated Yield
1	NEt_3	$4.68 \pm 0.42 \times 10^7$	15%
2	$i\text{Pr}_2\text{NEt}$	$2.44 \pm 0.24 \times 10^8$	23%
3	TMEDA	$3.41 \pm 0.42 \times 10^8$	47%

Reaction Conditions: 3-Methylindole (0.3 mmol, 39 mg), Togani's reagent (II) (0.45 mmol, 149 mg), MB (0.003 mmol, 1.1 mg), electron donor (0.6 mmol), and MeCN (10 mL) were irradiated in 10 mL test tubes under air for 24 hours in a Luzchem photoreactor equipped with visible light bulbs. Yields are reported as isolated yields.

Next, different electrophilic CF_3 reagents were screened to determine the most efficient source for the generation of $^{\bullet}\text{CF}_3$ radicals (Table 4.2). Initially, it was hypothesized that Umemoto's reagent would be the most efficient source of $^{\bullet}\text{CF}_3$ radicals, based on a thermodynamic perspective. The reduction potential ($E_{1/2}^{\text{red}}$) of Umemoto's reagent (-0.75 V vs. Cp_2Fe) is significantly more positive than both analogues of Togani's reagents tested, meaning that it is more easily reduced.³³ Since all three reagents tested rely on a single-electron reduction to release a $^{\bullet}\text{CF}_3$ radical, thermodynamically speaking Umemoto's reagent should be the most efficient $^{\bullet}\text{CF}_3$ radical source. However, after 24 hours of irradiation, it was observed that the reaction employing Togani's reagent (I) (Table 4.2, Entry 2) resulted in the highest yield of the desired trifluoromethylated product (77%), whereas the reaction employing Umemoto's reagent (Table 4.2, Entry 1) gave the lowest yield (35%). Therefore, because thermodynamics was not able to predict the reactivity of this photocatalytic system, we turned to kinetics to help explain this disparity in reactivity.

Table 4.2. Screening of the CF₃ source for the radical trifluoromethylation of 3-methylindole.

Entry	CF ₃ Source	$E_{1/2}^{\text{red}}$ (V vs. Cp ₂ Fe)	Isolated Yield
1	Umemoto's Reagent	-0.75 V	35%
2	Togni's Reagent (I)	-1.34 V	77%
3	Togni's Reagent (II)	-1.49 V	47%

Reaction Conditions: 3-Methylindole (0.3 mmol, 39 mg), CF₃ source (0.45 mmol), MB (0.003 mmol, 1.1 mg), TMEDA (0.6 mmol, 90 μ L), and MeCN (10 mL) were irradiated in 10 mL test tubes under air for 24 hours in a Luzchem photoreactor equipped with visible light bulbs. Yields are reported as isolated yields.

In order to develop a kinetic understanding of the reaction system, the bimolecular rate constants (k_q) of all the reaction components and ³MB were measured using laser flash photolysis techniques (described in Chapter 3). The corresponding data are presented in Table 4.3. For this reaction to proceed efficiently, ³MB must be intercepted by TMEDA so that it may proceed via a reductive quenching photoredox cycle, generating the two desired reducing agents, [•]MB and an α -aminoalkyl radical. In other words, TMEDA must out-compete the other reaction components for the quenching of ³MB. Interestingly, it was determined that Umemoto's reagent quenches ³MB at a rate constant of $4.75 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ (Table 4.3, Entry 4). This rate is an order of magnitude greater than the corresponding rate constant for TMEDA (Table 4.3, Entry 1). By employing the following equation:

$$\% \text{ } ^3M \text{ Quenching} = \frac{100\% \times k_q^{\text{Quencher}} [\text{Quencher}]}{\tau_0^{-1} + k_q^{\text{TMEDA}} [\text{TMEDA}] + k_q^{3\text{-MeI}} [3\text{-MeI}] + k_q^{\text{CF}_3 \text{ Source}} [\text{CF}_3 \text{ Source}] + k_q^{\text{O}_2} [\text{O}_2]} \quad (1)$$

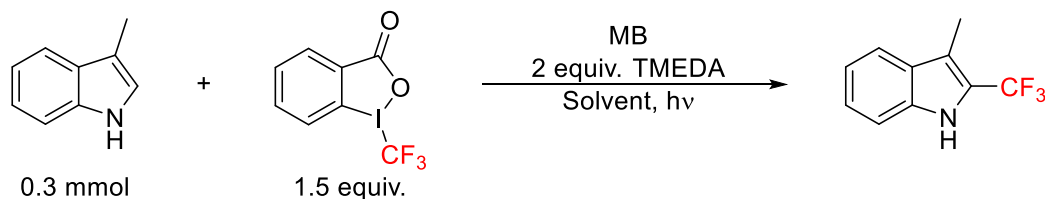
it is possible to calculate the percentage of the generated MB triplets which are intercepted by each component of the reaction under initial reaction conditions. When employing Umemoto's reagent, only 8% of MB triplets are intercepted by TMEDA, the desired reaction to promote this transformation, whereas Umemoto's reagent intercepts 85% of MB triplets. It is important to note that quenching by Umemoto's reagent does not proceed through electron-transfer and does not lead to any productive quenching events. The observed quenching is most likely the result of energy-transfer or exciplex formation.

Table 4.3. Bimolecular rate constants for the quenching of ^3MB by the reaction components for the radical trifluoromethylation of 3-methylindole.

Entry	Quencher	$^3\text{MB } k_q (\text{M}^{-1}\text{s}^{-1})$
1	TMEDA	$3.41 \pm 0.42 \times 10^8$
2	3-Methylindole	$4.09 \pm 0.27 \times 10^8$
3	3-Methyl-2-(trifluoromethyl)indole	$2.57 \pm 0.18 \times 10^8$
4	Umemoto's Reagent	$4.75 \pm 0.51 \times 10^9$
5	Togni's Reagent (I)	$4.83 \pm 0.24 \times 10^7$
6	Togni's Reagent (II)	$2.33 \pm 0.34 \times 10^8$
7	O_2	$2.46 \pm 0.25 \times 10^9$

On the other hand, it is observed that Togni's reagent (I) only quenches ^3MB at a rate constant of $4.83 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, two orders of magnitude lower compared to the corresponding rate constant with Umemoto's reagent. When employing equation (1), it can be calculated that under initial reaction conditions, the probability of quenching by TMEDA, the desired reaction, is increased to 51%, where Togni's reagent (I) only quenches 5% of MB's triplets. This increase in probability for the desired quenching by TMEDA resulted in an observed increase in reaction efficiency for the radical trifluoromethylation of 3-methylindole. Therefore, even though it is thermodynamically more favourable to generate $\bullet\text{CF}_3$ radicals from Umemoto's reagent, it is less efficient for this reaction because it inhibits the quenching of ^3MB by TMEDA. This demonstrates that even though a reaction is thermodynamically favourable, it is ultimately kinetics that dictates if the reaction will occur.

With the optimal substrates determined, the reaction conditions were then optimized using two warm-white LEDs as the light source (Table 4.4). The rate of the reaction was found to increase when the solvent was switched from MeCN to DMF (Entries 1 and 2). Reducing the amount of solvent, thereby increasing the concentration of the reaction components, also resulted in an increase in yield of the desired product (Entries 3-5). A higher concentration of the reaction components ensures that the ^3MB formed are quenched by increasing the probability of collisions rather than decaying back to the ground state. Finally removing O_2 from the system by purging with Ar resulted in an increase to 70% yield (Entry 6), as O_2 is a potent quencher of ^3MB (Table 4.3, Entry 7), therefore removing O_2 from the system increases the probability of ^3MB being quenched by TMEDA to 58%. Control experiments demonstrated that both MB and light are required for the trifluoromethylation of 3-methylindole (Entries 7 and 8). Interestingly, trifluoromethylation is still observed upon removal of TMEDA (Entry 9). Upon further investigation, it was discovered that SeT from 3-methylindole ($E_{1/2}^{\text{ox}} = 1.12 \text{ V vs. SCE}$)³⁴ to ^3MB (0.97 V vs. SCE) could be thermodynamically feasible. It is worth noting that these potentials are calculated based on peak potentials, and electron-transfer is still possible in the region of potential onset. The high observed triplet-quenching constant (Table 4.3, Entry 2) makes this a kinetically favourable process upon removal of TMEDA. Therefore, we propose that upon removal of TMEDA, electron-transfer occurs between ^3MB and 3-methylindole, resulting in the indole radical-cation and $^{\bullet}\text{MB}$, which could then initiate the trifluoromethylation reaction. Since no other products are observed after the reaction, it is hypothesized that the oxidized indole is reduced back to its original form. In addition, as discussed in Chapter 3, amines are common impurities in DMF and could be responsible for the generation of $^{\bullet}\text{MB}$.³⁵ These reasons could explain the observed reactivity in the absence of TMEDA.

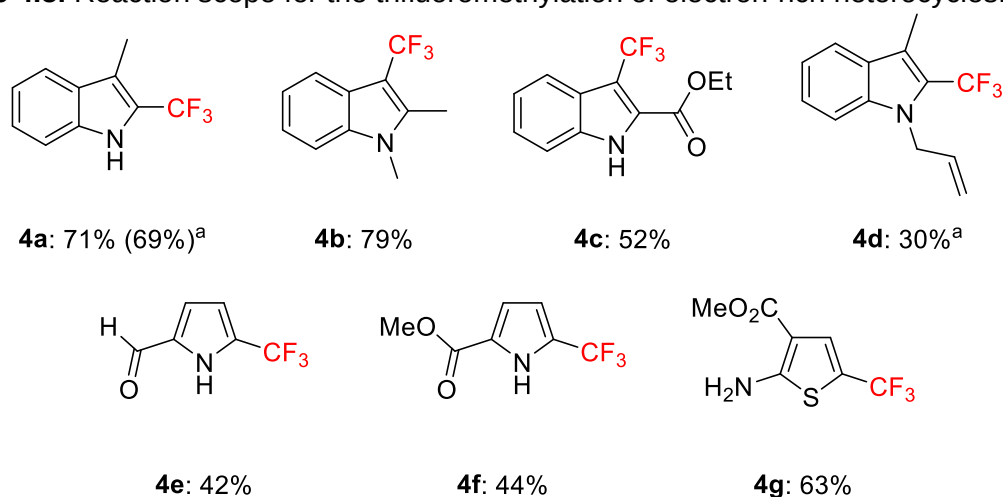
Table 4.4. Optimization of reaction conditions and control reactions for the radical trifluoromethylation of 3-methylindole.

Entry	[3-Methylindole]	MB	Solvent	Atm.	Time	Isolated Yield
1	30 mM	1 mol%	MeCN	air	12 h	25%
2	30 mM	1 mol%	DMF	air	6 h	23%
3	59 mM	1 mol%	DMF	air	6 h	44%
4	59 mM	2 mol%	DMF	air	6 h	59%
5	97 mM	2 mol%	DMF	air	6 h	59%
6	97 mM	2 mol%	DMF	Ar	6 h	70%
7	97 mM	-	DMF	Ar	6 h	Trace
8 ^a	97 mM	2 mol%	DMF	Ar	6 h	No Reaction
9 ^b	97 mM	2 mol%	DMF	Ar	6 h	35%

Irradiation was performed with two warm-white LEDs. ^aReaction was performed in the dark. ^bReaction was performed in the absence of TMEDA.

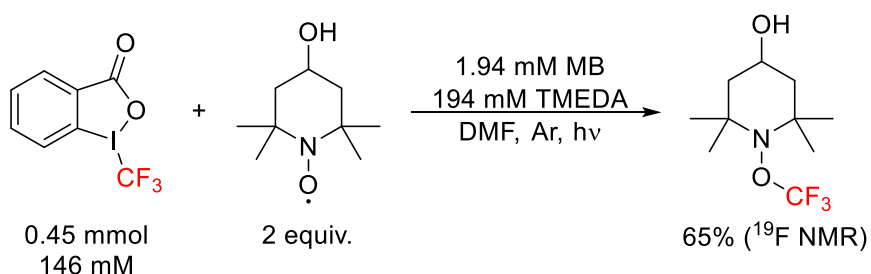
4.4 Trifluoromethylation of Electron-Rich Heterocycles

With the optimized conditions established, the scope of electron-rich heterocycles was then investigated Table 4.5. The trifluoromethylation of various electron-rich indoles proceeded in moderate to good yields (Compounds **4a-4d**). For example **4d**, the radical addition demonstrated selectivity for the most nucleophilic site, in accordance with the highly electrophilic nature of the $\cdot\text{CF}_3$ radical, however side products from radical addition to the terminal alkene were detected in low quantities by ^{19}F NMR. No side products from the result of trifluoromethylation of the aromatic portion of the indole were observed in all cases. The trifluoromethylation of pyrroles, as well as a thiophene derivative, also proceeded in moderate yields (**4e-4g**).

Table 4.5. Reaction scope for the trifluoromethylation of electron-rich heterocycles.

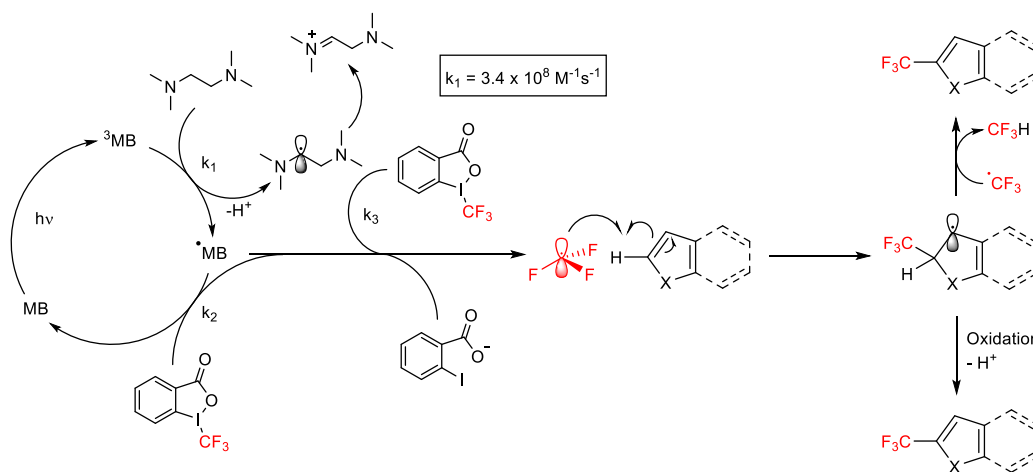
Yields were determined by ^{19}F NMR using C_6F_6 as an external standard. For reaction conditions, see Section 4.8.2. ^aIsolated yield.

In order to confirm that the reaction was proceeding through a free radical mechanism, 4-hydroxy-TEMPO was subjected to the general reaction conditions (Scheme 4.4). When the reaction was performed with 2 equivalents of 4-hydroxy-TEMPO compared to Togni's Reagent (I), the trifluoromethylated TEMPO adduct was observed in 65% yield on the basis of ^{19}F NMR. This result confirms the involvement of free $\cdot\text{CF}_3$ radicals in the underlying mechanism.

**Scheme 4.4.** Radical trapping experiment with 4-hydroxy-TEMPO.

A proposed mechanism for the trifluoromethylation of electron-rich heterocycles is presented in Scheme 4.5. Upon excitation using visible light, MB is excited to its triplet excited state (^3MB). ^3MB is then quenched by TMEDA (k_1) to give $\cdot\text{MB}$ and an amine radical-cation. As previously discussed, it is likely that ^3MB is also quenched by the

heterocycle which would also lead to the generation of $\bullet\text{MB}$. $\bullet\text{MB}$ is then quenched by Togni's reagent (I) (k_2) to regenerate the ground state, releasing a $\bullet\text{CF}_3$ radical and 2-iodobenzoate as a by-product. Due to the spectral overlap between ^3MB and $\bullet\text{MB}$, the corresponding bimolecular rate constant (k_2) could not be determined. The TMEDA radical-cation is also in equilibrium with its deprotonated form, an α -aminoalkyl radical, which can act as a reducing agent to generate another $\bullet\text{CF}_3$ radical (k_3). The CF_3 radical then adds to the most nucleophilic position of the electron-rich heterocycle, and the final product can be generated via one of two possible mechanisms. The first proposed pathway involves the oxidation of the heterocyclic radical intermediate, which could be performed by either ^3MB or Togni's reagent, followed by deprotonation to yield the final product. The second proposed pathway involves a H-atom abstraction from the heterocyclic radical intermediate by a $\bullet\text{CF}_3$ radical to generate the final product and CF_3H .



Scheme 4.5. Proposed mechanism for the trifluoromethylation of electron-rich heterocycles employing MB photocatalysis, where X = N or S.

4.5 Hydrotrifluoromethylation of Terminal Alkenes and Alkynes

Upon discovering radical addition side products to the terminal alkene moiety when analyzing the trifluoromethylation of 1-allyl-3-methylindole (see Table 4.5, **4d**), we decided

to investigate the possibility of employing MB photocatalysis to promote the radical trifluoromethylation of terminal alkenes and alkynes. Therefore, the potential for MB photocatalysis to promote these transformations was tested by employing the previously optimized conditions for the radical trifluoromethylation of electron-rich heterocycles, and 1-dodecene as the model substrate. Interestingly, not only was the product corresponding to the addition of a $\bullet\text{CF}_3$ radical observed, but the major product of the reaction corresponded to both the addition of a $\bullet\text{CF}_3$ radical and a H-atom, formally known as hydrotrifluoromethylation (Table 4.6, Entry 1). In a more recent contribution by Cho and coworkers, they reported the radical trifluoromethylation of terminal alkenes employing 1,8-diazobicyclo-[5.4.0]undec-7-ene (DBU) as the sacrificial electron donor to quench the excited state of $\text{Ru}(\text{bpy})_3\text{Cl}_2$.³⁶ In an attempt to control the selectivity of trifluoromethylation versus hydrotrifluoromethylation, the reaction was repeated and TMEDA was replaced with DBU (Table 4.6, Entry 2). Surprisingly, the same distribution of final products was observed compared to when TMEDA was employed, however with increased reaction efficiency. Notably, the reaction was also complete after only 3 hours of irradiation when employing DBU. More interestingly, despite the increased reaction efficiency, the bimolecular rate constant (k_q) for the triplet quenching of MB for DBU was determined to be a full order of magnitude lower ($k_q = 1.05 \pm 0.15 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$) compared to that of TMEDA ($k_q = 3.41 \pm 0.42 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$). It is important to note here that these quenching constants take into account all forms of quenching for ^3MB because not all quenching events result in electron-transfer.³⁷

Table 4.6. Radical trifluoromethylation of 1-dodecene photocatalyzed by MB.

Entry	Electron Donor	Time	Major Product	Minor Product
1	 TMEDA	6 h	 53%	 10% (<i>E</i> : <i>Z</i> = 13:1)
2	 DBU	3 h	 67%	 22% (<i>E</i> : <i>Z</i> = 20:1)

Reaction Conditions: 1-dodecene (0.3 mmol, 67 μ L), Togni's reagent (I) (0.45 mmol, 142 mg), MB (0.006 mmol, 2.2 mg), electron-donor (0.6 mmol), and DMF (3 mL) were irradiated in a 10 mL Schlenk tube under argon using two warm-white LEDs. Yields were determined by ^{19}F NMR using C_6F_6 as an external standard.

Interestingly, upon addition of DBU to a solution of MB, a drastic change in the colour of the solution was observed. This also correlated with a drastic change in the absorption profile in MB upon addition of 2 mM DBU, as confirmed by UV-vis spectroscopy (Figure 4.3). This change was not observed upon the addition of 2 mM TMEDA to a solution of MB. 2 mM of each electron donor was chosen to match the concentration equivalents employed under typical reaction conditions. It was postulated that the new absorption profile was due to a ground state charge-transfer complex (CTC) forming between MB and DBU and that this CTC was responsible for the increased reaction efficiency observed for the hydrotrifluoromethylation of 1-dodecene.

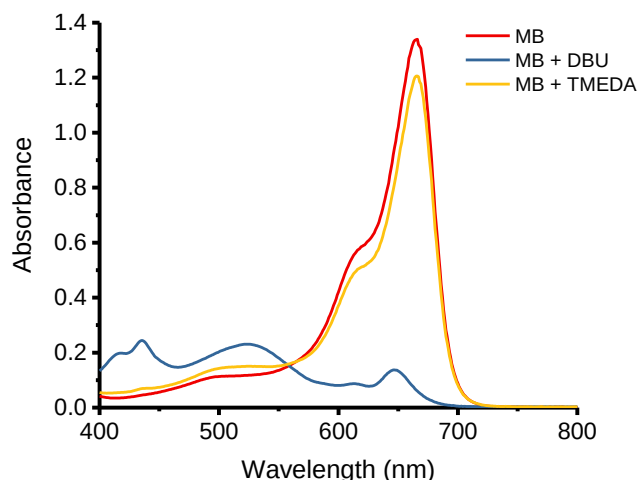


Figure 4.3. Effect on the absorption of a 0.02 mM solution of MB in the presence of 2 mM TMEDA and 2 mM DBU. The amine concentrations were selected to correlate with the concentration equivalents used under typical reaction conditions.

In order to confirm the presence of a CTC, a Benesi-Hildebrand analysis was performed to determine the association constant (K_A) of the CTC between MB and DBU.³⁸ In a quartz cuvette, the absorbance of a freshly prepared 0.02 mM solution of MB in DMF was measured using a UV-vis spectrophotometer. To the solution of MB, 5 μ L of a 1 mM solution of DBU in DMF was added to give a concentration of 0.1 equivalents compared to the concentration of MB. The absorbance of this solution was then measured, and this procedure was repeated for a range of 0.1 to 3 equivalents of DBU (Figure 4.4a). From these spectra, the corresponding CTC can be observed, with maxima at 435 and 520 nm and a clearly defined isosbestic point located at 557 nm.

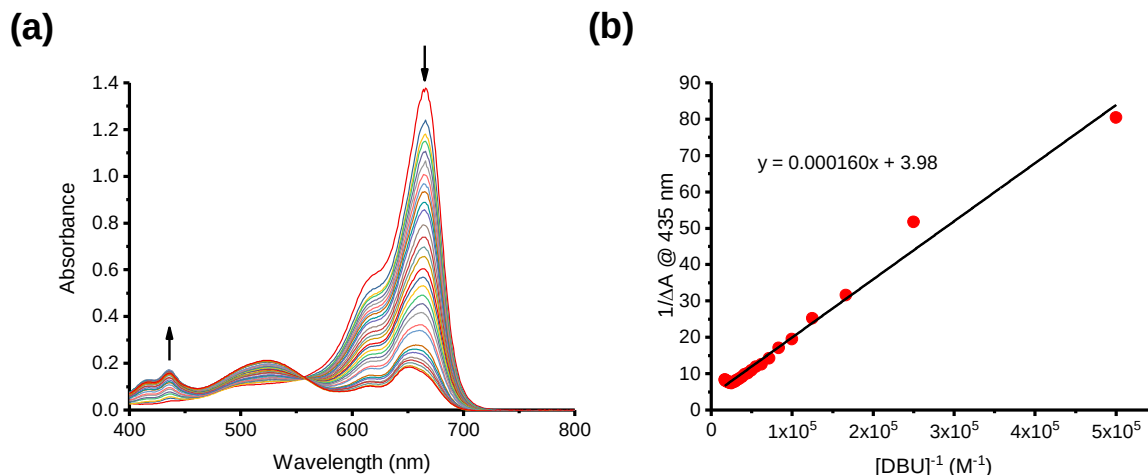


Figure 4.4. (a) The effect on the absorption of MB (0.02 mM) in the presence of an increasing concentration (0.1-3 equiv.) of DBU. (b) Plot of $1/\Delta A$ of the MB-DBU CTC at 435 nm versus $[\text{DBU}]^{-1}$.

In order to analyze the data using the Benesi-Hildebrand method, the reciprocal of the change in absorbance of the CTC (ΔA_{CTC}) at 435 nm was plotted against the reciprocal of the concentration of DBU (Figure 4.4b).³⁸ The linear relationship obtained confirms that the stoichiometry of the CTC between MB and DBU is 1:1. Performing a linear fit of the data, the following equation can be obtained:

$$y = 0.000160x + 3.98 \quad (2)$$

By employing the Benesi-Hildebrand equation:

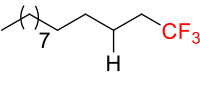
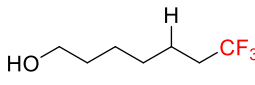
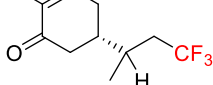
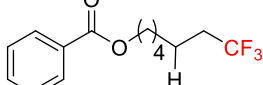
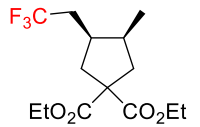
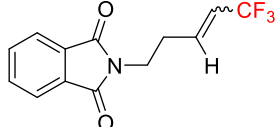
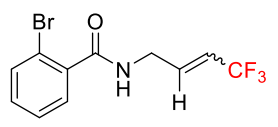
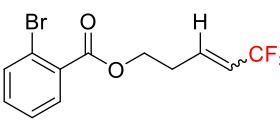
$$\frac{1}{\Delta A_{\text{CTC}}} = \frac{1}{A_{\text{CTC}}} \times \frac{1}{K_A [\text{DBU}]} + \frac{1}{A_{\text{CTC}}} \quad (3)$$

where $\frac{1}{A_{\text{CTC}}} = 3.98$ and $\frac{1}{A_{\text{CTC}}} \times \frac{1}{K_A} = 0.000160$, the K_A for the CTC can be calculated. By rearranging the equation to solve for K_A , it can be determined that the K_A for the CTC between MB and DBU is $2.5 \times 10^4 \text{ M}^{-1}$. Due to the excess concentration of DBU compared to MB under typical reaction conditions (100 equivalents), and the magnitude of the K_A , it is probable that all MB present in solution is complexed with DBU under typical reaction conditions. Therefore, the observed increased reaction efficiency obtained for the hydro-

trifluoromethylation of 1-dodecene is likely due to the formation of a ground state CTC between MB and DBU, increasing the probability of electron-transfer.

With the optimized conditions in hand for the hydrotrifluoromethylation of 1-dodecene, the scope of the reaction with terminal alkenes and alkynes was examined (Table 4.7). In the case of all terminal alkene examples (**4h-4l**), small amounts of the radical addition product (no hydrogenation of the double bond) was obtained. For all terminal alkyne examples (**4m-4o**), only the hydrotrifluoromethylated product was obtained. This selectivity will be discussed *vide infra*. When compared to the recently reported hydrotrifluoromethylation protocols by Gouverneur and Nicewicz, MB was able to promote this transformation at lower catalyst loadings under shorter irradiation times.^{19,28} For the terminal alkyne examples, improved *E:Z* ratios were also observed when directly comparing to Gouverneur's system.

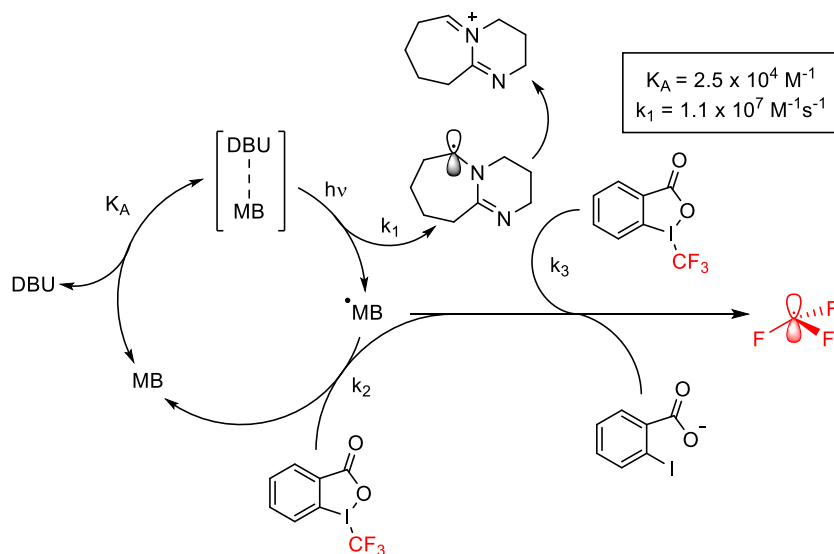
Table 4.7. Reaction scope for the hydrotrifluoromethylation of terminal alkenes and alkynes.

			
4h : 67%	4i : 48%	4j : 40%	4k : 83%
			
4m : 81%	4n : 70% (<i>E:Z</i> = 4:1)	4o : 66% (<i>E:Z</i> = 10:1)	4p : 79% (<i>E:Z</i> = 6:1)

Yields and *E:Z* ratios were calculated by ¹⁹F NMR using C₆F₆ as an external standard. For reaction conditions, see Section 4.8.3.

The proposed mechanism for the generation of •CF₃ radicals in a MB-DBU photocatalytic system is presented in Scheme 4.6. In the ground state, MB and DBU form a CT complex, with a *K_A* of 2.5 × 10⁴ M⁻¹ as determined by a Benesi-Hildebrand analysis. This CT complex is then excited by visible light irradiation, resulting in SeT to generate •MB and an α-aminoalkyl radical (upon deprotonation) (*k*₁). •MB is then quenched by Togni's reagent (I)

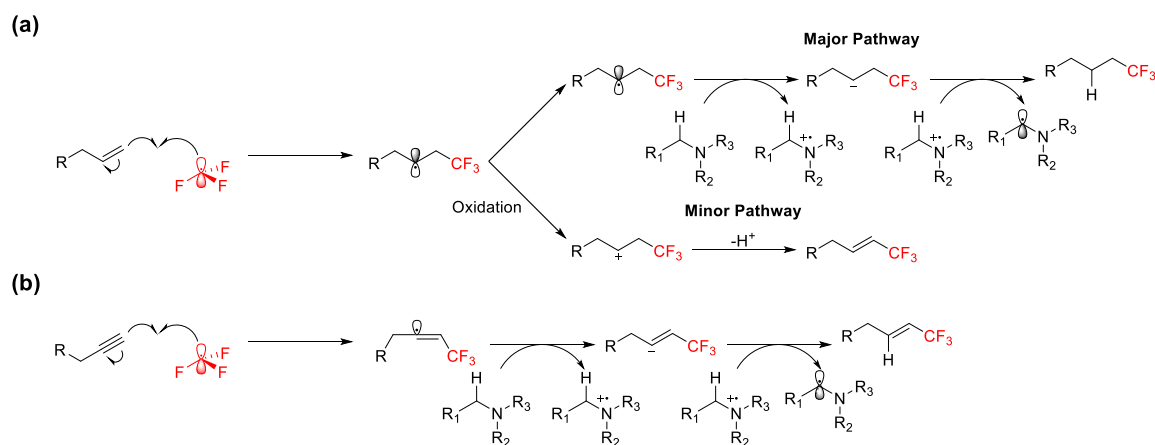
to generate a $\bullet\text{CF}_3$ and 2-iodobenzoate as a by-product (k_2). Due to the highly reducing nature of α -aminoalkyl radicals, the DBU α -aminoalkyl radical could also reduce Togni's reagent (I) (k_3).



Scheme 4.6. $\bullet\text{CF}_3$ radical generation in a MB-DBU photocatalytic system.

For terminal alkenes, there exist two possible pathways to account for both the major hydrotrifluoromethylated product and the unsaturated trifluoromethylated product (Scheme 4.7a). The addition of a $\bullet\text{CF}_3$ radical to the terminal double bond results in the formation of an aliphatic carbon-centered radical. In the early 1980s, Steenken and Neta demonstrated that carbon-centered radicals can oxidize amines to form amine radical-cations at rates approaching diffusion control.³⁹ Therefore, we propose that the hydrotrifluoromethylated major product results from oxidation of DBU by the aliphatic carbon-centered radical intermediate, followed by a proton-transfer to give the desired hydrotrifluoromethylated product and an α -aminoalkyl radical. This process is more formally known as a proton-coupled electron-transfer (PCeT). The minor product is proposed to be the result of either radical disproportionation or a one-electron oxidation of the aliphatic carbon-centered radical intermediate, followed by deprotonation by excess

base. The one-electron oxidation could be performed by ^3MB or an amine radical-cation, however, both of these species would be present in very low concentrations in solution at a given period of time. With that being said, the low concentration of these oxidizing agents in solution could account for why only small amounts of the unsaturated trifluoromethylated products are observed. Finally, it is also possible that the aliphatic carbon-centered radical intermediate could be oxidized by Togni's reagent (I), creating a propagating chain.



Scheme 4.7. Proposed mechanisms for the hydrotrifluoromethylation of (a) terminal alkenes and (b) terminal alkynes.

The proposed mechanism for the hydrotrifluoromethylation of terminal alkynes is presented in Scheme 4.7b. The addition of a $\cdot\text{CF}_3$ radical to the terminal triple bond results in the formation of a vinyl carbon-centered radical intermediate. Due to the high reactivity of this vinyl radical intermediate, it is immediately quenched by DBU, which is present in excess, via a PCeT mechanism similar to that observed for the hydrotrifluoromethylation of terminal alkenes. Due to the high reactivity of the vinyl radical intermediate compared to the aliphatic carbon-centered radical intermediate, the vinyl radical does not live long enough in solution to be intercepted by either ^3MB or an amine radical-cation, resulting in complete selectivity for the hydrotrifluoromethylated product. Due to the linearity of the

vinyl radical intermediate (see Scheme 4.7b), addition of a H-atom may result in the formation of either the *E* and *Z* isomers.⁴⁰ However, the majority of the observed product does correspond to the more stable *E* isomer.

4.6 Conclusion

For the first time, the use of a photocatalytic system based on MB has been successfully employed for the radical trifluoromethylation of electron-rich heterocycles and for the hydrotrifluoromethylation of terminal alkenes and alkynes. This method avoids the use of potentially toxic and expensive transition-metal photocatalysts such as ruthenium and iridium complexes, while also demonstrating improved reaction efficiencies with lower catalyst loadings compared to previously developed photoredox protocols. Importantly, MB is able to access the same scope of reactivity compared to the transition-metal photocatalysts typically employed for reductive quenching photoredox trifluoromethylation protocols.

Once again, it is important to highlight the use of excited state kinetics, as an understanding of the rate constants of the mechanistically key steps aided in the overall optimization of the reaction conditions, allowing for improved reaction efficiencies. Importantly, it was also demonstrated during the screening of electrophilic CF₃ reagents that even though a reaction is thermodynamically favourable, it is ultimately kinetics that determines if the reaction will occur. This was demonstrated by the reduced probability of reductive quenching by TMEDA in the presence of Umemoto's reagent compared to when Togni's reagent (I) was employed.

For future considerations, the role of the α -aminoalkyl radical in this transformation should be elucidated. For example, the bimolecular rate constant for the quenching of an α -aminoalkyl radical by Togni's reagent (I) (k_3 in Figures 4.4 and 4.7) could be determined

using the “probe technique”.⁴¹ The probe technique involves using methyl viologen, which upon reduction by a reducing agent such as an α -aminoalkyl radical, yields a strong signal in the visible region that can be easily monitored. By monitoring the growth of the reduced methyl viologen as a function of increasing concentration of Togni’s reagent (I), the rate at which the α -aminoalkyl radical reduces Togni’s reagent (I) (k_3) could be elucidated.

The presence of a propagating chain reaction could also be determined by monitoring the conversion over time using different “light on, light off” flashing parameters during irradiation, a method traditionally known as the “rotating sector” method. This method can be used qualitatively to determine the presence of a propagating chain, as well as quantitatively to determine the average lifetime of chain events. A more detailed discussion of the rotating sector method can be found in Chapter 6.

4.7 Experimental Details

4.7.1 General Information. Reaction substrates, triethylamine (TEA), *N, N*-diisopropylethylamine (*i*Pr₂NEt), *N, N, N', N'*-tetramethylethylenediamine (TMEDA), 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU), and DMF were purchased from chemical suppliers and used with no further purification. The light source, unless otherwise noted, was two warm white 90 W LEDs purchased from LEdEngin. Reaction products were purified by either flash column chromatography using 230-400 mesh silica gel, or by preparative thin layer chromatography using 1000 μ m thick glass baked TLC plates purchased from Silicycle. All ¹H NMR and proton-decoupled ¹⁹F NMR were recorded using a Bruker Avance 400 spectrometer.

4.7.2 General Procedure for the Trifluoromethylation of Electron-Rich Heterocycles.

Heteroarene (0.3 mmol), MB (0.006 mmol, 2.2 mg), Togni’s reagent (0.45 mmol, 142 mg),

and DMF (3 mL) were added to a 10 mL Schlenk tube equipped with a magnetic stir bar. The reaction mixture was then purged with argon for 10-15 minutes, and TMEDA (0.6 mmol, 90 μ L) was added under argon. The reaction mixture was then stirred and irradiated for 6 h. After irradiation, the reaction mixture was diluted with H₂O and extracted with ether (x3). The organic phase was then washed with brine (x5) to remove traces of DMF, dried over MgSO₄, and concentrated by rotary evaporation. The crude reaction mixture was purified by either flash column chromatography or preparative thin layer chromatography.

4.7.3 General Procedure for the Hydrotrifluoromethylation of Terminal Alkenes and

Alkynes. Reaction substrate (0.3 mmol), MB (0.006 mmol, 2.2 mg), Togni's reagent (0.45 mmol, 142 mg), and DMF (3 mL) were added to a 10 mL Schlenk tube equipped with a magnetic stir bar. The reaction mixture was then purged with argon for 10-15 minutes, and DBU (0.6 mmol, 90 μ L) was added under argon. The reaction mixture was then stirred and irradiated for 3 h. After irradiation, the reaction mixture was diluted with ether (30 mL) and washed with brine (x5). The organic phase was then dried over MgSO₄, and concentrated by rotary evaporation. The crude reaction mixture was purified by either flash column chromatography or preparative thin layer chromatography.

4.7.4 Synthesis of Togni's Reagent (I). NaIO₄ (33.8 mmol, 7.24 g) and 2-iodobenzoic acid (32.2 mmol, 8.0 g) and 50 mL of 30% acetic acid in H₂O (v/v) was added to a 500 mL round bottom flask equipped with a reflux condenser and a magnetic stir bar, and the reaction mixture was refluxed for 4 h with vigorous stirring. The reaction mixture was then diluted with 180 mL of cold H₂O and allowed to cool to room temperature. The crude solid was collected via suction filtration. The crude white solid was then washed with cold water (3 x 20 mL) and acetone (3 x 20 mL), and air dried overnight to afford the first intermediate, 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one.

1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (21.1 mmol, 6.00 g) and acetic anhydride (50 mL) was then added to a 3-neck 250 mL round bottom flask equipped with a reflux condenser and a magnetic stir bar. The reaction mixture was then heated to reflux until the solution became clear. The reaction was then slowly cooled to -20 °C for 4 hours using a dry ice/ethylene glycol:ethanol (9:1) bath. The acetic anhydride was then decanted, and the white solid was dried under vacuum with stirring for 24 hours to afford the second intermediate, 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one. After drying, the flask was back-filled with argon, and dry MeCN (50 mL) was added. To the reaction mixture, trimethyl(trifluoromethyl)silane (30.4 mmol, 4.5 mL) and cesium fluoride (0.33 mmol, 50 mg) were added under argon. The reaction was then stirred vigorously for 22 h at room temperature. The MeCN was then removed by rotary evaporation, and the crude reaction mixture was purified by column chromatography (15:1 CH₂Cl₂:MeOH) to afford Togni's reagent (I) as an off-white solid in 67% isolated yield (4.5 g).

4.7.5 Synthesis of Reaction Substrates.

Hex-5-en-1-yl benzoate: Hex-5-en-1-ol (5 mmol, 502 mg) and 10 mL of anhydrous CH₂Cl₂ was added to an oven-dried two-neck 250 mL round bottom flask equipped with a magnetic stir bar, and the reaction was purged with argon. The reaction mixture was cooled to 0 °C using an ice bath, followed by successive addition of DMAP (0.5 mmol, 61 mg) and pyridine (15 mmol, 1.2 mL). Benzoyl chloride (10 mmol, 1.2 mL) was then added dropwise, and the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was then quenched with H₂O (20 mL) and extracted with DCM (x3). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated by rotary evaporation. The crude was purified by flash column chromatography (Hex → 16:1 Hex:EtOAc) to give the desired product as a colourless oil in 75% isolated yield (765 mg).

2-Bromo-N-(prop-2-yn-1-yl)benzamide: Propargylamine (5 mmol, 0.32 mL), NEt_3 (10 mmol, 1.4 mL), and anhydrous DCM (35 mL) were added to an oven-dried three-neck round bottom flask equipped with a magnetic stir bar. The reaction mixture was cooled to 0 °C using an ice bath, and 2-bromobenzoyl chloride (5.5 mmol, 0.72 mL) was added dropwise. The reaction mixture was then stirred for 3 h, allowed to warm to room temperature, and was quenched with H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (x3), and the combined organic phases were washed with brine, dried over MgSO_4 , and concentrated by rotary evaporation. The crude was purified by flash column chromatography (3:2 Hex:EtOAc) to afford the desired product as a white solid in quantitative yield (1.2 g).

But-3-yn-1-yl 2-bromobenzoate: 3-butyne-1-ol (5 mmol, 0.38 mL), NEt_3 (10 mmol, 1.4 mL), and anhydrous DCM (35 mL) were added to an oven-dried three-neck round bottom flask equipped with a magnetic stir bar. The reaction mixture was cooled to 0 °C using an ice bath, and 2-bromobenzoyl chloride (5.5 mmol, 0.72 mL) was added dropwise. The reaction mixture was then stirred for 3 h, allowed to warm to room temperature, and was quenched with H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (x3), and the combined organic phases were washed with brine, dried over MgSO_4 , and concentrated by rotary evaporation. The crude was purified by flash column chromatography (9:1 Hex:EtOAc) to afford the desired product as a colourless oil in 95% isolated yield (1.4 g).

1-Allyl-3-methylindole: 3-Methylindole (1.91 mmol, 250 mg), cesium carbonate (9.55 mmol, 3.1 g) and MeCN were added to an oven-dried 50 mL round bottom flask equipped with a magnetic stir bar. The reaction mixture was then stirred, followed by dropwise addition of allyl bromide (5.7 mmol, 500 μL). The reaction mixture was left to stir overnight, and the consumption of 3-methylindole was monitored by TLC. After complete

consumption of 3-methylindole, the reaction was filtered through a celite plug, diluted with CH_2Cl_2 , and washed with brine (x2). The resulting organic phase was then dried over MgSO_4 and concentrated by rotary evaporation. The crude was purified by flash column chromatography (60:1 Hex:EtOAc) to afford the desired product as a colourless oil in 63% isolated yield (206 mg).

4.7.6 Trifluoromethyl Radical Trapping Experiment. Togni's reagent (0.45 mmol, 142 mg), 4-hydroxy-TEMPO (0.9 mmol, 155 mg), MB (0.006 mmol, 2.2 mg) and DMF (3 mL) were added to a 10 mL Schlenk tube. The reaction mixture was then purged with argon for 10-15 minutes, and TMEDA (0.6 mmol, 90 μL) was added under argon. The reaction mixture was then stirred and irradiated for 6 h. After irradiation, the reaction mixture was diluted with H_2O and extracted with ether (x3). The organic phase was then washed with brine (x5) to remove traces of DMF, dried over MgSO_4 , and concentrated by rotary evaporation. C_6F_6 (0.45 mmol, 52 mL) was added to the crude to serve as an external standard for ^{19}F NMR. From ^{19}F NMR, which was consistent with the literature (δ -55.79, s, CF_3), the yield of the trifluoromethylated 4-hydroxy-TEMPO adduct was calculated to be 65%.

4.8 Laser Flash Photolysis Data

The triplet quenching experiments of MB were performed using an excimer laser (308 nm, 10 mJ/pulse) in a LFP-111 laser flash photolysis system (Luzchem Inc., Ottawa, CA). The samples were measured in 1 x 1 cm LFP-Luzchem cuvettes or 1 x 1 cm flow system. Samples of MB were prepared in a 4:1 solution of MeCN: H_2O with a total volume of 3 mL and an absorbance of ~ 0.1 at 308 nm. The samples were purged with N_2 for 30 minutes prior to use. The solutions of quenchers examined in these studies were prepared in 4:1 MeCN: H_2O which was also degassed for the duration of the experiment.

Due to the overlap of triplet MB (420 nm) and semi-reduced MB (430 nm) signals, it was necessary to monitor the recovery of the ground state (650 nm) to measure triplet quenching of MB.

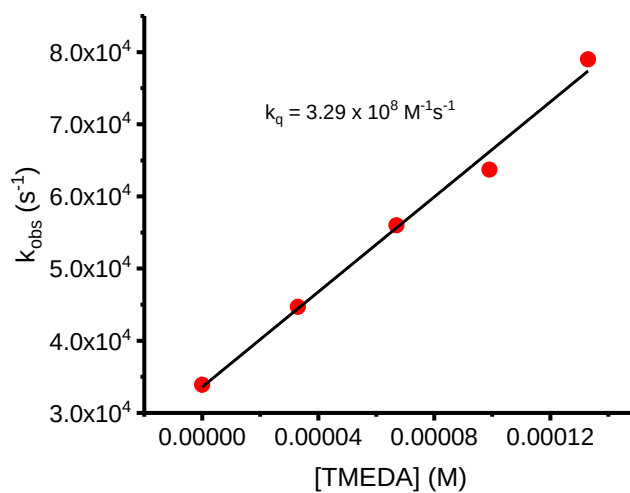


Figure 4.5. Representative kinetic plot for the quenching of ^3MB by TMEDA in 4:1 MeCN:H₂O using 308 nm laser excitation.

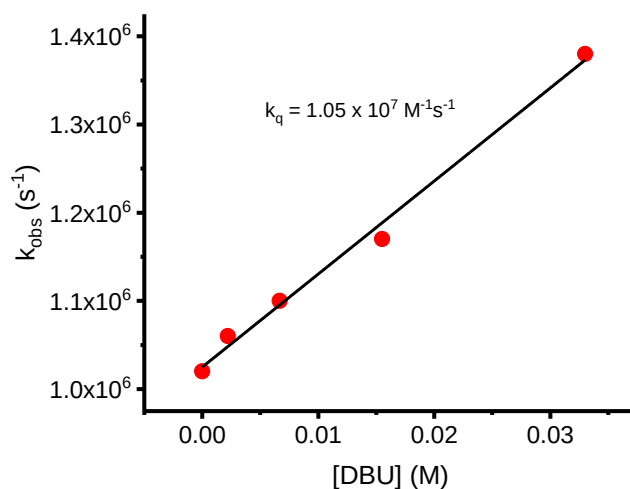


Figure 4.6. Representative kinetic plot for the quenching of ^3MB by DBU in 4:1 MeCN:H₂O using 308 nm laser excitation.

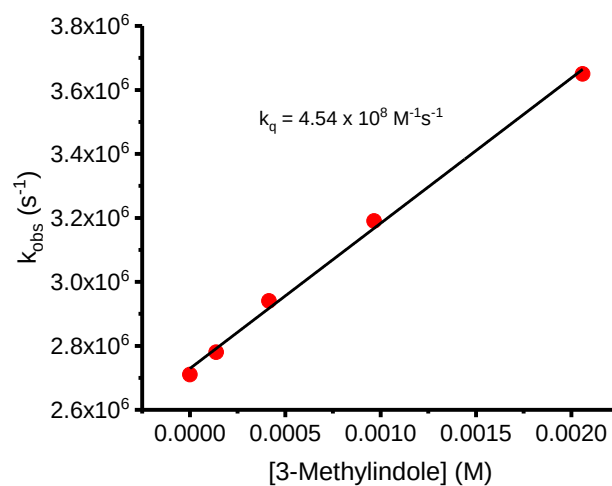


Figure 4.7. Representative kinetic plot for the quenching of ^3MB by 3-methylindole in 4:1 MeCN:H₂O using 308 nm laser excitation.

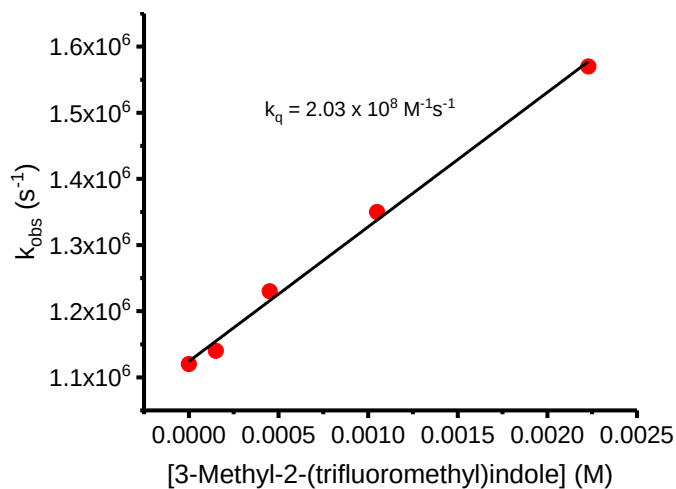


Figure 4.8. Representative kinetic plot for the quenching of ^3MB by 3-methyl-2-(trifluoromethyl)indole in 4:1 MeCN:H₂O using 308 nm laser excitation.

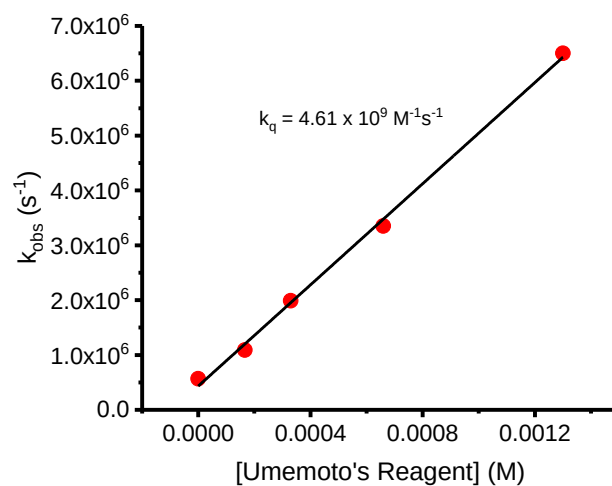


Figure 4.9. Representative kinetic plot for the quenching of ^3MB by Umemoto's reagent in 4:1 MeCN:H₂O using 308 nm laser excitation.

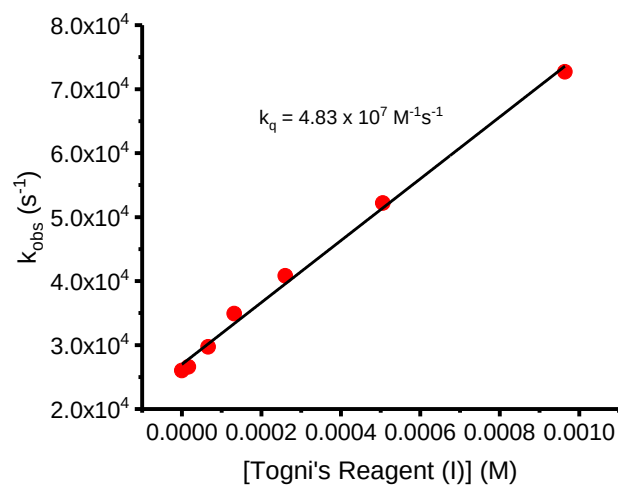


Figure 4.10. Representative kinetic plot for the quenching of ^3MB by Togni's reagent (I) in 4:1 MeCN:H₂O using 308 nm laser excitation.

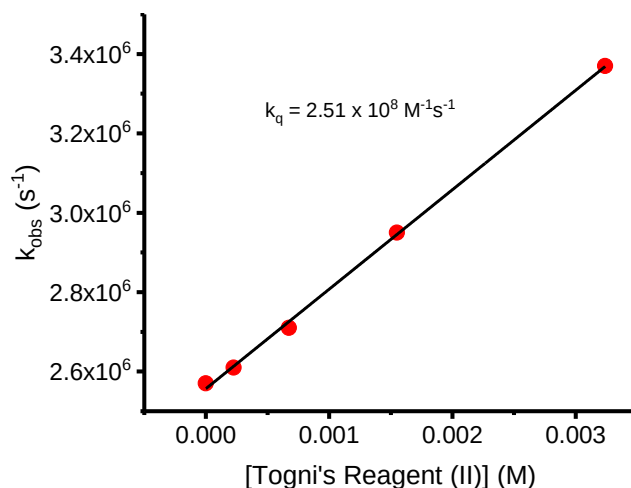


Figure 4.11. Representative kinetic plot for the quenching of ^3MB by Togni's reagent (II) in 4:1 MeCN:H₂O using 308 nm laser excitation.

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5. A Library of Organic Dyes for Photoredox Transformations

5.1 Organic Photoredox Catalysis

In recent years, the field of light-mediated redox catalysis has experienced a remarkable growth, as light can provide spatial and temporal control in organic synthesis under generally mild conditions. Transition-metal complexes, such as Ru(II) and Ir(III) bipyridyl complexes, have been extensively employed in these transformations.¹ The use of organic photosensitizers as catalysts for these reactions has also been examined, albeit to a lesser extent, which include examples with Eosin Y, Rose Bengal, benzophenone, acridinium and pyrylium salts, and our own contributions with Methylene Blue which have been highlighted in Chapters 3 and 4 of this dissertation (Figure 5.1).²⁻⁴

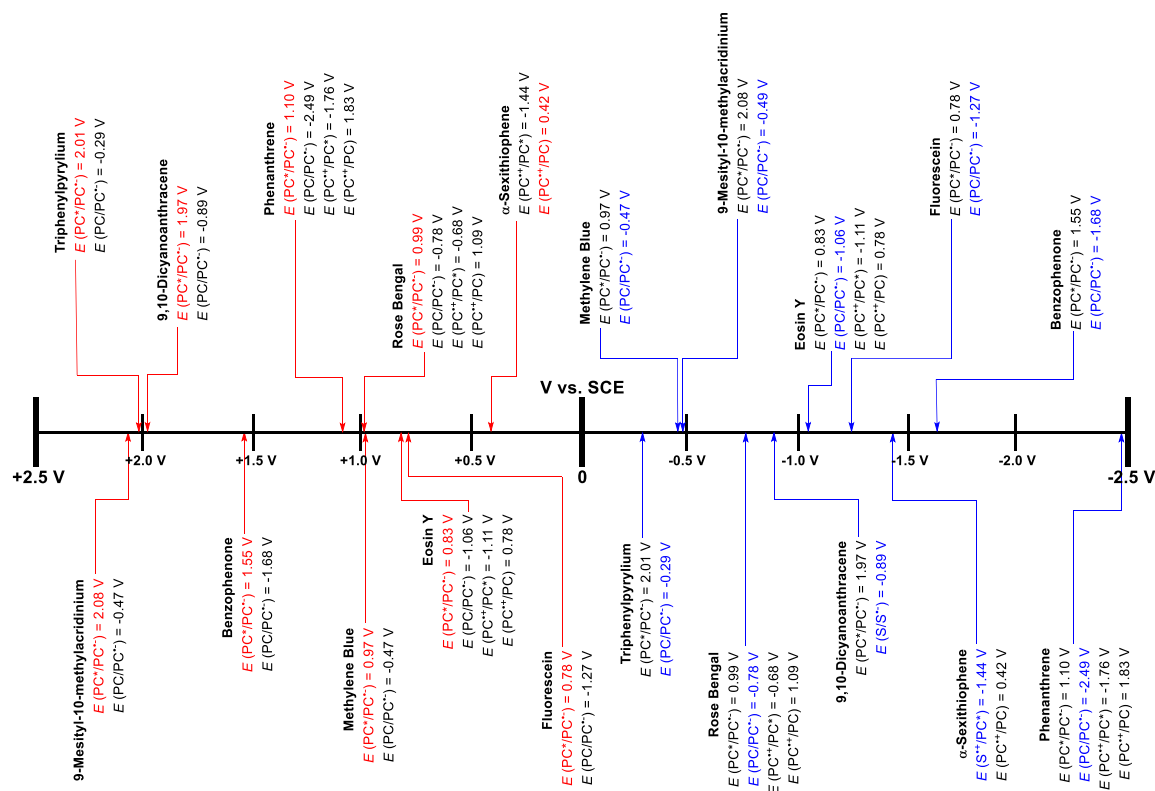


Figure 5.1. Common organic photosensitizers employed for photoredox transformations, and their ground and excited state redox properties.⁴⁻¹⁰ Potentials highlighted in red correspond to reduction potentials, while potentials highlighted in blue correspond to oxidation potentials.

Given the low price, low toxicity and demonstrated ability to perform as redox photocatalysts, the limited use of organic photosensitizers is rather surprising. We hypothesize that one of the primary reasons underlying the popularity of Ru(II) and Ir(III) complexes is that both their photophysical and electrochemical properties have been readily available for over 30 years.¹¹⁻¹³ Therefore, labs that lack the necessary equipment or expertise to determine the photophysical data of their catalyst can easily turn to the literature to acquire all the necessary information to perform their photochemical reaction. A few organic dyes are just as well understood, for example, Methylene Blue^{6,14,15}, but this is not the case for many of the dye options available. In fact, while in some cases organic dyes can be even more reactive than their transition-metal counterparts^{16,17}, the same exhaustive collection of photophysical data does not exist in the literature for these photosensitizers. We hypothesized that this information would be extremely valuable for those in the field, as some of the techniques required to characterize the photophysical data of these photosensitizers, which can be performed with ease in our laboratory, are not widely available to practitioners of synthetic organic chemistry.

In this chapter, the essential photochemical and electrochemical data for a collection four distinct classes of cationic dyes that may aid in increasing their usage in photoredox catalysis is presented (Figure 5.2).¹⁸ Cationic dyes are excellent candidates for photocatalysis as they provide the advantage of being economically viable, while also displaying improved photophysical properties such as increased light absorption across the visible spectrum, and longer triplet excited state lifetimes in comparison to their transition-metal counterparts. Herein, the efficiencies of 13 cationic dyes were compared with two ubiquitous photoredox catalysts, Ru(bpy)₃Cl₂ and *fac*-Ir(ppy)₃, along with 9-mesityl-10-methylacridinium cation originally synthesized by Fukuzumi and co-workers.¹⁹ The photosensitizers were compared in both the reduction of *meso*-1,2-dibromo-1,2-

diphenylethane originally studied by Willner in 1990²⁰, and the light-mediated Aza-Henry reaction originally studied by Stephenson in 2010.²¹ Importantly, we also demonstrate that favorable kinetics of electron-transfer for mechanistically key steps can correlate to increased reaction efficiency, highlighting the importance of investigating not only the thermodynamic feasibility but also the kinetic feasibility of the catalytic system. Finally, a comprehensive summary of both the photochemical and electrochemical properties of all the cationic dyes studied in this work is provided in an Appendix section at the end of this chapter (see Section 5.8).

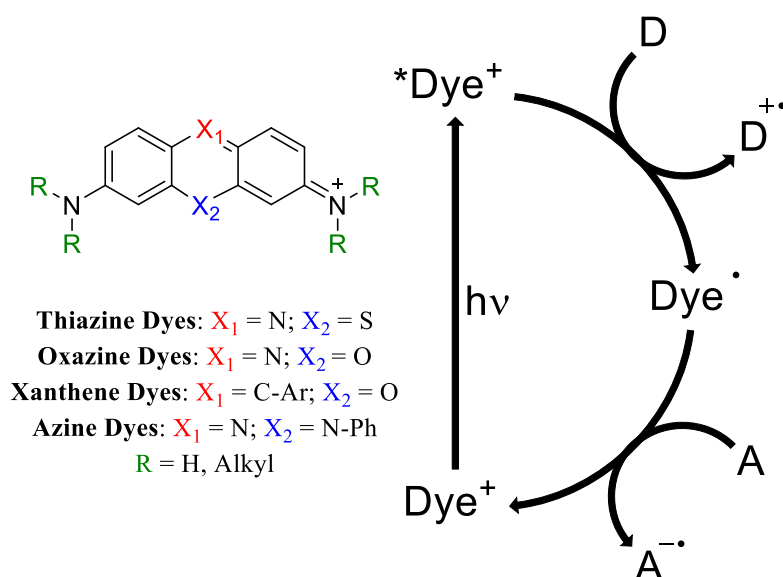


Figure 5.2. Basic structural representation of the organic dyes characterized in this chapter, and a typical reductive quenching photoredox cycle.

5.2 Dehalogenation of *meso*-1,2-dibromo-1,2-diphenylethane

The dehalogenation of *vicinal*-dibromo compounds employing photoredox techniques has been extensively studied in the literature, including examples from the Willner and Rieser groups employing $Ru(bpy)_3Cl_2$ as the photosensitizer^{20,22}, and more recently by the Scaiano group employing α -sexithiophene.²³ Due to the analytical simplicity of this

reaction, and the mechanistic data being extensively studied and readily available, we decided it would be an ideal system to compare the efficiencies of the cationic organic dyes.

We began by examining the dehalogenation of *meso*-1,2-dibromo-1,2-diphenylethane under visible light irradiation employing Methylene Blue as the photosensitizer (Table 5.1). After only 1 hour of irradiation, near quantitative conversion to the dehalogenated product, *trans*-stilbene, was observed. In order to compare the photocatalytic efficiency of Methylene Blue with other cationic dyes, a time point was required in order to compare the initial reaction efficiencies of the dyes. It was found that decreasing the irradiation time down to only 5 minutes was enough to decrease the conversion of the dibromo compound to 66%. It is important to note here that in these cases, only the *trans*-isomer of stilbene was observed under short periods of irradiation time.

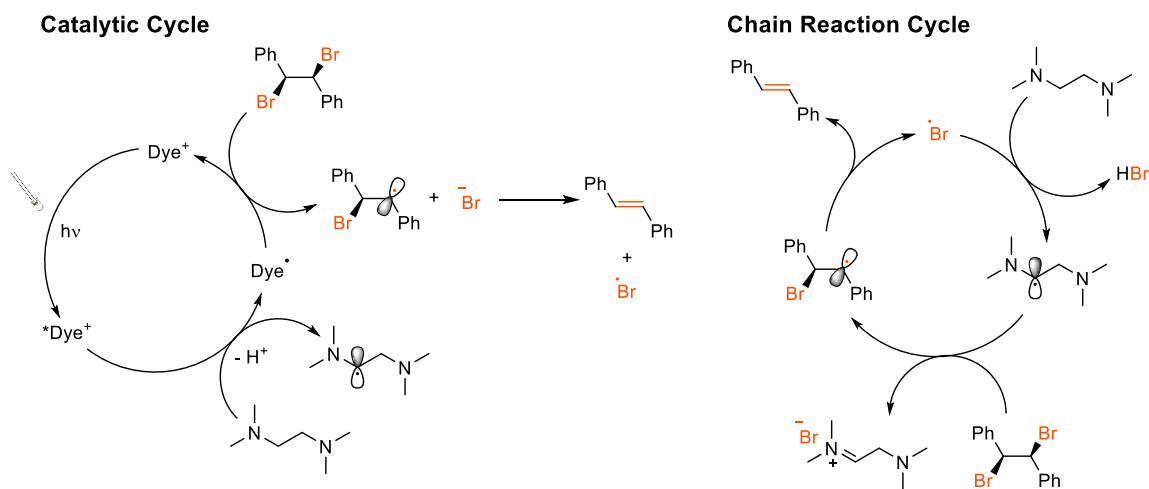
Table 5.1. Reductive dehalogenation of *meso*-1,2-dibromo-1,2-diphenylethane using Methylene Blue photocatalysis.

Entry	Irradiation Time	Percent Conversion	<i>E:Z</i> Ratio
1	18 h	Quantitative	13:1
2	1 h	96%	99:1
3	30 min	92%	99:1
4	10 min	83%	99:1
5	5 min	66%	99:1

For reaction conditions, see Section 5.6.2.

The reaction mechanism for this transformation is shown in Scheme 5.1. Upon excitation with visible light, the photosensitizer's excited state is generated (either singlet or triplet, depending on the photosensitizer studied), which can be quenched by an electron donor, in this case, *N,N,N',N'*-tetramethylethylenediamine (TMEDA), generating the reduced form of the dye and an amine radical-cation. The amine radical-cation will be readily

deprotonated to form an α -aminoalkyl radical²⁴, which along with the reduced form of the dye can reduce the dibromo compound.²⁵ Consistent with this mechanism, control experiments in which the photosensitizer or visible light is omitted do not give any conversion (Table 5.2). Importantly, experiments performed under UV-irradiation in the presence of TMEDA, but in the absence of a photosensitizer efficiently dehalogenate the dibromo compound. This is consistent with the proposed chain mechanism in Scheme 5.1 in which a liberated $\cdot\text{Br}$ produced in the reductive dehalogenation of *meso*-1,2-dibromo-1,2-diphenylethane can abstract a hydrogen atom from the amine to yield an α -aminoalkyl radical, which can, in turn, propagate the chain.^{26,27} No decomposition of the dibromo compound was observed in the absence of both the photosensitizer and the amine (Table 5.2).



Scheme 5.1. Proposed catalytic cycle and chain reaction for the reductive dehalogenation of *meso*-1,2-dibromo-1,2-diphenylethane photocatalyzed by cationic organic dyes.

Table 5.2. Control reactions for the reductive dehalogenation of *meso*-1,2-dibromo-1,2-diphenylethane.

Entry	Photon Source	TMEDA	Time	Percent Conversion	<i>E:Z</i> Ratio
1	Warm-White LEDs	+	5 min.	No Reaction	N.A.
2	Warm-White LEDs	+	1 h	< 5%	N.A.
3	Warm-White LEDs	-	1 h	No Reaction	N.A.
4	UVA Photoreactor	+	1 h	96%	5.4:1
5	UVA Photoreactor	-	1 h	No Reaction	N.A.
6	UVB Photoreactor	+	1 h	91%	1.5:1
7	UVB Photoreactor	-	1 h	No Reaction	N.A.

For reaction conditions, see Section 5.6.3.

We then proceeded to test a variety of cationic organic photosensitizers for the reductive dehalogenation of *meso*-1,2-dibromo-1,2-diphenylethane (Table 5.3). Importantly, the bimolecular rate constants (k_q) for excited state quenching for each cationic organic dye with TMEDA, the electron donor, were also obtained. As demonstrated in Table 5.3, the overall efficiency of the reaction correlates well with the magnitude of the bimolecular quenching constant, indicating the importance the kinetics of this electron-transfer step plays on the overall mechanism. One exception is the reactivity of 9-mesityl-10-methyl acridinium perchlorate (Mes-Acr⁺), which should be among the most reactive photosensitizers based on the kinetic data listed in Table 5.3. It is possible, however, that this is a thermodynamic issue, as the reduction potential of 9-mesityl-10-methyl acridinium perchlorate (-0.49 V vs. SCE)¹⁹ is not sufficiently negative to reduce *meso*-1,2-dibromo-1,2-diphenylethane (-1.10 V vs. SCE).²⁸ The xanthene and oxazine dyes are also less active than their k_q values would suggest, which can likely be attributed to their short singlet state lifetimes (ns timescales). The short singlet state lifetimes of these dyes greatly decreases the probability of excited state electron-transfer events compared to the thiazine and azine dyes with longer triplet state lifetimes (μ s timescales). This

demonstrates the preference for using triplet photosensitizers to increase the probability of the excited state interacting with a quencher before relaxing back to the ground state, and this will be expanded on further *vide infra*. It is also important to note here that the k_q value observed for Rhodamine B is greater than the diffusion control limit of DMF, which can be attributed to static quenching due to ground state complexation with TMEDA. Once again, it is important to note that the *trans*-isomer was the only isomer observed for all organic photosensitizers employed.

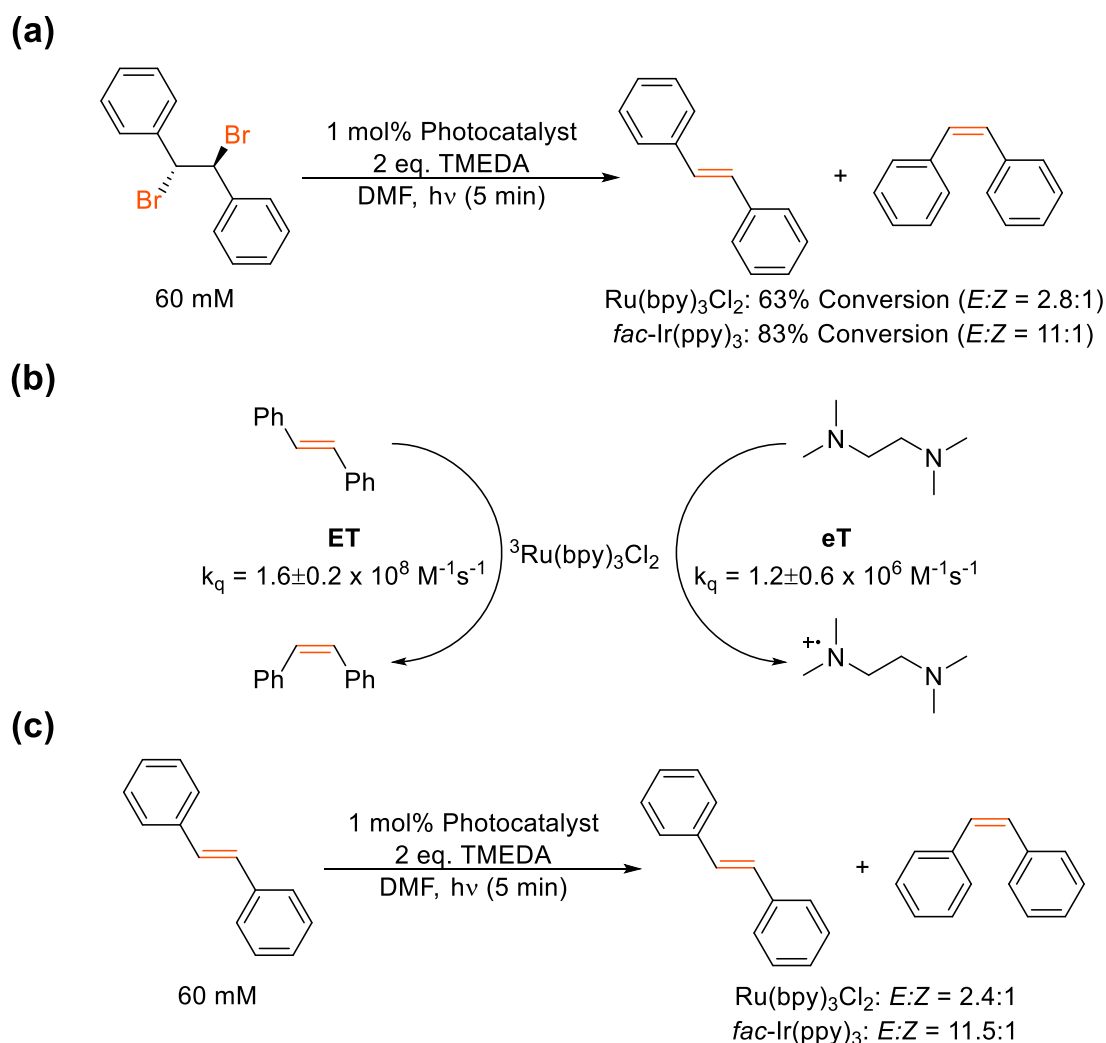
Table 5.3. Photocatalyzed reductive dehalogenation of *meso*-1,2-dibromo-1,2-diphenylethane, and the corresponding bimolecular rate constants (k_q) for excited state quenching by TMEDA.

Entry	Class	Photosensitizer	$k_q(\text{TMEDA}) \text{ (M}^{-1}\text{s}^{-1}\text{)}$	Conversion
1	Thiazine	Methylene Blue	$3.4 \pm 0.1 \times 10^8$	66%
2	Thiazine	Thionin	$7.2 \pm 0.7 \times 10^9$	73%
3	Thiazine	New Methylene Blue N	$3.3 \pm 0.1 \times 10^9$	93%
4	Thiazine	1,9-dimethyl Methylene Blue	$7.2 \pm 0.6 \times 10^9$	94%
5	Thiazine	Methylene Green	$1.0 \pm 0.1 \times 10^{10}$	81%
6	Oxazine	Brilliant Cresyl Blue ALD	$1.0 \pm 0.1 \times 10^{10}$	41%
7	Oxazine	Nile Blue	$7.5 \pm 1.0 \times 10^7$	18%
8	Xanthene	Pyronin Y	$5.2 \pm 0.3 \times 10^{10}$	68%
9	Xanthene	Rhodamine 6G	$8.1 \pm 0.3 \times 10^9$	77%
10	Xanthene	Rhodamine B	$2.7 \pm 0.5 \times 10^{13}$	58%
11	Azine	Phenosafranin	$4.8 \pm 0.2 \times 10^9$	62%
12	Azine	Safranin O	$2.0 \pm 0.3 \times 10^9$	56%
13	Azine	Methylene Violet 3RAX	$2.8 \pm 0.2 \times 10^9$	53%
16	Acridinium	Mes-Acr ⁺	$4.0 \pm 0.4 \times 10^{10}$	10%

For reaction conditions, see Section 5.6.2.

The reductive dehalogenation of *meso*-1,2-dibromo-1,2-diphenylethane employing $\text{Ru}(\text{bpy})_3\text{Cl}_2$ and *fac*- $\text{Ir}(\text{ppy})_3$, two ubiquitous complexes employed in the field of photoredox catalysis, was also investigated. While both complexes performed well under the standard employed conditions, we were surprised to observe both the *cis*- and *trans*-isomers of stilbene (Scheme 5.2a). However, by examining the kinetics of the system for the $\text{Ru}(\text{bpy})_3\text{Cl}_2$ example, it was determined that the loss in selectivity stems from the unfavourable kinetics of the initial electron-transfer step. As shown in Scheme 5.2b, the

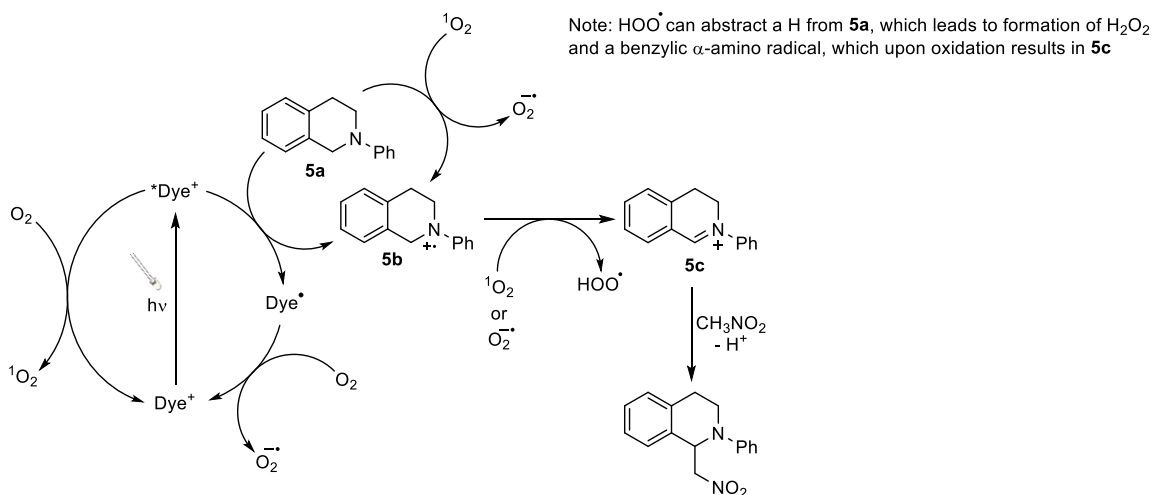
bimolecular rate constant for *trans*-stilbene and $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$ is two orders of magnitude higher than the corresponding bimolecular rate constant with TMEDA, the electron donor. Therefore, any *trans*-stilbene formed is able to outcompete TMEDA in the quenching of $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$, resulting in energy-transfer and isomerization of the double bond. In good agreement with this, irradiating *trans*-stilbene in the presence of either $\text{Ru}(\text{bpy})_3\text{Cl}_2$ or *fac*- $\text{Ir}(\text{ppy})_3$ results in the same *E:Z* ratio observed in the reductive dehalogenation experiments (Scheme 5.2c).



Scheme 5.2. (a) Reductive dehalogenation of *meso*-1,2-dibromo-1,2-diphenylethane by $\text{Ru}(\text{bpy})_3\text{Cl}_2$ and $\text{Ir}(\text{ppy})_3$. (b) Competitive quenching of $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$ by *trans*-stilbene and TMEDA. (c) Isomerization of *trans*-stilbene by $\text{Ru}(\text{bpy})_3\text{Cl}_2$ and $\text{Ir}(\text{ppy})_3$.

5.3 Light-Mediated Aza-Henry Reaction

The visible light-mediated Aza-Henry reaction of 2-phenyl-1,2,3,4-tetrahydroisoquinoline (PhTHIQ, **5a**) with nitromethane (MeNO_2) as the nucleophile was first studied by Stephenson and co-workers in 2010, and since has become one of the most studied reactions in the field of photoredox catalysis (Scheme 5.3).^{21,29} In fact, this reaction has become one of the gold standards when testing the activity of newly developed photocatalysts.³⁰⁻³⁶ Due to the popularity of the reaction and the availability of in depth mechanistic studies³⁷, we decided it would be another excellent test reaction for the cationic dyes employed in this chapter. Moreover, the simplicity of the reaction greatly facilitates the kinetic analysis of these catalytic systems, allowing for the examination of any possible correlations between excited state quenching efficiency and the overall efficiency of the reaction. Since the only quenchers in this system under initial reaction conditions are PhTHIQ and molecular oxygen, by measuring the bimolecular rate constants for excited state quenching of both, the probability at which the excited state of the photocatalyst will be quenched by PhTHIQ can be calculated.



Scheme 5.3. Proposed mechanism for the visible-light mediated Aza-Henry reaction. Note that reactions of $^1\text{O}_2$ are only viable for examples in which triplet-state dyes are employed.

The results for the Aza-Henry photocatalyzed reaction are summarized in Table 5.4. Here, the difference is more pronounced between the triplet and singlet state dyes, highlighting the importance of selecting a photocatalyst with a long excited state lifetime. Once again, Mes-Acr⁺ was observed to be much less efficient than the high bimolecular quenching constant would suggest, which we attribute to the lack of reactivity of the intermediate acridinium radical toward molecular oxygen ($E_{1/2} = -0.73$ V vs. SCE)³⁸, the required step for catalytic turnover. Similarly to the reductive dehalogenation reactions, the light-mediated Aza-Henry reaction was also performed employing both Ru(bpy)₃Cl₂ and *fac*-Ir(ppy)₃, which gave 27% and 26% yield of the final Aza-Henry product, respectively. One would expect similar results for both photocatalysts, as their rate constants for bimolecular quenching with PhTHIQ are on the same order of magnitude (2.9×10^7 and 3.1×10^7 M⁻¹s⁻¹ for Ru(bpy)₃Cl₂ and *fac*-Ir(ppy)₃, respectively).

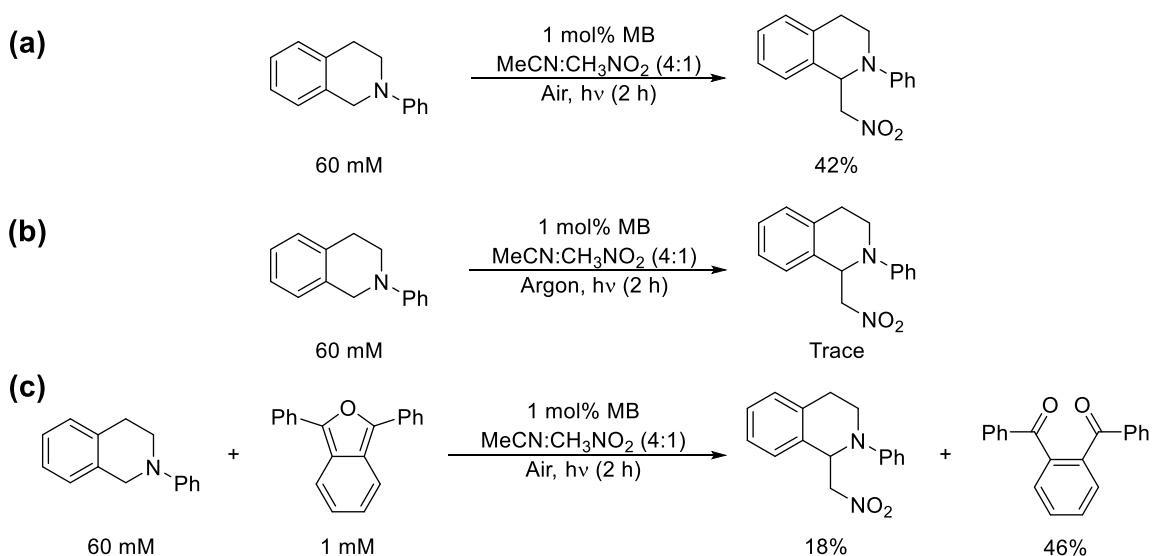
Table 5.4. Light-mediated Aza-Henry reaction with 2-phenyl-1,2,3,4-tetrahydro-isoquinoline (PhTHIQ), and the corresponding bimolecular rate constants (k_q) for excited state quenching by PhTHIQ.

Entry	Class	Photosensitizer	$k_q(\text{TMEDA})$ (M ⁻¹ s ⁻¹)	Conversion
1	Thiazine	Methylene Blue	$8.3 \pm 0.1 \times 10^9$	66%
2	Thiazine	Thionin	$4.3 \pm 0.4 \times 10^9$	15%
3	Thiazine	New Methylene Blue N	$5.9 \pm 0.8 \times 10^9$	48%
4	Thiazine	1,9-dimethyl Methylene Blue	$1.5 \pm 0.4 \times 10^9$	50%
5	Thiazine	Methylene Green	$7.4 \pm 0.5 \times 10^9$	34%
6	Oxazine	Brilliant Cresyl Blue ALD	$2.5 \pm 0.1 \times 10^{10}$	9%
7	Oxazine	Nile Blue	$1.4 \pm 0.3 \times 10^9$	10%
8	Xanthene	Pyronin Y	$3.2 \pm 0.7 \times 10^{10}$	25%
9	Xanthene	Rhodamine 6G	$1.6 \pm 0.1 \times 10^9$	17%
10	Xanthene	Rhodamine B	$3.3 \pm 0.1 \times 10^{11}$	15%
11	Azine	Phenosafranin	$2.5 \pm 0.5 \times 10^9$	40%
12	Azine	Safranin O	$2.7 \pm 0.2 \times 10^9$	40%
13	Azine	Methylene Violet 3RAX	$8.4 \pm 0.7 \times 10^9$	24%
16	Acridinium	Mes-Acr ⁺	$7.1 \pm 0.8 \times 10^9$	26%

For reaction conditions, see Section 5.6.5.

Control experiments were also performed with MB as the photocatalyst, and it was demonstrated that the reaction did not proceed in the absence of oxygen, consistent with the previously reported mechanisms (Scheme 5.4b). More specifically, it has been

proposed that either singlet oxygen ($^1\text{O}_2$) or superoxide ($\text{O}_2^{\cdot-}$) play a prominent role in the overall mechanism (see Scheme 5.3)^{21,37}, and upon addition of 1,3-diphenylisobenzofuran (DPBF), an efficient $^1\text{O}_2$ and $\text{O}_2^{\cdot-}$ quencher^{39,40}, the reactivity is substantially diminished and formation of 1,2-phenylenebis(phenylmethanone) is observed as a result of the oxidation of DPBF, consistent with the proposed mechanism of previous reports (Scheme 5.4c).³⁷



Scheme 5.4 Light-mediated Aza-Henry reaction promoted by MB (a) in the presence of air and (b) under inert atmosphere. (c) Effect of 1,3-diphenylbenzofuran (DPBF) on the reaction efficiency. For reaction conditions, see section 5.6.6.

While the addition of DPBF to the reaction mixture results in a decrease in yield of the Aza-Henry product, this information alone is not enough to rule out that the decrease in yield of the Aza-Henry product is due to quenching of reactive oxygen species, as it could also stem from DPBF outcompeting PhTHIQ in the bimolecular quenching of ^3MB . In order to rule out this possibility, the excited state kinetics of MB and all the reaction substrates were examined, and are summarized in Table 5.5.

Table 5.5. Bimolecular quenching data for triplet Methylene Blue and the reaction substrates of the light-mediated Aza-Henry reaction.

Entry	Substrate	$^3\text{MB kq (M}^{-1}\text{s}^{-1})$
1	O_2	$2.5 \pm 0.3 \times 10^9$
2	2-phenyl-1,2,3,4-tetrahydroisoquinoline	$8.3 \pm 0.1 \times 10^9$
3	1,3-diphenylisobenzofuran	$< 10^6$
4	MeNO_2	$< 10^6$

For experimental conditions, see section 5.7.

Since we could not detect any bimolecular quenching of ^3MB by DPBF, it can be assumed that the observed decrease in reactivity is due to DPBF trapping reactive oxygen species, and not from DPBF outcompeting PhTHIQ for ^3MB .

Since it is well known that MB is an excellent sensitizer of $^1\text{O}_2$, the bimolecular quenching of $^1\text{O}_2$ by the reaction substrates was examined to determine the role of $^1\text{O}_2$ in the overall reaction mechanism. Moreover, it is well known that $^1\text{O}_2$ is capable of oxidizing amines⁴¹, an important step in the proposed mechanism for the Aza-Henry reaction.^{21,37} The results of this kinetic investigation are summarized in Table 5.6.

Table 5.6. Bimolecular quenching data for singlet oxygen and the reaction substrates of the light-mediated Aza-Henry reaction.

Entry	Substrate	$^3\text{MB kq (M}^{-1}\text{s}^{-1})$
1	2-phenyl-1,2,3,4-tetrahydroisoquinoline	$1.1 \pm 0.2 \times 10^8$
2	1,3-diphenylisobenzofuran	$1.2 \pm 0.2 \times 10^9$
3	MeNO_2	$< 10^6$

For experimental conditions, see section 5.7.7.

From these data, it can be concluded that any $^1\text{O}_2$ produced by MB can indeed be trapped by PhTHIQ. In good agreement, a value approaching diffusion control was obtained for DPBF, an excellent known $^1\text{O}_2$ quencher.⁴⁰ Therefore, it is possible that $^1\text{O}_2$ is indeed playing a role in the mechanism, as the addition of another potent $^1\text{O}_2$ quencher (DPBF) significantly impacts the yield. However, DPBF is not solely specific to $^1\text{O}_2$, as it has been reported to trap other reactive oxygen species, such as superoxide ($\text{O}_2^{\cdot-}$).³⁹ Therefore, it cannot be concluded from these data alone that the trapping of $^1\text{O}_2$ is what is responsible

for the decrease in the yield, but that the decrease is due to the trapping of reactive oxygen species.

5.4 Thermodynamics versus Kinetics in Photoredox Transformations

With all the kinetic data in hand, equation (1) can be employed to calculate the probability that the excited state of the photosensitizer (*PC) is quenched by PhTHIQ under our initial reaction conditions.

$$\% \text{ *PC Quenched by PhTHIQ} = \frac{k_q^{\text{PhTHIQ}}[\text{PhTHIQ}]}{\tau_0^{-1} + k_q^{\text{PhTHIQ}}[\text{PhTHIQ}] + k_q^{\text{O}_2}[\text{O}_2]} \quad (1)$$

This calculation was performed with all 13 cationic dyes that were examined in this study, and the results were plotted against the yield of the corresponding Aza-Henry reaction (Figure 5.3). While the correlation is not strong, this plot still demonstrates that the majority of the more efficient reactions are for the larger probabilities of excited state quenching. It is also important to note that the highest probabilities for *PC quenching by PhTHIQ occur when triplet state dyes (●) are employed, which one would predict considering the effect that the excited state lifetime plays in equation (1). Furthermore, the rate-limiting step of this reaction is the addition of MeNO₂, and not the initial excited state electron-transfer to the amine, which could affect the correlation observed in Figure 5.3.^{21,37} However, it is still clear that by optimizing the mechanistically key steps of the system, even if it is not the rate-limiting step, one can increase the overall efficiency of the reaction.

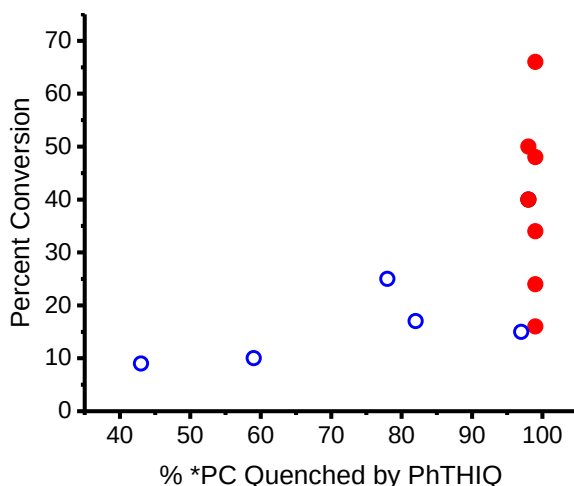


Figure 5.3. Plot of percent yield of the Aza-Henry product versus the percent of *Dye quenched by PhTHIQ for all cationic dyes examined in this study. Legend: triplet photosensitizers (●), singlet photosensitizers (○).

A similar analysis on the thermodynamic feasibility of these reactions can also be performed. Since the oxidation potential of PhTHIQ is known (0.90 V vs. SCE)⁴², this value along with the ground state reduction potentials and the excited state energies of each dye can be used to calculate the Gibbs free energy of photoinduced electron-transfer (ΔG_{eT}) for each reaction using equation (2)^{43,44}:

$$\Delta G_{\text{eT}} = E_{1/2}^{\text{ox}}(\text{PhTHIQ}) - E_{1/2}^{\text{red}}(\text{Dye}) - E_{\text{S or T}}^*(\text{Dye}) + \Delta E_{\text{Coulombic}} \quad (2)$$

This calculation was performed for all 13 cationic dyes examined in this chapter, and the results were plotted against the yield of the Aza-Henry product (Figure 5.4). It should be noted that $\Delta E_{\text{Coulombic}}$ was neglected for these calculations, as the values are usually negligible for solvents with high dielectric constants. One would typically expect that a more negative ΔG_{eT} would lead to a more favourable and therefore more efficient reaction. However, essentially the opposite trend is observed in Figure 5.4, as the more favourable reactions (more negative ΔG_{eT}) give the lowest yields after two hours of irradiation. Upon further examination, it can be seen that the more negative ΔG_{eT} correspond to the singlet

excited state dyes ($\circ$), which can be correlated to their higher excited state energies compared to the triplet state dyes. However, due to their short singlet state lifetimes, the probability of electron-transfer is greatly decreased, as seen in Figure 5.3, even though the electron-transfer event is more thermodynamically favourable. This highlights the importance of performing kinetic studies, as even though a reaction can have favourable thermodynamics, it is ultimately kinetics that determines to what extent the reaction proceeds.

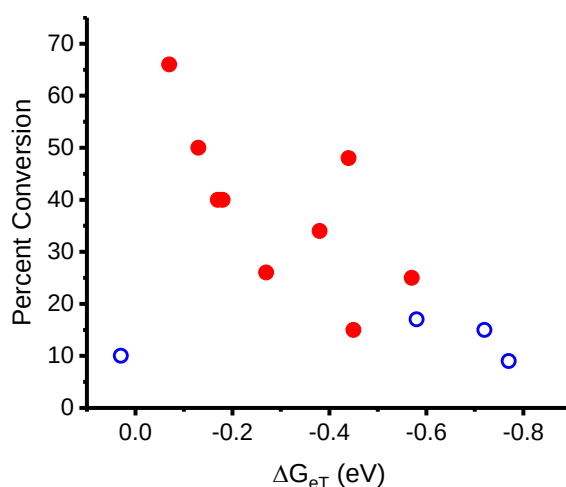


Figure 5.4. Plot of percent yield of Aza-Henry product versus the Gibb's free energy for photoinduced electron transfer (ΔG_{ET}) for all cationic dyes examined in this study. Legend: triplet photosensitizers ($\bullet$), singlet photosensitizers ($\circ$).

5.5 Conclusion

In this chapter, it was demonstrated that cationic dyes can act as viable metal-free alternatives to transition-metal complexes for visible light-mediated photoredox transformations. The utility of these dyes for both the reductive dehalogenation of a *vicinal*-dibromo compound, as well as the visible light mediated Aza-Henry reaction of PhTHIQ was examined. In the majority of these examples, improved kinetics of electron-transfer between the excited state of the photocatalyst and the amine resulted in an overall

increase in the reaction efficiency. For the light-mediated Aza-Henry reaction, the probability of excited state quenching by PhTHIQ was found to correlate with the reaction efficiency. In these cases, the triplet state photosensitizers were found to be more efficient than the singlet state photosensitizers, demonstrating the importance of choosing photosensitizers with long lived excited states to increase the probability of being quenched before returning to the ground state. Moreover, no correlation could be observed between the Gibbs free energy of electron-transfer and the efficiency of the reaction. This highlights the importance of optimizing the kinetics of all the mechanistically key steps, even if it is not the rate-limiting step of the reaction, and that even if a reaction is thermodynamically favourable, it is ultimately kinetics that will determine to what extent the reaction proceeds.

Importantly, a summary of all the photophysical and electrochemical properties of these cationic dyes has been provided and can be found in the Appendix (Section 5.8). With this information in hand, we envision that this will result in an increase in popularity of these cationic dyes being employed in visible light photoredox processes, as this information will now be readily available to laboratories who may lack the necessary equipment and/or expertise to perform the characterization of their photophysical properties.

With all the organic photosensitizers examined in this work, as well as the examples listed in Figure 5.1, the breadth of redox potentials attainable is competitive with those of Ru and Ir complexes.¹ This range covers oxidation potentials of -2.4 V vs. SCE to reduction potentials of 2.1 V, with the majority of these potentials being achievable employing visible light irradiation. An important question in regards to the advancement of this field is what can be done to increase the range of potentials available in order to tackle more thermodynamically challenging transformations. In essence, in order to achieve more

oxidizing and/or reducing capabilities, higher excited energies are required, which can be seen mathematically when examining the equation for Gibb's free energy of photoinduced electron-transfer (e.g. equation (2)). However, one of the limitations in this regard is that in order to obtain higher excited state energies, higher energy photons, such as UV photons, must be employed. This is undesirable in organic synthesis, as many organic compounds absorb in the UV range, and direct irradiation could lead to undesired side reactions and/or decomposition. This ultimately means that expanding the potential window beyond what is already available may not be possible without compromising the stability and reactivity of the transformations, therefore more focus should be shifted towards developing novel transformations that can be achieved with this thermodynamic window.

5.6 Experimental Details

5.6.1 General Information. All dyes were purchased from chemical suppliers and used without further purification. *meso*-1,2-Dibromo-1,2-diphenylethane and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) were purchased from Sigma Aldrich and Acros Organics, respectively, and used as received. All reactions were irradiated with two 90 W warm-white LEDs unless otherwise noted. Products were isolated using flash column chromatography using 230-400 mesh silica gel. All ^1H and ^{13}C NMR spectra were recorded using a Bruker Avance 400 spectrometer.

5.6.2 General Procedure for the Dehalogenation of *meso*-1,2-dibromo-1,2-diphenyl ethane. *meso*-1,2-dibromo-1,2-diphenylethane (0.3 mmol, 102 mg), photosensitizer (0.003 mmol), and 5 mL of dry DMF were added to an oven-dried 10 mL Schlenk tube equipped with a magnetic stir bar. TMEDA (0.6 mmol, 90 μL) was then added, and the reaction mixture was purged with argon for 15 minutes, followed by irradiation for 5

minutes with two warm white LEDs. The reaction was then diluted with H₂O, extracted with ether (3 x 20 mL), and the organic phase was washed with brine (5 x 20 mL) to remove traces of DMF. The organic phase was then dried over MgSO₄, and concentrated by rotary evaporation. Percent conversion and *E:Z* ratios were determined by ¹H NMR analysis.

5.6.3 Procedure for Dehalogenation Control Reactions. *meso*-1,2-Dibromo-1,2-diphenylethane (0.3 mmol, 102 mg) and 5 mL of dry DMF were added to an oven-dried 10 mL Schlenk tube equipped with a magnetic stir bar. TMEDA (0.6 mmol, 90 μL) was then added (unless otherwise noted), and the reaction mixture was purged with argon for 15 minutes, followed by irradiation for 1 h with two warm white LEDs or a Luzchem photoreactor equipped with either UVA or UVB bulbs. The reaction was then diluted with H₂O, extracted with ether (3 x 20 mL), and the organic phase was washed with brine (5 x 20 mL) to remove traces of DMF. The organic phase was then dried over MgSO₄, and concentrated by rotary evaporation. Percent conversion and *E:Z* ratios were determined by ¹H NMR analysis.

5.6.4 Procedure for *trans*-Stilbene Isomerization with Ru(bpy)₃Cl₂ and Ir(ppy)₃. *trans*-Stilbene (0.3 mmol, 54 mg), Ru(bpy)₃Cl₂ or Ir(ppy)₃ (0.003 mmol), and 5 mL of dry DMF were added to an oven-dried 10 mL Schlenk tube equipped with a magnetic stir bar. TMEDA (0.6 mmol, 90 μL) was then added, and the reaction mixture was purged with argon for 15 minutes, followed by irradiation for 5 minutes with two warm white LEDs. The reaction was then diluted with H₂O, extracted with ether (3 x 20 mL), and the organic phase was washed with brine (5 x 20 mL) to remove traces of DMF. The organic phase was then dried over MgSO₄, and concentrated by rotary evaporation. *E:Z* ratios were determined by ¹H NMR analysis.

5.6.5 General Procedure for Light-Mediated Aza-Henry Reactions. 2-Phenyl-1,2,3,4-tetrahydroisoquinoline (0.3 mmol, 63 mg), photosensitizer (0.003 mmol), and MeCN:MeNO₂ (4:1, 5 mL) were added to an oven-dried 10 mL Schlenk tube equipped with a magnetic stir bar. The reaction was stirred and irradiated for 1 h with two warm white LEDs, then diluted with ether (20 mL) and H₂O (20 mL). The aqueous phase was extracted with ether (2 x 20 mL), and the combined organic phases were washed with brine, dried over MgSO₄, and concentrated by rotary evaporation. Crude was purified by flash column chromatography (20:1 Hex:EtOAc) to give the desired product as a yellow oil.

5.6.6 Procedure for Aza-Henry Control Reactions using Methylene Blue. For the following control experiments, a 10 W 660 nm LED purchased from LedEngin was used as the irradiation source in order to avoid direct irradiation of 1,3-diphenylisobenzofuran (DPBF).

Standard Conditions: 2-Phenyl-1,2,3,4-tetrahydroisoquinoline (0.3 mmol, 63 mg), MB (0.003 mmol, 1.1 mg), and MeCN:MeNO₂ (4:1, 5 mL) were added to an oven-dried 10 mL Schlenk tube equipped with a magnetic stir bar. The reaction was stirred and irradiated for 2 h with one 660 nm LED, then diluted with ether (20 mL) and H₂O (20 mL). The aqueous phase was extracted with ether (2 x 20 mL), and the combined organic phases were washed with brine, dried with MgSO₄, and concentrated by rotary evaporation. The crude was purified by flash column chromatography (20:1 Hex:EtOAc) to give the desired Aza-Henry product as a yellow oil in 42% isolated yield (34 mg).

No Oxygen Control: 2-Phenyl-1,2,3,4-tetrahydroisoquinoline (0.3 mmol, 63 mg), MB (0.003 mmol, 1.1 mg), and MeCN:MeNO₂ (4:1, 5 mL) were added to an oven-dried 10 mL Schlenk tube equipped with a magnetic stir bar. The reaction was purged with argon for

15 minutes to remove any trace of O₂. The reaction was stirred and irradiated for 2 h with two warm white LEDs, then diluted with ether (20 mL) and H₂O (20 mL). The aqueous phase was extracted with ether (2 x 20 mL), and the combined organic phases were washed with brine, dried with MgSO₄, and concentrated by rotary evaporation. Purification of the crude by flash column chromatography resulted in only trace quantities of the desired product.

DPBF Control: 2-Phenyl-1,2,3,4-tetrahydroisoquinoline (0.3 mmol, 63 mg), MB (0.003 mmol, 1.1 mg), DPBF (0.05 mmol, 14 mg) and MeCN:MeNO₂ (4:1, 5 mL) were added to an oven-dried 10 mL Schlenk tube equipped with a magnetic stir bar. The reaction was stirred and irradiated for 2 h with two warm white LEDs, then diluted with ether (20 mL) and H₂O (20 mL). The aqueous phase was extracted with ether (2 x 20 mL), and the combined organic phases were washed with brine, dried with MgSO₄, and concentrated by rotary evaporation. The crude was purified by flash column chromatography (20:1 Hex:EtOAc) to give the desired Aza-Henry product as a yellow oil in 18% isolated yield (14 mg) and the oxidation product of DPBF (1,2-phenylenebis(phenylmethanone)) as a white solid in 46% isolated yield (6.5 mg). Yields are reported as an average over two trials.

5.6.7 Synthesis of 2-Phenyl-1,2,3,4-tetrahydroisoquinoline. CuI (3.0 mmol, 600 mg) and K₃PO₄ (60 mmol, 12.75 g) were added to an oven-dried three-neck 250 mL round bottom flask equipped with a magnetic stir bar. The flask was evacuated and back-filled with argon, followed by syringe addition of 2-propanol (30 mL), ethylene glycol (30 mmol, 3.33 mL), 1,2,3,4-tetrahydroisoquinoline (45 mmol, 6.0 mL), and iodobenzene (30 mmol, 3.36 mL). The reaction mixture was stirred and heated to 90 °C for 24 h and allowed to cool to room temperature. The reaction mixture was diluted with ether (60 mL) and H₂O

(60 mL), and the aqueous phase was further extracted with ether (2 x 60 mL). The combined organic phases were dried with MgSO_4 and concentrated by rotary evaporation. The crude was purified by flash column chromatography (20:1 Hex:EtOAc) to give the final product as an off-white solid in 58% isolated yield (3.66 g).

5.7 Laser Flash Photolysis and Steady-State Quenching Data

5.7.1 General Procedure for Laser Flash Photolysis Experiments. The triplet quenching experiments were performed using either an Nd:YAG (355 or 532 nm) or a Surelite plus OPO (430-700 nm) in a LFP-111 laser flash photolysis system (Luzchem Inc., Ottawa, CA). The samples were measured in 1 x 1 cm LFP-Luzchem cuvettes. Samples were prepared with a total volume of 3 mL and an absorbance of ~ 0.1 at the excitation wavelength. The samples were purged with N_2 for 30 minutes prior to use.

5.7.2 General Procedure for Steady-State Experiments. The fluorescence emission measurements required for the singlet quenching experiments were carried out in a Photon Technology International (PTI) spectrofluorimeter using 1 x 1 cm quartz cuvettes. The fluorescent lifetimes were measured in an Easy-Life (PTI) system and calculated using the integrated Easy-Life software. Samples were prepared with a total volume of 3 mL and an absorbance of ~ 0.1 at the excitation wavelength. The substrates used in the quenching studies were also prepared in this solution to ensure that the observed quenching is not due to dilution of the fluorophore.

5.7.3 Excited State Quenching by TMEDA.

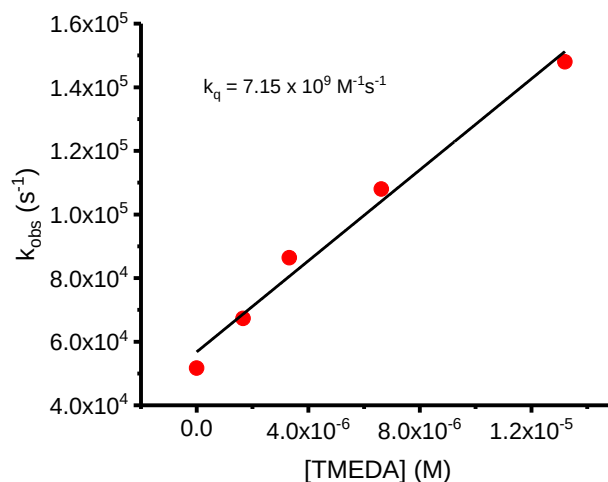


Figure 5.5. Representative kinetic quenching plot for the quenching of $^3\text{Thionin}$ by TMEDA in 4:1 MeCN:H₂O using 532 nm laser excitation.

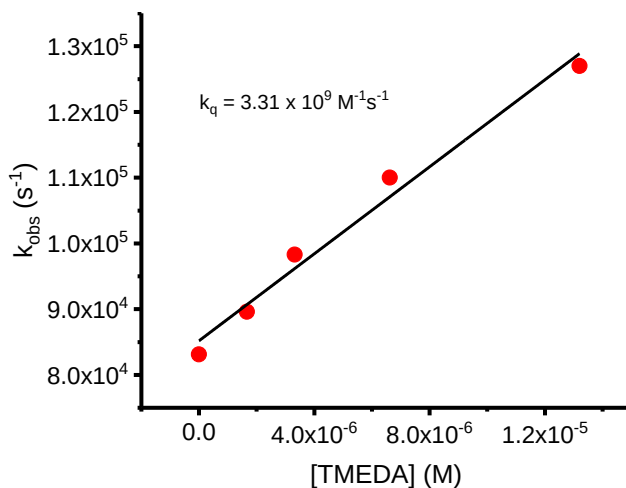


Figure 5.6. Representative kinetic quenching plot for the quenching of $^3\text{New Methylene Blue N}$ by TMEDA in MeCN using 532 nm laser excitation.

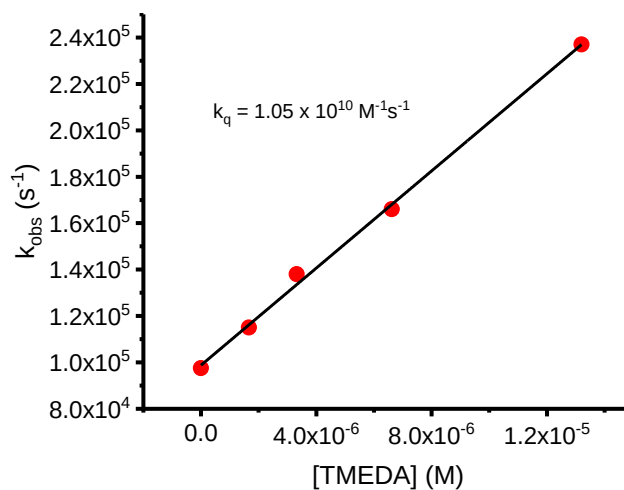


Figure 5.7. Representative kinetic quenching plot for the quenching of ^{3} 1,9-dimethyl Methylene Blue by TMEDA in MeCN using 532 nm laser excitation.

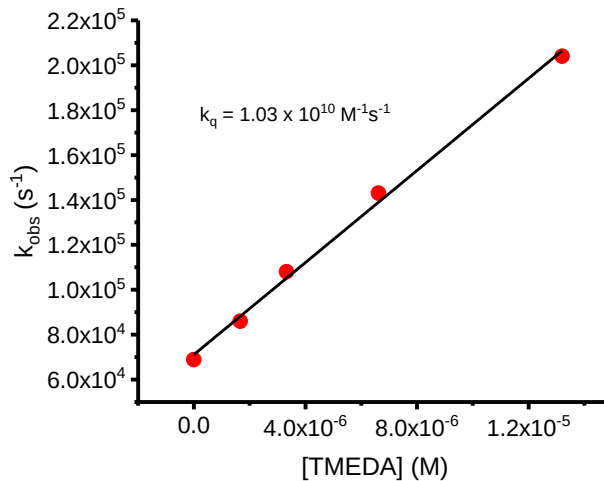


Figure 5.8. Representative kinetic quenching plot for the quenching of ^{3} Methylene Green by TMEDA in MeCN using 532 nm laser excitation.

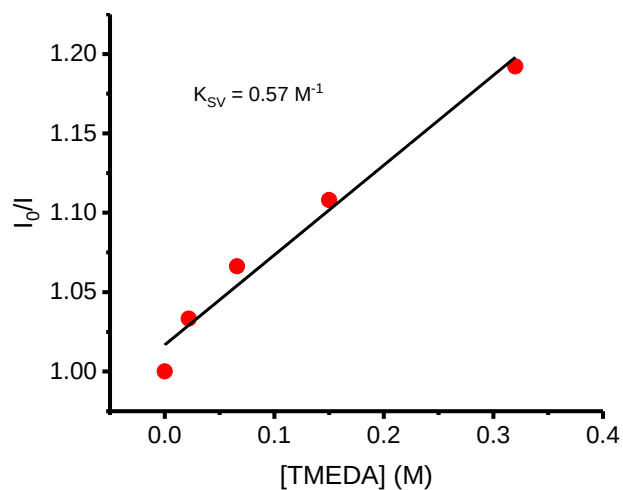


Figure 5.9. Representative Stern-Volmer plot for the quenching of ¹Brilliant Cresyl Blue ALD by TMEDA in MeCN using 605 nm excitation.

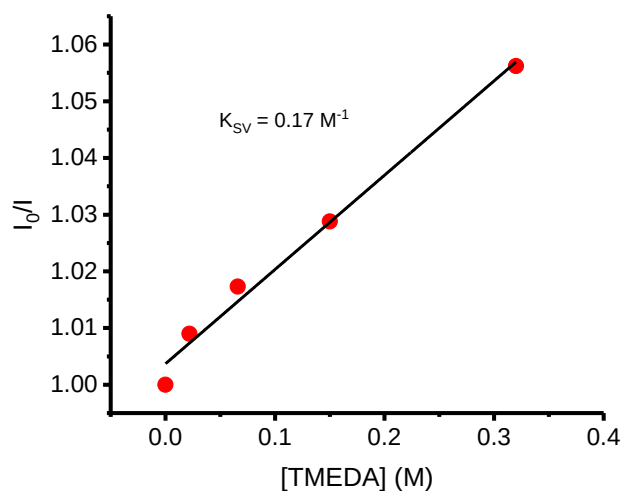


Figure 5.10. Representative Stern-Volmer plot for the quenching of ¹Nile Blue by TMEDA in MeCN using 605 nm excitation.

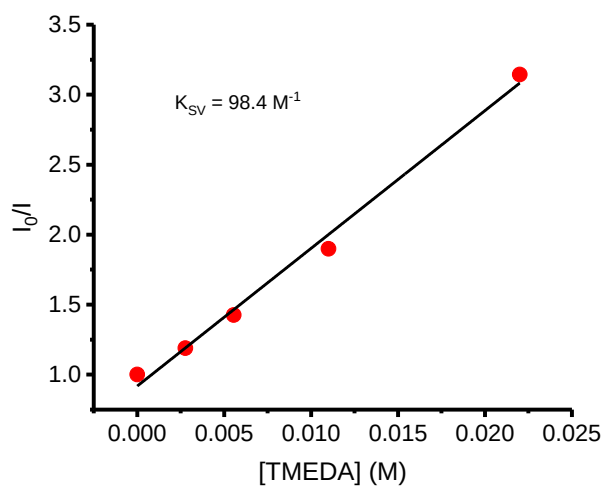


Figure 5.11. Representative Stern-Volmer plot for the quenching of ¹Pyronin Y by TMEDA in MeCN using 485 nm excitation.

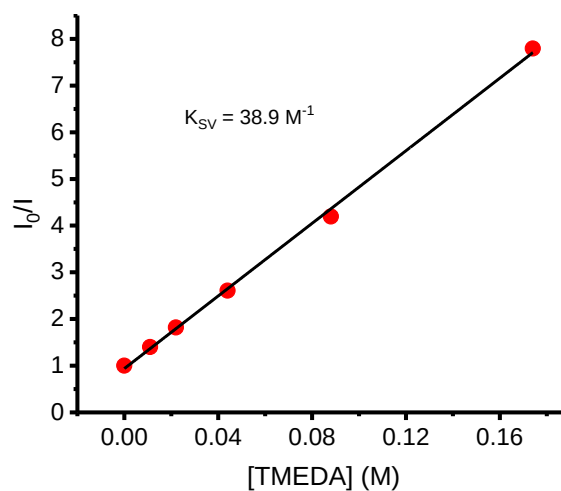


Figure 5.12. Representative Stern-Volmer plot for the quenching of ¹Rhodamine 6G by TMEDA in MeCN using 460 nm excitation.

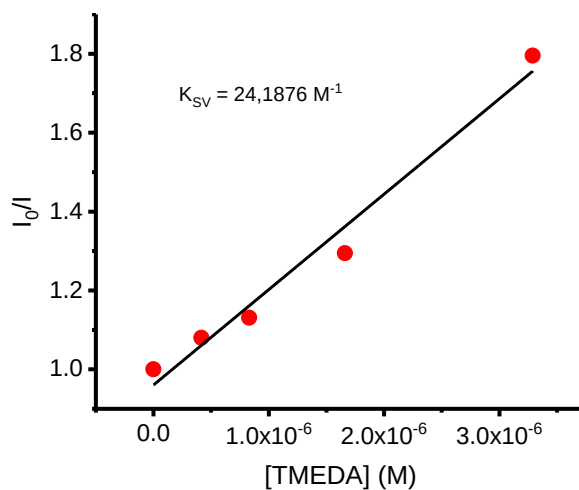


Figure 5.13. Representative Stern-Volmer plot for the quenching of ¹Rhodamine B by TMEDA in MeCN using 485 nm excitation.

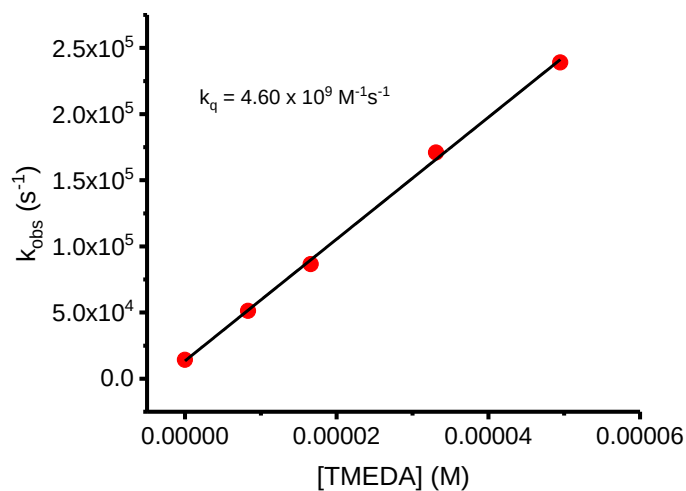


Figure 5.14. Representative kinetic quenching plot for the quenching of ³Phenosafranin by TMEDA in MeCN using 532 nm laser excitation.

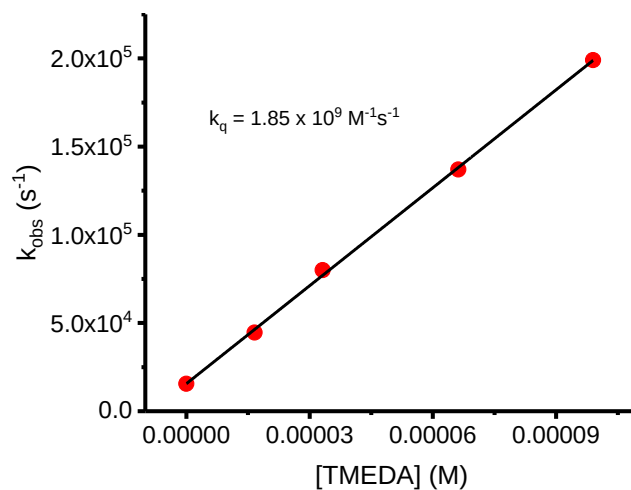


Figure 5.15. Representative kinetic quenching plot for the quenching of $^3\text{Safranin O}$ by TMEDA in MeCN using 532 nm laser excitation.

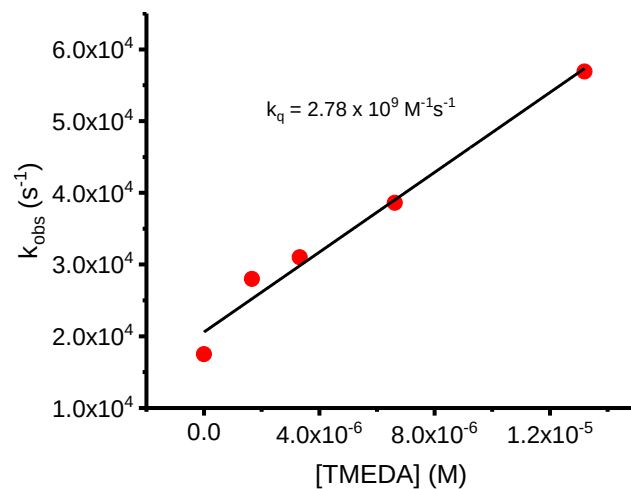


Figure 5.16. Representative kinetic quenching plot for the quenching of $^3\text{Methylene Violet 3RAX}$ by TMEDA in MeCN using 532 nm laser excitation.

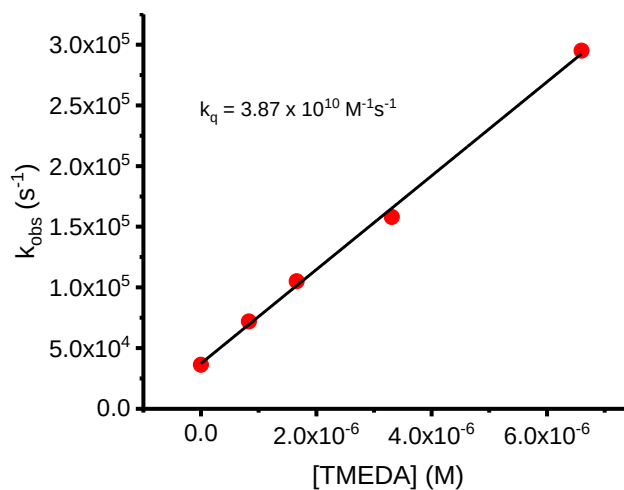


Figure 5.17. Representative kinetic quenching plot for the quenching of $^3\text{Mes-Acr}^+$ by TMEDA in MeCN using 430 nm laser excitation.

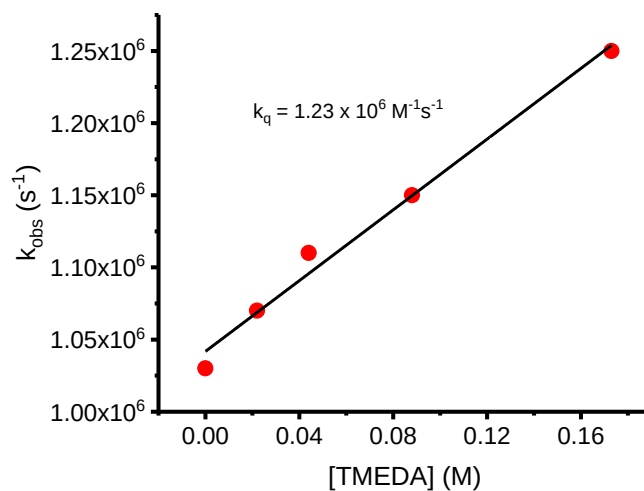


Figure 5.18. Representative kinetic quenching plot for the quenching of $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$ by TMEDA in MeCN using 355 nm laser excitation.

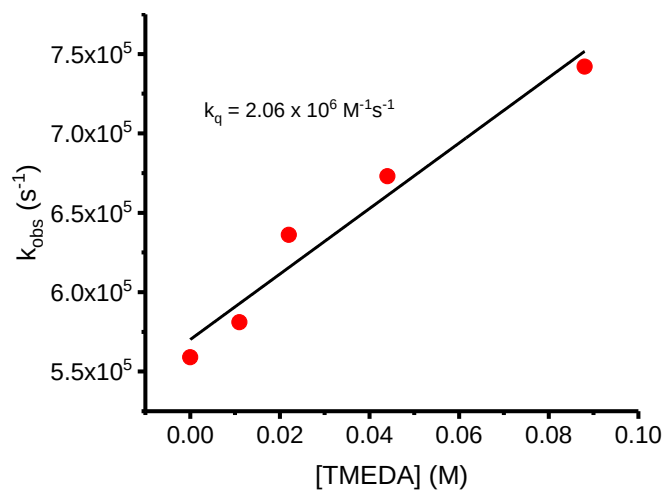


Figure 5.19. Representative kinetic quenching plot for the quenching of $^3\text{Ir}(\text{ppy})_3$ by TMEDA in MeCN using 355 nm laser excitation.

5.7.4 Quenching of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ by *trans*-Stilbene.

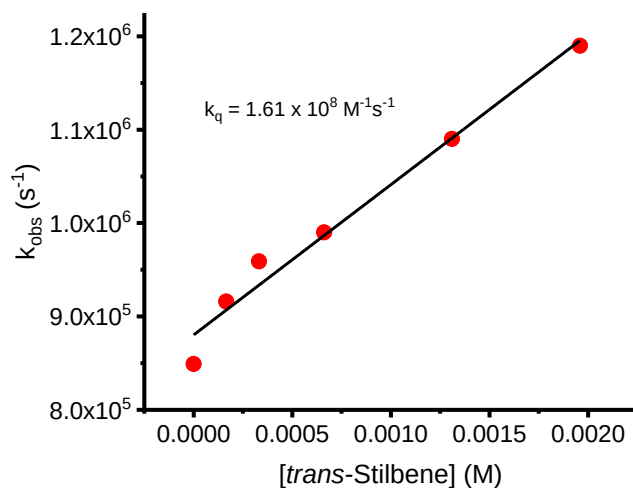


Figure 5.20. Representative kinetic quenching plot for the quenching of $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$ by *trans*-Stilbene in MeCN using 355 nm laser excitation.

5.7.7 Singlet Oxygen ($^1\text{O}_2$) Quenching Experiments.

The $^1\text{O}_2$ quenching experiments were performed using a Nd-YAG laser (532 nm, 10 mJ/pulse) in a LFP-111 laser flash photolysis system (Luzchem Inc., Ottawa, CA). The samples were measured in 1 x 1 cm LFP-Luzchem cuvettes. The LFP system was fitted with a Hamamatsu NIR-PMT which monitored the phosphorescence of $^1\text{O}_2$ at 1270 nm. Excitation of Rose Bengal in CD_3CN at 532 nm was used to sensitize the formation of $^1\text{O}_2$.

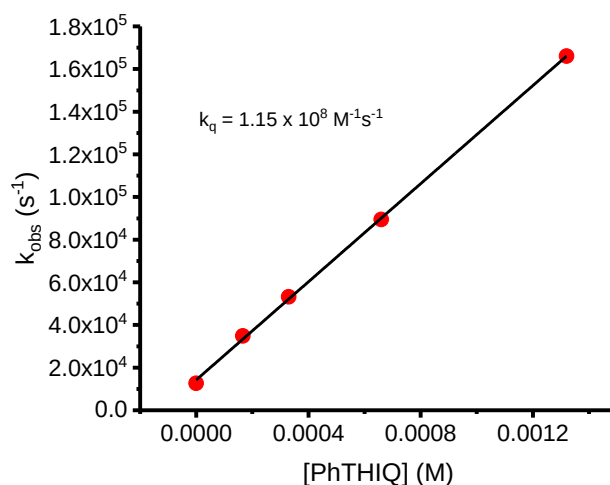


Figure 5.21. Representative kinetic plot for the quenching of $^1\text{O}_2$ by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in CD_3CN . $^1\text{O}_2$ was sensitized by Rose Bengal using 532 nm laser excitation.

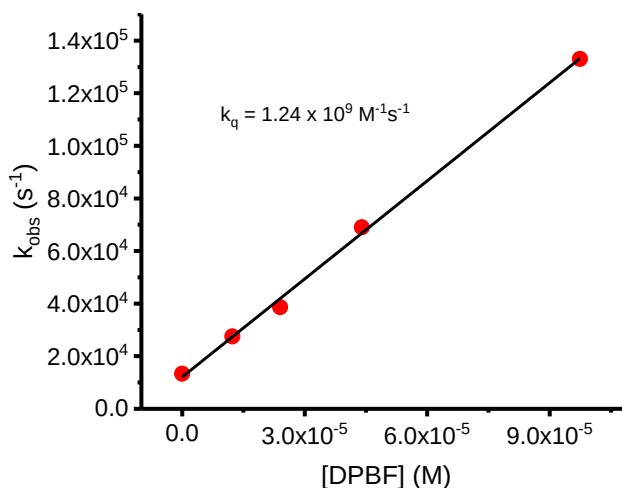


Figure 5.22. Representative kinetic plot for the quenching of $^1\text{O}_2$ by 1,3-diphenylisobenzofuran in CD_3CN . $^1\text{O}_2$ was sensitized by Rose Bengal using 532 nm laser excitation.

5.7.8 Excited State Quenching by 2-Phenyl-1,2,3,4-tetrahydroisoquinoline.

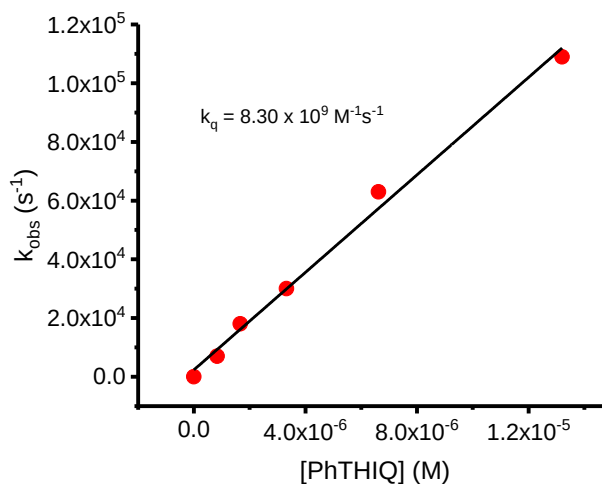


Figure 5.23. Representative kinetic quenching plot for the quenching of $^3\text{Methylene Blue}$ by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 650 nm laser excitation.

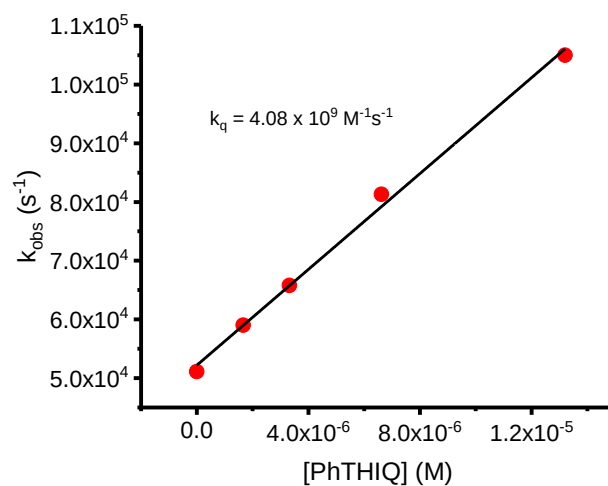


Figure 5.24. Representative kinetic quenching plot for the quenching of $^3\text{Thionin}$ by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in 4:1 MeCN:H₂O using 532 nm laser excitation.

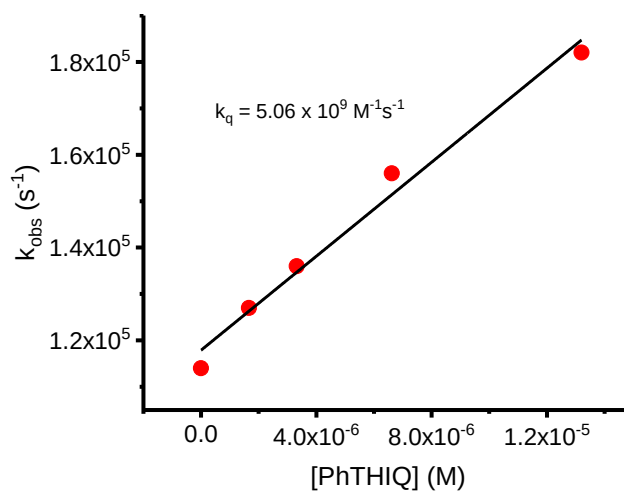


Figure 5.25. Representative kinetic quenching plot for the quenching of $^3\text{New Methylene Blue N}$ by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 532 nm laser excitation.

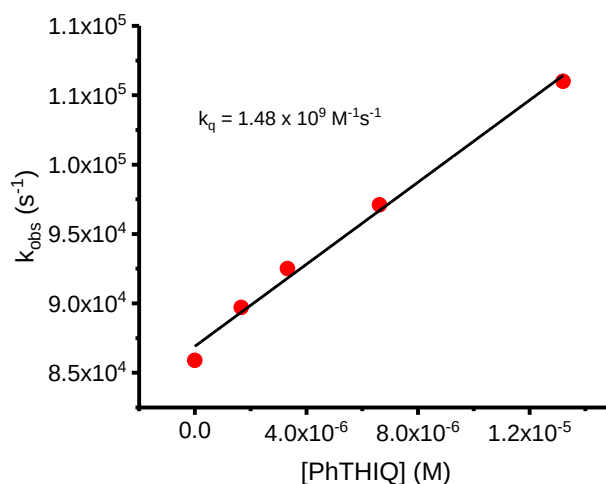


Figure 5.26. Representative kinetic quenching plot for the quenching of ^{3} 1,9-dimethyl Methylene Blue by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 532 nm laser excitation.

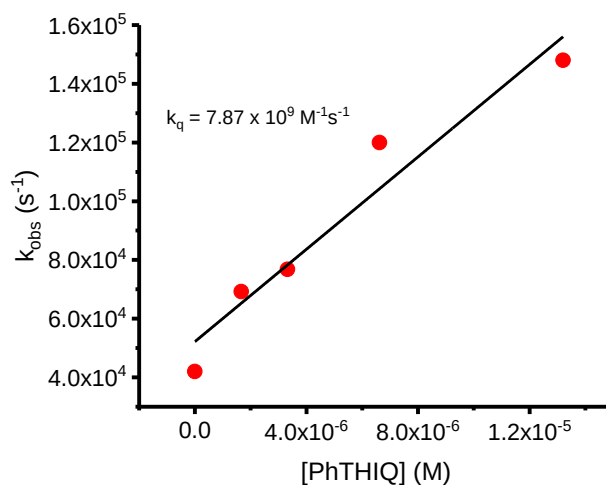


Figure 5.27. Representative kinetic quenching plot for the quenching of ^{3} Methylene Green by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 532 nm laser excitation.

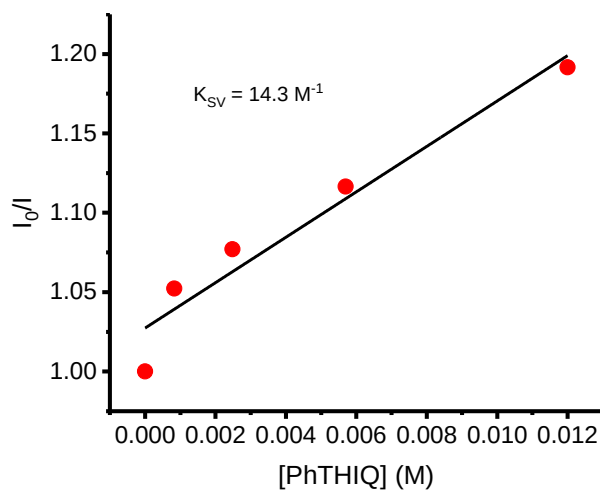


Figure 5.28. Representative Stern-Volmer plot for the quenching of ^{1} Brilliant Cresyl Blue ALD by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 605 nm excitation.

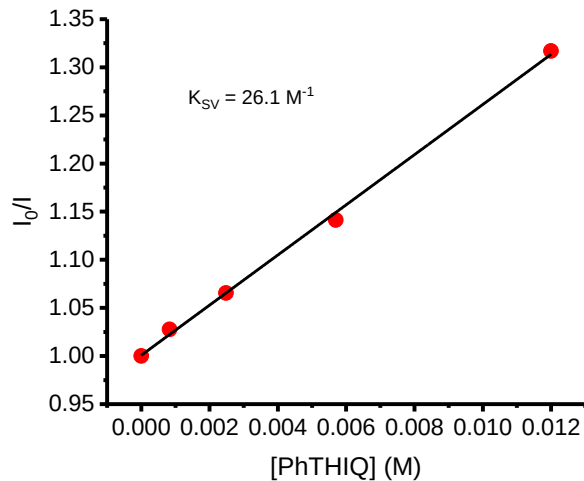


Figure 5.29. Representative Stern-Volmer plot for the quenching of ^{1} Nile Blue by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 605 nm excitation.

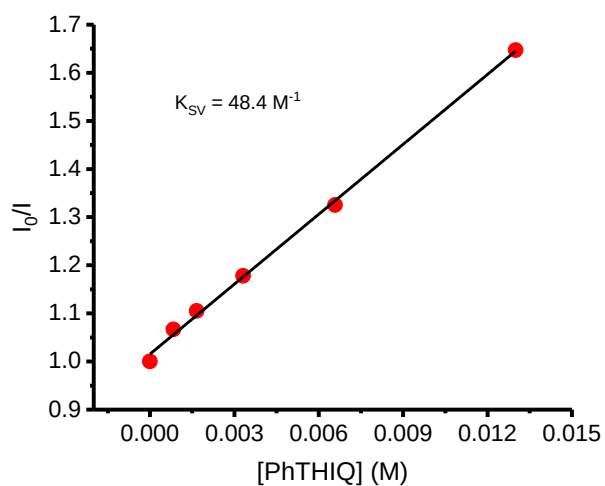


Figure 5.30. Representative Stern-Volmer plot for the quenching of ¹Pyronin Y by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 485 nm excitation.

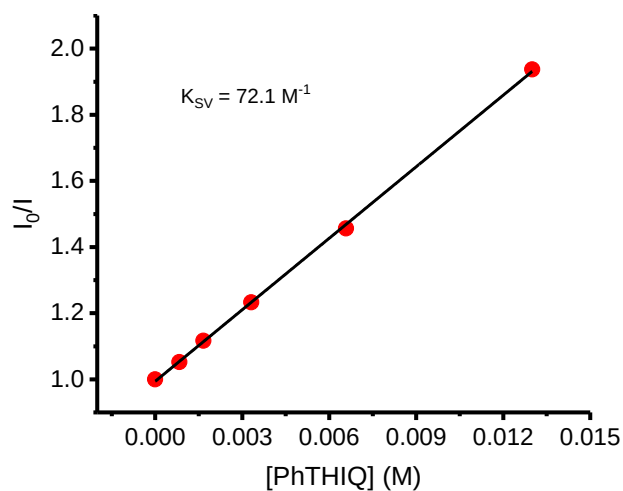


Figure 5.31. Representative Stern-Volmer plot for the quenching of ¹Rhodamine 6G by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 460 nm excitation.

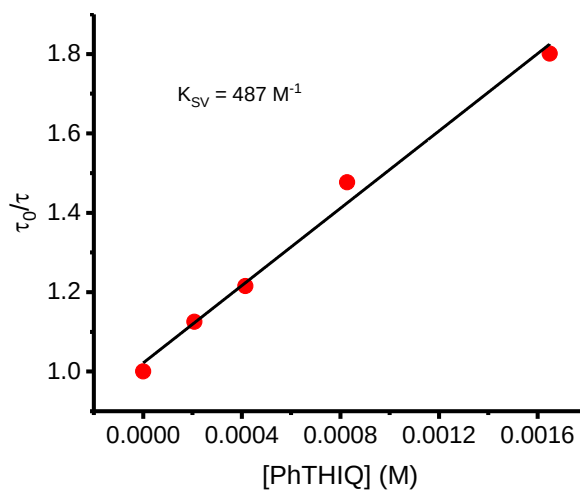


Figure 5.32. Representative Stern-Volmer plot for the quenching of ¹Rhodamine B by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 485 nm excitation.

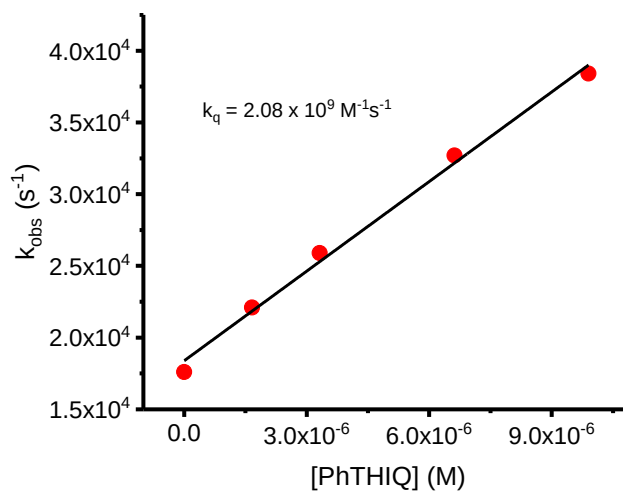


Figure 5.33. Representative kinetic quenching plot for the quenching of ³Phenosafranin by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 532 nm laser excitation.

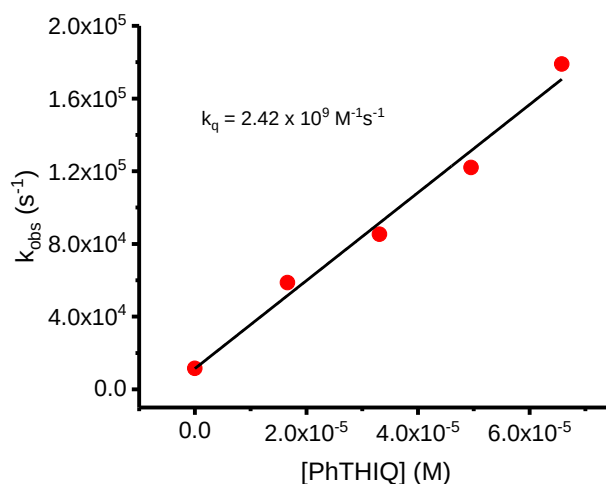


Figure 5.34. Representative kinetic quenching plot for the quenching of $^3\text{Safranin O}$ by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 532 nm laser excitation.

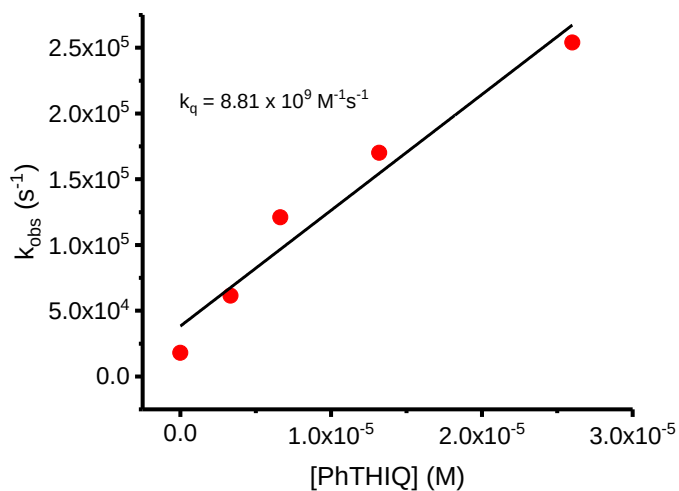


Figure 5.35. Representative kinetic quenching plot for the quenching of $^3\text{Methylene Violet 3RAX}$ by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 532 nm laser excitation.

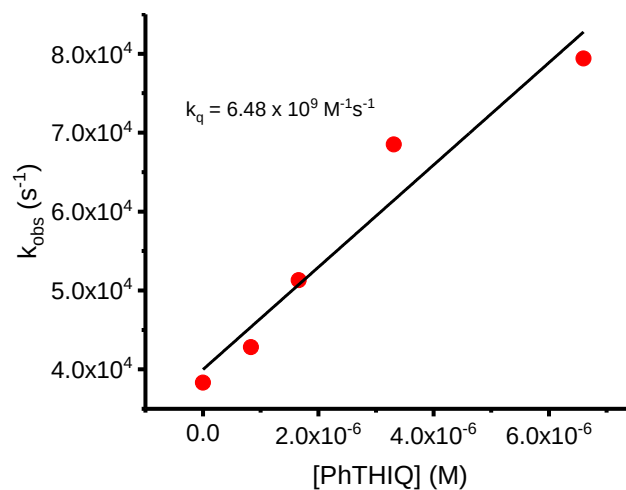


Figure 5.36. Representative kinetic quenching plot for the quenching of $^3\text{Mes-Acr}^+$ by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 430 nm laser excitation.

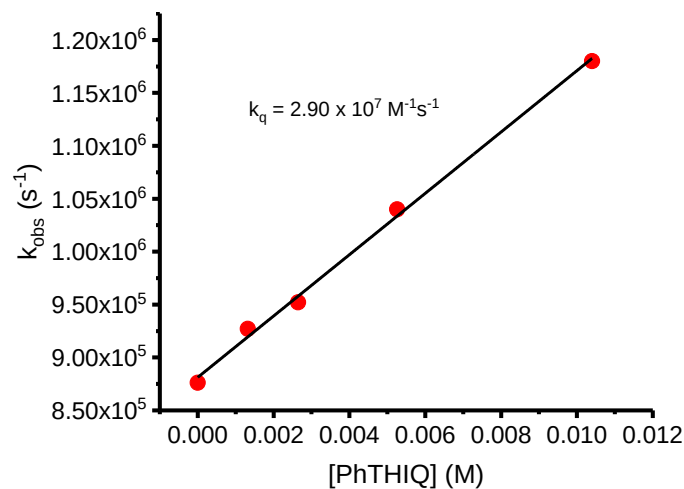


Figure 5.37. Representative kinetic quenching plot for the quenching of $^3\text{Ru}(\text{bpy})_3\text{Cl}_2$ by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 355 nm laser excitation.

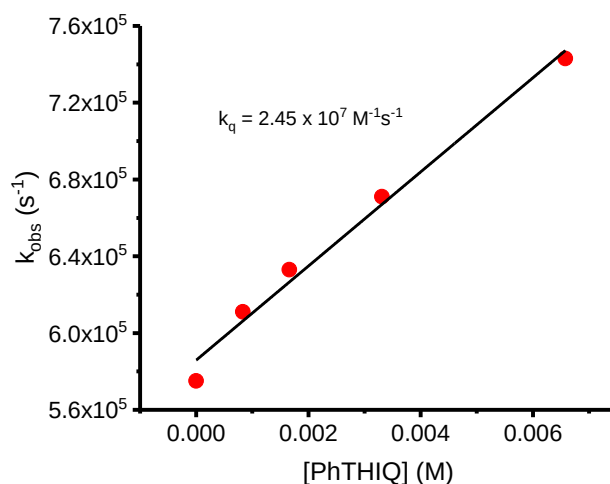


Figure 5.38. Representative kinetic quenching plot for the quenching of $^3\text{Ir}(\text{ppy})_3$ by 2-phenyl-1,2,3,4-tetrahydroisoquinoline in MeCN using 355 nm laser excitation.

5.7.9 Excited State Quenching by O_2 .

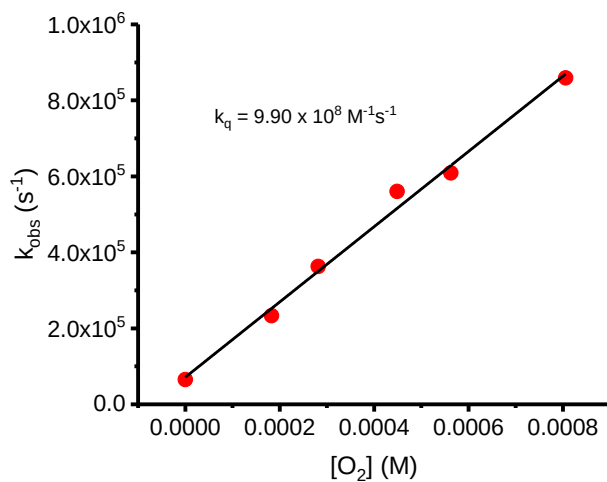


Figure 5.39. Representative kinetic plot for the quenching of $^3\text{New Methylene Blue N}$ by O_2 in MeCN using 532 nm laser excitation.

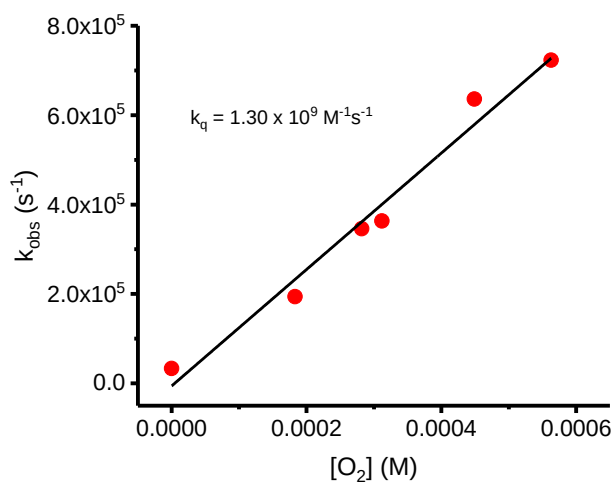


Figure 5.40. Representative kinetic plot for the quenching of $^3\text{1,9-dimethyl Methylene Blue}$ by O_2 in MeCN using 532 nm laser excitation.

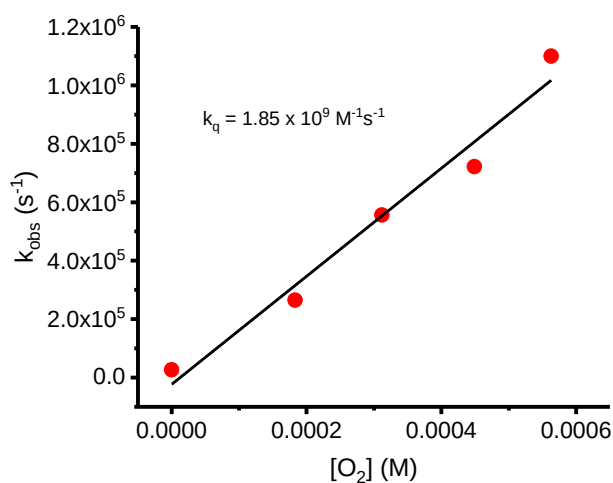


Figure 5.41. Representative kinetic plot for the quenching of $^3\text{Methylene Green}$ by O_2 in MeCN using 532 nm laser excitation.

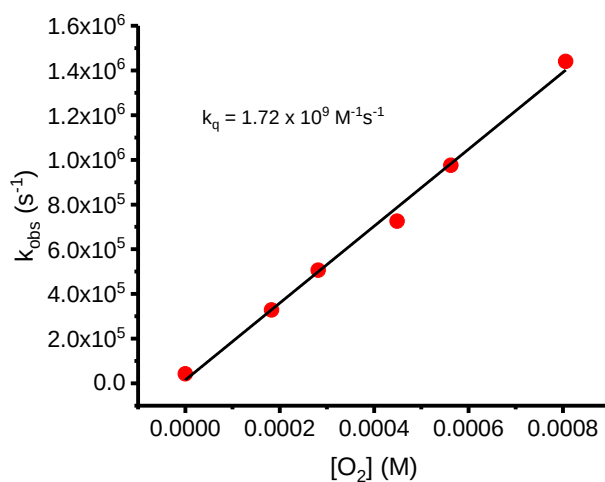


Figure 5.42. Representative kinetic plot for the quenching of $^3\text{Phenosafranin}$ by O_2 in MeCN using 532 nm laser excitation.

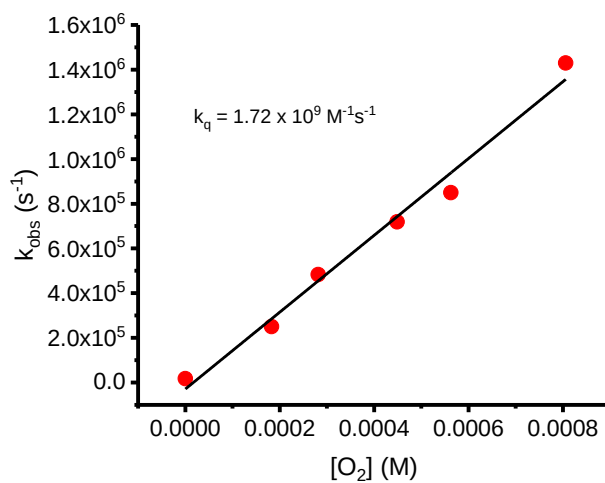


Figure 5.43. Representative kinetic plot for the quenching of $^3\text{Safranin O}$ by O_2 in MeCN using 532 nm laser excitation.

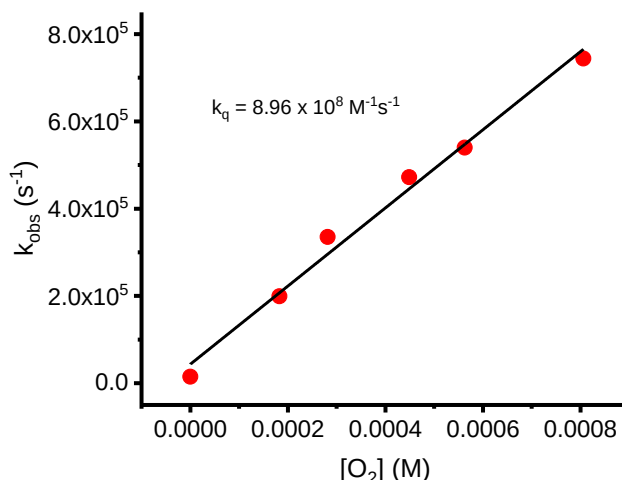


Figure 5.44. Representative kinetic plot for the quenching of ³Methylene Violet 3RAX by O₂ in MeCN using 532 nm laser excitation.

5.8 Determination of Triplet Energies by Laser Flash Photolysis

In order to estimate the triplet energy of the newly characterized dyes, quenchers with known triplet energies were employed, and their bimolecular quenching constants were determined using laser flash photolysis. Once no bimolecular quenching between the dye triplet-state and the quencher was observed ($<10^6 \text{ M}^{-1}\text{s}^{-1}$), the triplet energy was calculated to be the midpoint between the failed quencher and the last successful quencher employed. The data for the determination of the triplet energies are summarized in Tables 5.7-5.10, followed by their corresponding bimolecular quenching plots. All measurements were performed in acetonitrile, unless otherwise noted, using the same general procedure previously described in Section 5.7.1.

Table 5.7. Bimolecular quenching values for New Methylene Blue N and a series of quenchers.

Quencher	Quencher E _T (eV)	k _q (M ⁻¹ s ⁻¹)
O ₂	0.91	9.9 × 10 ⁸
1,3-diphenylisobenzofuran	1.47	2.9±0.5 × 10 ⁸
Perylene ¹	1.53	2.3±0.3 × 10 ⁸
Azulene	1.69	1.2±0.1 × 10 ⁸
9,10-diphenylanthracene ¹	1.77	10 ⁶

¹Performed in CH₂Cl₂

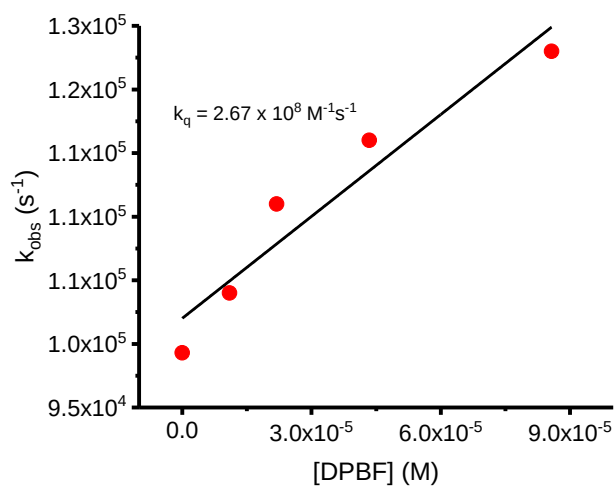


Figure 5.45. Representative kinetic quenching plot for $^3\text{New Methylene Blue N}$ and 1,3-diphenylisobenzofuran in MeCN using 532 nm laser excitation.

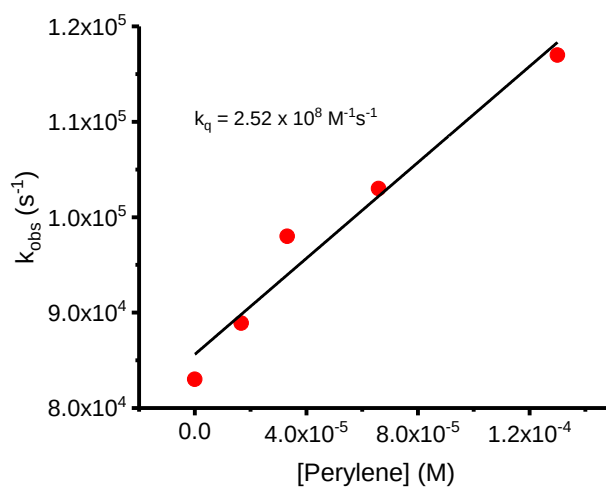


Figure 5.46. Representative kinetic quenching plot for $^3\text{New Methylene Blue N}$ and Perylene in CH_2Cl_2 using 532 nm laser excitation.

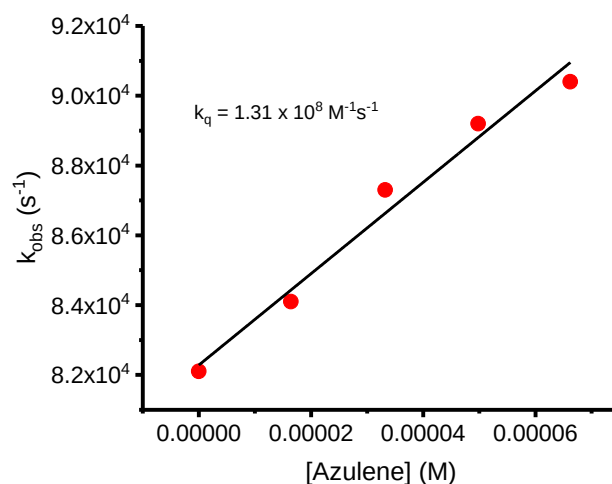


Figure 5.47. Representative kinetic quenching plot for ³New Methylene Blue N and Azulene in MeCN using 532 nm laser excitation.

Table 5.8. Bimolecular quenching values for 1,9-dimethyl Methylene Blue and a series of quenchers.

Quencher	Quencher E_T (eV)	k_q ($M^{-1} s^{-1}$)
O ₂	0.91	1.2×10^9
1,3-diphenylisobenzofuran	1.47	$1.2 \pm 0.4 \times 10^9$
Perylene ¹	1.53	$< 10^6$

¹Performed in CH₂Cl₂.

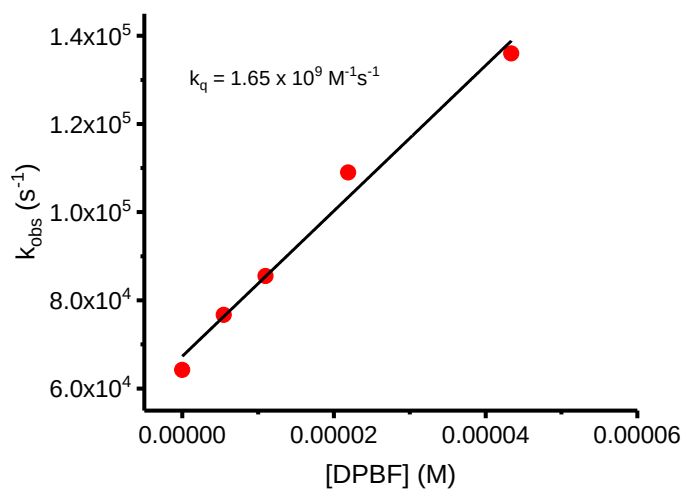
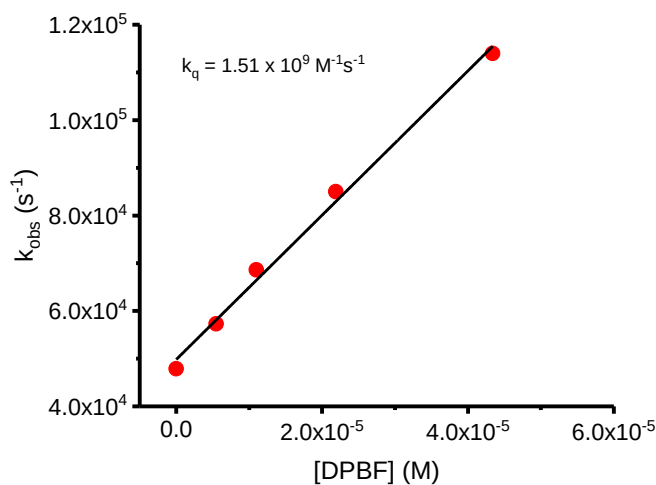


Figure 5.48. Representative kinetic quenching plot for ³1,9-dimethyl Methylene Blue and 1,3-diphenylisobenzofuran in MeCN using 532 nm laser excitation.

Table 5.9. Bimolecular quenching values for Methylene Green and a series of quenchers.

Quencher	Quencher E_T (eV)	k_q ($M^{-1} s^{-1}$)
O ₂	0.91	1.2×10^9
1,3-diphenylisobenzofuran	1.47	$1.6 \pm 0.1 \times 10^9$
Perylene ¹	1.53	$< 10^6$

¹Performed in DMSO.**Figure 5.49.** Representative kinetic quenching plot for ³Methylene Green and 1,3-diphenylisobenzofuran in MeCN using 532 nm laser excitation.**Table 5.10.** Bimolecular quenching values for Methylene Violet 3RAX and a series of quenchers.

Quencher	Quencher E_T (eV)	k_q ($M^{-1} s^{-1}$)
O ₂	0.91	1.2×10^9
Azulene	1.69	$1.8 \pm 0.2 \times 10^9$
9-Anthracenecarboxaldehyde	1.89	$4.1 \pm 0.4 \times 10^8$
Phenazine	1.92	$< 10^6$

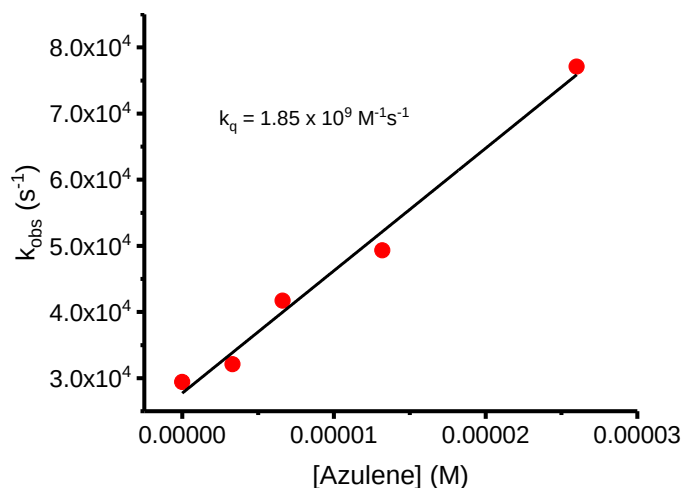


Figure 5.50. Representative kinetic quenching plot for $^3\text{Methylene Violet 3RAX}$ and Azulene in MeCN using 532 nm laser excitation.

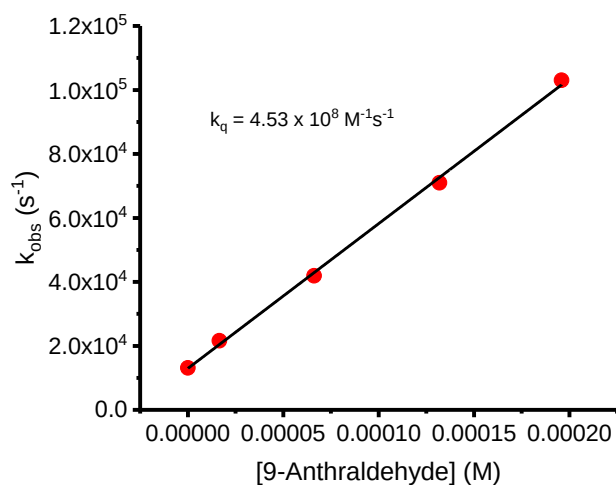


Figure 5.51. Representative kinetic quenching plot for $^3\text{Methylene Violet 3RAX}$ and 9-Anthracenecarboxaldehyde in MeCN using 532 nm laser excitation.

5.9 Cyclic Voltammetry Data

Conditions for cyclic voltammetry measurements: scan rate: 100 mVs^{-1} ; 0.5-2.0 mM of Dye in MeCN (degassed with argon) containing 100 mM Bu_4NClO_4 as the supporting electrolyte; platinum wire working electrode; platinum wire counter electrode; silver wire

pseudo-reference electrode; Fc/Fc⁺ redox couple as an internal reference (0.41 V vs. SCE); reduction potentials reported as peak cathodic (E_{pc}) potentials.

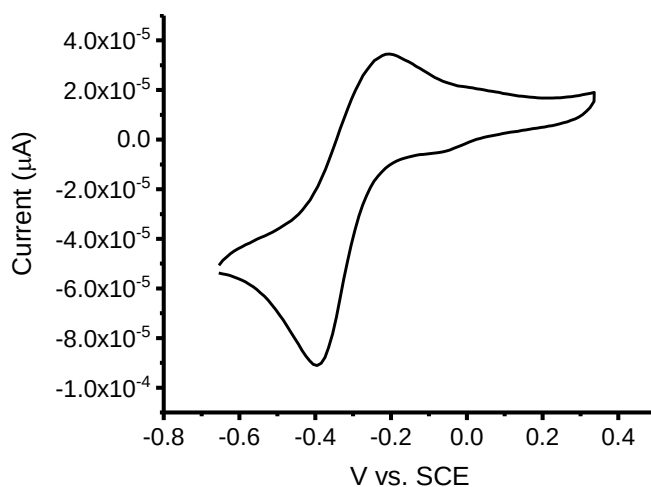


Figure 5.52. Cyclic voltammogram of New Methylene Blue N [Cathodic Scan].

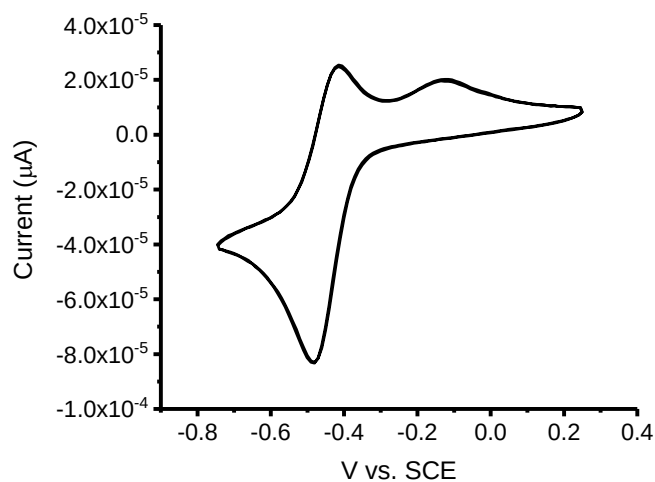


Figure 5.53. Cyclic voltammogram of 1,9-dimethyl Methylene Blue [Cathodic Scan].

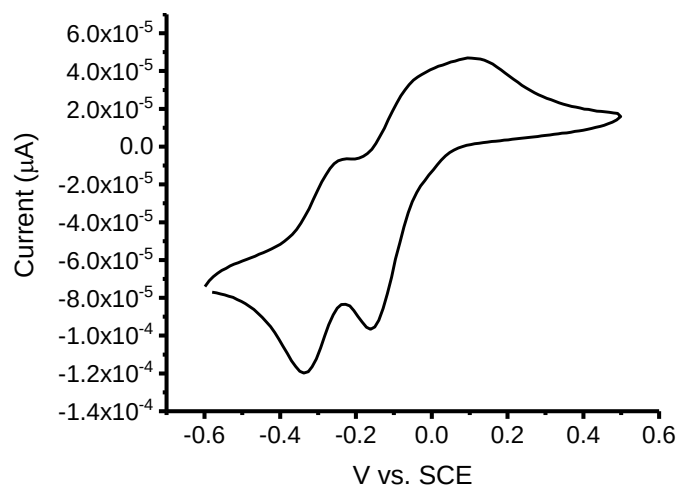


Figure 5.54. Cyclic voltammogram of Methylene Green [Cathodic Scan].

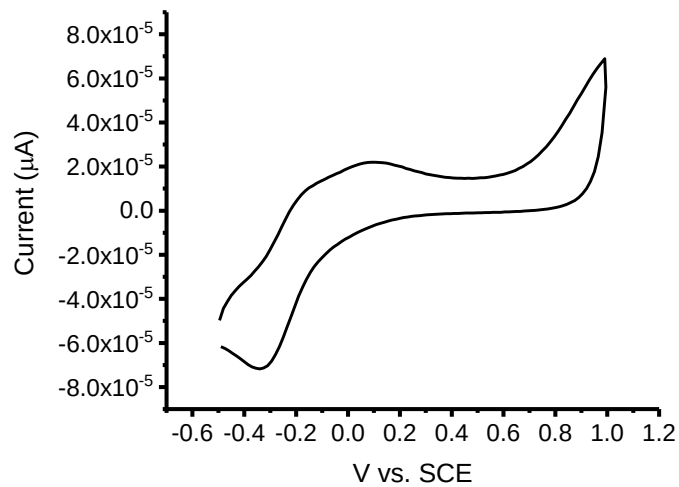


Figure 5.55. Cyclic voltammogram of Brilliant Cresyl Blue ALD [Cathodic Scan].

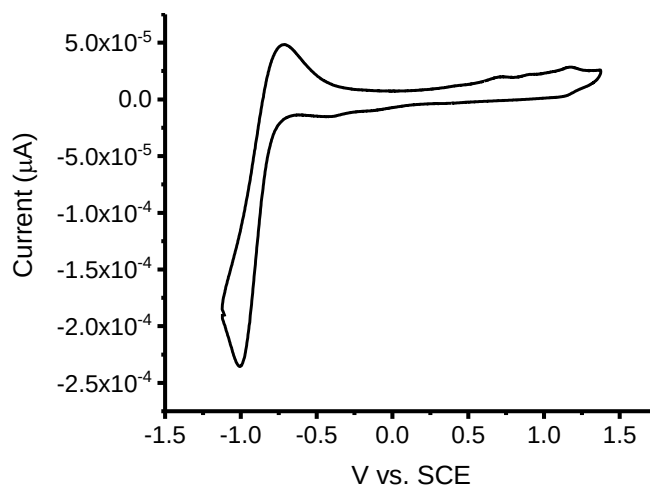


Figure 5.56. Cyclic voltammogram of Nile Blue [Cathodic Scan].

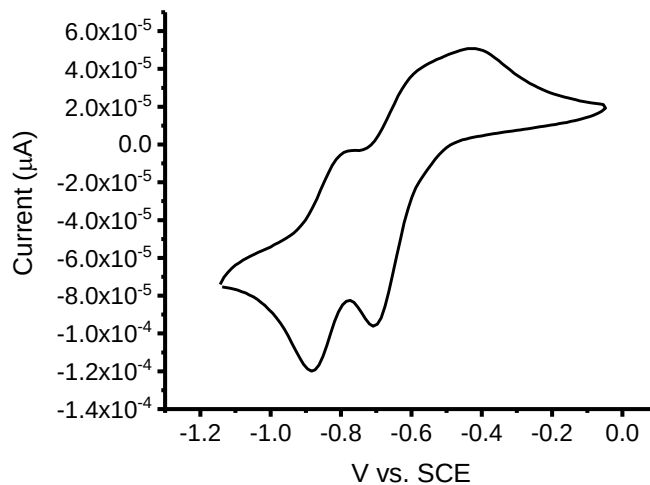


Figure 5.57. Cyclic voltammogram of Pyronin Y [Cathodic Scan].

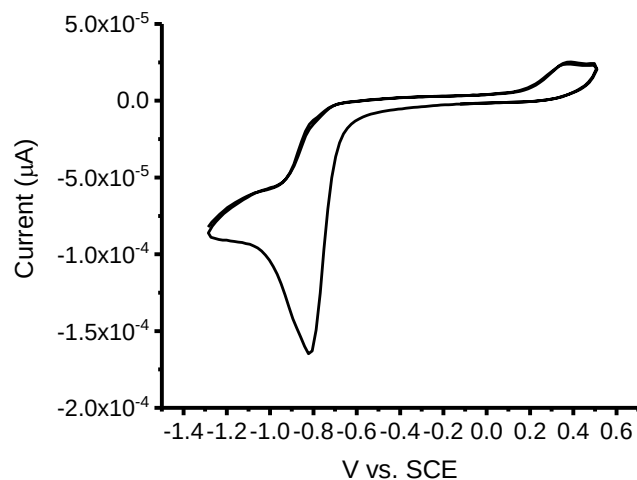


Figure 5.58. Cyclic voltammogram of Rhodamine 6G [Cathodic Scan].

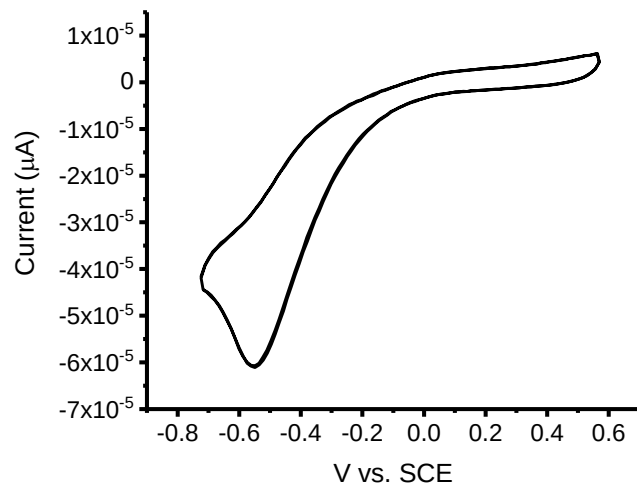


Figure 5.59. Cyclic voltammogram of Rhodamine 6B [Cathodic Scan].

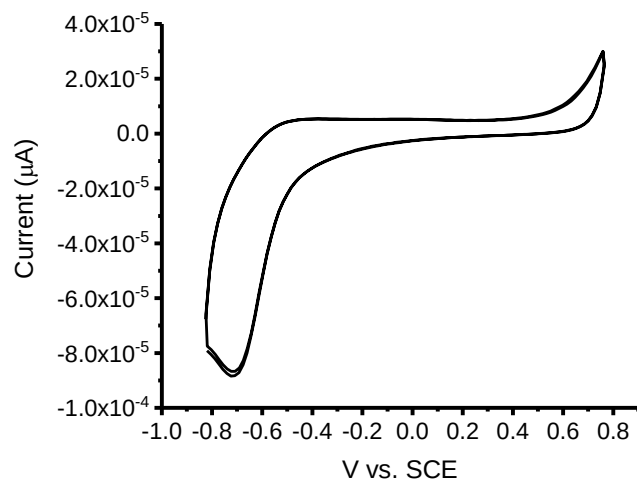


Figure 5.60. Cyclic voltammogram of Phenosafranin [Cathodic Scan].

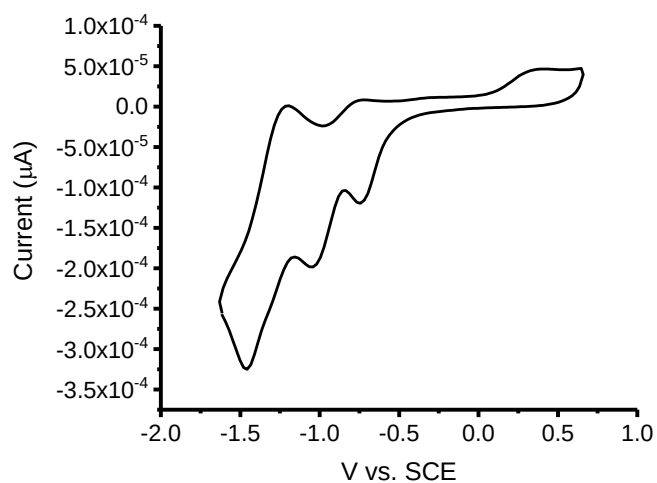


Figure 5.61. Cyclic voltammogram of Safranin O [Cathodic Scan].

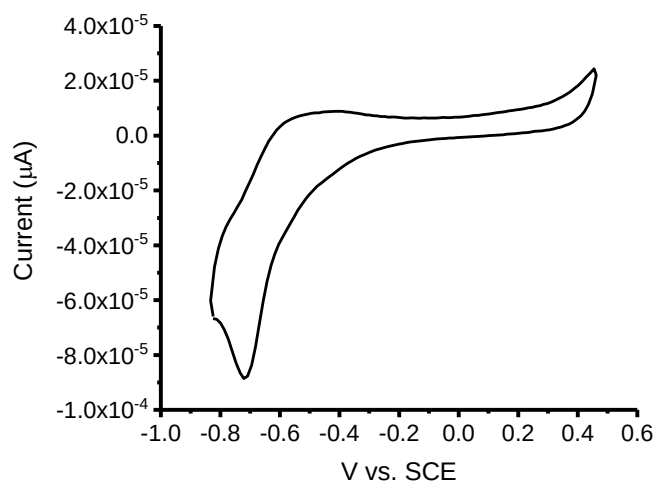
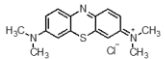
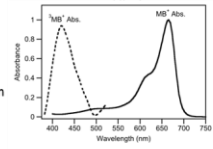


Figure 5.62. Cyclic voltammogram of Methylene Violet 3RAX [Cathodic Scan].

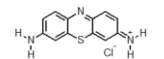
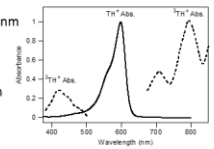
5.10 Appendix of Organic Dyes

Legend

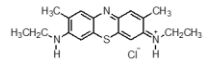
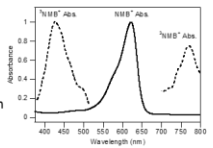
Thiazine Dyes	Oxazine Dyes	Xanthene Dyes	Azine Dyes	Others

Methylene Blue
Formula: $C_{16}H_{18}ClN_3S \cdot xH_2O$ M/W: 319.86 (anhydrous) CAS#: 122965-43-9

Photophysical Properties
Absorption λ_{max} : 664 nm $\epsilon_{664} = 90,000 \text{ M}^{-1}\text{cm}^{-1}$ Triplet Energy: 1.50 eV Triplet τ_0 (MeCN) = 32 μs Transient Absorption λ_{max} : 420 nm Triplet $\epsilon_{420} = 11,000 \text{ M}^{-1}\text{cm}^{-1}$

Electrochemical Properties
$E_{1/2}(\text{MB}^+/\text{MB}) = -0.47 \text{ V vs. SCE}$ $E_{1/2}(\text{MB}^+/\text{MB}) = 0.97 \text{ V vs. SCE}$
Quenching by $^3\text{O}_2$ & Common Amines
$^3\text{O}_2$: $k_q = 2.5 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ <i>N,N,N',N'</i> -tetramethylethylenediamine: $k_q = 3.4 \pm 0.1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ 2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 8.3 \pm 0.1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$
References
<i>J. Chem. Soc. Faraday Trans.</i> 1992 , 88, 2329. <i>J. Am. Chem. Soc.</i> 1980 , 102, 4636. <i>Photochem. Photobiol.</i> 1976 , 24, 395.

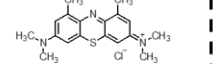
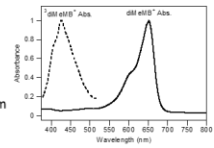
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Thionin
Formula: $C_{12}H_9N_3S \cdot xC_2H_4O_2$ M/W: 287.34 CAS#: 78338-22-4

Photophysical Properties
Absorption λ_{max} (MeCN:H ₂ O): 598 nm $\epsilon_{598}(\text{MeCN:H}_2\text{O}) = 58,000 \text{ M}^{-1}\text{cm}^{-1}$ Triplet Energy: 1.69 eV Triplet τ_0 (MeCN:H ₂ O) = 20 μs Transient Absorption λ_{max} : 780 nm Triplet $\epsilon_{780} = 13,200 \text{ M}^{-1}\text{cm}^{-1}$

Electrochemical Properties
$E_{pc}(\text{TH}^+/\text{TH}^*) = -0.34 \text{ V vs. SCE}$ $E_{pc}(\text{TH}^+/\text{TH}^*) = 1.35 \text{ V vs. SCE}$
Quenching by $^3\text{O}_2$ & Common Amines
$^3\text{O}_2$: $k_q = 4.5 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ <i>N,N,N',N'</i> -tetramethylethylenediamine: $k_q = 7.2 \pm 0.7 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ 2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 4.3 \pm 0.4 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$
References
<i>J. Chem. Soc. Faraday Trans.</i> 1992 , 88, 2329. <i>J. Phys. Chem.</i> 1977 , 81, 1104. <i>Z. Phys. Chem.</i> 1970 , 69, 113.

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New Methylene Blue N
Formula: $C_{18}H_{22}ClN_3S$ M/W: 347.91 CAS#: 1934-16-3

Photophysical Properties
Absorption λ_{max} : 622 nm $\epsilon_{622} = 18,000 \text{ M}^{-1}\text{cm}^{-1}$ Triplet Energy: $1.73 \pm 0.05 \text{ eV}$ Triplet τ_0 (MeCN) = 11 μs Transient Absorption λ_{max} : 430 nm

Electrochemical Properties
$E_{pc}(\text{NMB}^+/\text{NMB}^*) = -0.39 \text{ V vs. SCE}$ $E_{pc}(\text{NMB}^+/\text{NMB}^*) = 1.34 \text{ V vs. SCE}$
Quenching by $^3\text{O}_2$ & Common Amines
$^3\text{O}_2$: $k_q = 9.9 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ <i>N,N,N',N'</i> -tetramethylethylenediamine: $k_q = 3.3 \pm 0.1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ 2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 5.9 \pm 0.8 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$

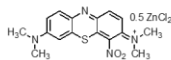
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1,9-Dimethyl Methylene Blue
Formula: $C_{18}H_{22}ClN_3S$ M/W: 347.91 CAS#: 931418-92-7

Photophysical Properties
Absorption λ_{max} : 652 nm $\epsilon_{652} = 85,000 \text{ M}^{-1}\text{cm}^{-1}$ Triplet Energy: $1.50 \pm 0.04 \text{ eV}$ Triplet τ_0 (MeCN) = 12 μs Transient Absorption λ_{max} : 425 nm

Electrochemical Properties
$E_{pc}(\text{diMeMB}^+/\text{diMeMB}^*) = -0.47 \text{ V vs. SCE}$ $E_{pc}(\text{diMeMB}^+/\text{diMeMB}^*) = 1.03 \text{ V vs. SCE}$
Quenching by $^3\text{O}_2$ & Common Amines
$^3\text{O}_2$: $k_q = 1.2 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ <i>N,N,N',N'</i> -tetramethylethylenediamine: $k_q = 7.2 \pm 0.6 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ 2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 1.5 \pm 0.4 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$

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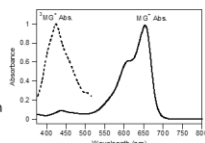
Methylene Green

Formula: $C_{18}H_{22}ClN_3S \cdot 0.5ZnCl_2$
M/W: 416.05
CAS#: 931418-92-7



Photophysical Properties

Absorption λ_{max} : 654 nm
 $\epsilon_{654} = 60,000 \text{ M}^{-1}\text{cm}^{-1}$
Triplet Energy: $1.50 \pm 0.04 \text{ eV}$
Triplet τ_0 (MeCN) = 14 μs
Transient Absorption λ_{max} : 425 nm



Electrochemical Properties

$E_{PC}(\text{MG}^+/\text{MG}^{\bullet}) = -0.22 \text{ V vs. SCE}$
 $E_{PC}^*(\text{MG}^+/\text{MG}^{\bullet}) = 1.28 \text{ V vs. SCE}$

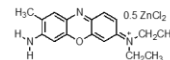
Quenching by $^3\text{O}_2$ & Common Amines

$^3\text{O}_2$: $k_q = 1.9 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$
N,N,N',N'-tetramethylethylenediamine: $k_q = 1.0 \pm 0.1 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$
2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 7.4 \pm 0.5 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$



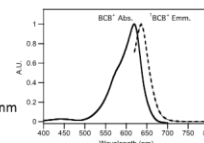
Brilliant Cresyl Blue ALD

Formula: $C_{17}H_{20}N_3OCl \cdot 0.5ZnCl_2$
M/W: 385.96
CAS#: 81029-05-2



Photophysical Properties

Absorption λ_{max} : 616 nm
 $\epsilon_{616} = 45,000 \text{ M}^{-1}\text{cm}^{-1}$
Singlet Energy: 1.98 eV
Singlet τ_0 (MeCN) = 0.51 ns
Fluorescence Emission λ_{max} : 636 nm



Electrochemical Properties

$E_{PC}(\text{BCB}^+/\text{BCB}^{\bullet}) = -0.31 \text{ V vs. SCE}$
 $E_{PC}^*(\text{BCB}^+/\text{BCB}^{\bullet}) = 1.67 \text{ V vs. SCE}$

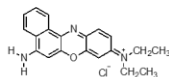
Quenching by Common Amines

N,N,N',N'-tetramethylethylenediamine: $k_q = 1.0 \pm 0.1 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$
2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 2.5 \pm 0.1 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$



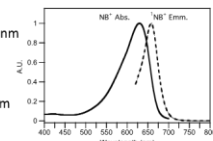
Nile Blue

Formula: $C_{20}H_{20}N_3OCl$
M/W: 353.85
CAS#: 2381-85-3



Photophysical Properties

Absorption λ_{max} (MeCN:H₂O): 630 nm
 ϵ_{630} (MeCN:H₂O) = $56,000 \text{ M}^{-1}\text{cm}^{-1}$
Singlet Energy: 1.92 eV
Singlet τ_0 (MeCN) = 1.76 ns
Fluorescence Emission λ_{max} : 660 nm



Electrochemical Properties

$E_{PC}(\text{NB}^+/\text{NB}^{\bullet}) = -1.05 \text{ V vs. SCE}$
 $E_{PC}^*(\text{NB}^+/\text{NB}^{\bullet}) = 0.87 \text{ V vs. SCE}$

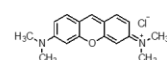
Quenching by Common Amines

N,N,N',N'-tetramethylethylenediamine: $k_q = 7.5 \pm 1.0 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$
2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 1.4 \pm 0.3 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$



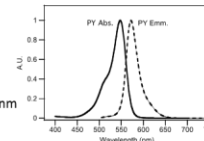
Pyronin Y

Formula: $C_{17}H_{19}N_3OCl$
M/W: 302.80
CAS#: 92-32-0



Photophysical Properties

Absorption λ_{max} : 547 nm
 $\epsilon_{547} = 62,000 \text{ M}^{-1}\text{cm}^{-1}$
Singlet Energy: 2.21 eV
Singlet τ_0 (MeCN) = 1.87 ns
Fluorescence Emission λ_{max} : 572 nm



Electrochemical Properties

$E_{PC}(\text{PY}^+/\text{PY}^{\bullet}) = -0.74 \text{ V vs. SCE}$
 $E_{PC}^*(\text{PY}^+/\text{PY}^{\bullet}) = 1.47 \text{ V vs. SCE}$

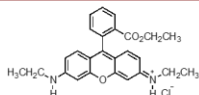
Quenching by Common Amines

N,N,N',N'-tetramethylethylenediamine: $k_q = 5.2 \pm 0.3 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$
2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 3.2 \pm 0.7 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$



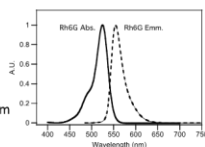
Rhodamine 6G

Formula: $C_{26}H_{27}N_2O_3Cl$
M/W: 450.96
CAS#: 989-38-8



Photophysical Properties

Absorption λ_{max} : 524 nm
 $\epsilon_{524} = 78,000 \text{ M}^{-1}\text{cm}^{-1}$
Singlet Energy: 2.29 eV
Singlet τ_0 (MeCN) = 4.65 ns
Fluorescence Emission λ_{max} : 555 nm



Electrochemical Properties

E_{PC} (Rh6G[•]/Rh6G^{•+}) = -0.81 V vs. SCE
 E_{PC}^* (Rh6G[•]/Rh6G^{•+}) = 1.48 V vs. SCE

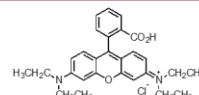
Quenching by Common Amines

N,N,N',N'-tetramethylethylenediamine: $k_q = 8.1 \pm 0.3 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$
2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 1.6 \pm 0.1 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$



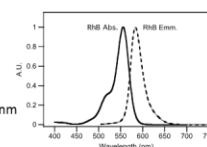
Rhodamine B

Formula: $C_{28}H_{31}N_2O_3Cl$
M/W: 479.01
CAS#: 81-88-9



Photophysical Properties

Absorption λ_{max} : 555 nm
 $\epsilon_{555} = 108,000 \text{ M}^{-1}\text{cm}^{-1}$
Singlet Energy: 2.17 eV
Singlet τ_0 (MeCN) = 1.50 ns
Fluorescence Emission λ_{max} : 583 nm



Electrochemical Properties

E_{PC} (RhB[•]/RhB^{•+}) = -0.55 V vs. SCE
 E_{PC}^* (RhB[•]/RhB^{•+}) = 1.62 V vs. SCE

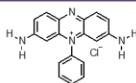
Quenching by Common Amines

N,N,N',N'-tetramethylethylenediamine: $k_q = 2.7 \pm 0.5 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$
2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 3.3 \pm 0.1 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$



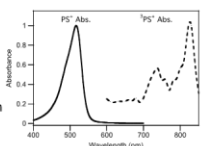
Phenosafranin

Formula: $C_{18}H_{15}N_4Cl$
M/W: 322.79
CAS#: 81-93-6



Photophysical Properties

Absorption λ_{max} : 517 nm
 $\epsilon_{517} = 44,000 \text{ M}^{-1}\text{cm}^{-1}$
Triplet Energy: 1.77 eV
Triplet τ_0 (MeCN) = 63 μs
Transient Absorption λ_{max} : 830 nm
Triplet $\epsilon_{830} = 20,400 \text{ M}^{-1}\text{cm}^{-1}$



Electrochemical Properties

E_{PC} (PS[•]/PS^{•+}) = -0.69 V vs. SCE
 E_{PC}^* (PS[•]/PS^{•+}) = 1.08 V vs. SCE

Quenching by $^3\text{O}_2$ & Common Amines

$^3\text{O}_2$: $k_q = 1.7 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$
N,N,N',N'-tetramethylethylenediamine: $k_q = 4.8 \pm 0.2 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$
2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 2.5 \pm 0.5 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$

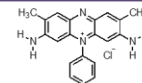
References

J. Chem. Soc. Faraday Trans. **1992**, 88, 2329.
J. Photochem. Photobiol., A. **2005**, 173, 115.



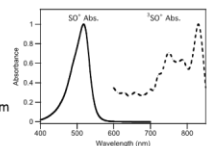
Safranin O

Formula: $C_{20}H_{19}N_4Cl$
M/W: 350.84
CAS#: 477-73-6



Photophysical Properties

Absorption λ_{max} : 518 nm
 $\epsilon_{518} = 46,000 \text{ M}^{-1}\text{cm}^{-1}$
Triplet Energy: 1.78 eV
Triplet τ_0 (MeCN) = 67 μs
Transient Absorption λ_{max} : 845 nm
Triplet $\epsilon_{845} = 22,200 \text{ M}^{-1}\text{cm}^{-1}$



Electrochemical Properties

E_{PC} (SO[•]/SO^{•+}) = -0.71 V vs. SCE
 E_{PC}^* (SO[•]/SO^{•+}) = 1.07 V vs. SCE

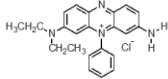
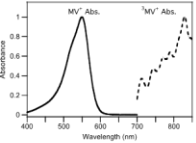
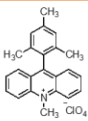
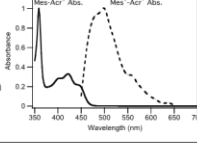
Quenching by $^3\text{O}_2$ & Common Amines

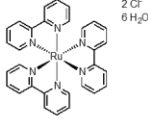
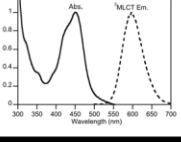
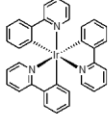
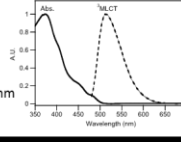
$^3\text{O}_2$: $k_q = 1.7 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$
N,N,N',N'-tetramethylethylenediamine: $k_q = 2.0 \pm 0.3 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$
2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 2.7 \pm 0.2 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$

References

J. Chem. Soc. Faraday Trans. **1992**, 88, 2329.
J. Photochem. Photobiol., A. **2005**, 173, 115.



Methylene Violet 3RAX Formula: $C_{23}H_{23}N_4Cl$ M/W: 378.90 CAS#: 4569-86-2  Photophysical Properties Absorption λ_{max}: 550 nm $\epsilon_{550} = 44,000 \text{ M}^{-1}\text{cm}^{-1}$ Triplet Energy: $1.90 \pm 0.01 \text{ eV}$ Triplet τ_0 (MeCN) = 78 μs Transient Absorption λ_{max}: 830 nm  Electrochemical Properties E_{PC} (MV3RAX/MV3RAX*) = -0.73 V vs. SCE E_{PC} (3MV3RAX*/MV3RAX*) = 1.17 V vs. SCE Quenching by $^3O_2$ & Common Amines $^3O_2$: $k_q = 8.9 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ <i>N,N,N',N'</i>-tetramethylethylenediamine: $k_q = 2.8 \pm 0.2 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ 2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 8.4 \pm 0.7 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ References <i>J. Am. Chem. Soc.</i> 2004, 126, 1600. <i>J. Am. Chem. Soc.</i> 2005, 127, 16054.	9-Mesityl-10-methylacridinium Formula: $C_{23}H_{22}ClNO_4$ M/W: 411.88 CAS#: 674783-97-2  Photophysical Properties Absorption λ_{max}: 422 nm $\epsilon_{422} = 5,600 \text{ M}^{-1}\text{cm}^{-1}$ Triplet Energy: 2.37 eV Triplet τ_0 (MeCN) = 27 μs Transient Absorption λ_{max}: 500 nm  Electrochemical Properties E_{PC} (Mes-Acr*/Mes-Acr*) = -0.47 V vs. SCE E_{PC} (1 Mes*-Acr*/Mes-Acr*) = 2.08 V vs. SCE Quenching by $^3O_2$ & Common Amines $^3O_2$: $k_q = 6.8 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ <i>N,N,N',N'</i>-tetramethylethylenediamine: $k_q = 4.1 \pm 0.4 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$ 2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 7.1 \pm 0.8 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ References <i>J. Am. Chem. Soc.</i> 2004, 126, 1600. <i>J. Am. Chem. Soc.</i> 2005, 127, 16054.

Tris(2,2'-bipyridyl)dichlororuthenium(II) Formula: $C_{30}H_{24}Cl_2N_6Ru \cdot 6H_2O$ M/W: 748.62 CAS#: 50525-27-4  Photophysical Properties Absorption λ_{max}: 454 nm $\epsilon = 15,000 \text{ M}^{-1}\text{cm}^{-1}$ Triplet Energy: 2.12 eV Triplet τ_0 (MeCN) = 1.1 μs Phosphorescence Emission λ_{max}: 605 nm  Electrochemical Properties $E_{1/2}$ (Ru^{3+}/Ru^{2+}) = 1.25 V vs. SCE $E_{1/2}$ (Ru^{3+}/Ru^+) = -1.28 V vs. SCE $E_{1/2}$ (Ru^{3+}/Ru^{2+}) = -0.86 V vs. SCE $E_{1/2}$ ($^3Ru^{2+}/Ru^+$) = 0.84 V vs. SCE Quenching by $^3O_2$ & Common Amines $^3O_2$: $k_q = 3.0 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ <i>N,N,N',N'</i>-tetramethylethylenediamine: $k_q = 1.2 \pm 0.6 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ 2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 2.9 \pm 0.7 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ References <i>Coord. Chem. Rev.</i> 1988, 84, 85.	fac-Tris(2-phenylpyridinato-$C^{2'}$, N)iridium(III) Formula: $C_{33}H_{24}N_3Ir$ M/W: 654.78 CAS#: 94928-86-6  Photophysical Properties Absorption λ_{max}: 375 nm $\epsilon_{375} = 7,200 \text{ M}^{-1}\text{cm}^{-1}$ Triplet Energy: 2.51 eV Triplet τ_0 (MeCN) = 1.7 μs Phosphorescence Emission λ_{max}: 512 nm  Electrochemical Properties $E_{1/2}$ (Ir^{4+}/Ir^{3+}) = 0.77 V vs. SCE $E_{1/2}$ (Ir^{3+}/Ir^{2+}) = -2.19 V vs. SCE $E_{1/2}$ (Ir^{3+}/Ir^{2+}) = -1.73 V vs. SCE $E_{1/2}$ ($^3Ir^{2+}/Ir^+$) = 0.31 V vs. SCE Quenching by $^3O_2$ & Common Amines $^3O_2$: $k_q = 4.6 \times 10^{10} \text{ M}^{-1}\text{s}^{-1}$ <i>N,N,N',N'</i>-tetramethylethylenediamine: $k_q = 2.6 \pm 0.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ 2-Phenyl-1,2,3,4-tetrahydroisoquinoline: $k_q = 3.1 \pm 0.7 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ References <i>Top. Curr. Chem.</i> 2007, 281, 143.

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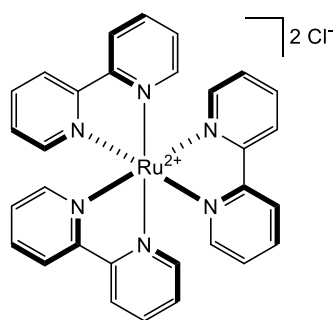
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6. A Ru(bpy)₃Cl₂ Based Visible Light Actinometer

6.1 Characterization of Chain Processes in Photoredox Catalysis

The field of photoredox catalysis has gained increasing attention in recent years due to its wide applicability in sustainable organic synthesis. One of the key driving forces responsible for the growth of this field relies on the use of photosensitizers that take advantage of the “visible light” wavelengths of the electromagnetic spectrum (400-700 nm), providing less harsh conditions than traditional UV-promoted photochemical reactions. This is enticing for chemists looking for “greener” reaction conditions, however, perhaps more importantly, it also aids in avoiding possible side reactions or product decomposition as most simple organic molecules do not absorb in the “visible light” range. Large ranges of photosensitizers including transition-metal complexes and metal-free compounds have been employed in a wide variety of chemical transformations.¹⁻³ With that being said, the vast majority of reported photoredox transformations employ the photocatalyst *tris*(2,2'-bipyridyl)ruthenium(II) chloride (Ru(bpy)₃Cl₂, Figure 6.1). Ru(bpy)₃Cl₂, despite being a precious-metal catalyst, offers a variety of advantages, which include a visible light absorbing metal-to-ligand charge-transfer band (MLCT), and a relatively long-lived and stable excited state.⁴ Like all diamagnetic molecules, upon excitation to the lowest energy excited state, Ru(bpy)₃Cl₂ becomes both a stronger electron-donor and acceptor than in the ground state.⁵ Coupled with its long-lived ³MLCT excited state, this allows for favourable conditions for single-electron-transfer (SeT) reactions, which has been highly exploited in the recent literature.

**Photochemical Properties**

Absorption λ_{max} : 454 nm
 $\epsilon = 14,600 \text{ M}^{-1} \text{ cm}^{-1}$
 Excited State: $^3\text{MLCT}$
 Triplet Energy: 2.12 eV
 τ_0 (MeCN): 1100 ns
 Emission λ_{max} : 605 nm

Redox Properties

$E_{1/2} (\text{Ru}^{2+}/\text{Ru}^{3+}) = +1.29 \text{ V vs. SCE}$
 $E_{1/2} (\text{Ru}^{2+}/\text{Ru}^+) = -1.33 \text{ V vs. SCE}$
 $E_{1/2} (\text{Ru}^{3+}/^*\text{Ru}^{2+}) = -0.81 \text{ V vs. SCE}$
 $E_{1/2} (^*\text{Ru}^{2+}/\text{Ru}^+) = +0.77 \text{ V vs. SCE}$

Figure 6.1. The photophysical and electrochemical properties of the popular Ru(bpy)₃Cl₂ photocatalyst. Properties listed correspond to data presented in Chapter 5.

Despite all the recent advancements in this field, many of the new discoveries take place in the absence of excited state kinetics as well as an understanding of the underlying mechanisms. Throughout this dissertation, the usefulness of laser flash photolysis (LFP) techniques for determining bimolecular rate constants of mechanistically key steps, which provided insights into the overall reaction mechanism, was demonstrated. Other techniques that could be powerful tools are visible light actinometry and the “rotating sector” method (*vide infra*).^{6,7} In many cases throughout the literature, the proposed mechanisms often suggest the possibility of a chain propagating reaction and are generally probed through intermittent irradiation with on/off times in the minute timescale. This method, however, does not provide any insights into a possible chain reaction, as chain reactions are normally terminated within milliseconds-to-seconds after the illumination source is turned off. While intermittent illumination can be a useful technique to characterize chain propagation, the on/off times must be on the same order of the lifetime of the propagating chain to gain any insights on the possible participation of chain propagation. This can be achieved by employing the “rotating sector” method, which can achieve light pulses in the millisecond time regime.⁷

The use of intermittent illumination in photochemical reactions was initially suggested in 1929 by Briers, Chapman, and Walters⁸, but was not put into practice until 1946 when Burnett and Melville applied it to the photo-polymerization of vinyl acetate.⁷ The technique has since become known as the “rotating sector” method as they employed a rotating sectorized disk in the path of the light source to produce the intermittent illumination. Using this set-up, the light/dark ratio could be controlled by modifying the size and/or number of sectors on the disk, and the light on/off periods could be adjusted by changing the speed at which the disk rotated.

In a typical rotating sector experiment, the light is interrupted in such a way that the period of irradiation (t_{on}) is followed by an off time (t_{off}) that is equal to or longer than that of t_{on} . When the flashing rate is slow, t_{on} is much longer than the radical lifetime which causes the radical concentration to quickly increase to the value reached during steady-state irradiation.⁹ However, since the period over which the radicals decay is short in comparison to the dark period (t_{off}), during the slow flashing cycle, the radical concentration drops off to essentially zero whenever the light is off. On the other hand, if the flashing rate is increased to the point where t_{on} and t_{off} are significantly shorter than chain lifetime (τ_s), the situation becomes much different. Under these conditions, the radicals generated during a single t_{on} period will continue to grow through several successive on-off cycles until the concentration of radicals eventually levels off.⁹ Experimentally, this translates to a higher probability of chain terminating events occurring, therefore it would be expected that fast flashing will result in lower yields compared to when slow flashing is employed, where the radical chains are longer lived due to the decreased probability of termination. Therefore, as long as the intensity of irradiation and the total irradiation time are kept constant, a difference in the average rate of reaction for the fast and slow flashing

experiments should be observed, with the change in rate becoming apparent as the t_{off} time reaches that of the radical chain lifetime (τ_s).⁹

One of the simplest ways to observe the change in reaction rate when moving from fast to slow flashing is to plot the percent conversion of the reaction versus $\log(t_{on})$ of the flashing cycle. Qualitatively, the presence of chain propagation can be confirmed by demonstrating a non-linear relationship between short and long flashing times. Semi-quantitatively, the average lifetime of the propagating chain (τ_s) can also be estimated and is equal to the point of 50% change if a non-linear relationship is observed. For example, for the oxidation of diphenylmethanol mediated by Ru(bpy)₃Cl₂ and 4-cyano-*N*-methoxypyridinium tetrafluoroborate (Figure 6.2), τ_s was estimated to be 19 ms.¹⁰

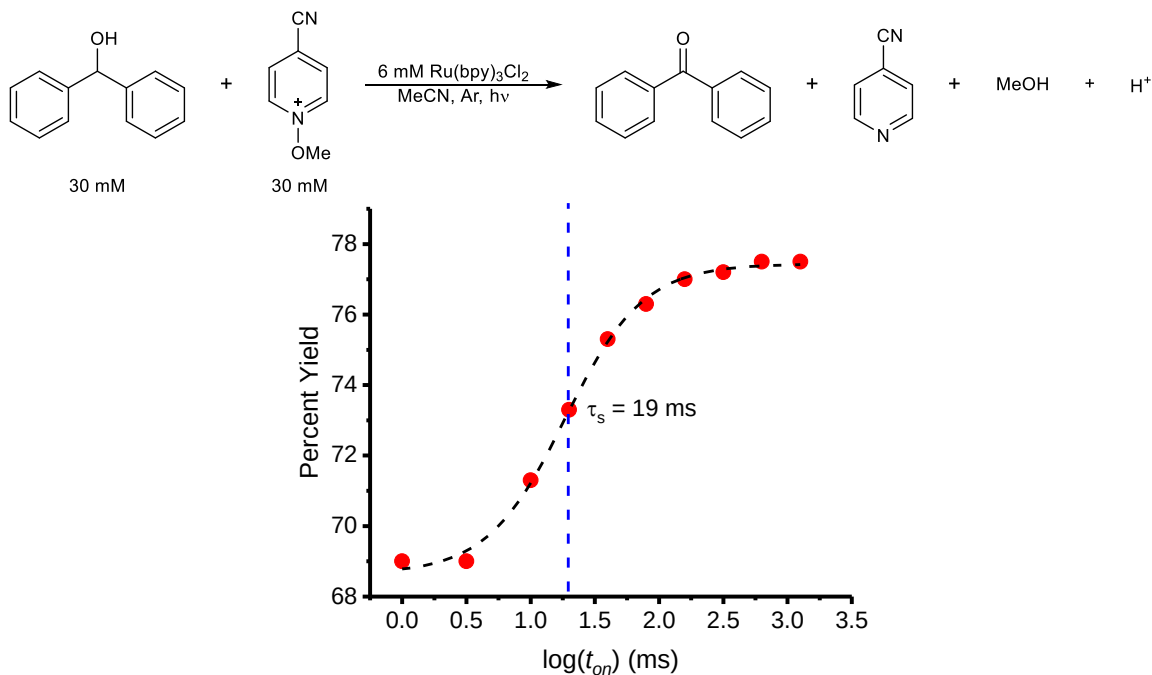


Figure 6.2. Conversion of diphenylmethanol to benzophenone as a function of $\log(t_{on})$ in milliseconds.¹⁰

While intermittent illumination employing the “rotating sector” method may be one of the more conclusive ways to demonstrate the presence of a chain reaction, and perhaps the

simplest way to determine the average lifetime of chain propagation, the requirement for specialized equipment renders widespread implementation of the technique difficult. Another technique for probing chain propagation in photochemical reactions is to determine the quantum yield (Φ) of a reaction.¹¹ Determining the Φ of a photochemical reaction requires the ability to measure the number of molecules consumed or produced during a given period of irradiation as well as the number of photons absorbed by the sample during the same time period. It is important to make the distinction here between incident and absorbed photons, as only photons that are absorbed by the sample can produce a chemical change. For this reason, the Φ of a photochemical reaction can be defined by equation (1), below.

$$\Phi = \frac{\text{\# of molecules consumed or produced per unit time}}{\text{\# of photons absorbed per unit time}} \quad (1)$$

Considering that in most cases the number of moles consumed or produced can be easily determined through a variety of different analytical techniques, all that is required to determine the Φ of a reaction is the moles of photons (i.e., einsteins) absorbed by the sample during the irradiation period. One such method to obtain this number is to perform chemical actinometry experiments, where the energy delivered to a particular sample within a defined spectral range and geometry can be determined.¹⁰ Although any photoactive system for which the Φ is known could be used as an actinometer, the ability to quickly and conveniently determine the number of actinometer molecules reacted can influence the utility and applicability of the system. For example, one of the most widely employed chemical actinometers for UV and visible light wavelengths up to 500 nm is the ferrioxalate actinometer, in which the number of molecules reacted can easily be determined by UV-Vis spectrophotometry.¹² However, there exist some drawbacks to this system. For example, the Φ of the ferrioxalate system is dependent on the wavelength of

irradiation, therefore requiring precise spectral matching with the photosensitizer of the reaction of interest, which can be cumbersome. The ferrioxalate actinometer is also extremely sensitive, and can therefore only withstand short irradiation periods at low powers. This is particularly disadvantageous for practitioners of photoredox catalysis, who typically employ high powered LED light sources. In order to overcome these issues, we envisioned that a visible light actinometer based on Ru(bpy)₃Cl₂ would be the perfect solution. With such a system, one could perform a photoredox transformation using Ru(bpy)₃Cl₂ as the photocatalyst with the same concentration of Ru(bpy)₃Cl₂ as the actinometer, and the Φ could easily be determined. The need for spectral matching would be completely eliminated, as the actinometer and the photocatalyst would be the same molecule, greatly simplifying the determination of Φ for the photoredox reaction of interest.

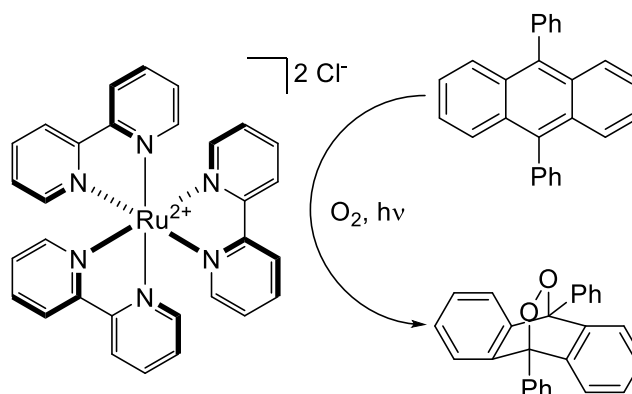
When employing chemical actinometry to study photochemical reactions, a $\Phi > 2$ is needed to confirm the presence of propagating chains. Technically speaking, a $\Phi > 1$ should imply the presence of a chain reaction, as more than 1 mole is consumed or produced per photon absorbed. However, there can be cases where the Φ is greater than 1 and does not involve a chain reaction. For example, one could envision a reaction involving a homolytic cleavage of a symmetrical molecule as easily having a Φ as high as 2 if a single cleaving event results in two product molecules; in other words, stoichiometric factors can result in values in the 1-to-2 range. On the other hand, having a $\Phi < 1$ does not imply that no chain reaction is involved. If the initiation step is inefficient, this could result in a lower value for the Φ , even if chain propagation is involved. In summary, chemical actinometry can confirm the presence of a chain reaction if the value for Φ is greater than 2. However, if the value for Φ is less than 1, it does not necessarily rule out the involvement of propagating chains.

Another implication of these types of mechanistic investigations for photoredox catalysis is that one could determine if a photoredox reaction is truly catalytic in nature, or if it is simply a means to initiate radical chain propagation. While actinometry would be a powerful tool in this regard, this technique alone would not be enough to differentiate between a truly catalytic reaction and an initiated chain reaction with low initiation efficiencies. In this case, actinometric measurements should be coupled with intermittent illumination experiments, such as those described in this chapter, as a truly catalytic reaction should not be affected by the temporal profile of illumination.

In this chapter, the development and characterization of a visible light actinometer to probe chain reactions in photoredox catalysis based on the popular photocatalyst, Ru(bpy)₃Cl₂, is presented. The utility of the newly developed Ru(bpy)₃Cl₂ actinometric system was also examined by employing the actinometer to characterize the Ru(bpy)₃Cl₂-catalyzed oxidation of diphenylmethanol to benzophenone employing a pyridinium salt as the chain amplifier, a known chain reaction.

6.2 Development of a Ru(bpy)₃Cl₂ Based Visible Light Actinometer

In order to develop a simple but yet effective visible light actinometer, it was important to base the new Ru(bpy)₃Cl₂ actinometer on well-established photochemistry. Therefore, we decided to base the actinometer on well-known singlet oxygen (¹O₂) chemistry, specifically, the oxidation of 9,10-diphenylanthracene (DPA) to its corresponding endoperoxide.¹³ A general scheme outlining the proposed actinometric system is presented in Scheme 6.1. Following photosensitization of Ru(bpy)₃Cl₂ with visible light irradiation, the ³MLCT excited state is quenched by oxygen to form ¹O₂, which occurs at an efficiency of 0.57.¹⁴ ¹O₂ can then be quenched by DPA to form the corresponding endoperoxide.



Scheme 6.1. General scheme for the proposed Ru(bpy)₃Cl₂ visible light actinometer based on the singlet oxygen-mediated oxidation of 9,10-diphenylanthracene.

DPA exhibits a distinct absorption band at 372 nm, which is not obscured by the MLCT band of Ru(bpy)₃Cl₂ ($\lambda_{\text{max}} = 454$ nm), that can be easily monitored by UV-Vis spectroscopy, allowing for facile quantification of this actinometric system. Furthermore, employing DPA in a visible light actinometric system comes with the added advantage that DPA does not absorb in the visible light region (Figure 6.3). Since Ru(bpy)₃Cl₂ is generally excited with visible light in photoredox processes, side reactions from the direct excitation of DPA by the light source can be avoided.

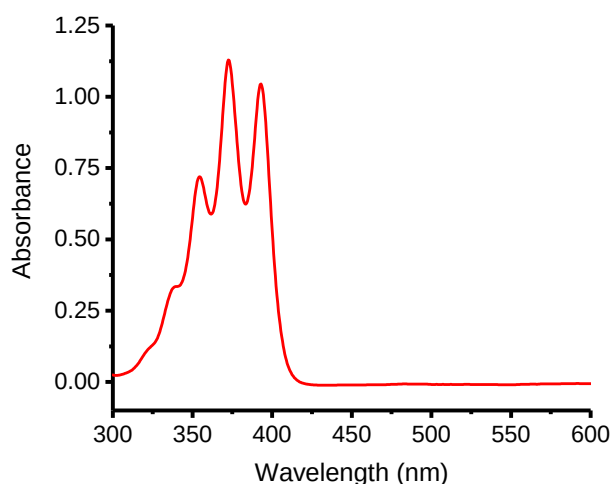


Figure 6.3. Absorption spectrum of 9,10-diphenylanthracene (0.10 mM) in MeCN.

In order to monitor the consumption of DPA when employing the actinometer, the extinction coefficient at 372 nm was needed in order to determine the concentration of DPA at a given period of irradiation using the Beer Lambert law.¹⁵ By measuring the absorption at 372 nm as a function of the concentration of DPA, the extinction coefficient can be calculated from the slope of the corresponding plot and was determined to be 11,100 M⁻¹cm⁻¹ (Figure 6.4).

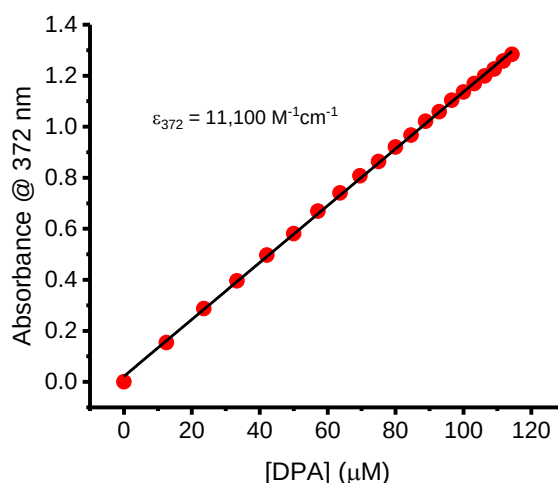


Figure 6.4. Absorption at 372 nm as a function of the concentration of 9,10-diphenylanthracene in MeCN for the determination of the extinction coefficient at 372 nm.

The typical results of a visible light actinometry experiment with the newly developed Ru(bpy)₃Cl₂/DPA system can be seen in Figure 6.5. As mentioned, the consumption of DPA can be easily monitored by following the band at 372 nm, and by using the extinction coefficient at 372 nm, which was measured to be 11,100 M⁻¹cm⁻¹, the concentration of DPA can be easily calculated using the Beer Lambert Law at any given irradiation time. It is important to note here that when employing this actinometer system, the user should always measure a spectrum of a separate solution of Ru(bpy)₃Cl₂ at the same concentration employed in the actinometer. This will ensure that all of the DPA was not consumed during the period of irradiation, as Ru(bpy)₃Cl₂ also absorbs at 372 nm.

Complete consumption of all the DPA before the period of irradiation is finished could result in inaccurate values when calculating the number of photons absorbed, ultimately affecting Φ calculations.

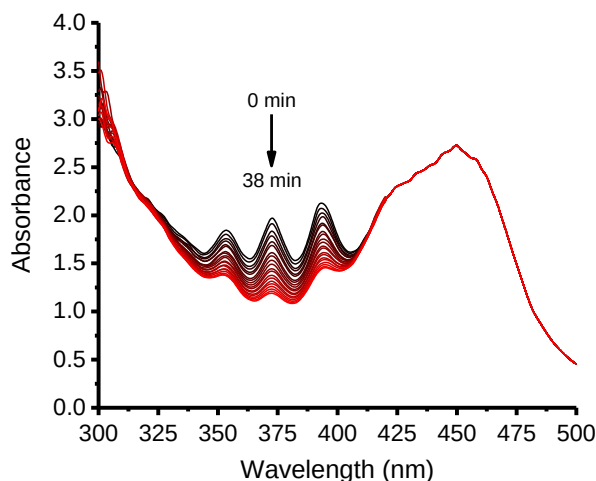


Figure 6.5. Absorption spectra of a typical Ru(bpy)₃Cl₂ actinometer experiment performed with 0.19 mM Ru(bpy)₃Cl₂ and 0.10 mM DPA in MeCN and irradiated with a 460 nm LED equipped with a 440 nm notch filter.

In order to determine the Φ of the actinometric system, the intensity of our light source was required. In order to determine this value, an actinometer with a known quantum yield at the same wavelength as the LED light source employed needed to be chosen. For this task, the ferrioxalate system was chosen due to its known reliability in the wavelength range we required.¹² Both the absorbance of the sample and actinometer were matched at 440 nm, and a 440 nm notch filter was employed to simplify lamp-sample spectral overlap (Figure 6.6). It is important to note that this filter was used only to calibrate the Ru(bpy)₃Cl₂ actinometer, and is not needed by users employing the Ru(bpy)₃Cl₂ actinometer itself. The only requirement is that the light source has no significant emission below 400 nm to avoid direct excitation of DPA.

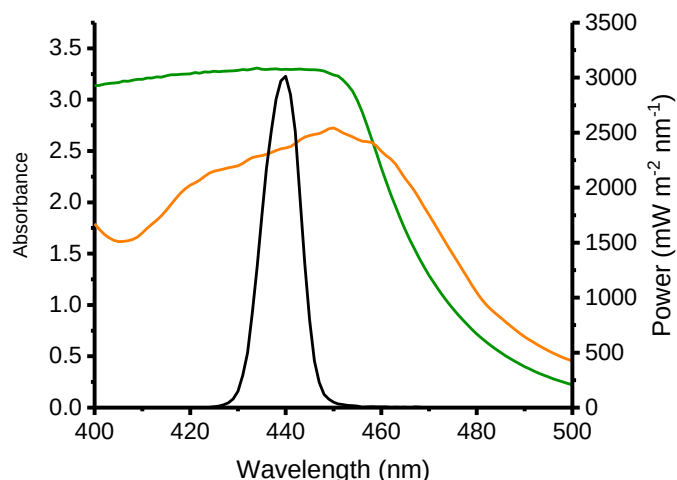


Figure 6.6. Overlay of the emission spectrum of the 460 nm LED fitted with 440 nm notch filter (FWHM 10 nm, black) with the absorption spectra of the Ru(bpy)₃Cl₂ (orange) and potassium ferrioxalate (green) solutions.

In order to determine the effective intensity of the 460 nm LED fitted with a 440 nm notch filter (FWHM 10 nm), the ferrioxalate actinometer was employed. The results of these experiments are presented in Table 6.1.

Table 6.1. Results from ferrioxalate actinometry experiments.

Trial	Sample absorption @ 510 nm		
	A _{Light}	A _{Dark}	A _{Light} - A _{Dark}
1	1.402	0.121	1.281
2	1.400	0.134	1.266
3	1.381	0.148	1.233
Average	1.394	0.134	1.260

Experimental Details: 3 mL samples were irradiated for 1 minute in 1 cm x 1 cm quartz cuvettes. [Potassium ferrioxalate] = 0.15 M. Samples were developed by adding 500 μ L of 0.1% buffered phenanthroline solution.

From these data, the concentration of ferrous ions produced after 1 minute of irradiation can be calculated using equation (2):

$$[Fe^{2+}] = \frac{A_{Light} - A_{Dark}}{\epsilon_{510} l} \quad (2)$$

where A_{Light} is the absorbance of the actinometer after 1 minute of irradiation, A_{Dark} is the absorbance of a second actinometer sample which was left in the dark, ϵ_{510} is the extinction coefficient of the actinometer at 510 nm, and *l* is the pathlength. After 1 minute

of irradiation, it was determined that the concentration of ferrous ions was 1.135×10^{-4} M. Knowing the volume of the sample employed was 3.5 mL (see Section 6.5.3), the moles of ferrous ions produced can be calculated, which was found to be 3.97×10^{-7} mol. Finally, the moles of photons, or einsteins, being absorbed by the ferrioxalate actinometer can be calculated using equation (3):

$$\frac{N h \nu}{t} = \frac{\text{moles of } Fe^{2+}}{\Phi t F} \quad (3)$$

where Φ is the quantum yield of the actinometer, which is known to be 1.01, and F is the fraction of light absorbed.¹² By using the previously mentioned values obtained after 1 minute of irradiation, the intensity of the light source being absorbed by the ferrioxalate sample was calculated to be 6.5×10^{-9} einsteins s⁻¹. Therefore, any sample with an absorbance above 2 (>99% photons absorbed) within the wavelengths of irradiation and using the same geometry will absorb 6.5×10^{-9} einsteins s⁻¹. Finally, by employing equation (4):

$$\Phi = \frac{-d/dt[DPA]}{6.5 \times 10^{-9} \text{ einsteins s}^{-1}} \quad (4)$$

the Φ for the newly developed visible light Ru(bpy)₃Cl₂ actinometer was calculated to be 0.019 ± 0.001 . While the Φ of the actinometer is considerably lower than other visible light systems, such as the ferrioxalate system, it provides the advantage of being easier to work with compared to the other chemical actinometers, as it can withstand the longer irradiation times and higher light intensities typically employed in photoredox transformations. Further, no developing agent is required, as is the case in the ferrioxalate system.¹² This system is also comprised of all commercially available reagents, shows a linear relationship to the power dependence of the light source (Figure 6.7), and there are no concerns relating to wavelength specificity, as the actinometer is also the photocatalyst.

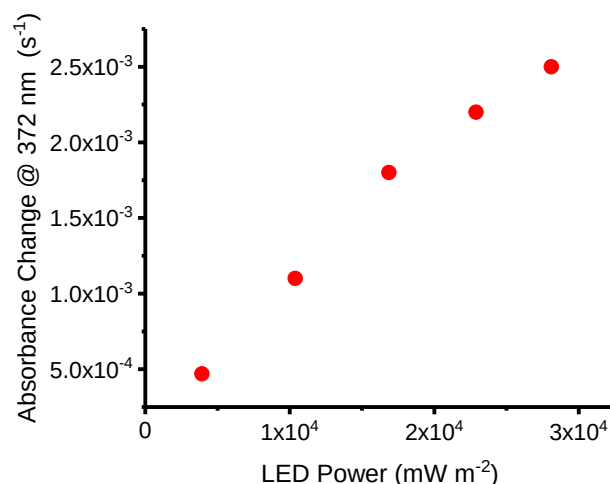


Figure 6.7. Rate of change in absorbance at 372 nm as a function of LED power. Data was plotted as an average over 3 trials.

In order to explain the low efficiency of the Ru(bpy)₃Cl₂/DPA actinometer, the kinetics of the system was examined using LFP (Table 6.2). By determining the bimolecular quenching constants for the mechanistically key steps, equations (5) and (6) can be used to calculate the percentage of ³MLCTs quenched by oxygen and the percentage of ¹O₂ quenched by DPA under initial reaction conditions.

Table 6.2. Bimolecular rate constants (k_q) and ¹O₂ generation efficiency (f_{Δ}^T) of all the mechanistically key steps in our actinometer system.^{14,16,17}

Quenching of ³ Ru(bpy) ₃ Cl ₂			
Quencher	k _q (M ⁻¹ s ⁻¹)	f _Δ ^T	
O ₂	2.97±0.30 x 10 ⁹	0.57	
DPA	5.13±0.39 x 10 ⁹		
Quenching of ³ DPA			
Quencher	k _q (M ⁻¹ s ⁻¹)	f _Δ ^T	
O2	3 x 10 ⁹	1.0	
Quenching of ¹ O ₂			
Quencher	k _q (M ⁻¹ s ⁻¹)		
DPA	2.00±0.25 x 10 ⁶		

For experimental conditions, see section 6.6.

$$\% \text{ } ^3\text{Ru(bpy)}_3\text{Cl}_2 \text{ quenched by O}_2 = \frac{100\% \times k_q^{O_2}[\text{O}_2]}{\tau_0^{-1} + k_q^{O_2}[\text{O}_2] + k_q^{DPA}[\text{DPA}]} \quad (5)$$

$$\% \text{ } ^1\text{O}_2 \text{ quenched by DPA} = \frac{100\% \times k_q^{DPA}[\text{DPA}]}{\tau_0^{-1} + k_q^{DPA}[\text{DPA}]} \quad (6)$$

From the bimolecular quenching constants reported in Table 6.2, equations (5) and (6) can be used to calculate that under initial reaction conditions, 77% of the ³Ru(bpy)₃Cl₂ are intercepted by oxygen, while only 1.5% of the ¹O₂ produced is intercepted by DPA. Although it can be concluded that the low Φ obtained for the Ru(bpy)₃Cl₂ actinometer stems from the low quenching efficiency of ¹O₂ by DPA, given the aforementioned efficiencies the Φ of this system is too large, even without considering the fact that only 57% of ³Ru(bpy)₃Cl₂ quenching events lead to ¹O₂ generation.¹⁴ A possible explanation for the higher than expected Φ is that ³Ru(bpy)₃Cl₂ is acting as a triplet sensitizer, producing ³DPA which can, in turn, sensitize the production of ¹O₂. In order to demonstrate that ³Ru(bpy)₃Cl₂ can indeed sensitize the formation of ³DPA, LFP was employed in order to observe the growth of the triplet-triplet absorption of DPA at 440 nm.¹⁸ As seen in Figure 6.8, a sample containing Ru(bpy)₃Cl₂ and DPA produced a long-lived growth at 440 nm characteristic of the triplet-triplet absorption of DPA, whereas the sample containing only Ru(bpy)₃Cl₂ did not.

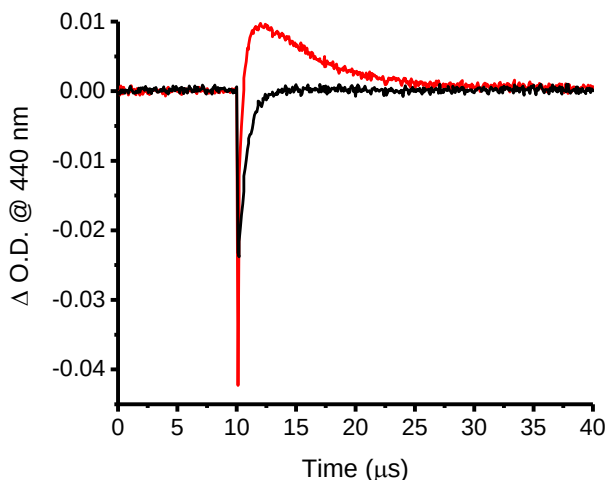
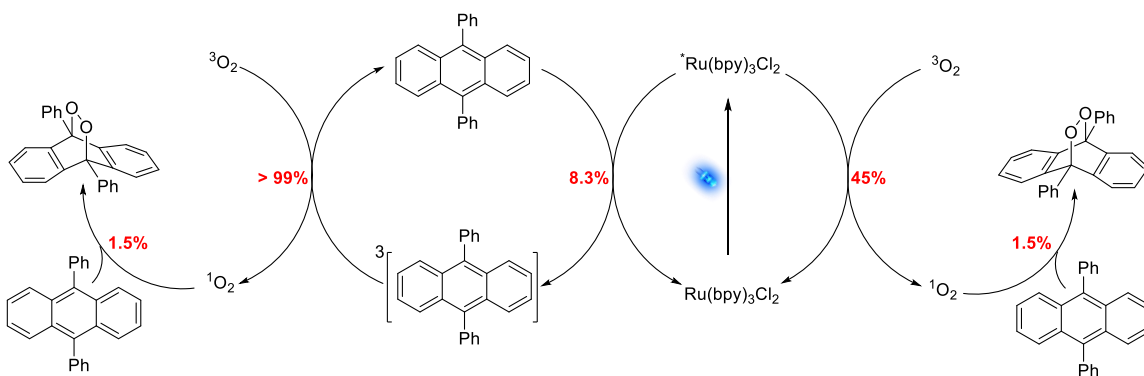


Figure 6.8. Laser flash photolysis traces obtained upon 460 nm excitation (10 mJ per pulse) of a deaerated solution of Ru(bpy)₃Cl₂ in MeCN (black) and Ru(bpy)₃Cl₂ and 1,9-diphenylanthracene in MeCN (red) while monitoring at 440 nm.

Knowing that ³Ru(bpy)₃Cl₂ is capable of sensitizing the production of ³DPA, equation (5) can be rearranged in order to determine the probability at which ³Ru(bpy)₃Cl₂ is quenched by DPA under the initial reaction conditions. This probability was calculated to be 8.3%. Considering the long lifetime of ³DPA (approximately 3 ms)¹⁸, and that ³DPA quenches O₂ at a rate of 3 × 10⁹ M⁻¹s⁻¹, one can employ equation (7):

$$\% \text{ } ^3\text{DPA quenched by O}_2 = \frac{100\% \times k_q^{O_2}[O_2]}{\tau_0^{-1} + k_q^{O_2}[O_2]} \quad (7)$$

to calculate that 99.9% of ³DPA is quenched by O₂. Combining this with the fact that the efficiency for ¹O₂ generation (*f*_Δ^T) by ³DPA is 100%^{16,17}, it becomes clear that this secondary route to ¹O₂ can account for the higher than expected Φ that is observed. A summary of the underlying mechanism for the Ru(bpy)₃Cl₂/DPA actinometer is can be seen in Scheme 6.2.



Scheme 6.2. Generalized reaction scheme for the Ru(bpy)₃Cl₂ actinometer system. Note that the extreme left and right reactions are identical, with singlet oxygen being produced from different sensitization steps.

Importantly, the Φ for this actinometer is ultimately an experimental value, and the preceding discussion behind the efficiency of the actinometer does not affect the obtained value of 0.019.

6.3 Characterization of the Photo-oxidation of Diphenylmethanol

In order to illustrate the usefulness of the Ru(bpy)₃Cl₂-based actinometer, it was important to use the actinometer to characterize a known chain reaction. It has been previously reported that in the presence of *N*-alkoxypyridium salts, the photocatalyzed oxidation of diphenylmethanol to benzophenone becomes a chain reaction.¹⁹ Since the underlying mechanism of this reaction was well established, it was found to be an ideal candidate to test the utility of the newly developed Ru(bpy)₃Cl₂ actinometric system.

In a typical reaction, diphenylmethanol (30 mM), Ru(bpy)₃Cl₂ (6 mM), and 4-cyano-*N*-methoxypyridinium (30 mM) in degassed MeCN were irradiated with a 10 W 460 nm LED (Scheme 6.3). Under these conditions, 77% conversion of diphenylmethanol to benzophenone was obtained after only 2 minutes of irradiation. In order to determine the Φ of this reaction, it was first necessary to determine the rate at which a 6.0 mM solution of Ru(bpy)₃Cl₂ absorbs photons under these irradiation conditions. This task was greatly simplified using the newly developed Ru(bpy)₃Cl₂-based actinometer. By simply performing the previously described actinometry experiment with a 6.0 mM solution of Ru(bpy)₃Cl₂, it was calculated that the sample absorbs 1.53×10^{-7} einsteins s⁻¹. With this information, equation (1) can be employed to find that the 77% conversion obtained in 2 minutes of irradiation corresponds to a Φ of 3.8. This signifies that for every photon absorbed, roughly 4 molecules of diphenylmethanol are oxidized, indicating the presence of a chain reaction. This aligns with previous reports that this reaction possesses a chain propagating component¹⁹, demonstrating the utility of the Ru(bpy)₃Cl₂-based actinometer.

Finally, the utility of the actinometer system was examined using the Ru(bpy)₃Cl₂-mediated oxidation of benzhydrol using 4-cyano-*N*-methoxypyridinium tetrafluoroborate as the chain amplifier. Using the Ru(bpy)₃Cl₂ actinometer, the Φ for this reaction was calculated to be 3.8. This supports previous studies on this reaction, unequivocally confirming the presence of chain propagation, and in turn, demonstrating the utility of the visible light Ru(bpy)₃Cl₂ actinometer.

It is envisioned that these methods will have great implications on the field of photoredox catalysis, as it will provide researchers with useful tools to properly characterize chain mechanisms. This visible light actinometer provides the advantage that the actinometer is also the photocatalyst, greatly simplifying the determination Φ for a Ru(bpy)₃Cl₂ catalyzed photoredox transformation.

6.5 Experimental Details

6.5.1 General Information. Tris(2,2'-bipyridyl)ruthenium(II) chloride (Ru(bpy)₃Cl₂) was purchased from Fisher Scientific and used as received. Diphenylanthracene (DPA), diphenylmethanol, 4-cyanopyridine *N*-oxide, and trimethyloxonium tetrafluoroborate were purchased from Sigma Aldrich and used as received. Flash column chromatography was performed using 230-400 mesh silica gel. All ¹H and ¹³C NMR were recorded on a Bruker AVANCE 400 spectrometer.

6.5.2 General Procedure for the Ru(bpy)₃Cl₂ Actinometer Experiments. The Ru(bpy)₃Cl₂ actinometer experiments were performed using a 10 W 460 nm LED in a dark room. Samples were stirred and irradiated as 3 mL samples in a precision 1 × 1 cm quartz cuvette equipped with a magnetic stir bar. Initially, experiments performed with the aim of determining the quantum yield (Φ) for the Ru(bpy)₃Cl₂ mediated oxidation of 1,9-

diphenylanthracene (DPA) to its corresponding endoperoxide were performed with a 440 nm notch filter (FWHM 10 nm). Once the Φ of the reaction was known the notch filter could be removed so long as there was no overlap between the absorption of Ru(bpy)₃Cl₂ and any of the reaction components, within the LED wavelengths of irradiation. In order to determine the Φ and power dependence of the actinometer, solutions consisting of 0.194 mM Ru(bpy)₃Cl₂ and 0.10 mM DPA in MeCN were utilized. By monitoring the disappearance of the signal at 372 nm, the amount of DPA consumed over a given period of irradiation using $\epsilon_{372 \text{ nm}}$ for DPA (11,100 M⁻¹cm⁻¹) can be determined.

6.5.3 General Procedure for the Ferrioxalate Actinometer Experiments. The ferrioxalate actinometer experiments were performed using a 10 W 460 nm LED equipped with a 440 nm notch (FWHM 10 nm) filter in a dark room. The samples were stirred and irradiated as 3 mL samples in a precision 1 x 1 cm quartz cuvette equipped with a magnetic stir bar.

In performing the experiment, two solutions are required: 1) a 0.15 M potassium ferrioxalate and 2) a 0.1% buffered phenanthroline solution.

1) Preparation of 0.15 M potassium ferrioxalate. Potassium ferrioxalate (7.37 g), 80 mL of H₂O, and 10 mL of 1.0 N H₂SO₄ were mixed in a 100 mL volumetric flask. Upon complete dissolution of the potassium ferrioxalate, the solution was topped up to 100 mL with H₂O to give a final concentration of 0.15 M.

2) Preparation of 0.1% buffered phenanthroline. Sodium acetate (22.5 g), and phenanthroline (100 mg) were dissolved in 100 mL of 0.5 M H₂SO₄.

Both solutions were stored in the dark in amber bottles and used as required.

In a typical experiment, two cuvettes containing 3 mL of 0.15 M potassium ferrioxalate were prepared. One sample was irradiated for 1 minute using the LED, while the other was left in the dark as a control. Upon completion of irradiation, 500 μ L of the 0.1% buffered phenanthroline solution was added to both samples. The samples were then allowed to develop in the dark for another 5 minutes before the absorption of each of the samples were measured at 510 nm. Using the optical difference ($\Delta A_{510 \text{ nm}}$) between the irradiated and control (dark) sample and the $\epsilon_{510 \text{ nm}} = 11,100 \text{ M}^{-1}\text{cm}^{-1}$, the amount of Fe²⁺ produced during the irradiation can be determined. Knowing that the quantum yield for Fe²⁺ production is 1.01 and that the samples absorbs > 99% of the incident light, the photon flux absorbed by the sample can be calculated.

6.5.4 Preparation of Potassium Ferrioxalate. In Milli-Q H₂O, a solution of 1.5 M potassium oxalate and 1.5 M ferric chloride were prepared. The two solutions were then combined with stirring in a 3:1 ratio of potassium oxalate:ferric chloride. After stirring for 2 h, the resulting precipitate was filtered off and recrystallized three times from warm H₂O. The solid was then dried under vacuum, and stored in the dark until use.

6.5.5 Procedure for the Oxidation of Diphenylmethanol. Diphenylmethanol (0.09 mmol, 16.6 mg), 4-methoxy-*N*-cyanopyridinium tetrafluoroborate (0.09 mmol, 20 mg), Ru(bpy)₃Cl₂ (0.018 mmol, 13.5 mg), and MeCN (3 mL) were added to a 1 x 1 cm quartz cuvette equipped with a magnetic stir bar and fitted with a septum. The reaction mixture was degassed with argon for 15 minutes, and irradiated with a 10 W 460 nm LED for 2 minutes. The MeCN was removed by rotary evaporation, and dimethylsulfone (0.09 mmol, 8.5 mg) was added as an external ¹H NMR standard.

6.5.6 Synthesis of 4-Cyano-*N*-methoxypyridinium Tetrafluoroborate. 4-cyanopyridine *N*-oxide (6 mmol, 720 mg) and trimethyloxonium tetrafluoroborate (11.37 mmol, 1.68 g)

were added to an oven-dried 100 mL round bottom flask equipped with a magnetic stir bar. The contents were dissolved in dry CH₂Cl₂ (30 mL), and the reaction was purged with argon and stirred overnight at room temperature. The reaction was quenched with MeOH (15 mL), and the solvent was removed by rotary evaporation. The crude solid was recrystallized in MeOH to afford the desired product as a white crystalline solid in 68% isolated yield (910 mg).

6.6 Laser Flash Photolysis Data

6.6.1 General Procedure for Laser Flash Photolysis Experiments. The triplet quenching experiments of Ru(bpy)₃Cl₂ were performed using a Nd-YAG laser (355 nm, 10 mJ/pulse) in a LFP-111 laser flash photolysis system (Luzchem Inc., Ottawa, CA) and 1 x 1 cm quartz cuvettes. Samples of Ru(bpy)₃Cl₂ were prepared in MeCN with a total volume of 3 mL and an absorbance of ~0.1 at 355 nm. The samples were degassed with N₂ 30 minutes prior to use. Experiments probing the sensitization of DPA by ³Ru(bpy)₃Cl₂ were performed using a Surelite plus OPO (460 nm and 10 mJ/pulse) as to avoid direct excitation of the DPA.

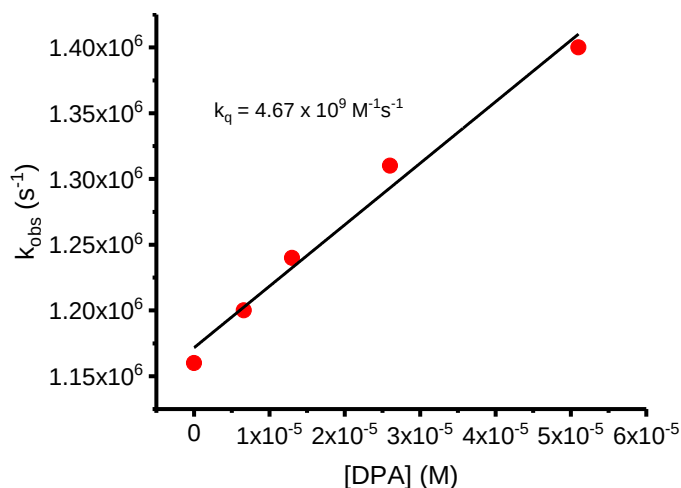


Figure 6.9. Representative kinetic plot for the quenching of ³Ru(bpy)₃Cl₂ by DPA in MeCN using 355 nm laser excitation.

6.6.2 General Procedure for Singlet Oxygen Quenching Experiments. The singlet oxygen (¹O₂) quenching experiments by DPA were performed using a Nd-YAG laser (532 nm, 10 mJ/pulse) in a LFP-111 laser flash photolysis system (Luzchem Inc., Ottawa, CA) and a 1 x 1 cm reduced path length quartz cuvette fitted with a Hamamatsu NIR-PMT which monitored the phosphorescence of ¹O₂ at 1270 nm. Excitation of Rose Bengal in 1 mL of CD₃CN at 532 nm was used to sensitize the production of ¹O₂. A solution of 5 mM DPA prepared in CD₃CN was used for the quenching studies.

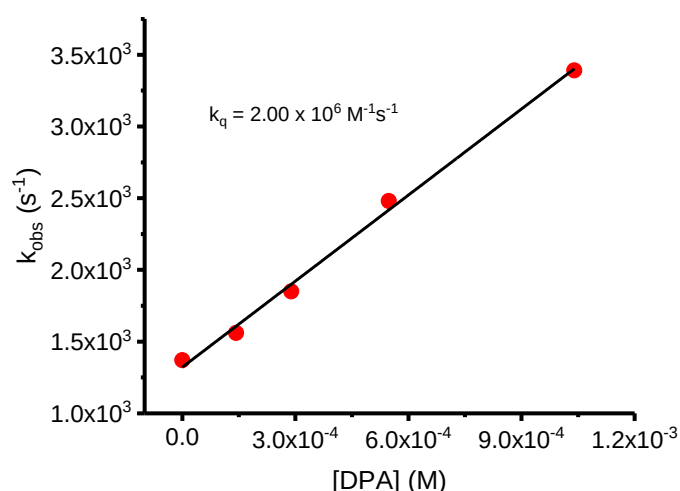


Figure 6.10. Representative kinetic plot for the quenching of ¹O₂ by DPA in CD₃CN. ¹O₂ was sensitized by Rose Bengal and 532 nm laser excitation.

6.7 References

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7. Photocatalytic Diels-Alder Reactions of Indoles Mediated by TiO₂

In Collaboration with Dr. Tehshik P. Yoon at the University of Wisconsin-Madison

7.1 An Introduction to Semiconductor Photocatalysis

Semiconductors, unlike metals, do not possess a continuum of electronic states.^{1,2} Instead, they possess a void energy region where no energy levels are available to promote the recombination of an electron and a hole produced in the photoactivation of a solid. This void region, which extends from the top of the filled valence band (VB) to the bottom of the empty conduction band (CB) is known as the band gap (Figure 7.1).^{1,2} Upon excitation of a semiconductor particle with photons of equal or greater energy than the band gap (ΔE_{BG}) of the material, an exciton, or an electron-hole pair, is created. The electron-hole pair can then undergo charge-transfer reactions at the surface of the semiconductor with species from the solution (or gas) phase. If the semiconductor remains intact and charge-transfer reactions at the surface of the semiconductor are continuous and exothermic, the process is known as heterogeneous photocatalysis.¹

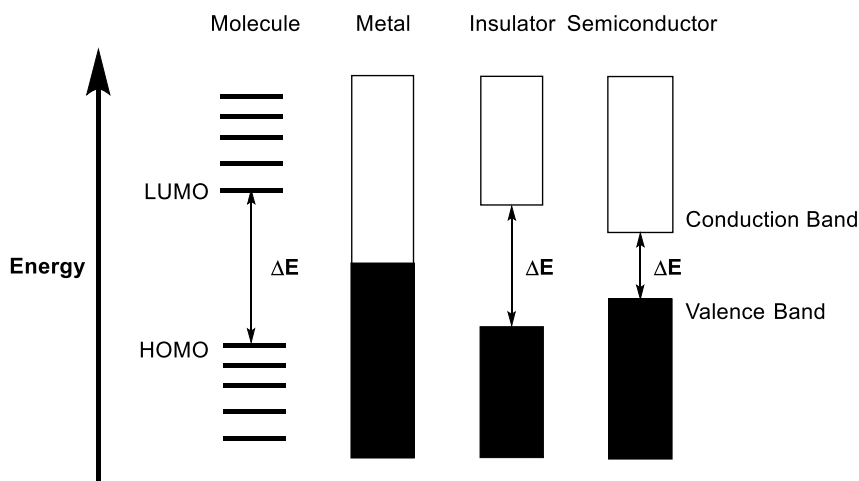


Figure 7.1. Molecular orbital representation of an atom, a metal, an insulator, and a semiconductor material.

The initial process for heterogeneous photocatalysis by semiconductors is the generation of electron-hole pairs in the semiconductor particles. Figure 7.2 shows the excitation of an electron from the VB to the CB initiated by light absorption with energy equal to or greater than the band gap of the semiconductor.¹⁻³ Upon excitation, the fate of the separated electron and hole can follow several pathways. Figure 7.2 illustrates possible pathways for photogenerated electrons and holes in a semiconductor particle.¹⁻³

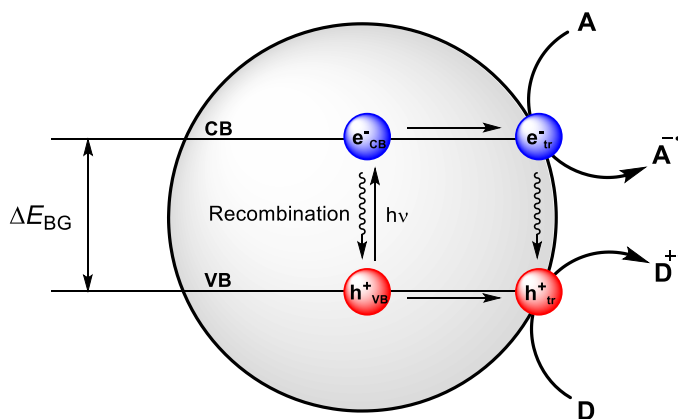


Figure 7.2. General scheme for photocatalysis employing inorganic semiconductor particles. Legend: ΔE_{BG} = band gap energy CB = conduction band; VB = valence band; tr = trapped on semiconductor surface.

The photoinduced electron-transfer from the semiconductor to either organic or inorganic species or to the solvent results from electrons and holes which have migrated and become trapped at the semiconductor surface (e^-_{tr} and h^+_{tr} , respectively).¹⁻³ The electron-transfer process is more efficient if the species are pre-adsorbed on the surface. While at the surface the semiconductor, e^-_{tr} and h^+_{tr} can be quenched by an electron acceptor (A) or an electron donor (D), respectively.¹⁻³ The probability and rate of these charge-transfer processes depend upon the respective positions of the band edges for the conduction and valence bands and the redox potential levels of the acceptor/donor. In competition with these charge-transfer pathways is electron-hole recombination.¹⁻³ Recombination of the

separated electron and hole can occur in the volume of the semiconductor particle or on the surface with the release of heat. While not shown in Figure 7.2, the process of back-donation after electron-transfer with a donor or acceptor species may also occur, depending on the affinity of the acceptor/donor to the semiconductor surface.¹

7.2. Titanium Dioxide Photocatalysis

One of the most well studied inorganic semiconductors employed in photocatalysis is titanium dioxide (TiO₂). TiO₂ particles exist in three main phases: anatase, rutile, and brookite⁴, and is commonly sold as a roughly 3:1 mixture of anatase and rutile known as TiO₂ P25.⁵ TiO₂, especially TiO₂ P25, has been demonstrated to be an excellent, inexpensive photocatalyst due to its high chemical stability, nontoxicity, and high chemical reactivity. In particular, TiO₂ has been employed in applications such as the purification of polluted water and air, photoelectrochemical solar energy conversion, photoinduced hydrophilicity for self-cleaning materials, and photocatalysts for many organic photoreactions.^{2,3,6-8} However, its relatively large band gap (3.0 eV for rutile, 3.2 eV for anatase)⁹ requires ultraviolet irradiation for excitation, and its relatively low photonic efficiencies (ζ_p) limits its applications in organic synthesis.¹⁰ In this light, investigations have been carried out to develop visible light responsive TiO₂ materials, typically through the addition of cations or metal oxides by both chemical doping and physical ion-implantation methods.¹¹ Similarly, the addition of dopants, such as platinum (Pt) nanoparticles, can help increase the photonic efficiency of TiO₂ semiconductors by trapping the electron, effectively slowing down the rate of charge recombination.¹²⁻¹⁶

Heterogeneous semiconductors, such as TiO₂, provide an excellent alternative to homogeneous photoredox catalysts, due not only to their ability to be easily separated and recycled, but they also possess many of the same properties as homogeneous

photocatalysts required to promote photoredox reactions. As demonstrated in Figure 7.3a, upon excitation of TiO₂, an exciton (or electron-hole pair) is formed, where an electron is promoted to the CB of TiO₂ (e^-_{CB}), leaving a hole in the VB (h^+_{VB}).¹⁷ Roughly 90% of these excitons will recombine within picoseconds of formation, however the remainder become trapped on the surface of the TiO₂.^{7,17} In these cases, e^-_{tr} can be quenched by a variety of electron acceptors (e.g. O₂, viologens, etc.) and h^+_{tr} can be quenched by a variety of electron donors (e.g. aliphatic amines, MeOH, etc.). Similar to the relaxation of the excited state of a homogeneous photocatalyst, the surface e^-_{tr} and h^+_{tr} must be quenched before charge recombination occurs, which is on the nanosecond to microsecond regime.¹⁷ In order to minimize charge recombination, Pt nanoparticles can be functionalized onto the surface of TiO₂ in order to act as a sink for the trapped electrons (Figure 7.3b).⁷ This functionalization generally occurs through an electrostatic interaction between the TiO₂ surface and the Pt nanoparticles, leaving the surface and semiconductor properties of TiO₂ unchanged. Many examples have demonstrated that the functionalization of TiO₂ with Pt nanoparticles results in an increase in photonic efficiencies by slowing down electron-hole recombination. In previous work from the Scaiano group, it was demonstrated that by adding a small loading (0.2% w/w) of Pt nanoparticles onto TiO₂, the overall reaction efficiency of the reductive dehalogenation of ethyl 4-iodobenzoate was increased by ~1.5 times compared to that of unfunctionalized TiO₂.¹⁸

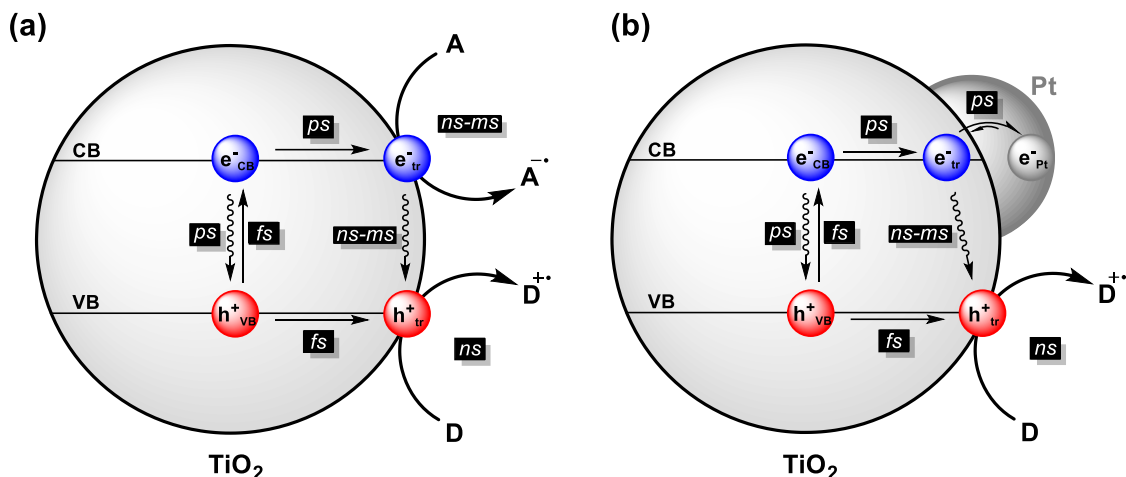
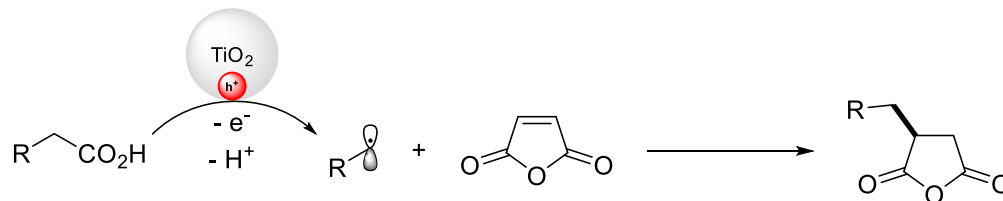
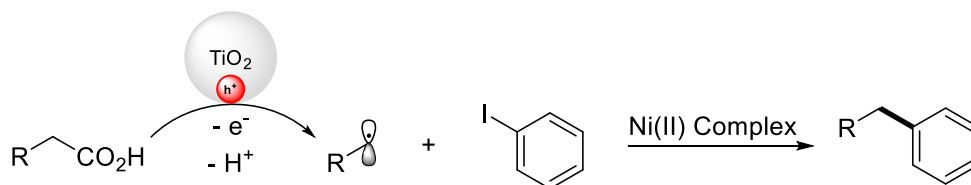


Figure 7.3. The fate of charge carriers formed upon excitation of semiconductor particles for **(a)** unfunctionalized TiO₂ and **(b)** TiO₂ functionalized with Pt nanoparticles, along with the timescales for each possible event. Legend: CB = conduction band; VB = valence band; tr = trapped on semiconductor surface.^{7,17}

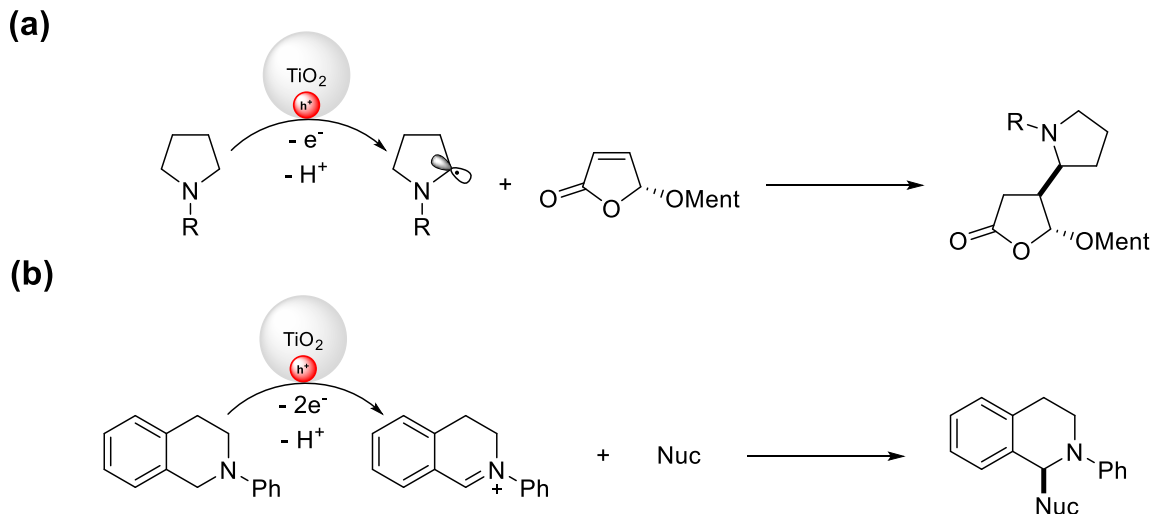
In recent years, the use of TiO₂ as an inexpensive photocatalyst to drive photochemical transformations has been gaining interest.¹⁰ While few examples exist in which CB electrons are employed in photoreductive transformations, the photogenerated holes of TiO₂ have proven useful in promoting oxidation reactions in organic synthesis. For example, Albini and Walton have demonstrated that holes from TiO₂ are efficient at performing oxidative decarboxylations of carboxylic acids to generate carbon-centered radicals, which can be trapped by a variety of radical acceptors, such as maleic anhydride (Scheme 7.1a).^{16,19–22} More recently, the Scaiano group also employed TiO₂ for the generation of carbon-centered radicals from simple carboxylic acids. Following oxidative decarboxylation, the radicals were then trapped by a homogeneous nickel complex to undergo cross coupling with a variety of aryl iodides (Scheme 7.1b).²³ This protocol, originally developed by MacMillan and coworkers, enabled the cross coupling of carboxylic acids employing an inexpensive, reusable TiO₂ photocatalyst, in comparison to the homogenous iridium bipyridyl complex employed in the seminal work by MacMillan.²⁴

(a)**(b)**

R = Aryl, Alkyl

Scheme 7.1. Generation of carbon-centered radicals (alkyl or benzylic) through the oxidative decarboxylation of carboxylic acids mediated by TiO₂, which can be trapped by radical acceptors such as **(a)** maleic anhydride or **(b)** homogeneous nickel complexes to facilitate cross coupling with aryl iodides.^{16,19-23}

TiO₂ photocatalysis has also been widely employed in the oxidation of amines. For example, TiO₂ and its functionalized derivatives have been extensively utilized for the aerobic oxidation of amines to their corresponding imines. In the early 2000s, Hoffmann and coworkers demonstrated that TiO₂ could be employed to oxidize amines to generate α -aminoalkyl radicals, which could be trapped by electron-deficient alkenes (Scheme 7.2a).²⁵⁻²⁷ In 2012, Rueping and König demonstrated that TiO₂ could be employed to oxidize *N*-phenyltetrahydroisoquinolines to their corresponding iminium ions, which could then be trapped by a variety of nucleophiles (Scheme 7.2b).^{28,29} These select examples highlight that TiO₂ semiconductor particles possess all the necessary photochemical properties to efficiently promote photoredox transformations, with the added advantages typically attributed to heterogeneous catalysts, such as easy purification and reusability.

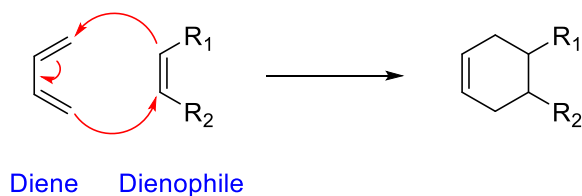


Scheme 7.2. Oxidation of amines mediated by TiO₂ to generate α -aminoalkyl radicals **(a)** and iminium ions **(b)** for photoredox transformations. Ment = menthol, Nuc = nucleophile.^{25–29}

7.3 The Diels–Alder Reaction

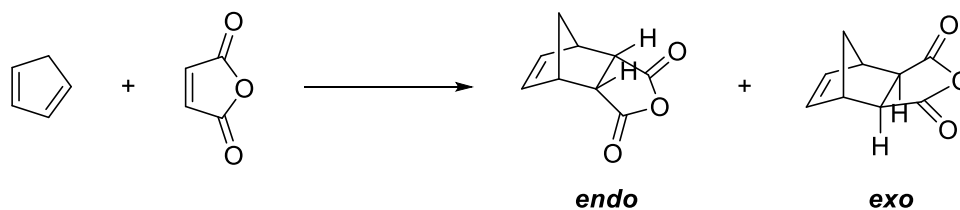
The Diels–Alder reaction is a particularly important reaction in organic chemistry because it creates two new carbon-carbon bonds and forms a cyclic molecule in the process. The importance of this reaction was highlighted when Otto Diels and Kurt Alder were awarded the Nobel Prize in chemistry in 1950.³⁰

In a Diels–Alder reaction, a conjugated diene reacts with a compound containing a carbon-carbon double bond, also known as the dienophile (Scheme 7.3).³¹ More precisely, the Diels–Alder reaction can be described as a [4+2] cycloaddition reaction because of the six π electrons participating in the cyclic transition state, four from the conjugated diene and two from the dienophile.³¹ The result, in essence, is the conversion of two π bonds into two σ bonds.



Scheme 7.3. General scheme describing a Diels–Alder reaction between a conjugated diene and a dienophile.

Many Diels–Alder reactions employing cyclic dienes can yield two stereoisomers, as seen in Scheme 7.4 in the reaction between cyclopentadiene and maleic anhydride.³² For the *endo* isomer, carbonyl groups or other unsaturated substituents on the dienophile are *cis* to the double bond of the newly formed cyclohexene ring. For the *exo* isomer, the unsaturated substituents are *trans* to the double bond.



Scheme 7.4. The Diels–Alder reaction between cyclopentadiene and maleic anhydride resulting in a mixture of *endo* and *exo* stereoisomers.

In the 1930s, Alder and Stein formulated the *endo* rule, which simply states that *endo* products from Diels–Alder reactions are usually obtained in higher yields than *exo* products.³² This may at first seem surprising because *endo* isomers tend to be less thermodynamically stable compared to *exo* isomers due to steric considerations. This can be demonstrated by the fact that *endo* isomers are frequently converted to *exo* isomers upon heating.

In the 1960s, Woodward and Hoffmann were able to rationalize the *endo* rule using frontier orbital theory.³² In order to demonstrate their rationalization of the *endo* rule, the transition states of the Diels–Alder reaction between cyclopentadiene and maleic anhydride will be

examined. As seen in Figure 7.4, the HOMO of the diene (cyclopentadiene) interacts with the LUMO of the dienophile (maleic anhydride). The atomic orbitals of carbon atoms 1 and 4 of the diene interact with the atomic orbitals of the double bond of the dienophile. However, in the transition state leading to the *endo* product, the atomic orbitals of carbons 2 and 3 of the diene also interact with the dienophile. These are commonly referred to as secondary orbital interactions, and this interaction lowers the energy of the transition state for the *endo* cycloaddition compared to the *exo* cycloaddition. Therefore, while the *exo* stereoisomer is more thermodynamically favoured due to steric considerations, the lower energy transition state for the *endo* cycloaddition results in the *endo* product being kinetically favoured.³²

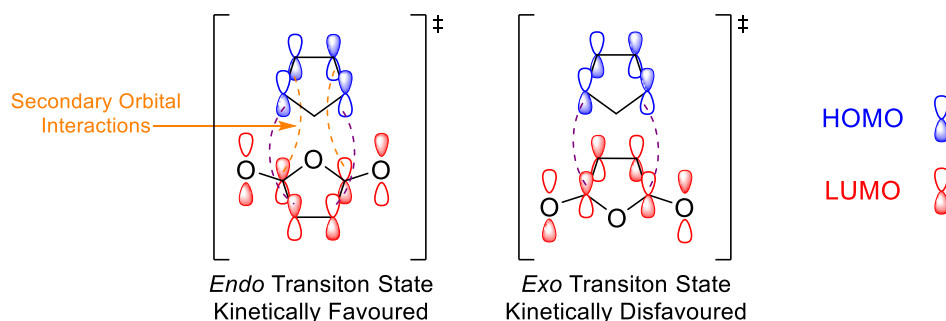


Figure 7.4. Transition states for the Diels–Alder reaction between cyclopentadiene and maleic anhydride, highlighting Woodward and Hoffmann’s rationalization of the *endo* rule.

Both steric and electronic effects can affect the rate of Diels–Alder reactions. For example, a diene will only undergo a Diels–Alder reaction in the *cis* conformation. Therefore, the most reactive dienes are those that are forced to maintain a *cis* conformation, such as dienes in which double bonds are contained in a ring structure. For instance, cyclopentadiene will undergo Diels–Alder dimerization simply on prolonged standing at room temperature.³²

In general, for a Diels–Alder reaction to take place in high yields at reasonable rates, the sp^2 carbons of the dienophile must be substituted with an electron-withdrawing group, such as carbonyl or carboxyl groups.³² This fact may be interpreted more simply that reactions occur more readily if one reactant is a good electron-donor while the other is a good electron-acceptor.

Once again, frontier molecular orbital theory can be used to rationalize this principle.³² The interaction of any two orbitals will result in the formation of two new orbitals in the transition state, one orbital that is lower in energy than either of the original orbitals and another orbital higher in energy. The extent of the differences between the new and original orbitals will depend on the relative energies of the two original orbitals. If the LUMO of one molecule is higher in energy than the HOMO of the other, the newly formed HOMO will not be much lower in energy compared to the original. If the original orbitals are closer in energy, the difference in energy between the original and transition state orbitals should be larger. Therefore, the reaction should proceed at a higher rate, because the electrons in the original HOMO will go into transition state orbitals that are lower in energy.

For the Diels–Alder reaction, placing electron-donating substituents on one reactant would raise the energy of its HOMO, while placing electron-withdrawing substituents on the other would lower the energy of its LUMO. Therefore, it would be expected that a Diels–Alder reaction would be most efficient when one reactant bears strongly electron-donating substituents (typically the diene), while the other strongly electron-withdrawing substituents (typically the dienophile).³² This situation is more commonly referred to as a *normal electron-demand* Diels–Alder reaction. On the other hand, Diels–Alder reactions can also proceed efficiently if the dienophile bears electron-donating substituents while the diene bears electron-withdrawing substituents, which is commonly referred to as an

inverse electron-demand Diels–Alder reaction.³³ However, the synthesis of dienes that bear electron-donating groups and of dienophiles with electron-withdrawing groups is generally easier than the reverse, therefore the majority of Diels–Alder reactions tend to be *normal electron-demand* reactions.

7.4 Diels–Alder Reactions of Indoles

Indole alkaloids represent one of the largest family of alkaloids, which houses a variety of complex natural products which possess a broad range of chemical diversity and potent biological activity.³⁴ Many of these alkaloid structures, including the subfamily *Strychnos* alkaloids, for example, possess common, tetrahydrocarbazole cores (Figure 7.5).³⁵ [4+2] cycloadditions, in particular, the Diels–Alder reaction, have proven to be powerful tools for the efficient synthesis of these complex structures. Indoles, being an electron-rich dienophile, have been reported to undergo a variety of *inverse electron-demand* Diels–Alder with electron-poor dienes to access these cyclic motifs.^{35,36} Indoles have also been reported to undergo *normal electron-demand* Diels–Alder with electron rich dienes, albeit these reactions require an electron-withdrawing group at the C-3 position, an electron-withdrawing protecting group on the indole nitrogen, and require either high temperatures or high pressures to give the [4+2] product.^{37–44} Microwave-assisted conditions^{45,46} or the addition of Lewis acids^{47,48} have been demonstrated to facilitate these reactions by diminishing reaction times and improving reactivity and selectivity. However, due to the poor tolerability of many common functional groups due to the harsh conditions required, there is a need to develop milder, more efficient conditions to access these alkaloids.

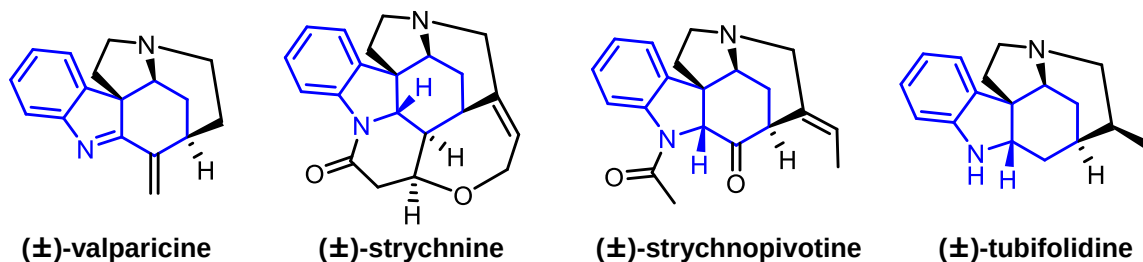
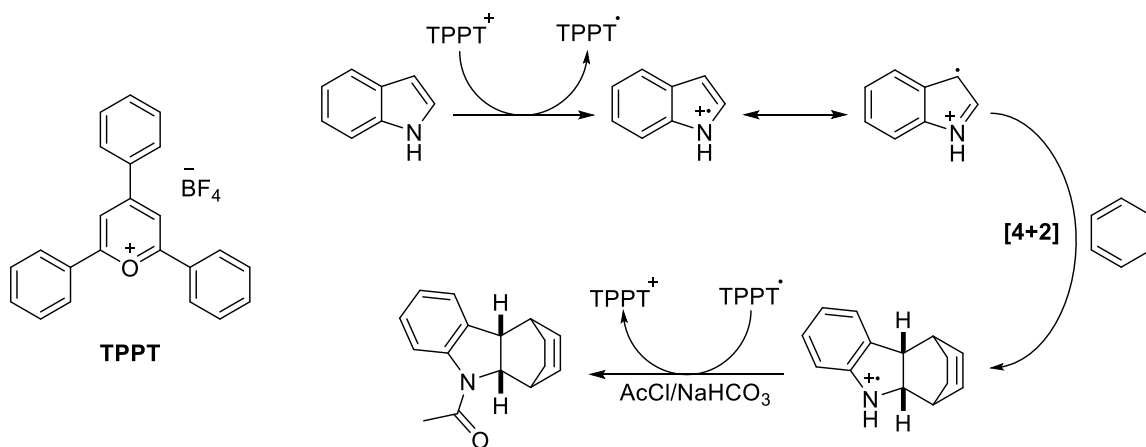


Figure 7.5. Selected examples from the Strychnos subfamily of indole alkaloids, all which possess a common tetrahydrocarbazole core, highlighted in blue.

Another strategy to perform normal electron-demand Diels–Alder was developed by Steckhan and coworkers, in which indole is oxidized by a single electron-transfer reaction with an excited photocatalyst, generating an indole radical-cation which undergoes a [4+2] radical cyclization with electron rich dienes.^{49–52} This enables chemists to start with an electron rich dienophile and convert it to an electron poor dienophile by simply removing an electron from the indole. In the seminal report from Steckhan, the excited state of triphenylpyrylium tetrafluoroborate (TPPT) ($E_{1/2} = 2.29$ V vs. SCE) was used to oxidize indole ($E_{1/2} = 1.07$ V vs. SCE) to the indole radical-cation, an electron deficient radical that undergoes a [4+2] radical cyclization with 1,3-cyclohexadiene (1,3-CHD, see Scheme 7.5).⁴⁹ The newly formed tetrahydrocarbazole radical-cation is then reduced by the TPPT radical-anion, closing the photocatalytic cycle. However, due to the fact that the newly formed tetrahydrocarbazole is significantly easier to oxidize than indole itself ($E_{1/2} = 0.46$ V vs. SCE), 1 equivalent of acetyl chloride and 2 equivalents of NaHCO₃ is added at the beginning of the reaction to protect the tetrahydrocarbazole product *in situ*, to give a *N*-acetylated tetrahydrocarbazole that is now considerably more stable towards oxidation ($E_{1/2} = 1.30$ V vs. SCE), giving the acylated product in 70% yield. More recently, the Miranda laboratory has developed other homogeneous variants^{53,54}, however to date no heterogeneous photocatalytic Diels–Alder reactions has been developed. Due to the recent success from the Scaiano group in employing Pt(0.2%)/TiO₂ for reductive

dehalogenation and cyclization reactions¹⁸, the fact that the conduction band of TiO₂ should be sufficiently oxidizing to oxidize indole ($E_{1/2} = 1.00$ V vs. SCE in MeCN, 2.25 V vs. SCE in H₂O, pH 7)²⁸, and that it is well accepted that h^+_{tr} can be quenched by nitrogen-based compounds^{25–29}, we decided to test the ability of Pt(0.2%)/TiO₂ to catalyze this reaction. Importantly, the broad absorption of the catalyst allows for the possibility to employ visible light irradiation to excite the photocatalyst, avoiding the use of ultraviolet irradiation such as the light sources employed in the aforementioned examples.



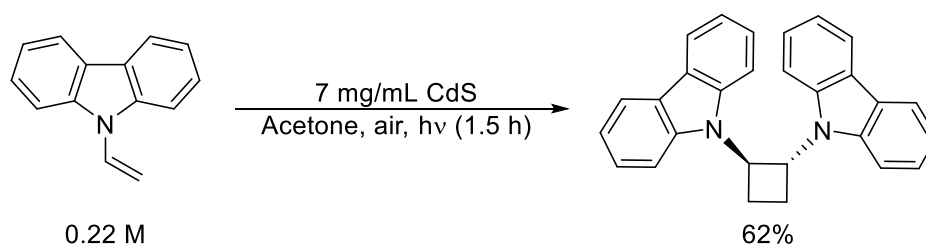
Scheme 7.5. Proposed mechanism for the photocatalytic Diels–Alder reaction between indole and 1,3-cyclohexadiene catalyzed by triphenylpyrylium tetrafluoroborate developed by Steckhan and coworkers.⁴⁹

In this chapter, the photocatalytic Diels–Alder reaction of indoles with *cis*-1,3 dienes in the presence of Pt(0.2%)/TiO₂ as the photocatalyst was studied. The reaction (*vide infra*) was found to proceed efficiently with irradiation from a simple, inexpensive 10 W blue LED (460 nm). When developing new reactions, several control experiments are always performed, and in this case, an important control was to compare the performance of unfunctionalized TiO₂ (i.e. free of Pt nanoparticles) with the parent Pt(0.2%)/TiO₂ catalyst. Surprisingly, the reaction still proceeded efficiently after five hours of irradiation, despite none of the reagents possessing an absorption in the visible region. At first glance,

this result appears to violate the first law of photochemistry, which simply states that light must be absorbed in order to promote chemical change.⁵⁵ This chapter will present the interpretation of these results, which is based on the fact that while the individual components do not absorb visible light, a surface interaction between the TiO₂ semiconductor and indole provides a new, weak absorption band that was determined to be crucial in promoting the photocatalytic Diels–Alder reaction.

7.5 Photocatalytic Diels–Alder Reaction of Indoles Mediated by Pt(0.2%)@TiO₂

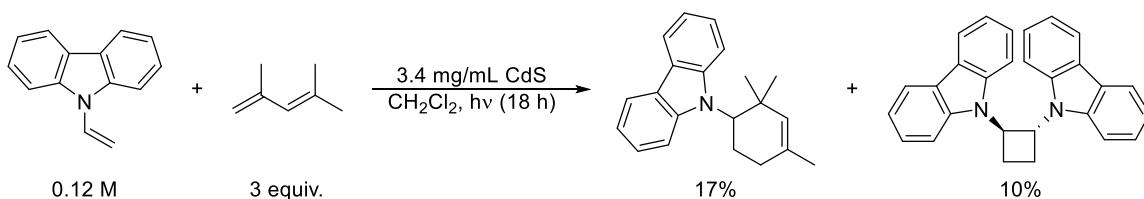
While the use of TiO₂ has not been widespread in organic synthesis due to the requirement for UV excitation, other semiconductors such as Bi₂O₃ and CdS, which absorb in the visible region, have been employed for visible light photoredox applications.⁵⁶ For example, CdS possesses a band gap of 2.4 eV, with a visible light absorption that extends to roughly 600 nm. One of the first examples employing CdS in organic synthesis was by De Mayo and coworkers in 1986, where they successfully promoted the radical-cation [2+2] cyclodimerization of *N*-vinylcarbazole (Scheme 7.6).⁵⁷



Scheme 7.6. [2+2] cyclodimerization of *N*-vinylcarbazole photocatalyzed by CdS semiconductor particles developed by De Mayo and coworkers.⁵⁷

In order to test if heterogeneous semiconductors could promote radical-cation [4+2] cycloadditions, the [2+2] cyclodimerization of *N*-vinylcarbazole photocatalyzed by CdS, originally developed by De Mayo was repeated in the presence of 3 equivalents of 2,4-dimethyl-1,3-pentadiene (Scheme 7.7). Gratifyingly, the major product of the reaction was

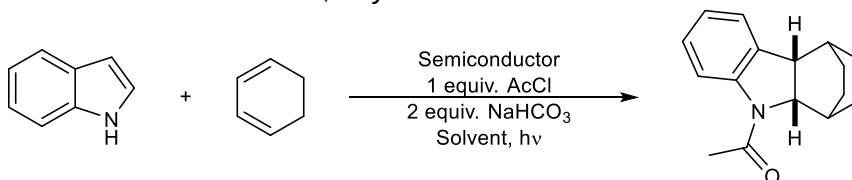
found to be the [4+2] cycloadduct between *N*-vinylcarbazole and 2,4-dimethyl-1,3-pentadiene. This aligns with previous reports by Bauld, who reported that *N*-vinylcarbazole could undergo radical-cation [4+2] reactions with cyclopentadiene and cyclohexadiene.⁵⁸ This provides sufficient evidence that heterogeneous semiconductors can also be employed as a strategy to mediate these [4+2] radical-cation cycloadditions. Therefore, it was hypothesized that this strategy could be used as a means to access substituted tetrahydrocarbazoles, an important structural motif in medicinal chemistry, through [4+2] radical-cation cycloadditions of indoles and electron-rich dienes.



Scheme 7.7. The effect of added diene on the [2+2] radical-cation cyclodimerization of *N*-vinylcarbazole. For reaction conditions, see section 7.7.5.

On this basis, we began investigating the use of heterogeneous semiconductors to promote the photocatalytic Diels–Alder reaction of indoles by investigating the seminal system developed by Steckhan and coworkers.⁴⁹ Using 5 equivalents of 1,3-CHD, 1 equivalent of AcCl and 2 equivalents of NaHCO₃, CdS was able to successfully promote the [4+2] cycloaddition with indole, reaching 51% yield after 24 hours of irradiation with a blue LED light source (Table 7.1, Entries 1-4). Increasing the loading of CdS was found to have an adverse effect on the reaction (Entry 5). Other attempts to increase the yield employing CdS were futile, and it was determined that photo-erosion of the catalyst, a process known to occur with sulfide-based semiconductors, was the result of the observed plateau in reactivity. However, it is well known that oxide based semiconductors are not prone to these photodecomposition processes, making them more suitable for applications in photocatalysis.⁵⁹ Since it was desirable to continue employing visible light

irradiation, a titanium dioxide catalyst decorated with Pt nanoparticles with a loading of 0.2% (w/w) (Pt(0.2%)/TiO₂) was chosen due to its broad absorption across the visible region, and due to the recent success from the Scaiano group in employing this catalyst in dehalogenation and cycloaddition reactions.¹⁸ The catalyst can also be easily synthesized in one step⁶⁰, and Pt nanoparticles offer the added advantage of slowing down electron-hole recombination by trapping the CB electrons.^{7,17} Using a concentration of 2 mg/mL of Pt(0.2%)/TiO₂, the tetrahydrocarbazole product was obtained in 31% yield after 24 hours of irradiation (Entry 6). Increasing the catalyst concentration to 4 mg/mL resulted in a 15% improvement in yield (Entry 7). Changing the solvent from CH₂Cl₂ to MeCN resulted in a sharp decrease in reactivity (Entry 8), however switching to MeNO₂ resulted in a yield of 63% after 24 hours of irradiation (Entry 9). While the role of MeNO₂ in this reaction is unclear, it has been found to be beneficial for other radical-cation cycloadditions.^{61,62} However, it was postulated that perhaps MeNO₂ is not an innocent solvent in this reaction and that it plays a role in the quenching of electrons trapped in the platinum nanoparticles/TiO₂ CB. In order to prove this idea, the reaction was performed in the absence of oxygen, another potent electron scavenger. As seen in Entry 10, the reaction still proceeded in 37% yield, indicating that MeNO₂ could be responsible for some of the observed electron scavenging, however it is clear that oxygen also plays an important role in this regard. Finally, by optimizing the light source and reaction concentrations, it was determined that the reaction reached 72% yield after only 5 hours of irradiation (Entries 11-14). Importantly, the observed *endo:exo* ratio of the tetrahydrocarbazole product was similar to that observed by Stechkan and coworkers⁴⁹, indicating that the heterogeneous nature of the reaction did not impart any negative effects on the observed stereoselectivity.

Table 7.1. Reaction optimization for the heterogeneous semiconductor photocatalyzed Diels–Alder reaction of indole and 1,3-cyclohexadiene.

Entry	Catalyst (Loading)	Solvent ([Indole])	Time	Yield	Endo:Exo
1	CdS (3 mg/mL)	CH ₂ Cl ₂ (0.11 M)	4 h ^a	20%	2.8:1
2	CdS (3 mg/mL)	CH ₂ Cl ₂ (0.11 M)	8 h ^a	37%	2.8:1
3	CdS (3 mg/mL)	CH ₂ Cl ₂ (0.11 M)	18 h ^a	47%	2.8:1
4	CdS (3 mg/mL)	CH ₂ Cl ₂ (0.11 M)	24 h ^a	51%	2.8:1
5	CdS (6.8 mg/mL)	CH ₂ Cl ₂ (0.11 M)	24 h ^a	33%	2.4:1
6	Pt(0.2%)/TiO ₂ (2 mg/mL)	CH ₂ Cl ₂ (0.11 M)	24 h ^a	31%	3.3:1
7	Pt(0.2%)/TiO ₂ (4 mg/mL)	CH ₂ Cl ₂ (0.11 M)	24 h ^a	46%	3.4:1
8	Pt(0.2%)/TiO ₂ (4 mg/mL)	MeCN (0.11 M)	24 h ^a	9%	N.D.
9	Pt(0.2%)/TiO ₂ (4 mg/mL)	MeNO ₂ (0.11 M)	24 h ^a	63%	2.8:1
10	Pt(0.2%)/TiO ₂ (4 mg/mL)	MeNO ₂ (0.11 M)	24 h ^{a,c}	37%	3.3:1
11	Pt(0.2%)/TiO ₂ (4 mg/mL)	MeNO ₂ (95 mM)	1 h ^b	42%	3.5:1
12	Pt(0.2%)/TiO ₂ (4 mg/mL)	MeNO ₂ (95 mM)	3 h ^b	53%	3.1:1
13	Pt(0.2%)/TiO ₂ (4 mg/mL)	MeNO ₂ (95 mM)	5 h ^b	72%	3.6:1
14	Pt(0.2%)/TiO ₂ (4 mg/mL)	MeNO ₂ (95 mM)	6 h ^b	72%	3.6:1

Reaction Conditions: Indole (0.3 mmol), 1,3-cyclohexadiene (1.5 mmol), acetyl chloride (0.3 mmol), NaHCO₃ (0.6 mmol), and solvent were irradiated with a blue LED light source. Yields and *Endo:Exo* ratios are reported based on ¹H NMR using trimethyl(phenyl)silane as an external standard. N.D. = not determined. ^a16 W blue LED floodlamp. ^b10 W 460 nm LED. ^cReaction purged with N₂.

Importantly for all newly developed photocatalyzed transformations, numerous control reactions were performed in order to gain a further mechanistic understanding of the transformation (Table 7.2). The reaction did not proceed in the absence of either Pt(0.2%)/TiO₂ or light (Entries 1 and 2). Aligning with previous observations by Stechkan, the reaction proceeds in low yields in the absence of AcCl and NaHCO₃, due to the unprotected tetrahydrocarbazole being easier to oxidize than the indole starting material (Entry 3).⁴⁹ Oxidation of the tetrahydrocarbazole product was hypothesized either to lead to degradation or to catalyze the retro Diels–Alder reaction. Substituting indole for *N*-acetylindole led to no reaction, indicating that acetylation occurs after the [4+2] cycloaddition (Entry 4). A reaction was also performed with a 630 nm LED, as only Pt nanoparticles absorb in this region, and no reaction was observed (Entry 5), indicating

that direct excitation of the Pt nanoparticles is not a viable mechanistic pathway. Finally, the reaction was performed with unfunctionalized TiO₂, in other words, in the absence of Pt nanoparticles. It was expected that this would not give any reactivity, as TiO₂ or any of the other reaction components do not possess an absorption in the visible region. Surprisingly, however, the reaction with unfunctionalized TiO₂ gave the desired product in 60% yield (Entry 6). This result was intriguing, as it appears to violate the first law of photochemistry that simply states that light must be absorbed in order to promote chemical change.⁵⁵ However, this result led to series of experiments that gave valuable mechanistic insight into the reaction and will be discussed further in section 7.5.

Table 7.2. Control reactions for the photocatalyzed Diels-Alder reaction of indole and 1,3-cyclohexadiene mediated by Pt(0.2%)/TiO₂.

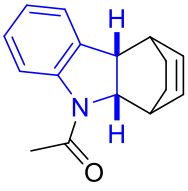
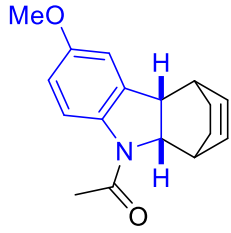
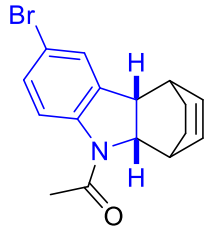
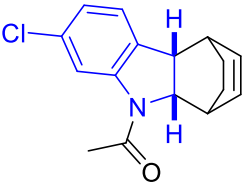
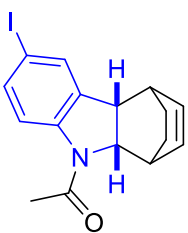
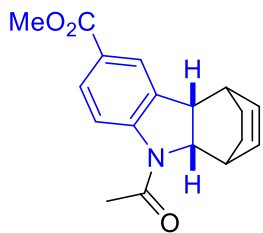
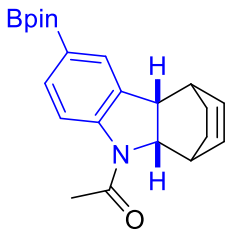
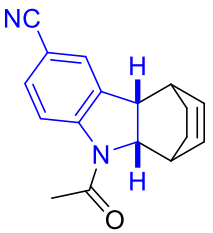
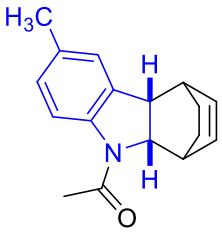
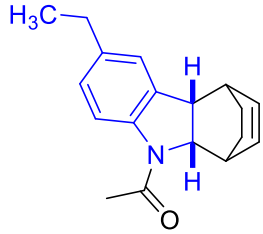
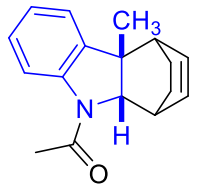
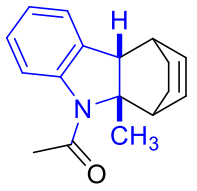
Entry	Modifications from Standard Conditions	Yield
1	No Pt(0.2%)/TiO ₂	No Reaction
2	Reaction performed in the dark	No Reaction
3	No AcCl/NaHCO ₃	11%
4	<i>N</i> -Acetylindole instead of indole	No Reaction
5	630 nm LED instead of 460 nm LED	No Reaction
6	TiO ₂ instead of Pt(0.2%)/TiO ₂	60%

Standard Conditions: Indole (0.3 mmol), 1,3-cyclohexadiene (1.5 mmol), acetyl chloride (0.3 mmol), NaHCO₃ (0.6 mmol), and MeNO₂ (3 mL) were irradiated under air with a 10 W 460 nm LED. Yields are reported based on ¹H NMR using trimethyl(phenyl)silane as an external standard.

Next, the scope of the heterogeneous photocatalytic Diels–Alder reaction was examined. First, the scope of the indole dienophile was examined (Table 7.3). In the cases for both **7a** and **7b**, Pt(0.2%)/TiO₂ was found to be more efficient than unfunctionalized TiO₂. While Pt(0.2%)/TiO₂ does provide increased yields, one of the drawbacks of this catalyst is the potential to leach trace Pt metal, which would limit its use in the pharmaceutical industry. However, in previous work by the Scaiano group, no leaching from the Pt(0.2%)/TiO₂ catalyst was detected after four uses using ICP-MS, circumventing the need for expensive trace Pt removal from the desired products.¹⁸ Ultimately, if trace Pt is still of concern during the synthesis of these compounds, unfunctionalized TiO₂ can still

be employed, albeit with decreased reactivity (Table 7.3, **7a** and **7b**). Other advantages of the Pt(0.2%)/TiO₂ catalyst include a facile one-step synthesis, and low cost compared to common transition-metal homogeneous photocatalysts. Based on these aforementioned advantages and the lack of any observable Pt leaching in previous reports, the scope of the reaction was examined with this catalyst. Both electron-withdrawing and donating functionalities on the aromatic ring are well tolerated under the standard reaction conditions. Interestingly, no reduction of the iodo-group was observed for example **7e**, despite this catalyst being employed in the reductive dehalogenation of iodo-compounds in a previous report by the Scaiano group.¹⁸ This is likely due to the presence of MeNO₂ and oxygen, both excellent electron scavengers that are present in this system which prevents reductive dehalogenation. Bis(pinacolato)diborane (Bpin) groups were also well tolerated (**7g**), giving an important synthetic handle that allows for further functionalization of the tetrahydrocarbazole product. Unfortunately, functionalization at the C2 and C3 positions of the indole led to a sharp decrease in reactivity, most likely due to steric considerations (**7k** and **7l**). The addition of a nitro group was also found to completely inhibit the reactivity, and 7-azaindole also did not yield any [4+2] product, as *N*-acylation occurred at a faster rate than the [4+2] cycloaddition in this case.

Table 7.3. Indole scope for the photocatalytic Diels–Alder reaction of indoles mediated by Pt(0.2%)/TiO₂.

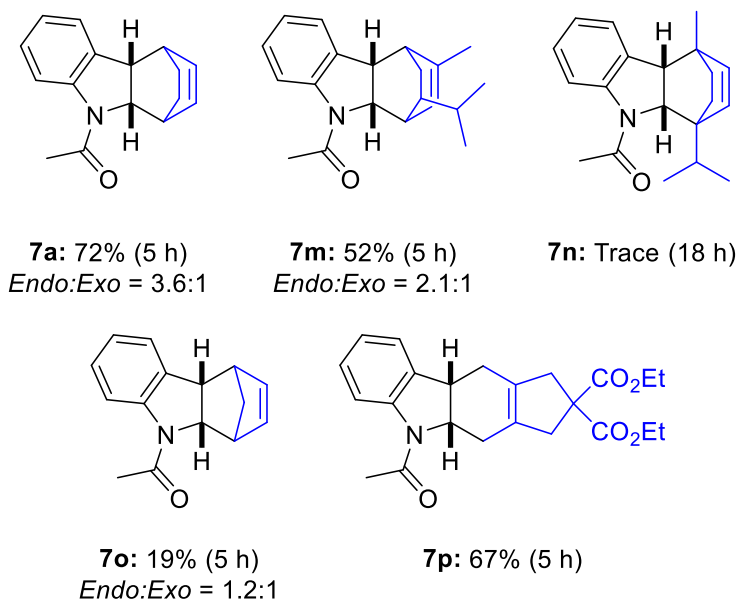
			
7a: 72% (5 h) 60% (TiO ₂ , 5 h) <i>Endo:Exo</i> = 3.6:1	7b: 48% (5 h) 31% (TiO ₂ , 5 h) <i>Endo:Exo</i> = 3.9:1	7c: 62% (5 h) <i>Endo:Exo</i> = 3.3:1	7d: 56% (5 h) <i>Endo:Exo</i> = 3.2:1
			
7e: 52% (5 h) <i>Endo:Exo</i> = 3.9:1	7f: 59% (5 h) <i>Endo:Exo</i> = 3.4:1	7g: 52% (5 h) <i>Endo:Exo</i> = 3.4:1	7h: 40% (7 h) <i>Endo:Exo</i> = 2.2:1
			
7i: 55% (5 h) <i>Endo:Exo</i> = 3.8:1	7j: 57% (5 h) <i>Endo:Exo</i> = 2.8:1	7k: 11% (5 h) <i>Endo:Exo</i> = 2.7:1	7l: Trace (5 h)

Yields reported as isolated yields. *Endo:Exo* ratio determined from ¹H NMR analysis of crude reaction mixture. For reaction conditions, see Section 7.7.2.

The diene scope was only briefly examined, as Steckhan and coworkers examined this scope in detail in a series of publications (Table 7.4).^{49–52} In agreement with Steckhan's observations, only dienes that are structurally locked in the *cis*-isomer yielded any reactivity for the photocatalytic Diels–Alder reaction. Interestingly, α -terpinene (**7n**) only gave trace amounts of the [4+2] product, in contrast to Steckhan's results when employing TPPT as the photocatalyst.⁴⁹ It is hypothesized that if the reaction takes place near the

vicinity of the TiO₂ surface that substitution at the C1 and C4 position of the diene could create too large of a steric hindrance for the reaction to proceed efficiently. It was also surprising to observe that 1,3-cyclopentadiene, which is known to be significantly more reactive than 1,3-CHD in Diels–Alder reactions, gave only 19% of the desired [4+2] product (**7o**). In this case, it is likely that the increased reactivity of the diene resulted in increase rates of dimerization or polymerization, leading to a lesser amount of the desired [4+2] product being formed.

Table 7.4. Diene scope for the photocatalytic Diels–Alder reaction of indoles mediated by Pt(0.2%)@TiO₂.

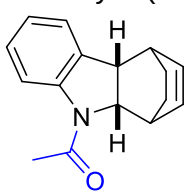
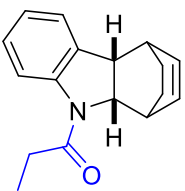
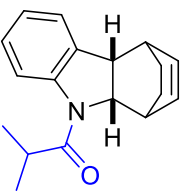
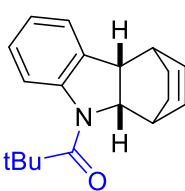
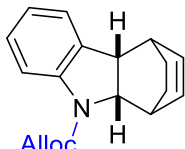
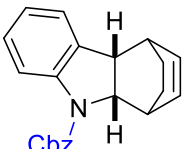
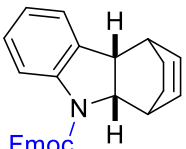
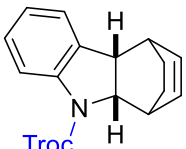


Yields reported as isolated yields. *Endo:Exo* ratio determined from ¹H NMR analysis of crude reaction mixture. For reaction conditions, see Section 7.7.2.

While this protocol has proven effective for a variety of cyclic 1,3-dienes, *cis*-1,3-exocyclic dienes, such as example **7p**, are also well tolerated.^{51,52} This demonstrates that this protocol provides a useful strategy for generating complex indole alkaloids quickly and efficiently, as compound **7p** could be accessed after only 3 synthetic steps, with an isolated yield of 32% over those 3 steps.

Finally, the scope of the protecting group can be seen in Table 7.5. Increasing the bulk of the acetyl chloride was found to have a negative effect on the yield, either due to steric considerations or decreased electrophilicity. Due to the acetyl group being an undesirable protecting group in organic synthesis, as it traditionally requires either harsh acidic or basic conditions to remove⁶³, chloroformate protecting groups were also examined. While the reactions proceed poorly with allyl chloroformate (**7t**) and benzyl chloroformate (**7u**), both 9-fluorenylmethyl chloroformate (Fmoc chloride, **7v**) and 2,2,2-trichloroethyl chloroformate (Troc chloride, **7w**) were found to proceed in moderate yields. In all cases with the exception of Fmoc chloride for the chloroformate protecting groups, a significant loss in yield occurred upon isolation. It is proposed that this is the result of decomposition or deprotection occurring during isolation by column chromatography, as these protecting groups are sensitive to acidic conditions. Tosyl chloride was also found to be an inefficient protecting group for this reaction (11% yield by ¹H NMR). Other protecting groups commonly employed in organic synthesis such as Boc anhydride (di-*tert*-butyl dicarbonate) and benzyl chloride did not yield any of the desired [4+2] product. Therefore, if removal of the protecting group is desirable for the further functionalization of these tetrahydrocarbazoles, Troc and Fmoc chloride could be considered, albeit with decreased isolated yields compared to acetyl chloride.

Table 7.5. Protecting group scope for the photocatalytic Diels–Alder reaction of indoles mediated by Pt(0.2%)/TiO₂.

			
7a: 72% (5 h) <i>Endo:Exo</i> = 3.6:1	7q: 49% (5 h) <i>Endo:Exo</i> = 3.1:1	7r: 45% (5 h) <i>Endo:Exo</i> = 3.2:1	7s: 16% (5 h) ^a <i>Endo:Exo</i> = 2.9:1
			
7t: 16% (5 h) (29%) ^a <i>Endo:Exo</i> = 4.8:1	7u: 14% (5 h) (30%) ^a <i>Endo:Exo</i> = 3.5:1	7v: 29% (5 h) <i>Endo:Exo</i> = 2.7:1	7w: 32% (7 h) (50%) ^a <i>Endo:Exo</i> = 4.6:1

Yields reported as isolated yields. *Endo:Exo* ratio determined from ¹H NMR analysis of crude reaction mixture. For reaction conditions, see Section 7.7.2. ^aYield determined from ¹H NMR analysis of crude reaction mixture using trimethyl(phenyl)silane as an external standard.

Having established the scope for the heterogeneous photocatalytic Diels–Alder reaction, we were interested in how this protocol compared to the seminal example by Steckhan and coworkers with TPPT.⁴⁹ Typically, quantum yields, the amount of chemical change per photon absorbed in a given period of time, are used to compare photochemical reactions. However, in heterogeneous reactions some of the photons are scattered off the surface of the catalyst, making it difficult to determine the exact number of photons the sample has absorbed over a given period of irradiation. Therefore, to overcome these intrinsic problems in comparing these two photoreactions, the number of photons absorbed at a given wavelength per units of time and volume (I_a) is replaced by I_0 , the number of photons of a given wavelength per time and volume arriving at the sample.⁵⁹ This apparent quantum yield is more formally known as photonic efficiency (ζ_p), and can be described as equation (1).

$$\zeta_p = \frac{rate}{I_0} \quad (1)$$

Therefore, in order to compare our heterogeneous protocol to the seminal work by Steckhan, the ζ_p of both reactions needed to be determined. In order to determine the amount of photons arriving at the sample, the Ru(bpy)₃Cl₂ actinometer developed in Chapter 6 was employed. By employing the actinometer with a Ru(bpy)₃Cl₂ concentration of 0.19 mM, the absorption of Ru(bpy)₃Cl₂ was found to have an absorbance of 2 or greater over the entire emission spectrum of the 460 nm LED employed. Therefore, it can be assumed that greater than 99% of the photons arriving at the sample would be absorbed by Ru(bpy)₃Cl₂, therefore the actinometer could be employed to determine the amount of photons arriving at the sample in a given period of time and volume. By performing a typical actinometry experiment (Figure 7.6), and by employing equations (2) and (3):

$$moles\ of\ DPA\ consumed = \frac{(A_{initial} - A_{final})}{(\epsilon_{372\ nm})(l)} (V) \quad (2)$$

$$\frac{Nh\nu}{t} = I_0 = \frac{moles\ of\ DPA\ consumed}{(\Phi)(t)} \quad (3)$$

where $A_{initial}$ and A_{final} are the absorbances at 372 nm before and after irradiation, $\epsilon_{372\ nm}$ is the extinction coefficient of DPA at 372 nm, l is the pathlength and Φ is the quantum yield of the actinometer, it was calculated that I_0 for the 460 nm LED set up employed was $4.7 \pm 0.1 \times 10^{-7} \text{ mol } h\nu \text{ s}^{-1}$.

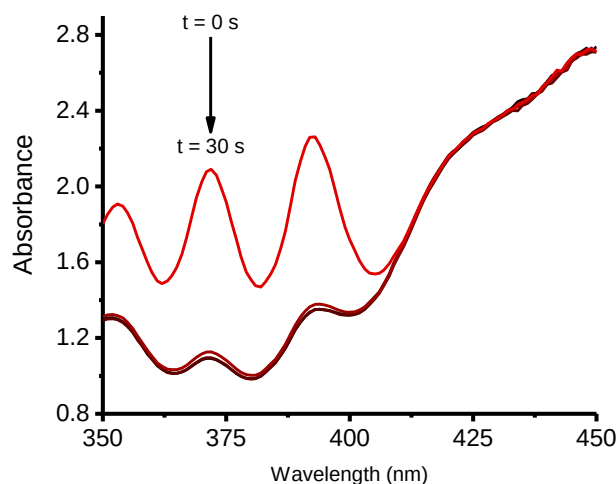
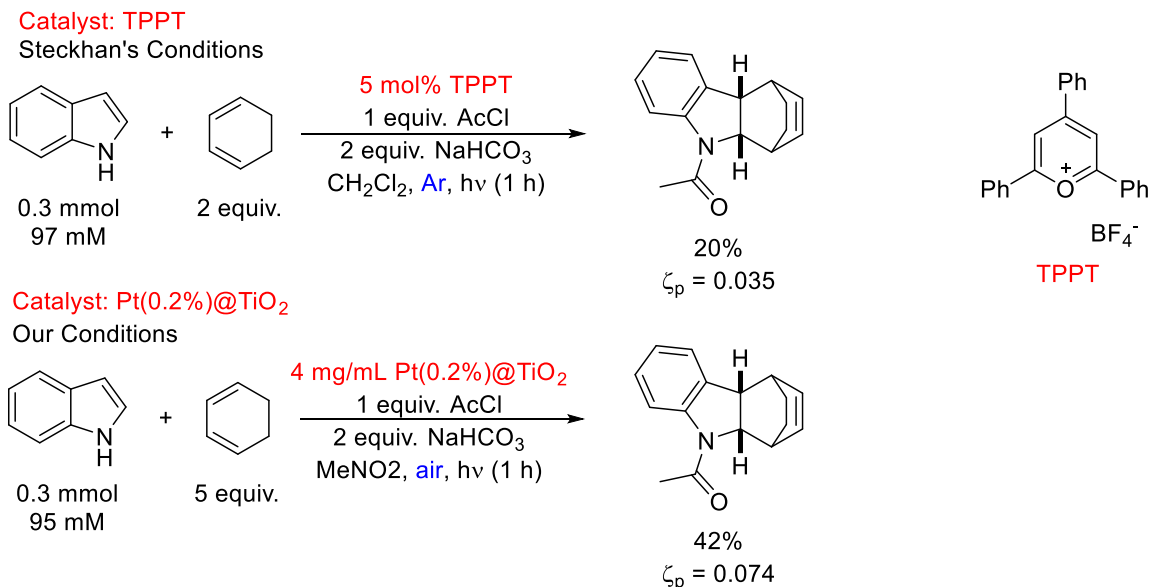


Figure 7.6. Raw data for the $\text{Ru}(\text{bpy})_3\text{Cl}_2$ actinometry experiment performed to calculate the number of photons arriving at the sample in a given period of time for the typical set up employed for the photocatalytic Diels–Alder reaction. For full procedure, see section 7.7.6.

Now that I_0 was calculated, the ζ_p for both the homogeneous photocatalytic Diels–Alder reaction developed by Steckhan and coworkers and our newly developed heterogeneous protocol mediated by $\text{Pt}(0.2\%)\text{@TiO}_2$ could be determined. In order to more accurately compare both systems, the initial reaction rates after 1 hour of irradiation from a 10 W 460 nm LED were determined (Scheme 7.8). By employing equation (1), the ζ_p for Steckhan's protocol was calculated to be 0.035, while the ζ_p for the heterogeneous protocol mediated by $\text{Pt}(0.2\%)\text{@TiO}_2$ was calculated to be 0.074. While our protocol was found to be more than twice as efficient as Steckhan's protocol, it is perhaps unfair to directly compare the homogeneous and heterogeneous protocols, as the reaction conditions differ for both protocols and it is difficult to determine the exact number of active catalytic sites on the semiconductor. However, it is clear that in the work presented in this chapter, a heterogeneous protocol for the photocatalytic Diels–Alder reaction of indoles was successfully developed, and after further optimization of the reaction condition, we were able to further improve the overall ζ_p of the reaction.



Scheme 7.8. Determination of the photonic efficiencies (ζ_p) for the homogeneous photocatalytic Diels–Alder reaction developed by Steckhan and coworkers (top), and the newly developed heterogeneous protocol mediated by Pt(0.2%)/TiO₂ (bottom).

An important aspect of any heterogeneous photocatalyst is the ability to easily separate the catalyst, and reusability. In this light, the reusability of the Pt(0.2%)/TiO₂ catalyst was examined. After irradiation, the reaction was centrifuged to separate the catalyst from the reaction mixture, and the catalyst was dried overnight under vacuum in an attempt to remove any volatile organic compounds from the catalyst surface. As seen in Figure 7.7, it was observed that the catalyst activity decreases sharply on its third and fourth use. The loss in activity is hypothesized to be due to surface poisoning from organics, in this case, indole. This is evidenced by the diffuse reflectance spectrum taken of a TiO₂ catalyst after only one use (*vide infra*).

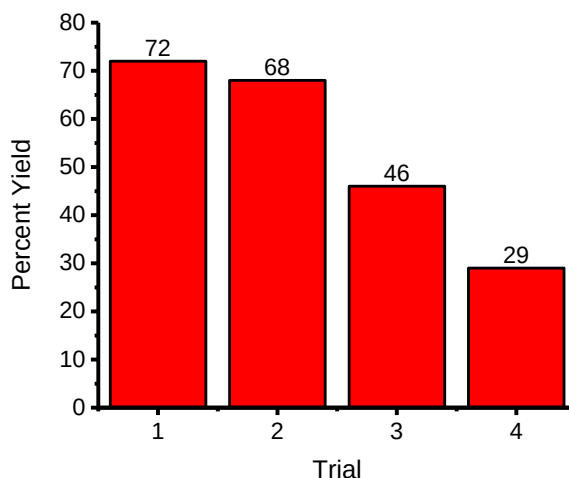


Figure 7.7. Reusability of the Pt(0.2%)@TiO₂ catalyst for the photocatalytic Diels–Alder reaction of indole and 1,3-cyclohexadiene. After irradiation, the catalyst was separated by centrifugation and dried overnight under vacuum. For full procedure, see section 7.7.8.

7.6 Mechanistic Investigation

As discussed in Section 7.4, the control experiment performed with unfunctionalized TiO₂ resulted in 60% yield of the desired tetrahydrocarbazole product (Table 7.2, Entry 6). This is an intriguing result, as none of the individual reaction components absorb at the emission wavelengths of the blue LED employed (Figure 7.8). Since light must be absorbed to promote chemical change, it is likely that a new, visible light absorbing species is produced *in situ*, and the formation of this species is what is responsible for the observed photochemistry.

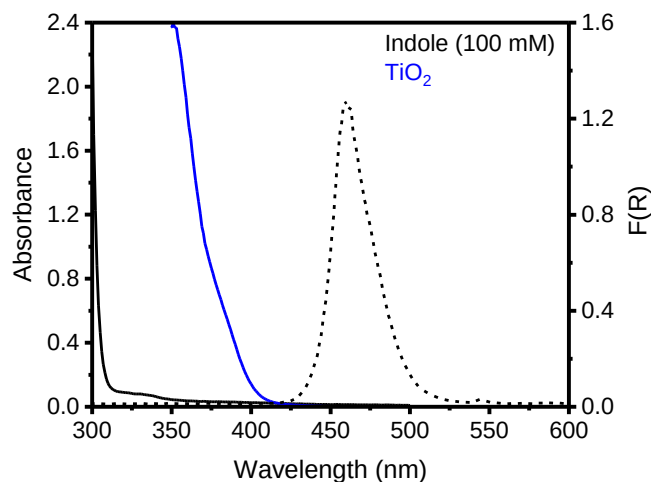


Figure 7.8. Absorption and diffuse reflectance spectra of the reaction components for the photocatalytic Diels–Alder reaction compared to the emission spectrum of the 10 W 460 nm LED employed as the irradiation source.

In order to investigate this phenomenon further, the effect of indole on the absorption spectrum of the TiO_2 photocatalyst was examined. It has been proposed that amines can associate to the surface of TiO_2 , which can facilitate the single electron oxidation of the amine.^{25–27} In previous studies, Chen and coworkers observed charge-transfer interactions between TiO_2 and benzylamine that resulted in approximately 20 nm shift of the TiO_2 band edge.^{64,65} Through the use of a sharp long pass filter at 400 nm they were able to show that part of the visible light from a xenon lamp could promote aerobic benzylamine and sulfide oxidations. Therefore, it was hypothesized that indole might be engaging in a similar interaction with the TiO_2 surface and that perhaps this interaction was responsible for a new absorption in the visible region. Thus, diffuse reflectance measurements were performed, one with TiO_2 that was exposed to MeNO_2 , and a second measurement in which the TiO_2 sample was exposed to a solution of indole in MeNO_2 . The results of these measurements are presented in Figure 7.9a. No change was observed in the absorption of TiO_2 in the presence of MeNO_2 alone; however, in the presence of the solution of indole, the formation of a new weak absorption in the visible region was observed, which

extended to roughly 520 nm. These results are also consistent with the characterization of TiO_2 that was recovered by centrifugation after the reaction (Figure 7.9b).

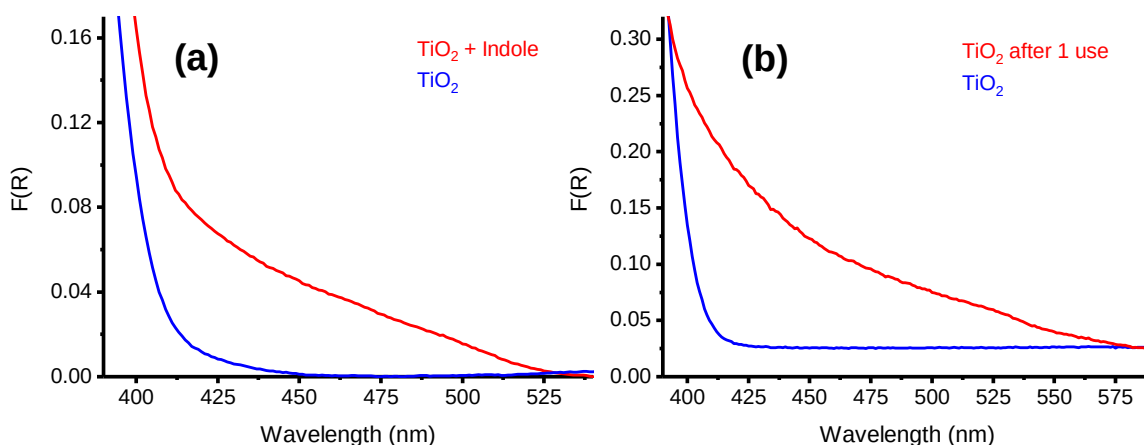


Figure 7.9. (a) Effect on the absorption of TiO_2 in the presence of indole, clearly displaying the formation of a new absorption band that extends into the visible region. Similar effects were observed with catalyst recovered by centrifugation after the reaction (b).

To confirm that formation of the absorption band was occurring due to the association of indole to the TiO_2 surface, Fourier transform infrared spectroscopy (FTIR) analysis was performed on a sample of TiO_2 that had been exposed to a 0.1 M solution of indole, the same concentration employed under standard reaction conditions. As seen in Figure 7.10, the TiO_2 -indole sample contained bands characteristic of indole, while the sample of pure TiO_2 contained no bands in this region. Interestingly, the band corresponding to the N-H stretch of indole was not present in the TiO_2 -indole sample (Figure 7.10). These results are consistent with previous studies by Busca and coworkers, who observed similar IR spectral features when indole was combined with other metal oxides such as zirconia and alumina.⁶⁶ From these data, they concluded that the adsorption of indole onto the surface of metal oxides is dissociative. Due to the lack of an observable indole N-H stretch band in the presence of TiO_2 , a similar type of interaction is proposed for this system.

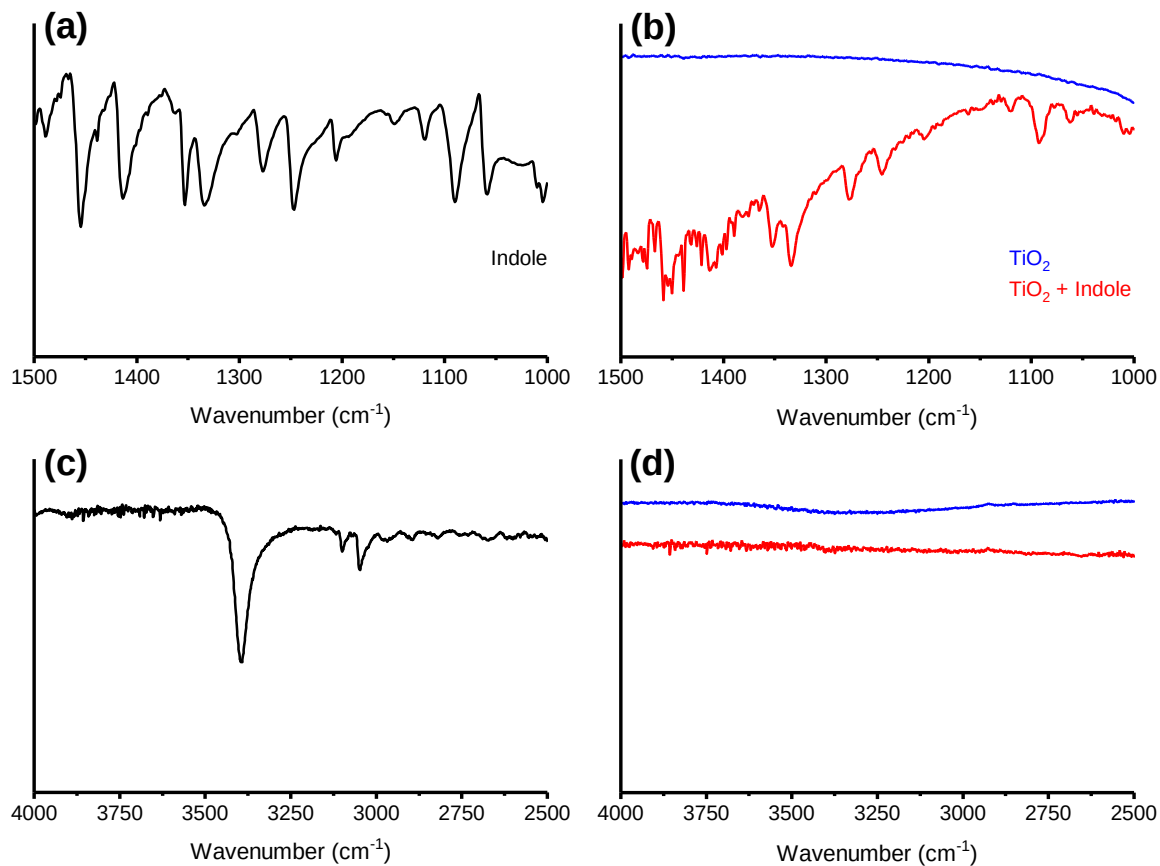


Figure 7.10. FTIR spectra of (a) pure indole (black), (b) TiO_2 and TiO_2 that was exposed to a 100 mM solution of indole (blue and red, respectively). The region of the N–H stretch band of indole (c) is not present in the TiO_2 sample that was exposed to a 100 mM solution of indole (d), indicating that adsorption occurs dissociatively.

In order to test if the absorption of this complex was responsible for the observed Diels–Alder reactivity, an action spectrum was obtained. An action spectrum can be described as a plot of the apparent quantum yield of the reaction versus the wavelength of incident photons.⁵⁹ An action spectrum can be used to help differentiate if the photoreaction is simply the consequence of direct photosensitization of the photocatalyst, or due to the photosensitization of the weak interaction leading to a band that extends to longer wavelengths (ca. 520 nm in this case). If the mechanism only involves excitation of TiO_2 (sometimes referred as *direct photocatalysis*, Figure 7.11)⁵⁹, the action spectrum would simply resemble the absorption profile of the photocatalyst. If, however, the mechanism

requires excitation of the weak complex (sometimes referred as *indirect photocatalysis*, Figure 7.11)⁵⁹, then the action spectrum would resemble the absorption profile of the TiO₂-indole complex.

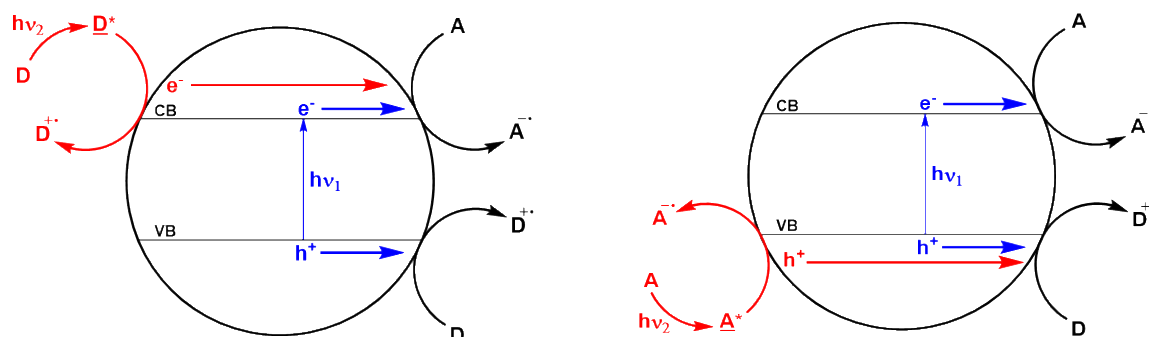


Figure 7.11. Comparison of direct (blue, $h\nu_1$) and indirect (red, $h\nu_2$) semiconductor photocatalysis. Indirect photocatalysis can occur through photosensitization of dye molecule, or through the photosensitization of an absorbed complex.⁵⁹

In order to construct an action spectrum, four experiments were performed, irradiating with LEDs of varying wavelengths (405 nm, 460 nm, 500 nm and 520 nm). The results of each experiment after 2 h of irradiation are displayed in Table 7.6.

Table 7.6. Experimental and calculated data for the construction of an action spectrum.

LED Wavelength	Yield	ν_0 (mol min ⁻¹)	Φ_{ph} (mol m ⁻² min ⁻¹)	ν_0/Φ_{ph}
405 nm	40%	1.00×10^{-6}	6.09×10^{-3}	1.64×10^{-4}
460 nm	35%	8.75×10^{-7}	6.91×10^{-3}	1.27×10^{-4}
500 nm	26%	6.50×10^{-7}	7.52×10^{-3}	8.64×10^{-5}
520 nm	28%	7.00×10^{-7}	7.82×10^{-3}	8.95×10^{-5}

Reaction Conditions: Indole (0.3 mmol, 35 mg), 1,3-CHD (1.5 mmol, 150 μ L), acetyl chloride (0.3 mmol, 21 μ L), NaHCO₃ (0.6 mmol, 50 mg), TiO₂ (12 mg), and MeNO₂ (3 mL) were placed in a 10 mL Schlenk tube and irradiated for 2 h under air using a LED light source set at 30 W/m². Yields are reported based on ¹H NMR using trimethyl(phenyl)silane as an external standard. For information on experimental set up, see section 7.7.9.

In order to simplify the calculations for the apparent quantum yields, all four LEDs were set to an irradiance of 30 W/m². The energy of a photon (E_{ph}) at each wavelength can be defined as equations (4), where h is Planck's constant (6.626×10^{-34} J s or W s²), c is the speed of light (2.998×10^8 m s⁻¹), and λ is the wavelength of the light source in nm.

$$E_{ph} = h \times (c/\lambda) \quad (4)$$

From this relationship, the number of photons arriving at the sample can be determined from the irradiance. Dividing this value by Avogadro's number gives the photon flux (Φ_{ph}), or the moles of photons (i.e., einsteins) arriving at the sample per unit time, resulting in equation (5).

$$\Phi_{ph} = \frac{(30 \text{ W m}^{-2})(\lambda)/(h)(c)}{(6.022 \times 10^{23} \text{ mol}^{-1})} \quad (5)$$

The photon flux was calculated for each LED used, and the initial rate was corrected by the photon flux for each experiment to obtain the apparent quantum yield (Table 7.6). Finally, an action spectrum can be obtained by plotting the apparent quantum yield (v_0 / Φ_{ph}) versus the wavelength of the incident photons.

In order to gain insight into the mechanism of the photocatalytic Diels–Alder reaction, the action spectrum was compared to both the diffuse reflectance spectrum of the TiO₂ catalyst and the absorption spectrum of the TiO₂-indole complex. As demonstrated in Figure 7.12, it is unlikely that the photocatalytic Diels–Alder reaction is proceeding through direct band gap excitation, as it would be expected that only the reaction performed at 405 nm would yield reactivity in that case. However, when the action spectrum is compared to the absorption spectrum of the TiO₂-indole complex, as seen in Figure 7.12, an excellent correlation between the two spectra is observed. This is compelling evidence that excitation of this complex is an integral step in initiating the photocatalytic Diels–Alder reaction.

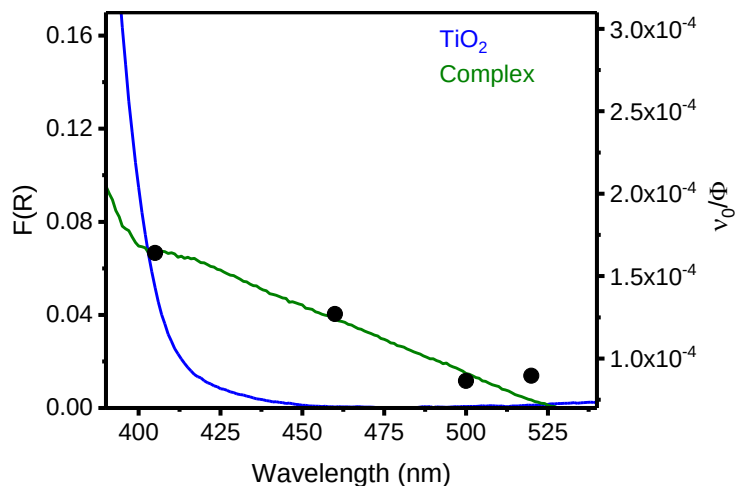


Figure 7.12. Comparison of the acquired action spectrum with the diffuse reflectance spectrum of the TiO_2 photocatalyst (blue), and with the absorption of the TiO_2 -indole complex (green).

In order to demonstrate that this phenomenon is also present in the model system employing $\text{Pt}(0.2\%)\text{@TiO}_2$, the effect of indole on the diffuse reflectance spectrum of $\text{Pt}(0.2\%)\text{@TiO}_2$ was also examined. As seen in Figure 7.13, a new absorption band extending beyond 500 nm was also observed in this case.

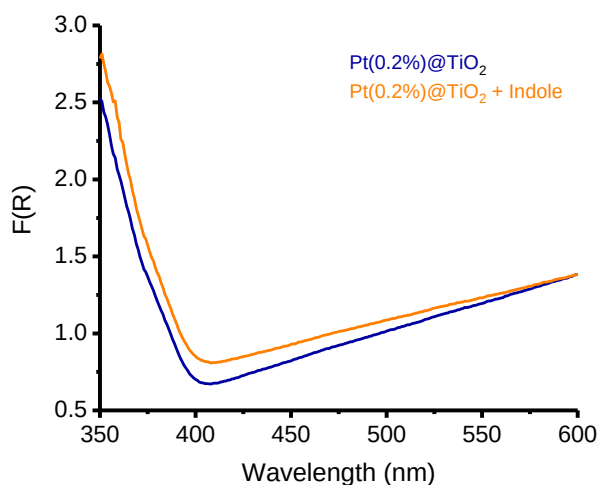


Figure 7.13. Diffuse reflectance spectra of $\text{Pt}(0.2\%)\text{@TiO}_2$ demonstrating the effect of indole on the absorption of the catalyst.

Next, the reaction was examined using the intermittent illumination technique in order to determine if there was chain propagation involved in the underlying mechanism. It was

hypothesized after the [4+2] cyclization occurred that perhaps the resulting tetrahydrocarbazole radical-cation could oxidize an indole molecule, creating a propagating chain. As discussed in Chapter 6, if chain propagation was present, a non-linear relationship between reaction conversion and the temporal profile of the intermittent illumination would exist. On the other hand, if the underlying mechanism does not contain a chain propagation component, the reaction conversion should not be affected by the temporal profile of the intermittent illumination, as the total number of photons absorbed by the sample is always the same.

In order to investigate chain propagation for this reaction, the original homogeneous variant developed by Steckhan and coworkers employing TPPT as the photocatalyst was employed.⁴⁹ For these studies, it is important that each sample absorbs the same number of photons during the period of intermittent illumination. Due to the fact that heterogeneous samples tend to scatter a portion of the incident photons, the exact number of photons absorbed by the sample is difficult to determine.⁵⁹ Therefore, by utilizing a homogeneous system, issues with light scattering can be avoided. As seen in Figure 7.14, the temporal profile of the intermittent illumination did not affect the yield of [4+2] product, therefore it can be concluded that the underlying mechanism for the photocatalytic Diels–Alder reaction does not possess a chain propagation component.

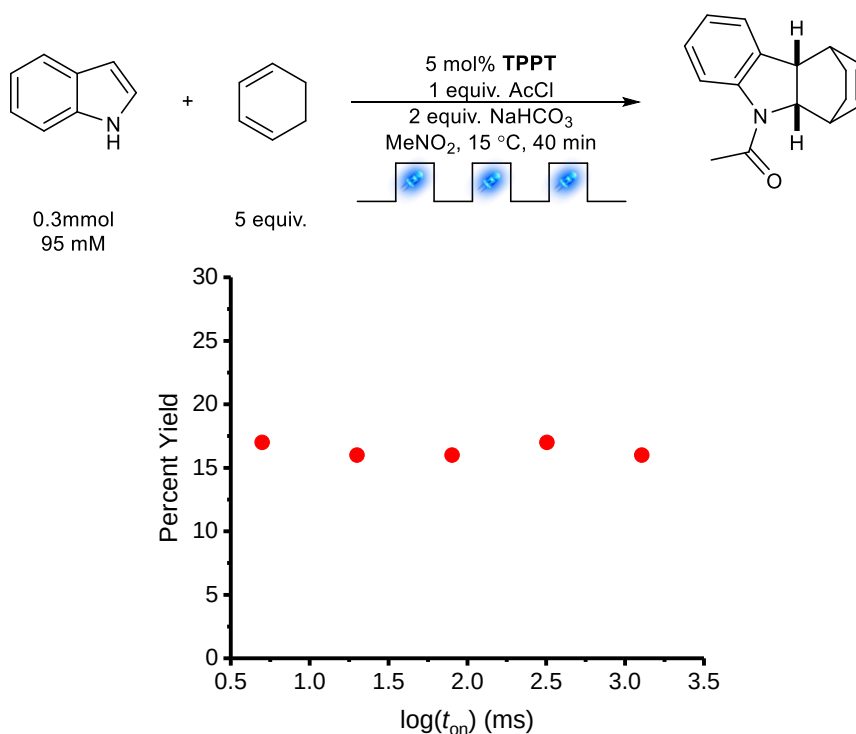
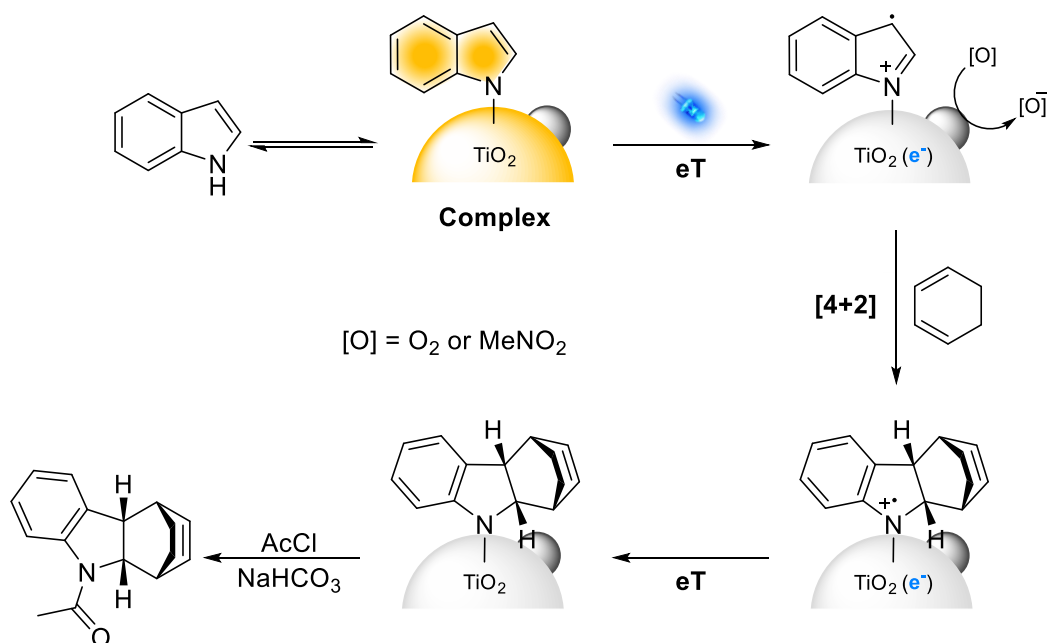


Figure 7.14. Plot of the yield of [4+2] product versus the log(*t*_{on}) for the photocatalytic Diels–Alder reaction of indole and 1,3-cyclohexadiene catalyzed by TPPT, where *t*_{on} is the length of the on-time. For information on the experimental set up and procedure, see section 7.7.10.

Based on these data, the following mechanism is proposed for the photocatalytic reaction presented in Scheme 7.9. Indole first adsorbs to the surface of TiO₂, giving rise to an absorption band that extends into the visible region. The adsorption of indole is proposed to be dissociative, similar to the behaviour observed with other metal oxides.⁶⁶ This complex can then be excited by a 460 nm LED light source, resulting in the injection of an electron into the CB of TiO₂. In order to prevent back-electron-transfer, the electron is first trapped by the Pt nanoparticles on the TiO₂ surface and then quenched by either MeNO₂ ($E_{1/2} = -0.91$ V vs. SCE)⁶⁷ or O₂ ($E_{1/2} = -0.73$ V vs. SCE)⁶⁸. Upon forming the indole radical-cation, the radical undergoes isomerization to be centered on the C3 position of the indole.⁴⁹ From there, it can then undergo a [4+2] radical cyclization with a diene. Next, another photogenerated electron from the Pt(0.2%)/TiO₂ catalyst can then reduce the

tetrahydrocarbazole radical-cation. Based on the results when employing intermittent illumination, it is unlikely that the tetrahydrocarbazole radical-cation oxidizes another indole molecule to create a propagating chain. Finally, the tetrahydrocarbazole is rapidly acylated in order to protect it from oxidation, as the corresponding tetrahydrocarbazole has a lower oxidation potential ($E_{1/2} = 0.46$ vs SCE) compared to the starting material, indole ($E_{1/2} = 1.07$ V vs. SCE).⁴⁹ Based on experimental evidence, it is likely that the majority of the reaction takes place in the vicinity of the TiO₂ surface.



Scheme 7.9. Proposed mechanism for the photocatalytic Diels–Alder reaction of indole with electron-rich dienes mediated by Pt(0.2%)@TiO₂.

7.7 Conclusion

In this chapter, the first example of employing a heterogeneous semiconductor photocatalyst for the photocatalytic Diels–Alder reaction of indoles was presented. TiO₂ functionalized with Pt nanoparticles was found to efficiently promote radical-cation [4+2] cycloadditions between indoles and 1,3-dienes in the *cis*-configuration. The reaction was

also found to tolerate common chloroformate protecting groups such as Fmoc and Troc, which is beneficial if further functionalization of the tetrahydrocarbazole product is desired.

In order to compare the efficiency of the newly developed heterogeneous protocol with the seminal homogeneous system developed by Steckhan and coworkers, the photonic efficiencies of each reaction was determined. A photonic efficiency takes into account all of the photons which arrive at the sample, which simplifies the quantitative comparison with heterogeneous photoreactions where it is difficult to determine the amount of photons which were absorbed. In doing this, it was found that our newly optimized heterogeneous system had a photonic efficiency of 0.074, over twice as efficient as the seminal homogeneous system by Steckhan. While it is difficult to directly compare homogeneous and heterogeneous protocols, it can be seen that upon optimization of our heterogeneous protocol, a system that is even more efficient than the homogeneous variant could be obtained. This heterogeneous protocol also offers the advantage easy catalyst separation from the reaction mixture, and the Pt(0.2%)/TiO₂ catalyst can also be reused several times before losing its photocatalytic activity.

Interestingly, when performing control reactions during the optimization of this protocol, it was discovered that the reaction performed with unfunctionalized TiO₂ gave the tetrahydrocarbazole product in 60% yield after 5 hours of irradiation with a 460 nm LED. This was surprising, as TiO₂ does not absorb in this region, and yet when compared to the model system with Pt(0.2%)/TiO₂, it was only 12% less efficient at mediating the photocatalytic Diels–Alder reaction. It was discovered that an interaction between indole and the surface of TiO₂, which was confirmed by FTIR spectroscopy, led to the formation of a new visible light absorbing band. Through the use of an action spectrum, it was determined that the excitation of this TiO₂-indole complex was crucial in initiating the [4+2]

cycloaddition. It is anticipated that the formation of these visible light absorbing complexes, now demonstrated with benzylamine by Chen and coworkers, and now in the work presented herein with indole, is perhaps a more general phenomenon that could greatly increase the utility of TiO₂ in organic synthesis.

7.8 Experimental Details

7.8.1. General Information. Indoles were purchased from Fisher Scientific and Sigma Aldrich and purified by recrystallization from hexanes before use. 1,3-Cyclohexadiene was purchased from Fisher Scientific and purified by distillation in the presence of NaBH₄ before use. Acetyl chloride was purchased from Fisher Scientific and purified by distillation in the presence of *N,N*-dimethylaniline before use. MeNO₂ was purchased from Sigma Aldrich, was purified by drying over CaCl₂ followed by distillation, and was then stored under an argon atmosphere. The TiO₂ P25 employed was provided as a gift from Nippon Aerosil Co., Ltd (Batch #: 4168091398) and used as received. Chloroplatinic acid hydrate was purchased from Sigma Aldrich and used as received. All LEDs employed in this work were purchased from LedEngin. Flash column chromatography was performed using 230-400 mesh silica gel. All ¹H and ¹³C were recorded on a Bruker AVANCE 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm from the solvent resonance as the internal standard (CDCl₃: δ 7.26 ppm); ((CD₃)₂CO: δ 2.05 ppm); ((CD₃)₂SO: δ 2.50 ppm). UV-Vis spectra were recorded using an Agilent Cary 7000 Spectrophotometer, and diffuse reflectance spectra were recorded using either an Agilent Cary 100 or Cary 7000 spectrophotometer. IR spectra were recorded with an Agilent Technologies Cary 630 FTIR spectrometer equipped with a diamond ATR module.

7.8.2. General Procedure for the Photocatalytic Diels–Alder Reaction. To an oven dried 10 mL Schlenk tube equipped with a magnetic stir bar was added indole (0.3 mmol,

35 mg), Pt(0.2%)TiO₂ (12 mg), and NaHCO₃ (0.6 mmol, 50 mg). The vessel was then charged with MeNO₂ (3 mL), and freshly distilled 1,3-cyclohexadiene (1.5 mmol, ~150 µL) and acetyl chloride (0.3 mmol, 21 µL) was added. The reaction mixture was then sonicated until the Pt(0.2%)@TiO₂ catalyst was completely dispersed. The reaction was then irradiated with a 10 W 460 nm LED for 5 h. Following irradiation, the reaction was transferred to a 15 mL centrifuge tube and centrifuged at 3,000 rpm for 10 min. The supernatant was then transferred to a round bottomed flask, and the solvent was evaporated by rotary evaporation. The crude reaction mixture was then analyzed by ¹H NMR to determine the *endo:exo* ratio, followed by purification by flash column chromatography to give pure *endo* and *exo* isomers of the desired final product.

7.8.3. Synthesis of Pt(0.2%)@TiO₂. To a 500 mL round bottom flask equipped with a magnetic stir bar was added 60 mg H₂PtCl₆, 60 mL of 1% sodium citrate in H₂O (w/w) and 240 mL of deionized H₂O. The mixture was then refluxed for 4 hours and then cooled back to room temperature. 100 mL of this solution was then added to a 250 mL Erlenmeyer flask containing TiO₂ P25 (2 g) and NaCl (10 g) and the mixture was stirred vigorously overnight. This procedure was repeated for the remaining 200 mL of the Pt nanoparticle solution from the first step of the synthesis. The catalyst was then distributed into 50 mL centrifuge tubes, and the catalyst was centrifuged at 5,000 rpm for 15 minutes. The supernatant was decanted, followed by the addition of freshwater and re-dispersion of the catalyst. The catalyst was then centrifuged again at 5,000 rpm for 15 minutes, and the entire washing procedure was repeated an additional two times. The catalyst was then dried in a vacuum desiccator overnight, crushed into a powder, and then dried for an additional two days at 120 °C. ICP-MS analysis in previous work by the Scaiano group determined the loading of Pt nanoparticles to be 0.2% (w/w).

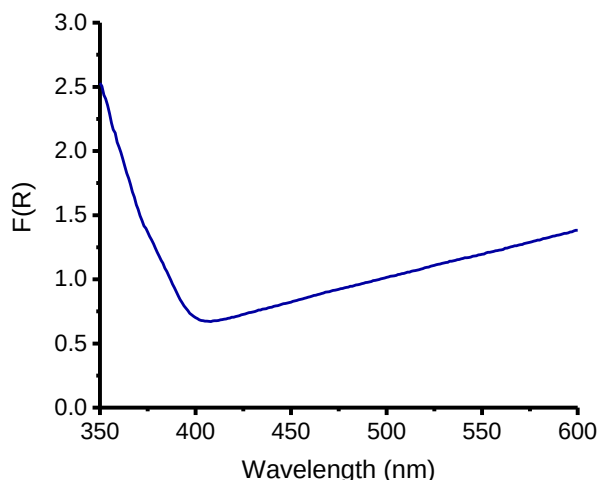


Figure 7.15. Diffuse reflectance spectrum of Pt(0.2%)@TiO₂.

7.8.4. Synthesis of Reaction Substrates.

5-Ethylindole: An oven-dried 50 mL round bottom flask equipped with a magnetic stir bar was charged with 5-bromoindole (3 mmol, 588 mg), Cs₂CO₃ (9 mmol, 2.93 g), and Pd(dpf)Cl₂ (0.06 mmol, 50 mg) under argon atmosphere, followed by the addition of 6 mL of dry THF. To this stirred suspension was added BEt₃ (1.0 M in THF, 9 mmol, 9 mL), and the mixture was refluxed for 6 hours. The reaction mixture was then cooled to 0 °C, and 9 mL of 50% aqueous acetic acid was added, and the reaction was heated to reflux for an additional 30 minutes. The reaction was then cooled to room temperature, and extracted with ether (x3). The combined organic phases were washed with water (x1) and brine (x1) and dried with MgSO₄. The crude was concentrated by rotary evaporation and purified by flash column chromatography (4:1 Hex:EtOAc) to give the title compound as a pale yellow oil in 50% isolated yield (216 mg).

Diethyl 3,4-diethylenecyclopentane-1,1-dicarboxylate: To an oven-dried 250 mL round bottom flask equipped with a magnetic stir bar was added NaH (18.8 mmol, 450 mg) and dry THF (60 mL) under an argon atmosphere. The mixture was cooled to 0 °C, and diethyl allylmalonate (15.2 mmol, 3 mL) was added dropwise. The reaction mixture was stirred

for 10 minutes at room temperature, and propargyl bromide (18.6 mmol, 3.2 mL of an 80% wt% solution in toluene) was added. The reaction mixture was stirred at room temperature overnight, and then 20 mL of a saturated aqueous solution of NH₄Cl was added. The aqueous layer was extracted with EtOAc (x3) and the combined organic phases were washed with brine, dried over MgSO₄, and concentrated by rotary evaporation. The crude was purified by flash column chromatography (95:5 Hex:EtOAc) to give diethyl 2-allyl-2-(prop-2-ynyl)malonate as a colourless oil in 94% isolated yield (3.40 g).

Next, an oven-dried 100 mL round bottom flask equipped with a magnetic stir bar was charged with Pd(OAc)₂ (0.226 mmol, 51 mg) and triphenylphosphine (0.228 mmol, 60 mg), followed by the addition of a solution of diethyl 2-allyl-2-(prop-2-ynyl)malonate (4.53 mmol, 1.08 g) in MeCN (45 mL). The reaction was heated to reflux for 1.5 hours and cooled to room temperature. The reaction was concentrated by rotary evaporation, and the crude was purified by flash column chromatography (95:5 Hex:EtOAc) to yield the title compound as a colourless oil in 51% isolated yield (550 mg). **Note:** The title compound polymerizes in the presence of light, so the final step was performed in the dark, and the diene was stored at -30 °C in a degassed round bottom flask covered with aluminum foil and was used within 24 hours.

7.8.5. Procedure for the [4+2] cycloaddition of *N*-Vinylcarbazole and 2,4-Dimethyl-1,3-pentadiene. To an oven-dried test tube equipped with a magnetic stir bar was added *N*-vinylcarbazole (0.6 mmol, 116 mg) and CdS (17 mg). Then, 5 mL of anhydrous CH₂Cl₂ was added, and the mixture was sonicated until the CdS was completely dispersed. The reaction was then irradiated for 18 hours using a 16 W blue LED floodlamp. The reaction was then filtered through a celite plug, washing with CH₂Cl₂, and then concentrated by

rotary evaporation. Yields were determined by ¹H NMR analysis employing 1,3,5-trimethoxybenzene as an external standard.

7.8.6. Ru(bpy)₃Cl₂ Visible Light Actinometry Experiments. A 100 mL stock solution of the actinometer was made with 0.19 mM Ru(bpy)₃Cl₂ (14.2 mg) and 0.10 mM DPA (3.3 mg) in MeCN. 3 mL of the stock solution was added to a quartz cuvette, and a UV-Vis spectrum was recorded from 450–350 nm (*A*_{initial}). The cuvette was then placed in the 460 nm LED set up employed for the photocatalytic Diels–Alder reactions, and was irradiated for 30 seconds. Following irradiation, the absorption spectrum was recorded again from 450–350 nm (*A*_{final}). This was repeated in triplicate, and employing the equations laid out in section 7.4, the amount of photons arriving at the sample (*I*₀) was calculated to be $4.7 \pm 0.1 \times 10^{-7} \text{ mol hv s}^{-1}$.

7.8.7. Procedure for the Homogeneous Photocatalytic Diels–Alder Reaction. To an oven dried 10 mL Schlenk tube equipped with a magnetic stir bar was added indole (0.3 mmol, 35 mg), triphenylpyrylium tetrafluoroborate (0.015 mmol, 6 mg), and NaHCO₃ (0.6 mmol, 50 mg). The vessel was then charged with CH₂Cl₂ (3 mL), and freshly distilled 1,3-cyclohexadiene (0.6 mmol, ~60 μL) and acetyl chloride (0.3 mmol, 21 μL) was added. The reaction mixture degassed by purging with argon for 15 minutes. The reaction was then irradiated with a 10 W 460 nm LED for 1 h, and then the solvent was evaporated by rotary evaporation. The crude reaction mixture was then analyzed by ¹H NMR employing trimethyl(phenyl)silane as an external standard to determine the yield and *endo:exo* ratio.

7.8.8. Procedure for Catalyst Reusability Experiments. To an oven dried 10 mL Schlenk tube equipped with a magnetic stir bar was added indole (0.3 mmol, 35 mg), Pt(0.2%)TiO₂ (12 mg), and NaHCO₃ (0.6 mmol, 50 mg). The vessel was then charged with MeNO₂ (3 mL), and freshly distilled 1,3-cyclohexadiene (1.5 mmol, ~150 μL) and acetyl

chloride (0.3 mmol, 21 μ L) was added. The reaction mixture was then sonicated until the Pt(0.2%)/TiO₂ catalyst was completely dispersed. The reaction was then irradiated with a 10 W 460 nm LED for 5 h. Following irradiation, the reaction was transferred to a 15 mL centrifuge tube and centrifuged at 3,000 rpm for 10 min. The supernatant was then transferred to a round bottomed flask, and the solvent was evaporated by rotary evaporation. The catalyst was then re-dispersed in CH₂Cl₂ and centrifuged at 3,000 rpm for 10 minutes. The CH₂Cl₂ washing was repeated once more. The catalyst was dried under vacuum overnight, and re-dispersed in 3 mL of MeNO₂ for the next trial.

7.8.9. Experimental Set Up for the Action Spectrum Experiments. In order to perform the action spectrum for the photocatalytic Diels–Alder reaction, a set up needed to be designed the photon flux delivered by each LED could be calculated. The simplest method was to employ a spectroradiometer to measure the output of each LED (in W/m²). Using the spectroradiometer, each LED was set to a total output power of 30 W/m², and using the equations outlined in section 7.5, the mole of photons being delivered from the LED per unit time was calculated. Figure 7.16 shows a photograph of the set up employed, and the emission spectra of each LED set to 30 W/m² are shown in Figure 7.17.

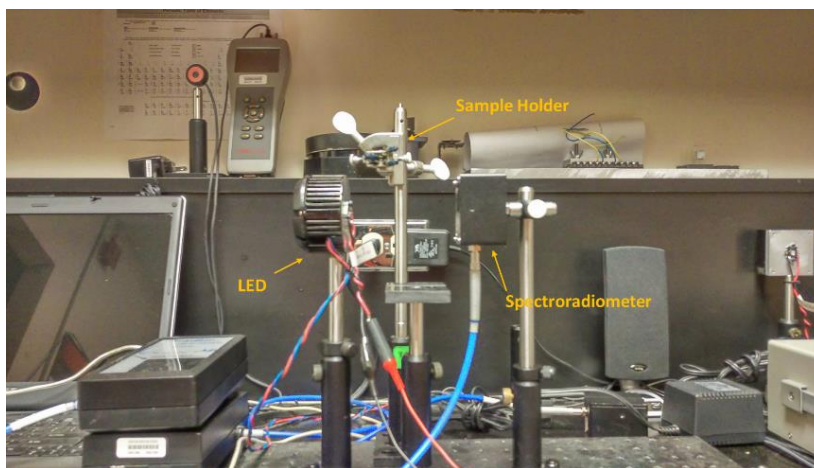


Figure 7.16. Photograph of the experimental set up employed for the action spectrum experiments.

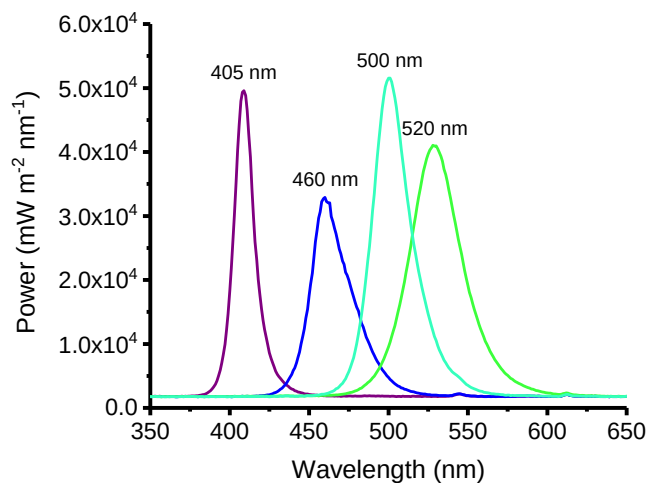


Figure 7.17. Emission spectra for LEDs utilized for the action spectrum measurements.

7.8.10. Experimental Set Up for the Intermittent Illumination Experiments. Typically, indole (0.3 mmol, 35 mg), 1,3-cyclohexadiene (1.5 mmol, ~150 μL), acetyl chloride (0.3 mmol, 21 μL), triphenylpyrylium tetrafluoroborate (0.015 mmol, 6 mg), NaHCO_3 (0.6 mmol, 50 mg) and CH_2Cl_2 (3 mL) were added to a glass test tube equipped with a magnetic stir bar and fitted with a septum. The reaction mixture was then degassed with argon for 15 minutes before it was intermittently irradiated at 15 °C for 40 minutes (total light on time) using a pulsed 460 nm LED, which was powered by a constant current driver (designed and built in house) and controlled by a digital delay/pulse generator (Stanford Research System Inc.- MODEL DG535). In all cases, the system was interfaced with an oscilloscope (Tektronix–MODEL TDS3052), which monitored the delivered voltage and resulting current of the system. The system was also interfaced with a photodiode, which allowed the shape and duration of the light pulse emitted from the LED to be monitored. This also allowed for real time monitoring of the light pulse to ensure that the appropriate light on:light off ratio was being employed. A light on:light off ratio of 1:2 was used in all trials, and the length of the on and off times were increased proportionally with each successive

trial. After the irradiation, the reaction mixture was concentrated by rotary evaporation, and the yield was determined using ¹H NMR using trimethyl(phenyl)silane as an external standard.

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8. Conclusions and Future Directions

8.1 Conclusions

The work presented in this thesis was inspired by three goals, which are summarized below.

The first goal was to develop inexpensive alternatives to catalyze photoredox transformations. As discussed throughout this dissertation, the vast majority of photoredox transformations presented require the use of expensive ruthenium and iridium precious metal catalysts. In chapters 3 to 5, we explored the use of organic dyes for photoredox transformations. In Chapter 3, we demonstrated that Methylene Blue, an inexpensive thiazine dye, could mediate the oxidative hydroxylation of a variety of arylboronic acids. More importantly, Methylene Blue was also found to be more efficient at promoting the transformation when directly compared to Ru(bpy)₃Cl₂, the photocatalyst employed in the seminal report.¹

In chapter 4, we demonstrated that Methylene Blue could also promote radical trifluoromethylation reactions, a reaction of importance to both the pharmaceutical and agricultural industries. Our system, which employed Methylene Blue as the photocatalyst and Togni's reagent as the trifluoromethyl source, was able to promote the radical trifluoromethylation of electron-rich heterocycles, as well as the radical hydrotrifluoromethylation of terminal alkenes and alkynes. A trapping experiment with TEMPO was able to confirm that the reaction was indeed proceeding through a free-radical mechanism.

While many of the reported photoredox transformations are mediated by ruthenium and iridium complexes, it was hypothesized that this was due to their photophysical and electrochemical properties being readily available for over 30 years. In order to help popularize organic dyes for photoredox transformations, we characterized both the photophysical and electrochemical properties of a variety of organic dyes, and provided all the necessary information required when

designing a photoredox system; these are presented in a convenient appendix. The efficacy of these dyes for photoredox transformations was also demonstrated with both the dehalogenation of a vicinal bromo compound, as well as the light mediated Aza Henry reaction.

Another strategy for developing inexpensive alternatives for photoredox transformations is to employ heterogeneous semiconductor particles, like TiO_2 , as the photocatalyst. These heterogeneous catalysts offer the advantage of being easily separated from the reaction mixture, which also allows for the photocatalyst to be reused. Due to the abundance and low cost of TiO_2 , we decided to employ a TiO_2 photocatalyst functionalized with Pt nanoparticles for the photocatalytic Diels–Alder reaction of indoles. The functionalized $\text{Pt}(0.2\%)\text{@TiO}_2$ catalyst offered the advantage of improved reaction efficiencies compared to unfunctionalized TiO_2 by slowing down electron-hole recombination events. The reaction was found to be broad in scope, the catalyst could be reused up to three times, and our protocol was also found to have a higher photonic efficiency compared to the seminal homogeneous reaction employing triphenylpyrylium as the photocatalyst.²

The second goal we aimed to achieve in this work was to gain an understanding of the excited state kinetics and the underlying mechanisms in order to rationalize and improve the overall reactivity of photoredox transformations. In chapter 2, we investigated the reactivity of α -aminoalkyl radicals in photoredox transformations, specifically, the 5-exo-trig cyclization of a (bis)enone. The fate of these radicals are often ignored during the development of photoredox transformations, which is puzzling due to their well-established ability to act as a reducing agent. Using two independent methods, we were able to demonstrate that α -aminoalkyl radicals can indeed promote reductive photoredox transformations, indicating that the reactivity of these radicals should not be ignored, and in fact, should be one of the parameters of optimization when developing novel photoredox protocols.

In chapter 3, we observed that Methylene Blue was more efficient at promoting the oxidative hydroxylation of phenylboronic acid compared to the seminal photocatalyst, $\text{Ru}(\text{bpy})_3\text{Cl}_2$. Using laser flash photolysis techniques, we were able to demonstrate that this difference in reactivity originated from the excited state quenching of the photocatalyst by $i\text{Pr}_2\text{NEt}$, the electron-donor. This is an integral step in the overall mechanism, as it generates the catalytically active reducing agents in each case. The rate constant for this electron-transfer step was found to be two orders of magnitude higher when employing Methylene Blue as the photocatalyst compared to $\text{Ru}(\text{bpy})_3\text{Cl}_2$, which ultimately led to a more efficient overall reaction.

Another example of how excited state kinetics can be employed to gain an understanding of the underlying reactivity was presented in chapter 3. For the oxidative hydroxylation of phenylboronic acid, an induction period was observed when following the reaction over time. Using laser flash photolysis techniques, we were able to determine that this was due to the starting material, phenylboronic acid, being a more efficient quencher of the triplet excited state than the final product, phenol. These quenching events are competing against quenching by $i\text{Pr}_2\text{NEt}$, the desired reaction to generate the catalytically active reducing agents in this system. As the greater quencher (phenylboronic acid) is consumed, the probability for triplet quenching by $i\text{Pr}_2\text{NEt}$ increases, and the reaction becomes more efficient.

Excited state kinetics can also be used to facilitate optimization of reaction conditions. In chapter 4, we employed laser flash photolysis techniques to examine the excited state kinetics of all the reaction components in our radical trifluoromethylation protocol in order to gain an understanding of how to improve the reaction conditions. In order to improve the first electron-transfer step to generate the semi-reduced form of Methylene Blue and an α -aminoalkyl radical, we employed TMEDA, which had the highest rate constant for electron-transfer of all the electron-donors tested. In order to increase the percentage of triplet excited states intercepted by TMEDA, the desired

quenching event, we chose the trifluoromethyl radical source which had the lowest rate constant for triplet quenching, and eliminated oxygen, a potent triplet quencher, from the system. This understanding of the behavior of all the components in our system allowed us to quickly reach the optimized reaction conditions for our photocatalytic radical trifluoromethylation protocol.

In chapter 7, during the development of a photocatalytic Diels–Alder reaction between indole and 1,3-cyclohexadiene mediated by Pt(0.2%)/TiO₂, we performed a simple control reaction with unfunctionalized TiO₂. To our surprise, the reaction proceeded with 60% yield, despite none of the reagents possessing an absorption in the region of irradiation. By examining the TiO₂ photocatalyst in the presence of indole, we discovered the formation of a new visible light absorption band, indicative of indole associating to the semiconductor surface. This association was confirmed using FTIR studies. By measuring an action spectrum, we were able to demonstrate that excitation of this complex was integral in promoting the Diels–Alder reaction. This is an example which highlights the importance of performing control reactions when developing novel photoredox transformations, as this key mechanistic insight would never have been discovered if we did not perform a control reaction with unfunctionalized TiO₂.

Finally, our third goal was to develop novel methods which would facilitate mechanistic investigations for synthetic laboratories who may not possess the specialized equipment or expertise to perform such studies. In chapter 6, we presented a visible light actinometer based on the ubiquitous photocatalyst, Ru(bpy)₃Cl₂, to aid in the characterization of chain propagation in photoredox transformations. This actinometer offers many advantages compared other visible light actinometers, such as the ferrioxalate actinometer, such as being easy to quantify, being able to withstand higher intensities common with LEDs typically employed for photoredox transformations, is highly reproducible, and shows a linear dependence with power. Perhaps most importantly, the actinometer is based off Ru(bpy)₃Cl₂, the photocatalyst of choice for many

practioners of photoredox. This completely eliminates the need for spectral matching, as the actinometer and the photocatalyst will be the same molecule.

8.2 Future Directions

The work presented in this thesis demonstrates that both organic dyes and heterogeneous semiconductor particles can be employed as inexpensive alternatives for photoredox catalysis. While organic dyes appear quite promising in this regard, it would be ideal to continue with heterogeneous photocatalysts for the future development of the field, as they provide the advantage of being easily separated and frequently recyclable. However, drawbacks still remain with employing heterogeneous semiconductors, most notably, the lack of visible light absorption of many oxide based semiconductors, and the fast rate of electron-hole recombination.

In chapter 7, we demonstrated that the association of indole to the surface of TiO_2 created a new absorption band that could be excited with visible light irradiation. This was also observed in previous reports by Chen in the presence of benzylamine.^{3,4} It is possible, therefore, that this may be a more general phenomenon, which would increase the utility of TiO_2 in organic synthesis. For example, glucose is also known to associate to the surface of TiO_2 , creating a visible light absorbing ligand-to-metal charge-transfer absorption band.⁵ Therefore, the generality of this phenomenon, and how it can be applied to visible light-mediated organic synthesis, merits further investigation.

In order to decrease electron-hole recombination, the general strategy has been to decorate TiO_2 with Pt nanoparticles, such as the work presented in chapter 7. However, due to the high cost of Pt, it would be beneficial to employ abundant and inexpensive first row transition metals, such as iron, cobalt, nickel, and copper for this purpose. Therefore, the efficiency of these metal or metal oxide nanoparticles for decreasing electron-hole recombination should be investigated. As an added benefit, the metallic nanoparticles could also be employed as an independent catalyst in a

reaction, opening the door to performing dual catalytic reactions with one simple and inexpensive catalyst. Dual catalytic reactions by coupling photoredox and transition metal catalysis has gained an increasing amount of interest over the last couple of years⁶, therefore creating a heterogeneous catalyst with dual functionality that can be easily separated and reused would be incredibly valuable in the field.

8.3 Claims to Original Research

- (i) The first example in which the participation of α -aminoalkyl radicals as a reducing agent in photoredox catalysis was demonstrated.
- (ii) Development of photocatalytic systems employing Methylene Blue as a homogeneous photoredox catalyst, which include the oxidative hydroxylation of arylboronic acids and radical trifluoromethylation reactions.
- (iii) Characterization of both the photophysical and electrochemical properties of a variety of organic dyes.
- (iv) Development of a visible light actinometric system based on $\text{Ru}(\text{bpy})_3\text{Cl}_2$ and 9,10-diphenylanthracene.
- (v) Development of a photocatalytic system employing $\text{Pt}(0.2\%)\text{@TiO}_2$ as a heterogeneous photoredox catalyst for the photocatalytic Diels–Alder reaction of indoles.
- (vi) Characterization of a complex between indole and the surface of TiO_2 , enabling visible light photochemistry with TiO_2 .

8.4 Publications

8.4.1 Publications Resulting from Work Presented in this Thesis

- (i) Ismaili, H.; Pitre, S. P.; Scaiano, J. C. Active participation of amine-derived radicals in photoredox catalysis as exemplified by a reductive cyclization. *Cat. Sci. Technol.*, **2013**, 3, 935.
- (ii) Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. Mechanistic Insights and Kinetic Analysis for the Oxidative Hydroxylation of Arylboronic Acids by Visible Light Photoredox Catalysis: A Metal-Free Alternative. *J. Am. Chem. Soc.*, **2013**, 135, 13286.
- (iii) Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. Metal-Free Photocatalytic Radical Trifluoromethylation Utilizing Methylene Blue and Visible Light Irradiation. *ACS Catal.*, **2014**, 4, 2530.
- (iv) Pitre, S. P.*; McTiernan, C. D.*; Vine, W.; DiPucchio, R.; Grenier, M.; Scaiano, J. C. Visible-Light Actinometry and Intermittent Illumination as Convenient Tools to Study Ru(bpy)₃Cl₂ Mediated Photoredox Transformations. *Sci. Rep.*, **2015**, 5, 16397. (*These authors contributed equally to this work)
- (v) Pitre, S. P.; McTiernan, C. D.; Scaiano, J. C. Library of Cationic Organic Dyes for Visible-Light-Driven Photoredox Transformations. *ACS Omega*, **2016**, 1, 66.
- (vi) Pitre, S. P.; Yoon, T. P.; Scaiano, J. C. Titanium dioxide visible light photocatalysis: surface association enables photocatalysis with visible light irradiation. *Chem. Commun.*, **2017**, 53, 4335.
- (vii) Pitre, S. P.; Scaiano, J. C.; Yoon, T. P. One-Pot Three-Component of Indoles Mediated by Visible Light Titanium Dioxide Photocatalysis. *Submitted*.

8.4.2 Publications Resulting from Work Not Presented in this Thesis

- (i) McTiernan, C. D.; Pitre, S. P.; Scaiano, J. C. Photocatalytic Dehalogenation of Vicinal Dibromo Compounds Utilizing Sexithiophene and Visible-Light Irradiation. *ACS Catal.*, **2014**, *4*, 4034.
- (ii) McTiernan, C. D.; Pitre, S. P.; Ismaili, H.; Scaiano, J. C. Heterogeneous Light-Mediated Reductive Dehalogenations and Cyclizations Utilizing Platinum Nanoparticles on Titania (PtNP@TiO₂). *Adv. Synth. Catal.*, **2014**, *356*, 2819.
- (iii) Garcia, A. M.; de Alwis Weerasekera, H.; Pitre, S. P.; McNeill, B.; Lissi, E.; Edwards, A. E.; Alarcon, E. I. Photodynamic performance of zinc phthalocyanine in HeLa cells: A comparison between DPCC liposomes and BSA as delivery systems. *J. Photochem. Photobiol., B*, **2016**, *163*, 385.
- (iv) McCallum, T.; Pitre, S. P.; Morin, M.; Scaiano, J. C.; Barriault, L. The Photochemical Alkylation and Reduction of Heteroarenes. *Submitted*.

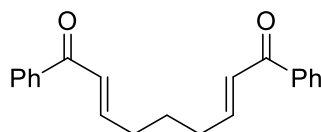
8.5 References

1. Zou, Y.-Q.; Chen, J.-R.; Liu, X.-P.; Lu, L.-Q.; Davis, R. L.; Jørgensen, K. A.; Xiao, W.-J., *Angew. Chem. Int. Ed.* **2012**, *51*, 784-788.
2. Gieseler, A.; Steckhan, E.; Wiest, O.; Knoch, F., *J. Org. Chem.* **1991**, *56*, 1405-1411.
3. Lang, X.; Leow, W. R.; Zhao, J.; Chen, X., *Chem. Sci.* **2015**, *6*, 1075-1082.
4. Lang, X.; Ma, W.; Zhao, Y.; Chen, C.; Ji, H.; Zhao, J., *Chem. Eur. J.* **2012**, *18*, 2624-2631.
5. Kim, G.; Lee, S.-H.; Choi, W., *Appl. Catal., B.* **2015**, *162*, 463-469.
6. Skubi, K. L.; Blum, T. R.; Yoon, T. P., *Chem. Rev.* **2016**, *116*, 10035-10074.

Supplementary Information

I. Compound Characterization

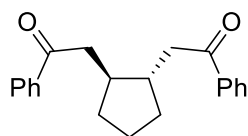
Chapter 2



(E,E)-1,7-Dibenzoyl-1,6-heptadiene (2a): Prepared according to the procedure described in section 2.5.2 (page 40). Purified by flash column chromatography (10:1 Hex:EtOAc) to give the title compound as a colourless oil in 41% isolated yield (262 mg).

^1H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.84 (m, 4H), 7.60 – 7.50 (m, 2H), 7.46 (dd, J = 8.3, 6.9 Hz, 4H), 7.06 (dt, J = 15.3, 6.8 Hz, 2H), 6.92 (dt, J = 15.4, 1.3 Hz, 2H), 2.46 – 2.31 (m, 4H), 1.78 (p, J = 7.5 Hz, 2H).

Reference: *Chem. Commun.* **2011**, 47, 1491.



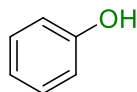
2,2'-((1S,2S)-Cyclopentane-1,2-diyl)bis(1-phenylethanone) (2e): Prepared according to procedures 2.5.3 and 2.5.4 (page 40) from reductive cyclization of (*E,E*)-1,7-Dibenzoyl-1,6-heptadiene using a source of α -aminoalkyl radicals. Purified by preparative thin layer chromatography (5:1 Hex:EtOAc) to give the title compound as a colourless oil as a single diastereomer in 73-

83% isolated yield.

^1H NMR (400 MHz, Chloroform-*d*) δ 7.99 – 7.91 (m, 4H), 7.61 – 7.50 (m, 2H), 7.45 (dd, J = 8.3, 6.9 Hz, 4H), 3.20 (dd, J = 16.5, 4.3 Hz, 2H), 2.95 (dd, J = 16.5, 8.2 Hz, 2H), 2.28 – 2.12 (m, 2H), 2.04-1.96 (m, 2H), 1.68-1.61 (m, 1H), 1.33-1.23 (m, 1H).

Reference: *Chem. Sci.* **2011**, 2, 2115.

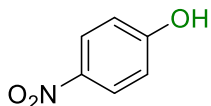
Chapter 3



Phenol (3b): Prepared according to general procedure 3.7.2 (page 68) from phenylboronic acid (0.6 mmol, 73 mg), *i*Pr₂Net (3 mmol, 520 μ L), and Methylene Blue (0.006 mmol, 2.2 mg) in 10 mL 4:1 MeCN:H₂O to give the title compound as a colourless solid in 100% conversion by ^1H NMR. Purified by flash column chromatography (5:1 Hex:EtOAc) to give the title compound in 94% isolated yield (53 mg).

^1H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.21 (m, 2H), 6.96 – 6.91 (m, 1H), 6.86 – 6.81 (m, 2H), 4.67 (br.s, 1H).

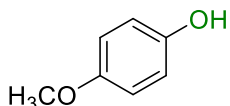
Reference: *Angew. Chem. Int. Ed.* **2012**, 51, 784.



4-Nitrophenol (3c): Prepared according to general procedure 3.7.2 (page 68) from 4-nitrophenylboronic acid (0.6 mmol, 100 mg), *i*Pr₂Net (3 mmol, 520 μ L), and Methylene Blue (0.006 mmol, 2.2 mg) in 10 mL 4:1 MeCN:H₂O to give the title compound as a brown solid in 100% conversion by ¹H NMR. Purified by flash column chromatography (5:1 Hex:EtOAc) to give the title compound in 98% isolated yield (81 mg).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.21 – 8.15 (m, 2H), 6.95 – 6.89 (m, 2H), 5.72 (br.s, 1H).

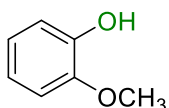
Reference: *Synlett*. **2014**, 25, 2613.



4-Methoxyphenol (3d): Prepared according to general procedure 3.7.2 (page 68) from 4-methoxyphenylboronic acid (0.6 mmol, 91 mg), *i*Pr₂Net (3 mmol, 520 μ L), and Methylene Blue (0.006 mmol, 2.2 mg) in 10 mL 4:1 MeCN:H₂O to give the title compound as a white solid in 100% conversion by ¹H NMR. Purified by flash column chromatography (5:1 Hex:EtOAc) to give the title compound in 96% isolated yield (71 mg).

¹H NMR (400 MHz, Chloroform-*d*) δ 6.83 – 6.71 (m, 4H), 4.40 (br.s, 1H), 3.76 (s, 3H).

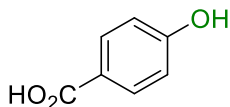
Reference: *Angew. Chem. Int. Ed.* **2012**, 51, 784.



2-Methoxyphenol (3e): Prepared according to general procedure 3.7.2 (page 68) from 2-methoxyphenylboronic acid (0.6 mmol, 91 mg), *i*Pr₂Net (3 mmol, 520 μ L), and Methylene Blue (0.006 mmol, 2.2 mg) in 10 mL 4:1 MeCN:H₂O to give the title compound as a white solid in 75% conversion by ¹H NMR. Purified by flash column chromatography (5:1 Hex:EtOAc) to give the title compound in 69% isolated yield (51 mg).

¹H NMR (400 MHz, Chloroform-*d*) δ 6.96 – 6.91 (m, 1H), 6.90 – 6.83 (m, 3H), 5.61 (br.s, 1H), 3.89 (s, 3H).

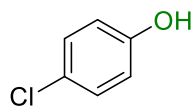
Reference: *Angew. Chem. Int. Ed.* **2012**, 51, 784.



4-Hydroxybenzoic acid (3f): Prepared according to general procedure 3.7.2 (page 68) from 4-carboxyphenylboronic acid (0.6 mmol, 100 mg), *i*Pr₂Net (3 mmol, 520 μ L), and Methylene Blue (0.006 mmol, 2.2 mg) in 10 mL 4:1 MeCN:H₂O. After quenching with 10% HCl, toluene was added to the reaction mixture and the mixture was concentrated under vacuum to give the title compound as a white solid in 100% conversion by ¹H NMR.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.92 – 7.66 (m, 2H), 6.91 – 6.71 (m, 2H).

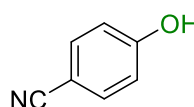
Reference: *Angew. Chem. Int. Ed.* **2012**, 51, 784.



4-Chlorophenol (3g): Prepared according to general procedure 3.7.2 (page 68) from 4-chlorophenylboronic acid (0.6 mmol, 94 mg), *i*Pr₂Net (3 mmol, 520 μ L), and Methylene Blue (0.006 mmol, 2.2 mg) in 10 mL 4:1 MeCN:H₂O to give the title compound as a yellow oil in 100% conversion by ¹H NMR.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.22 – 7.16 (m, 2H), 6.79 – 6.74 (m, 2H), 5.34 (br.s, 1H).

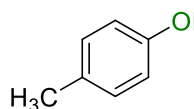
Reference: *Angew. Chem. Int. Ed.* **2012**, 51, 784.



4-Hydroxybenzonitrile (3h): Prepared according to general procedure 3.7.2 (page 68) from 4-cyanophenylboronic acid (0.6 mmol, 88 mg), *i*Pr₂Net (3 mmol, 520 μ L), and Methylene Blue (0.006 mmol, 2.2 mg) in 10 mL 4:1 MeCN:H₂O to give the title compound as a white solid in 99% conversion by ¹H NMR.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.60 – 7.50 (m, 2H), 6.97 – 6.86 (m, 2H), 5.69 (br.s, 1H).

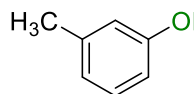
Reference: *Angew. Chem. Int. Ed.* **2012**, 51, 784.



***p*-Cresol (3i):** Prepared according to general procedure 3.7.2 (page 68) from *p*-tolylboronic acid (0.6 mmol, 82 mg), *i*Pr₂Net (3 mmol, 520 μ L), and Methylene Blue (0.006 mmol, 2.2 mg) in 10 mL 4:1 MeCN:H₂O to give the title compound as a colourless solid in 100% conversion by ¹H NMR.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.07 – 7.01 (m, 2H), 6.77 – 6.70 (m, 2H), 4.57 (br.s, 1H), 2.28 (s, 3H).

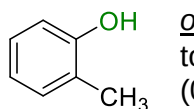
Reference: *Angew. Chem. Int. Ed.* **2012**, 51, 784.



***m*-Cresol (3j):** Prepared according to general procedure 3.7.2 (page 68) from *m*-tolylboronic acid (0.6 mmol, 82 mg), *i*Pr₂Net (3 mmol, 520 μ L), and Methylene Blue (0.006 mmol, 2.2 mg) in 10 mL 4:1 MeCN:H₂O to give the title compound as a colourless oil in 99% conversion by ¹H NMR.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.13 (t, *J* = 7.7 Hz, 1H), 6.76 (ddt, *J* = 7.6, 1.6, 0.8 Hz, 1H), 6.67 – 6.62 (m, 2H), 4.61 (br.s, 1H), 2.31 (d, *J* = 0.7 Hz, 3H).

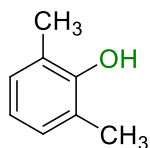
Reference: *Angew. Chem. Int. Ed.* **2012**, 51, 784.



***o*-Cresol (3k):** Prepared according to general procedure 3.7.2 (page 68) from *o*-tolylboronic acid (0.6 mmol, 82 mg), *i*Pr₂Net (3 mmol, 520 μ L), and Methylene Blue (0.006 mmol, 2.2 mg) in 10 mL 4:1 MeCN:H₂O to give the title compound as a yellow oil in 100% conversion by ¹H NMR.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.17 – 7.04 (m, 2H), 6.85 (td, *J* = 7.4, 1.2 Hz, 1H), 6.77 (dd, *J* = 7.9, 1.1 Hz, 1H), 4.62 (br.s, 1H), 2.26 (s, 3H).

Reference: *Angew. Chem. Int. Ed.* **2012**, 51, 784.

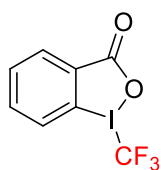


2,6-Dimethylphenol (3I): Prepared according to general procedure 3.7.2 (page 68) from 2,6-dimethylphenylboronic acid (0.6 mmol, 90 mg), *i*Pr₂Net (3 mmol, 520 μ L), and Methylene Blue (0.006 mmol, 2.2 mg) in 10 mL 4:1 MeCN:H₂O to give the title compound as a yellow solid in 100% conversion by ¹H NMR.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.01 – 6.96 (m, 2H), 6.76 (t, *J* = 7.5 Hz, 1H), 4.58 (br.s, 1H), 2.25 (s, 6H).

Reference: *Angew. Chem. Int. Ed.* **2012**, 51, 784.

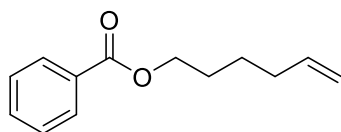
Chapter 4



Togni's Reagent (I): Prepared according to the procedure described in section 4.7.4 (page 104). Purified by flash column chromatography (15:1 CH₂Cl₂:MeOH) to give the title compound as an off-white solid in 67% isolated yield (4.5 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.47 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.86 – 7.74 (m, 3H). **¹⁹F NMR** (377 MHz, Chloroform-*d*) δ -33.97 (s, 3F).

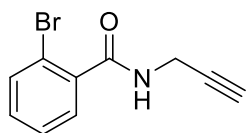
Reference: *J. Org. Chem.* **2008**, 73, 7678.



Hex-5-en-1-yl benzoate: Prepared according to the procedure described in section 4.7.5 (page 105). Purified by flash column chromatography (Hex $\rightarrow$ 16:1 Hex:EtOAc) to give the title compound as a colourless oil in 75% isolated yield (765 mg).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.08 – 8.01 (m, 2H), 7.59 – 7.51 (m, 1H), 7.47 – 7.39 (m, 2H), 5.82 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.10 – 4.93 (m, 2H), 4.33 (t, *J* = 6.6 Hz, 2H), 2.18 – 2.09 (m, 2H), 1.84 – 1.74 (m, 2H), 1.61 – 1.51 (m, 2H).

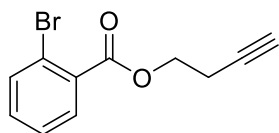
Reference: *J. Am. Chem. Soc.* **2013**, 135, 2505.



2-Bromo-N-(prop-2-yn-1-yl)benzamide: Prepared according to the procedure described in section 4.7.5 (page 106). Purified by flash column chromatography (3:2 Hex:EtOAc) to give the title compound as a white solid in quantitative yield (1.2 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.62 – 7.48 (m, 2H), 7.35 (tdd, *J* = 7.5, 3.4, 1.5 Hz, 1H), 7.31 – 7.23 (m, 1H), 6.29 (br.s, 1H), 4.29-4.20 (m, 2H), 2.31 – 2.26 (m, 1H).

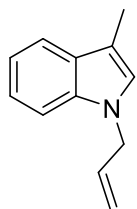
Reference: *J. Am. Chem. Soc.* **2013**, 135, 2505.



But-3-yn-1-yl 2-bromobenzoate: Prepared according to the procedure described in section 4.7.5 (page 105). Purified by flash column chromatography (9:1 Hex:EtOAc) to give the title compound as a colourless oil in 95% isolated yield (1.4 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.80 (m, 1H), 7.70 – 7.63 (m, 1H), 7.41 – 7.29 (m, 2H), 4.45 (t, *J* = 6.8 Hz, 2H), 2.69 (td, *J* = 6.8, 2.7 Hz, 2H), 2.04 (t, *J* = 2.7 Hz, 1H).

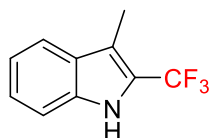
Reference: *J. Am. Chem. Soc.* **2013**, 135, 2505.



1-Allyl-3-methylindole: Prepared according to the procedure described in section 4.7.5 (page 105). Purified by flash column chromatography (60:1 Hex:EtOAc) to give the title compound as a colourless oil in 63% isolated yield (206 mg).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.59 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.29 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.21 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 6.88 (s, 1H), 5.99 (ddt, *J* = 17.0, 10.2, 5.4 Hz, 1H), 5.22 – 5.07 (m, 2H), 4.68 (dt, *J* = 5.5, 1.7 Hz, 2H), 2.35 (s, 3H).

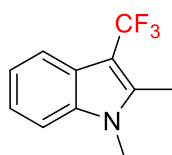
Reference: *J. Org. Chem.* **1996**, 61, 2594.



3-Methyl-2-(trifluoromethyl)indole (4a): Prepared according to general procedure 4.7.2 (page 104) from 3-methylindole (0.3 mmol, 39 mg), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and TMEDA (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ¹⁹F NMR using C₆F₆ as an external standard (71%). Purified by flash column chromatography (5:1 Hex:EtOAc) to afford the title compound as an off-white solid in 69% isolated yield (41 mg).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.16 (br.s, 1H), 7.67 – 7.61 (m, 1H), 7.39 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.32 (ddd, *J* = 8.2, 6.8, 1.1 Hz, 1H), 7.20 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 2.45 (q, *J* = 1.9 Hz, 3H). **¹⁹F NMR** (377 MHz, Chloroform-*d*) δ -58.65 (s, 3F).

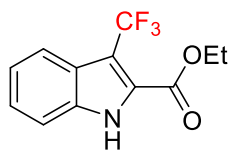
Reference: *Tetrahedron Lett.* **2012**, 53, 2005.



1,2-Dimethyl-3-(trifluoromethyl)indole (4b): Prepared according to general procedure 4.7.2 (page 104) from 1,2-dimethylindole (0.3 mmol, 44 mg), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and TMEDA (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ¹⁹F NMR using C₆F₆ as an external standard (79%). Purified by preparative thin layer chromatography (5:1 Hex:EtOAc) to afford the title compound as a white solid.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.71 (dq, *J* = 7.7, 1.2 Hz, 1H), 7.30 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.25 – 7.15 (m, 2H), 3.70 (s, 3H), 2.54 (q, *J* = 1.4 Hz, 3H). **¹⁹F NMR** (377 MHz, Chloroform-*d*) δ -53.74 (s, 3F).

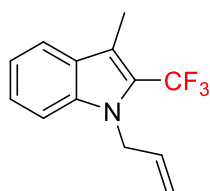
Reference: *Chem. Eur. J.* **2011**, 17, 6039.



Ethyl 3-(trifluoromethyl)indole-2-carboxylate (4c): Prepared according to general procedure 4.7.2 (page 104) from ethyl indole-2-carboxylate (0.3 mmol, 57 mg), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and TMEDA (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ^{19}F NMR using C_6F_6 as an external standard (52%). Purified by preparative thin layer chromatography (5:1 Hex:EtOAc) to afford the title compound as an off-white solid.

^1H NMR (400 MHz, Chloroform-*d*) δ 9.33 (br.s, 1H), 7.93 (d, J = 8.3, 2.2, 1.2 Hz, 1H), 7.47 (dt, J = 8.3, 1.0 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.30 – 7.27 (m, 1H), 4.48 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -53.77 (s, 3F).

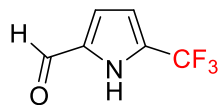
Reference: *Tetrahedron Lett.* **2012**, 53, 2005.



1-Allyl-3-methyl-2-(trifluoromethyl)indole (4d): Prepared according to general procedure 4.7.2 (page 104) from 1-allyl-3-methylindole (0.3 mmol, 51 mg), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and TMEDA (0.6 mmol, 90 μ L) in 3 mL of DMF. Purified by preparative thin layer chromatography (Hex) to afford the title compound as a pale brown oil in 30% isolated yield (20 mg).

^1H NMR (400 MHz, Chloroform-*d*) δ 7.65 (dt, J = 8.0, 1.0 Hz, 1H), 7.37 – 7.27 (m, 2H), 7.18 (ddd, J = 8.0, 6.4, 1.6 Hz, 1H), 5.92 (ddt, J = 17.2, 10.3, 5.1 Hz, 1H), 5.15 (dq, J = 10.3, 1.5 Hz, 1H), 4.98 (dq, J = 17.1, 1.6 Hz, 1H), 4.82 (dt, J = 5.2, 1.8 Hz, 2H), 2.47 (q, J = 2.6 Hz, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -55.45 (s, 3F).

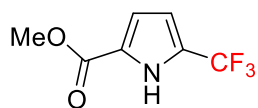
Reference: *J. Am. Chem. Soc.* **2011**, 134, 1298.



5-(trifluoromethyl)pyrrole-2-carbaldehyde (4e): Prepared according to general procedure 4.7.2 (page 104) from pyrrole-2-carboxaldehyde (0.3 mmol, 29 mg), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and TMEDA (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ^{19}F NMR using C_6F_6 as an external standard (42%). Purified by preparative thin layer chromatography (5:1 Hex:EtOAc) to afford the title compound as an off-white solid.

^1H NMR (400 MHz, Chloroform-*d*) δ 9.82 (br.s, 1H), 9.66 (s, 1H), 6.97 (ddt, J = 3.6, 2.3, 1.1 Hz, 1H), 6.68 (ddt, J = 3.9, 2.6, 1.1 Hz, 1H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -60.93 (s, 3F).

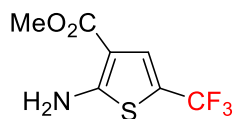
Reference: *Tetrahedron Lett.* **2012**, 53, 2005.



Methyl 5-(trifluoromethyl)pyrrole-2-carboxylate (4f): Prepared according to general procedure 4.7.2 (page 104) from methyl pyrrole-2-carboxylate (0.3 mmol, 38 mg), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and TMEDA (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ^{19}F NMR using C_6F_6 as an external standard (44%). Purified by preparative thin layer chromatography (5:1 Hex:EtOAc) to afford the title compound as white crystals.

^1H NMR (400 MHz, Chloroform-*d*) δ 9.57 (br.s, 1H), 6.88 (ddd, J = 3.7, 2.6, 1.1 Hz, 1H), 6.60 (ddq, J = 3.8, 2.3, 1.1 Hz, 1H), 3.90 (s, 3H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -60.45 (s, 3F).

Reference: *Tetrahedron Lett.* **2012**, 53, 2005.

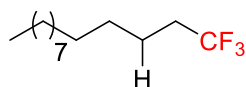


Methyl 2-amino-5-(trifluoromethyl)thiophene-3-carboxylate (4g): Prepared according to general procedure 4.7.2 (page 104) from methyl 2-aminothiophene-3-carboxylate (0.3 mmol, 47 mg), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and TMEDA (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ^{19}F NMR using C_6F_6 as an external standard (63%). Purified by preparative thin layer chromatography (5:1 Hex:EtOAc) to afford the title compound as a yellow solid.

^1H NMR (400 MHz, Chloroform-*d*) δ 7.36 (q, J = 1.4 Hz, 1H), 6.19 (br.s, 2H), 3.83 (s, 3H).

^{19}F NMR (377 MHz, Chloroform-*d*) δ -55.77 (s, 3F).

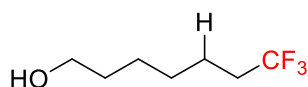
Reference: *Tetrahedron Lett.* **2012**, 53, 2005.



1,1,1-Trifluorotridecane (4h): Prepared according to general procedure 4.7.3 (page 104) from 1-dodecene (0.3 mmol, 67 μ L), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and DBU (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ^{19}F NMR using C_6F_6 as an external standard (70%).

^{19}F NMR (377 MHz, Chloroform-*d*) δ -66.45 (s, 3F).

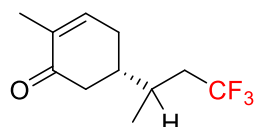
Reference: *J. Fluorine Chem.* **2007**, 128, 813.



7,7,7-trifluoroheptan-1-ol (4i): Prepared according to general procedure 4.7.3 (page 104) from 5-hexen-1-ol (0.3 mmol, 33 μ L), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and DBU (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ^{19}F NMR using C_6F_6 as an external standard (48%).

^{19}F NMR (377 MHz, Chloroform-*d*) δ -66.44 (s, 3F).

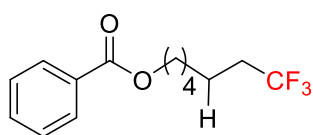
Reference: *J. Am. Chem. Soc.* **2013**, 135, 2505.

**(S)-2-Methyl-5-((S)-4,4,4-trifluorobutan-2-yl)cyclohex-2-enone (4j):**

Prepared according to general procedure 4.7.3 (page 104) from (*R*)-(-)-carvone (0.3 mmol, 47 μ L), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and DBU (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ^{19}F NMR using C_6F_6 as an external standard (40%). Purified by preparative thin layer chromatography (30:1 Hex:EtOAc) to afford the title compound as a colourless oil.

^1H NMR (400 MHz, Chloroform-*d*) δ 6.79 – 6.71 (m, 1H), 2.92 – 2.70 (m, 1H), 2.58 – 2.39 (m, 1H), 2.38 – 2.04 (m, 4H), 2.00 – 1.85 (m, 1H), 1.79 (ddt, J = 6.3, 2.6, 1.4 Hz, 3H), 1.12 – 0.97 (m, 2H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -63.54 (s, 3F).

Reference: *J. Am. Chem. Soc.* **2013**, 135, 2505.

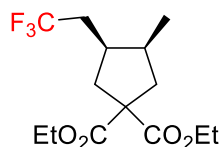


7,7,7-Trifluoroheptyl benzoate (4k): Prepared according to general procedure 4.7.3 (page 104) from hex-5-en-1-yl benzoate (0.3 mmol, 61 mg), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and DBU (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ^{19}F NMR using C_6F_6 as an external standard (83%).

Purified by preparative thin layer chromatography (20:1 Hex:EtOAc) to afford the title compound as a colourless oil.

^1H NMR (400 MHz, Chloroform-*d*) δ 8.08 – 8.01 (m, 2H), 7.60 – 7.53 (m, 1H), 7.48 – 7.40 (m, 2H), 4.33 (t, J = 6.6 Hz, 2H), 2.16 – 1.96 (m, 2H), 1.79 (dq, J = 7.8, 6.6 Hz, 2H), 1.68 – 1.53 (m, 3H), 1.53 – 1.38 (m, 4H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -66.40 (s, 3F).

Reference: *J. Am. Chem. Soc.* **2013**, 135, 2505.

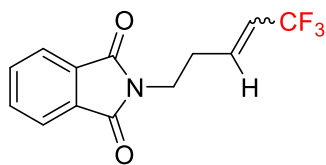


(3*S*,4*S*)-diethyl 3-methyl-4-(2,2,2-trifluoroethyl)cyclopentane-1,1-dicarboxylate (4l): Prepared according to general procedure 4.7.3 (page 104) from diethyl diallylmalonate (0.3 mmol, 73 μ L), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and DBU (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ^{19}F NMR using C_6F_6 as an external

standard (81%).

^{19}F NMR (377 MHz, Chloroform-*d*) δ -64.65 (s, 3F).

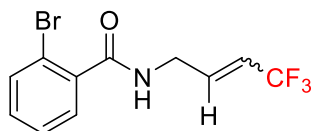
Reference: *J. Am. Chem. Soc.* **2013**, 135, 2505.



2-(5,5,5-Trifluoropent-3-en-1-yl)isoindoline-1,3-dione (4m): Prepared according to general procedure 4.7.3 (page 104) from *N*-(3-butynyl)phthalimide (0.3 mmol, 60 mg), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and DBU (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ^{19}F NMR using C_6F_6 as an external standard (70%, *E*:*Z* = 4:1). Purified by preparative thin layer chromatography (3:1 Hex:CH₂Cl₂) to afford the title compound as a white solid.

^1H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.81 (m, 2H, *E,Z*), 7.77 – 7.68 (m, 2H, *E,Z*), 6.37 (dddt, *J* = 16.1, 7.1, 4.8, 2.2 Hz, 1H, *E*), 6.05 (dt, *J* = 11.6, 7.8 Hz, 1H, *Z*), 5.75 – 5.62 (m, 1H, *E,Z*), 3.88 (t, *J* = 7.1 Hz, 1H, *Z*), 3.85 – 3.76 (m, 1H, *E*), 2.76 – 2.52 (m, 2H, *E,Z*). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -58.26 (s, 3F, *Z*), -64.47 (s, 3F, *E*).

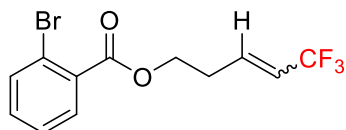
Reference: *J. Am. Chem. Soc.* **2013**, 135, 2505.



2-Bromo-N-(4,4,4-trifluorobut-2-en-1-yl)benzamide (4n): Prepared according to general procedure 4.7.3 (page 104) from 2-bromo-*N*-(prop-2-yn-1-yl)benzamide (0.3 mmol, 71 mg), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and DBU (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ^{19}F NMR using C_6F_6 as an external standard (66%, *E*:*Z* = 10:1). Purified by preparative thin layer chromatography (9:1 PET:EtOAc) to afford the title compound as a colourless solid.

^1H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 7.56 (m, 1H), 7.54 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.36 (tdd, *J* = 7.5, 4.4, 1.3 Hz, 1H), 7.32 – 7.27 (m, 1H), 6.54 – 6.41 (m, 1H), 6.27 (s, 1H), 5.97 – 5.83 (m, 1H), 4.28 – 4.17 (m, 2H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -58.49 (s, 3F, *Z*), -64.16 (s, 3F, *E*).

Reference: *J. Am. Chem. Soc.* **2013**, 135, 2505.



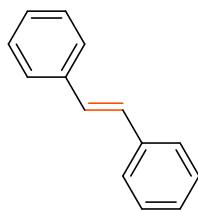
5,5,5-Trifluoropent-3-en-1-yl 2-bromobenzoate (4o): Prepared according to general procedure 4.7.3 (page 104) from but-3-yn-1-yl 2-bromobenzoate (0.3 mmol, 76 mg), Togni's Reagent (0.45 mmol, 142 mg), Methylene Blue (0.006 mmol, 2.2 mg) and DBU (0.6 mmol, 90 μ L) in 3 mL of DMF. Yield was calculated by ^{19}F NMR using C_6F_6

as an external standard (79%, *E*:*Z* = 6:1). Purified by preparative thin layer chromatography (99:1 PET:Et₂O) to afford the title compound as a colourless oil.

^1H NMR (400 MHz, Chloroform-*d*) δ 7.87 – 7.72 (m, 1H), 7.67 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.35 – 7.11 (m, 2H), 6.69 – 6.26 (m, 1H), 5.91 – 5.58 (m, 1H), 4.45 (t, *J* = 6.6 Hz, 2H), 2.76 – 2.58 (m, 2H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -58.40 (s, 3F, *Z*), -64.38 (s, 3F, *E*).

Reference: *J. Am. Chem. Soc.* **2013**, 135, 2505.

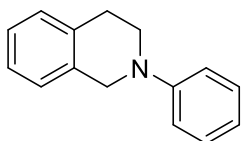
Chapter 5



trans-Stilbene: Prepared according to general procedure 5.6.2 (page 130) from *meso*-1,2-dibromo-1,2-diphenylethane (0.3 mmol, 102 mg), TMEDA (0.6 mmol, 90 μ L), and a photosensitizer (0.003 mmol) in 5 mL DMF to afford a crude product containing the title compound. Percent conversion was determined by ^1H NMR analysis of crude reaction mixture.

^1H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.50 (m, 4H), 7.40 – 7.33 (m, 4H), 7.30 – 7.24 (m, 2H), 7.12 (s, 2H).

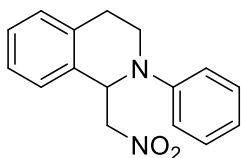
Reference: *J. Org. Chem.* **2015**, 80, 6922.



1-Phenyl-1,2,3,4-tetrahydroisoquinoline: Prepared according to the procedure described in section 5.6.7 (page 132). Purified by flash column chromatography (20:1 Hex:EtOAc) to give the title compound as an off-white solid in 58% isolated yield (3.66 g).

^1H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.27 (m, 2H), 7.24 – 7.14 (m, 4H), 7.04 – 6.97 (m, 2H), 6.84 (t, J = 7.3 Hz, 1H), 4.43 (s, 2H), 3.58 (t, J = 5.9 Hz, 2H), 3.00 (t, J = 5.8 Hz, 2H).

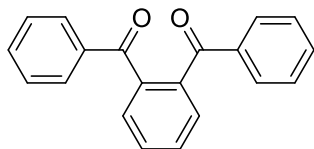
Reference: *Org. Biomol. Chem.* **2010**, 8, 4077.



1-(Nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline: Prepared according to general procedure 5.6.5 (page 131) from 1-phenyl-1,2,3,4-tetrahydroisoquinoline (0.3 mmol, 63 mg), and a photosensitizer (0.003 mmol) in 5 mL 4:1 MeCN:MeNO₂. Purified by flash column chromatography to afford the title compound as a yellow oil.

^1H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.18 (m, 5H), 7.15 (dd, J = 7.5, 1.5 Hz, 1H), 7.03 – 6.97 (m, 2H), 6.87 (t, J = 7.3 Hz, 1H), 5.57 (t, J = 7.2 Hz, 1H), 4.88 (dd, J = 11.8, 7.8 Hz, 1H), 4.57 (dd, J = 11.8, 6.6 Hz, 1H), 3.72 – 3.57 (m, 2H), 3.10 (ddd, J = 16.4, 8.7, 5.7 Hz, 1H), 2.81 (dt, J = 16.4, 5.0 Hz, 1H).

Reference: *J. Am. Chem. Soc.* **2010**, 132, 1464.

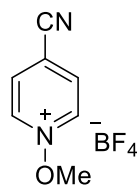


1,2-Phenylenebis(phenylmethanone): Prepared according to the procedure described in section 5.6.6 (page 132). Purified by preparative thin layer chromatography (20:1 Hex:EtOAc) to give the title compound as a white solid in 46% isolated yield (6.5 mg).

^1H NMR (400 MHz, Chloroform-*d*) δ 7.75 – 7.66 (m, 4H), 7.62 (s, 4H), 7.55 – 7.47 (m, 2H), 7.38 (t, J = 7.7 Hz, 4H).

Reference: *Eur. J. Org. Chem.* **2015**, 775.

Chapter 6

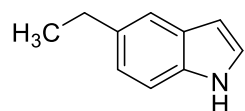


4-Cyano-*N*-methoxypyridinium tetrafluoroborate: Prepared according to the procedure described in section 6.5.6 (page 191). Purified by recrystallization in MeOH to give the title compound as a white crystalline solid in 68% isolated yield (910 mg).

^1H NMR (400 MHz, DMSO- d_6) δ 9.83 – 9.75 (m, 2H), 8.89 – 8.82 (m, 2H), 4.48 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 142.09, 132.44, 125.89, 114.45, 69.56.

Reference: *J. Org. Chem.* **2005**, 70, 6809.

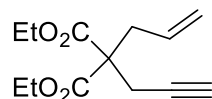
Chapter 7



5-Ethylindole: Prepared according to the procedure described in section 7.8.4 (page 234). Purified by flash column chromatography (4:1 Hex:EtOAc) to give the title compound as a pale yellow oil in 50% isolated yield (216 mg).

^1H NMR (400 MHz, Chloroform- d) δ 8.04 (br.s, 1H), 7.47 (s, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.19 – 7.16 (m, 1H), 7.07 (dd, J = 8.3, 1.7 Hz, 1H), 6.53 – 6.46 (m, 1H), 2.76 (q, J = 7.6 Hz, 2H), 1.30 (t, J = 7.6 Hz, 3H).

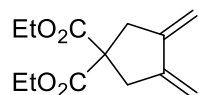
Reference: *Adv. Synth. Catal.* **2009**, 351, 415.



Diethyl 2-allyl-2-(prop-2-ynyl)malonate: Prepared according to the procedure described in section 7.8.4 (page 235). Purified by flash column chromatography (95:5 Hex:EtOAc) to give the title compound as a colourless oil in 94% isolated yield (3.4 g).

^1H NMR (400 MHz, Chloroform- d) δ 5.62 (ddt, J = 16.9, 10.1, 7.5 Hz, 1H), 5.18 (ddt, J = 17.0, 2.0, 1.3 Hz, 1H), 5.12 (ddt, J = 10.1, 1.9, 0.9 Hz, 1H), 4.20 (q, J = 7.1 Hz, 4H), 2.82 – 2.76 (m, 4H), 2.00 (t, J = 2.7 Hz, 1H), 1.24 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform- d) δ 169.82, 131.87, 119.94, 79.02, 71.51, 61.78, 56.74, 36.48, 22.68, 14.20.

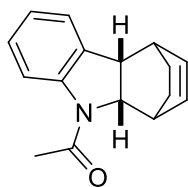
Reference: *J. Am. Chem. Soc.* **2010**, 132, 13214.



Diethyl 3,4-diethylenecyclopentane-1,1-dicarboxylate: Prepared according to the procedure described in section 7.8.4 (page 235). Purified by flash column chromatography (95:5 Hex:EtOAc) to give the title compound as a colourless oil in 51% isolated yield (550 mg).

^1H NMR (400 MHz, Chloroform- d) δ 5.38 (t, J = 2.2 Hz, 2H), 4.94 (t, J = 1.8 Hz, 2H), 4.18 (q, J = 7.1 Hz, 4H), 3.02 (t, J = 2.0 Hz, 4H), 1.23 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform- d) δ 171.32, 144.74, 105.58, 61.68, 57.76, 41.23, 14.14.

Reference: *J. Am. Chem. Soc.* **2010**, 132, 13214.



N-Acetyl-1,4,4a,9a-tetrahydro-1,4-ethanocarbazole (7a): Prepared according to general procedure 7.8.2 (page 233) from indole (0.3 mmol, 35 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (4:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a white solid in 72% isolated yield (52 mg, *endo:exo*

3.6:1).

Endo Isomer

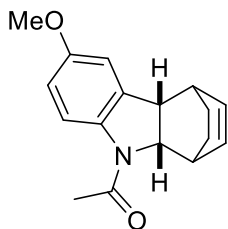
¹H NMR (500 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.22 – 7.07 (m, 2H), 6.98 (dt, *J* = 14.8, 7.7 Hz, 1H), 6.04 (dt, *J* = 16.7, 7.4 Hz, 1H), 5.93 (t, *J* = 7.5 Hz) and 5.86 (t, *J* = 7.4 Hz) (1H, two rotamers), 4.65 (dd, *J* = 9.5, 2.9 Hz) and 4.40 (dd, *J* = 9.3, 2.8 Hz) (1H, two rotamers), 3.69 (dd, *J* = 9.4, 3.1 Hz, 1H) and 3.59 – 3.48 (m) (1H, two rotamers), 3.45 – 3.31 (m) and 3.10 – 2.85 (m) (2H, two rotamers), 2.39 (s) and 2.31 (s) (3H, two rotamers), 1.80 – 1.52 (m, 2H), 1.47 – 1.19 (m, 2H). **¹³C NMR** (101 MHz, Acetone-*d*₆) δ 169.26, 146.03, 135.71, 135.07, 130.92, 127.59, 124.35, 123.85, 117.14, 64.83, 47.17, 35.73, 35.03, 24.21, 23.71, 22.96.

Reference: *J. Org. Chem.* **1991**, 56, 1405.

Exo Isomer

¹H NMR (500 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 8.1 Hz, 1H), 7.22 (td, *J* = 7.6, 1.1 Hz, 1H), 7.18 – 7.07 (m, 1H), 7.04 (td, *J* = 7.4, 1.0 Hz, 1H), 6.57 (t, *J* = 7.3 Hz, 1H), 6.30 (t, *J* = 7.5 Hz, 1H), 4.51 (d, *J* = 9.9 Hz) and 4.26 (dd, *J* = 10.9, 3.3 Hz) (1H, two rotamers), 3.54 (dd, *J* = 10.9, 3.9 Hz) and 3.47 – 3.34 (m) (1H, two rotamers), 3.34 – 3.23 (m) and 2.99 – 2.74 (m) (2H, two rotamers), 2.46 (s) and 2.28 (s) (3H, two rotamers), 1.60 – 1.38 (m, 1H), 1.31 – 1.20 (m, 1H), 1.15 – 0.96 (m, 2H). **¹³C NMR** (101 MHz, DMSO-*d*₆) δ 169.20, 144.31, 136.63, 132.68, 132.21, 127.44, 124.48, 123.33, 116.41, 63.02, 42.81, 33.21, 32.51, 23.42, 20.98, 16.88.

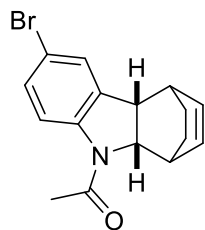
Reference: *J. Org. Chem.* **1991**, 56, 1405.



N-Acetyl-6-methoxy-1,4,4a,9a-tetrahydro-1,4-ethanocarbazole (7b): Prepared according to general procedure 7.8.2 (page 233) from 5-methoxyindole (0.3 mmol, 44 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (2:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a pale brown solid in 48% isolated yield (39 mg, *endo:exo* 3.9:1).

Endo Isomer

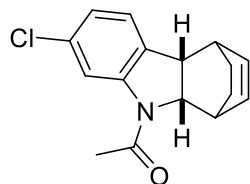
¹H NMR (400 MHz, Acetone-*d*₆) δ 7.96 (d, *J* = 8.8 Hz, 1H), 6.81 – 6.70 (m, 1H), 6.60 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.04 (t, *J* = 7.4 Hz, 1H), 5.90 (t, *J* = 7.4 Hz, 1H), 4.55 (dd, *J* = 9.3, 2.9 Hz, 1H), 3.74 (s, 3H), 3.68 (dd, *J* = 9.4, 3.2 Hz, 1H), 3.16 – 2.94 (m, 2H), 2.22 (s, 3H), 1.78 – 1.63 (m, 2H), 1.40 – 1.23 (m, 3H). **¹³C NMR** (101 MHz, Acetone-*d*₆) δ 167.58, 156.21, 138.82, 136.32, 134.03, 130.09, 116.84, 111.28, 109.55, 64.15, 54.83, 46.41, 34.70, 34.21, 23.28, 22.58, 22.09. **HRMS (EI)**: *m/z* cal'd for C₁₇H₁₉NO₂ [*M*⁺] 269.1416, found 269.1415. **IR (neat, cm⁻¹)**: 2934, 2867, 1647, 1487, 1389, 1262.



N-Acetyl-6-bromo-1,4,4a,9a-tetrahydro-1,4-ethanocarbazole (7c): Prepared according to general procedure 7.8.2 (page 233) from 5-bromoindole (0.3 mmol, 59 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (4:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a white solid in 62% isolated yield (59 mg, *endo:exo* 3.3:1).

Endo Isomer

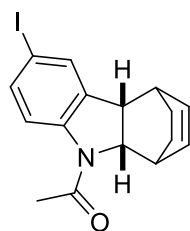
¹H NMR (400 MHz, Acetone-*d*₆) δ 7.96 (d, *J* = 8.6 Hz, 1H), 7.33 (s, 1H), 7.19 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.08 (t, *J* = 7.4 Hz, 1H), 5.93 (t, *J* = 7.4 Hz, 1H), 4.62 (dd, *J* = 9.4, 2.9, 1H), 3.18 – 3.00 (m, 2H), 2.26 (s, 3H), 1.79 – 1.67 (m, 2H), 1.40 – 1.23 (m, 2H). **¹³C NMR** (101 MHz, Acetone-*d*₆) δ 168.65, 144.52, 137.83, 134.13, 130.30, 129.55, 126.56, 117.72, 114.72, 64.23, 46.03, 34.70, 34.07, 23.24, 22.76, 21.98. **HRMS (EI):** *m/z* cal'd for C₁₆H₁₆BrNO [M⁺] 317.0415, found 317.0397. **IR (neat, cm⁻¹):** 2936, 2867, 1655, 1473, 1380.



N-Acetyl-7-chloro-1,4,4a,9a-tetrahydro-1,4-ethanocarbazole (7d): Prepared according to general procedure 7.8.2 (page 233) from 6-chloroindole (0.3 mmol, 45 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (4:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a white solid in 56% isolated yield (46 mg, *endo:exo* 3.2:1).

Endo Isomer

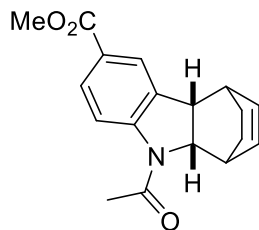
¹H NMR (400 MHz, Acetone-*d*₆) δ 8.18 – 7.99 (m, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 6.94 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.07 (t, *J* = 7.4 Hz, 1H), 5.91 (t, *J* = 7.5 Hz, 1H), 4.64 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.71 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.21 – 2.93 (m, 2H), 2.27 (s, 3H), 1.79 – 1.65 (m, 2H), 1.40 – 1.23 (m, 3H). **¹³C NMR** (101 MHz, Acetone-*d*₆) δ 169.77, 147.19, 135.05, 134.87, 132.56, 131.04, 125.45, 123.52, 116.98, 65.46, 46.67, 35.61, 34.91, 24.08, 23.64, 22.79. **HRMS (EI):** *m/z* cal'd for C₁₆H₁₆ClNO [M⁺] 273.0920, found 273.0943. **IR (neat, cm⁻¹):** 2936, 2867, 1655, 1475, 1387, 705.



N-Acetyl-6-iodo-1,4,4a,9a-tetrahydro-1,4-ethanocarbazole (7e): Prepared according to general procedure 7.8.2 (page 233) from 5-iodoindole (0.3 mmol, 73 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (4:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a white solid in 52% isolated yield (57 mg, *endo:exo* 3.9:1).

Endo Isomer

¹H NMR (400 MHz, Acetone-*d*₆) δ 7.84 (d, *J* = 8.5 Hz, 1H), 7.51 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 6.07 (t, *J* = 7.4 Hz, 1H), 5.93 (t, *J* = 7.5 Hz, 1H), 4.60 (dd, *J* = 9.5, 2.9 Hz, 1H), 3.76 – 3.69 (m, 1H), 2.26 (s, 3H), 1.79 – 1.66 (m, 2H), 1.39 – 1.24 (m, 2H). **¹³C NMR** (101 MHz, Acetone-*d*₆) δ 168.71, 145.18, 138.12, 135.71, 134.16, 132.47, 130.27, 118.26, 85.07, 64.12, 45.93, 34.71, 34.06, 23.25, 22.81, 21.99. **HRMS (EI):** *m/z* cal'd for C₁₆H₁₆I⁺NO [M⁺] 365.0277, found 365.0271. **IR (neat, cm⁻¹):** 2934, 2865, 1648, 1470, 1376, 1319, 1253, 818, 712.

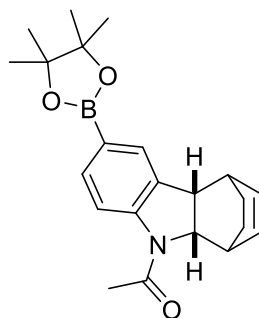


Methyl *N*-acetyl-1,4,4a,9a-tetrahydro-1,4-ethanocarbazole-6-carboxylate (7f): Prepared according to general procedure 7.8.2 (page 233) from 5-methylindole carboxylate (0.3 mmol, 53 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (2:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a white solid in 59% isolated yield (53 mg, *endo:exo*

3.4:1).

Endo Isomer

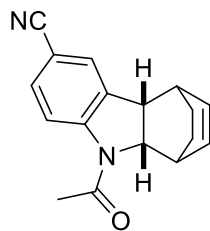
¹H NMR (400 MHz, Acetone-*d*₆) δ 8.08 (s, 1H), 7.82 – 7.71 (m, 2H), 6.06 (t, *J* = 7.6 Hz, 1H), 5.91 (t, *J* = 7.5 Hz, 1H), 4.73 – 4.65 (m, 1H), 3.83 (s, 3H), 3.81 – 3.73 (m, 1H), 3.24 – 3.03 (m, 2H), 2.32 (s, 3H), 1.82 – 1.68 (m, 2H), 1.41 – 1.26 (m, 2H). **¹³C NMR** (75 MHz, Acetone-*d*₆) δ 170.00, 166.93, 150.02, 136.43, 135.14, 131.12, 130.19, 125.63, 116.27, 65.43, 52.00, 46.64, 35.75, 34.86, 24.14, 23.84, 22.89. **HRMS (EI)**: *m/z* cal'd for C₁₈H₁₉NO₃ [M⁺] 297.1365, found 297.1341. **IR** (neat, cm⁻¹): 2948, 2868, 1713, 1665, 1444, 1380, 1257.



N-Acetyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4,4a,9a-tetrahydrohydro-ethanocarbazole (7g): Prepared according to general procedure 7.8.2 (page 233) from 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole (0.3 mmol, 73 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (4:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a white solid in 52% isolated yield (57 mg, *endo:exo* 3.4:1).

Endo Isomer

¹H NMR (400 MHz, Acetone-*d*₆) δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.38 (m, 2H), 6.04 (t, *J* = 7.5 Hz, 1H), 5.89 (t, *J* = 7.5 Hz, 1H), 4.60 (dd, *J* = 9.5, 2.9 Hz, 1H), 3.72 (d, *J* = 9.4 Hz, 1H), 3.19 – 2.93 (m, 2H), 2.28 (s, 3H), 1.80 – 1.65 (m, 2H), 1.39 – 1.25 (m, 14H). **¹³C NMR** (75 MHz, Acetone-*d*₆) δ 169.58, 148.68, 135.07, 130.86, 130.63, 116.29, 84.21, 65.02, 46.91, 35.77, 34.95, 25.33, 25.12, 24.24, 23.83, 22.96. **HRMS (EI)**: *m/z* cal'd for C₂₂H₂₈BNO₃ [M⁺] 365.2162, found 365.2147. **IR** (neat, cm⁻¹): 2976, 2935, 2867, 1660, 1605, 1428, 1348, 1255, 1143, 856, 677.

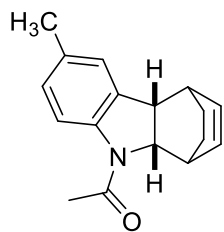


N-acetyl-1,4,4a,9a-tetrahydro-1,4-ethanocarbazole-6-carbonitrile (7h): Prepared according to general procedure 7.8.2 (page 233) from 5-cyanoindole (0.3 mmol, 43 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (2:1 → 1:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a white solid in 40% isolated yield (32 mg, *endo:exo* 2.2:1).

Endo Isomer

¹H NMR (400 MHz, Acetone-*d*₆) δ 8.13 (s, 1H), 7.56 (s, 1H), 7.47 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.09 (t, *J* = 7.6 Hz, 1H), 5.95 (t, *J* = 7.6 Hz, 1H), 4.71 (dd, *J* = 9.5, 2.8 Hz, 1H), 3.80 (d, *J* = 9.4 Hz, 1H), 3.30 – 3.01 (m, 2H), 2.33 (s, 3H), 1.80 – 1.68 (m, 2H), 1.40 – 1.25 (m, 2H). **¹³C NMR** (75 MHz, Acetone *d*₆) δ 169.35, 148.71, 136.63, 134.12, 131.94, 130.35, 127.32, 118.94, 116.20, 105.55,

68.38, 64.37, 45.66, 34.64, 33.79, 23.10, 21.87. **HRMS (EI):** m/z cal'd for $C_{17}H_{16}N_2O$ [M^+] 264.1263, found 264.1286. **IR (neat, cm^{-1}):** 2928, 2867, 2220, 1670, 1438, 1380, 1317, 1262, 1035.

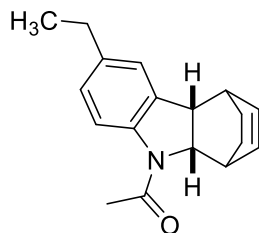


N-Acetyl-6-methyl-1,4,4a,9a-tetrahydro-1,4-ethanocarbazole (7i): Prepared according to general procedure 7.8.2 (page 233) from 5-methylindole (0.3 mmol, 39 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (4:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as an off-white solid in 55% isolated yield (42 mg, *endo:exo* 3.8:1).

Endo Isomer

¹H NMR (400 MHz, Acetone-*d*₆) δ 7.91 (d, J = 8.2 Hz, 1H), 6.98 (s, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.04 (t, J = 7.4 Hz, 1H), 5.88 (t, J = 7.5 Hz, 1H), 4.55 (dd, J = 9.4, 2.8 Hz, 1H), 3.67 (dd, J = 9.4, 3.1 Hz, 1H), 3.16 – 2.91 (m, 2H), 2.23 (s, 6H), 1.81 – 1.65 (m, 2H), 1.38 – 1.17 (m, 2H).

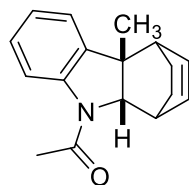
¹³C NMR (75 MHz, Acetone-*d*₆) δ 168.88, 143.82, 135.79, 135.07, 133.09, 130.88, 128.05, 124.88, 116.92, 64.96, 47.15, 35.71, 35.04, 24.22, 23.61, 22.99, 20.98. **HRMS (EI):** m/z cal'd for $C_{16}H_{17}NO$ [M^+] 253.1467, found 253.1450. **IR (neat, cm^{-1}):** 2934, 2866, 1649, 1487, 1384, 1327, 819, 708.



N-Acetyl-6-ethyl-1,4,4a,9a-tetrahydro-1,4-ethanocarbazole (7j): Prepared according to general procedure 7.8.2 (page 233) from 5-ethylindole (0.3 mmol, 44 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (4:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a colourless oil in 57% isolated yield (46 mg, *endo:exo* 2.8:1).

Endo Isomer

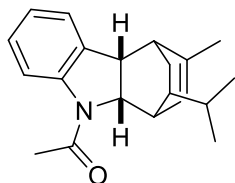
¹H NMR (400 MHz, Acetone-*d*₆) δ 7.94 (d, J = 8.2 Hz, 1H), 7.05 – 6.97 (m, 1H), 6.90 – 6.82 (m, 1H), 6.04 (t, J = 7.4 Hz, 1H), 5.87 (t, J = 7.5 Hz, 1H), 4.56 (dd, J = 9.3, 2.9 Hz, 1H), 3.68 (dd, J = 9.7, 3.1 Hz, 1H), 3.19 – 2.89 (m, 2H), 2.54 (q, J = 7.5 Hz, 2H), 2.23 (s, 3H), 1.78 – 1.65 (m, 2H), 1.40 – 1.23 (m, 2H), 1.16 (t, J = 7.6 Hz, 3H). **¹³C NMR** (101 MHz, Acetone-*d*₆) δ 168.89, 144.00, 139.87, 135.80, 135.09, 130.87, 126.91, 123.68, 116.99, 64.99, 47.19, 35.71, 35.06, 24.22, 23.62, 23.00, 16.35. **HRMS (EI):** m/z cal'd for $C_{18}H_{21}NO$ [M^+] 267.1628, found 267.1584. **IR (neat, cm^{-1}):** 2933, 2866, 1648, 1487, 1384, 1320, 830, 710.



N-Acetyl-4a-methyl-1,4,4a,9a-tetrahydro-1,4-ethanocarbazole (7k): Prepared according to general procedure 7.8.2 (page 233) from 3-methylindole (0.3 mmol, 39 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (4:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a pale yellow oil in 11% isolated yield (8 mg, *endo:exo* 2.7:1).

Endo Isomer

¹H NMR (400 MHz, Acetone-*d*₆) δ 8.03 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.95 – 6.89 (m, 1H), 5.96 – 5.89 (m, 2H), 4.07 (d, *J* = 2.8 Hz, 1H), 2.77 (dt, *J* = 5.9, 2.8 Hz, 1H), 2.25 (s, 3H), 1.78 – 1.67 (m, 1H), 1.46 (s, 3H), 1.38 – 1.15 (m, 3H). **¹³C NMR** (101 MHz, Acetone-*d*₆) δ 169.18, 145.04, 141.33, 137.76, 129.04, 127.42, 124.01, 122.75, 117.02, 72.81, 49.04, 40.68, 36.17, 26.82, 23.67, 22.31, 21.00. **HRMS (EI)**: *m/z* cal'd for C₁₇H₁₉NO [M⁺] 253.1467, found 253.1443. **IR (neat, cm⁻¹)**: 2954, 2924, 2868, 1655, 1481, 1389, 751, 707.

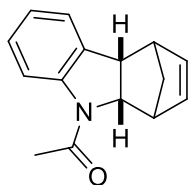


***N*-Acetyl-11-isopropyl-3-methyl-1,4,4a,9a-tetrahydro-1,4-ethanocarbazole (7m)**: Prepared according to general procedure 7.8.2 (page 233) from indole (0.3 mmol, 35 mg), α-phellandrene (1.5 mmol, 240 μL), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μL) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (10:1:1 Hex:EtOAc:CH₂Cl₂) to afford pure *endo* and *exo* isomers of the title compound as a colourless oil in 52% isolated yield (46 mg, *endo:exo* 2.1:1).

Endo Isomer

¹H NMR (400 MHz, Acetone-*d*₆) δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.96 – 6.83 (m, 1H), 5.52 (d, *J* = 6.5 Hz, 1H), 4.58 – 4.42 (m, 1H), 3.70 (dd, *J* = 9.8, 3.0 Hz, 1H), 3.11 (d, *J* = 6.4 Hz, 1H), 2.82 – 2.68 (m, 1H), 2.26 (s, 3H), 1.99 – 1.80 (m, 2H), 1.50 – 1.38 (m, 1H), 1.35 (s, 3H), 1.24 – 1.11 (m, 1H), 1.12 – 1.01 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H). **¹³C NMR** (101 MHz, Acetone-*d*₆) δ 169.20, 146.33, 143.72, 135.10, 127.60, 124.32, 123.52, 120.45, 117.10, 66.13, 46.36, 44.13, 41.85, 38.69, 33.54, 31.23, 23.67, 21.52, 21.40, 20.76.

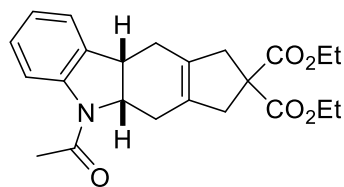
Reference: *J. Org. Chem.* **1991**, 56, 1405.



***N*-Acetyl-1,4,4a,9a-tetrahydro-1,4-methanocarbazole (7o)**: Prepared according to general procedure 7.8.2 (page 233) from indole (0.3 mmol, 35 mg), 1,3-cyclopentadiene (1.5 mmol, 123 μL), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μL) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (8:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a colourless oil in 19% isolated yield (13 mg, *endo:exo* 1.2:1).

Endo Isomer

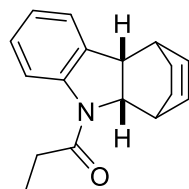
¹H NMR (400 MHz, Acetone-*d*₆) δ 8.05 (d, *J* = 8.1 Hz, 1H), 7.18 – 7.13 (m, 1H), 7.08 – 7.01 (m, 1H), 6.90 (td, *J* = 7.4, 1.1 Hz, 1H), 5.91 (dd, *J* = 5.8, 3.0 Hz, 1H), 5.66 – 5.59 (m, 1H), 4.88 (dd, *J* = 9.1, 3.9 Hz, 1H), 3.98 (dd, *J* = 9.1, 4.2 Hz, 1H), 3.50 (s, 1H), 3.27 (d, *J* = 3.6 Hz, 1H), 2.31 (s, 3H), 1.57 – 1.48 (m, 2H), 1.29 (s, 2H). **¹³C NMR** (101 MHz, Acetone-*d*₆) δ 169.22, 146.94, 137.47, 133.92, 132.58, 127.83, 124.56, 123.49, 117.11, 66.23, 48.90, 48.19, 47.98, 47.89, 24.23. **HRMS (EI)**: *m/z* cal'd for C₁₅H₁₅NO [M⁺] 225.1154, found 225.1150. **IR (neat, cm⁻¹)**: 2969, 2929, 2866, 1658, 1480, 1392, 1289, 754, 722.



Diethyl 5-acetyl-3,4,4a,5,9b,10-hexahydrocyclopenta[b]carbazole-2,2(1H)-dicarboxylate (7p): Prepared according to general procedure 7.8.2 (page 233) from indole (0.3 mmol, 35 mg), diethyl 3,4-diethylenecyclopentane-1,1-dicarboxylate (1.5 mmol, 360 mg), Pt(0.2%)/TiO₂ (12 mg), acetyl chloride (0.3 mmol, 21 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column

chromatography (4:1 $\rightarrow$ 2:1 Hex:EtOAc) to afford the title compound as a colourless oil in 67% isolated yield (80 mg).

¹H NMR (300 MHz, Acetone-*d*₆) δ 8.06 (s, 1H), 7.25 – 7.11 (m, 2H), 7.06 – 6.99 (m, 1H), 4.74 – 4.51 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.78 – 3.70 (m, 1H), 2.99 – 2.91 (m, 2H), 2.90 – 2.84 (m, 2H), 2.78 – 2.51 (m, 3H), 2.29 (s, 3H), 1.88 – 1.67 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (101 MHz, Acetone-*d*₆) δ 172.55, 172.33, 168.21, 142.65, 136.06, 130.44, 130.10, 128.03, 124.45, 123.35, 118.26, 61.97, 61.91, 60.23, 58.36, 44.25, 44.22, 38.97, 28.38, 24.38, 23.50, 14.32, 14.28. **HRMS (EI)**: *m/z* cal'd for C₂₃H₂₇NO₅ [*M*⁺] 397.1889, found 397.1872. **IR (neat, cm⁻¹)**: 2981, 2904, 1728, 1655, 1478, 1397, 1252, 1178, 1156, 1069, 756.

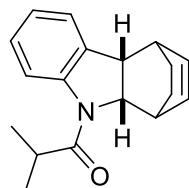


1,4,4a,9a-tetrahydro-1,4-ethanocarbazole-propan-1-one (7q): Prepared according to general procedure 7.8.2 (page 233) from indole (0.3 mmol, 35 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), propionyl chloride (0.3 mmol, 26 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (4:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a white solid in 47% isolated yield (36

mg, *endo:exo* 3.1:1).

Endo Isomer

¹H NMR (400 MHz, Acetone-*d*₆) δ 8.19 – 7.96 (m, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.95 – 6.85 (m, 1H), 6.03 (t, *J* = 7.4 Hz, 1H), 5.86 (t, *J* = 7.4 Hz, 1H), 4.66 – 4.53 (m, 1H), 3.71 (d, *J* = 9.3 Hz, 1H), 2.59 (q, *J* = 7.3, 2H), 1.74 (d, *J* = 8.3 Hz, 2H), 1.40 – 1.21 (m, 3H), 1.15 (t, *J* = 7.3 Hz, 3H). **¹³C NMR** (75 MHz, Acetone-*d*₆) δ 172.75, 146.17, 135.71, 135.06, 130.93, 127.60, 124.32, 123.72, 117.23, 64.13, 47.19, 35.76, 35.15, 24.20, 23.00, 9.72. **HRMS (EI)**: *m/z* cal'd for C₁₇H₁₉NO [*M*⁺] 253.1467, found 253.1425. **IR (neat, cm⁻¹)**: 2938, 2868, 1655, 1480, 1396, 1261, 753, 708.

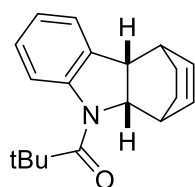


1,4,4a,9a-tetrahydro-1,4-ethanocarbazole-2-methylpropan-1-one (7r): Prepared according to general procedure 7.8.2 (page 233) from indole (0.3 mmol, 35 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), isobutyryl chloride (0.3 mmol, 31 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (4:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a white solid in 45% isolated yield (36

mg, *endo:exo* 3.2:1).

Endo Isomer

^1H NMR (400 MHz, Acetone- d_6) δ 8.12 (d, J = 8.1 Hz, 1H), 7.22 – 7.08 (m, 1H), 7.08 – 6.99 (m, 1H), 6.92 (td, J = 7.3, 1.1 Hz, 1H), 6.06 (t, J = 7.5 Hz, 1H), 5.88 (t, J = 7.4 Hz, 1H), 4.65 (dd, J = 9.4, 2.9 Hz, 1H), 3.76 – 3.70 (m, 1H), 3.09 – 2.92 (m, 3H), 1.80 – 1.69 (m, 2H), 1.42 – 1.26 (m, 2H), 1.21 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, Acetone- d_6) δ 176.54, 146.13, 136.00, 135.21, 130.81, 127.60, 124.32, 123.86, 117.45, 63.98, 47.07, 36.25, 35.79, 33.37, 24.25, 23.03, 20.46, 20.33. **HRMS (EI)**: m/z cal'd for $\text{C}_{18}\text{H}_{21}\text{NO}$ [M^+] 267.1623, found 267.1667. **IR (neat, cm^{-1})**: 2938, 2868, 1655, 1480, 1396, 1261, 753, 708.

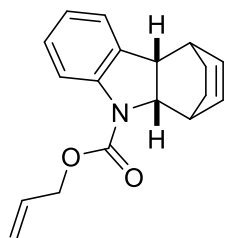
1,4,4a,9a-Tetrahydro-1,4-ethanocarbazole-2,2-dimethylpropan-1-one (7s):

Prepared according to general procedure 7.8.2 (page 233) from indole (0.3 mmol, 35 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μL), Pt(0.2%)/ TiO_2 (12 mg), pivaloyl chloride (0.3 mmol, 37 μL) and NaHCO_3 (0.6 mmol, 50 mg) in 3 mL MeNO_2 . Purified by flash column chromatography (8:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a colourless oil in 16% yield

(*endo:exo* 3.2:1).

Endo Isomer

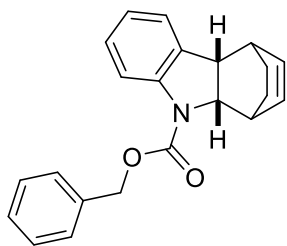
^1H NMR (400 MHz, Acetone- d_6) δ 7.90 – 7.85 (m, 1H), 7.14 – 7.09 (m, 1H), 7.04 – 6.97 (m, 1H), 6.89 (t, J = 7.4, 1H), 6.03 (t, J = 6.5 Hz, 1H), 5.81 (t, J = 6.6 Hz, 1H), 4.87 (ddd, J = 9.3, 2.6, 1.0 Hz, 1H), 3.79 (dd, J = 9.4, 3.5 Hz, 1H), 3.09 – 2.97 (m, 2H), 1.84 – 1.65 (m, 2H), 1.37 (s, 9H), 1.27 – 1.13 (m, 2H). ^{13}C NMR (101 MHz, Acetone- d_6) δ 177.90, 147.59, 135.56, 135.07, 130.85, 127.36, 124.22, 123.64, 117.61, 63.55, 47.43, 42.31, 36.73, 35.75, 23.65, 23.43. **HRMS (EI)**: m/z cal'd for $\text{C}_{19}\text{H}_{23}\text{NO}$ [M^+] 281.1780, found 281.1751. **IR (neat, cm^{-1})**: 2952, 2867, 1638, 1476, 1359, 753, 708.



Allyl 4,4a-dihydro-1H-1,4-ethanocarbazole-9(9aH)-carboxylate (7t): Prepared according to general procedure 7.8.2 (page 233) from indole (0.3 mmol, 35 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μL), Pt(0.2%)/ TiO_2 (12 mg), allyl chloroformate (0.3 mmol, 32 μL) and NaHCO_3 (0.6 mmol, 50 mg) in 3 mL MeNO_2 . Purified by flash column chromatography (16:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a colourless oil in 16% isolated yield (13 mg, *endo:exo* 4.8:1).

Endo Isomer

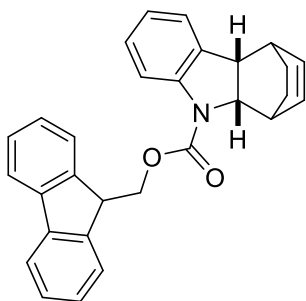
^1H NMR (400 MHz, Acetone- d_6) δ 7.71 (s, 1H), 7.18 (dd, J = 7.3, 1.4 Hz, 1H), 7.06 (ddt, J = 8.8, 8.0, 1.0 Hz, 1H), 6.89 (td, J = 7.4, 1.1 Hz, 1H), 6.13 – 5.99 (m, 2H), 5.90 (ddd, J = 8.1, 6.4, 1.3 Hz, 1H), 5.39 (dq, J = 17.2, 1.7 Hz, 1H), 5.24 (dq, J = 10.6, 1.4 Hz, 1H), 4.72 (s, 2H), 4.51 (d, J = 9.4 Hz, 1H), 3.62 (d, J = 8.4 Hz, 1H), 3.30 (s, 1H), 3.05 – 2.89 (m, 1H), 1.78 – 1.56 (m, 2H), 1.38 – 1.23 (m, 2H). ^{13}C NMR (75 MHz, Acetone- d_6) δ 153.34, 135.41, 134.73, 134.19, 131.42, 127.91, 124.70, 123.23, 117.56, 115.06, 66.18, 64.30, 46.61, 35.80, 33.78, 24.41, 22.54. **HRMS (EI)**: m/z cal'd for $\text{C}_{18}\text{H}_{19}\text{NO}_2$ [M^+] 281.1416, found 281.1462. **IR (neat, cm^{-1})**: 2935, 2868, 1707, 1485, 1399, 1309, 1263, 1048, 749, 709.



Benzyl 4,4a-dihydro-1H-1,4-ethanocarbazole-9(9aH)-carboxylate (7u): Prepared according to general procedure 7.8.2 (page 233) from indole (0.3 mmol, 35 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), benzyl chloroformate (0.3 mmol, 43 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (16:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a white solid in 14% isolated yield (14 mg, *endo:exo* 3.5:1).

Endo Isomer

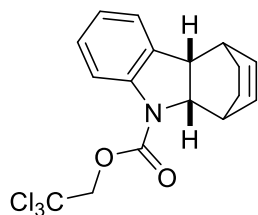
¹H NMR (400 MHz, Acetone-*d*₆) δ 7.74 (s, 1H), 7.51 – 7.45 (m, 2H), 7.44 – 7.37 (m, 2H), 7.37 – 7.30 (m, 1H), 7.17 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.06 (s, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 5.99 (ddt, *J* = 7.8, 6.5, 1.2 Hz, 1H), 5.89 (ddd, *J* = 8.1, 6.4, 1.3 Hz, 1H), 5.37 – 5.21 (m, 2H), 4.52 (d, *J* = 9.6 Hz, 1H), 3.61 (dd, *J* = 10.0, 2.9 Hz, 1H), 3.47 – 3.21 (m, 1H), 2.96 (tq, *J* = 4.3, 1.4 Hz, 1H), 1.75 – 1.54 (m, 2H), 1.36 – 1.19 (m, 2H). ¹³C NMR (101 MHz, Acetone-*d*₆) δ 153.48, 137.94, 135.40, 134.71, 131.41, 129.36, 128.83, 128.74, 127.91, 124.67, 123.26, 115.07, 67.23, 64.30, 46.61, 35.79, 33.84, 24.40, 22.51. **HRMS (EI):** *m/z* cal'd for C₂₂H₂₁NO₂ [M⁺] 331.1572, found 331.1580. **IR (neat, cm⁻¹):** 2937, 2866, 1701, 1483, 1401, 1307, 1263, 1137, 1023, 748, 698.



(9H-Fluoren-9-yl)methyl 4,4a-dihydro-1H-1,4-ethanocarbazole-9(9aH)-carboxylate (7v): Prepared according to general procedure 7.8.2 (page 233) from indole (0.3 mmol, 35 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), Fmoc chloride (0.3 mmol, 78 mg) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (8:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a white solid in 29% isolated yield (38 mg, *endo:exo* 2.7:1).

Endo Isomer

¹H NMR (300 MHz, Acetone-*d*₆, -40 °C) δ 7.94 (dd, *J* = 7.1, 2.0 Hz, 2H), 7.77 (dd, *J* = 7.7, 2.9 Hz) and 7.68 (d, *J* = 7.5 Hz) (2H, two rotamers), 7.59 (d, *J* = 8.0 Hz) and 6.24 (d, *J* = 8.0 Hz) (1H, two rotamers), 7.50 – 7.26 (m, 4H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 7.6 Hz) and 6.65 (t, *J* = 7.7 Hz) (1H, two rotamers), 6.83 (t, *J* = 7.4 Hz) and 6.73 (t, *J* = 7.3 Hz) (1H, two rotamers), 5.85 (t, *J* = 7.3 Hz) and 5.57 (t, *J* = 7.3 Hz) (1H, two rotamers), 5.79 – 5.66 (m, 1H), 4.89 (dd, *J* = 10.6, 4.1 Hz) and 4.72 (dd, *J* = 10.6, 4.2 Hz) (2H, two rotamers), 4.48 – 4.36 (m, 1H), 4.27 (dd, *J* = 9.7, 3.0 Hz) and 3.76 (dd, *J* = 9.8, 3.0 Hz) (1H, two rotamers), 2.90 – 2.73 (m, 1H), 1.64 – 1.40 (m, 1H), 1.28 – 1.01 (m, 2H), 0.95 – 0.79 (m, 1H). ¹³C NMR (75 MHz, Acetone-*d*₆, 25 °C) δ 153.30, 145.28, 142.50, 135.23, 134.38, 131.46, 128.47, 128.00, 127.79, 125.54, 124.58, 123.08, 120.85, 114.80, 66.61, 64.07, 48.20, 46.35, 35.64, 33.04, 24.31, 22.60. **HRMS (EI):** *m/z* cal'd for C₂₉H₂₅NO₂ [M⁺] 419.1885, found 419.1885. **IR (neat, cm⁻¹):** 2932, 2865, 1705, 1485, 1406, 1309, 1264, 741.



2,2,2-Trichloroethyl 4,4a-dihydro-1H-1,4-ethanocarbazole-9(9aH)-carboxylate (7w): Prepared according to general procedure 7.8.2 (page 233) from indole (0.3 mmol, 35 mg), 1,3-cyclohexadiene (1.5 mmol, 150 μ L), Pt(0.2%)/TiO₂ (12 mg), 2,2,2-trichloroethyl chloroformate (0.3 mmol, 41 μ L) and NaHCO₃ (0.6 mmol, 50 mg) in 3 mL MeNO₂. Purified by flash column chromatography (16:1 Hex:EtOAc) to afford pure *endo* and *exo* isomers of the title compound as a white solid in 32% isolated yield (36 mg,

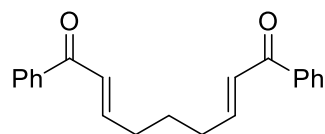
endo:exo 4.6:1).

Endo Isomer

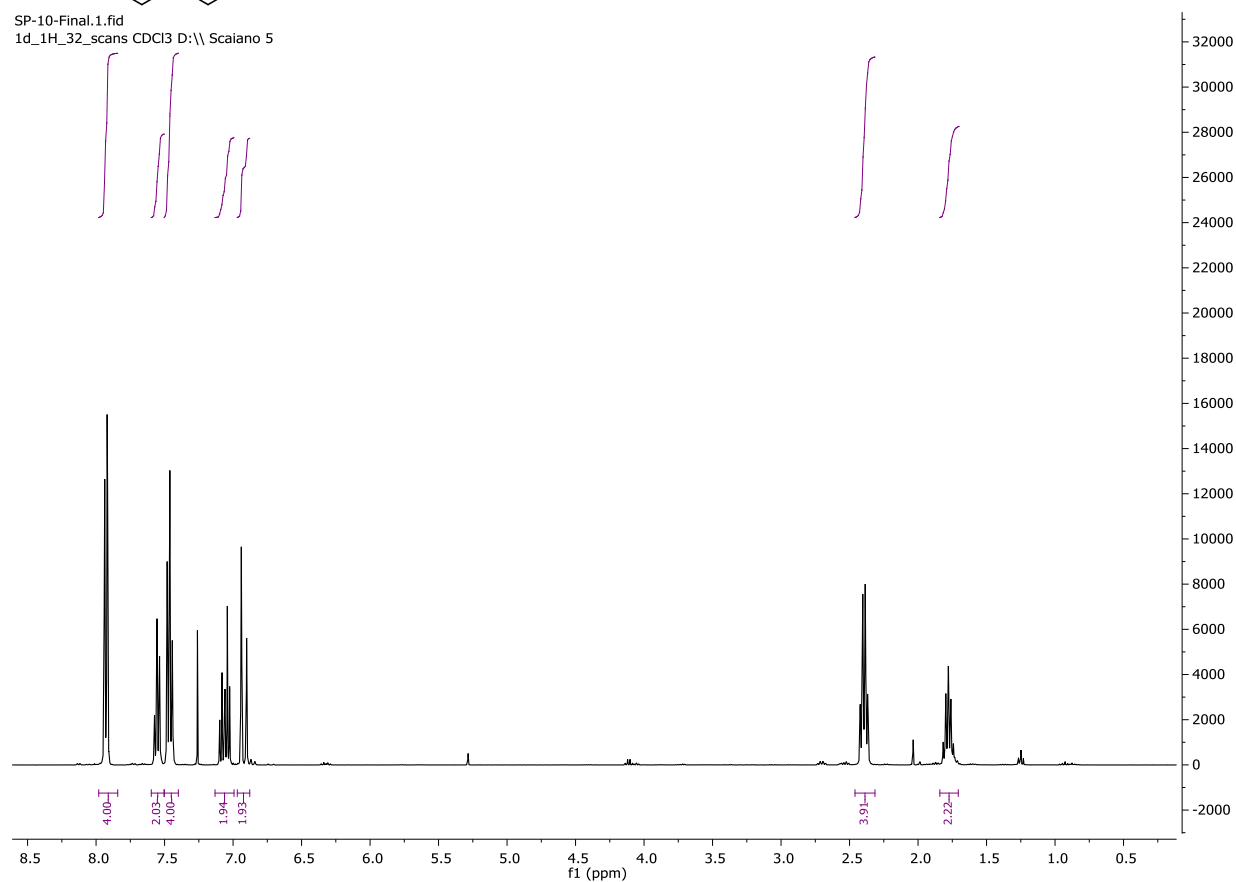
¹H NMR (400 MHz, Acetone-*d*₆) δ 7.72 (d, *J* = 8.1 Hz) and 7.60 (d, *J* = 8.1 Hz) (1H, two rotamers), 7.22 (d, *J* = 7.4 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 7.00 – 6.89 (m, 1H), 6.11 – 5.99 (m, 1H), 5.98 – 5.85 (m, 1H), 5.17 – 5.00 (m, 1H), 4.89 (d, *J* = 12.2 Hz, 1H), 4.62 (dd, *J* = 9.6, 3.0 Hz) and 4.53 (d, *J* = 9.7 Hz) (1H, two rotamers), 3.68 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.55 – 3.31 (m, 1H), 3.00 (dd, *J* = 6.5, 3.2 Hz, 1H), 1.78 – 1.57 (m, 2H), 1.42 – 1.23 (m, 2H). **¹³C NMR** (101 MHz, Acetone-*d*₆) δ 151.66, 144.51, 135.66, 134.84, 131.26, 128.01, 124.84, 123.98, 115.17, 96.69, 75.08, 64.55, 46.62, 35.74, 33.75, 24.32, 22.54. **HRMS (EI)**: *m/z* cal'd for C₁₇H₁₆Cl₃NO₂ [*M*⁺] 371.0247, found 371.0230. **IR (neat, cm⁻¹)**: 2940, 2868, 1713, 1485, 1403, 1309, 1264, 1135, 751, 709.

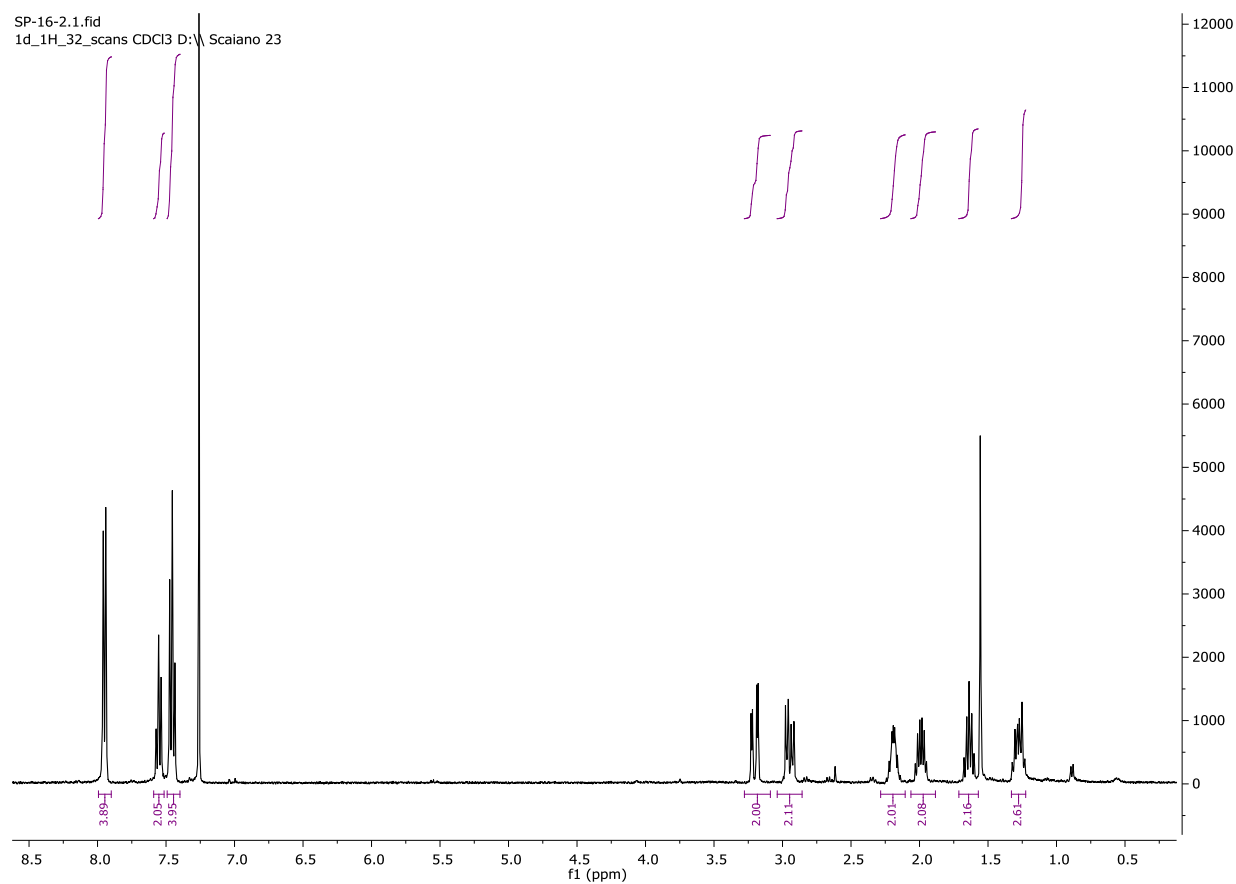
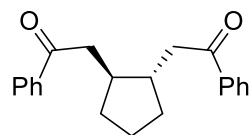
II. NMR Spectra

Chapter 2

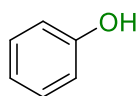


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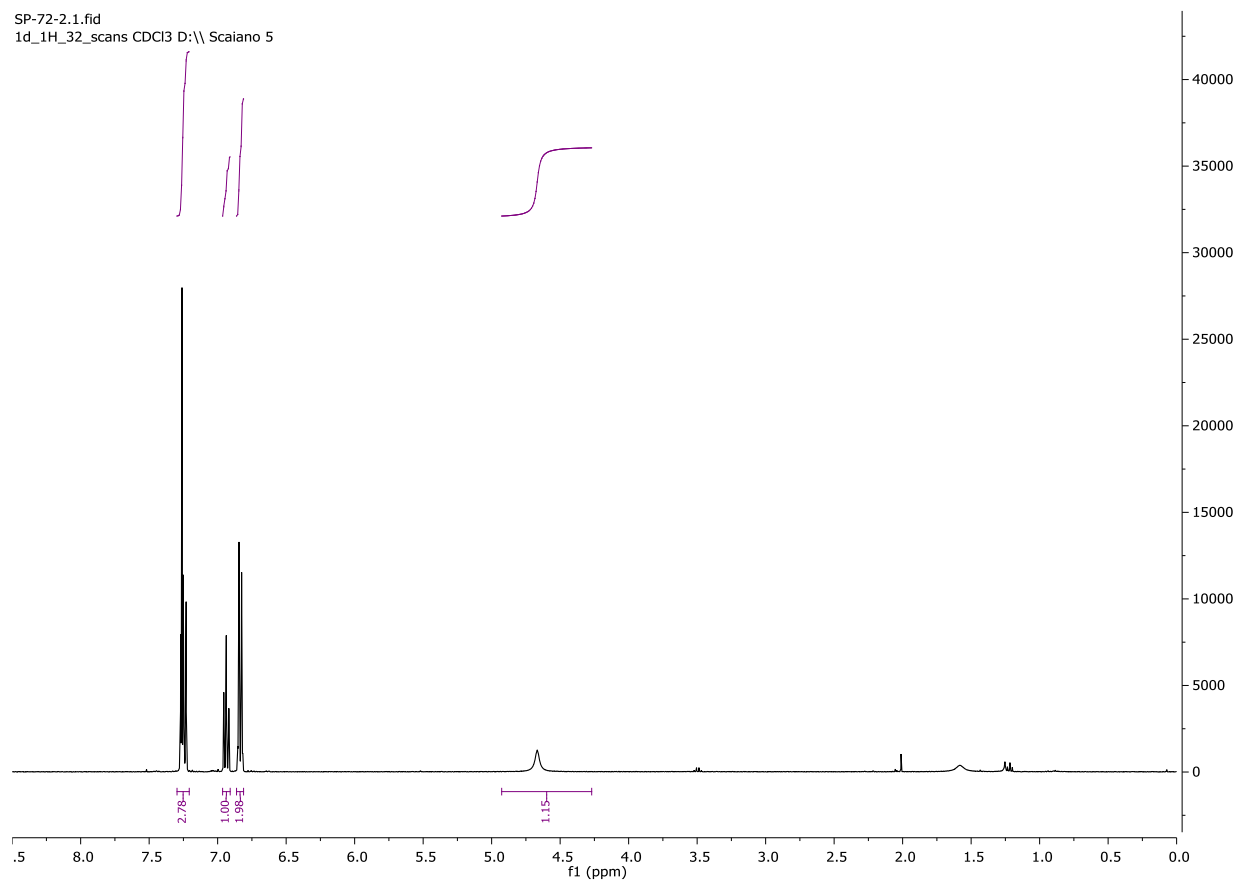


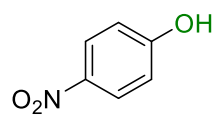


Chapter 3

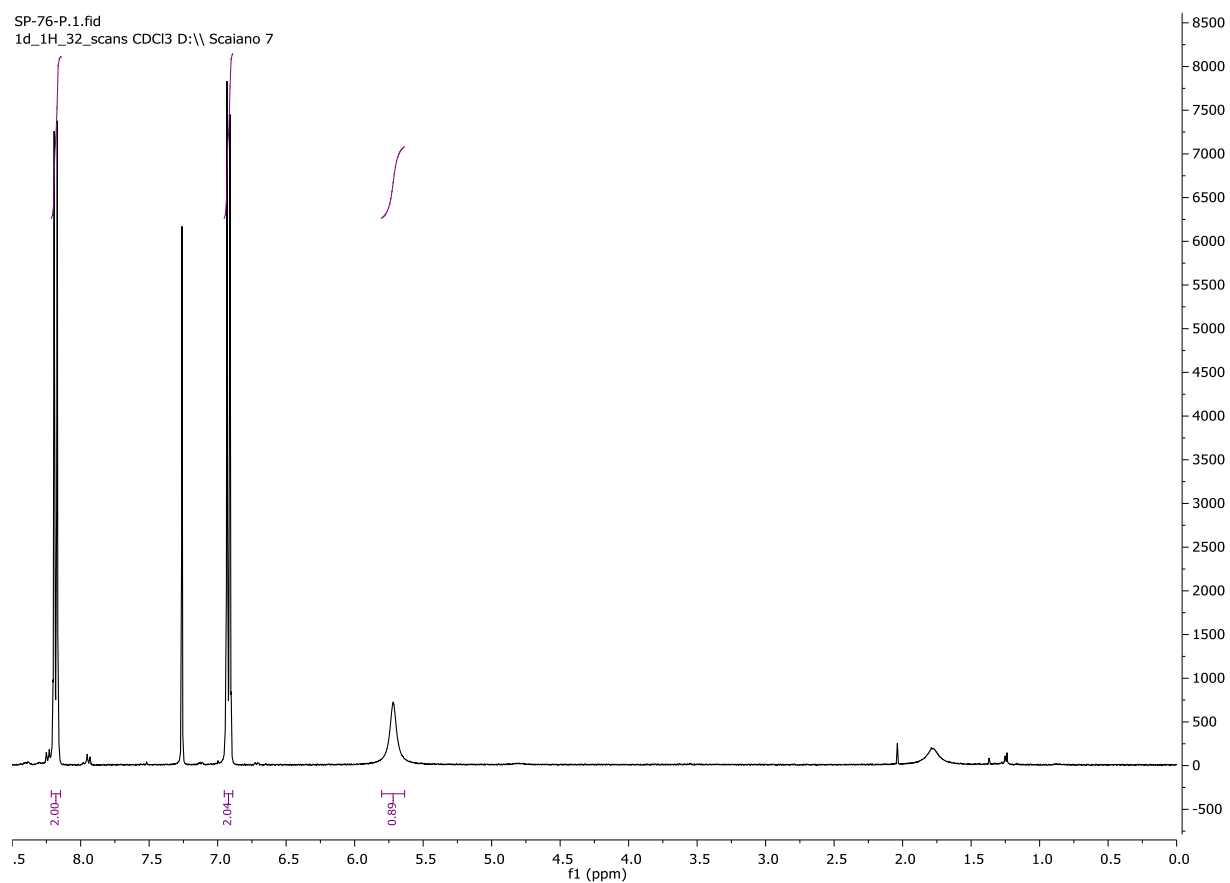


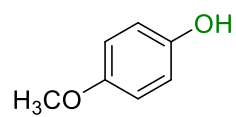
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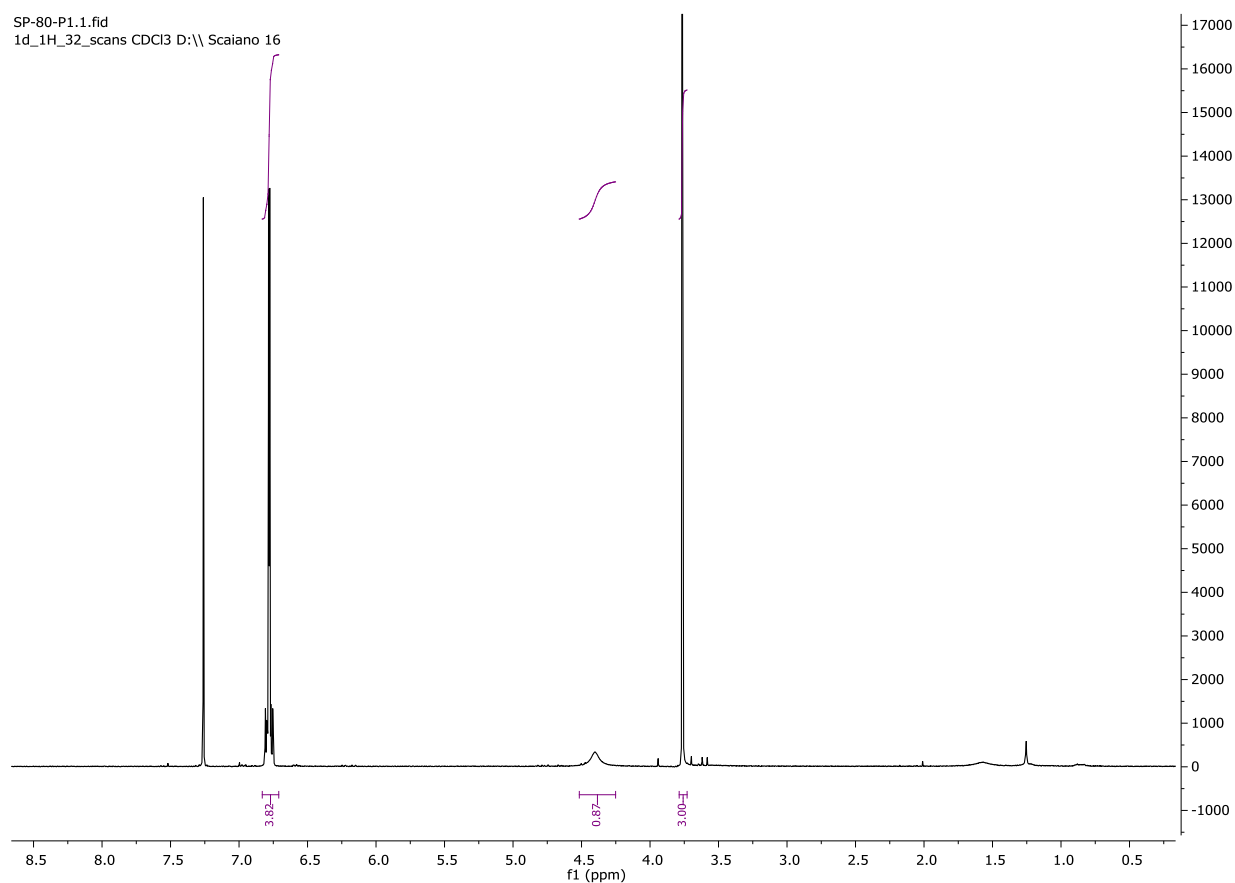


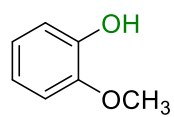
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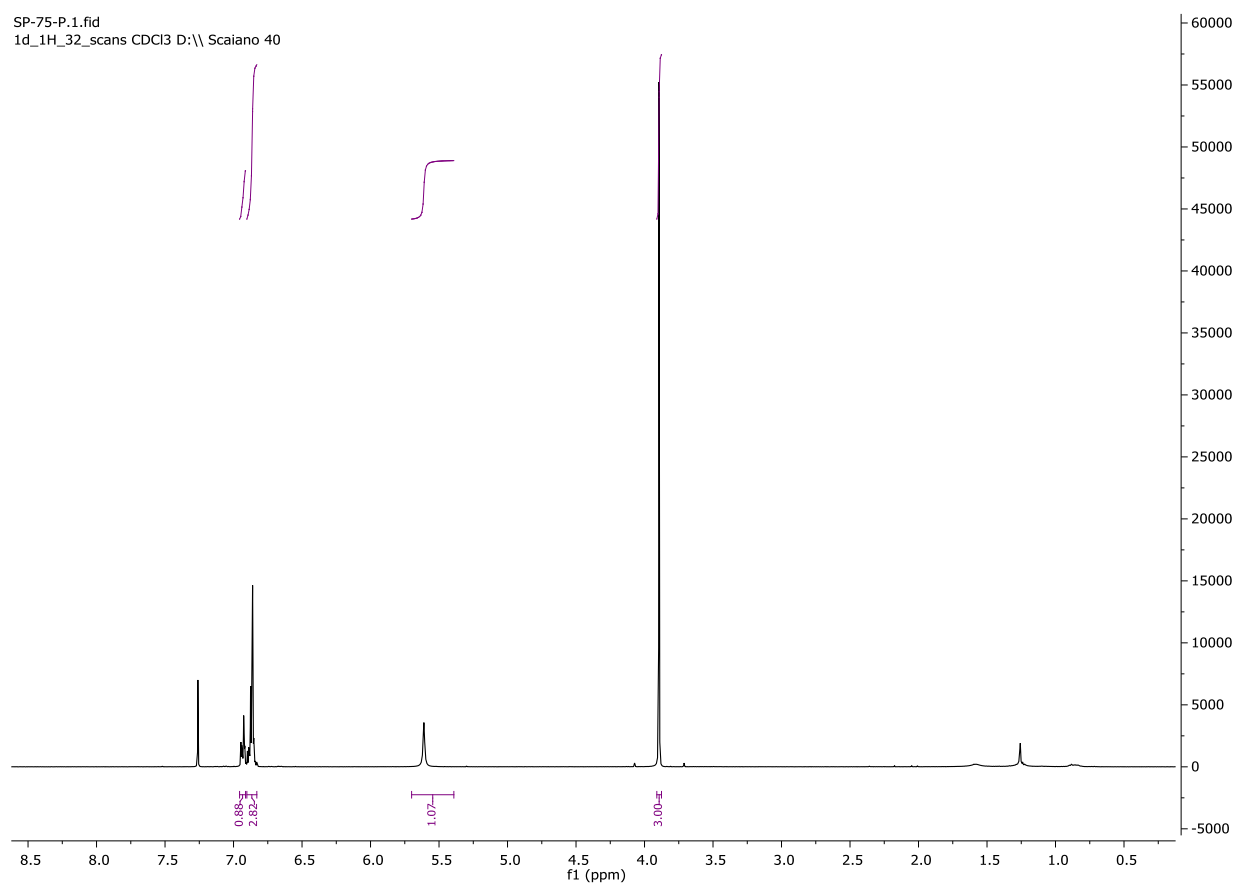


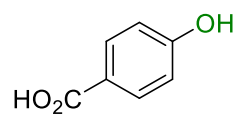
SP-80-P1.1.fid
1d_1H_32_scans CDCl3 D:\\ Scaiano 16



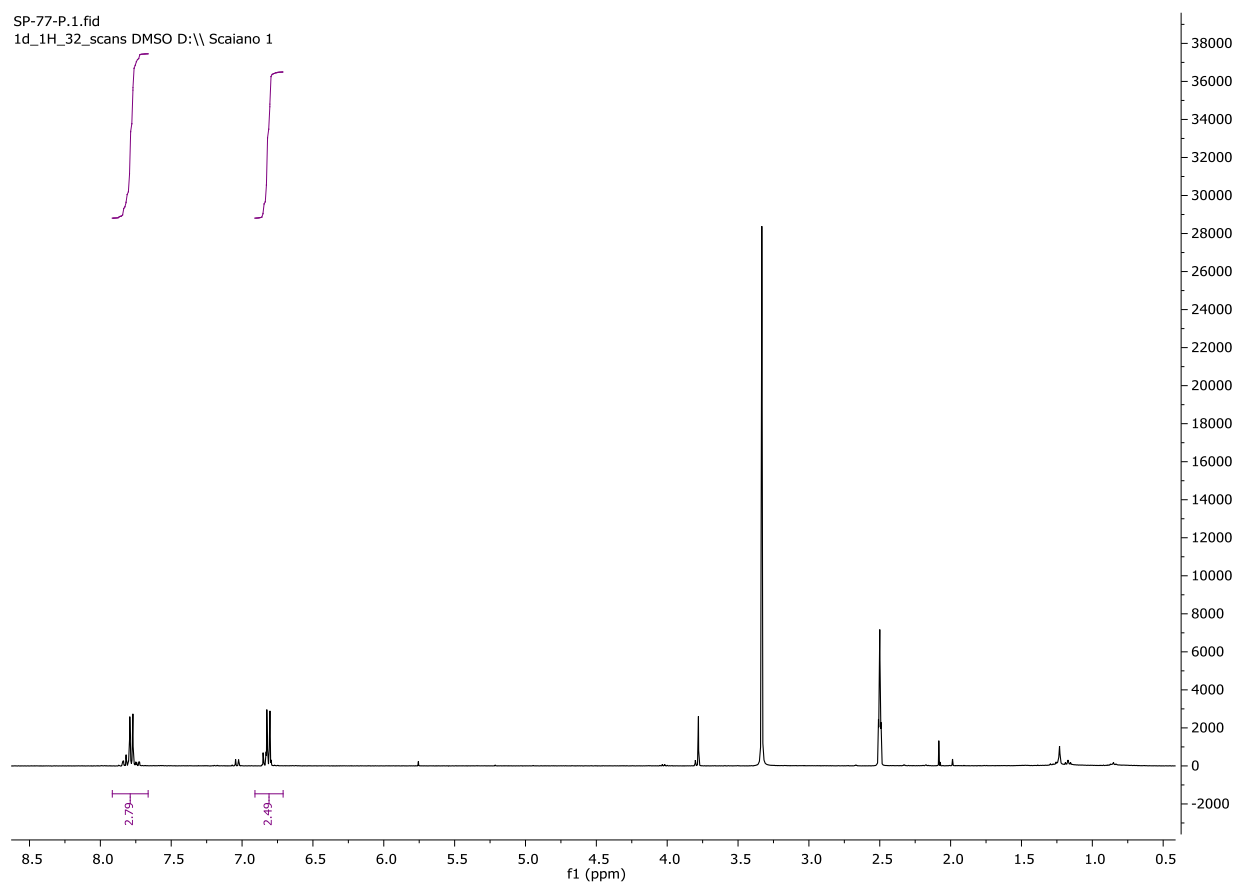


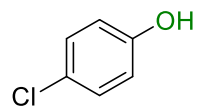
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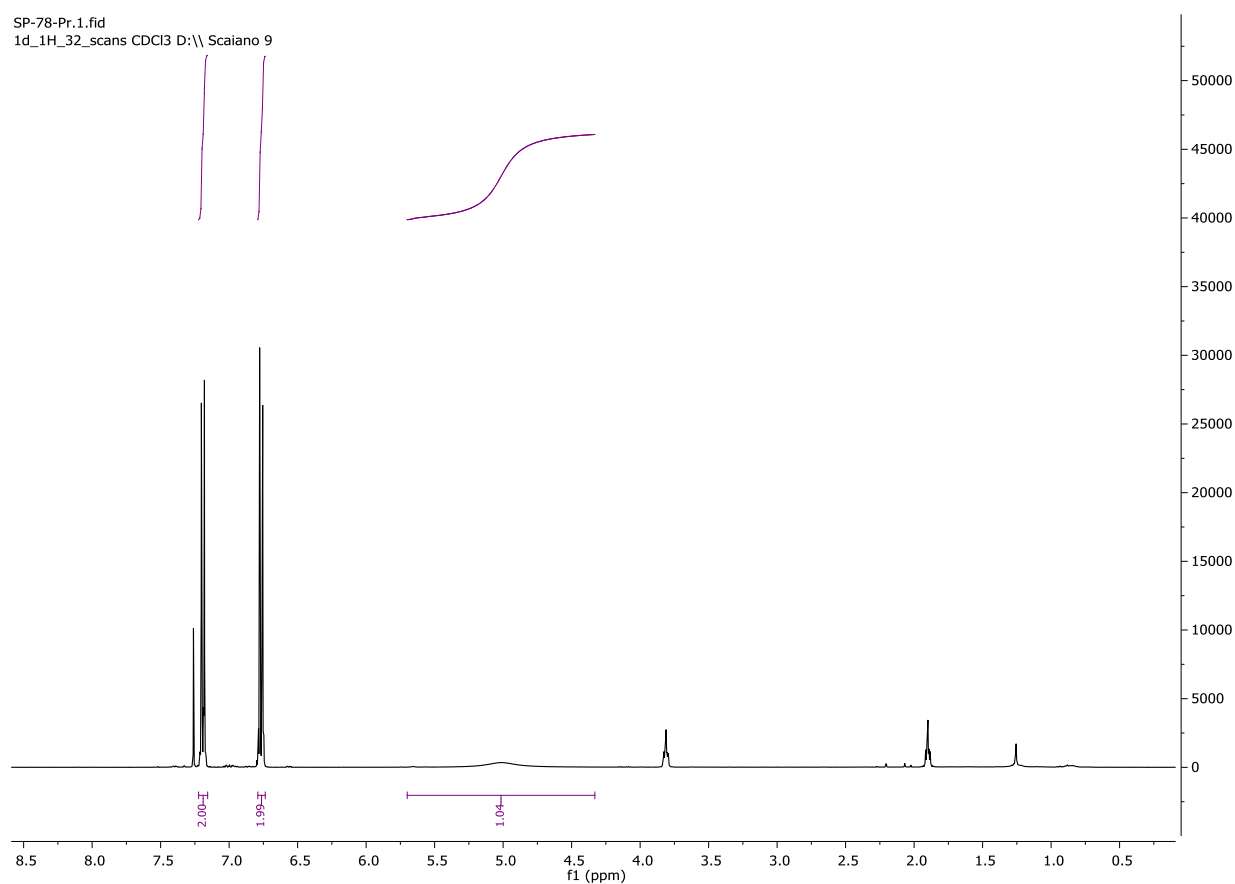


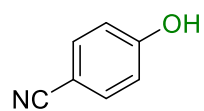
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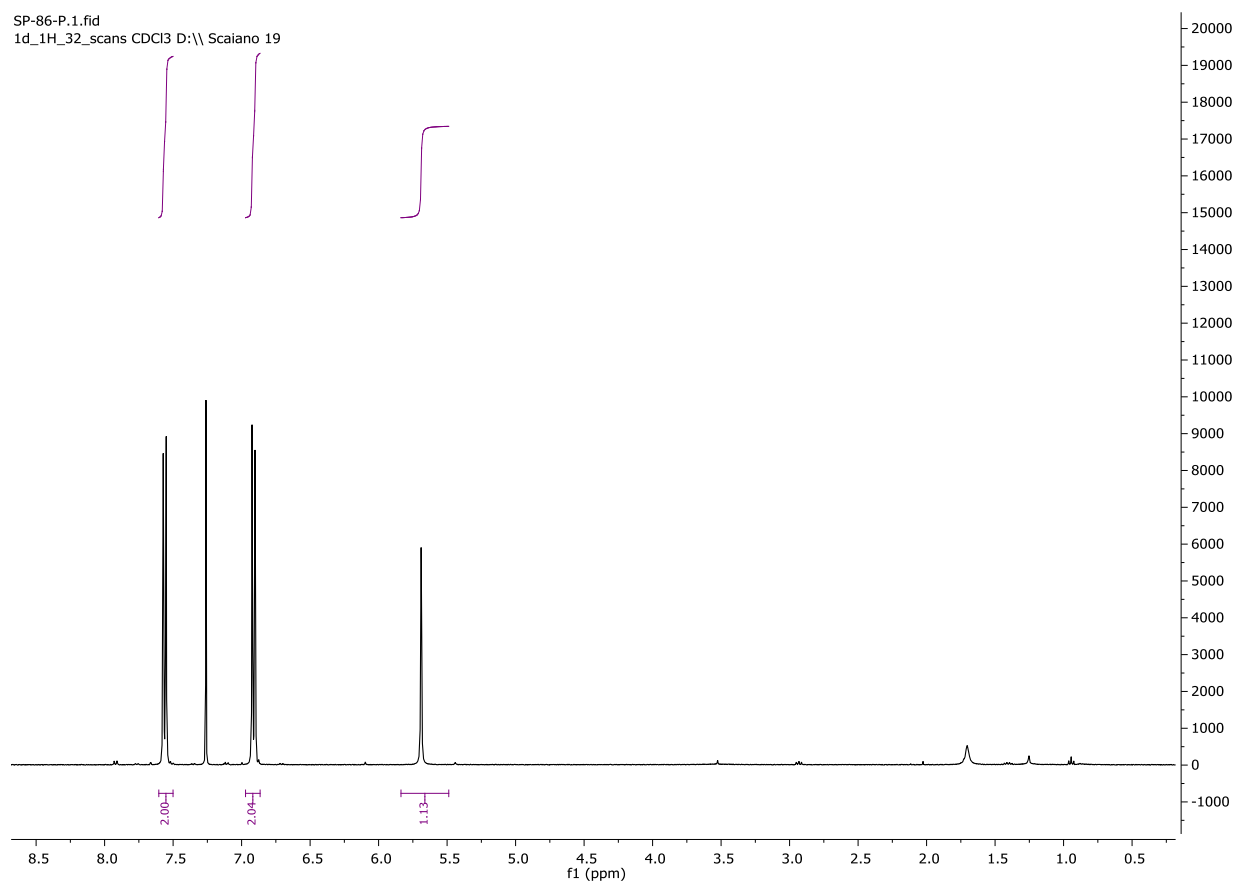


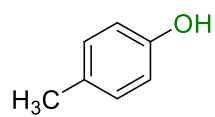
SP-78-Pr.1.fid
1d_1H_32_scans CDCl3 D:\\ Scaiano 9



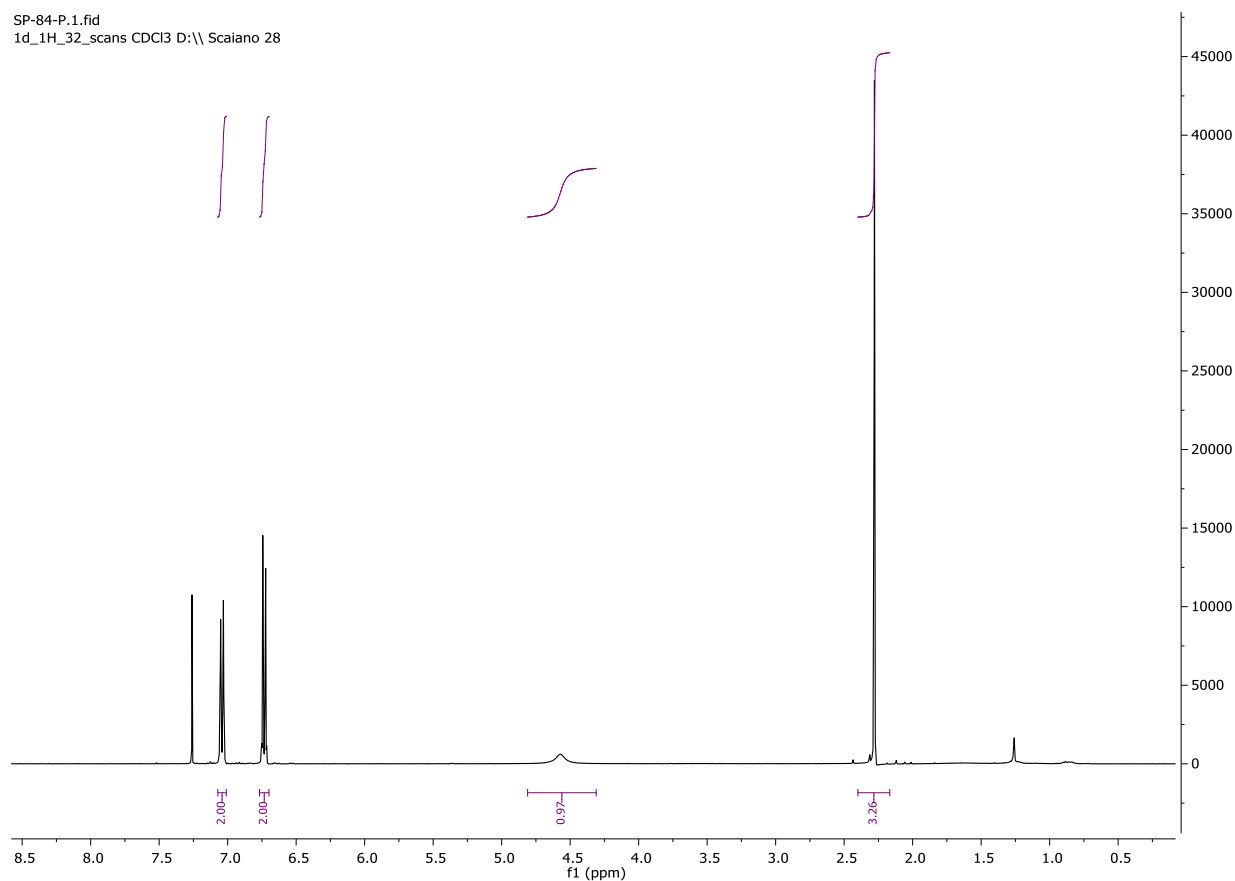


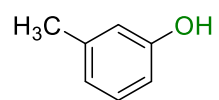
SP-86-P.1.fid
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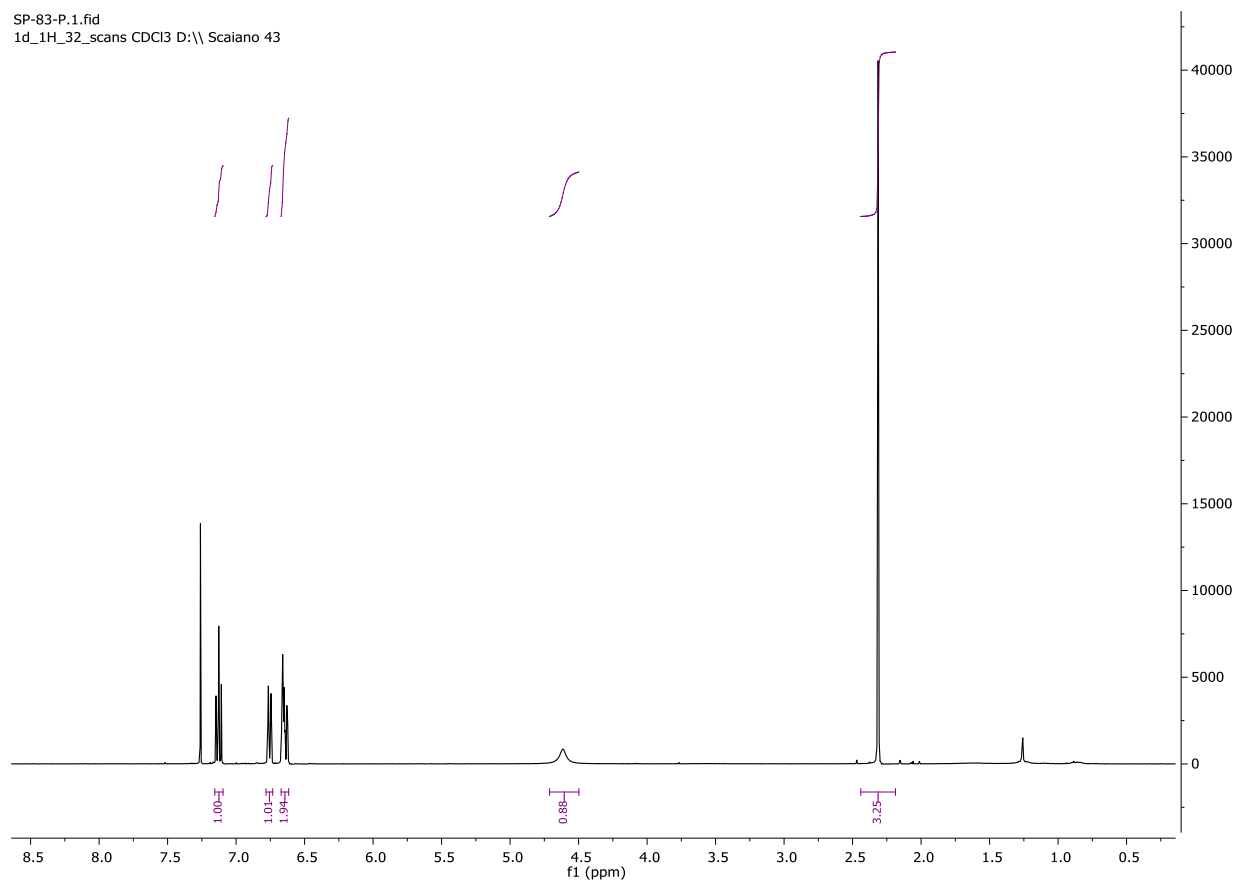
SP-84-P.1.fid
1d_1H_32_scans CDCl3 D:\ Scaiano 28

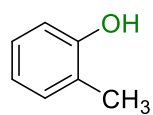




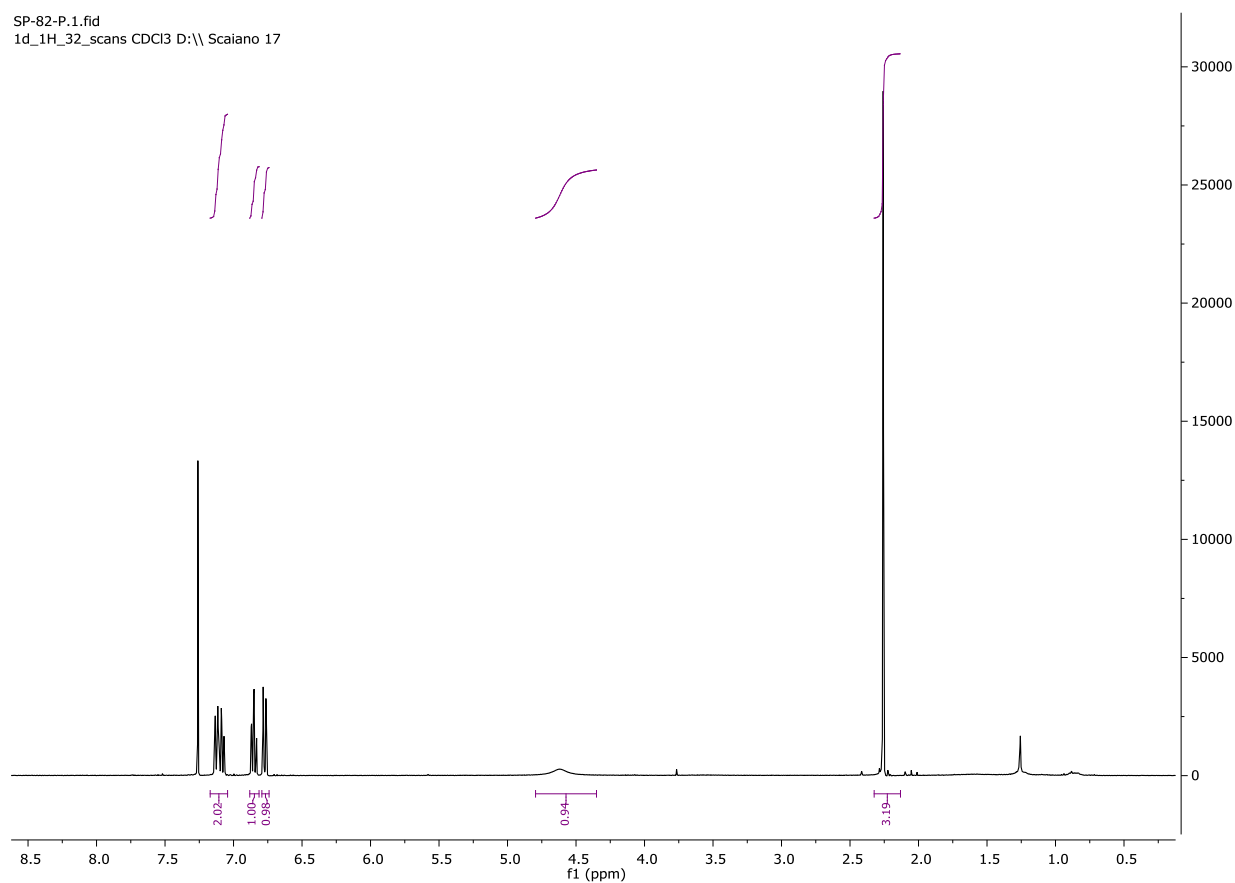
SP-83-P.1.fid

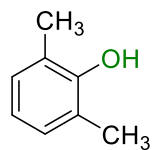
1d_1H_32_scans CDCl3 D:\ Scaiano 43



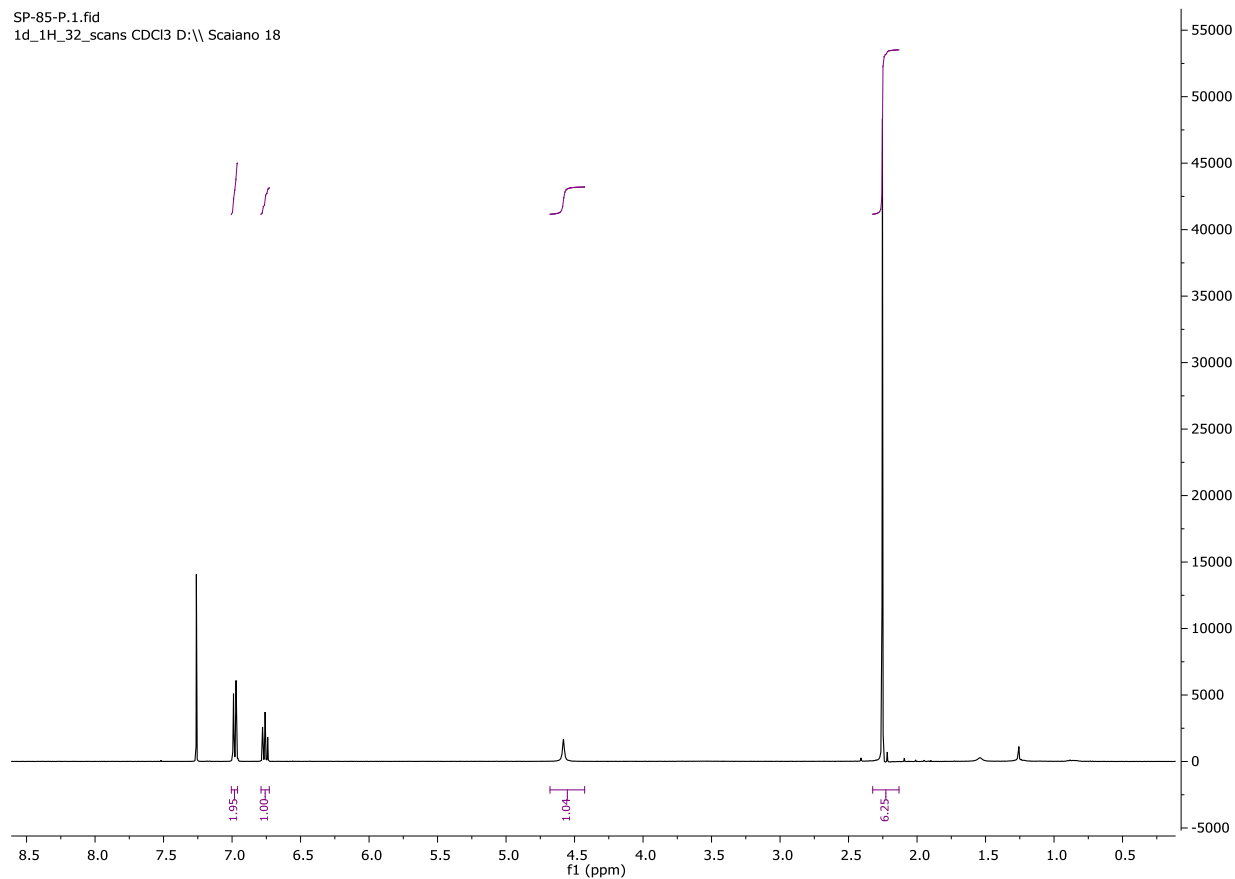


SP-82-P.1.fid
1d_1H_32_scans CDCl3 D:\ Scaiano 17

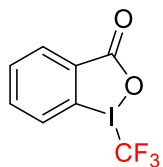




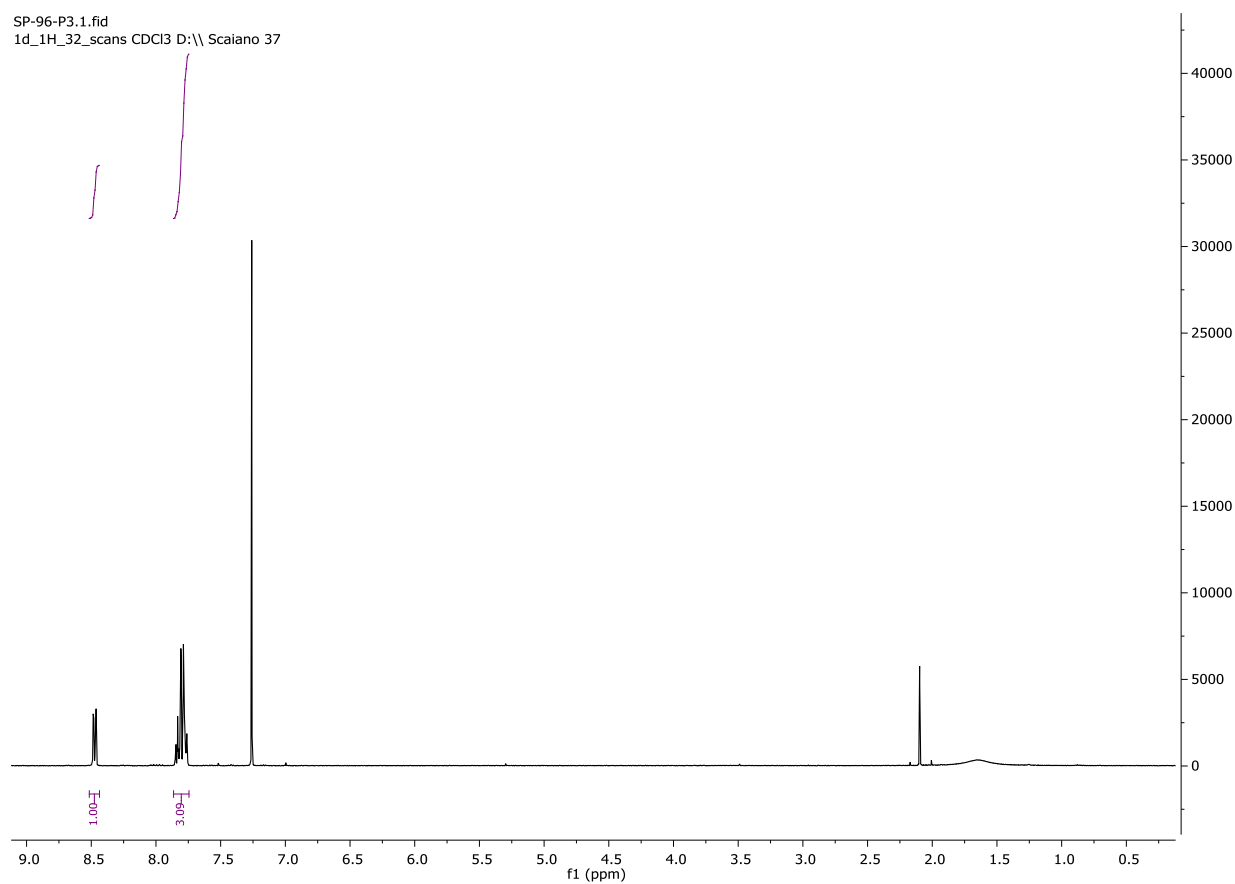
SP-85-P.1.fid
1d_1H_32_scans CDCl3 D:\\ Scaiano 18

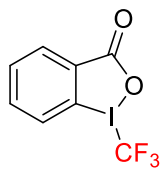


Chapter 4

 ^1H NMR

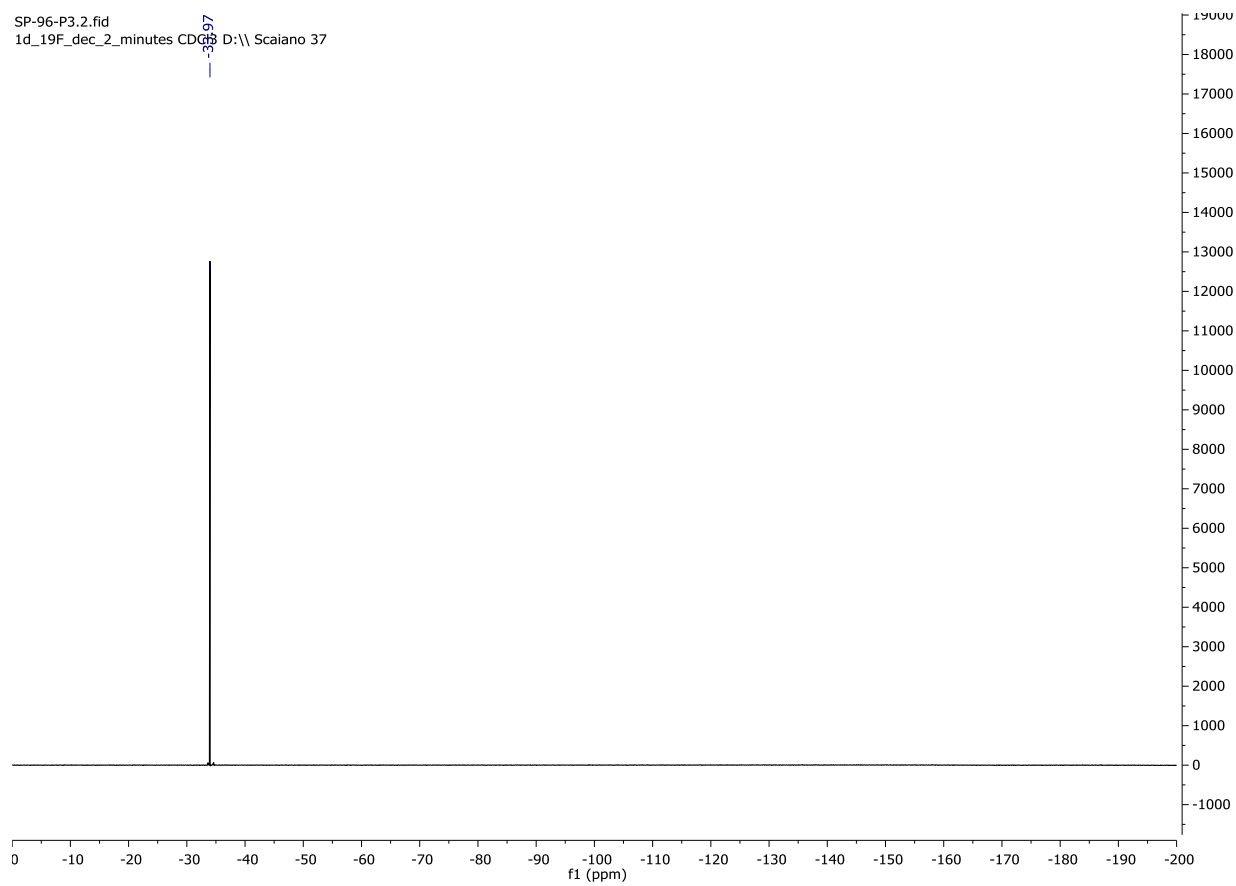
SP-96-P3.1.fid
1d_1H_32_scans CDCl₃ D:\ Scaiano 37

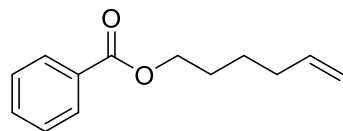




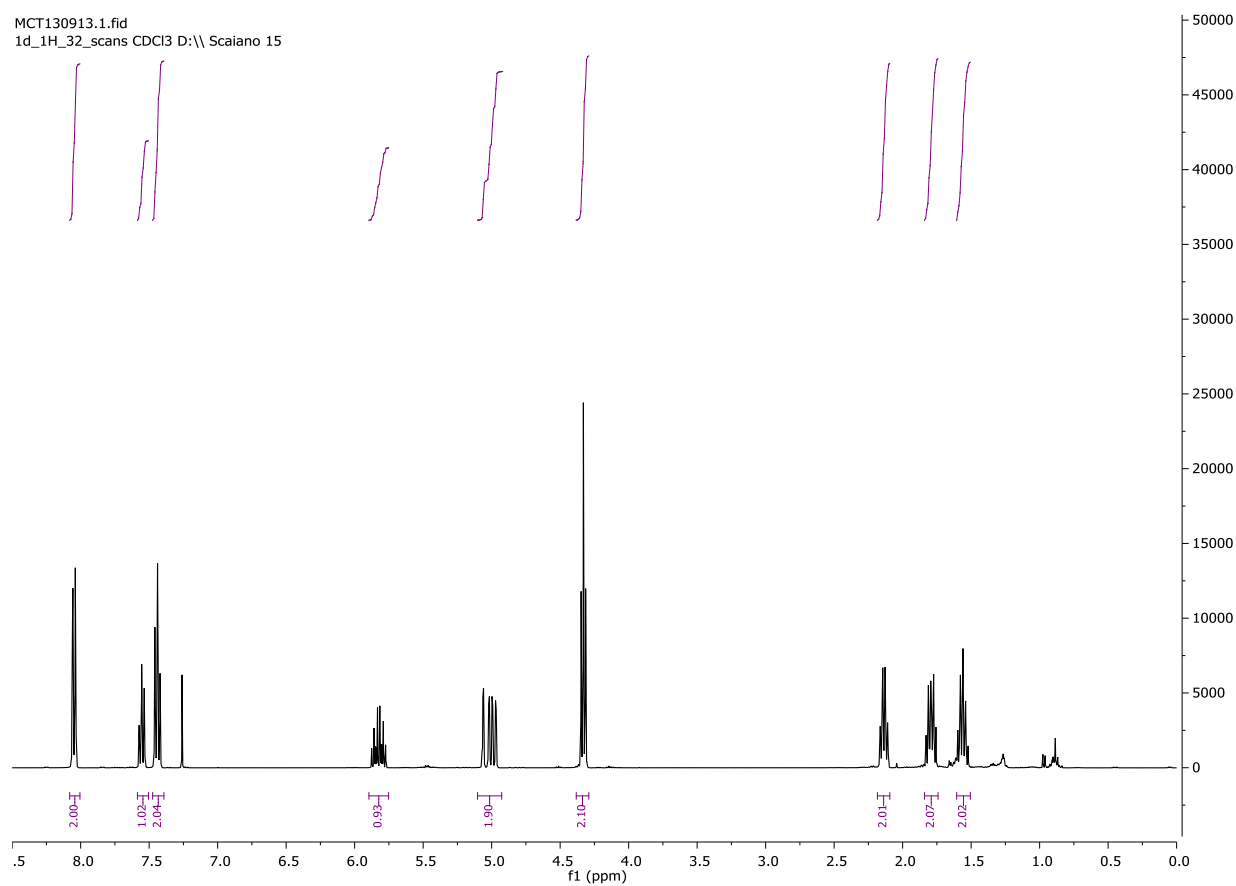
¹⁹F NMR

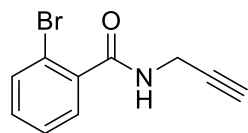
SP-96-P3.2.fid

1d_19F_dec_2_minutes CDCl₃ D:\\ Scaiano 37

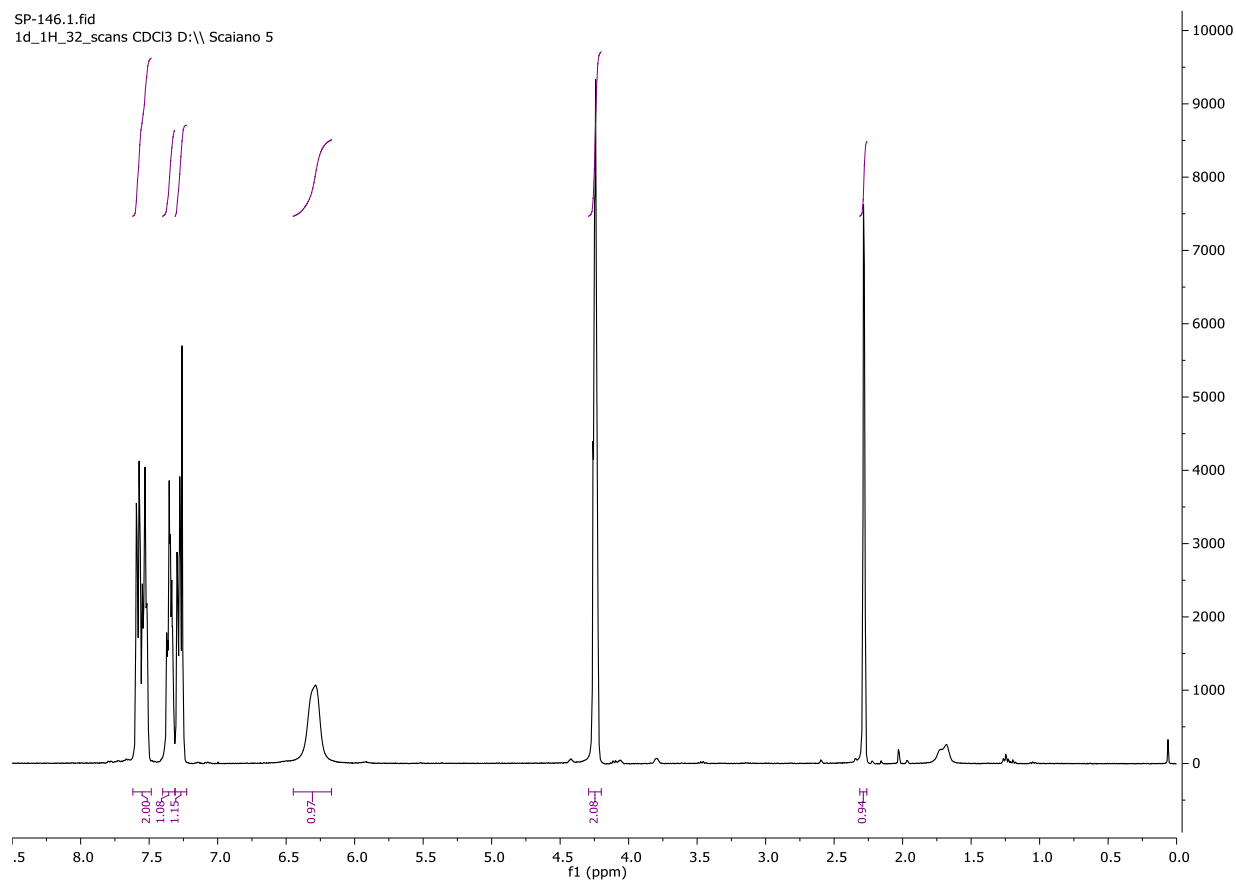


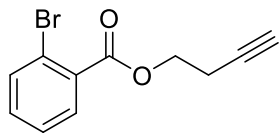
MCT130913.1.fid
1d_1H_32_scans CDCl3 D:\\ Scaiano 15





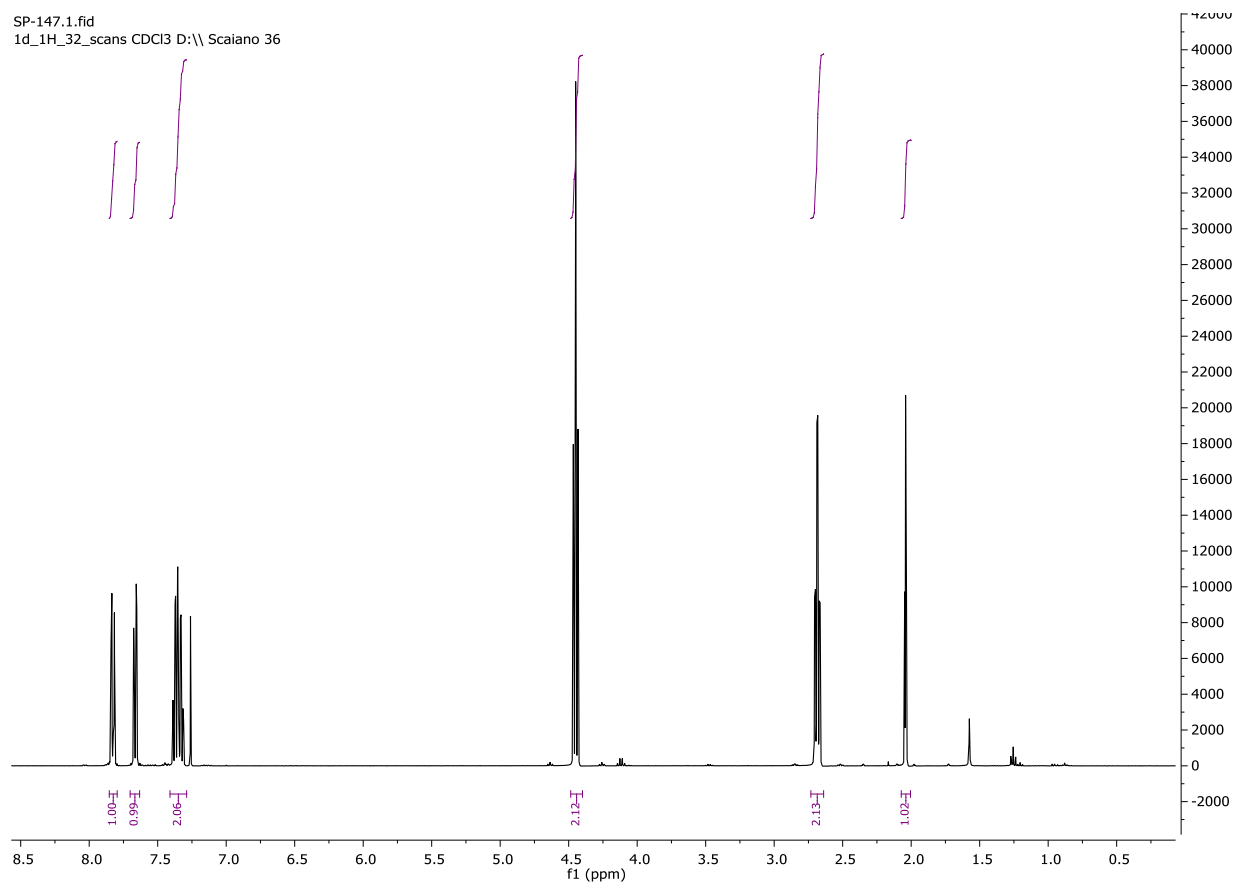
SP-146.1.fid
1d_1H_32_scans CDCl3 D:\\ Scaiano 5

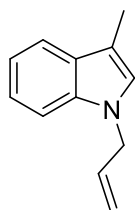




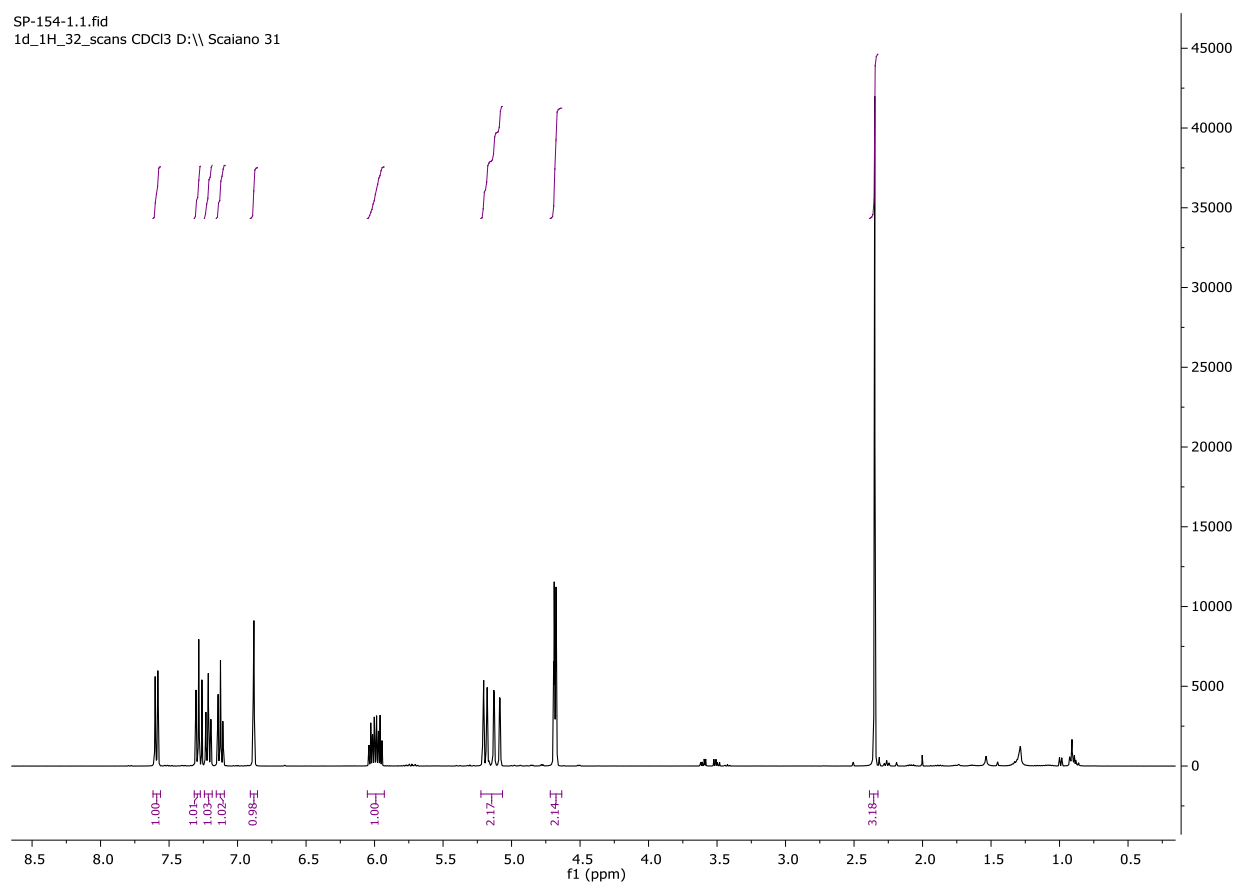
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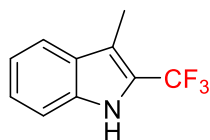
1d_1H_32_scans CDCl3 D:\\ Scaiano 36



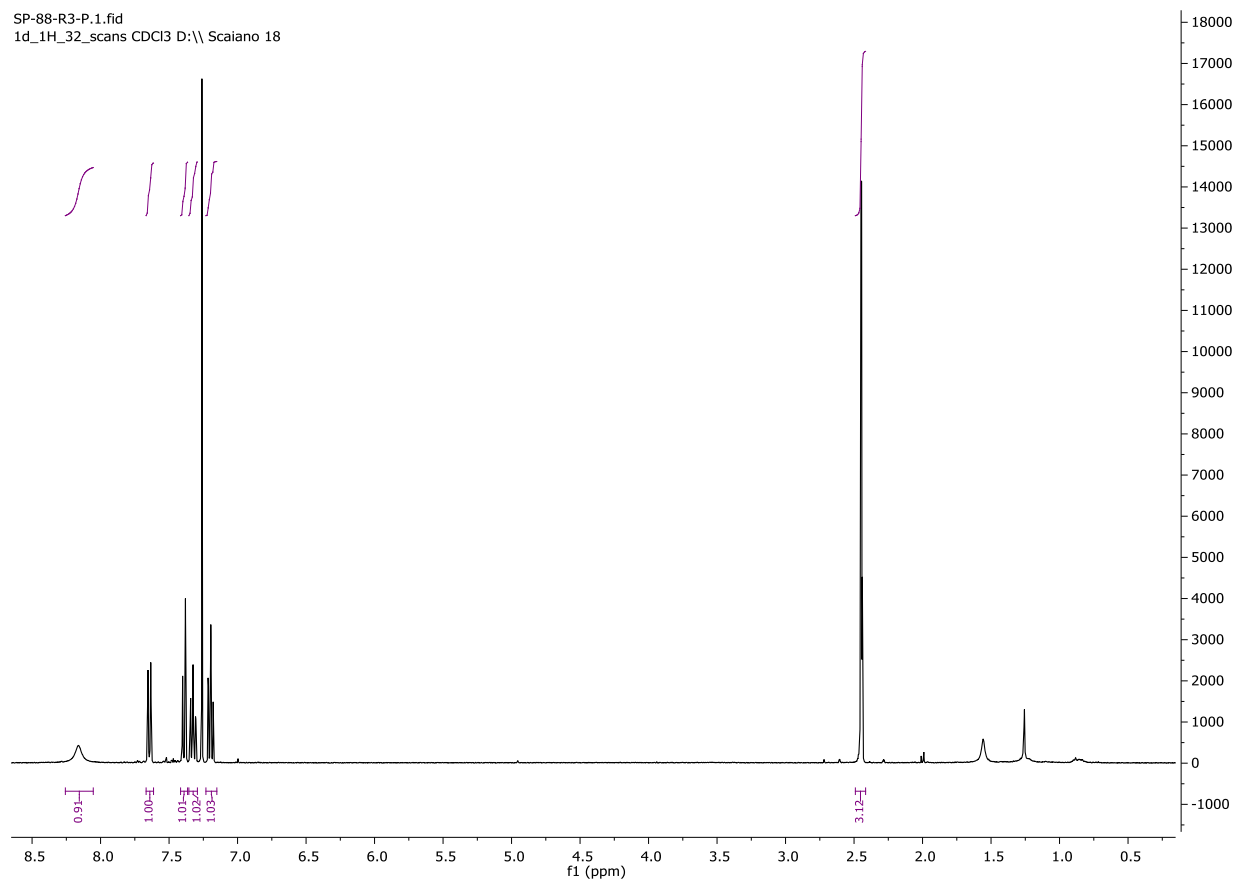


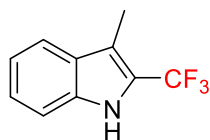
SP-154-1.1.fid
1d_1H_32_scans CDCl3 D:\\ Scaiano 31



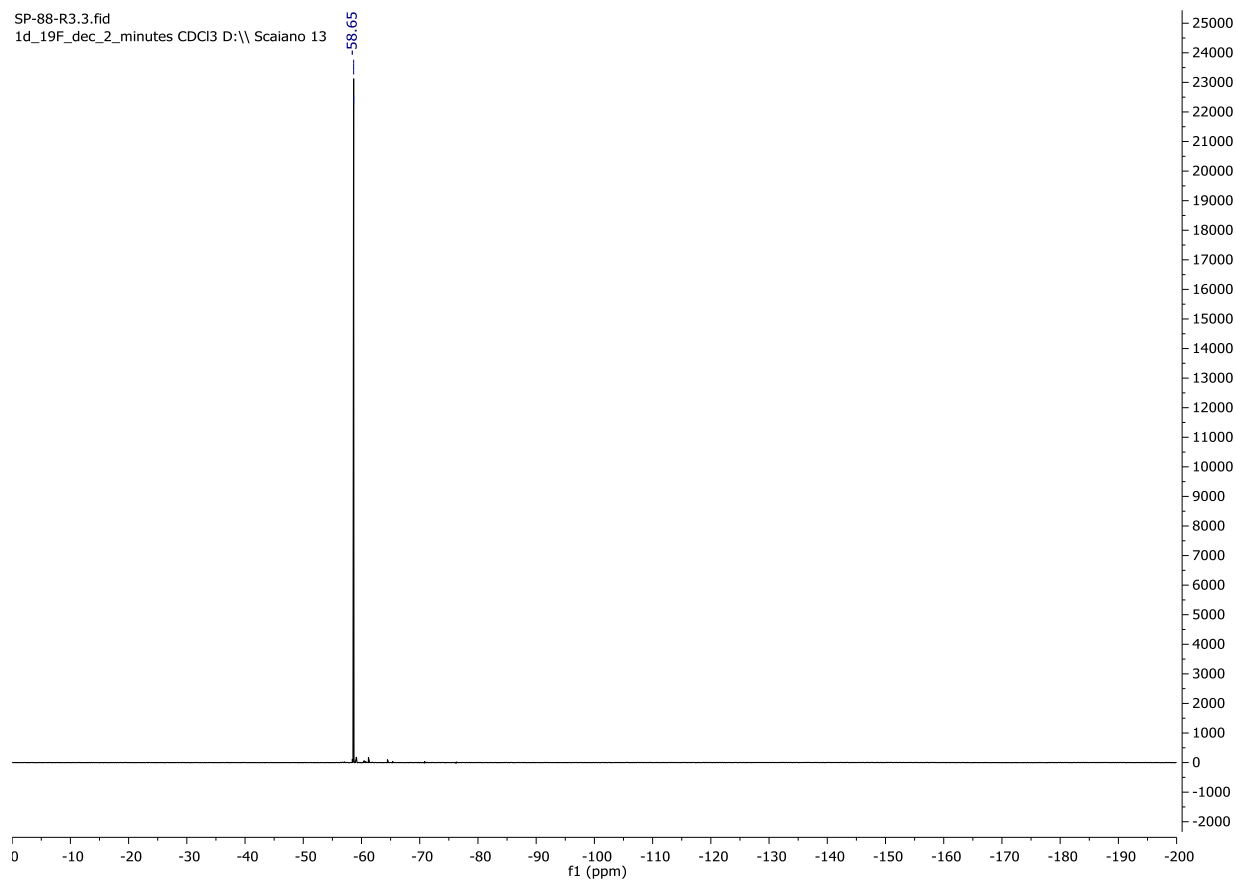
¹H NMR

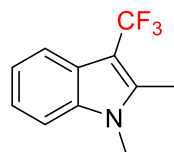
SP-88-R3-P.1.fid

1d_1H_32_scans CDCl₃ D:\\ Scaiano 18

 **^{19}F NMR**

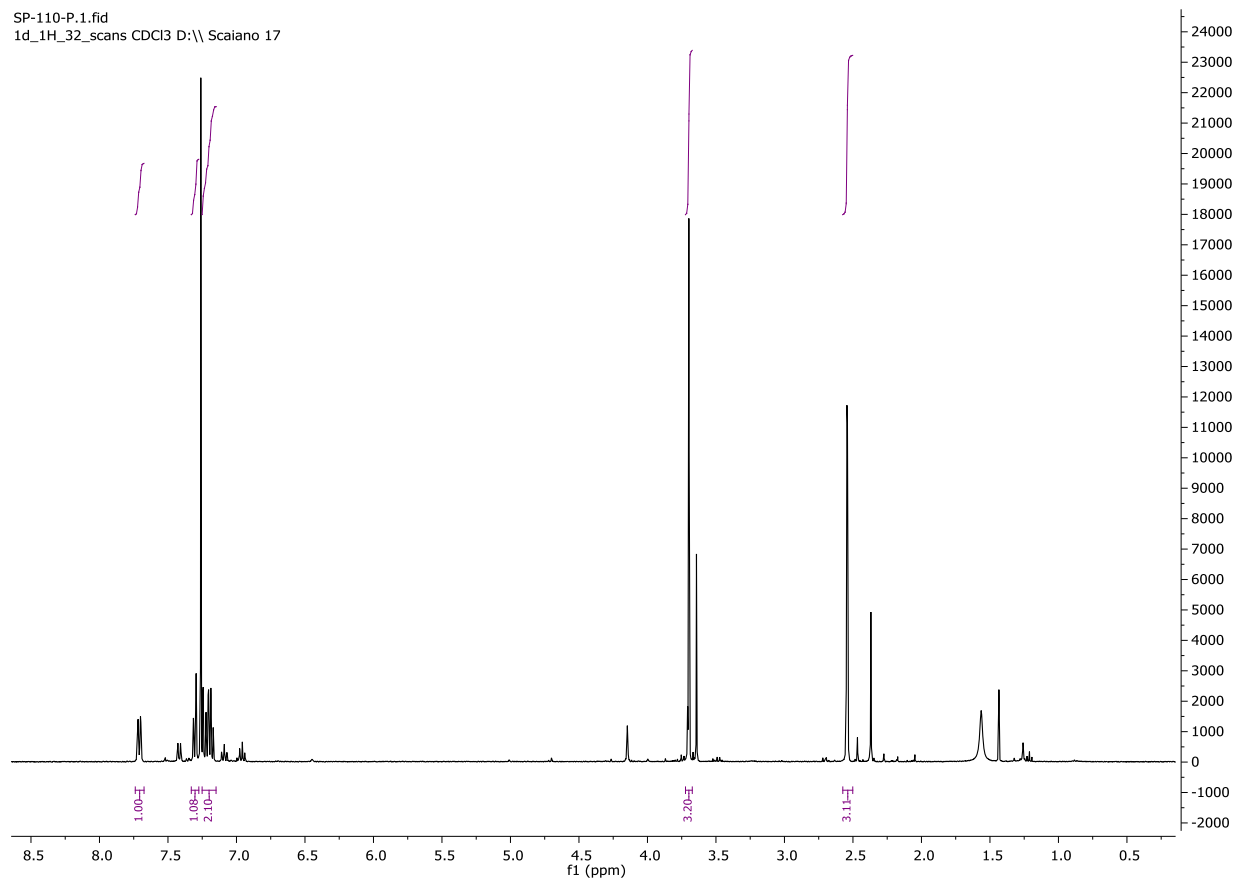
SP-88-R3.3.fid

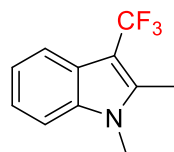
1d_19F_dec_2_minutes CDCl₃ D:\\ Scaiano 13



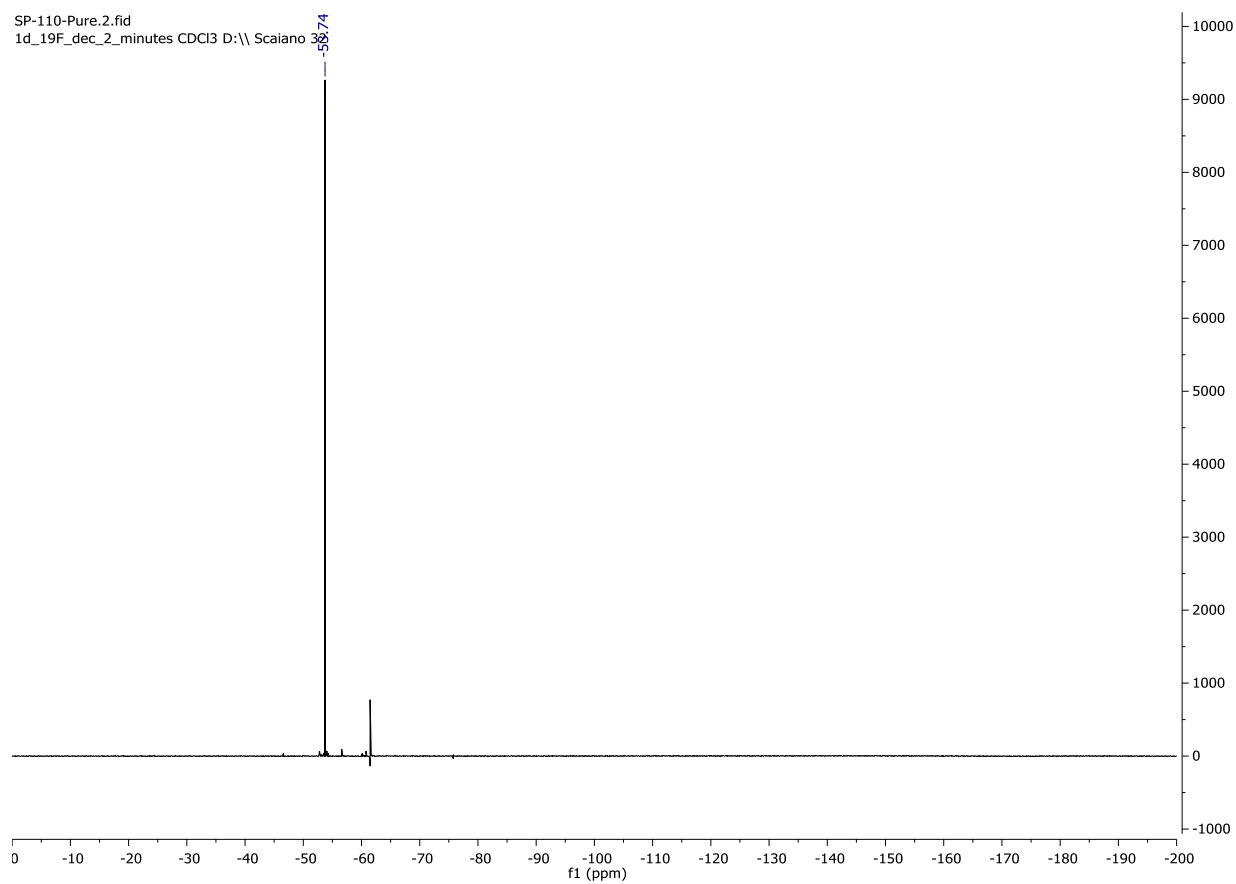
^1H NMR (Note: Product not stable to air, decomposition observed in ^1H NMR)

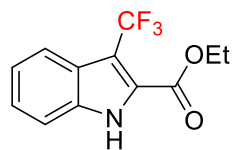
SP-110-P.1.fid
1d_1H_32_scans CDCl3 D:\Scaiano 17



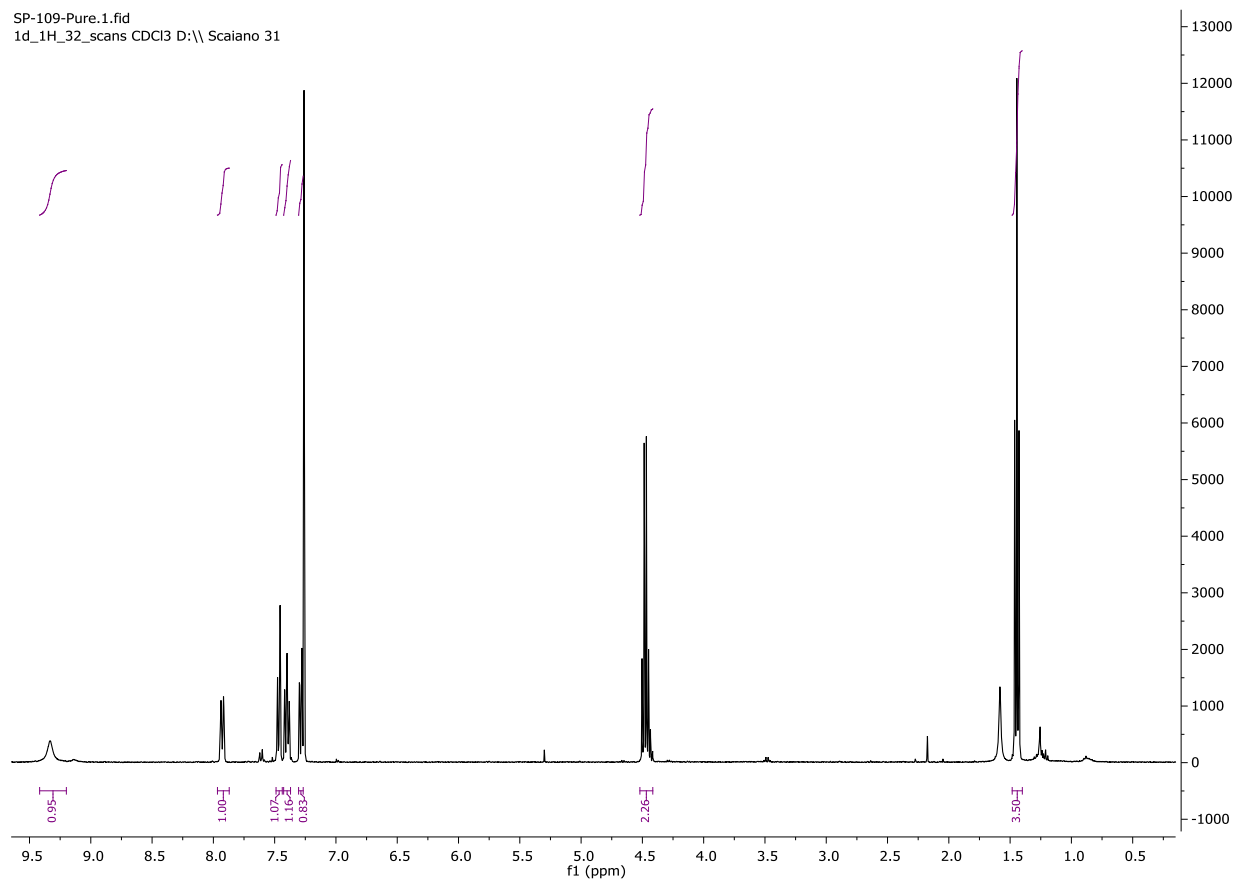


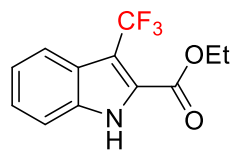
^{19}F NMR



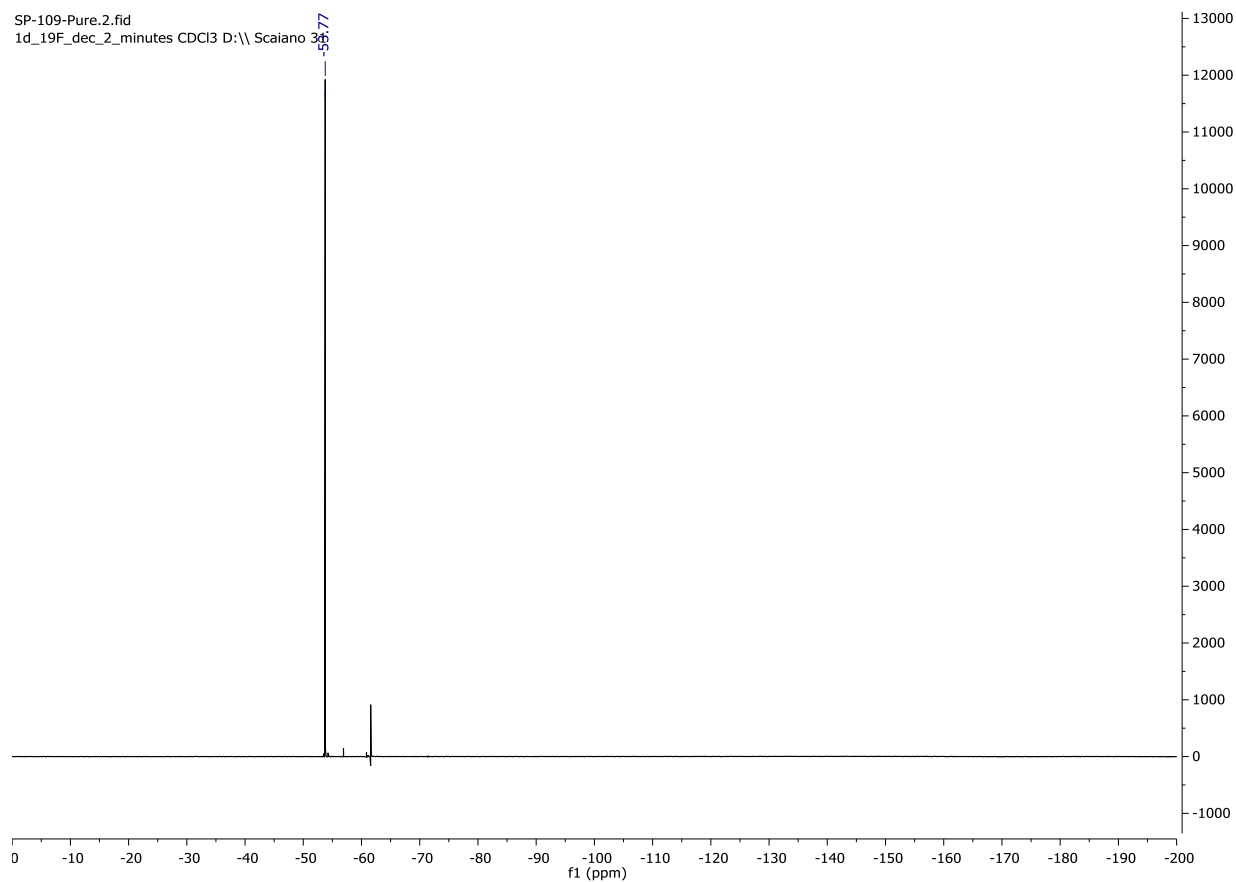
¹H NMR

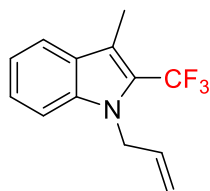
SP-109-Pure.1.fid
1d_1H_32_scans CDCl₃ D:\ Scaiano 31



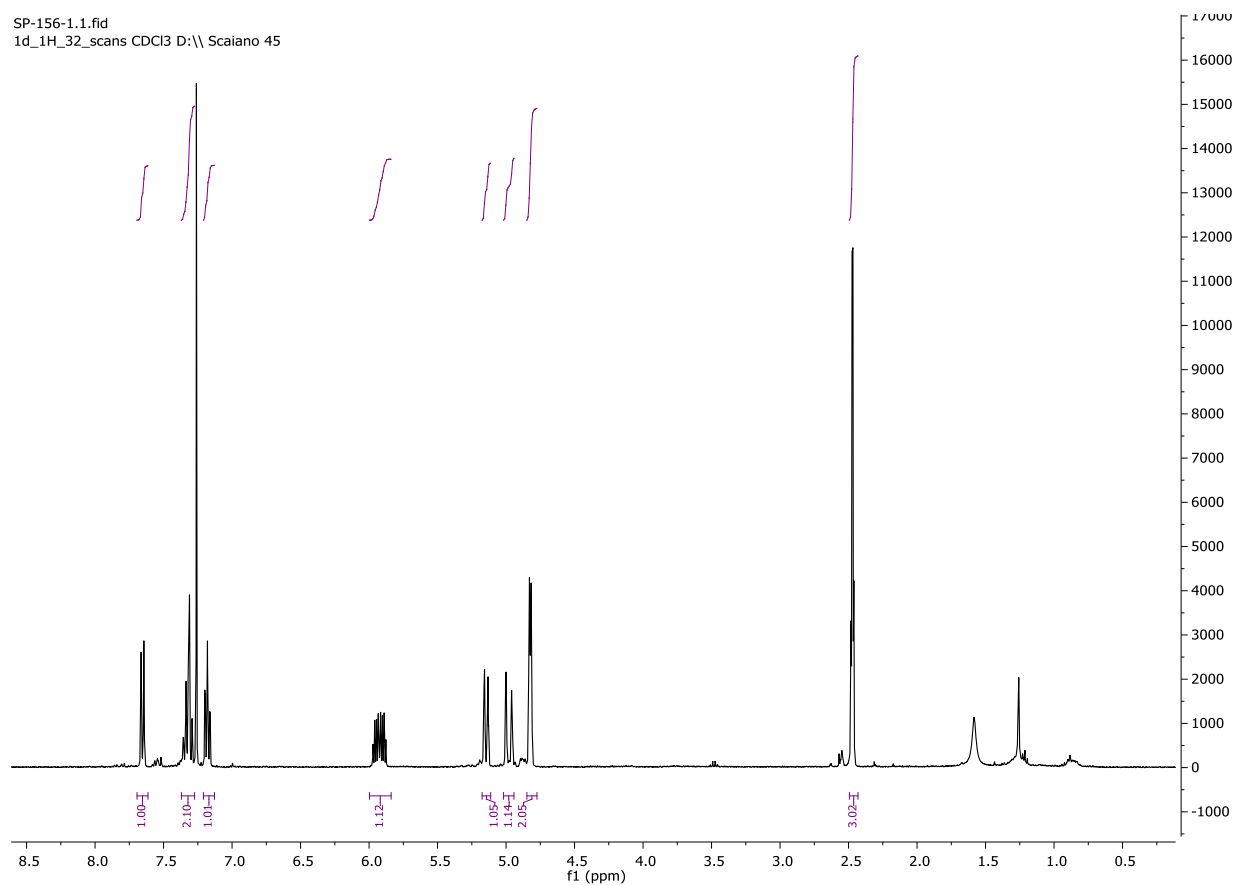
 **^{19}F NMR**

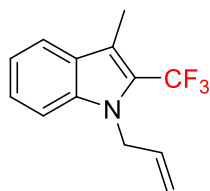
SP-109-Pure.2.fid
1d_19F_dec_2_minutes CDCl₃ D:\ Scaiano 3d



¹H NMR

SP-156-1.1.fid
1d_1H_32_scans CDCl₃ D:\\ Scaiano 45

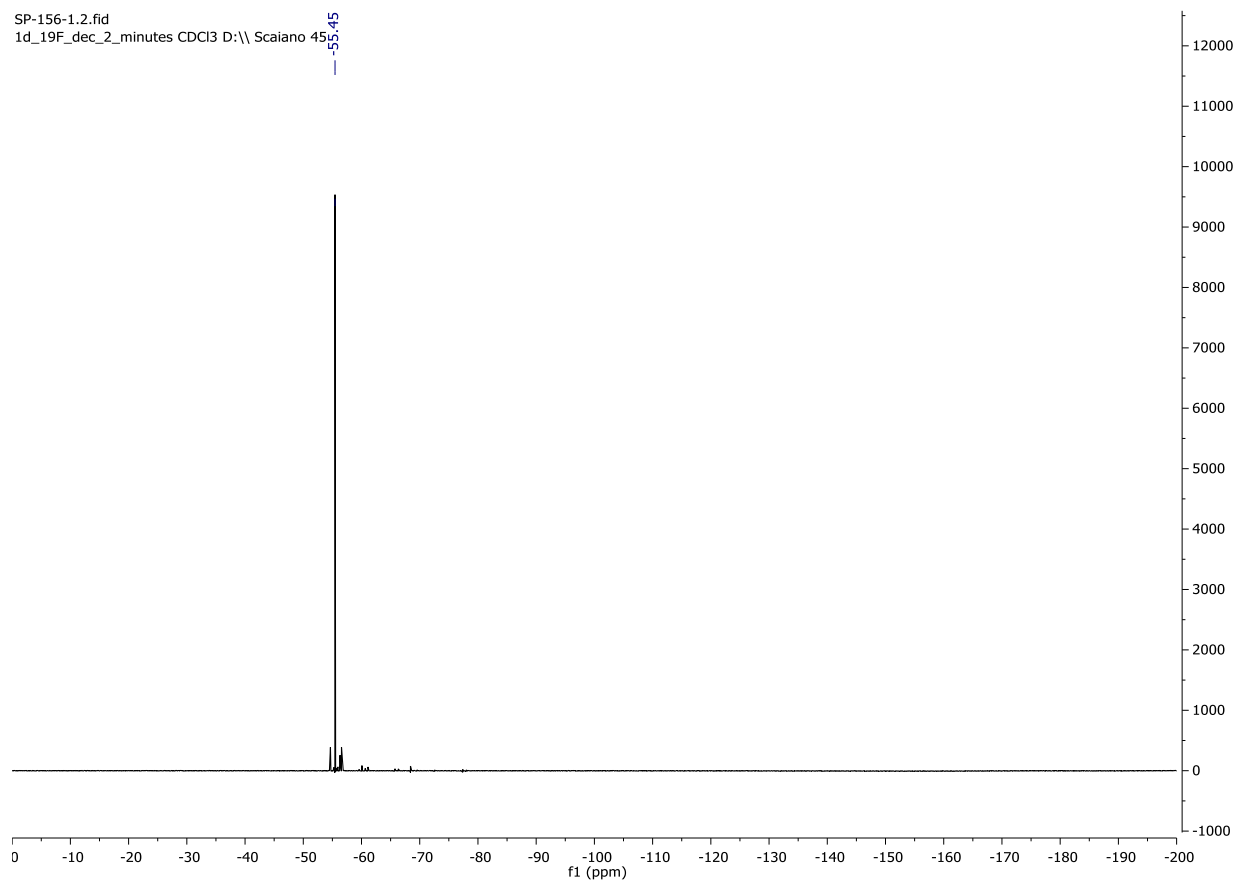


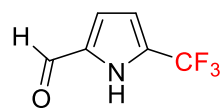


¹⁹F NMR

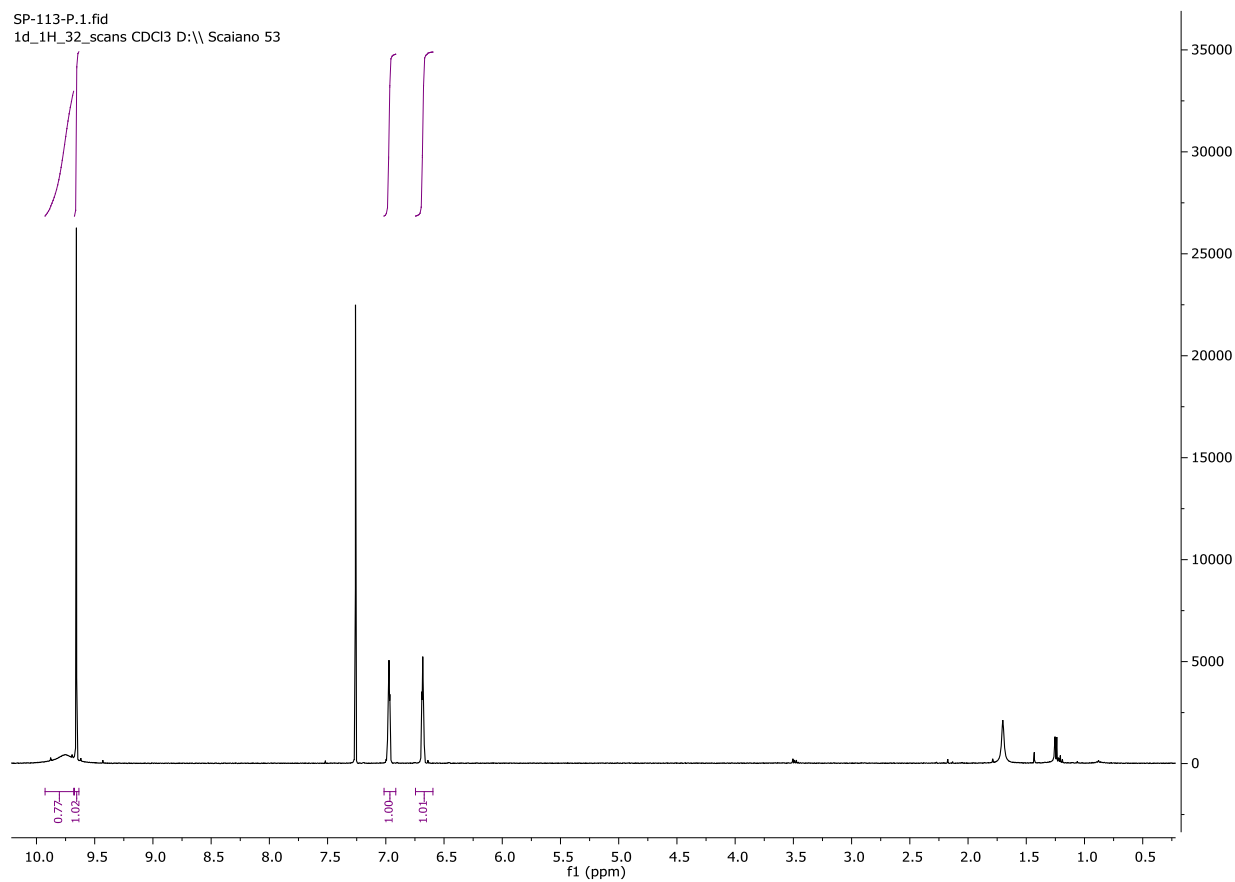
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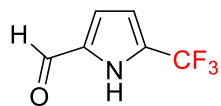
1d_19F_dec_2_minutes CDCl3 D:\\ Scaiano 45



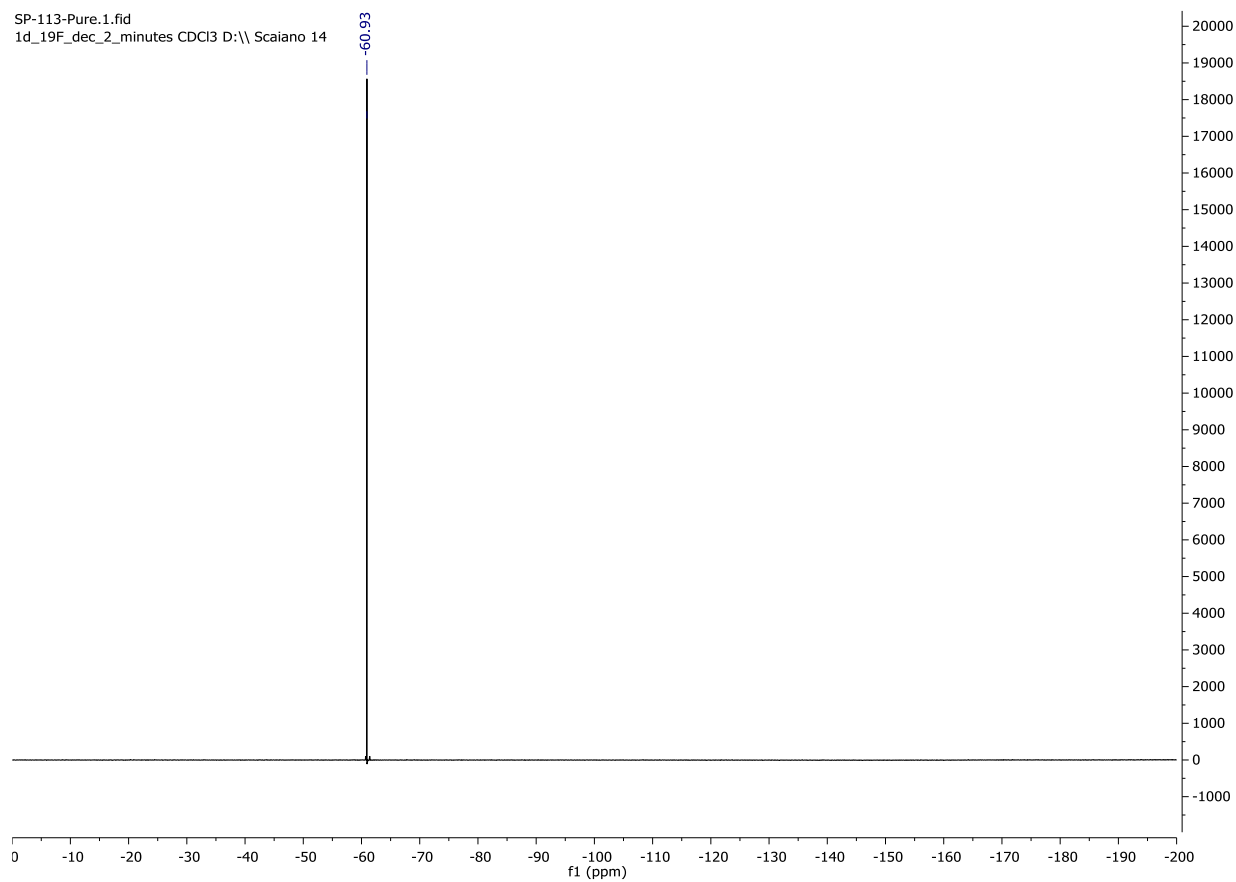
¹H NMR

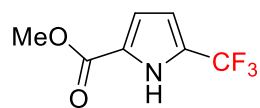
SP-113-P.1.fid
1d_1H_32_scans CDCl₃ D:\\ Scaiano 53



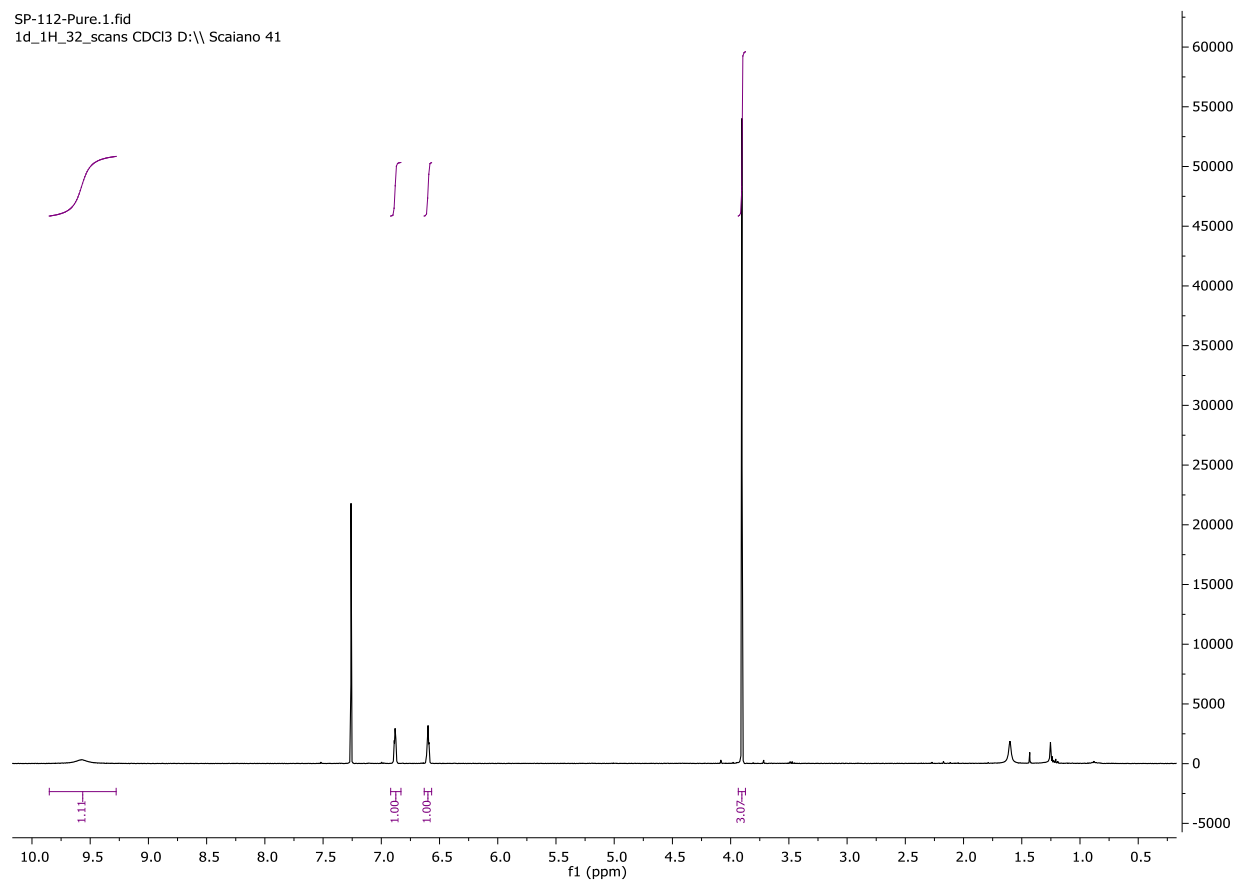
 **^{19}F NMR**

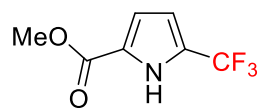
SP-113-Pure.1.fid
1d_19F_dec_2_minutes CDCl₃ D:\\ Scaiano 14



¹H NMR

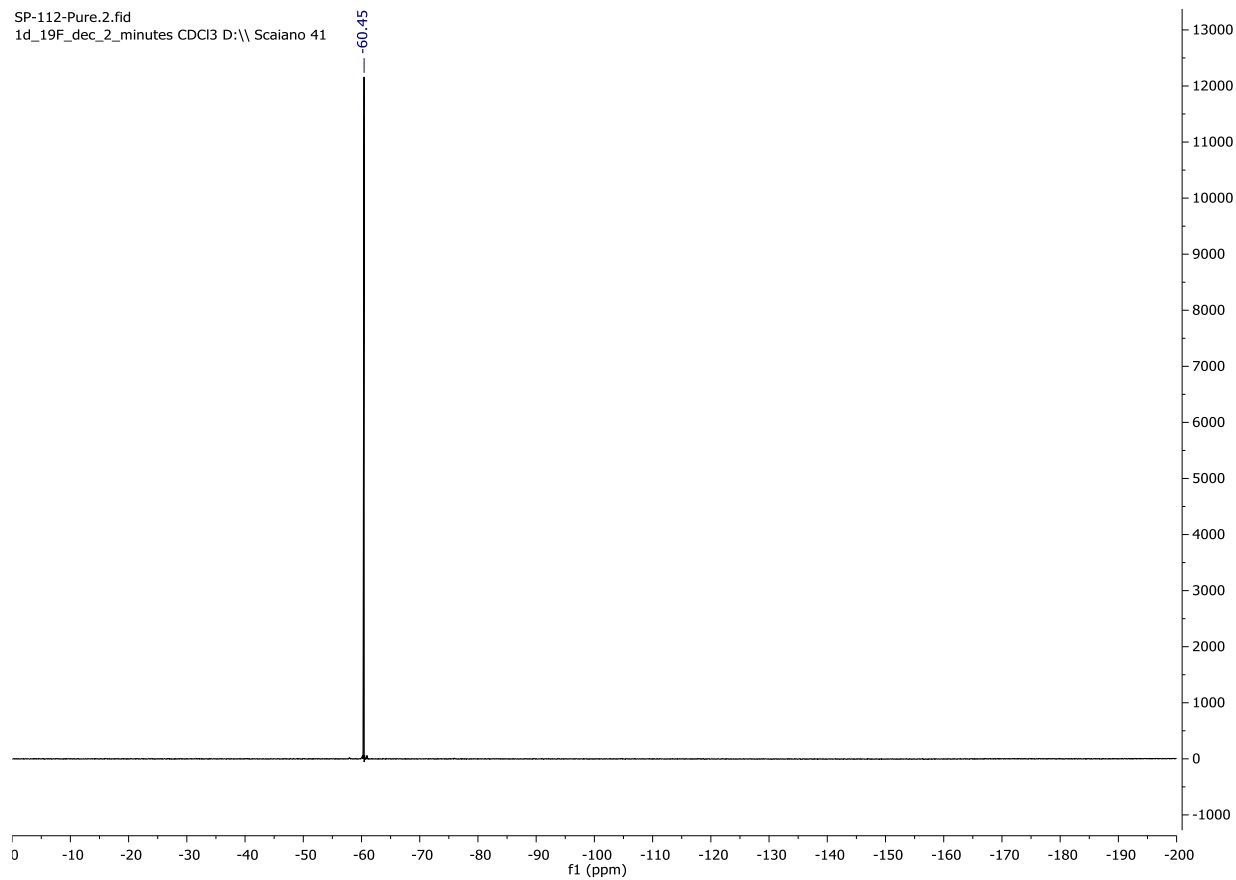
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1d_1H_32_scans CDCl₃ D:\\ Scaiano 41

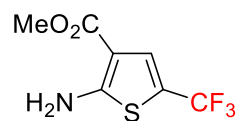




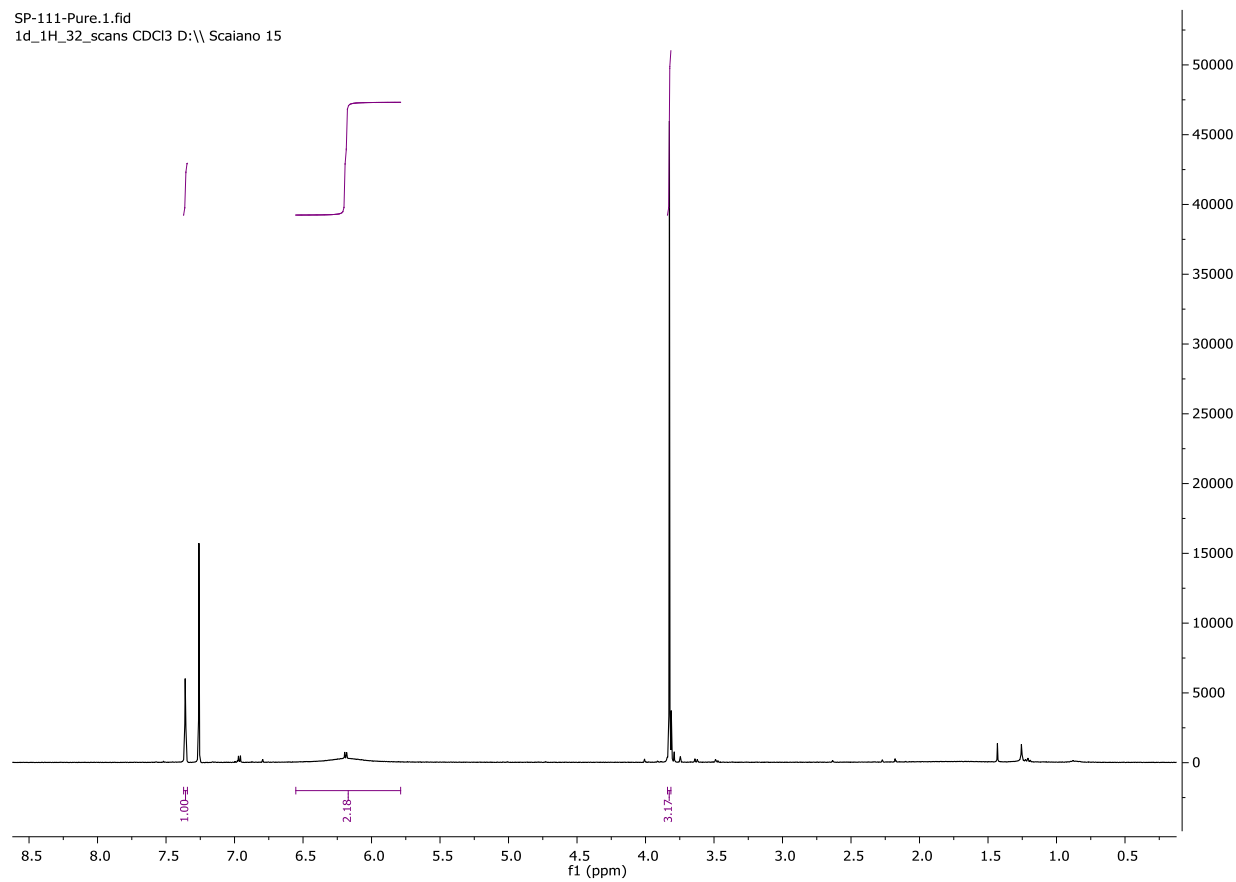
^{19}F NMR

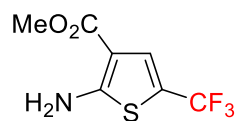
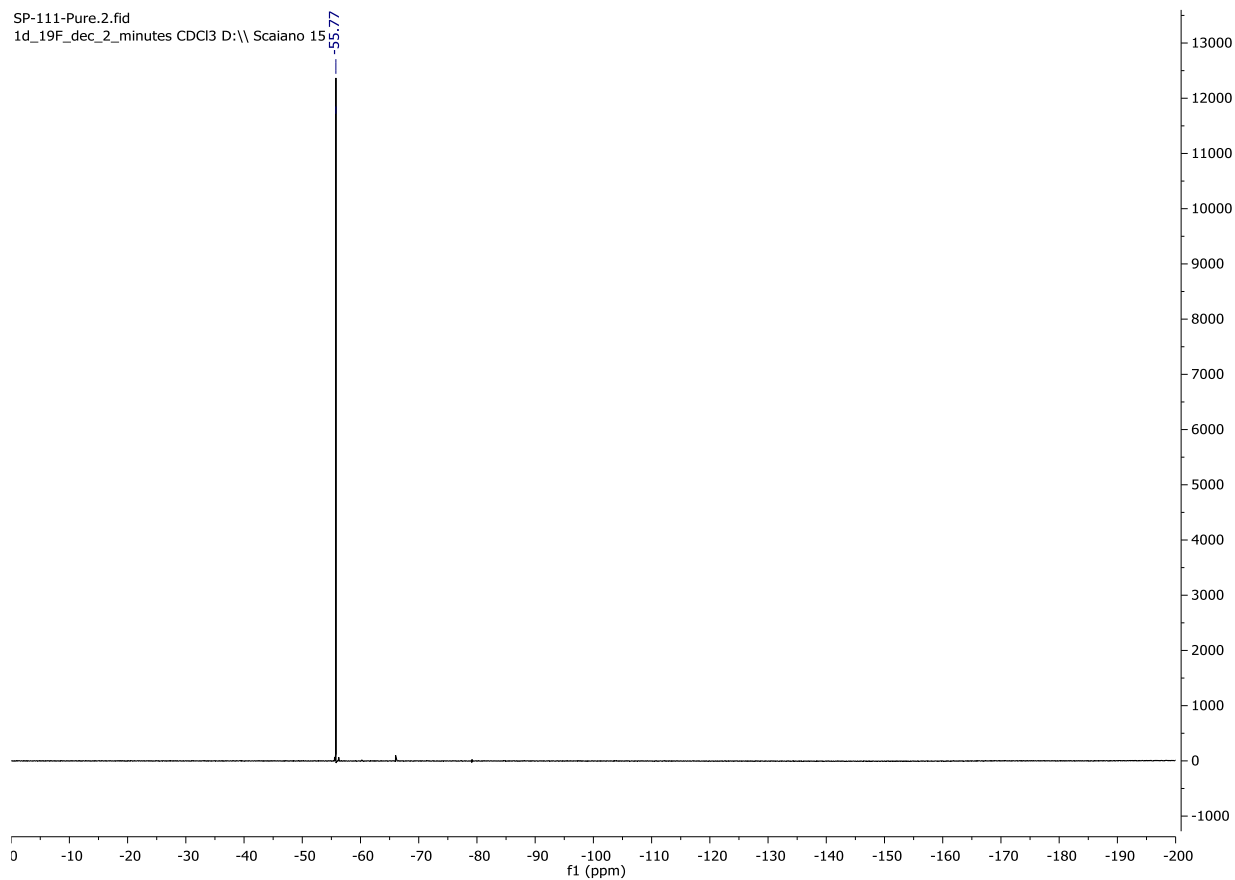
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1d_19F_dec_2_minutes CDCl₃ D:\\ Scaiano 41

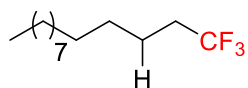


¹H NMR

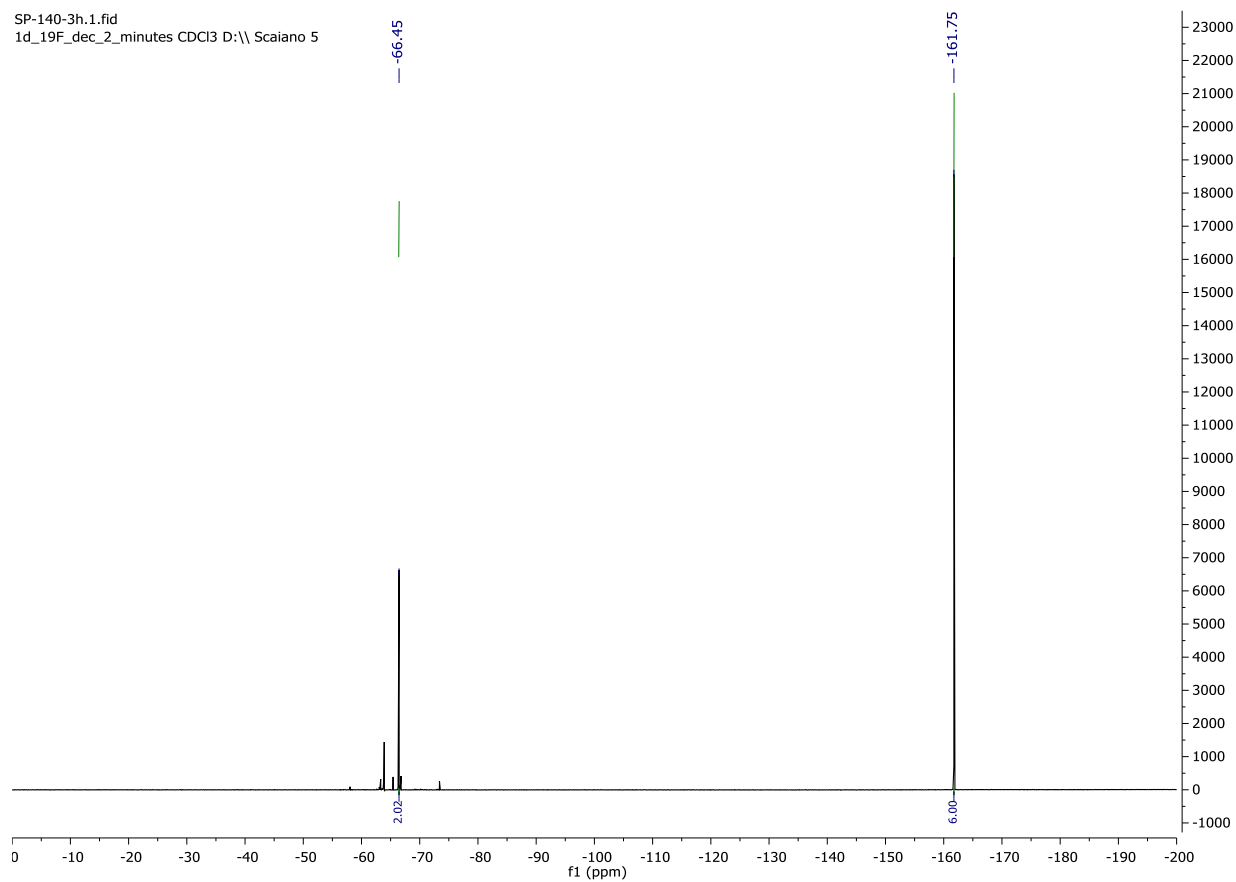
SP-111-Pure.1.fid
1d_1H_32_scans CDCl₃ D:\\ Scaiano 15

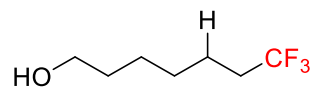


 **^{19}F NMR**



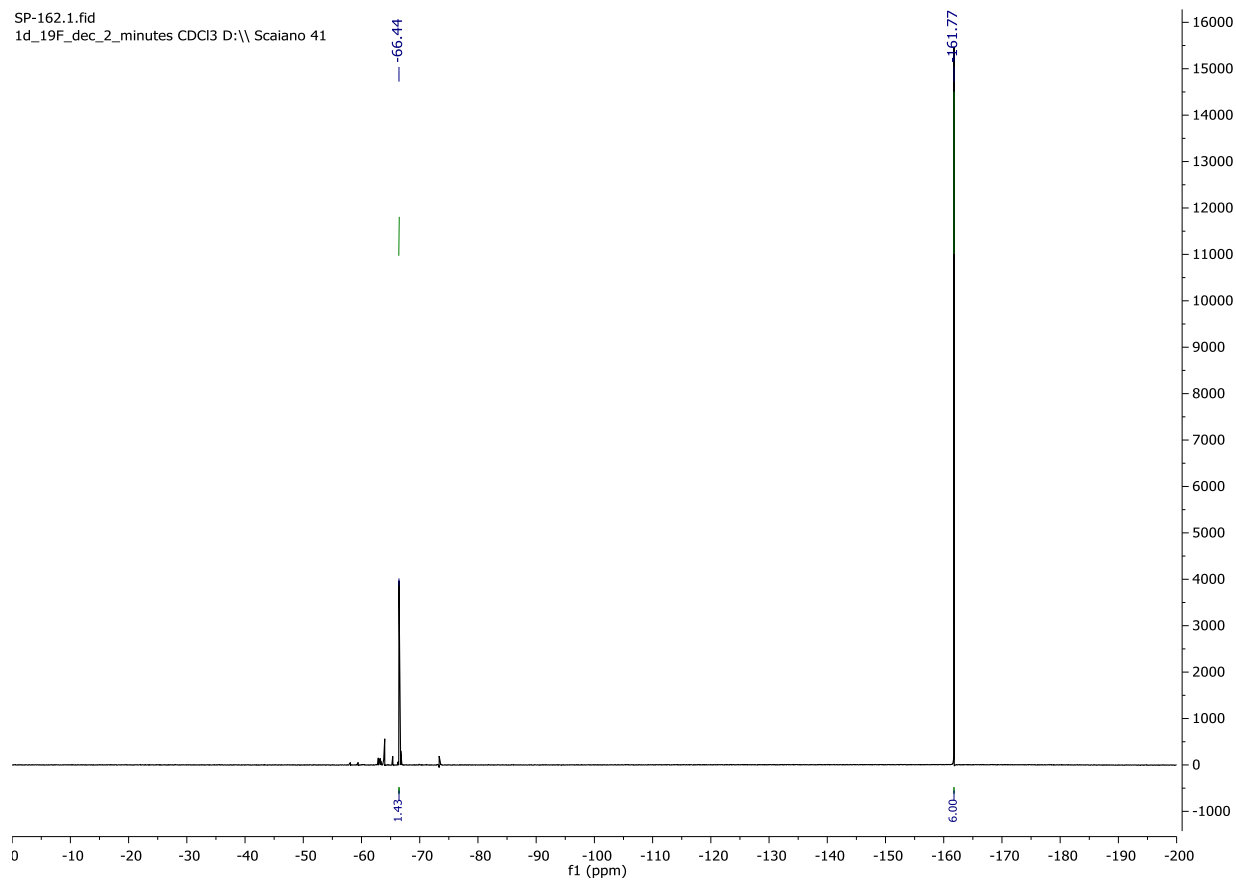
^{19}F NMR of crude reaction mixture

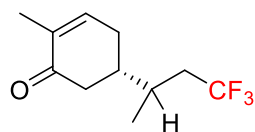




^{19}F NMR of crude reaction mixture

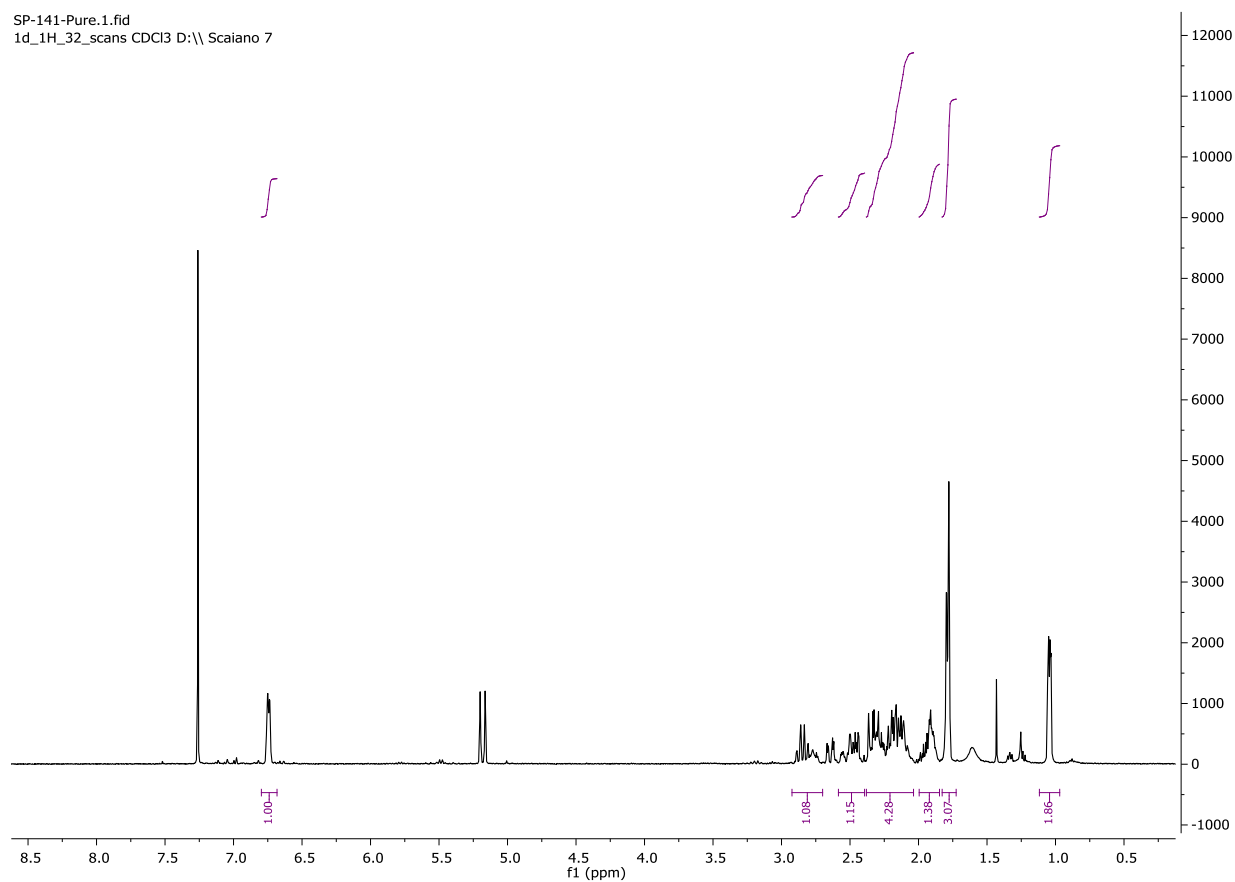
SP-162.1.fid

1d_19F_dec_2_minutes CDCl₃ D:\ Scaiano 41

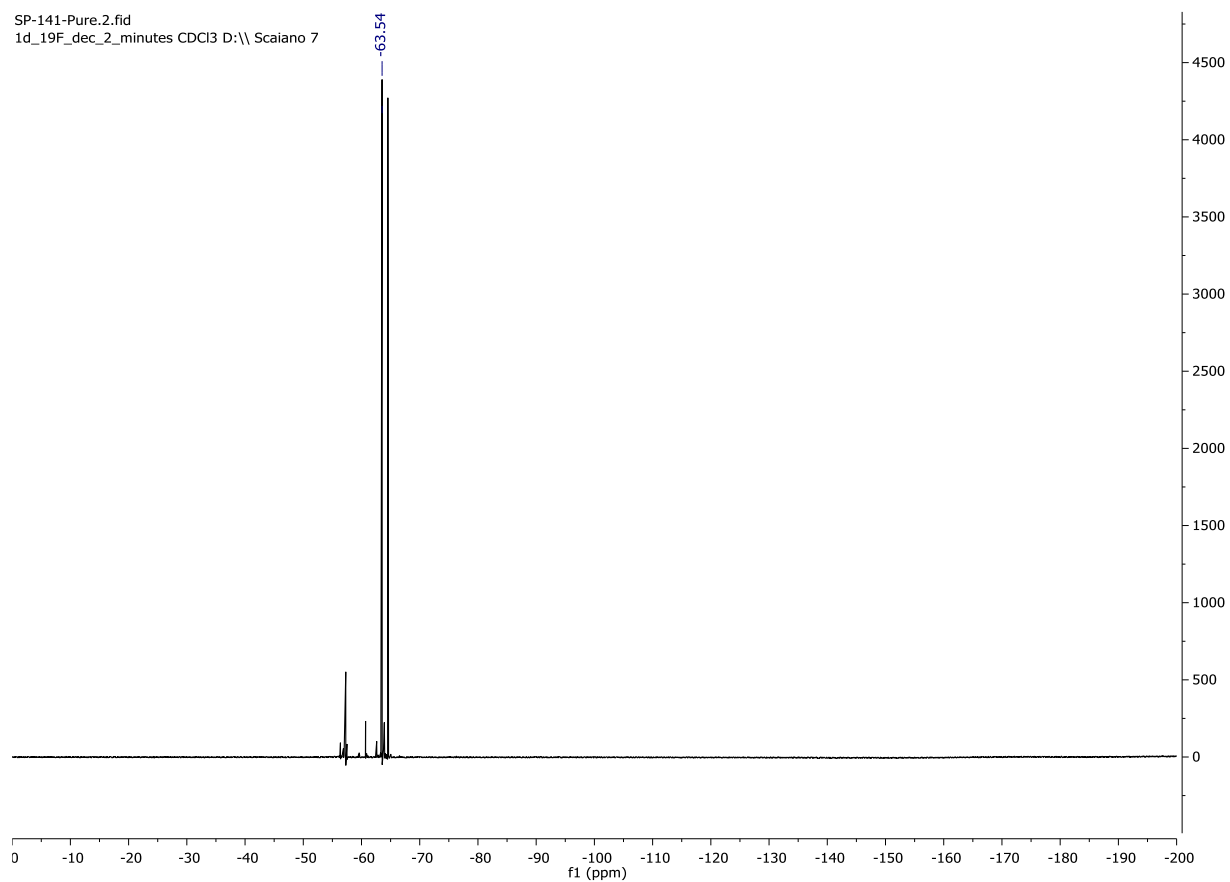


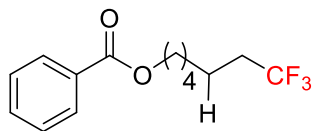
^1H NMR (Note: Contains peaks from inseparable non-hydrogenated minor product)

SP-141-Pure.1.fid
1d_1H_32_scans CDCl₃ D:\\ Scaiano 7



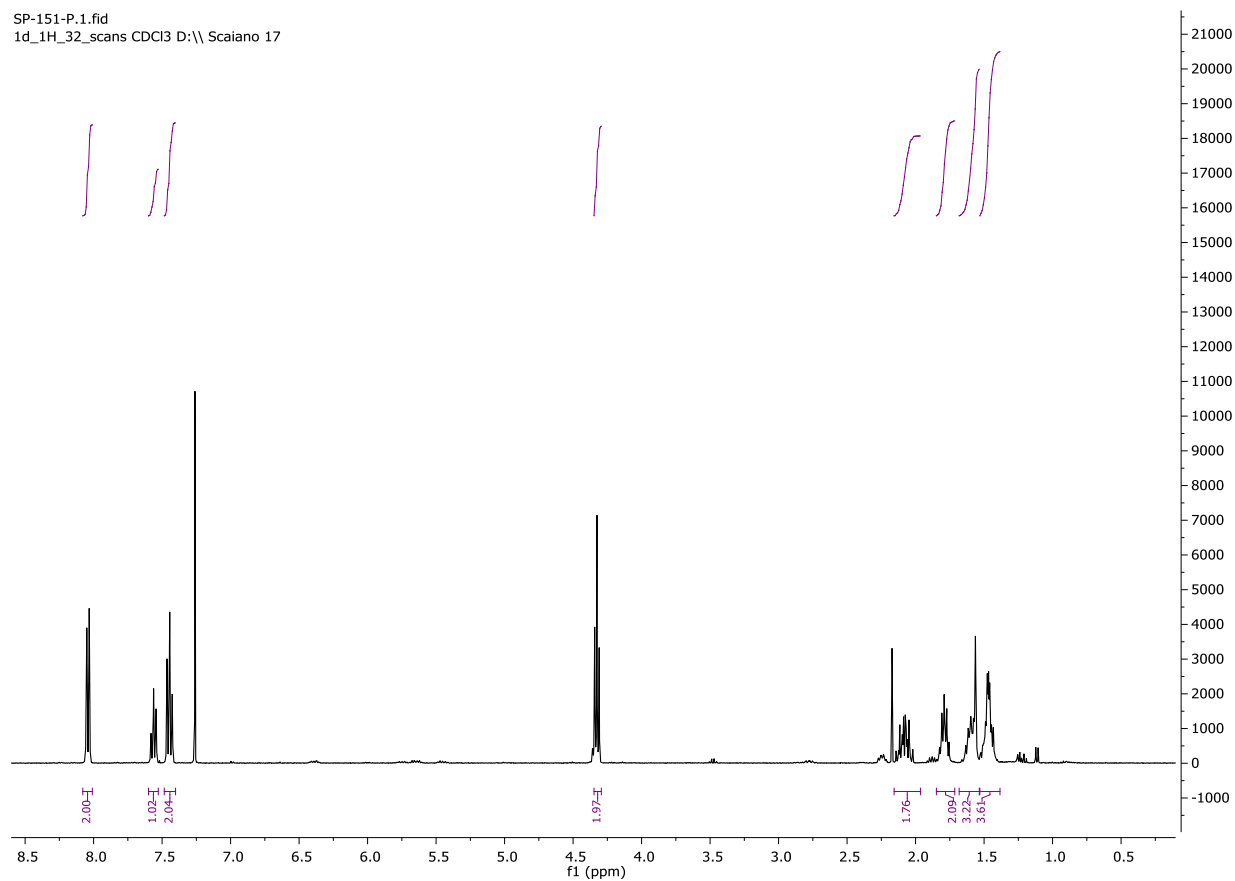
SP-141-Pure.2.fid
1d_19F_dec_2_minutes CDCl3 D:\ Scaiano 7

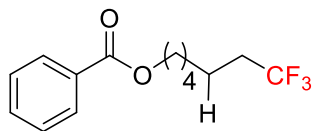




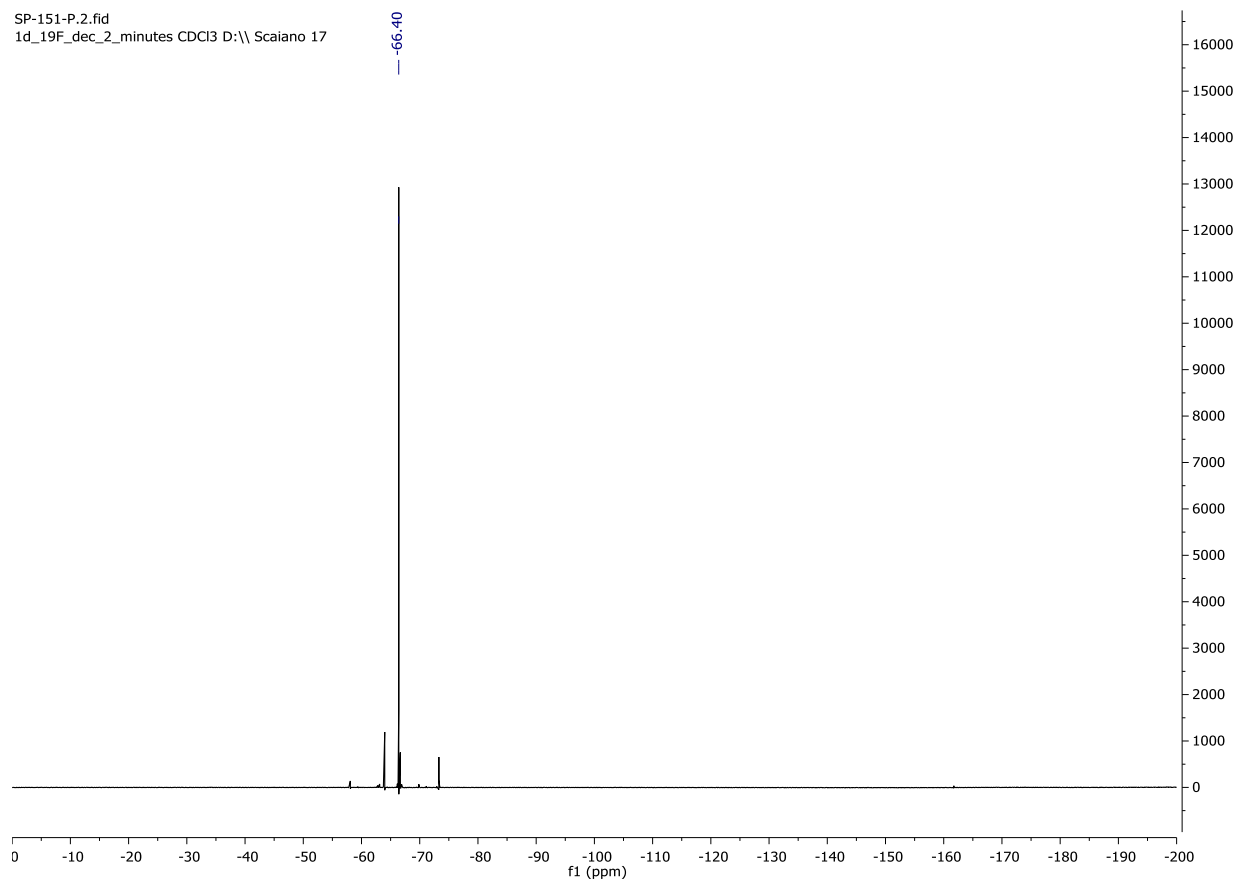
¹H NMR

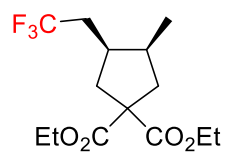
SP-151-P.1.fid

1d_1H_32_scans CDCl₃ D:\ Scalano 17

**¹⁹F NMR**

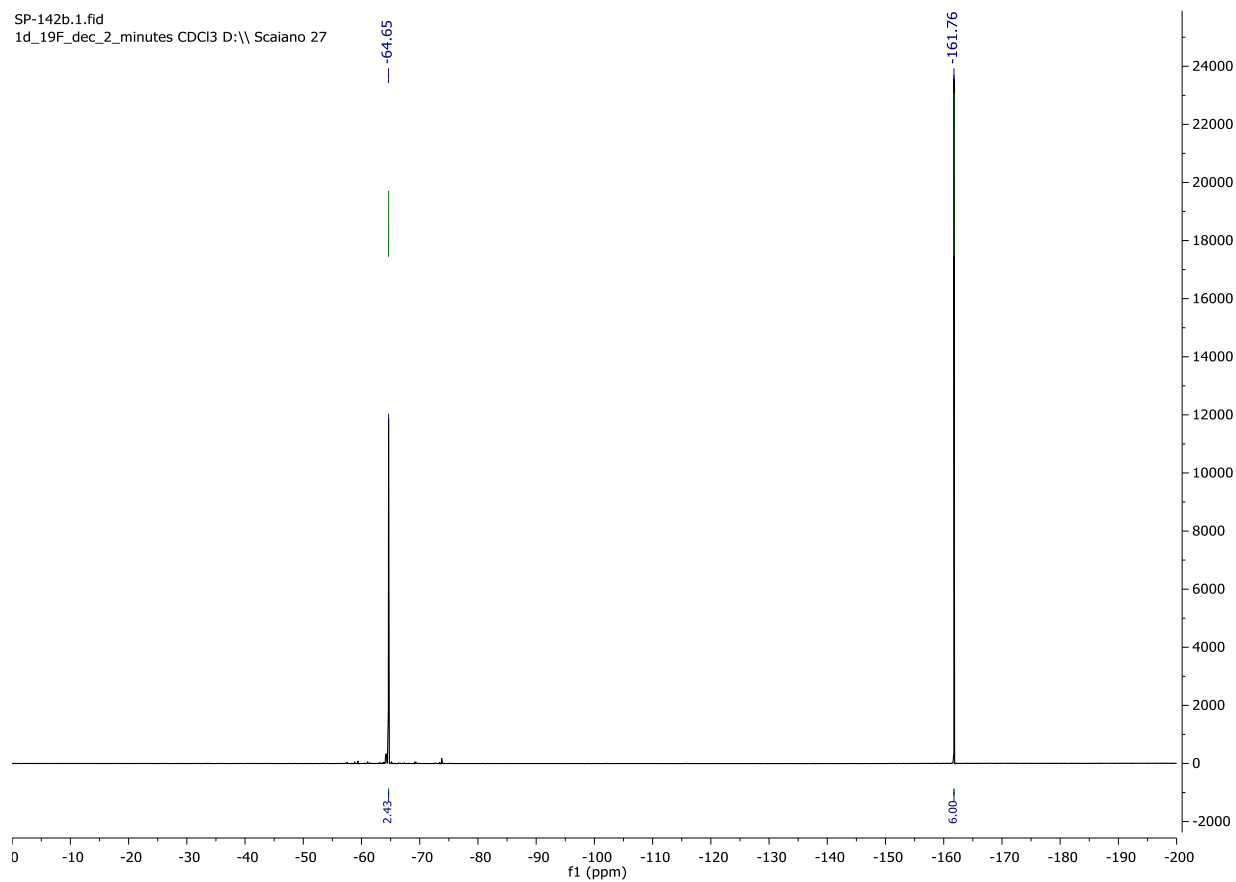
SP-151-P.2.fid

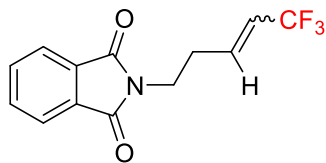
1d_19F_dec_2_minutes CDCl₃ D:\\ Scaiano 17



^{19}F NMR of crude reaction mixture

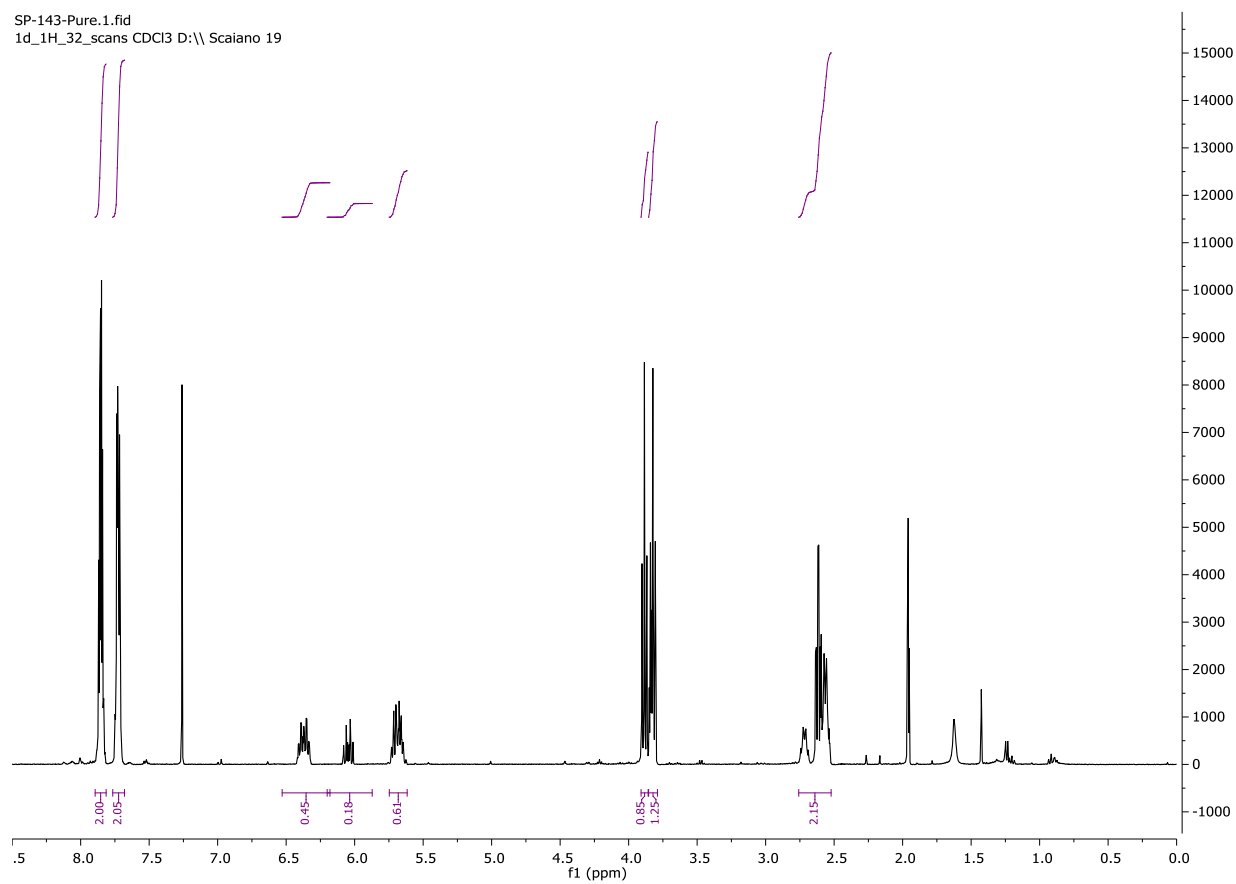
SP-142b.1.fid
1d_19F_dec_2_minutes CDCl₃ D:\Scaiano 27

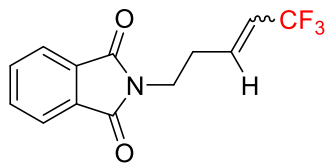




^1H NMR (Mixture of *E*:*Z*)

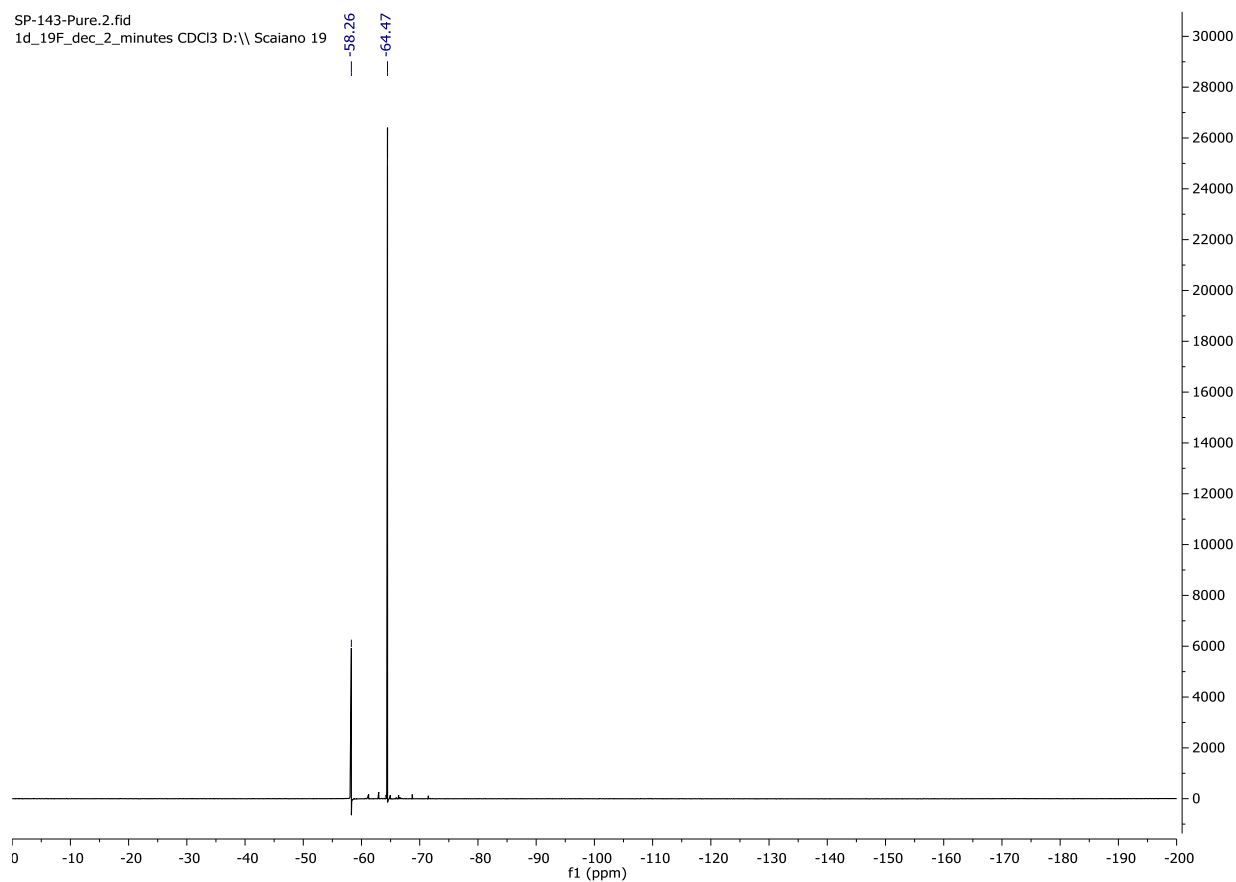
SP-143-Pure.1.fid

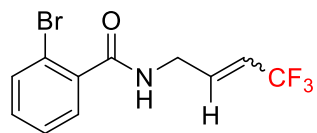
1d_1H_32_scans CDCl₃ D:\ Scalano 19



^{19}F NMR (Mixture of *E:Z*)

SP-143-Pure.2.fid
1d_19F_dec_2_minutes CDCl₃ D:\\ Scaiano 19

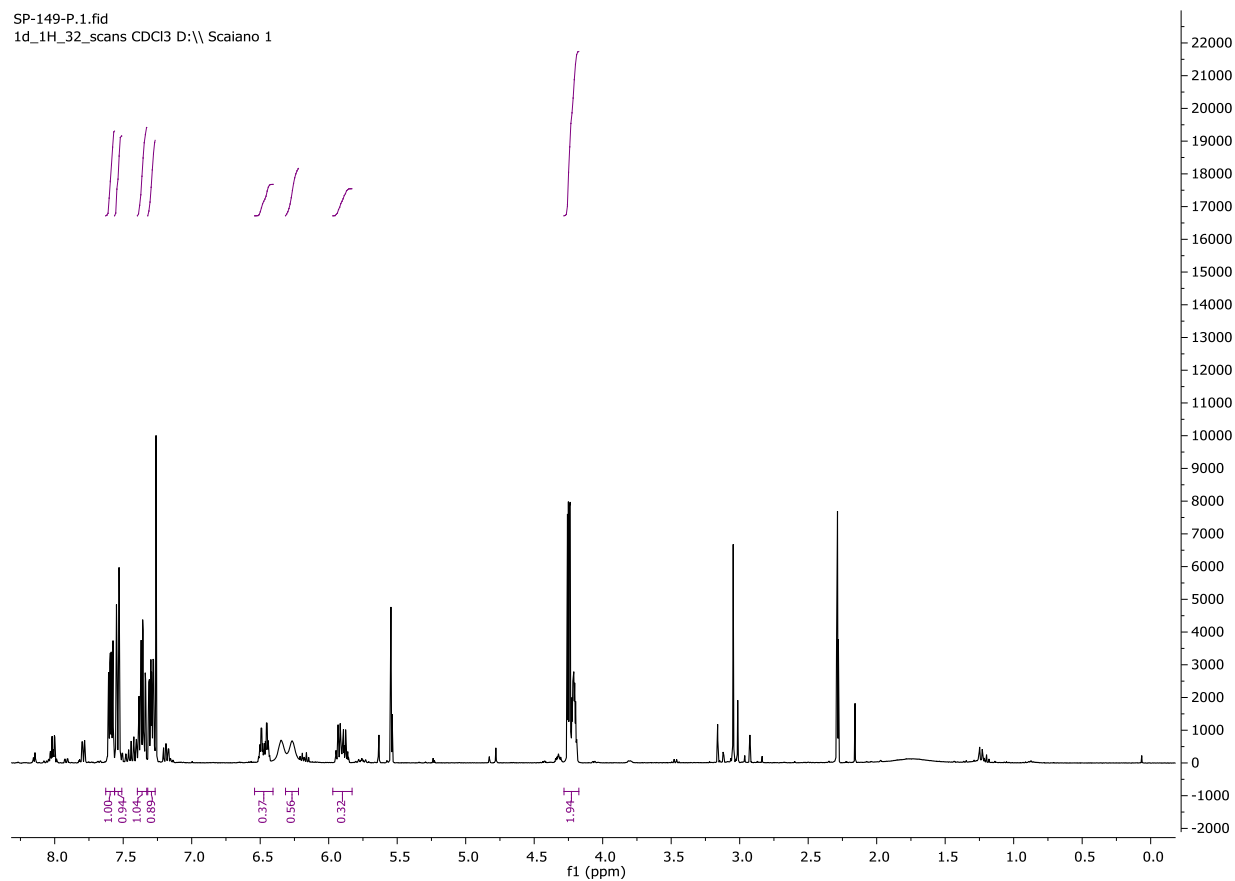


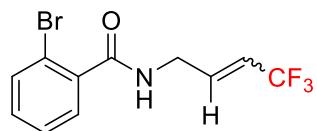


^1H NMR (Mixture of *E:Z*)

SP-149-P.1.fid

1d_1H_32_scans CDCl3 D:\ Scaiano 1

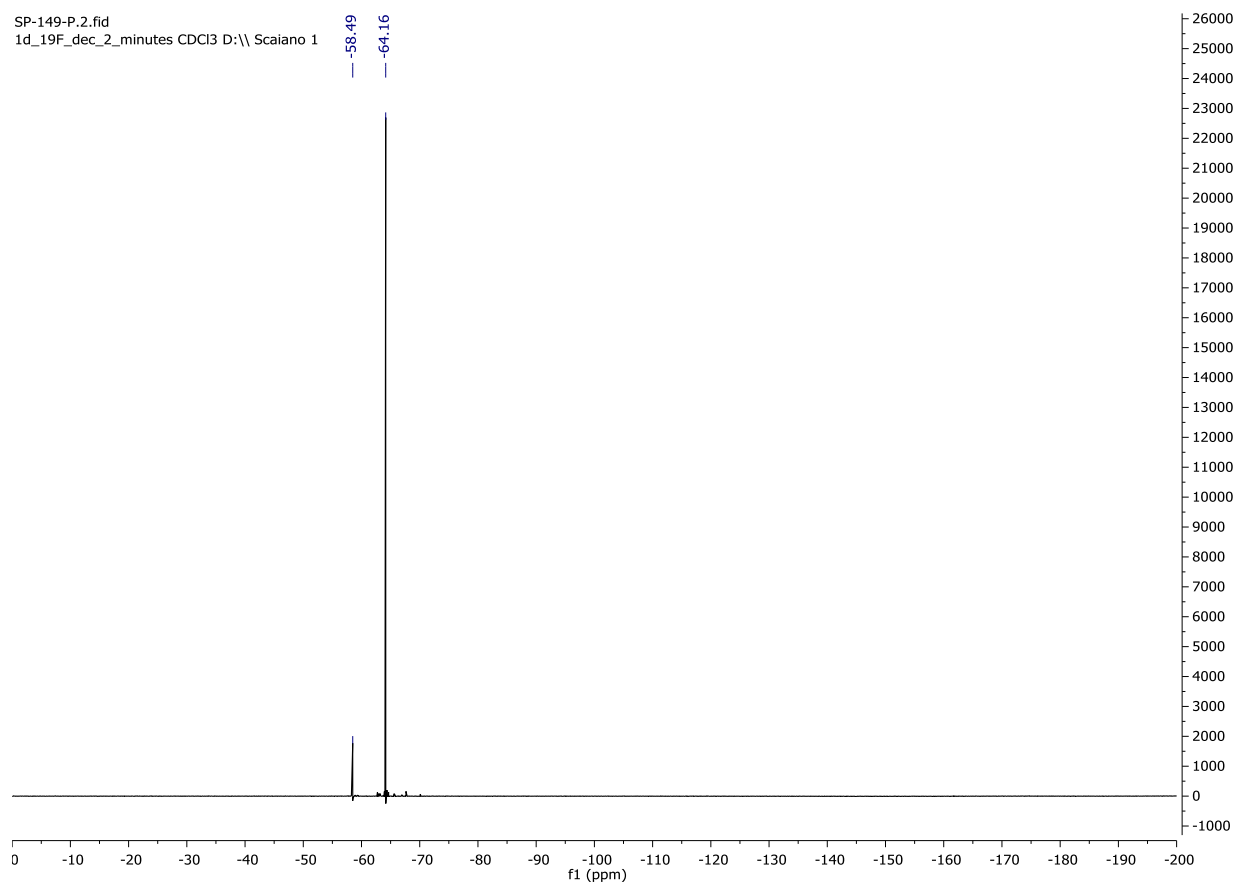


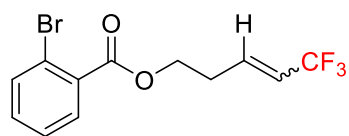


¹⁹F NMR (Mixture of *E:Z*)

SP-149-P.2.fid

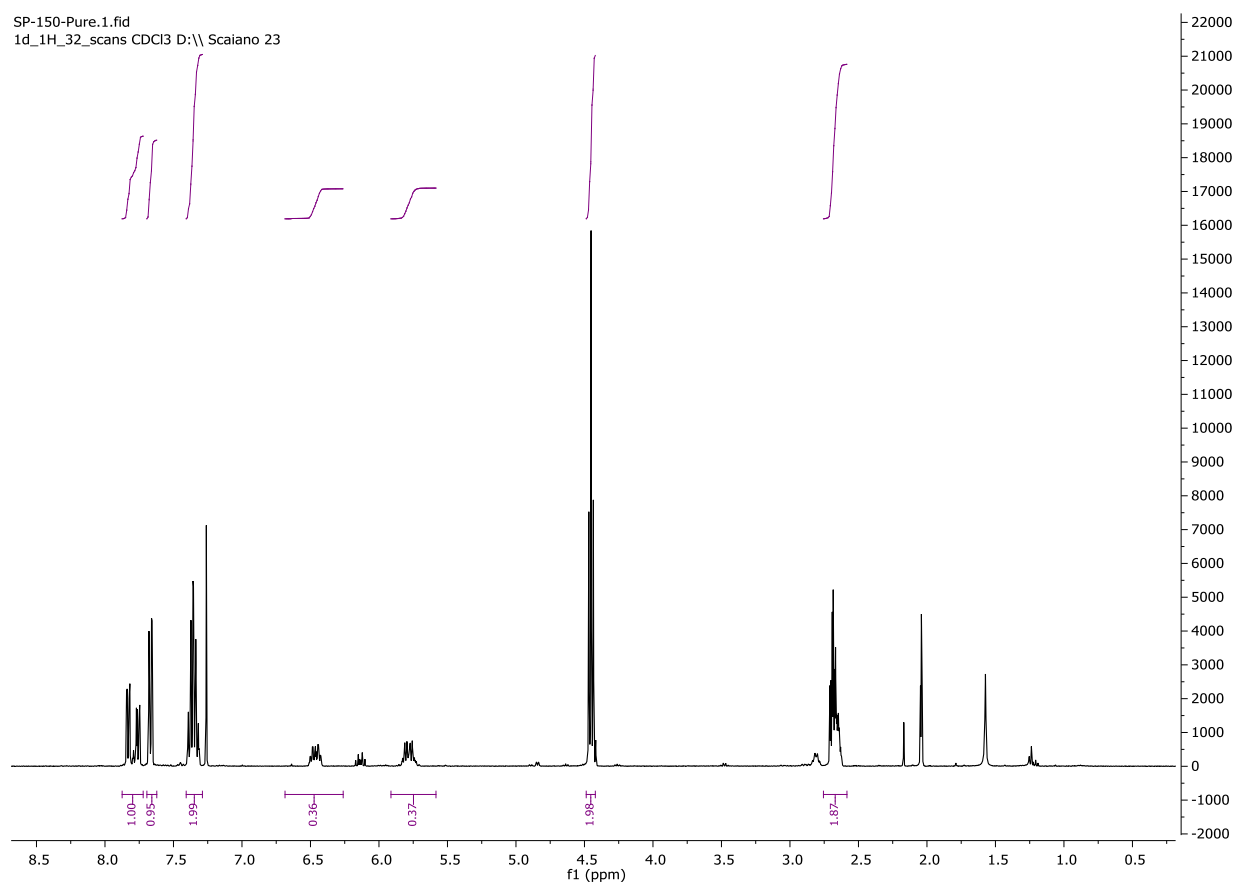
1d_19F_dec_2_minutes CDCl₃ D:\\ Scaiano 1

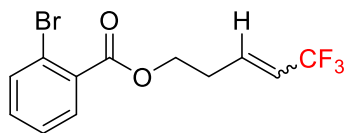




^1H NMR (Mixture of *E:Z*)

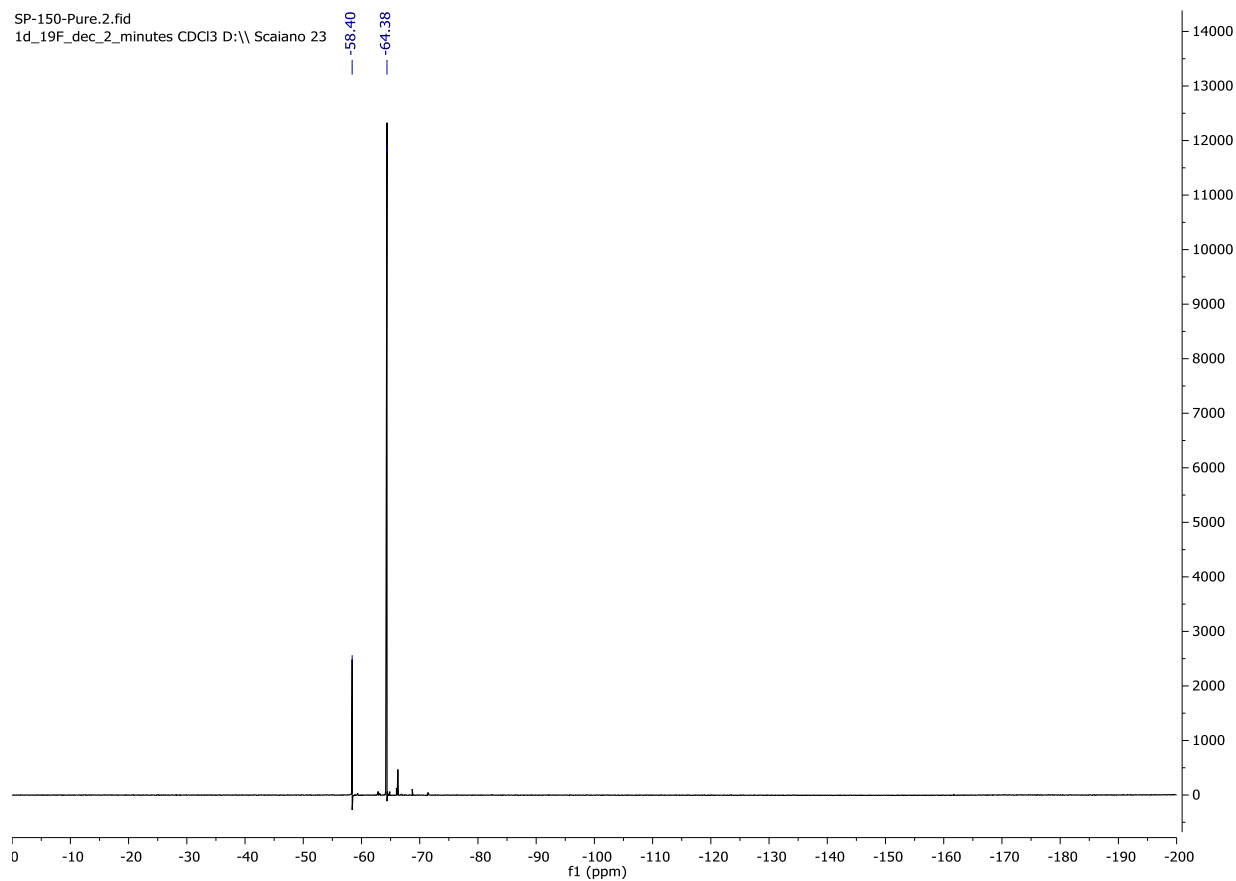
SP-150-Pure.1.fid
1d_1H_32_scans CDCl₃ D:\ Scaiano 23



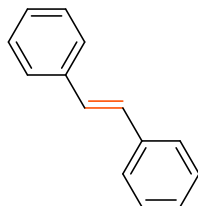


¹⁹F NMR (Mixture of *E:Z*)

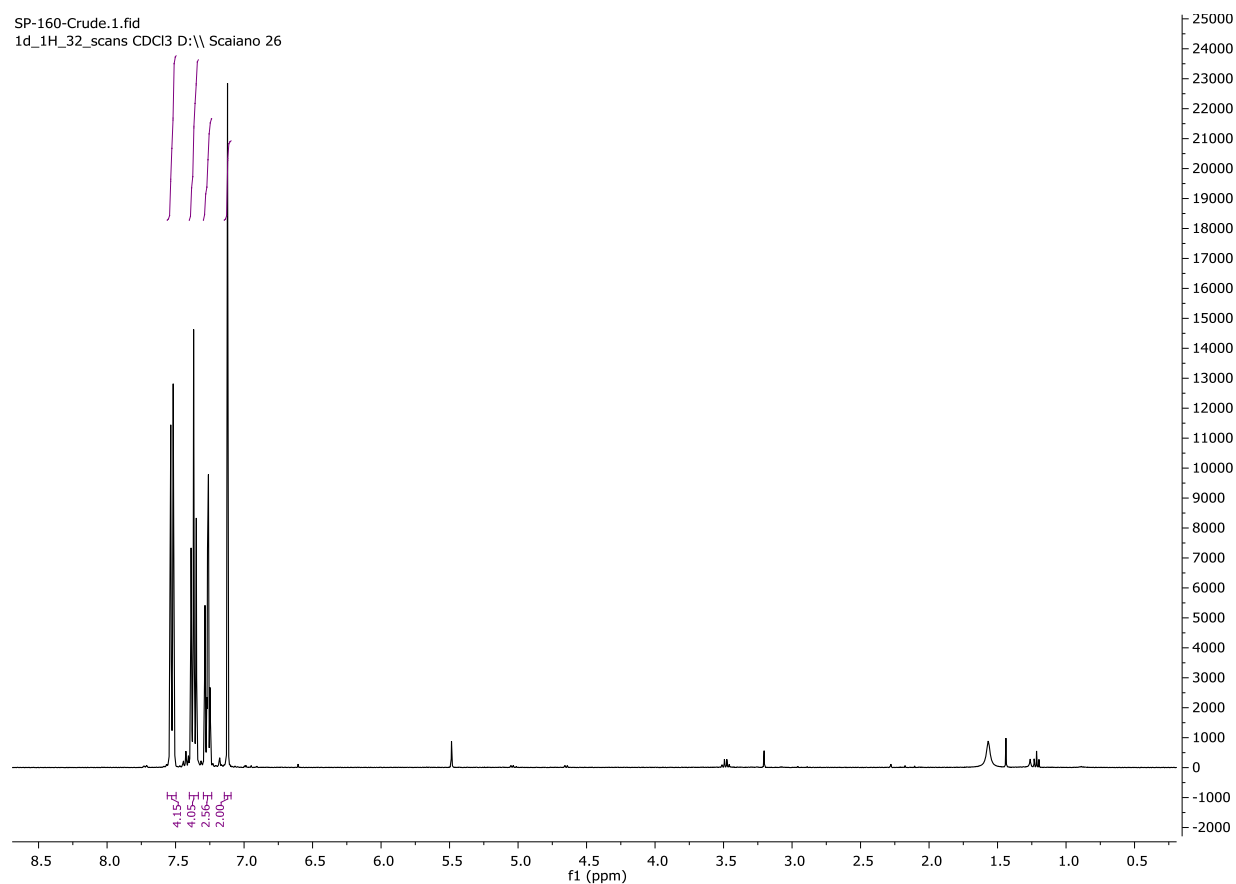
SP-150-Pure.2.fid
1d_19F_dec_2_minutes CDCl₃ D:\\ Scaiano 23

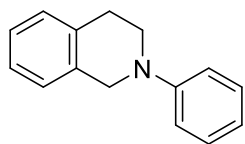


Chapter 5

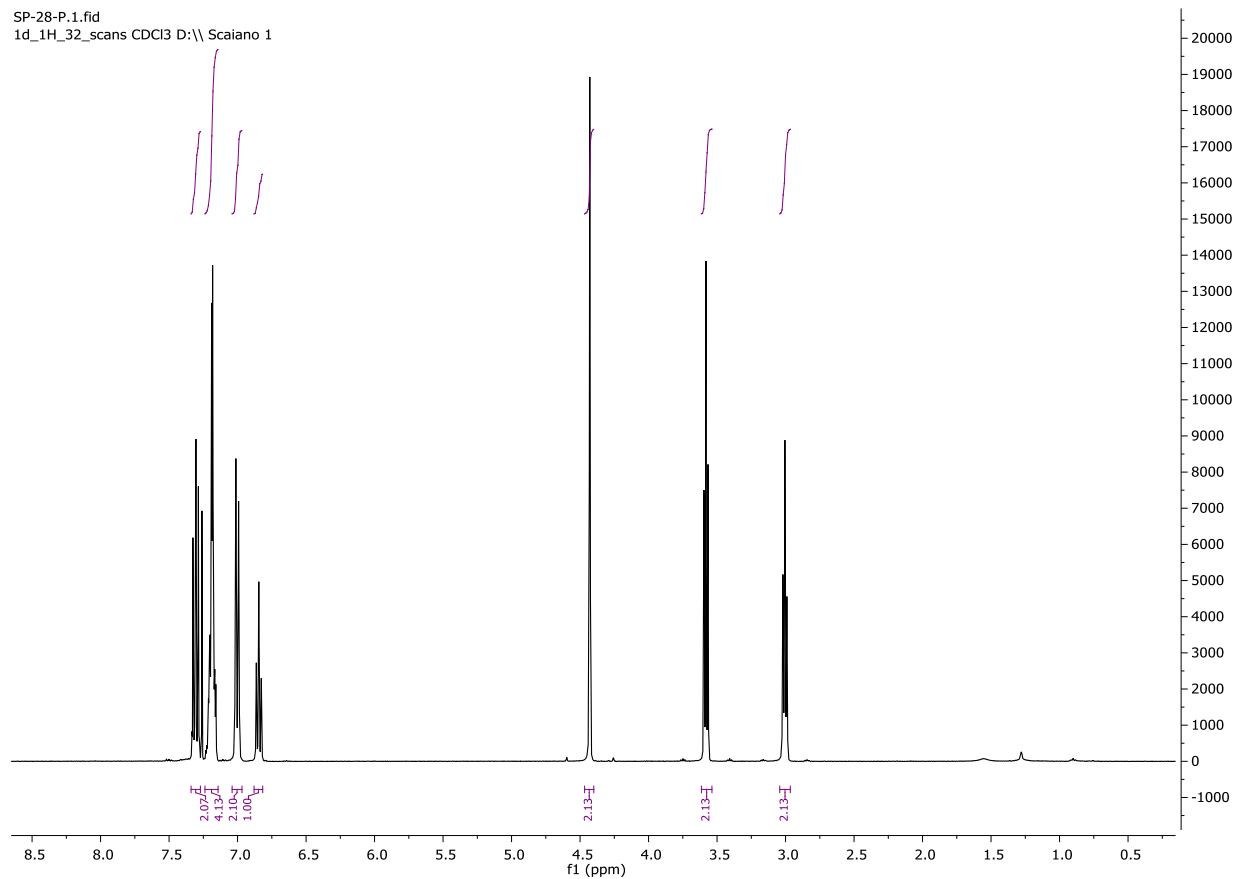


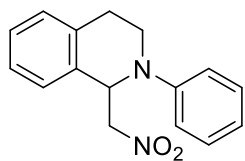
Representative ^1H NMR of crude reaction mixture (96% conversion)



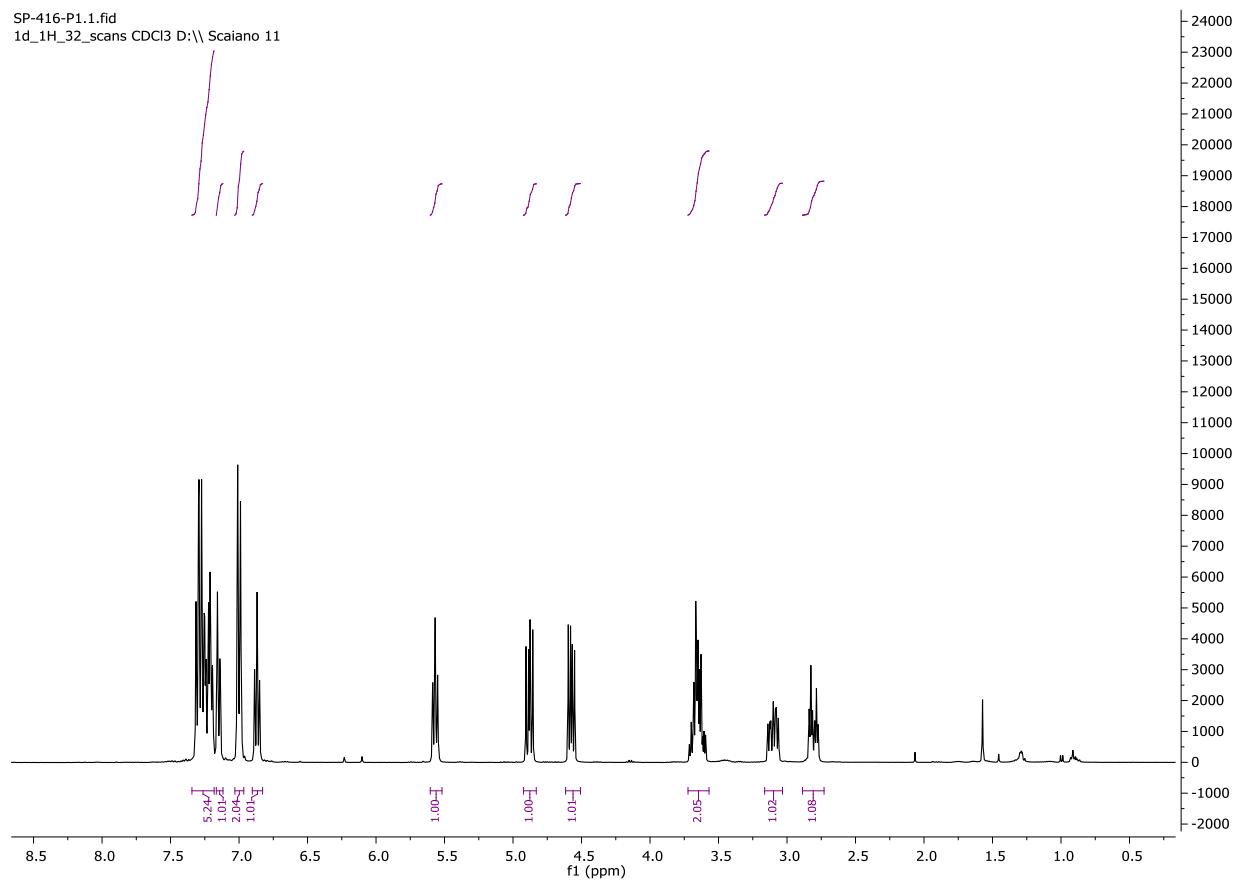


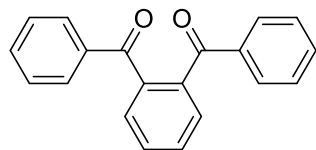
SP-28-P.1.fid
1d_1H_32_scans CDCl3 D:\ Scaiano 1



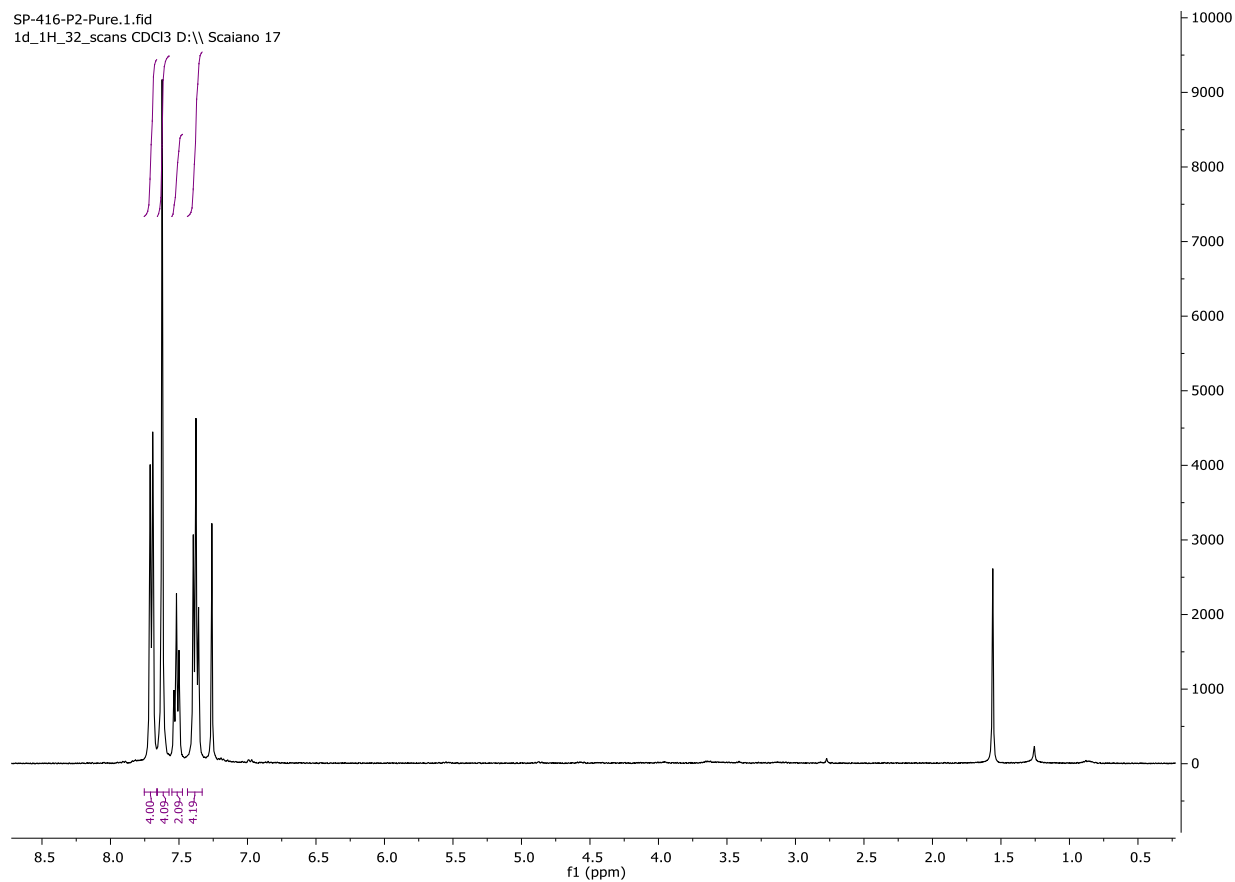


SP-416-P1.1.fid
1d_1H_32_scans CDCl3 D:\ Scalano 11

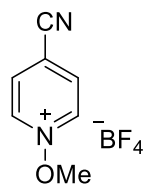




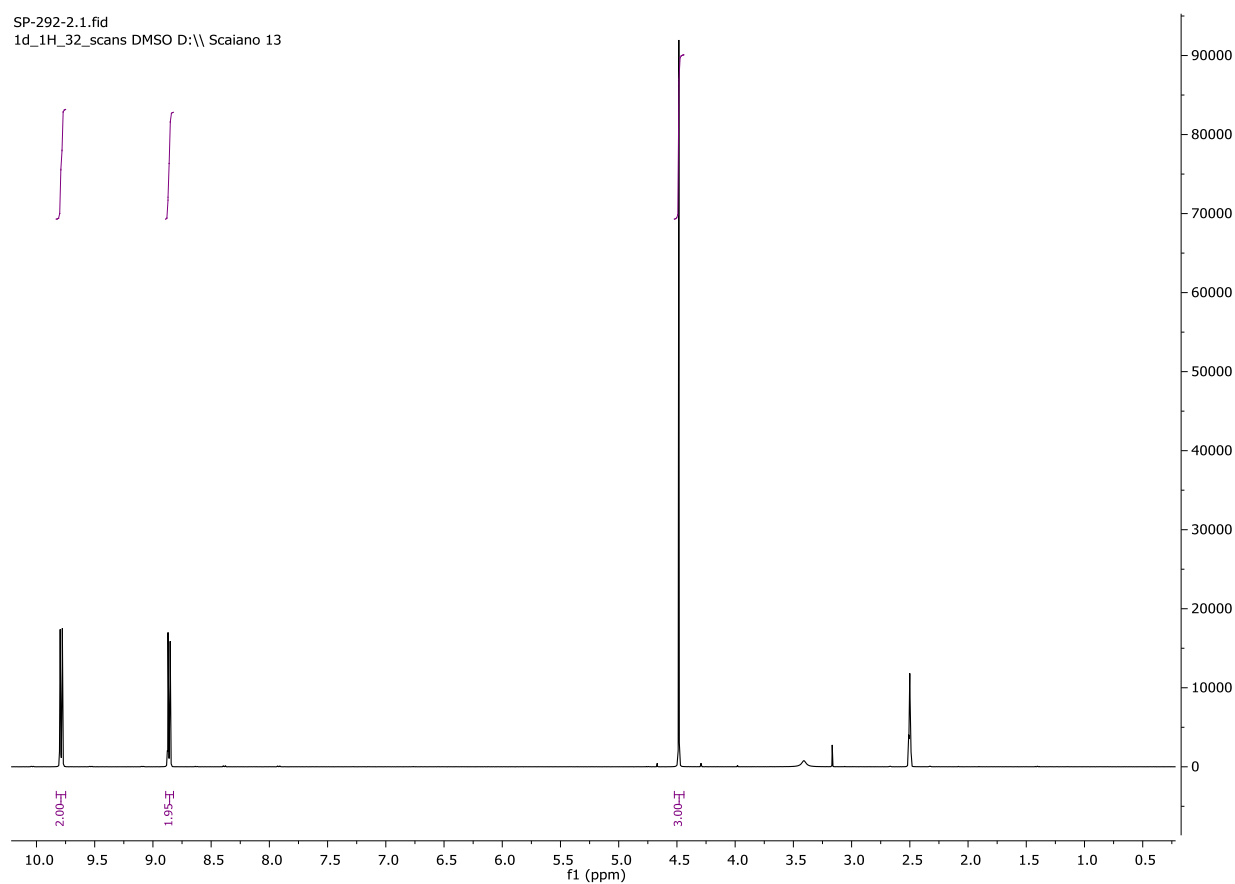
SP-416-P2-Pure.1.fid
1d_1H_32_scans CDCl3 D:\\ Scaiano 17

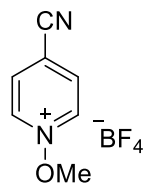


Chapter 6

¹H NMR

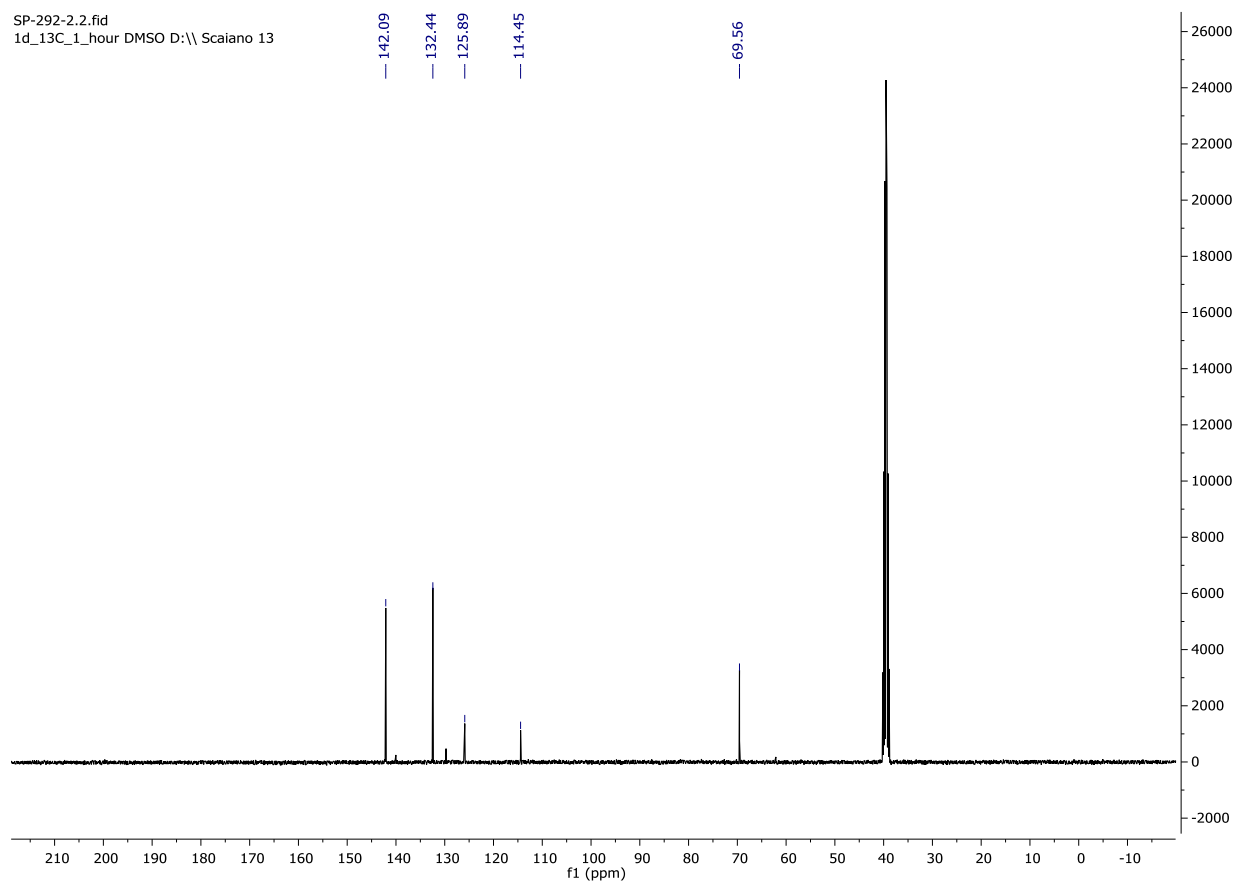
SP-292-2.1.fid
1d_1H_32_scans DMSO D:\\ Scaiano 13



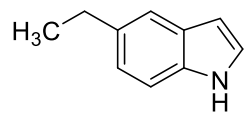


^{13}C NMR

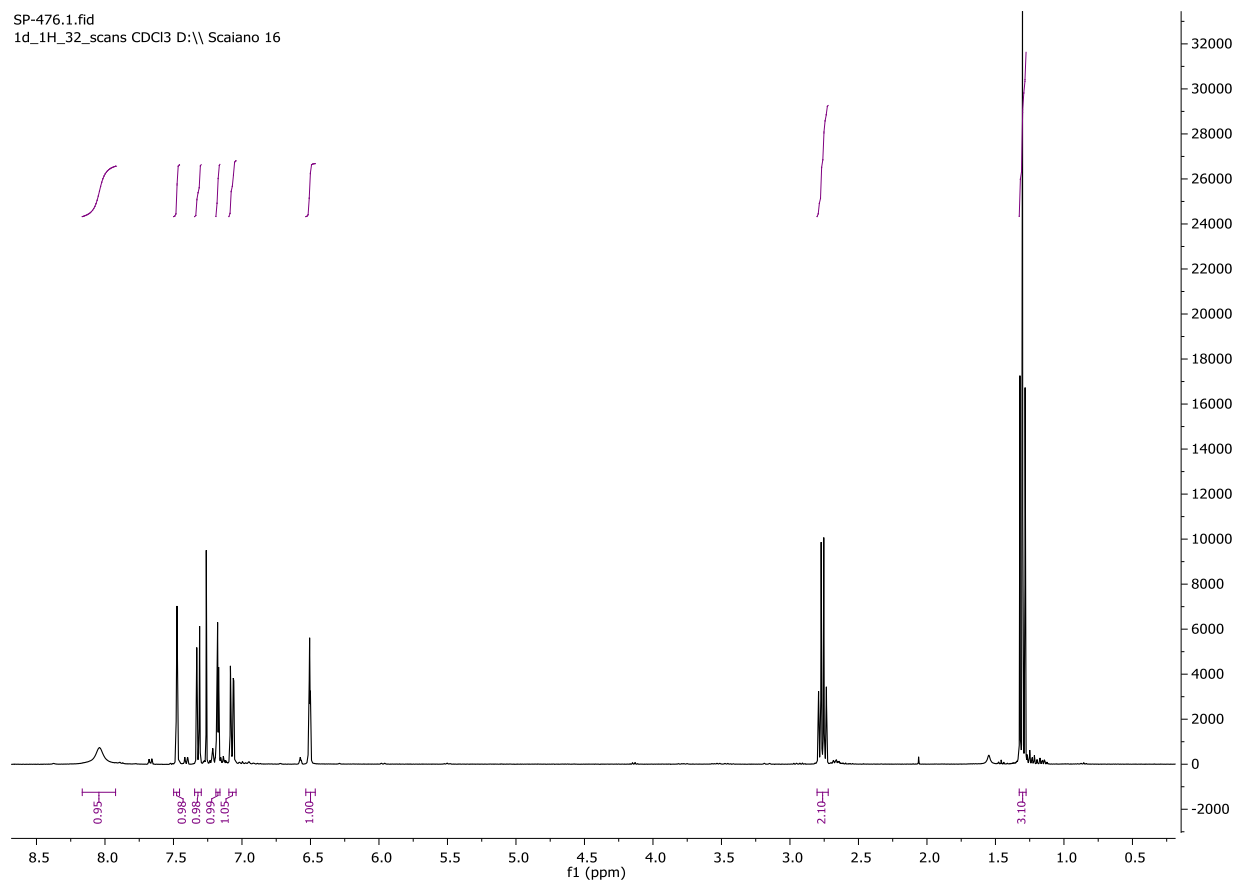
SP-292-2.2.fid
1d_13C_1_hour DMSO D: $\backslash$ Scaiano 13

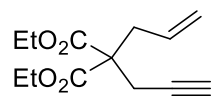


Chapter 7



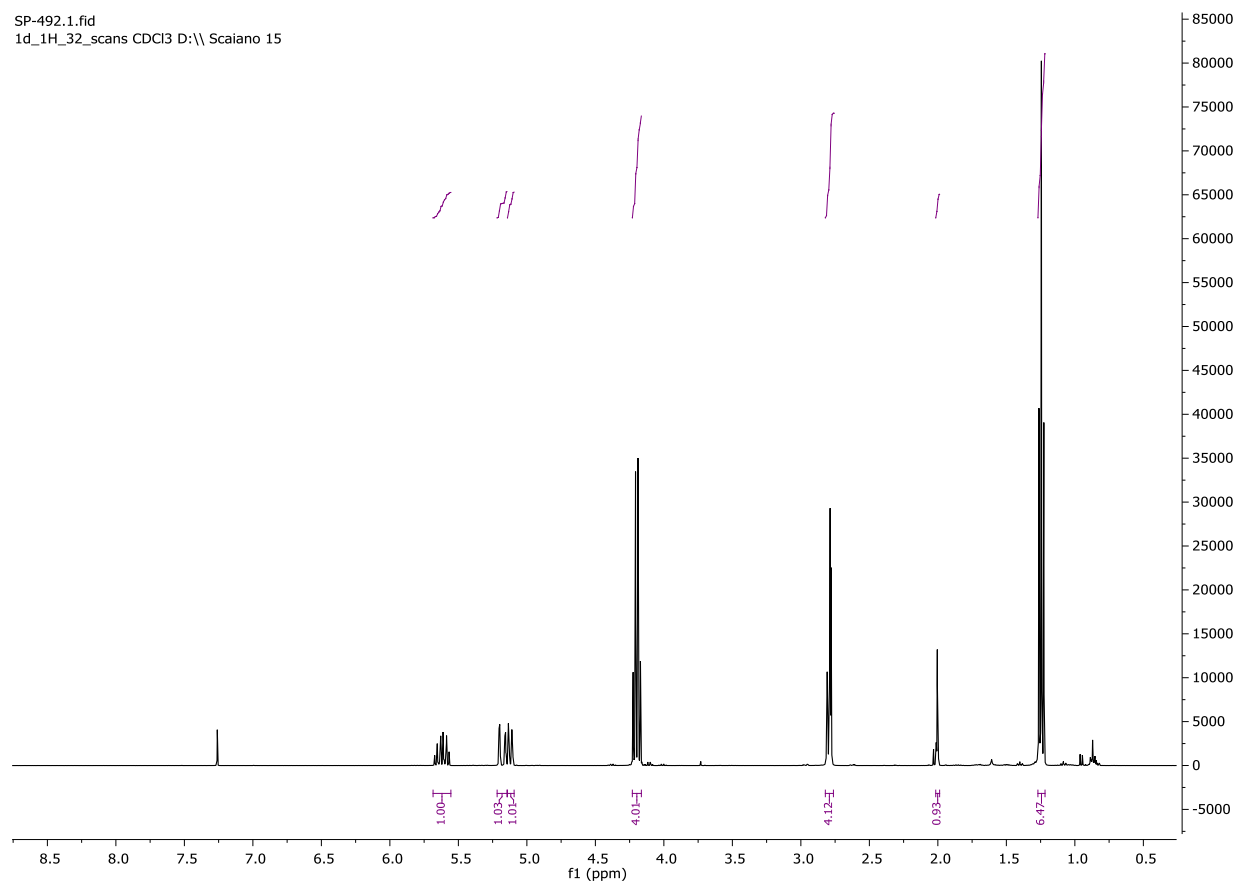
SP-476.1.fid
1d_1H_32_scans CDCl3 D:\ Scaiano 16

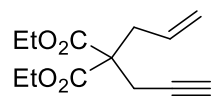
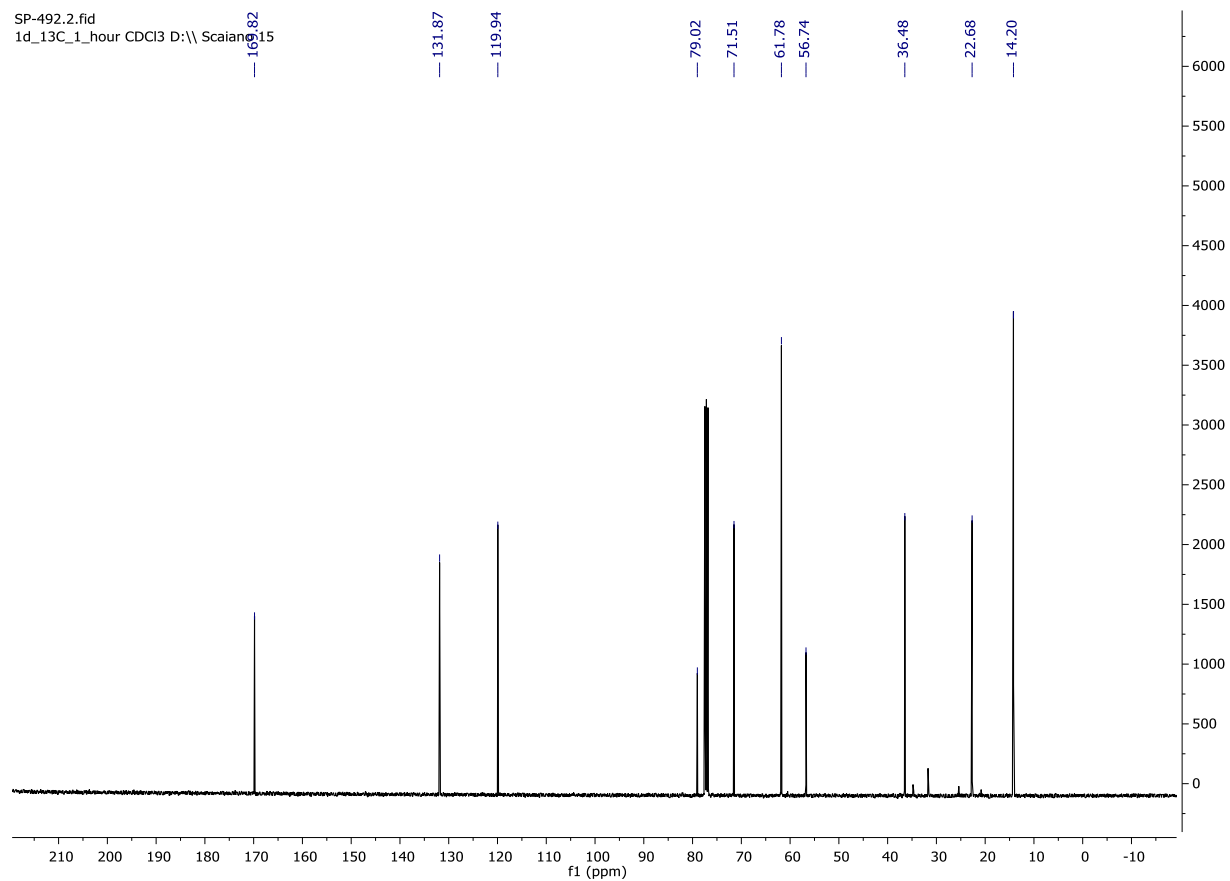


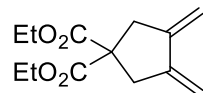


¹H NMR

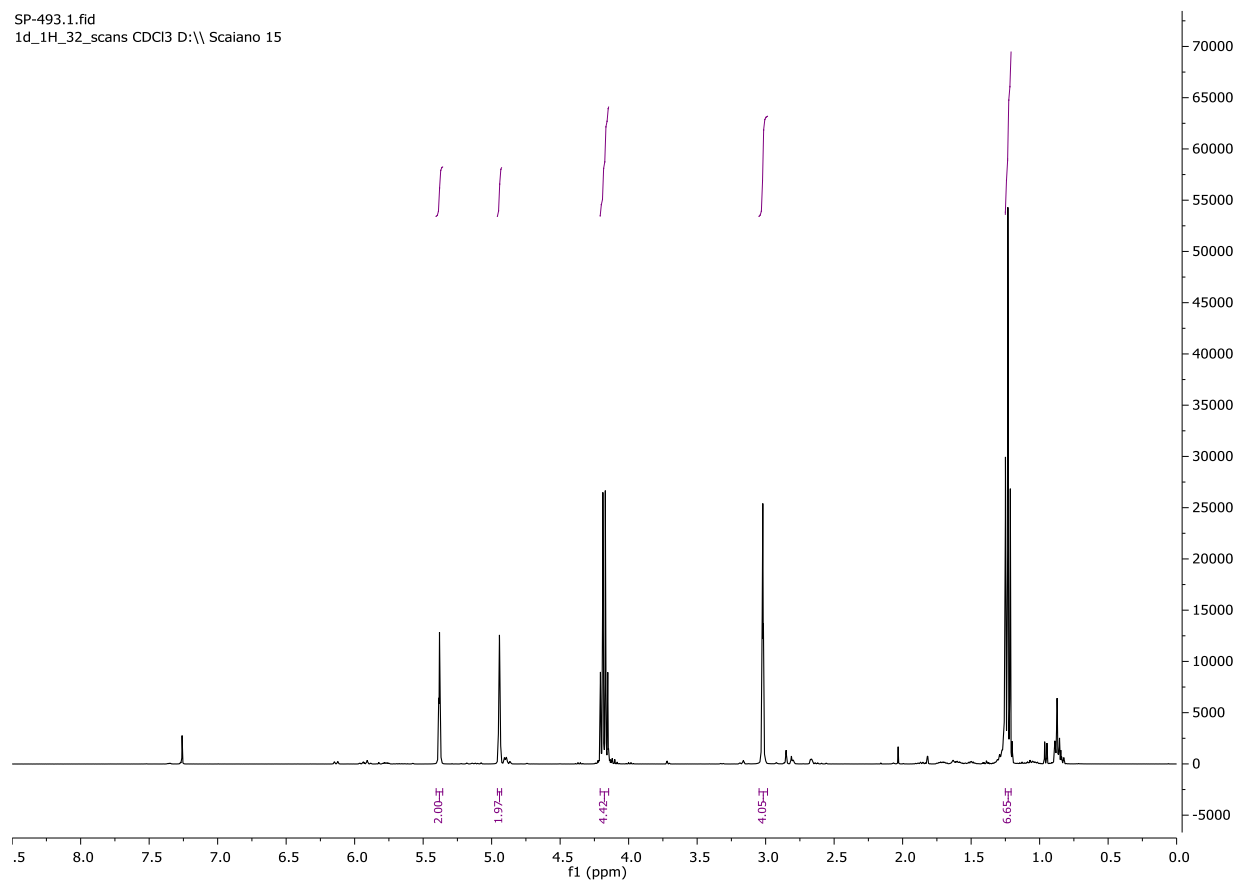
SP-492.1.fid
1d_1H_32_scans CDCl₃ D:\\ Scaiano 15

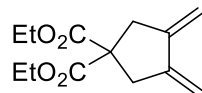


¹³C NMR

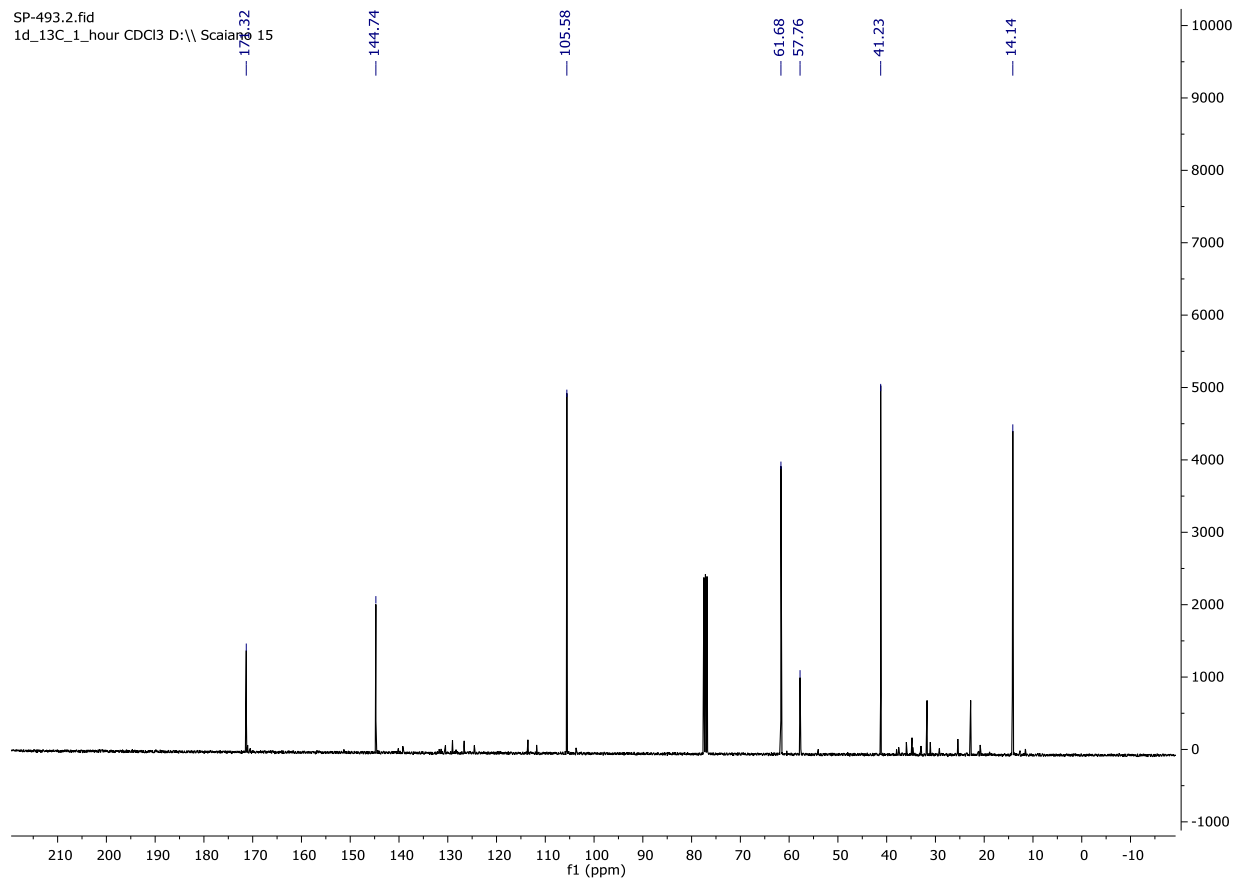
¹H NMR

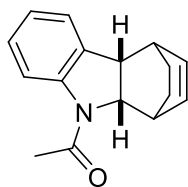
SP-493.1.fid
1d_1H_32_scans CDCl₃ D:\\ Scaiano 15



¹³C NMR

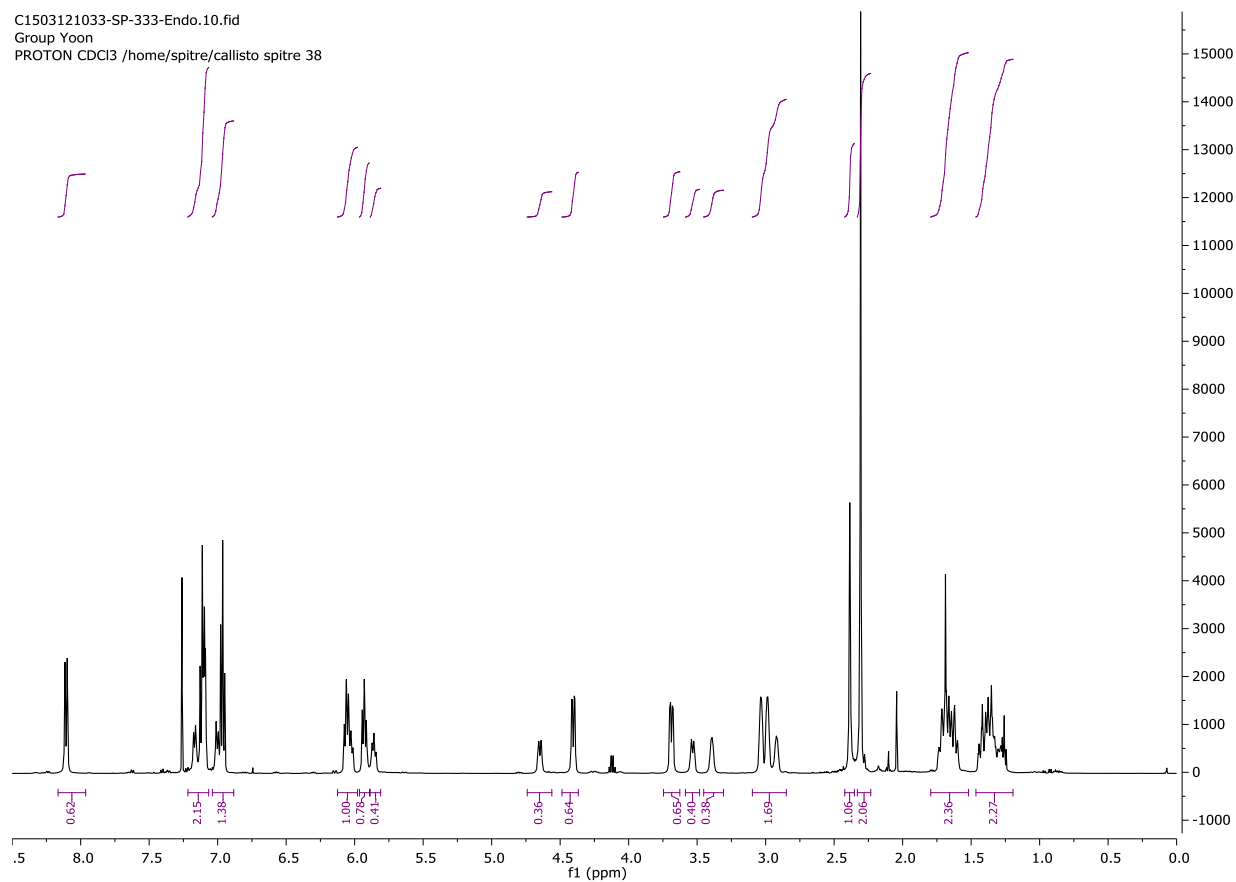
SP-493.2.fid
1d_13C_1_hour CDCl₃ D:\\ Scaia

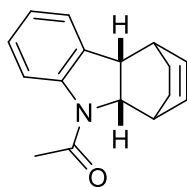




Endo

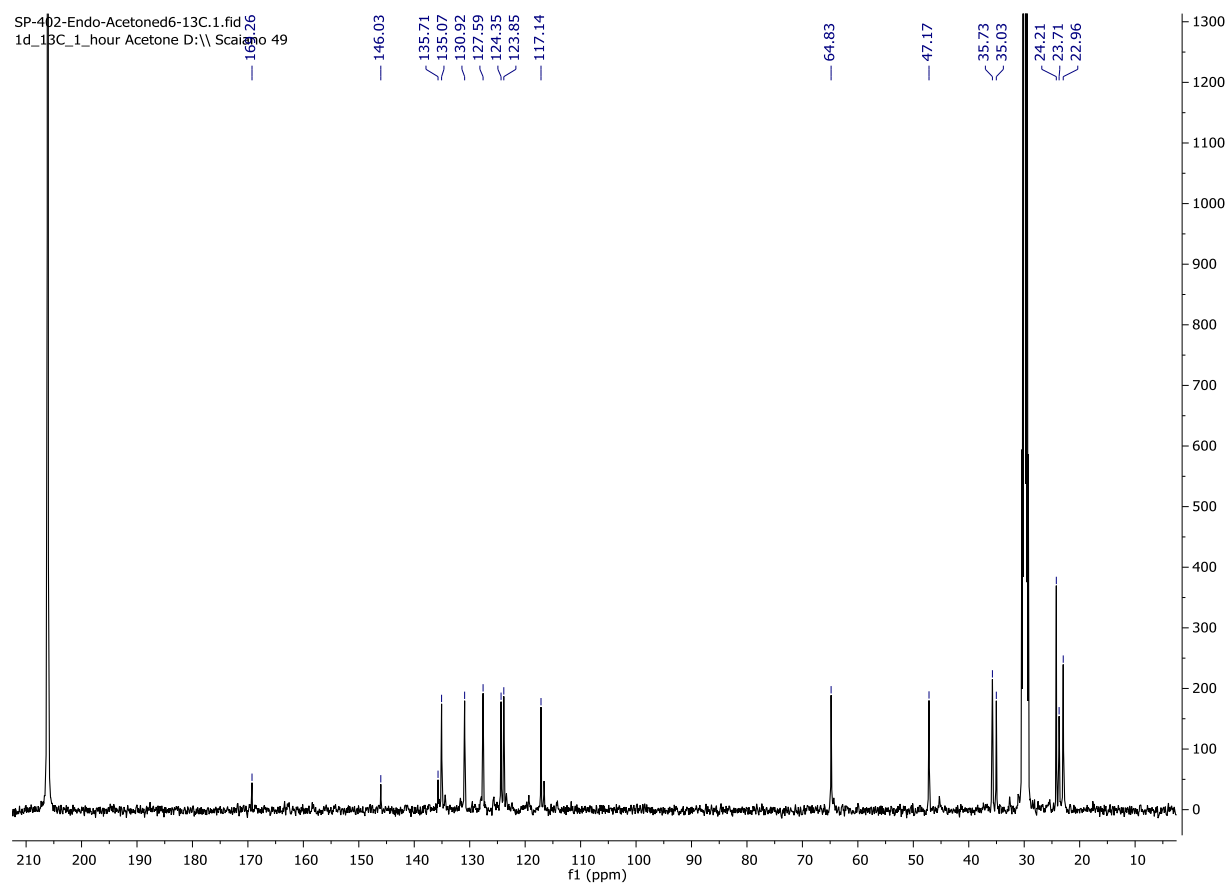
^1H NMR (peaks are doubled due to rotamers)

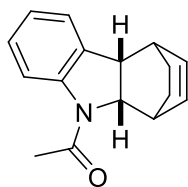




Endo

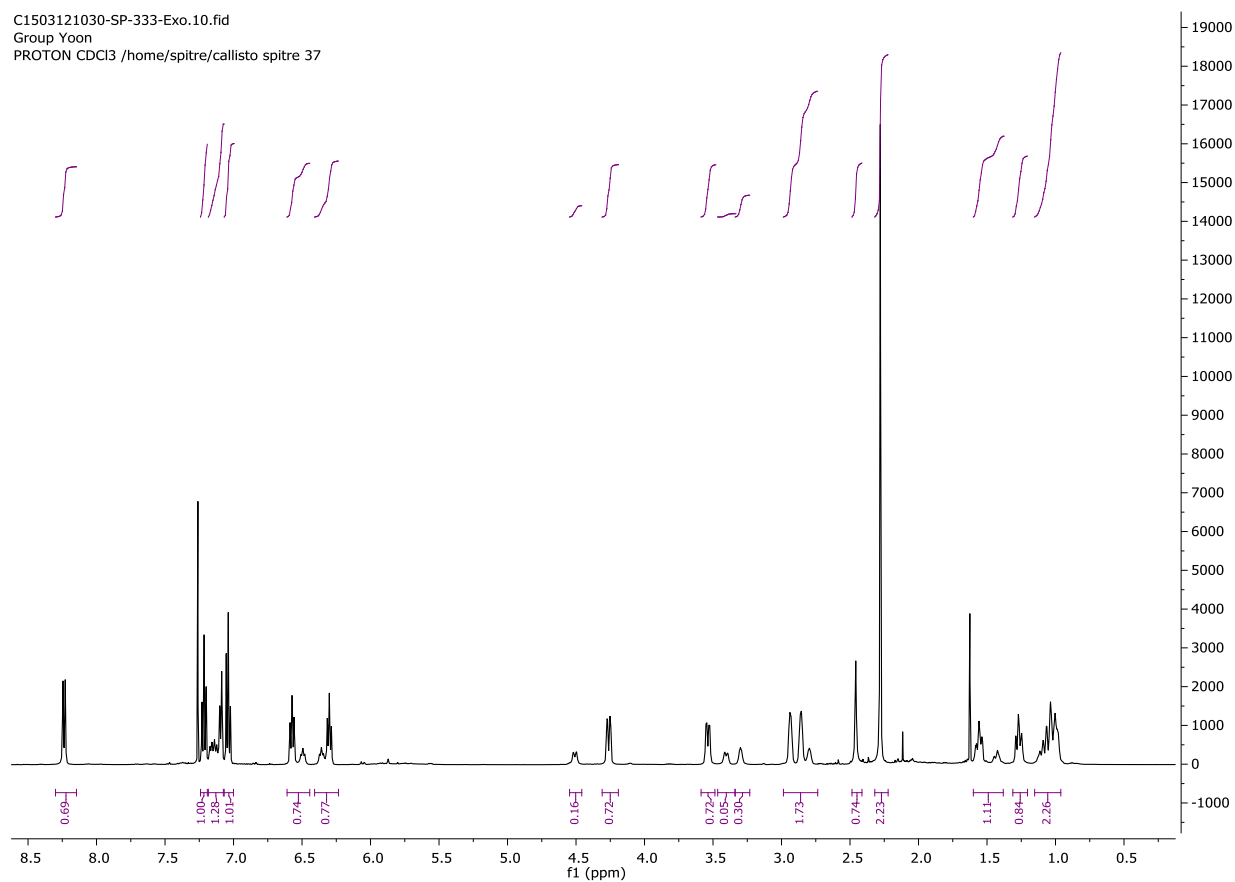
^{13}C NMR

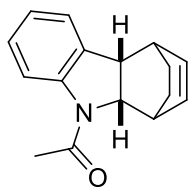
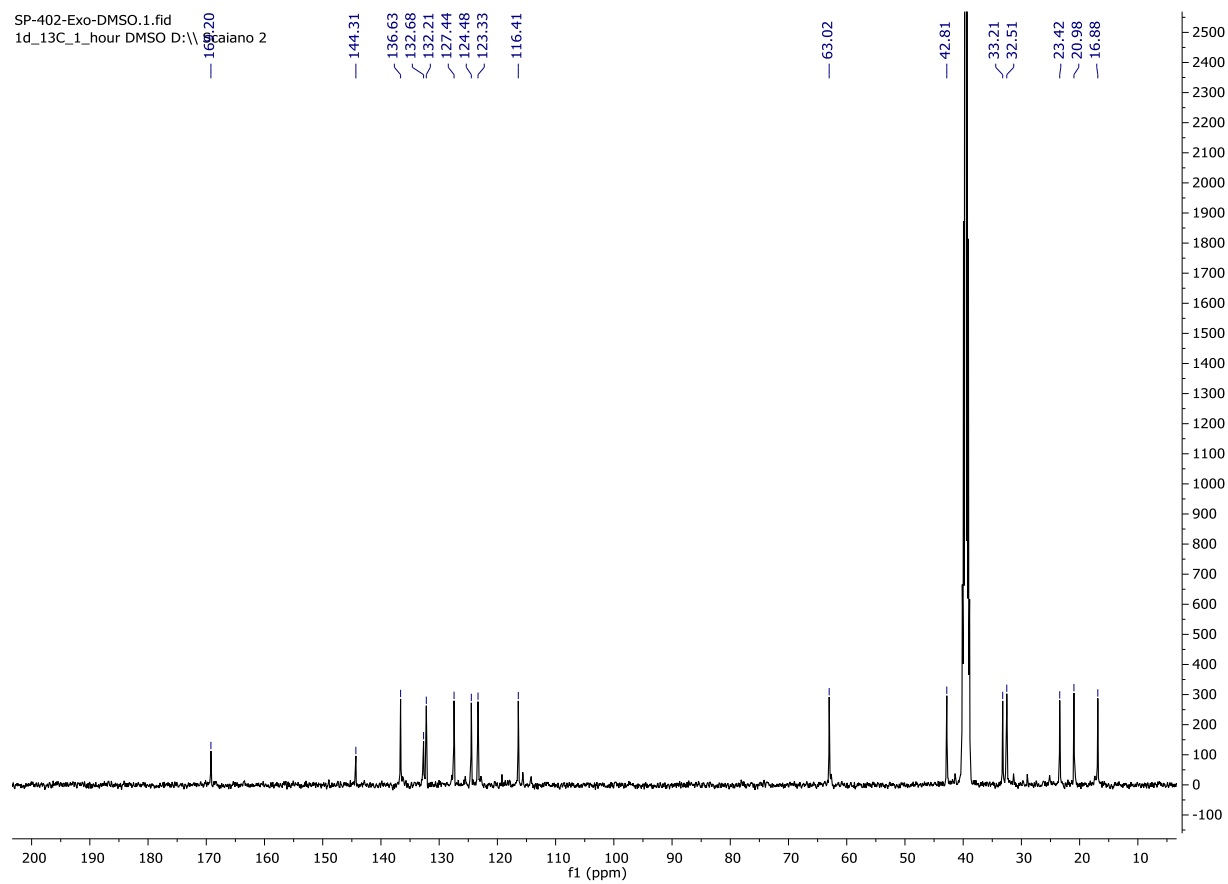


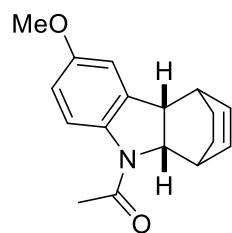


Exo

^1H NMR (peaks are doubled due to rotamers)



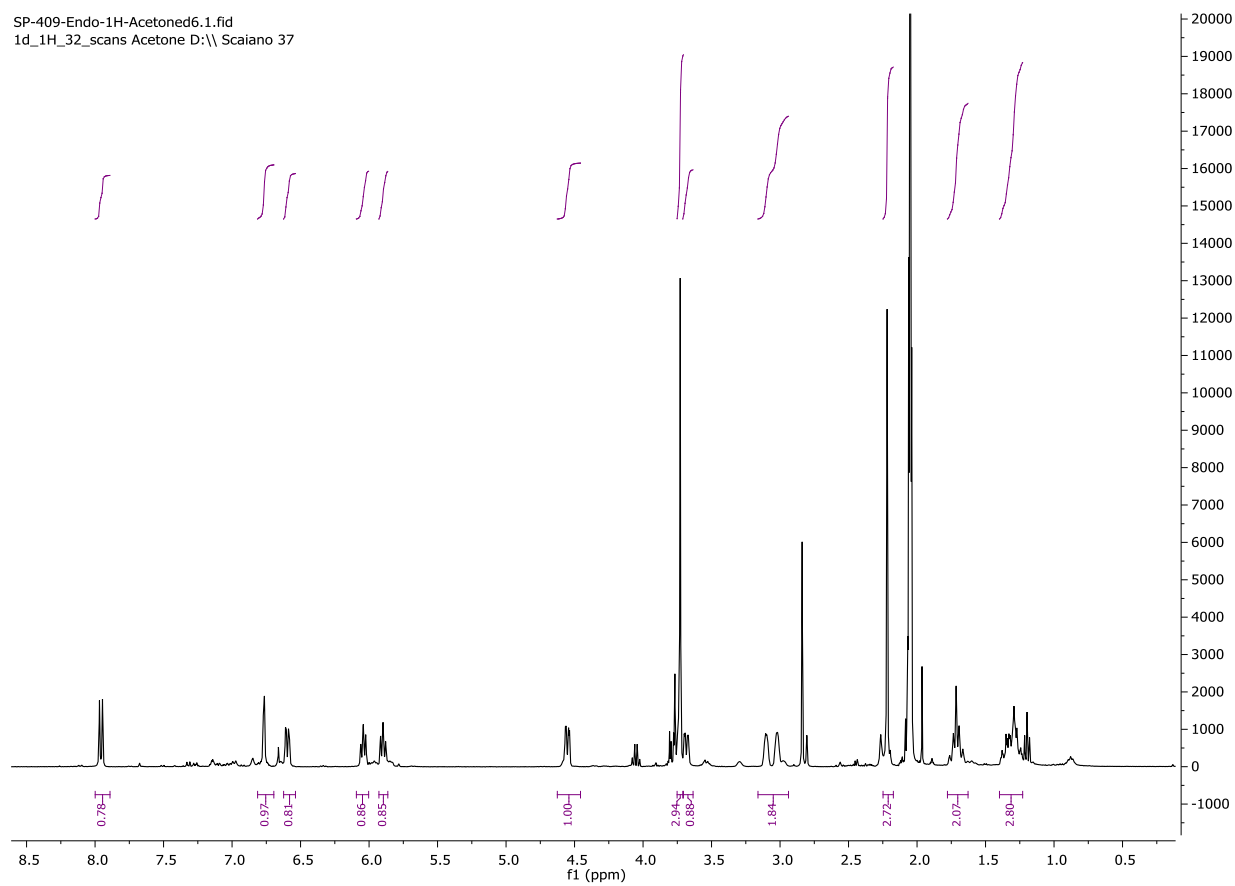
*Exo* ^{13}C NMR

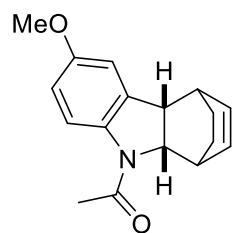


Endo

¹H NMR

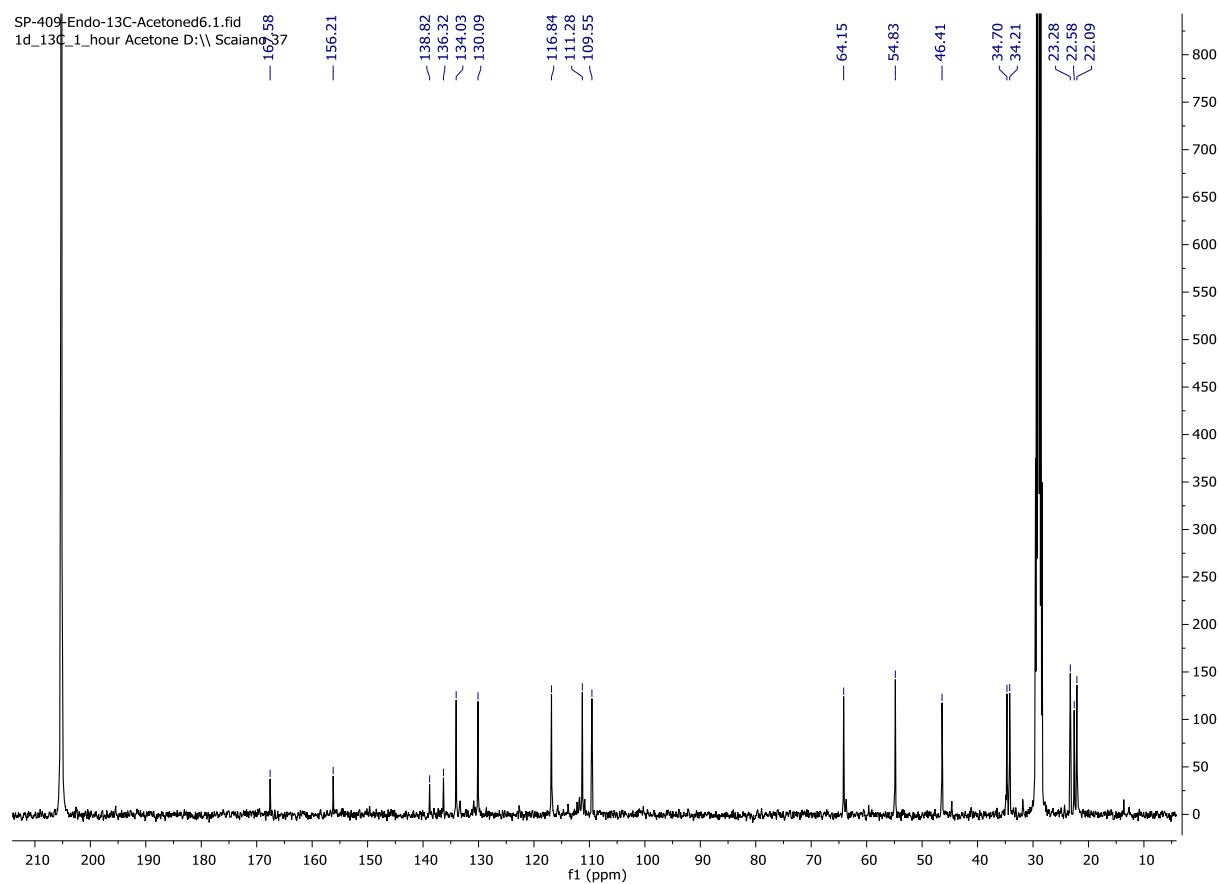
SP-409-Endo-1H-Acetone6.1.fid
1d_1H_32_scans Acetone D:\\ Scaiano 37

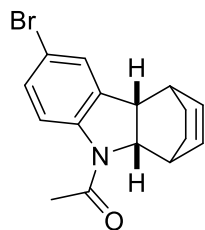




Endo

^{13}C NMR

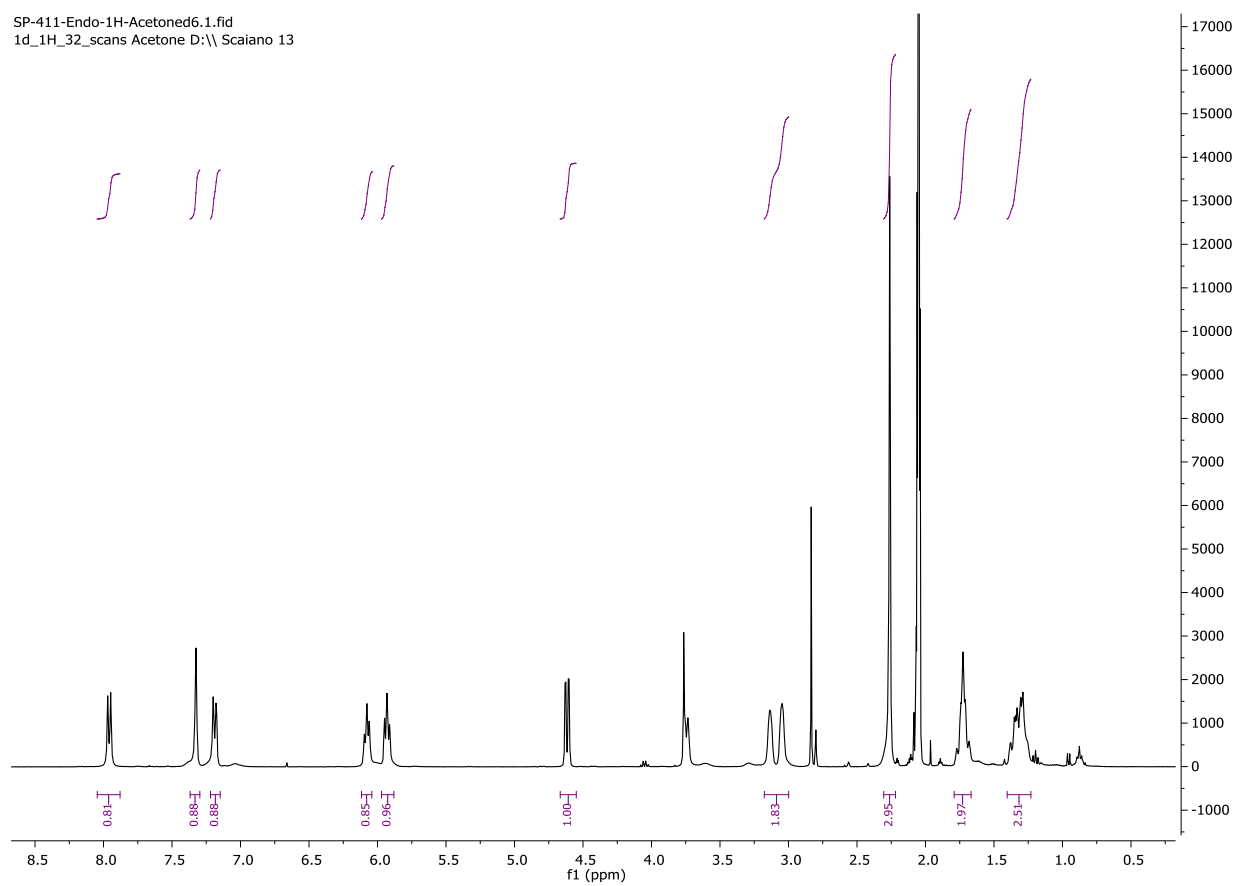


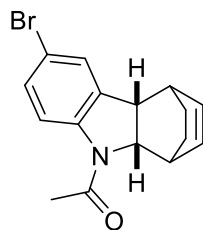
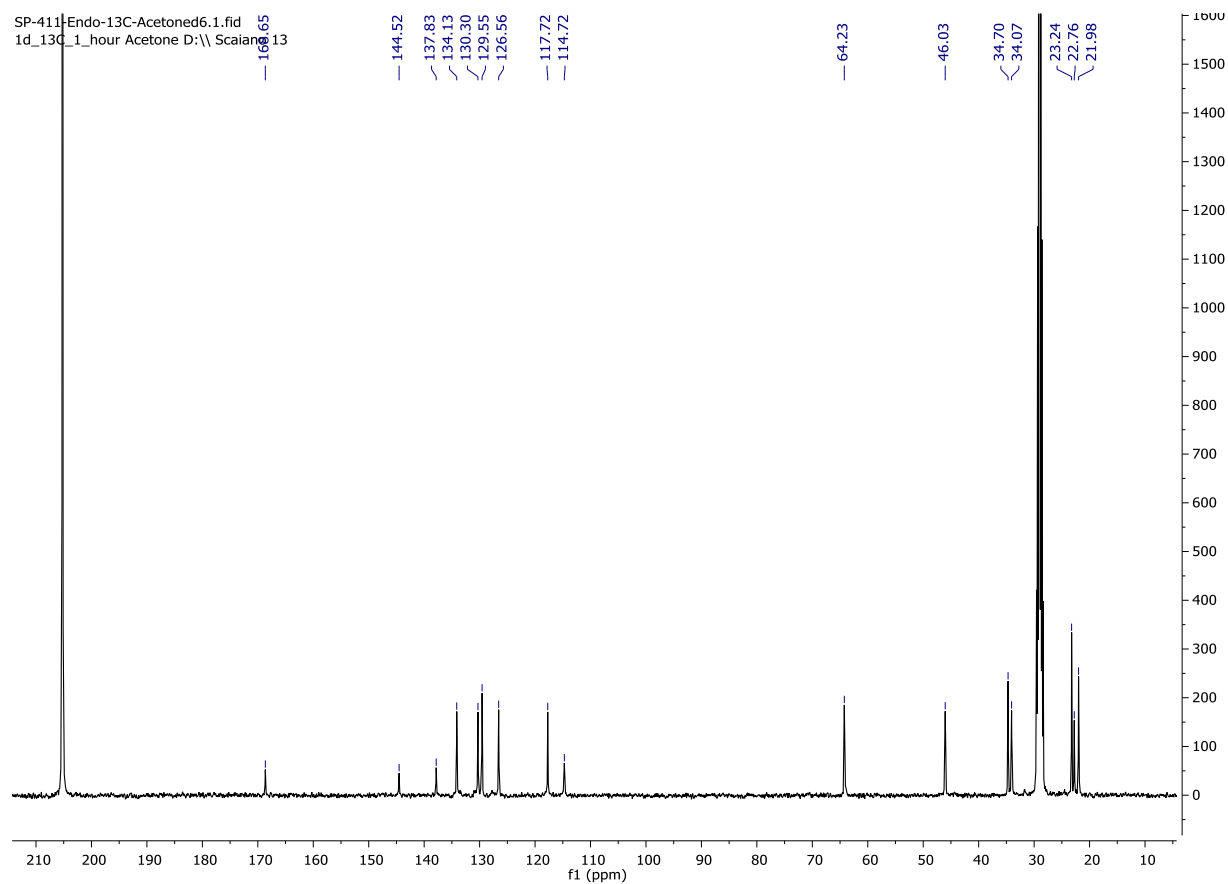


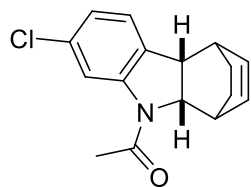
Endo

^1H NMR

SP-411-Endo-1H-Acetoned6.1.fid
1d_1H_32_scans Acetone D:\ Scaiano 13



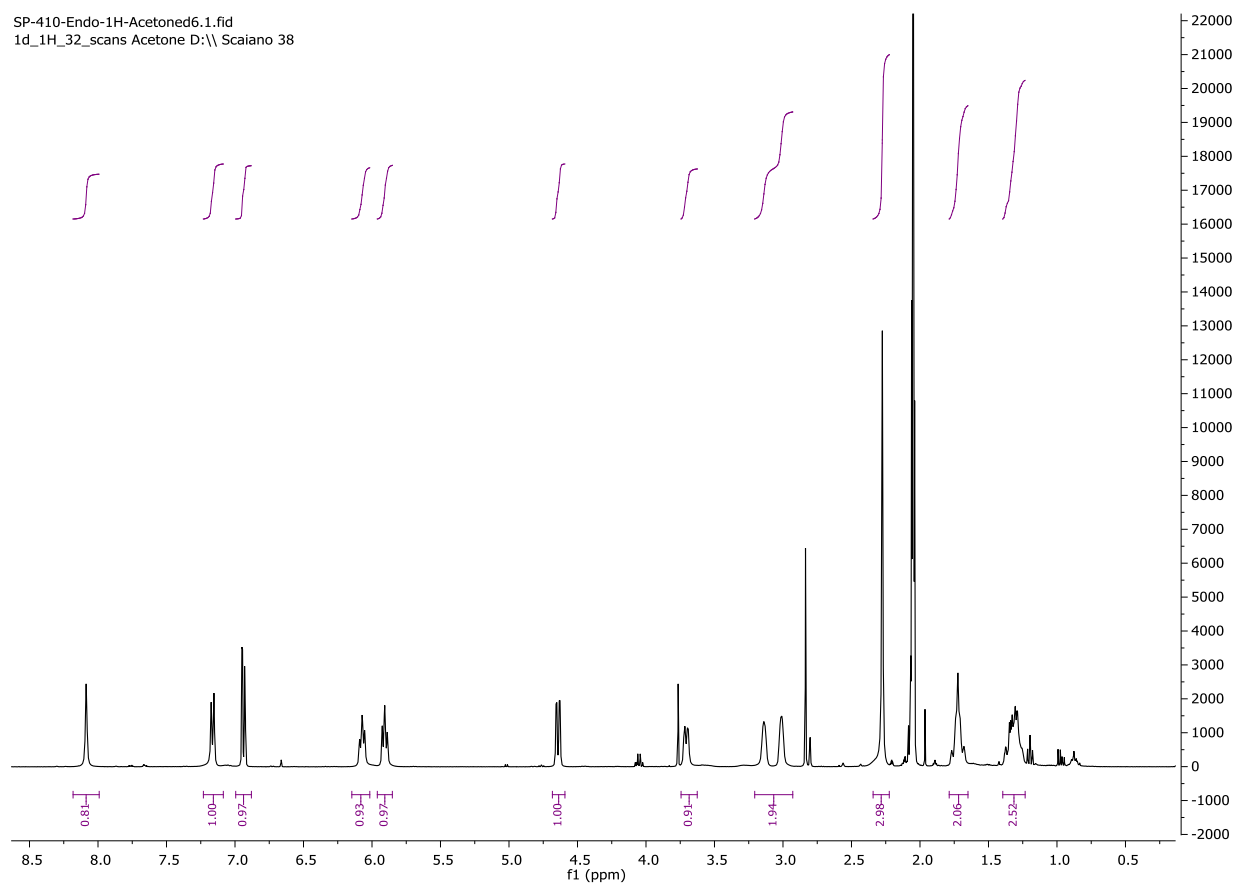
*Endo* ^{13}C NMR

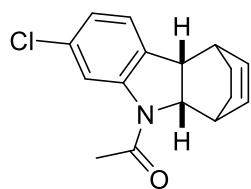


Endo

^1H NMR

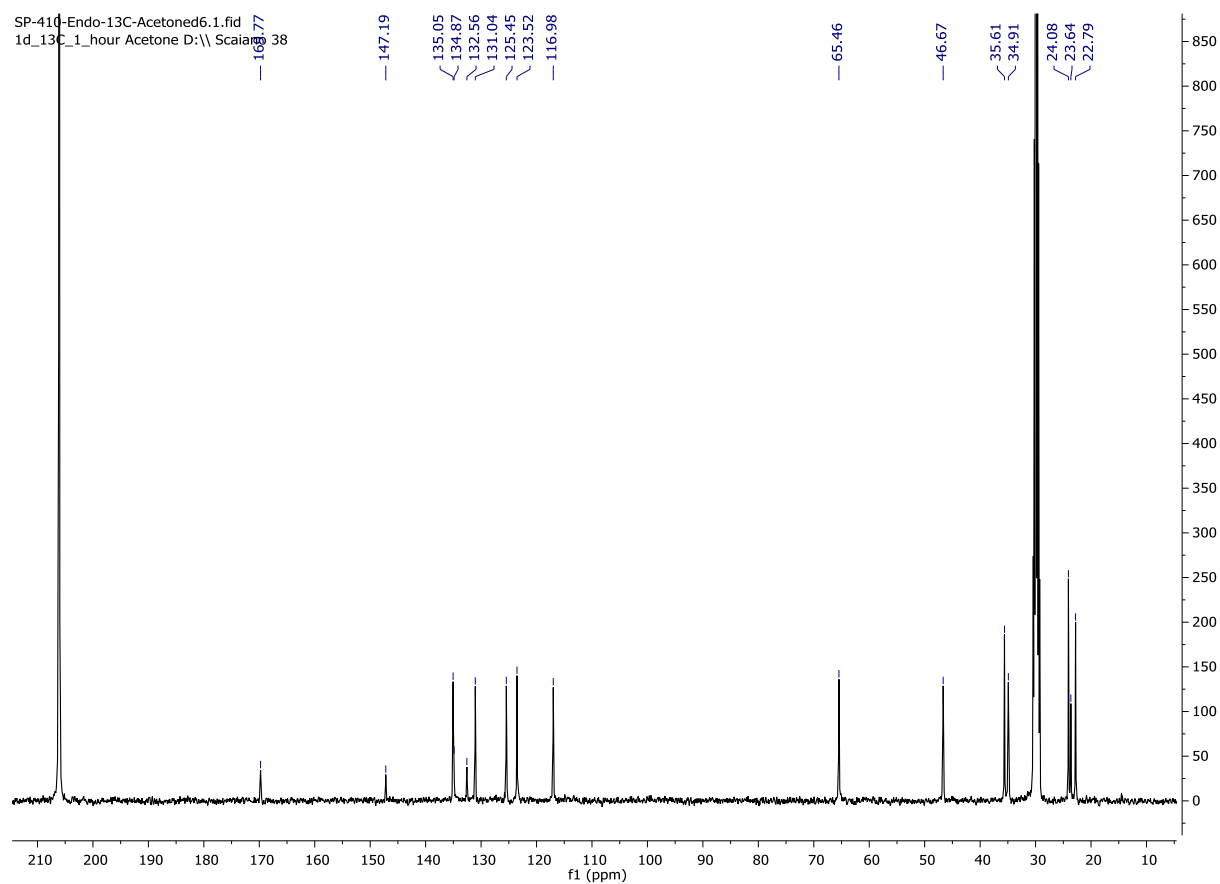
SP-410-Endo-1H-Acetoned6.1.fid
1d_1H_32_scans Acetone D:\ Scaiano 38

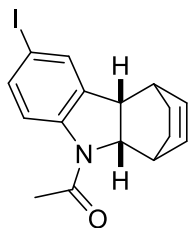




Endo

^{13}C NMR

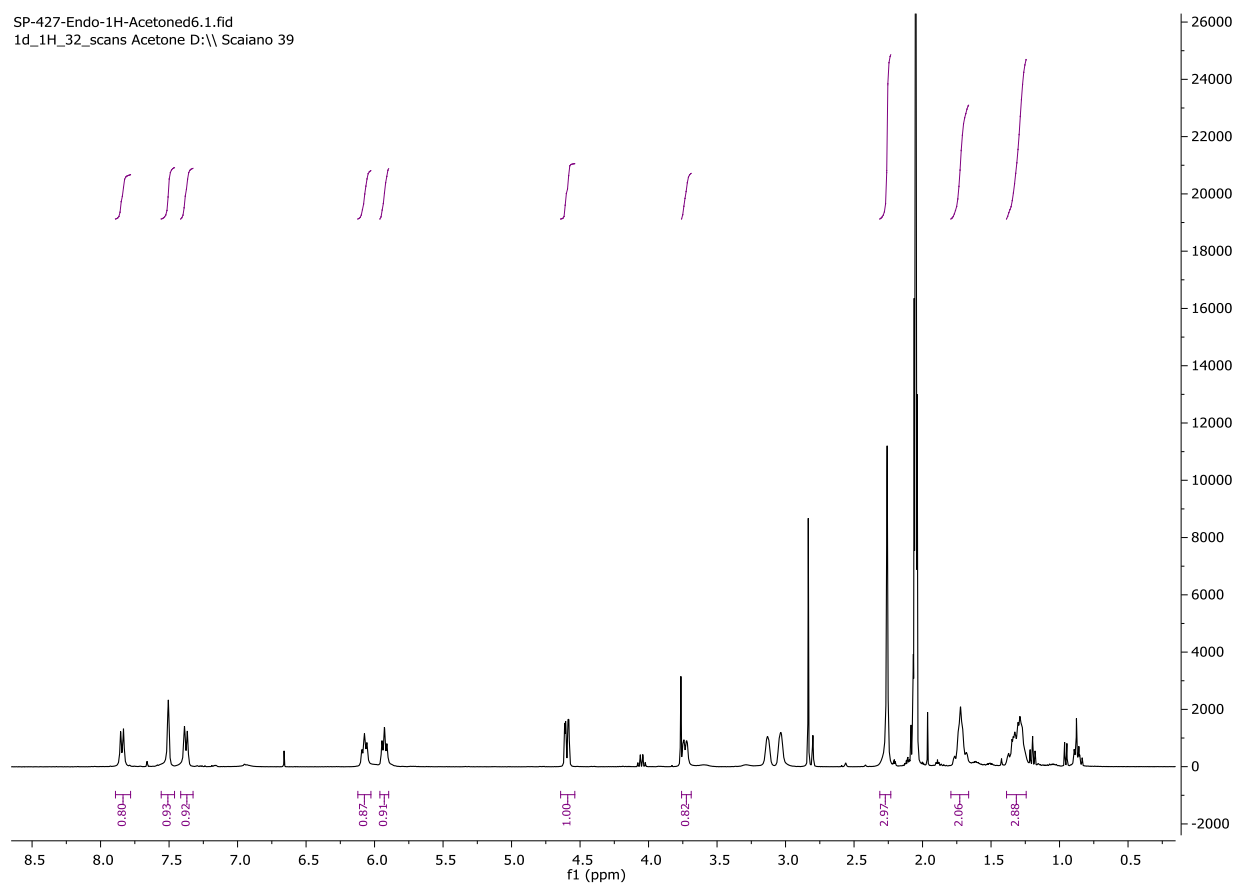


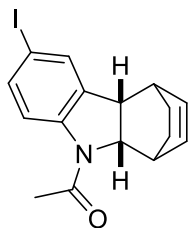


Endo

¹H NMR

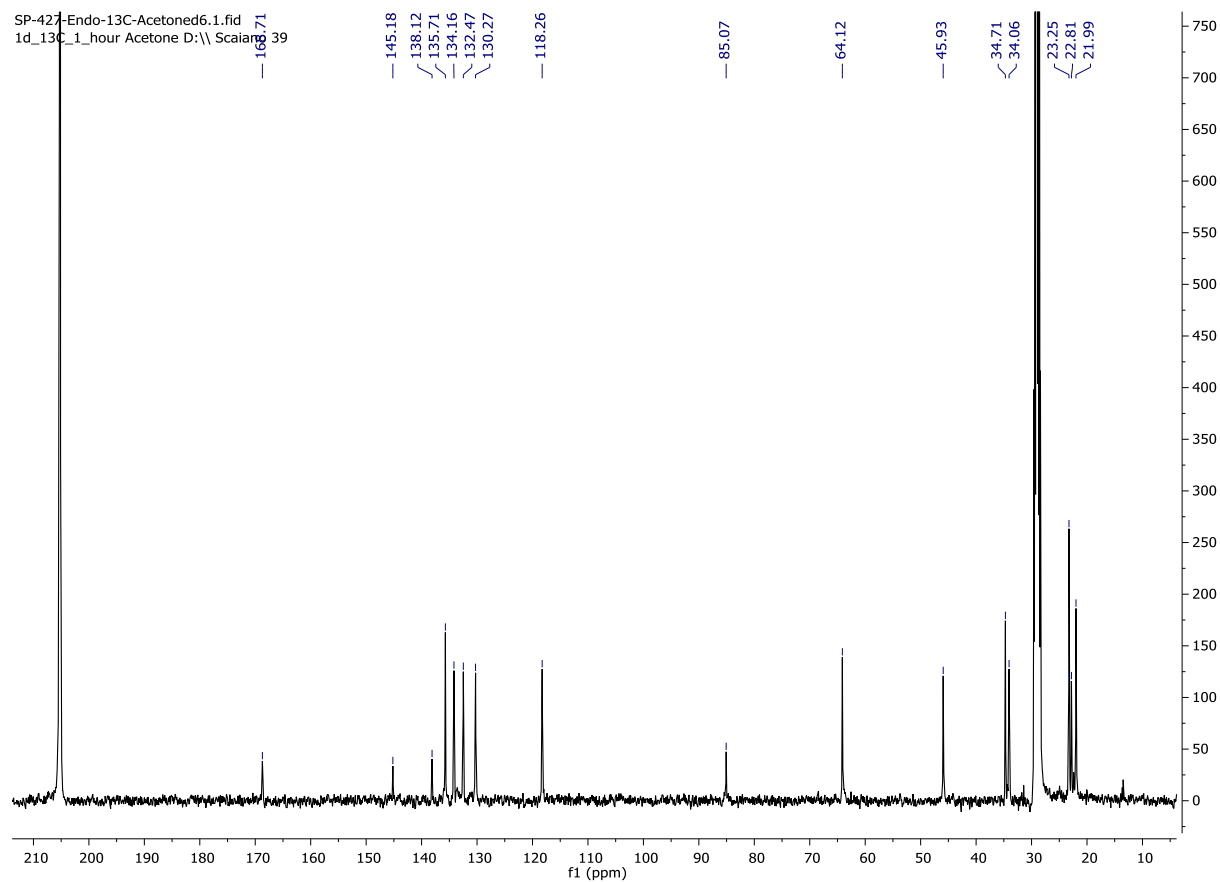
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1d_1H_32_scans Acetone D:\\ Scaiano 39

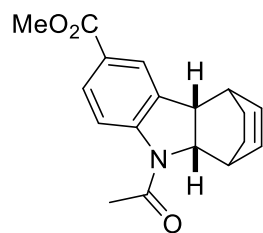




Endo

^{13}C NMR

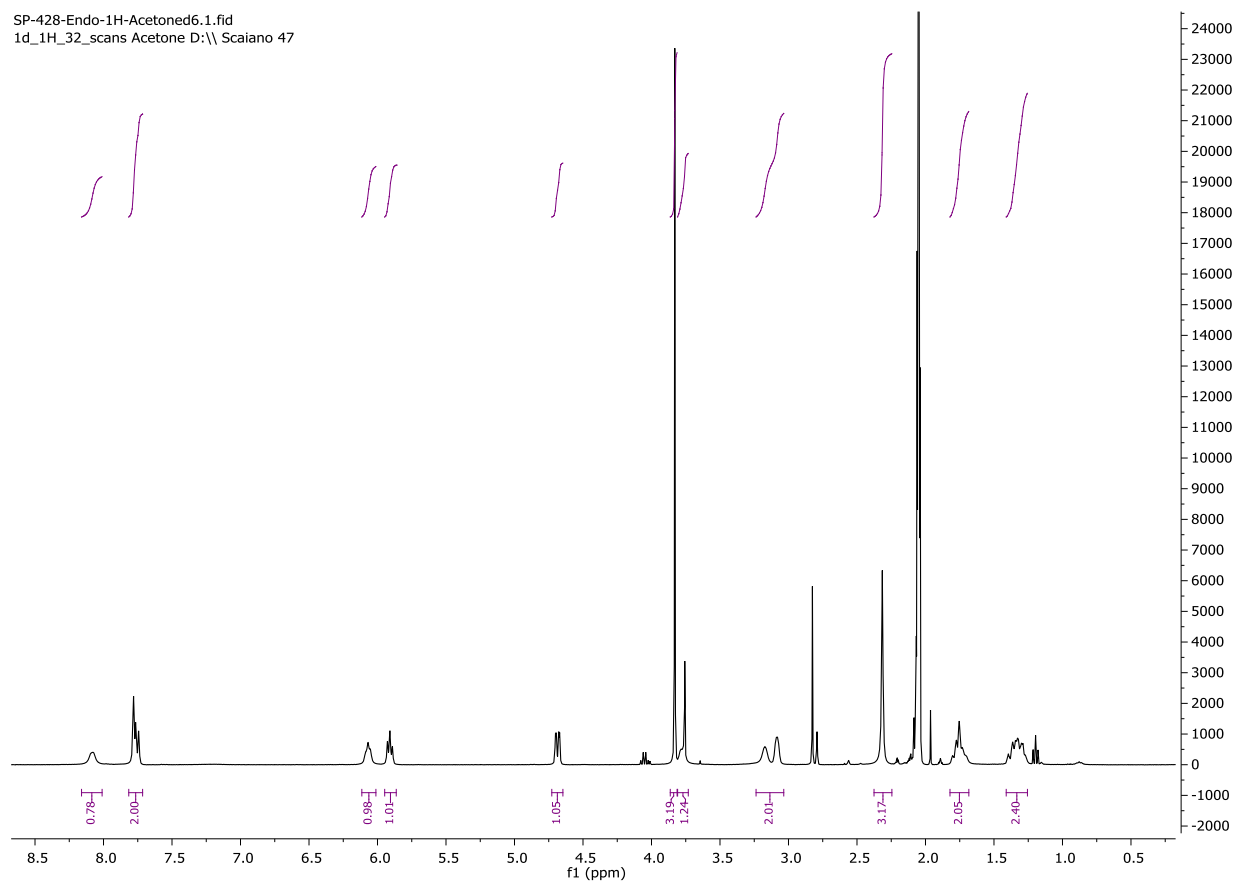


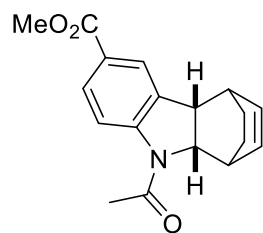


Endo

¹H NMR

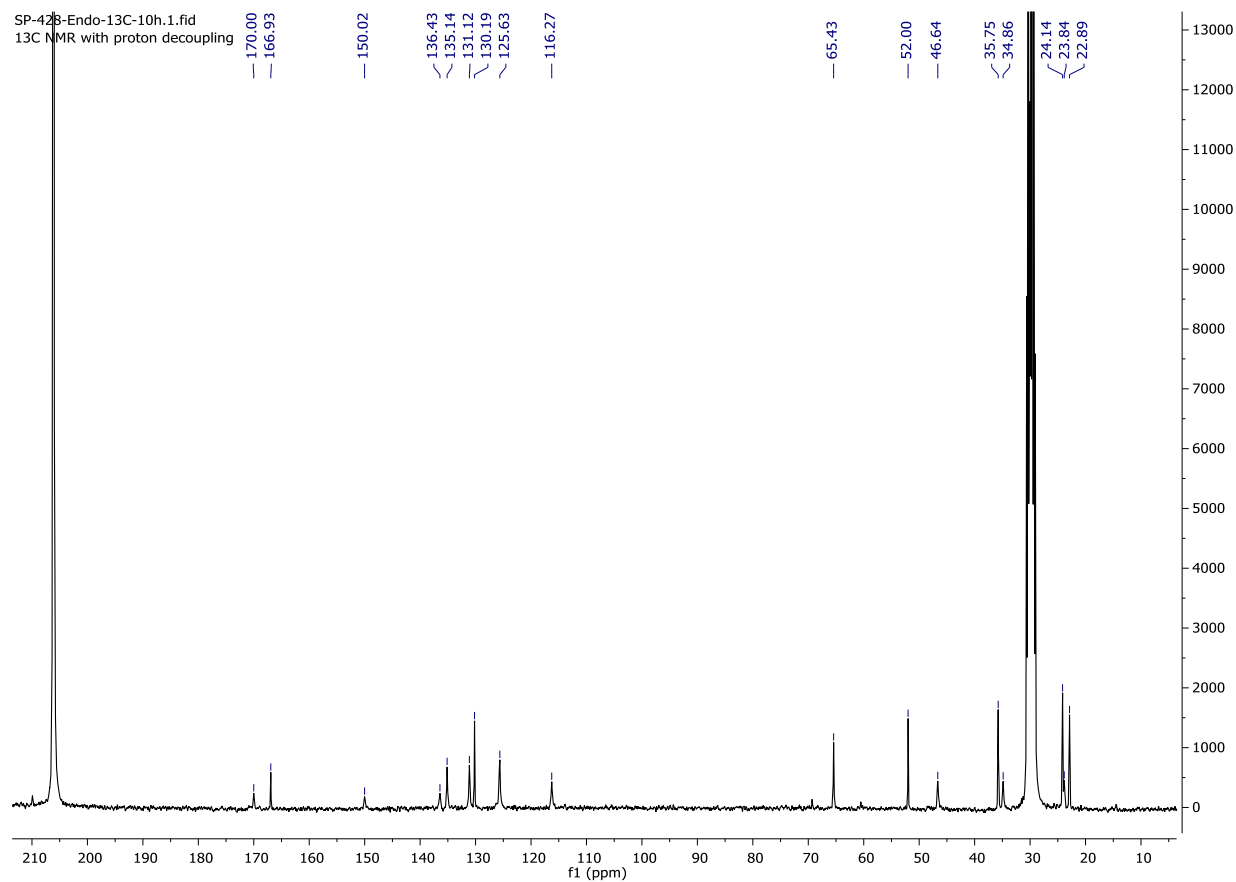
SP-428-Endo-1H-Acetoned6.1.fid
1d_1H_32_scans Acetone D:\\ Scaiano 47

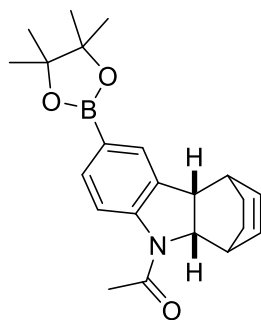




Endo

¹³C NMR

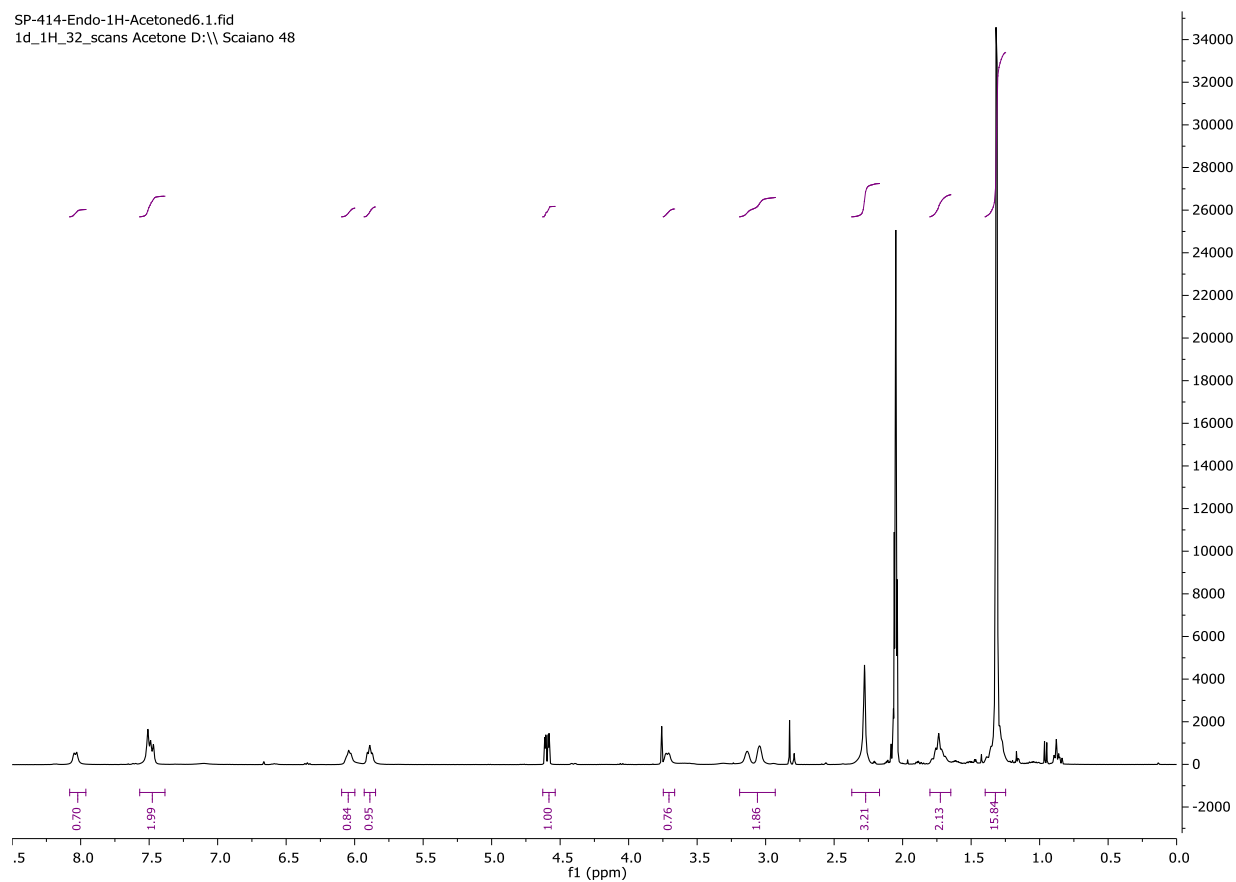


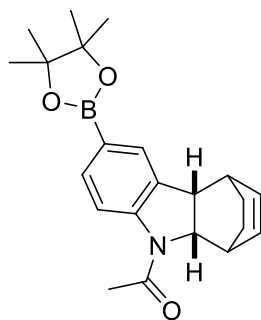


Endo

^1H NMR

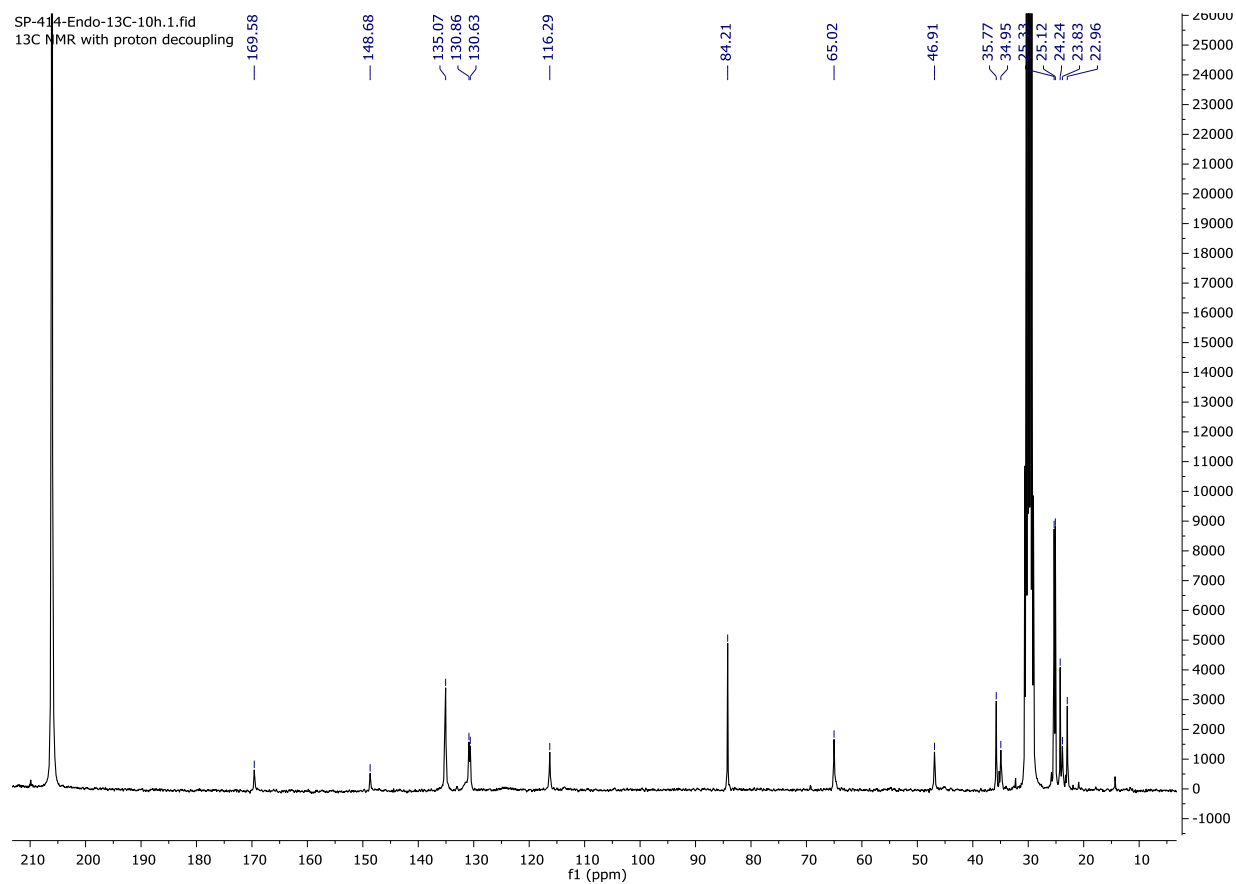
SP-414-Endo-1H-Acetoned6.1.fid
1d_1H_32_scans Acetone D: $\backslash$ Scaiano 48

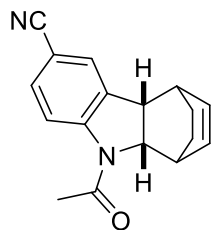




Endo

^{13}C NMR

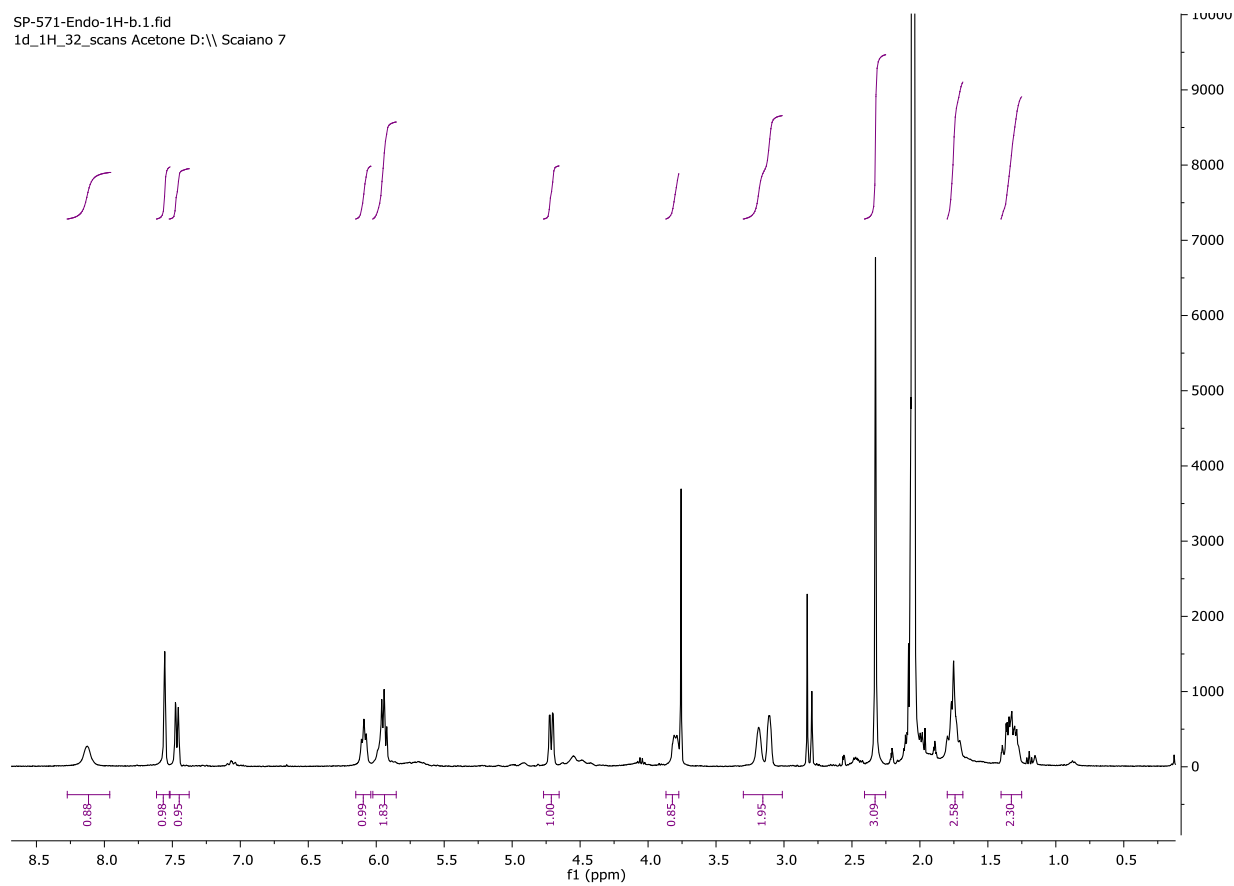


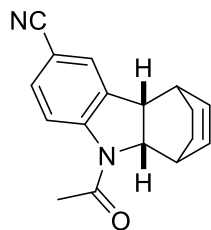
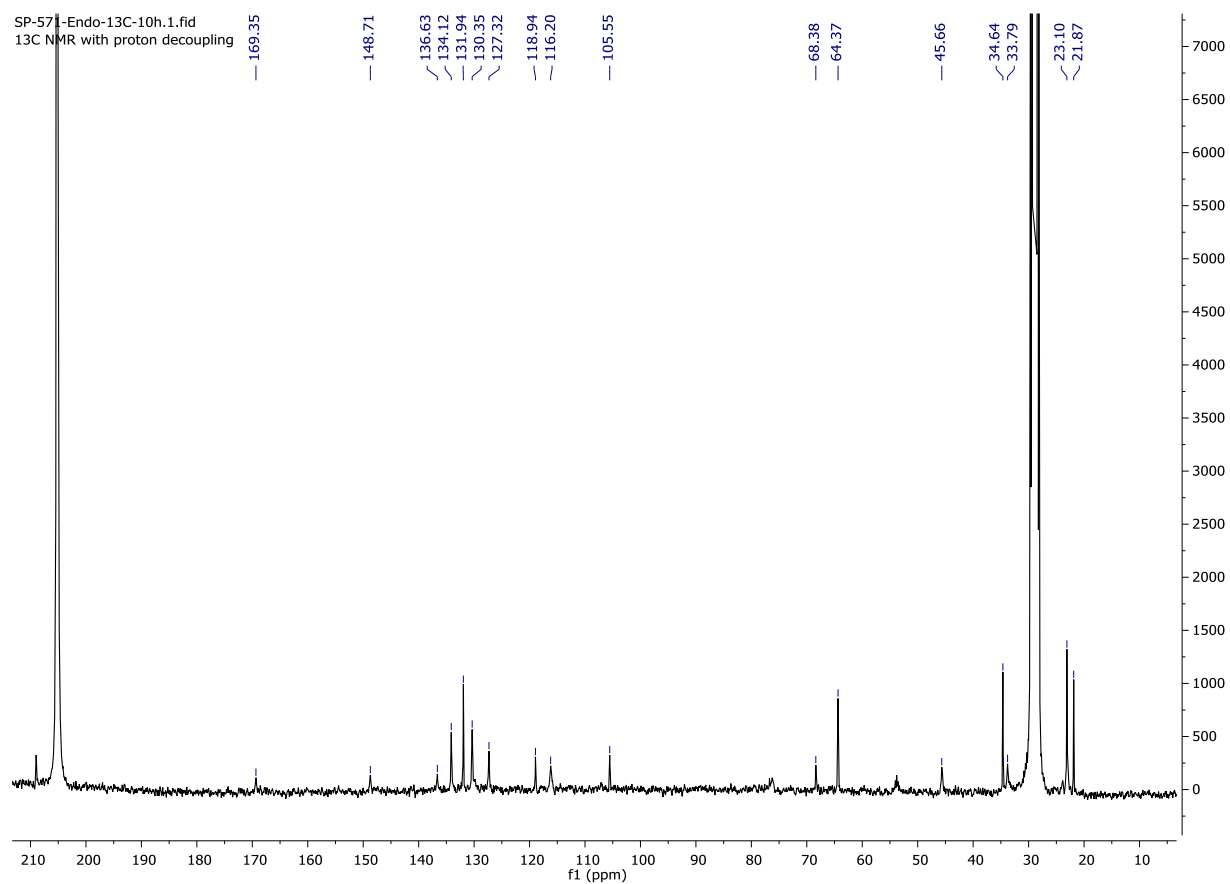


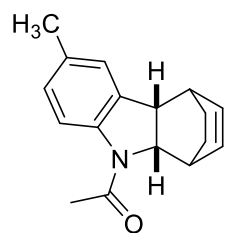
Endo

¹H NMR

SP-571-Endo-1H-b.1.fid
1d_1H_32_scans Acetone D:** Scaiano 7



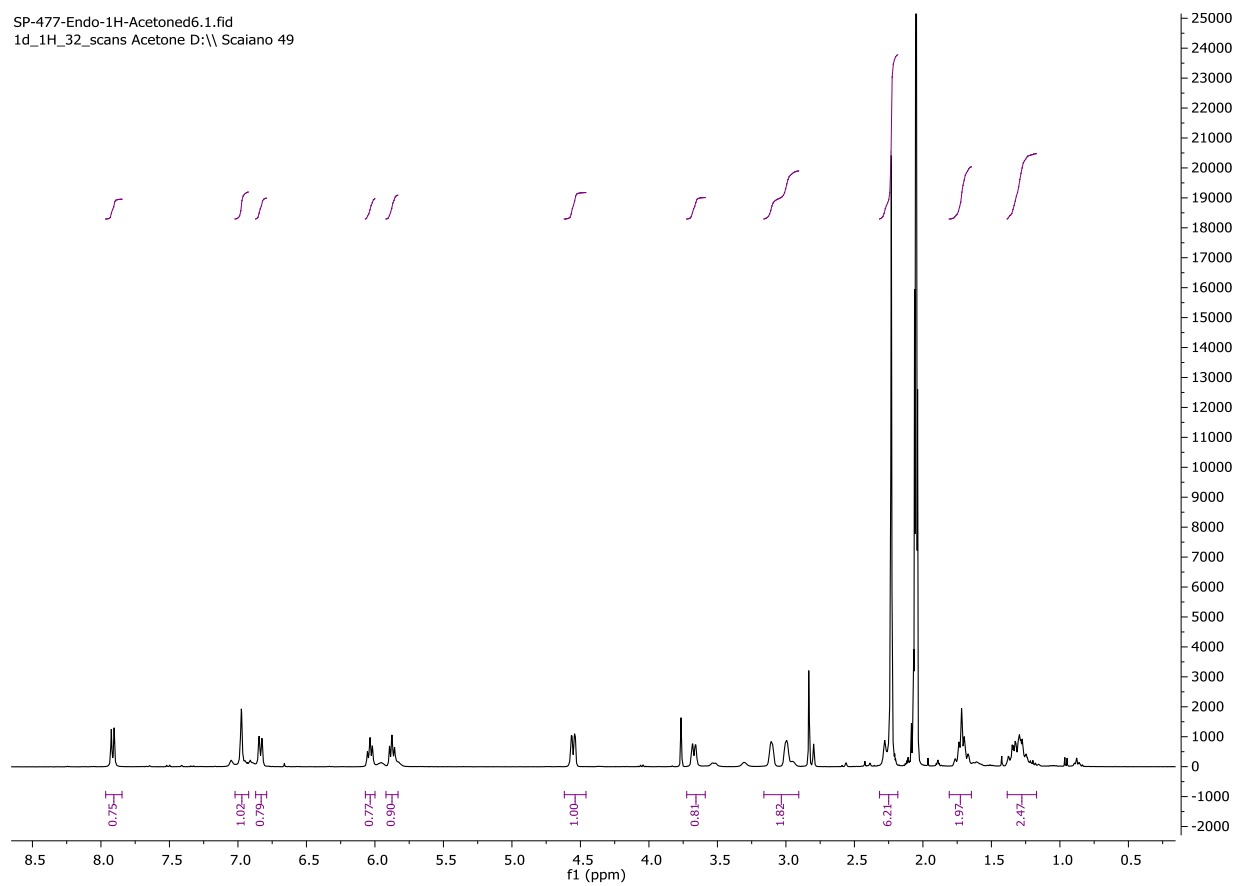
*Endo*¹³C NMR

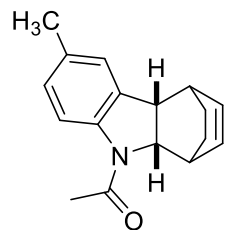


Endo

¹H NMR

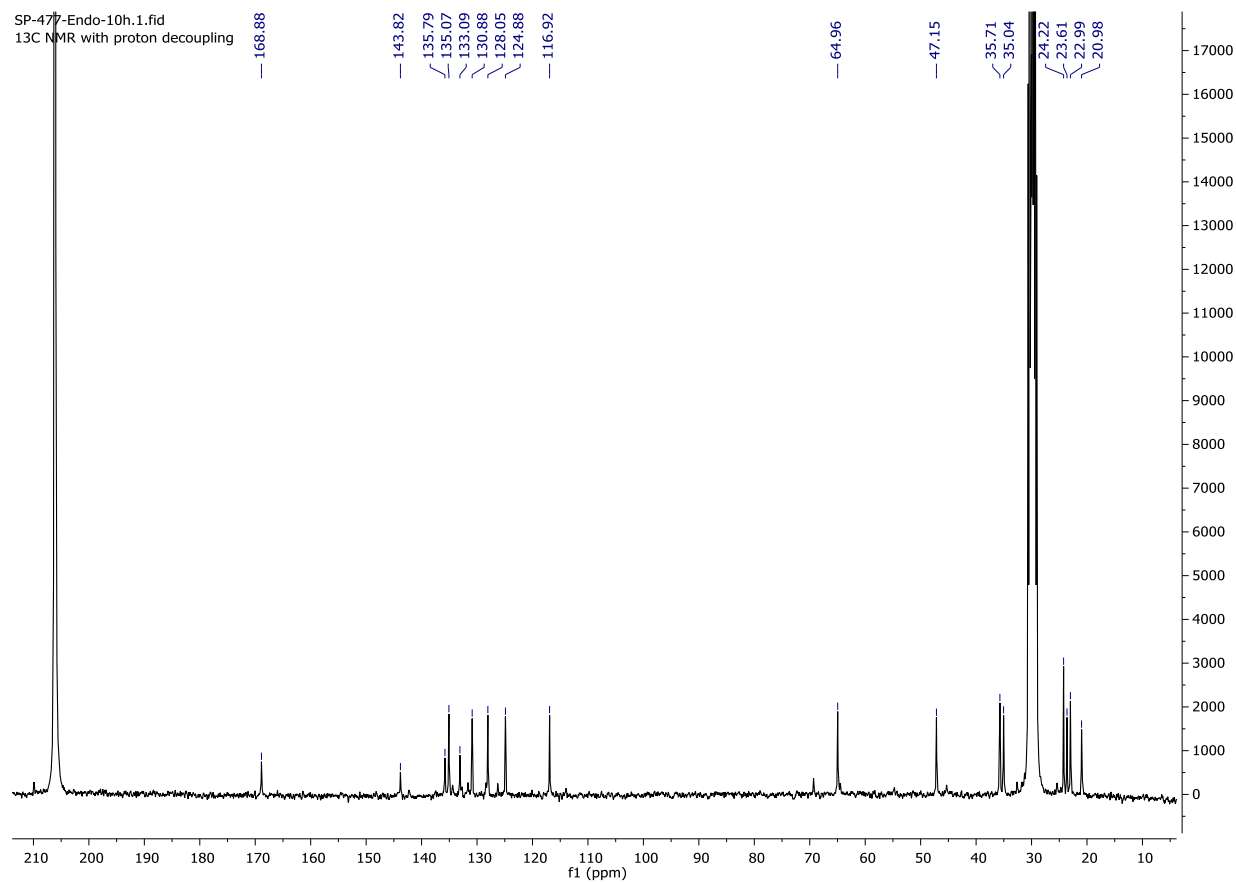
SP-477-Endo-1H-Acetoned6.1.fid
1d_1H_32_scans Acetone D:<>\ Scaiano 49

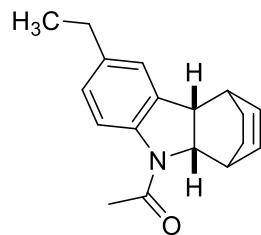




Endo

^{13}C NMR

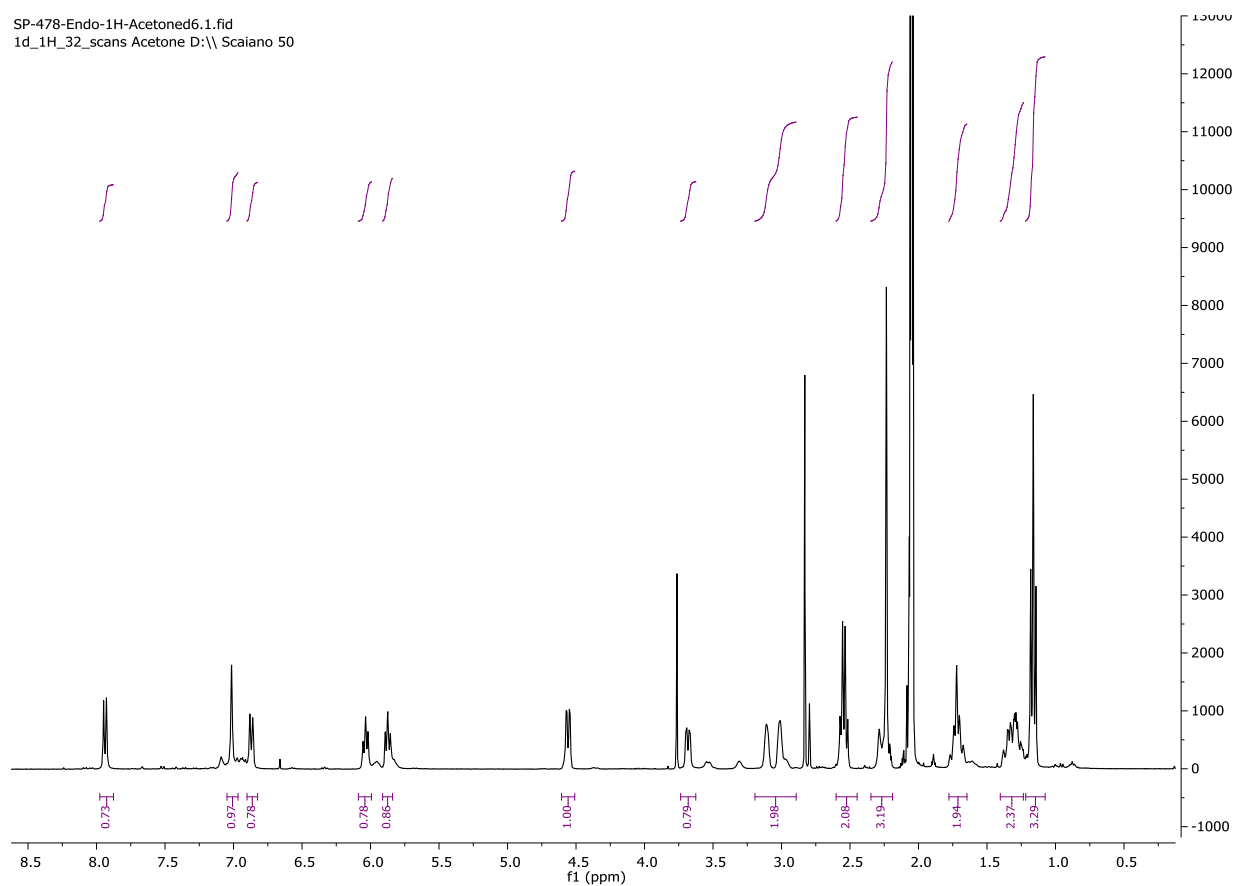


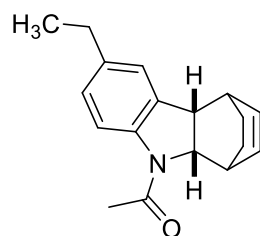
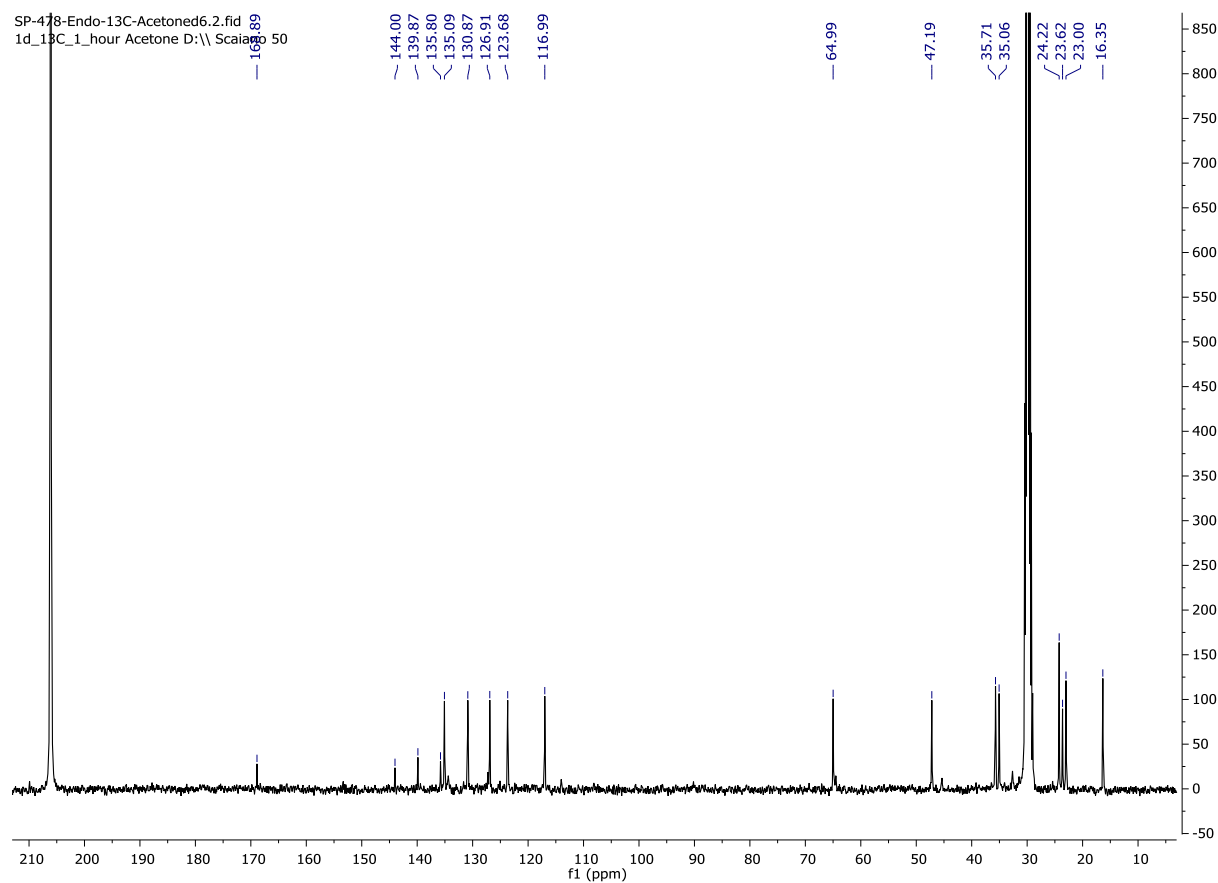


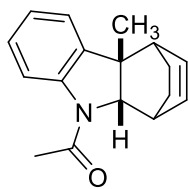
Endo

¹H NMR

SP-478-Endo-1H-Acetoned6.1.fid
1d_1H_32_scans Acetone D:\\ Scaiano 50



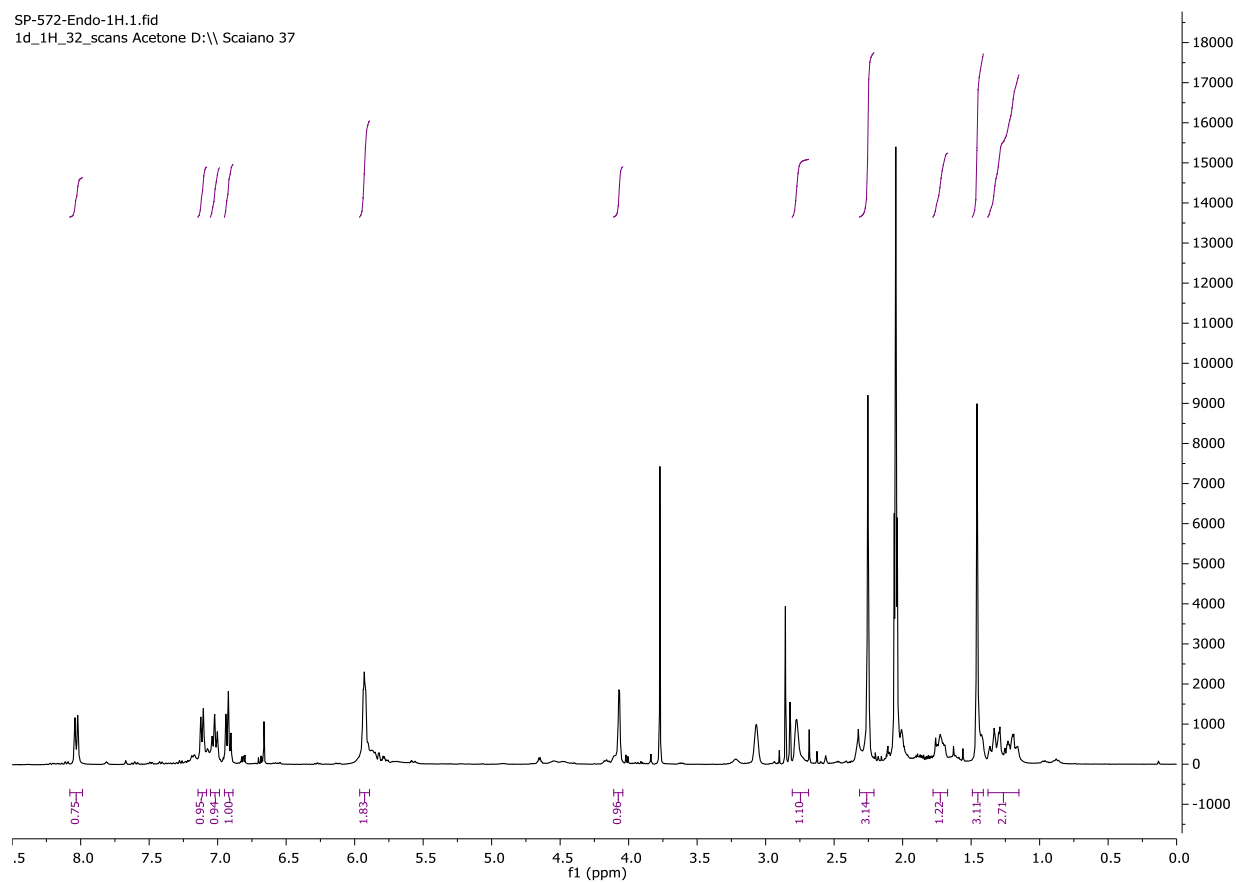
*Endo*¹³C NMR

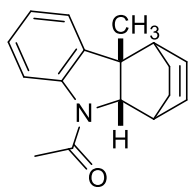
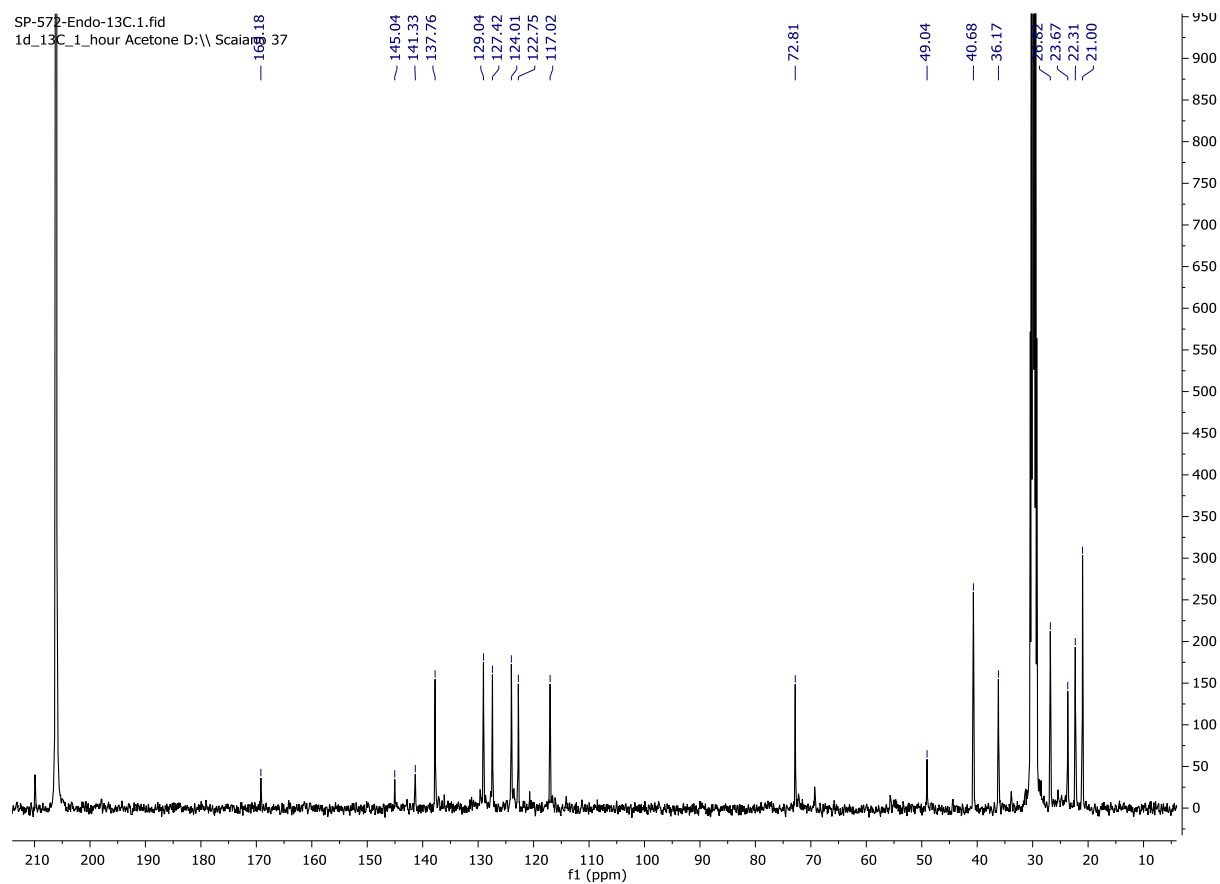


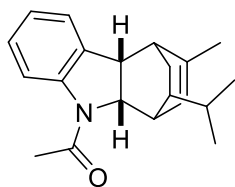
Endo

^1H NMR

SP-572-Endo-1H.1.fid
1d_1H_32_scans Acetone D: $\backslash\backslash$ Scaiano 37



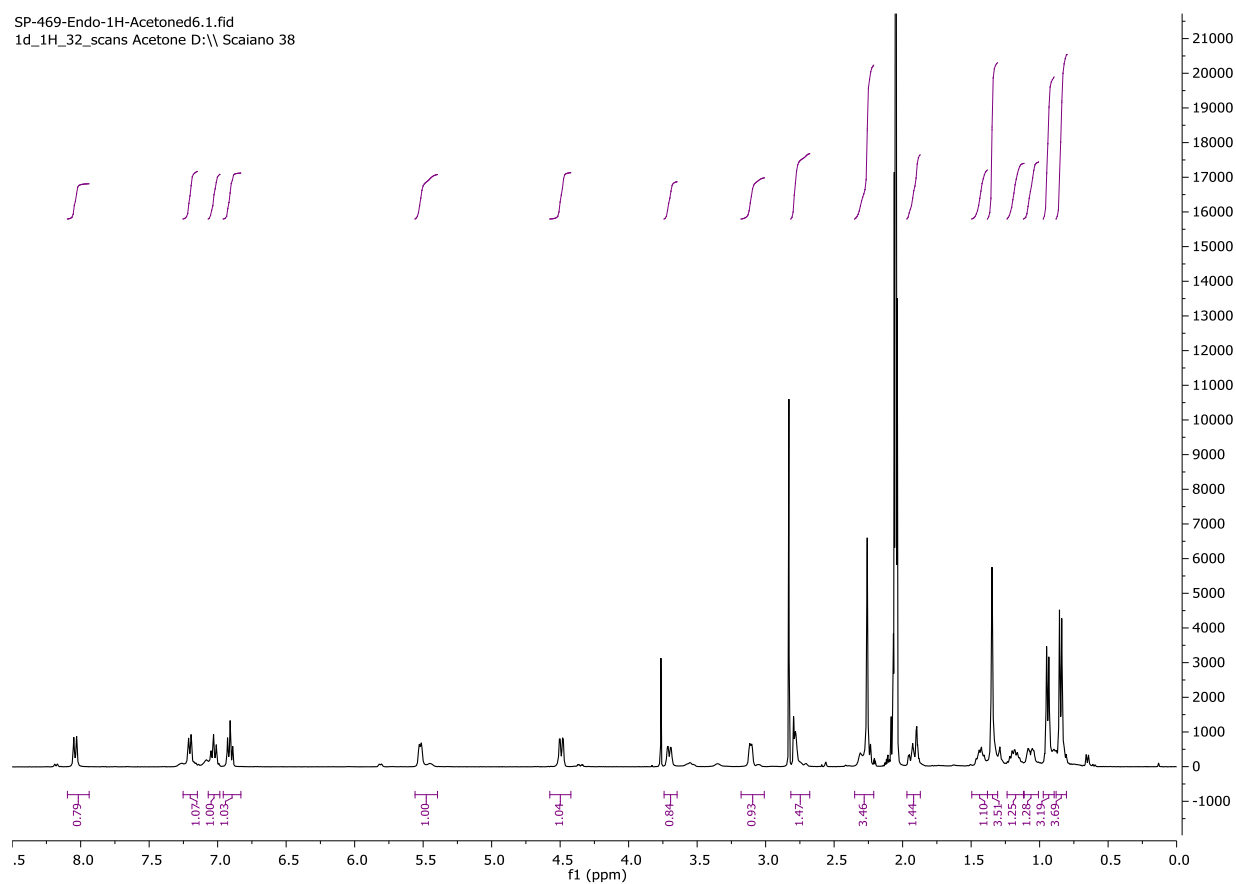
*Endo* ^{13}C NMR

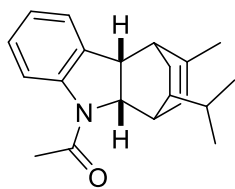


Endo

^1H NMR

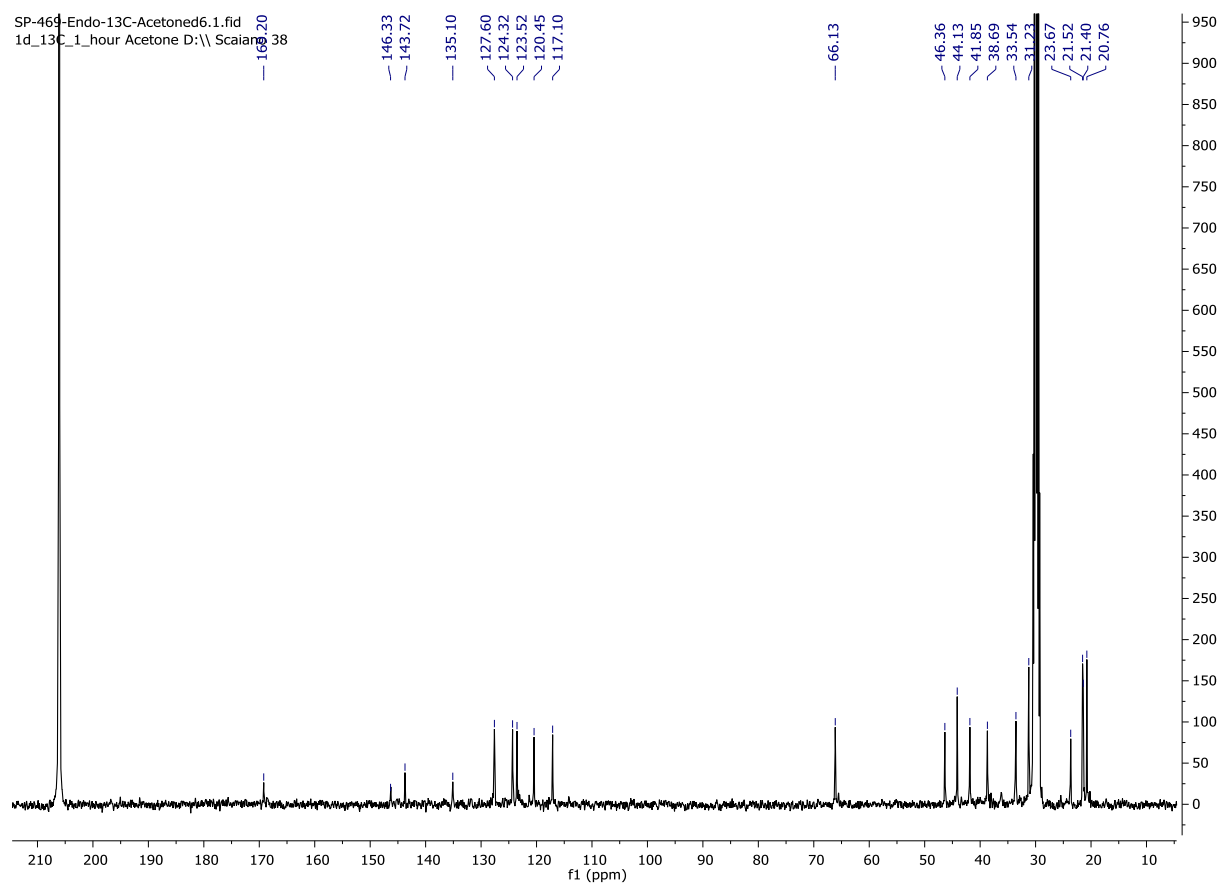
SP-469-Endo-1H-Acetoned6.1.fid
1d_1H_32_scans Acetone D: $\backslash$ Scaiano 38

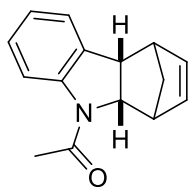




Endo

^{13}C NMR

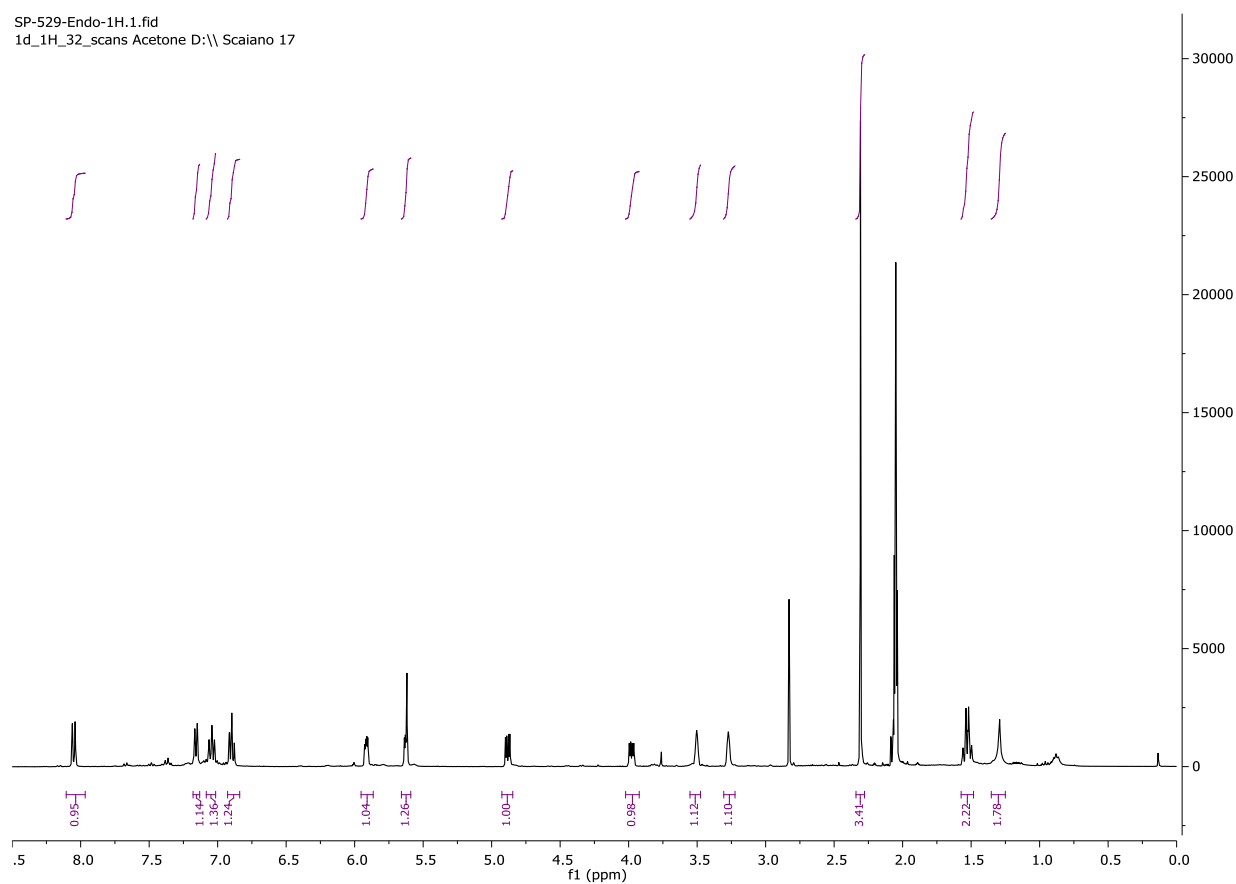


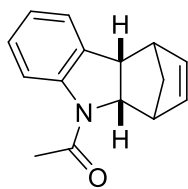
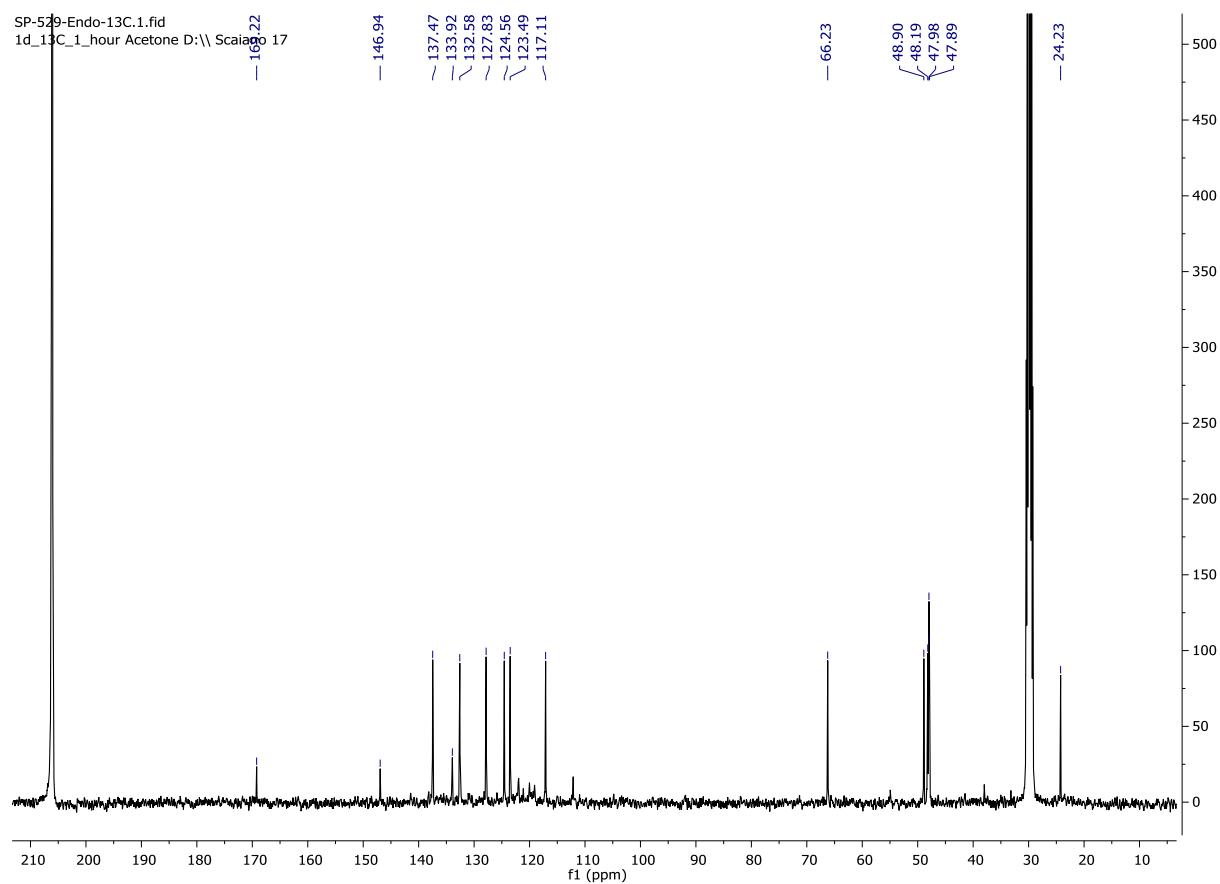


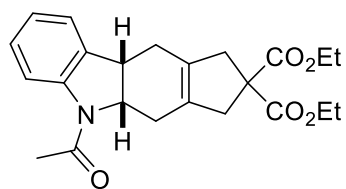
Endo

¹H NMR

SP-529-Endo-1H.1.fid
1d_1H_32_scans Acetone D:** Scaiano 17

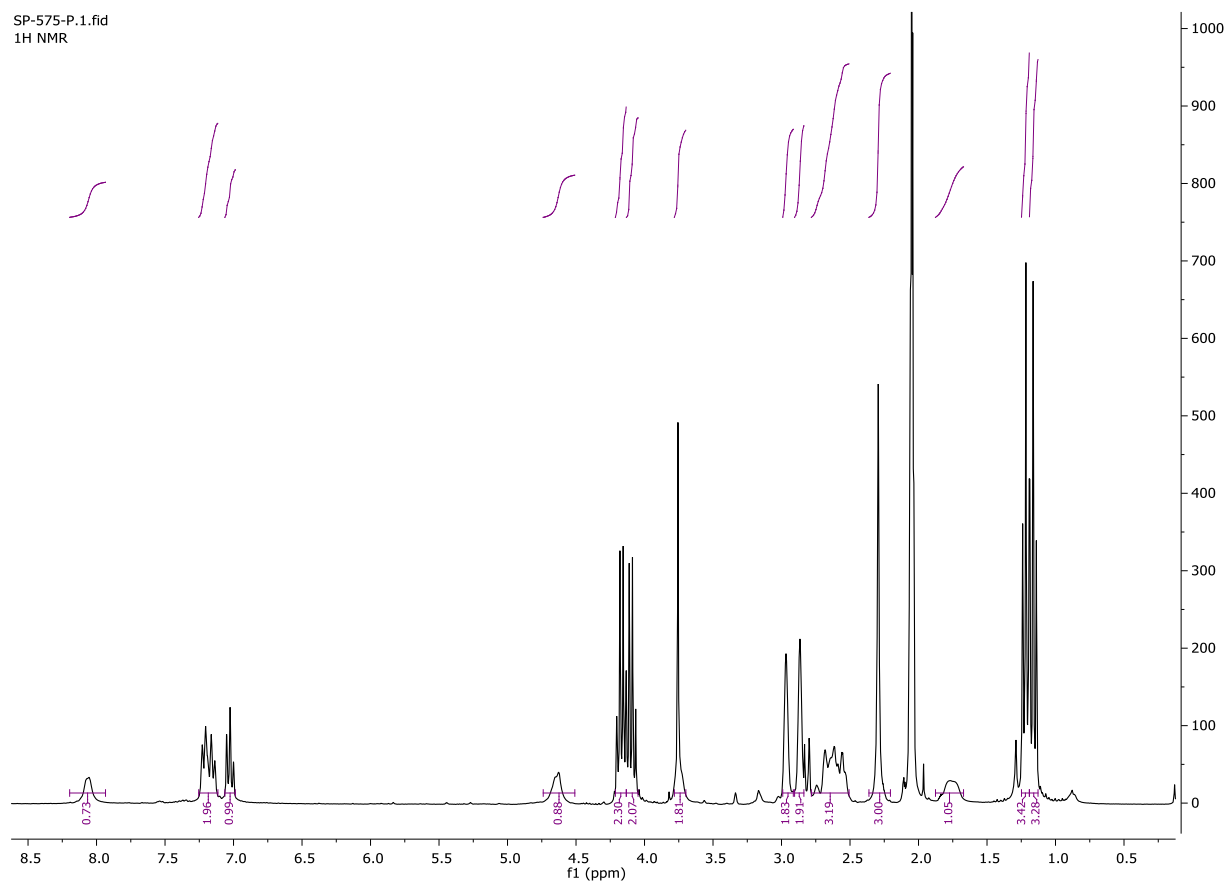


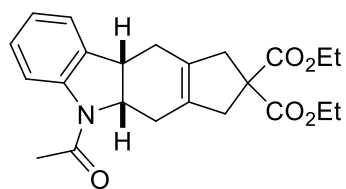
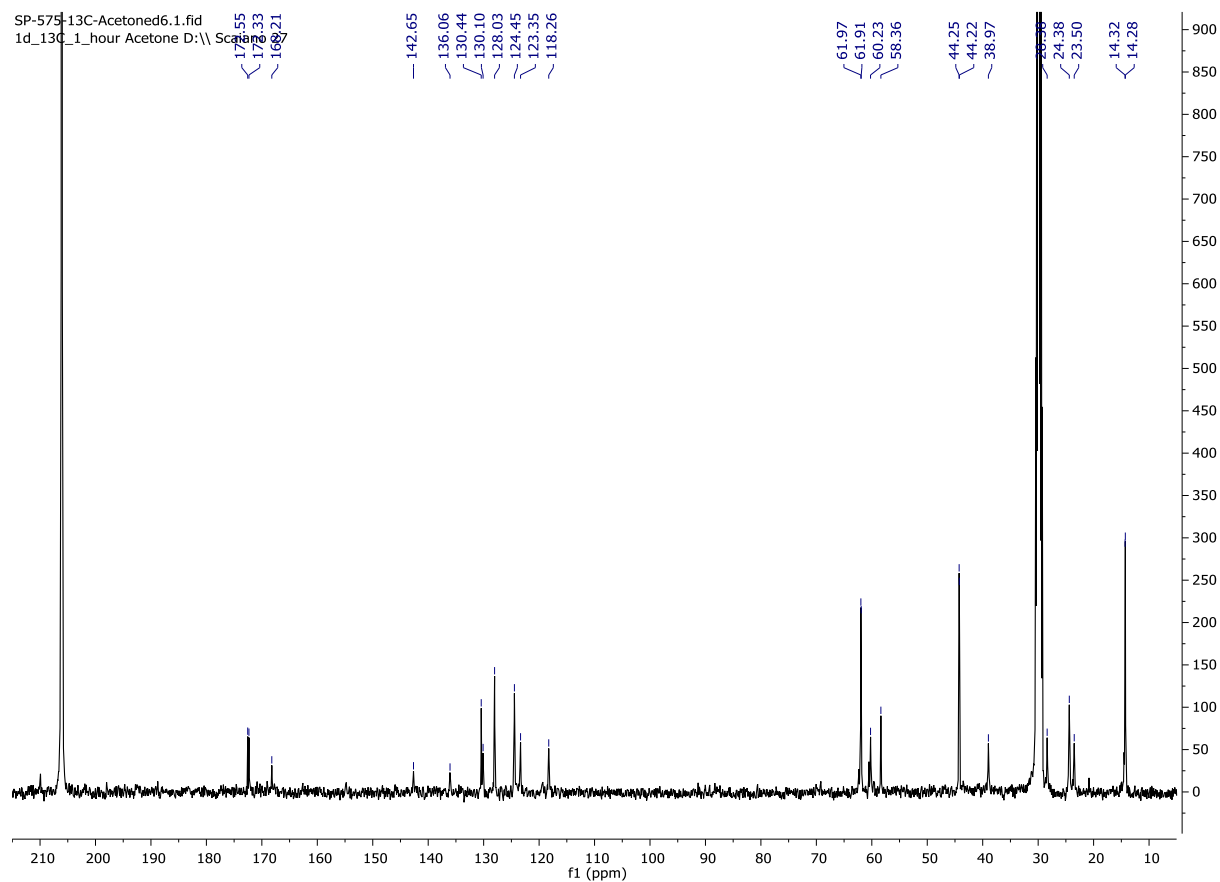
*Endo* ^{13}C NMR

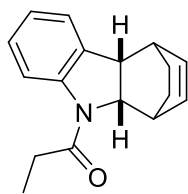


¹H NMR

SP-575-P.1.fid
1H NMR



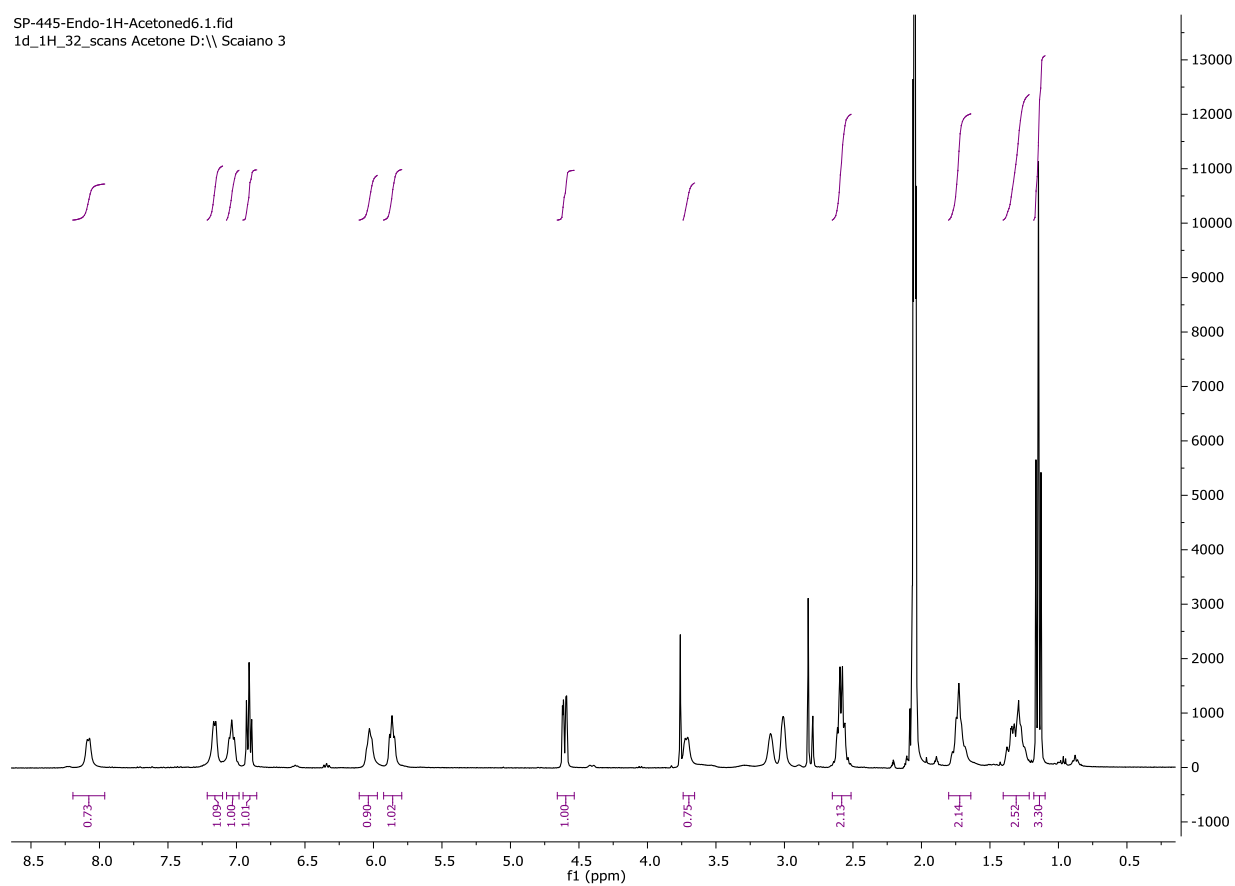
¹³C NMR

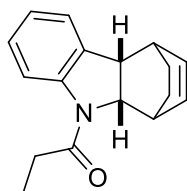
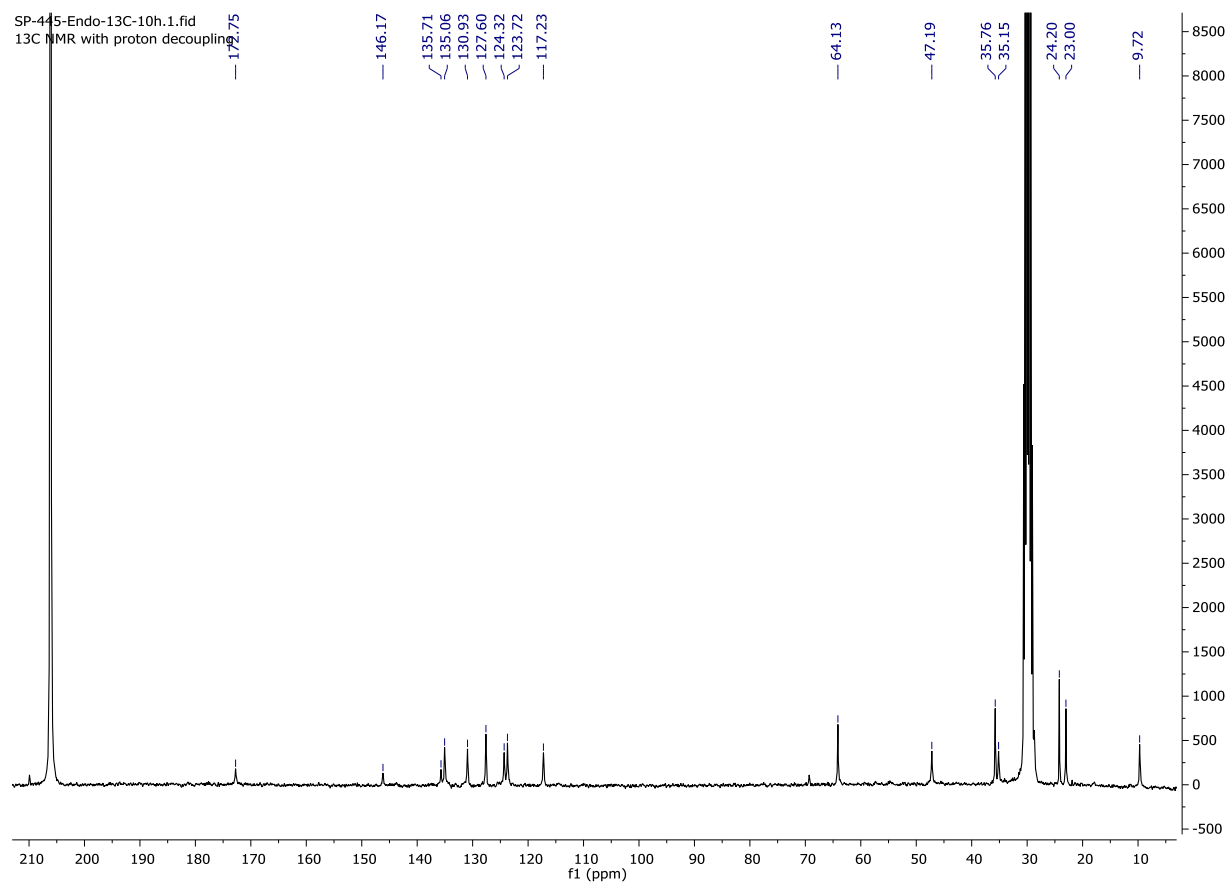


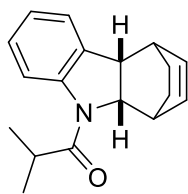
Endo

^1H NMR

SP-445-Endo-1H-Acetoned6.1.fid
1d_1H_32_scans Acetone D:\ Scaiano 3



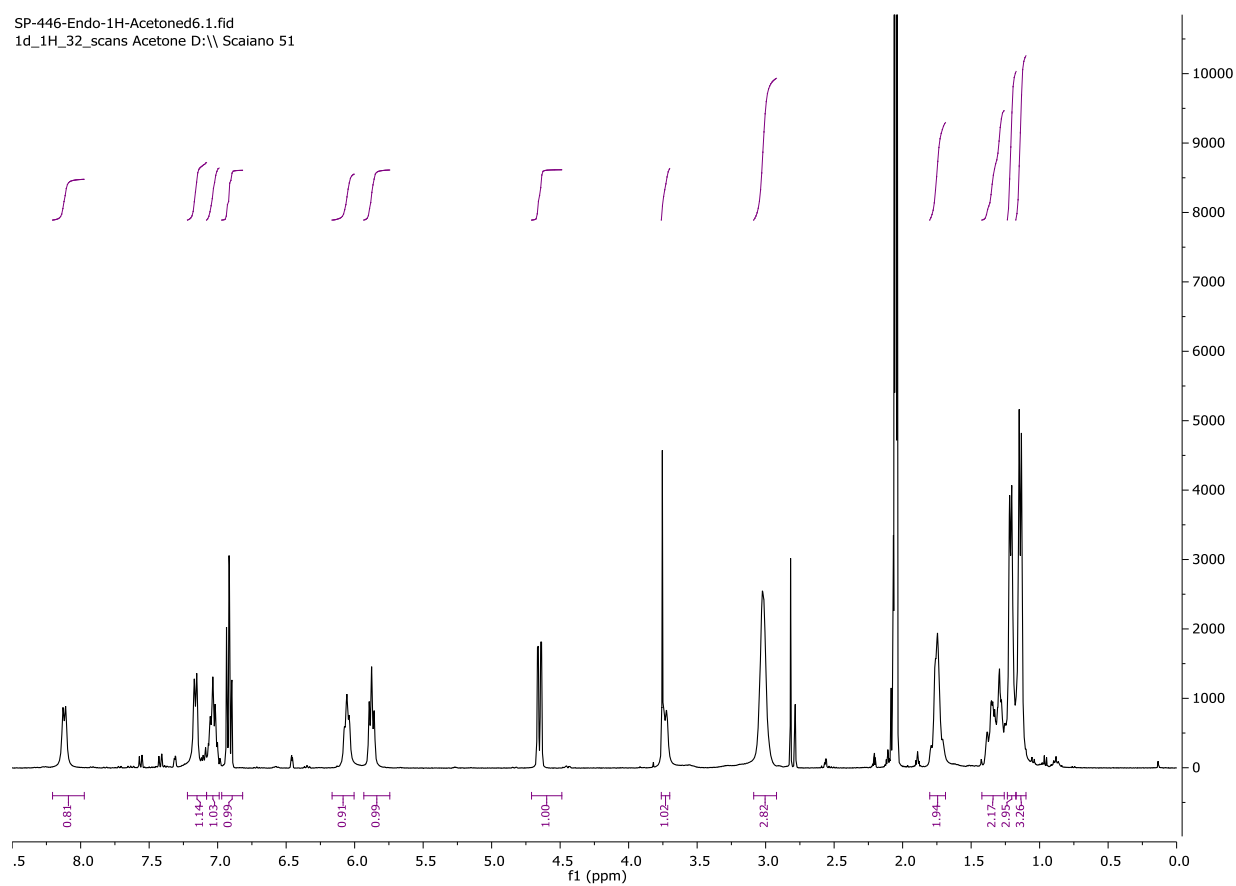
*Endo*¹³C NMR

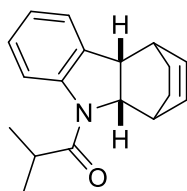


Endo

¹H NMR

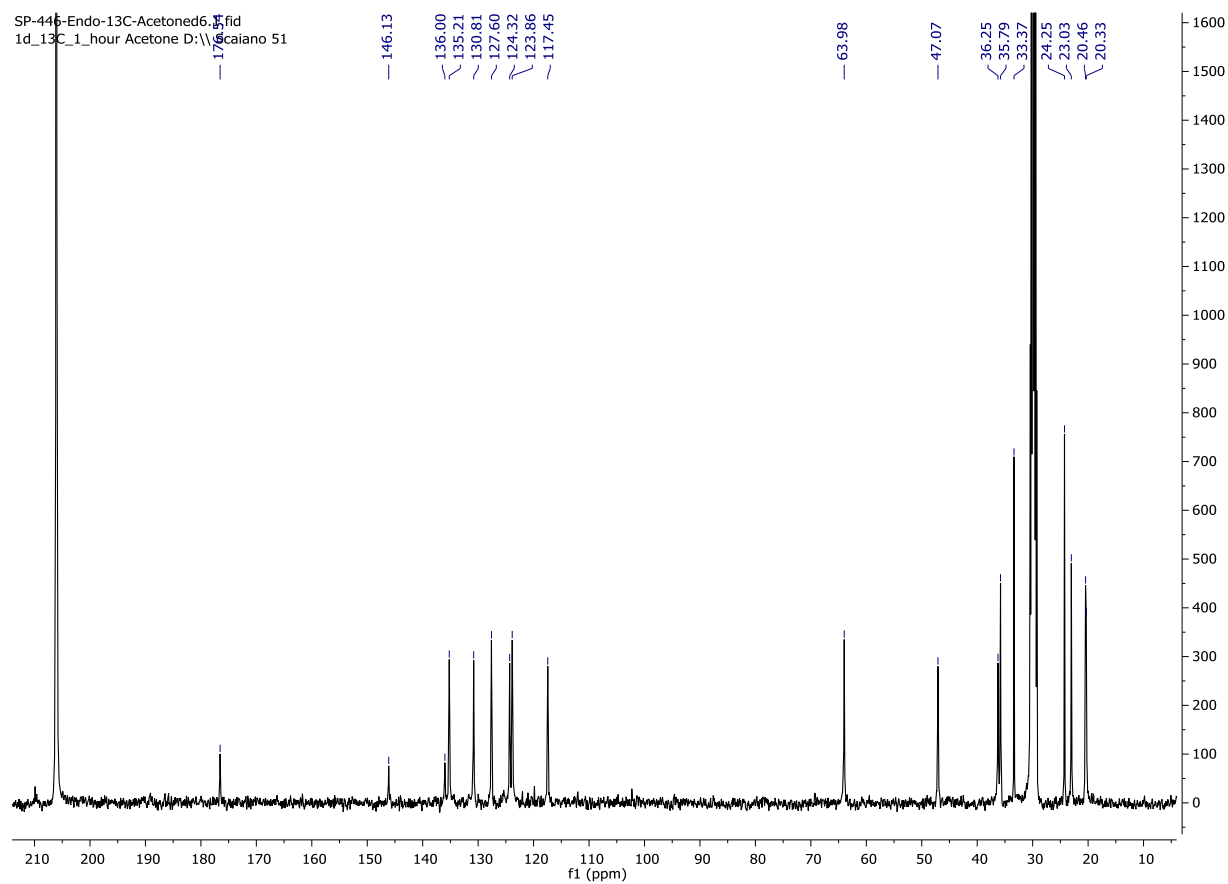
SP-446-Endo-1H-Acetone-d6.1.fid
1d_1H_32_scans Acetone D:\\ Scaiano 51

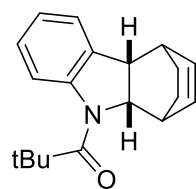




Endo

^{13}C NMR

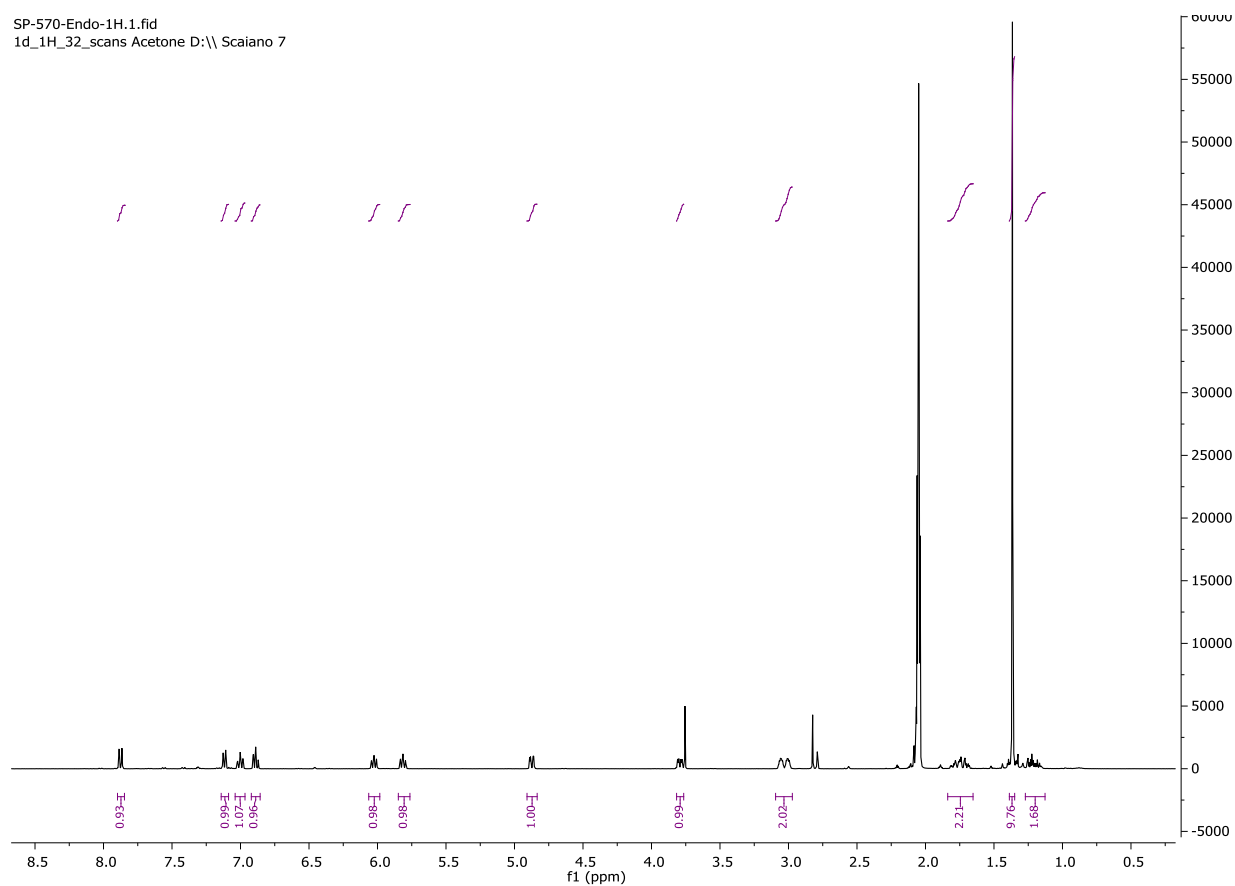


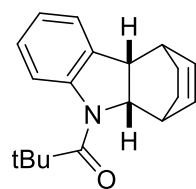


Endo

^1H NMR

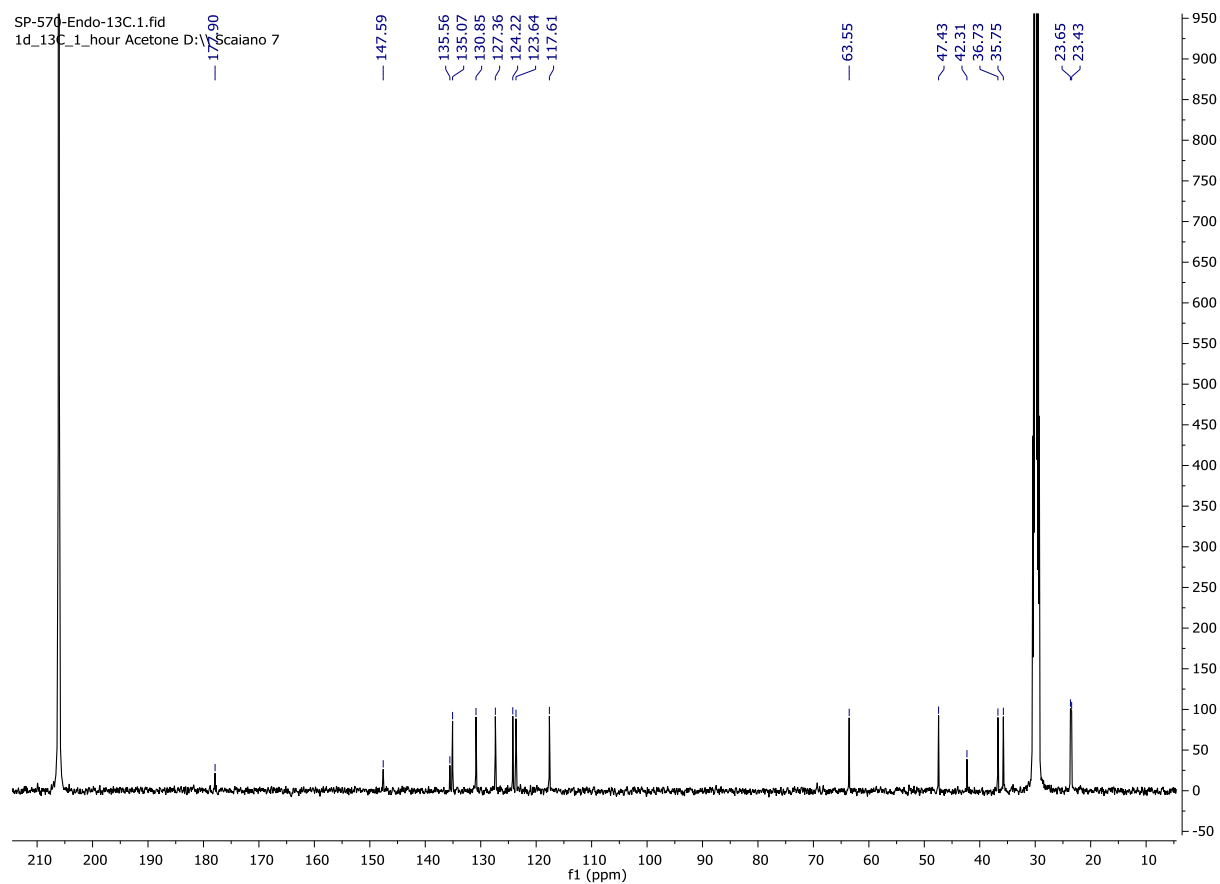
SP-570-Endo-1H.1.fid
1d_1H_32_scans Acetone D: $\backslash\backslash$ Scaiano 7

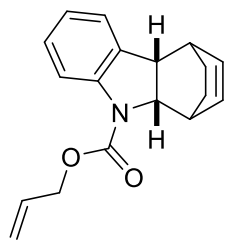




Endo

^{13}C NMR

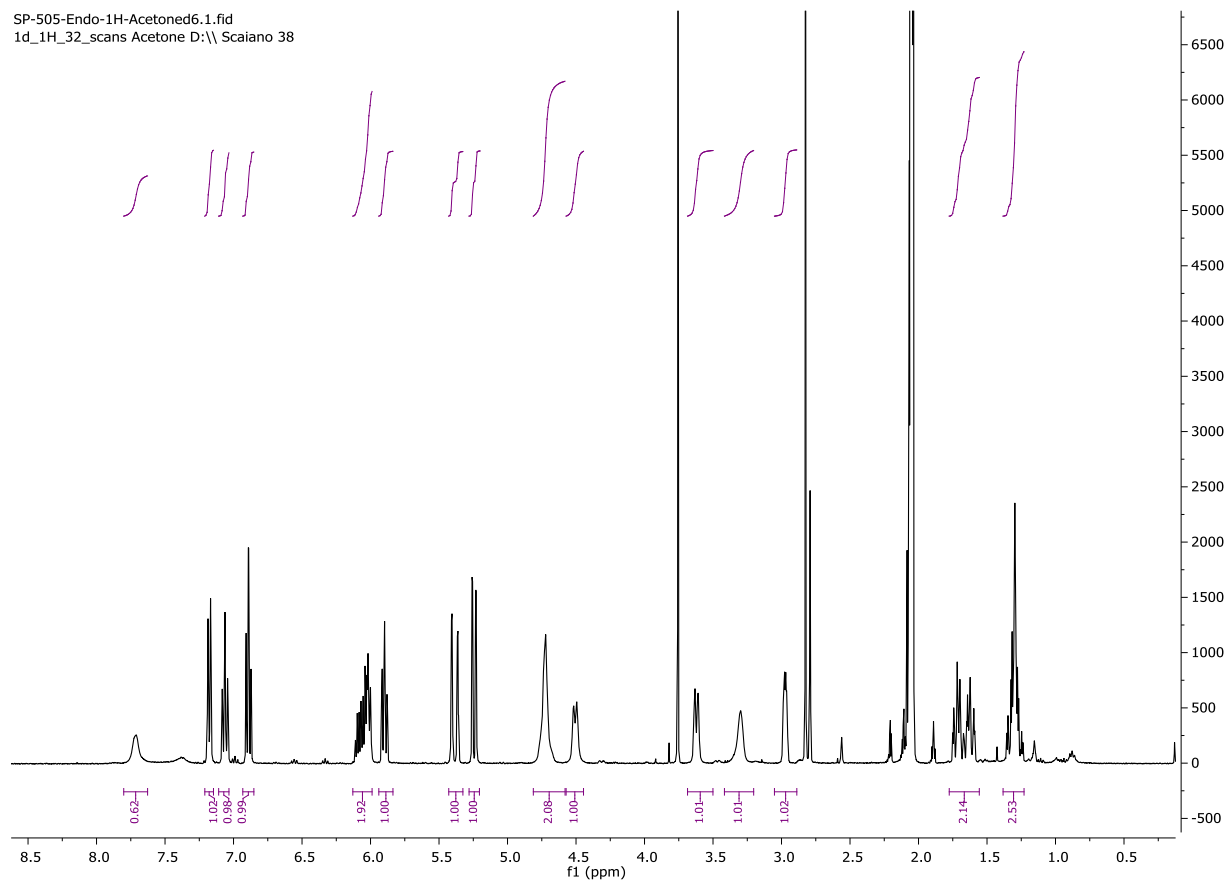


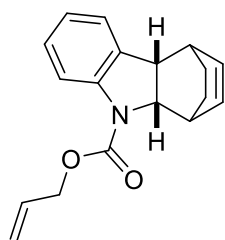


Endo

¹H NMR

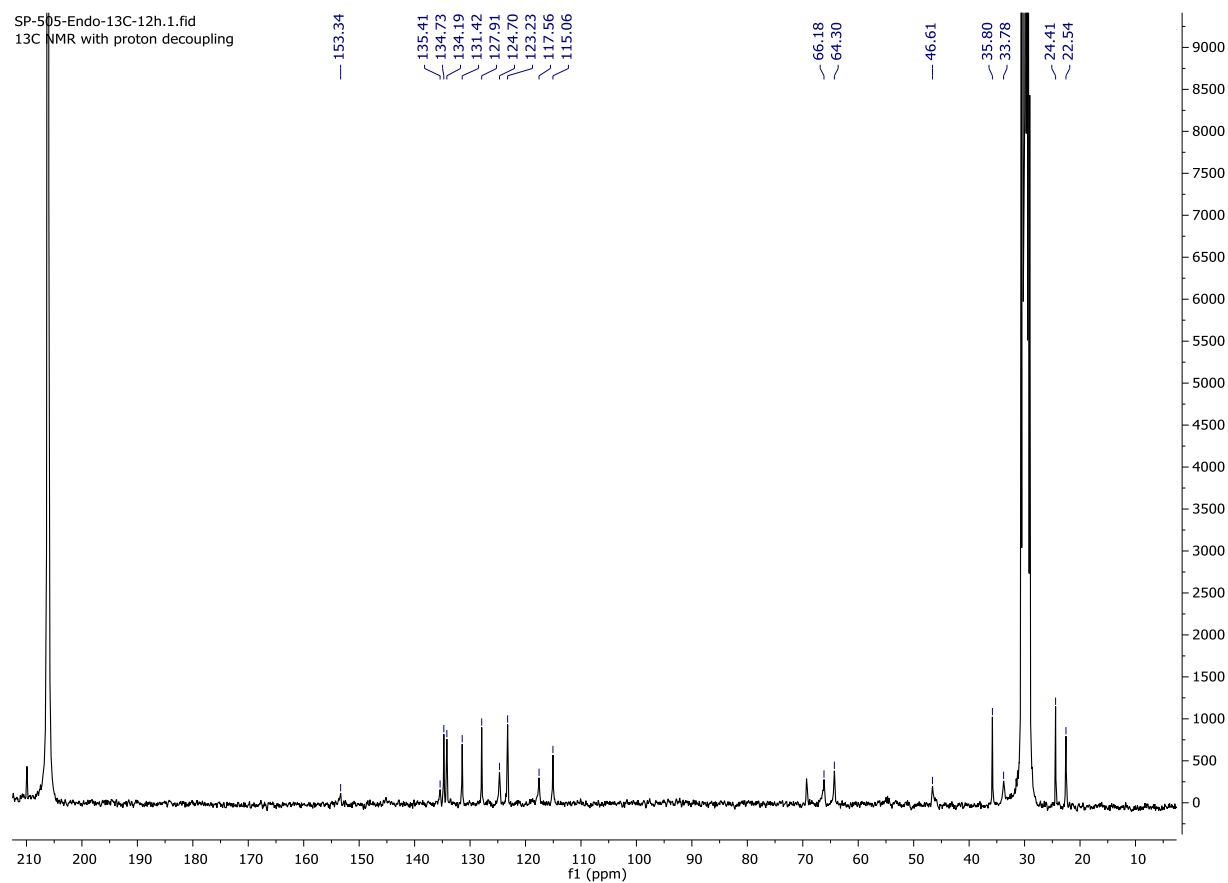
SP-505-Endo-1H-Acetone-d6.1.fid
1d_1H_32_scans Acetone D:\\ Scaiano 38

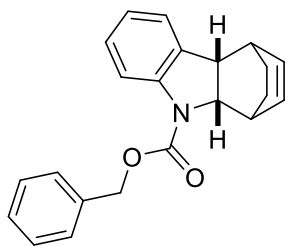




Endo

¹³C NMR

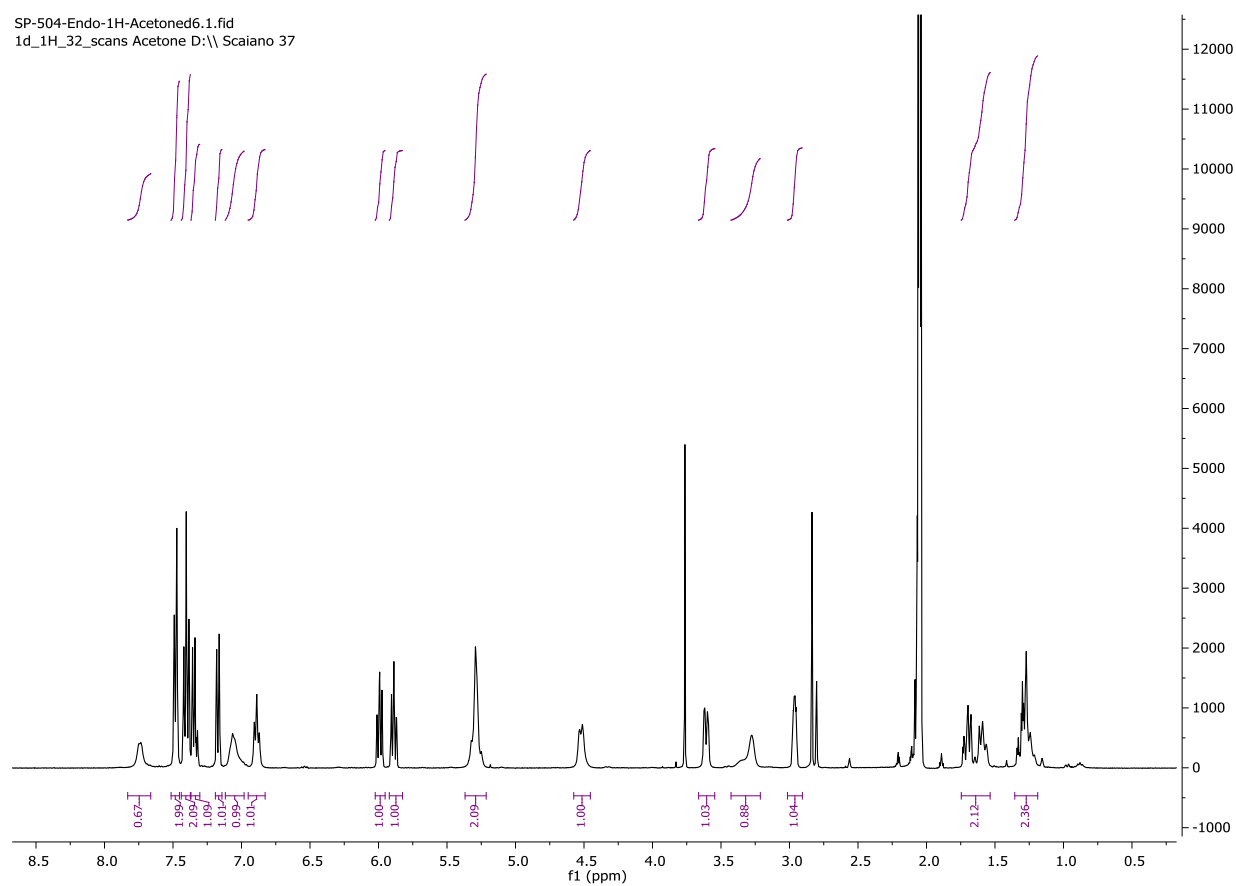


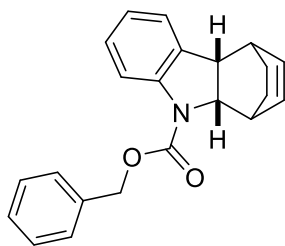


Endo

¹H NMR

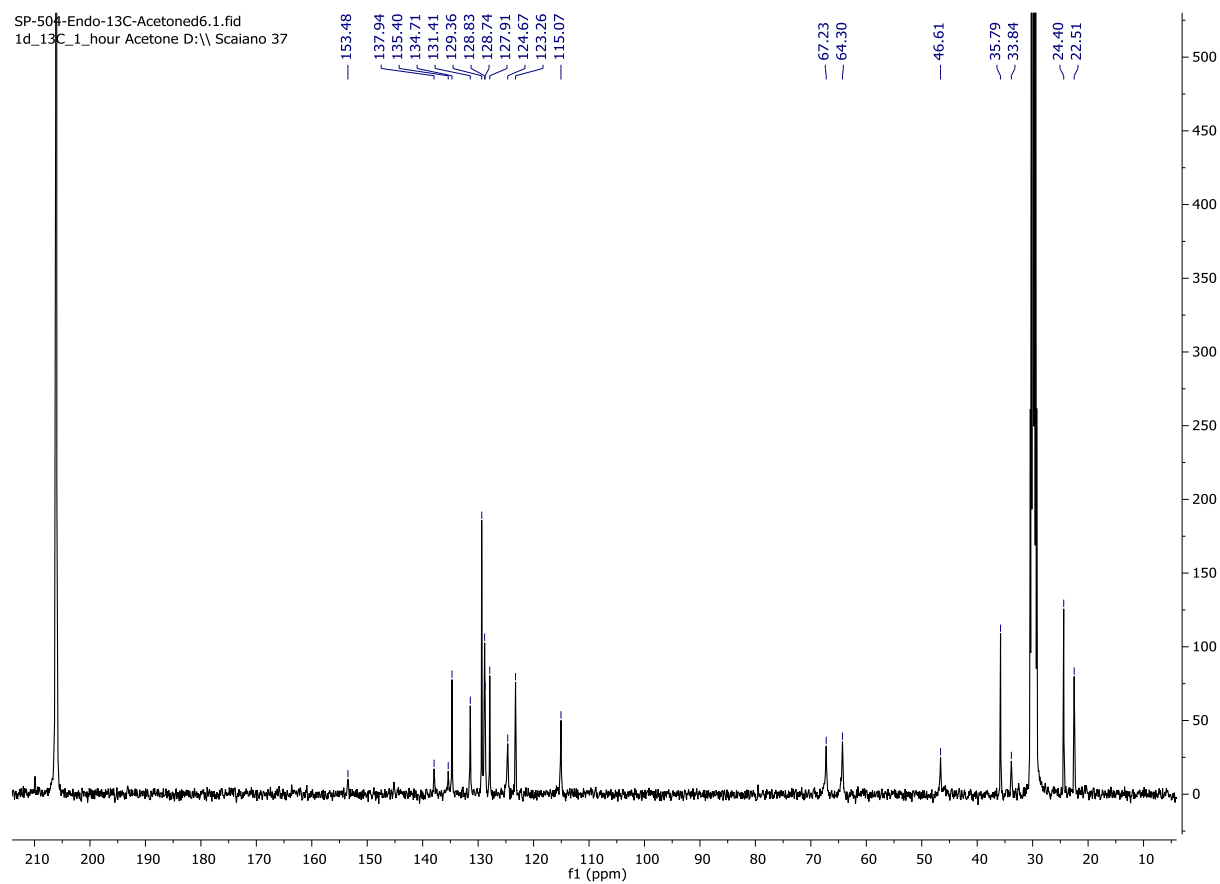
SP-504-Endo-1H-Acetoned6.1.fid
1d_1H_32_scans Acetone D:\\ Scaiano 37

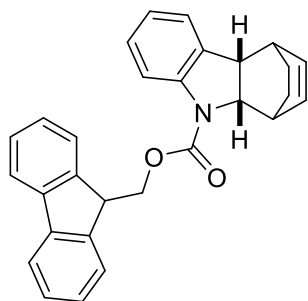




Endo

¹³C NMR

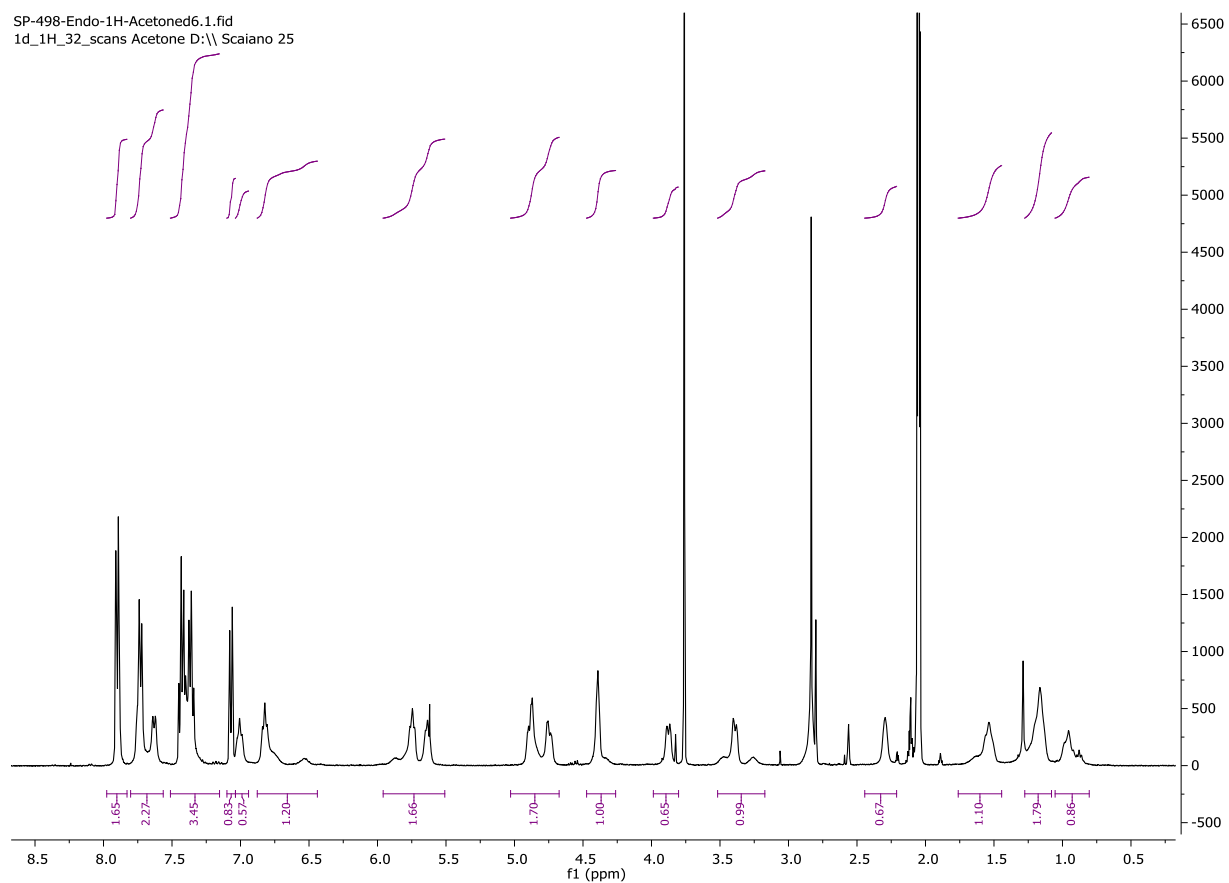


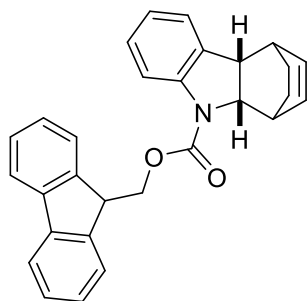


Endo

^1H NMR (25 °C)

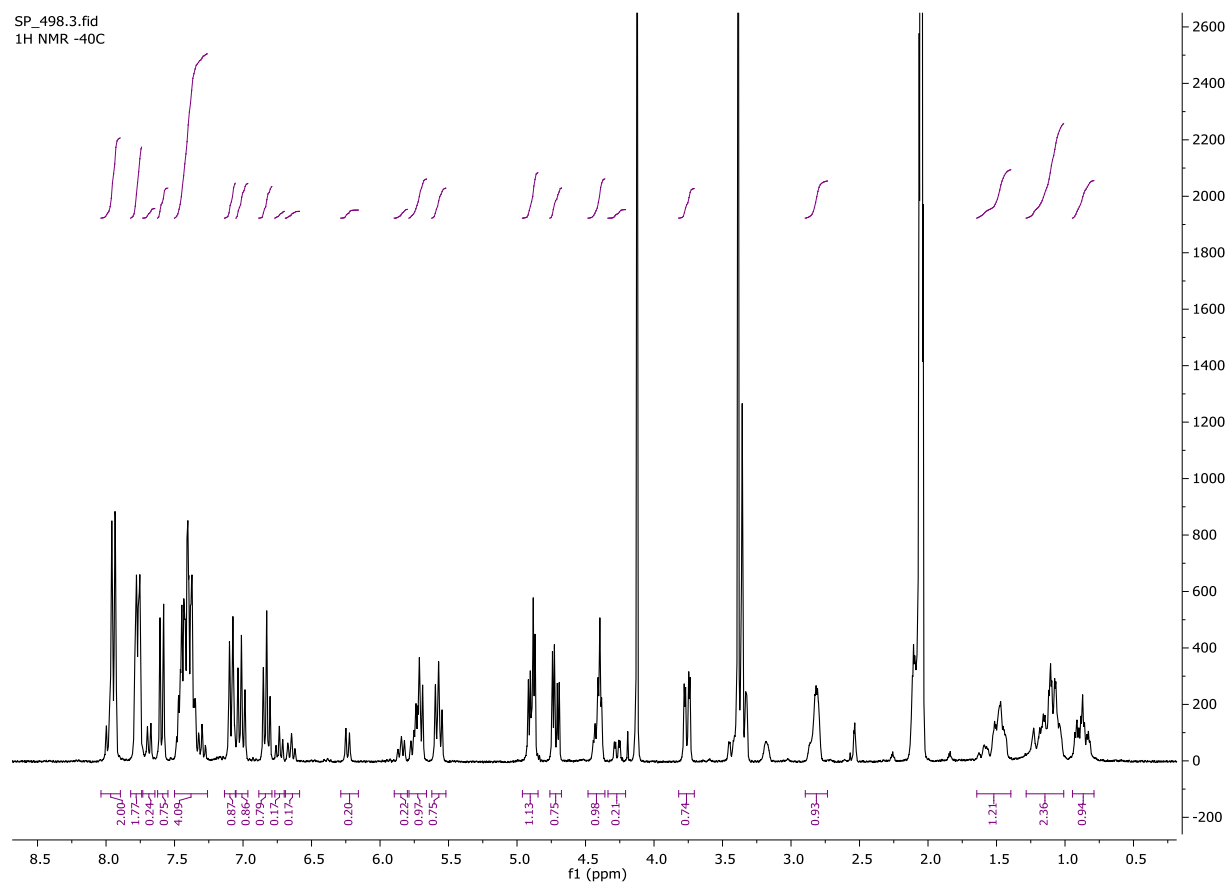
SP-498-Endo-1H-Acetone6.1.fid
1d_1H_32_scans Acetone D:\ Scaiano 25

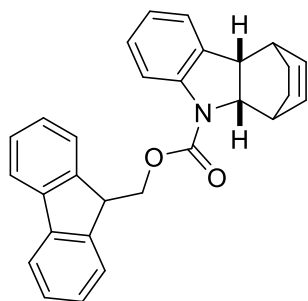




Endo

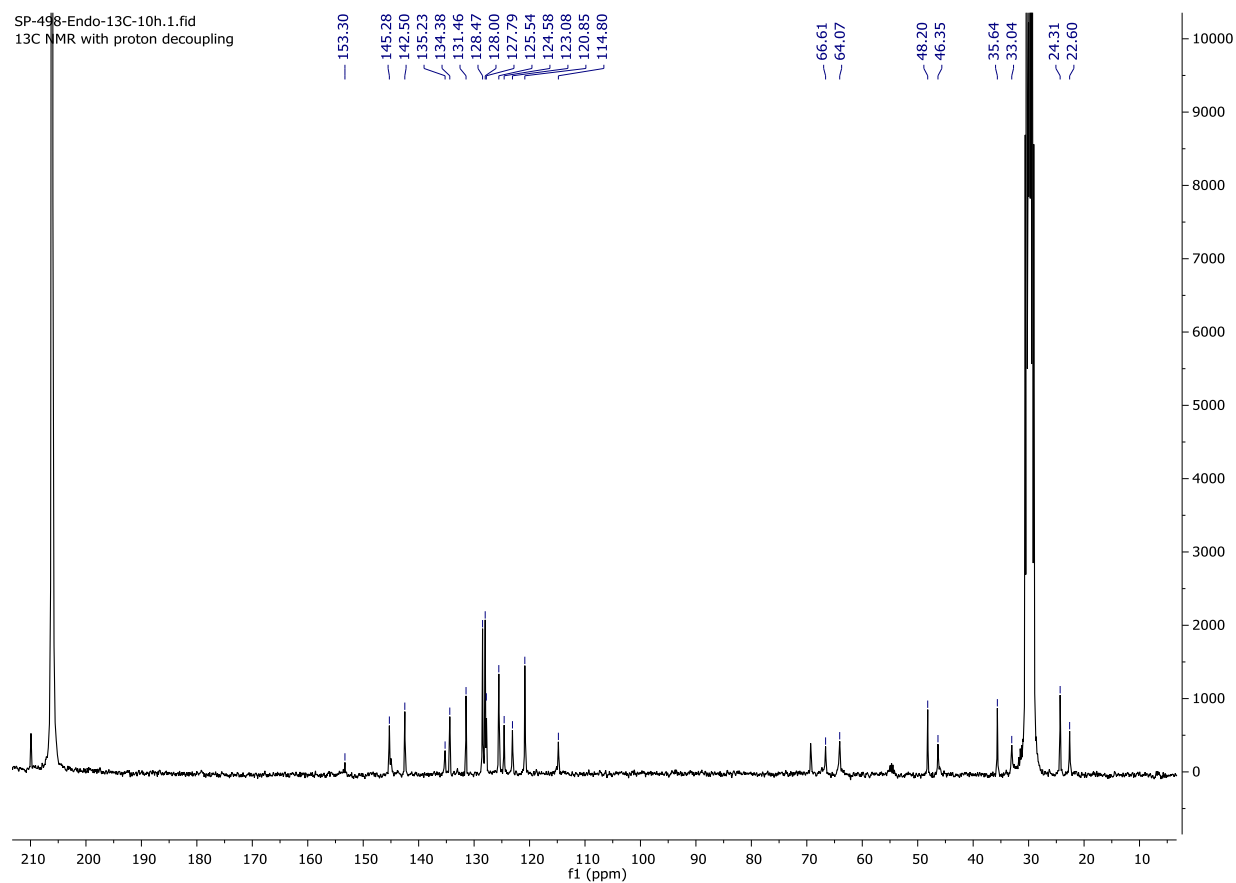
^1H NMR (-40 °C, peaks are doubled due to rotamers)

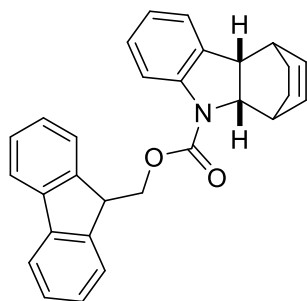




Endo

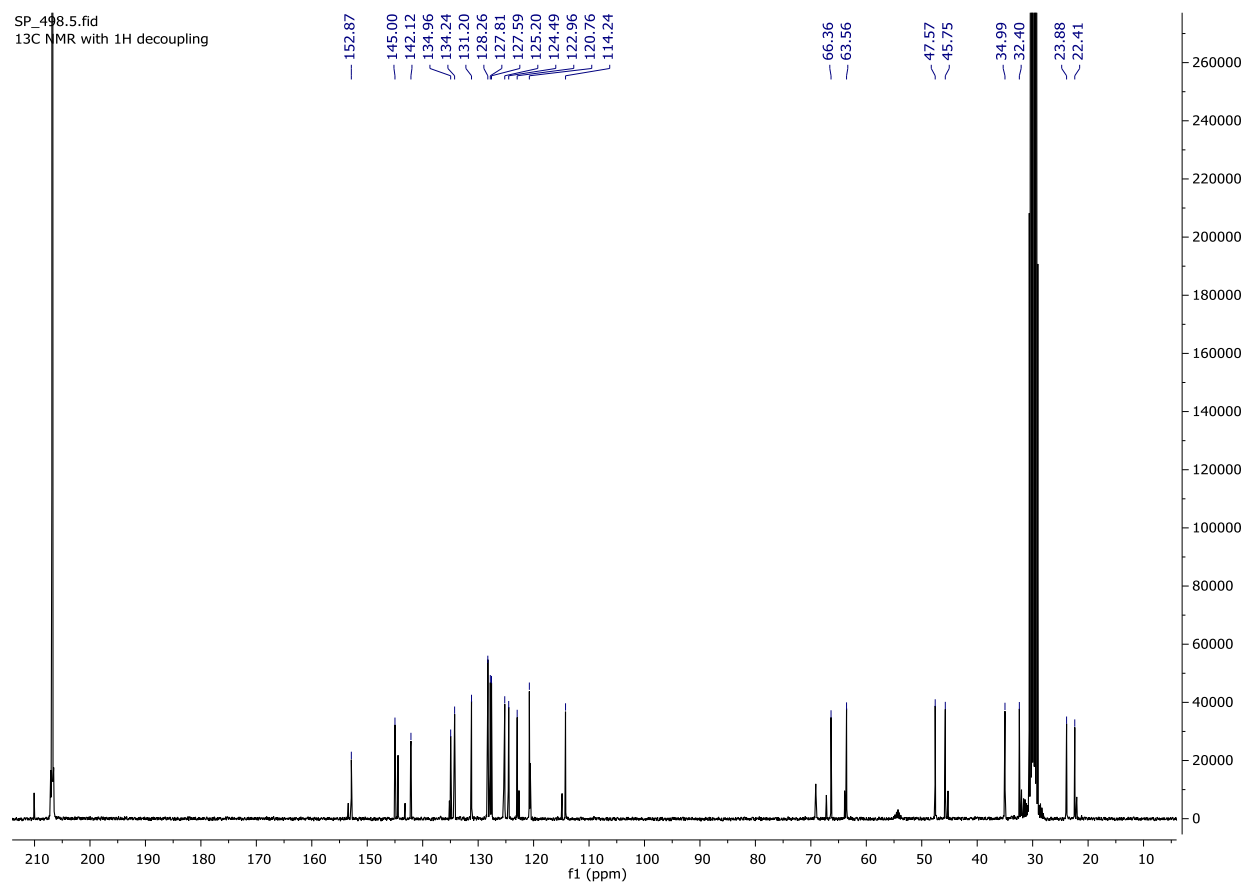
^{13}C NMR (25 °C)

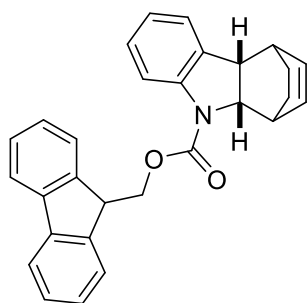




Endo

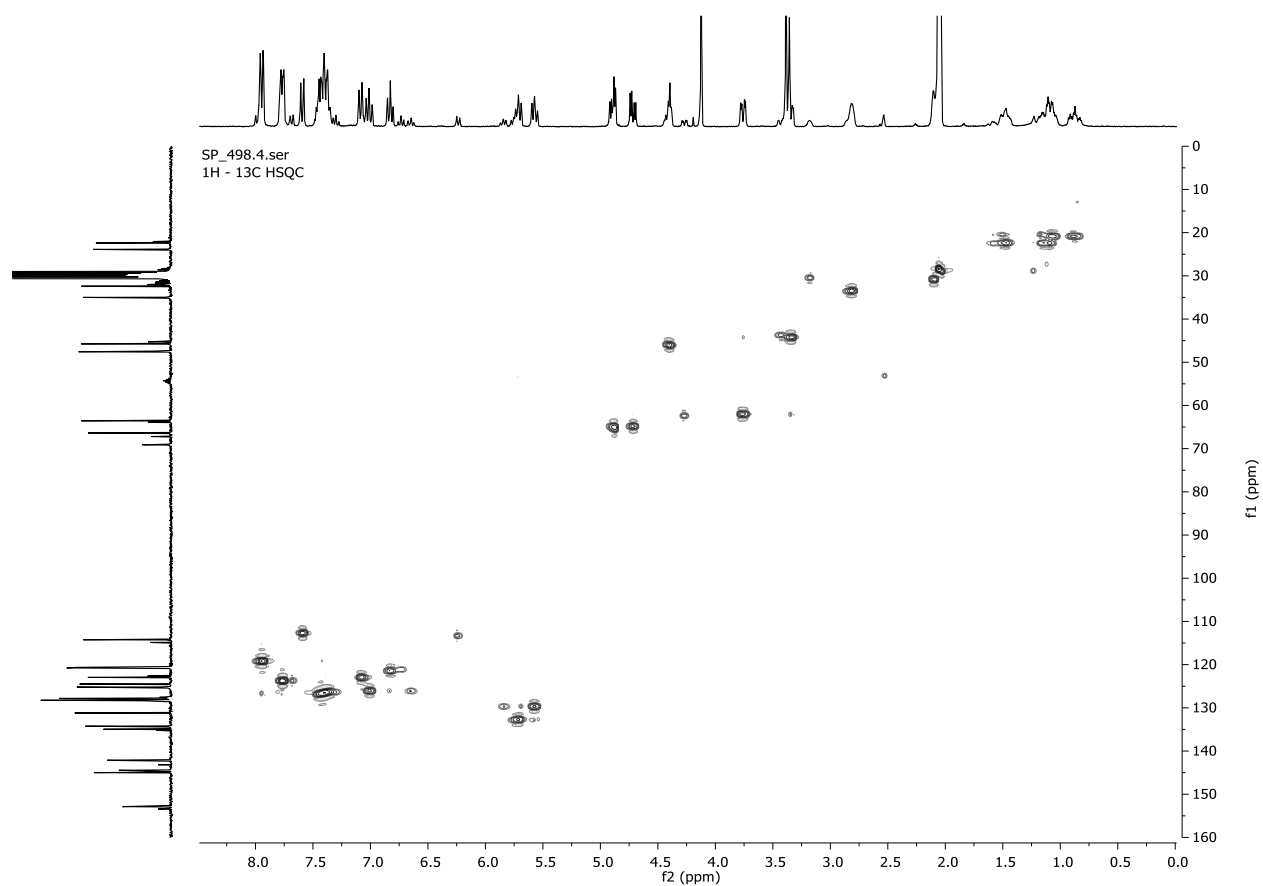
^{13}C NMR (-40 °C, peaks are doubled due to rotamers)

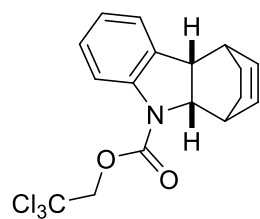




Endo

HSQC (-40 °C)

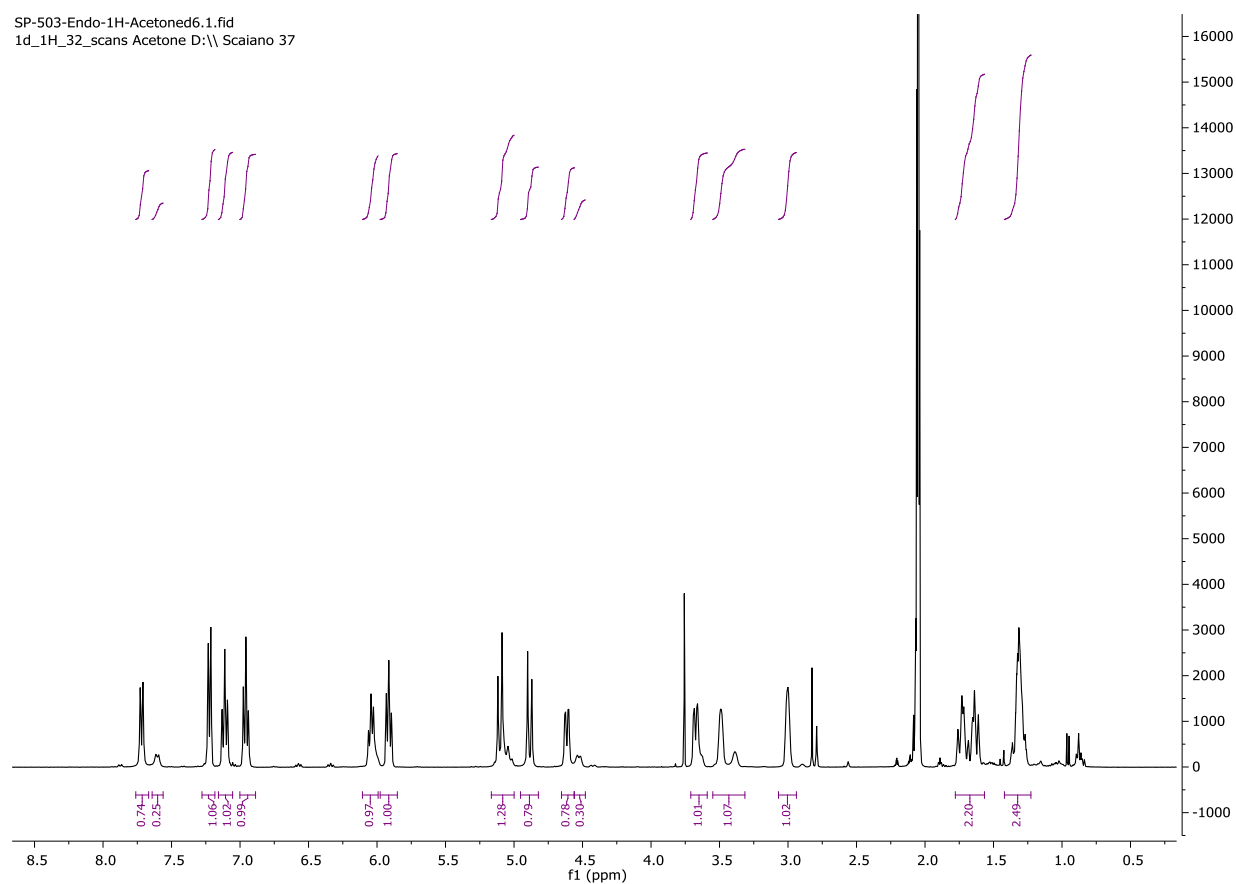


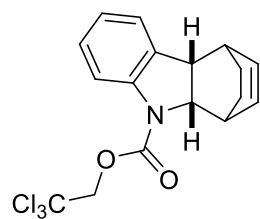


Endo

¹H NMR

SP-503-Endo-1H-Acetoned6.1.fid
1d_1H_32_scans Acetone D:\\ Scaiano 37





Endo

¹³C NMR

