Spring 5-20-2023

# Photoacid-Catalyzed C–C and C–O Bond Formation and the Synthesis of Triazole - Containing Bis(indolyl)methanes

Jason Saway
sawayjas@shu.edu

# *Photoacid-Catalyzed C–C and C–O Bond Formation and the Synthesis of Triazole - Containing Bis(indolyl)methanes*

by

Jason Saway

Advisor: Dr. Joseph Badillo, Ph.D.

Ph.D. Dissertation

Department of Chemistry and Biochemistry

Seton Hall University

South Orange, NJ

2023


College of Arts & Science
Department of Chemistry & Biochemistry

## APPROVAL FOR SUCCESSFUL DEFENSE

Jason Saway has successfully defended and made the required modifications to the text of the doctoral dissertation for the Ph.D. in Chemistry during Spring 2023

## DISSERTATION COMMITTEE

Dr. Joseph Badillo, Mentor Date

Dr. Gregory Wiedman, Committee Member Date

Dr. Cecilia Marzabadi, Committee Member Date

*Dedicated to my grandfather and mother. Los amo siempre*

Table of Contents

***Photoacid-Catalyzed C–C and C–O Bond Formation and the Synthesis of Triazole - Containing Bis(indolyl)methanes***


## Abstract

From photosynthesis to transition metal-type photocatalysts, the conversion of light energy into chemical energy is a fundamental process in chemistry. While photochemistry is not new to the world of science, there has been a renewed interest in the field, specifically with the use of photocatalysts. These catalysts convert light energy to chemical energy to promote chemical reactions. A wide variety of compounds function as photocatalysts, including transition metal complexes, organic dyes, and photoacids. A photoacid is a bench stable compound that upon irradiation becomes a strong acid. This dissertation describes using photoacids to catalyze several reactions including Friedel-Crafts alkylations, acetalizations, and the synthesis of building blocks for triazoles.

Chapter one describes an overview of recent advancements in photoacid catalysis. The overview is organized by different classes of photoacids and photoacid-catalyzed reactions. This includes the synthesis of both C–C and C–X bonds, (X = H,N,O). Chapter two describes the development of synthetic methodology using Schreiner's thiourea as a photoacid for the synthesis of triarylmethanes. The optimized conditions are elucidated for the model reaction and the evaluation of the catalytic activity for a variety of thiourea/urea derivatives is also investigated. In addition, these experiments helped develop the overall proposed photoactivation mechanism for

the photoacid-catalyzed Friedel-Crafts arylation. Finally, this chapter also establishes the chemistry for the parent compounds that are synthesized in chapter four.

Chapter three describes the development of synthetic methodology using 6-bromo-2-naphthol as a photoacid for the synthesis of acetals. The $S_1$ excited-state pKa for 6-bromo-2-naphthol was determined and shows that 6-bromo-2-naphthol exhibits enhanced excited-state acidity relative to 2-naphthol in water. In addition, we are also able to observe that 2-naphthol in the presence of a photosensitizer facilitates the acetalization of electron-deficient aldehydes.

Chapter four blends photochemistry with click chemistry. First the methodology developed in chapter two is used to synthesize parent compounds that contain alkyne functional handles. Afterwards, these parent compounds are then converted to triazoles using copper-catalyzed azide-alkyne cycloaddition (CuAAC) reactions. The goal of the project is to synthesize a triazole library consisting of mono-, bis- and tris-substituted triazoles and to investigate their biological activity.

**Acknowledgements**

Firstly, I'd like to thank God for letting me get to this point in my life. I know without him none of this would've been possible. Secondly, my family for supporting me and letting me pursue my studies and loving me always. I'd like to especially thank my mother and grandfather for instilling in me that education is the only way to separate yourself in this world and it's the only thing that no one can take from you. Thank you to my brother for being there with me whether it was playing video games or going on our adventures. I'd also like to thank my girlfriend, Claire, for supporting me through my Ph.D. career, she always had my back and knew how to keep me going through those late nights I would spend in lab. She always made sure I took time for myself and came up with new experiences for us to enjoy and I love you.

Thank you to my mentor, Dr. Joseph Badillo. From day one you taught me what it meant to be a Ph.D. student and always challenged me to become a better researcher and how to think critically. You showed me that there's always an answer to a question you just have to be willing to put in the work to find it. Thank you for not only making me a better scientist but also helping me realize my potential with each project and conference I went to. Thank you to my readers, Dr. Wiedman and Dr. Marzabadi for not only reading my dissertation but also being my professors and guides during my graduate student career.

Thank you to Maureen Grutt, for not only taking care of me like a son but also helping me find my mentor Dr. Badillo when I first began my Ph.D. journey. Thanks to you I was able to begin my journey as a graduate student and thanks to you I have completed it as well. Thank you to all my professors I have had during my Seton Hall career for teaching me. Thank you to the Educational Opportunity Program (EOP) for helping my through my transition from high school, through undergrad and even grad school.

Thank you to all the people in our research lab especially Zena Salem for helping me first get used to being in a new lab and showing me that organic chemistry isn't so scary lol. Thank you to Daniela Noguera-Urbina and Isaiah Torres for being my friends in and outside of lab. Thank you for the game nights and the adventures we took in New York, and all our Kpot runs lol.

Thank you to my friends Maham Bashir, Lana Hannineh and Patrycja Parafinska, even though you were Claire's friends first lol. You guys are the closest thing I know to a second family. We had a lot of adventures over the two years we spent together. I will never forget all the resturants we went to, the time we went to the zoo for Christmas or especially when we went to Maham's wedding. One special memory I will always remember is how you guys celebrated my birthday and all the little details and planning that went to it. I can't wait to see what the future has for us.

Thank you to my gradute school friends; Josh, Usha, Akilah, Brandon and Edrice for always listening to me vent or just giving me motivation to just keep going. Thank you to my friends outside of lab especially Marcos, Alonso and Manny; you guys have been there with me from undergrad and we still find time to check in on each other and play a game of soccer when we link up.

Thank you to Lambda Sigma Upsilon Latino Fraternity Inc., I became a brother in Spring 2021 and in return they gave me a second family. Thank you especially to the chapter I pledged the Anasazi Chapter and the Almirantes Chapter, the brothers in these chapters have and will always have a special place in my heart. Special thanks to Christian Perez-Colon, Franny Montesino, Grant Macalintal, Devon Hood, Felipe Rosario, Axel Martinez, Julian Rodriguez, Davion Delgado, Ricardo Vargas, Saul Martinez, Michael Georgevich, Jeffrey Heredia.

# List of Abbreviations

| | |
|---|---|
| ACS | American Chemical Society |
| ACN | acetonitrile |
| Å | angstrom |
| δ | chemical shift |
| BINOL | 1,1'-Bi-2-naphthol |
| BIM | bis(indolyl)methane |
| Bn | benzyl |
| Bp | boiling point |
| *c* | concentration (g/100 mL) |
| cat. | catalyst (catalytic amount) |
| CuAAC | copper-catalyzed azide-alkyne cycloaddition |
| DCM | dichloromethane |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| d | doublet |
| eq | equation |
| equiv | equivalents |
| ESI | electrospray ionization |
| Et | ethyl |
| ESPT | Excited State Proton Transfer |
| EtOAc | ethyl acetate |
| FTIR | Fourier-transform infrared spectroscopy |

| | |
|---|---|
| $F_2$Irpic | {bis[2-(4,6-difluorophenyl) pyridinato-$C^2$,*N*](picolinato) iridium (III)} |
| Δ | Heat |
| h | Hour |
| HOTf | triflic acid |
| HRMS | high resolution mass spectrometry |
| hν | Light |
| Hz | Hertz |
| IPA | isopropyl alcohol |
| *i-Pr* | Isopropyl |
| IR | infrared (spectrum) |
| *J* | coupling constant (in Hz) |
| LRMS | Low Resolution Mass Spectrometry |
| Me | Methyl |
| min | Minutes |
| mol | Mole |
| Mp | melting point |
| MS | molecular sieves |
| *m/z* | mass to charge ratio |
| NMR | Nuclear Magnetic Resonance |
| OTf | triflate (also trifluoromethylsulfonate) |
| Ph | Phenyl |
| ppm | parts per million |
| rt | room temperature |

| | |
|---|---|
| RCS | Royal Society of Chemistry |
| s | singlet |
| TEA | Triethylamine |
| TET | Triplet Energy Transfer |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin-layer chromatography |
| TMS | Trimethylsilyl |
| t | triplet |
| Ts | tosyl |

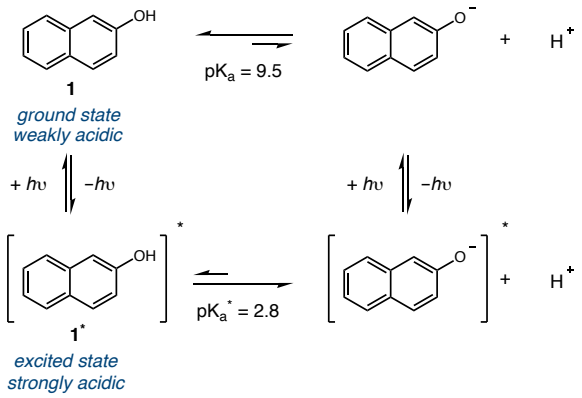
## *Chapter 1: Advances in photocatalysis*

# I. Introduction

Since Förster and Weller's first studies[3,4] the phenomena of photoacidity has been thoroughly investigated.[5] Photoacids are typically grouped into two categories: Photoacid generators (PAGs) and photoacids (PAHs). A PAH recombines with a proton and returns to its previous state without being destroyed, but a PAG experiences irreversible, proton dissociation upon irradiation, creating a strong acid and frequently leading to photoinduced destruction of the parent molecule. This chapter outlines many reaction classes that PAH-type photoacids have facilitated.

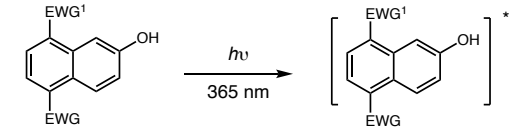
Aromatic alcohols such as phenols, naphthols, and pyrenols serve as prototypical photoacids. Tolbert and colleagues demonstrated that 2-naphthol (**1**) became $10^7$ times more acidic when exposed to 365 nm light over the course of one day (Scheme 1A). [6]

**Scheme 1A**: Photoacidic behavior of 2-naphthol.




The lifespan of this excited-state species is about 9 ns. Surprisingly, the presence of electron-withdrawing groups not only modifies excited-state durations and red shifts maxima, but also significantly enhances excited-state acidity (pKa*) (Scheme 1B).

**Scheme 1B**: Substituent effects on naphthol.



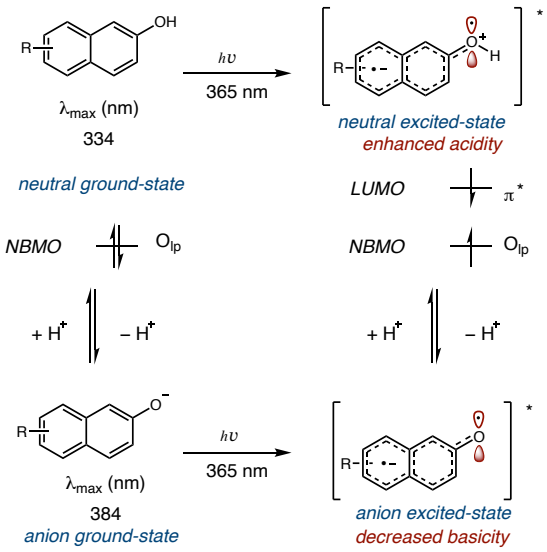

| EWG | EWG$^1$ | $\lambda_{max}$ (abs) | $\tau$ (ns) | $pK_a$ ($H_2O$) | $pK_a^*$ ($H_2O$) |
|---|---|---|---|---|---|
| H | H | 334 nm | 9 | 9.5 | 2.8 |
| CN | H | 337 nm | 3 | 8.8 | –1.2 |
| CN | CN | 351 nm | 12 | 7.8 | –4.5 |

2 CN > CN > H

***decreased $pK_a^*$ and increased $\lambda_{max}$***

The reason for the enhanced acidity of naphthol upon photoexcitation can be rationalized by considering Hückel molecular orbital theory (Scheme 2).

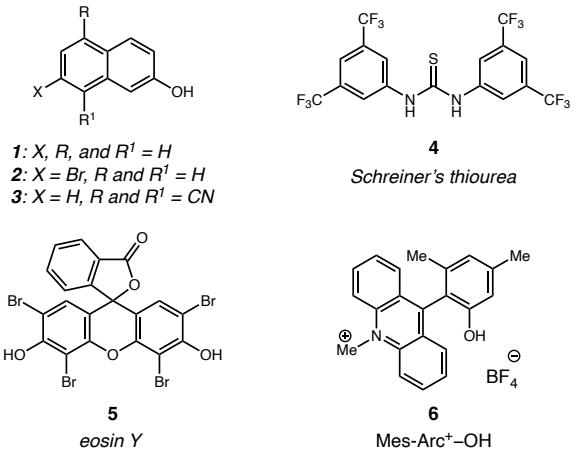
**Scheme 2**: Photoexcitation of 2-naphthol.




In the following scheme, photoexcitation removes one-electron from the nonbonding molecular orbital (NBMO) on oxygen and places it in the lowest unoccupied molecular orbital (LUMO), which is generally not located on oxygen. This charge redistribution results in an "intramolecular charge transfer state," which leads to increased acidity at oxygen.[6-8] The creation of novel photoacid catalysts is a fascinating topic of study due to the modularity of the photoacid

architecture and the effects structural modifications have on a photoacid's photophysical characteristics. The following figure displays a few of the photoacids covered here (Figure 1).

**Figure 1**: Representative structures of photoacid catalysts.

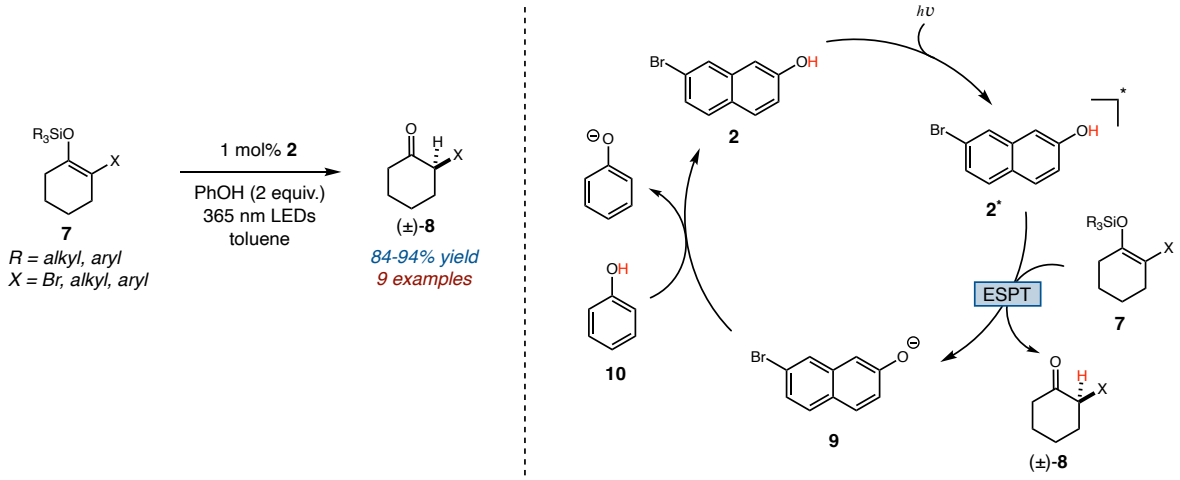



These compounds are typically bench stable weak acids in their ground state and only become strong acids upon light absorption. Even though many of the catalysts mentioned in this study have a $\lambda_{max}$ in the UV range (i.e. **1-4**), visible light can also be used to trigger photoactivity.

## II. Protonation

The control of hydrogen, the smallest element in nature, is a persistent problem in organic synthesis. While there are several sophisticated methods for the selective delivery of a proton,[9] photoacids have only lately been used to catalytically protonate substrates for chemical synthesis. In 2016, Hanson and co-workers showed that naphthols function as excited-state proton transfer (ESPT) catalysts for the protonation of a range of alkyl- and aryl-substituted enol silanes **7** to provide access to racemic α-substituted cyclohexanones **(±)-8** (Scheme 3).[10]

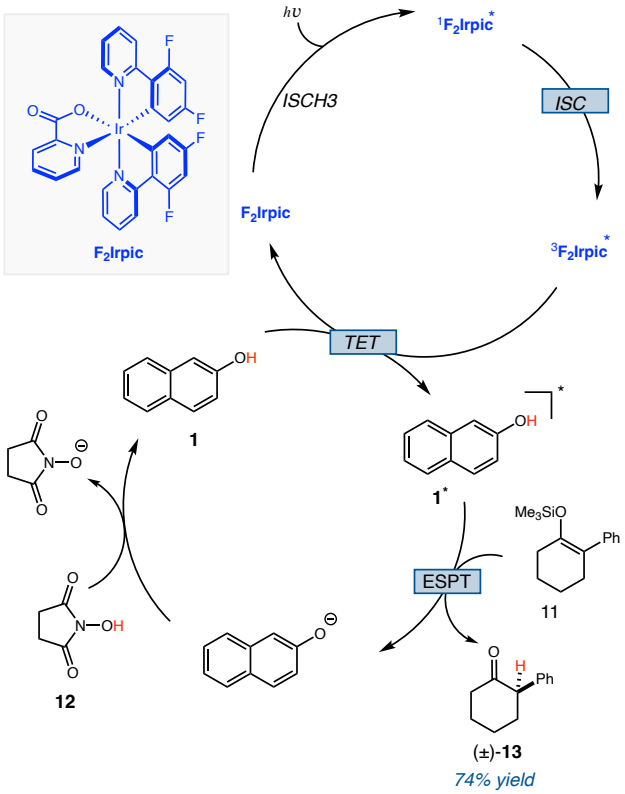
**Scheme 3**: Excited-state proton transfer catalysis using naphthol.




When 7-bromo-2-naphthol (**2**) is photoirradiated with 365 nm light, **2*** is created. **2*** is sufficiently acidic to protonate enol silane **7** and produce product **(±)-8**. After relaxation, deprotonated ground state catalyst **9** is sufficiently basic to deprotonate phenol **10**, regenerating the photoacid catalyst. The resultant phenoxide ion, PhO-$SiR_3$, is responsible for trapping the released silyl group. The heavy atom impact of bromine allows for quick intersystem crossing (ISC) into a long-lived triplet excited-state ( > 10 ms), which gives the enol silane and the excited-state catalyst enough time to engage in a bimolecular, diffusion-limited protonation process.[11]

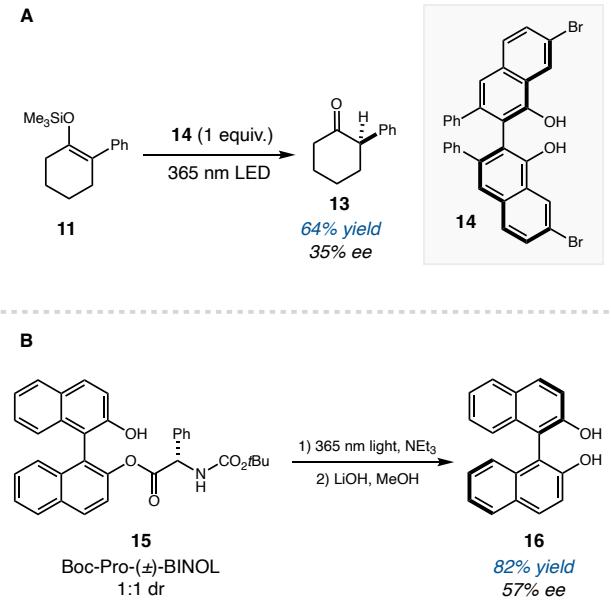
In the presence of an oxygen atmosphere, the reaction efficiency drops to 32% yield, while under nitrogen atmosphere the reaction yield is 96%. The catalyst's triplet excited-state being quenched by oxygen is the cause of this drop in its yield. The reaction is light-dependent; modulation between light and dark conditions show that the reaction only progresses under light irradiation. It's interesting to note that irradiating 50 mol% 2-naphthol (**1**) with 2 mol% photosensitizer **$F_2$Irpic** {bis[2-(4,6-difluorophenyl) pyridinato-$C^2$,*N*](picolinato) iridium (III)}, facilitates ESPT with 1-phenyl-2-(trimethylsiloxy) cyclohexene (**11**) using *N*-hydroxysuccinimide (**12**) as a sacrificial proton source to afford **(±)-13** in 74% yield (Scheme 4).[10]

**Scheme 4**: Photoacid protonation of enol silanes via triplet energy transfer.




Studies on emission quenching show that the triplet energy transfer (TET) between **1** and $^3$**F$_2$Irpic**$^*$ is efficient (~65%). The Hanson Lab went on to show that chiral naphthol-derived photoacids participate in enantioselective ESPT with enol ethers. Direct excitation of stochiometric (*R*)-3,3′-dibromoVANOL (**14**) facilitates the enantioselective protonation of enol silane **11** to give **13** in 64% yield, with 35% ee (Scheme 5A).[12] Due to BINOL's propensity to photoracemize under ESPT circumstances, the poor enantioselectivity for this transition was noted.[13] The Hanson Lab has exploited the photoracemization of BINOL to access enantioenriched biaryls (Scheme 5B).[14]

**Scheme 5A**: Enantioselective ESPT, **5B** Photoisomerization of BINOL.

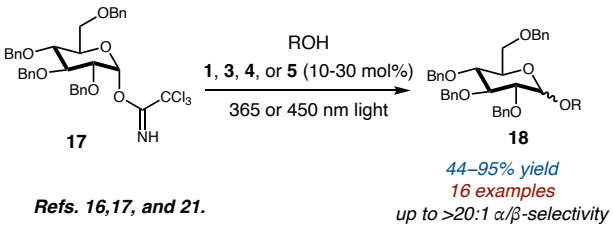



Selective mono-incorporation of a chiral auxiliary group onto one of the two alcohols of BINOL followed by light irradiation results in a diastereomeric, photostationary equilibrium that is dependent on the nature of the chiral auxiliary. Irradiation of Boc-Pro-(±)-BINOL (**15)** with 365 nm light followed by auxiliary cleavage gives enantioenriched BINOL (**16**) in 82% yield and 57% ee.

## III. Glycosylation

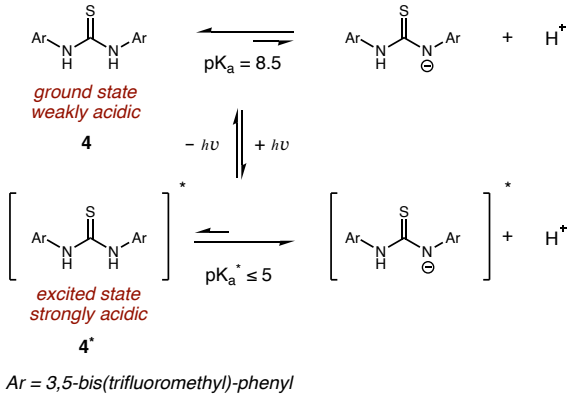
Due to the significance of glycomolecules in biology, several synthetic techniques have been developed to access them. [15] In 2014 and 2016, Toshima and co-workers demonstrated that photoirradiation of 30 mol% 2-naphthol (**1**) or Schreiner's thiourea (**4**) with long-wave UV light (365 nm) facilitates the glycosylation of alcohols with α-glucosyl trichloroacetimidates **17** to form the corresponding glycosides **18** (Scheme 6A).[16,17]

**Scheme 6A**: Glycosylation of alcohols using Schreiner's thiourea.




This is the first report of a thiourea acting as a photoacid catalyst, despite the fact that research on hydrogen bonding catalysts like ureas and thioureas has been intensive.[18] Thiourea **4** has a ground state pKa of 8.5 in dimethyl sulfoxide; nevertheless, it is proposed that with photoactivation, the excited state **4*** becomes $10^3$ times more acidic ($pK_a^* \leq 5$) in order to activate glucosyl trichloroacetimidate **17** (Scheme 6B).[20]

**Scheme 6B**: Photoactivation of Schreiner's thiourea.

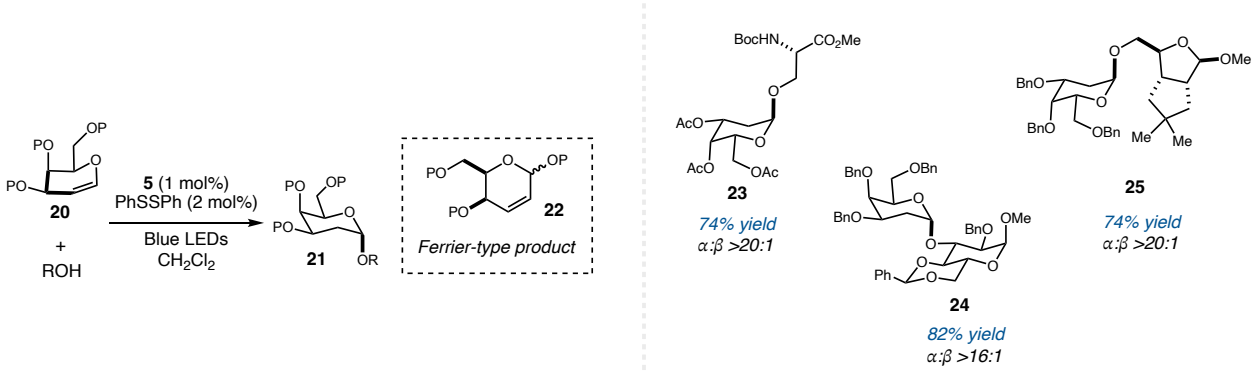



It's significant to note that by adjusting the reaction concentration, the thiourea photoacid catalyst **4**'s α/β-selectivity for glycosylation can be regulated. High levels of β-selectivity are obtained under high concentrations of substrate, whereas high levels of α-selectivity are obtained in low substrate concentrations.

Thiourea **4** and naphthol **1** are two examples of photoacid catalysts that may be recovered and reused in further processes without losing effectiveness. It should be noted that the catalyst

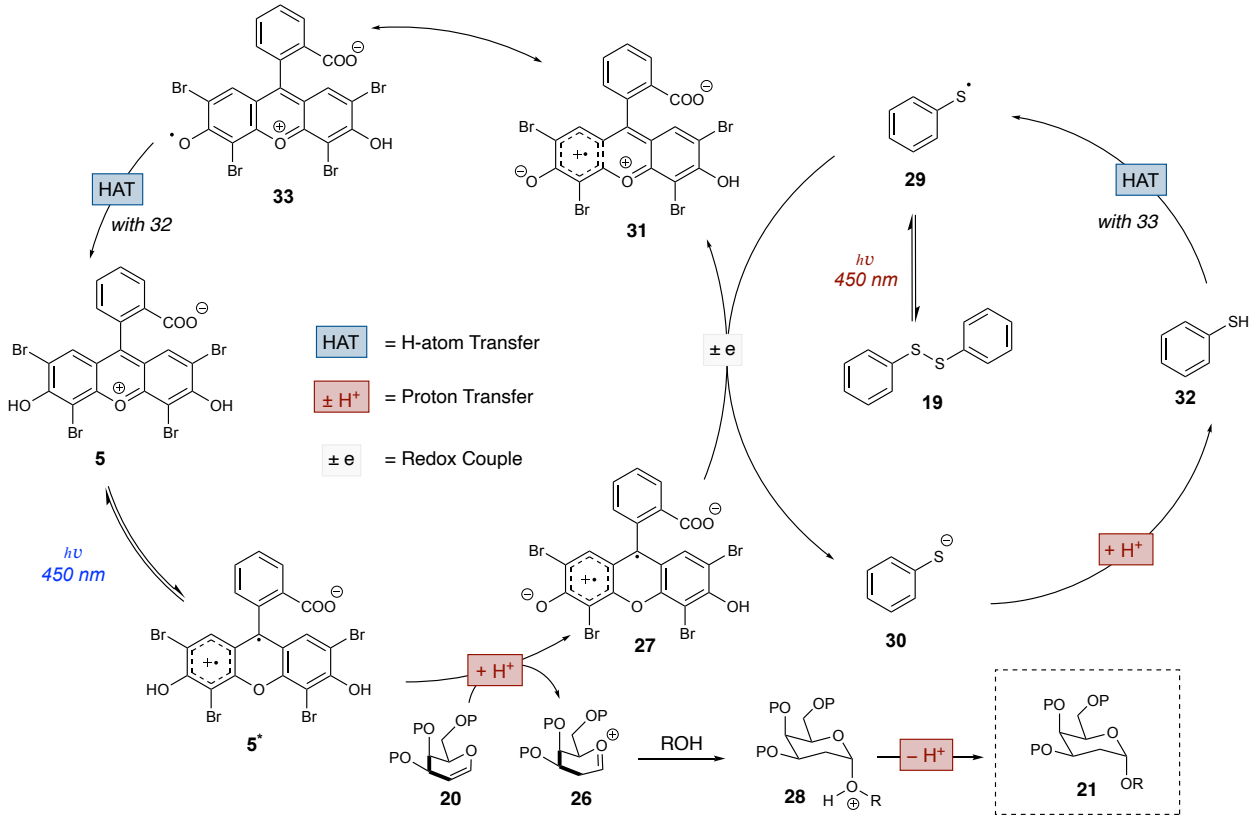
loading can be reduced to 10 mol% by employing the more acidic photoacid catalyst 6-hydroxynaphthalene-1,4-dicarbonitrile (**3**). In a subsequent report, Ni and co-workers showed that irradiation of 20 mol% Eosin Y (**5**) with visible light, 450 nm LEDs, also facilitates the glycosylation of alcohols with α-glycosyl trichloroacetimidates, although the α/β-selectivity is low (α:β ≈ 1:1).[21] The Wang Group has shown that photoirradiation of 1 mol% **5** in combination with 2 mol% diphenyl disulfide (**19**) additive, facilitates the α-stereoselective synthesis of 2-deoxyglycosides **21** from a variety of protected glycal donors **20** with a range of alcohol acceptors (Scheme 7).[22–24]

**Scheme 7**: Synthesis of 2-deoxyglycosides using Eosin Y.



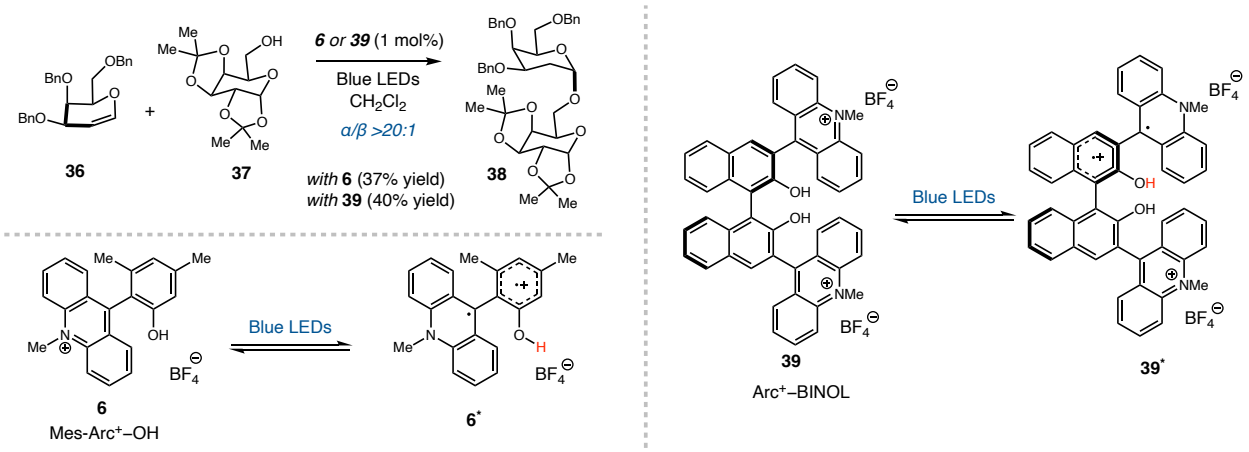

This photoacid-catalyzed technique is significant in that it prevents the competitive production of side products leading to an acid catalyzed rearrangement **22**, which result from facile elimination of C3-acyl protected glycals. The proposed mechanism for this transformation is described in (Scheme 8).

**Scheme 8**: Proposed mechanism for the Eosin Y catalyzed synthesis of 2-deoxyglucals.



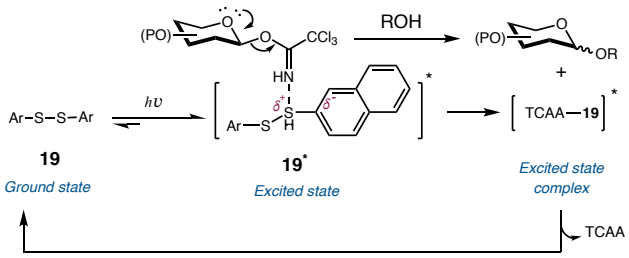

Photoexcitation of **5** gives rise to excited state radical cation **5**$^{*}$ which protonates glycal **20**, generating oxocarbenium intermediate **26** and deprotonated catalyst **27**. After proton transfer, 2-deoxyglycoside product **21** is produced by the nucleophilic attack of the hydroxyl acceptor ROH on the oxocarbenium **26** in the axial position. Disulfide **19** serves as a co-catalyst in the reaction. Homolytic cleavage of the S–S bond generates thiyl radical **29**, which can oxidize deprotonated photocatalyst **27** to generate thiolate **30** and oxidized photocatalyst **31**. Aryl thiol **32** is produced when **30** is protonated by the oxonium intermediate **28**. The ground state photoacid catalyst **5** and thiyl radical **29** are regenerated by hydrogen atom transfer (HAT) from **32** to **33**. Interestingly, taking inspiration from the 9-mesityl-10-methylacridinium ion photocatalyst developed by Fukuzumi and co-workers (structure not shown),[25] novel phenol-substituted photoacid catalysts **6** and **39** were synthesized (Scheme 9).[22]

**Scheme 9**: Synthesis of 2-deoxyglycosides with acridinium derived photoacids.




While the absorption spectra for **6** and **39** were not provided, it is likely that these acridinium catalysts exhibit substantial visible absorption. To access 2-deoxglycoside **38** from glycal **36** and alcohol **37** in a modest yield (37% and 40%, respectively), photoirradiation with 450 nm LEDs produces phenolic radical cations **6*** and **39*** that exhibit increased acidity. When combined with the disulfide additive **19**, this yield can increase to up to 75% (with 1 mol% **6**). Recently, Toshima showed that diaryl sulfide **19** functions as an organo-Lewis photoacid (LPA) catalyst in photo-induced glycosylation reactions (Scheme 10).[26]

**Scheme 10**: Glycosylation via organo-Lewis photoacid catalysis (TCAA = trichloroacetamide).



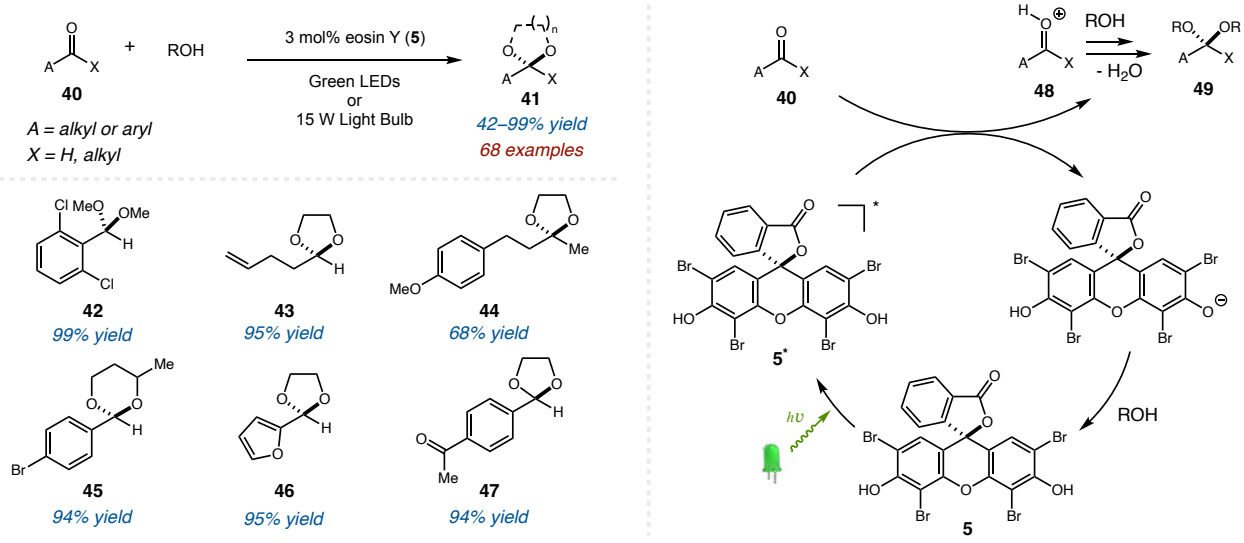

The glycosylation of alcohols with glucosyl trichloroacetimidates is facilitated by photoirradiating 5 mol% **19** with 365 nm light. Experiments employing nanosecond transient absorption spectroscopy indicate that increased Lewis acidity occurs as a result of photoirradiation

because a complex with triethylamine and **19** is formed. Interaction of the trichloroacetimidate nitrogen with the sulfur of excited-state catalyst **19**$^*$ is sufficient to facilitate glycosylation. The disulfide catalyst was recovered and used in subsequent reactions, indicating that **19** did not decompose through radical or non-radical reactions under photo irradiative conditions.

## IV. Acetalization

A crucial protective group technique for the synthesis of sophisticated medicines and natural products is the acetalization of carbonyl compounds. The use of photoacids for the catalytic acetalization of carbonyl compounds has only recently been utilized, despite techniques for the photoacid assisted cleavage of protecting groups having been reported.[27] In 2017, Lei and co-workers showed that irradiation of 3 mol% Eosin Y (**5**) with green LEDs, under $N_2$ atmosphere provides access to a wide range of dimethyl, diethyl, and cyclic acetals **41** derived from both alkyl and aryl ketones and aldehydes **40** (Scheme 11).[28]

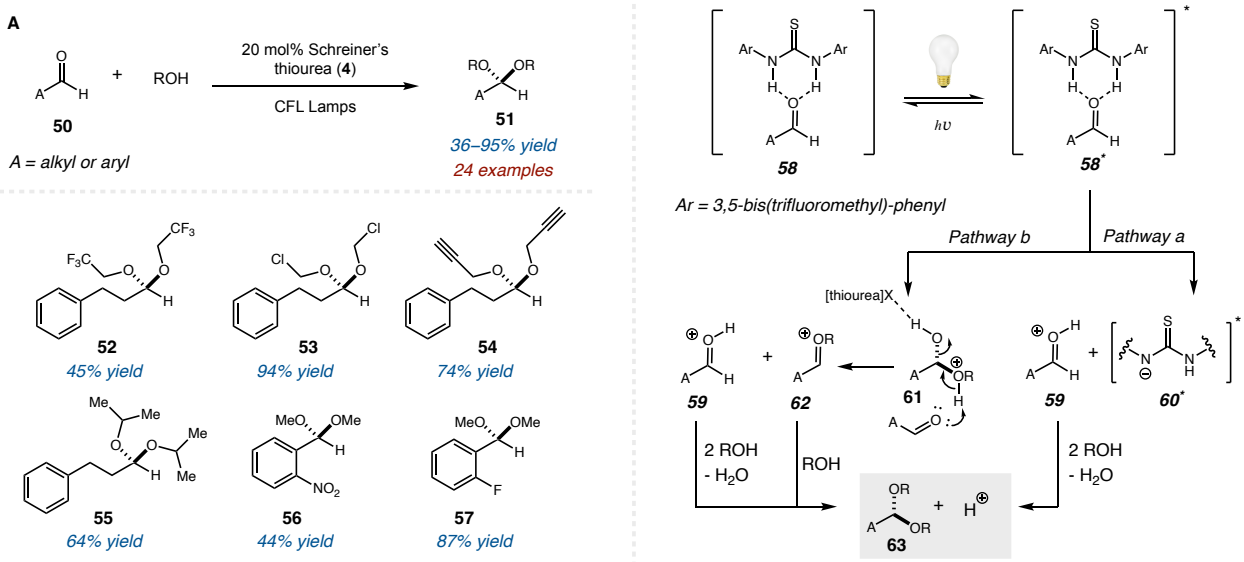
**Scheme 11**: Acetalization using Eosin Y.



This method is suitable with aryl aldehydes that are sterically inhibited (**42**), acid-sensitive substrates (**43**), and preferentially reacts with aldehydes rather than ketones (**47**). Mechanistic research has shown that the reaction must be initiated by visible light. After irradiation for 5 mins and placement of the reaction in the dark and monitoring by *in situ* IR, an acetalization product was obtained in high yield, although the efficiency was slightly diminished relative to a similar reaction placed under constant light irradiation. The reaction was entirely stopped when $Na_2CO_3$ was introduced to the solution in a catalytic quantity (5 mol%). The authors suggest that the catalysis is caused by an acidic species produced *in situ*. Interestingly, the Feng group was able to show that irradiation of 2 mol% of **5** with 15 W household light bulbs provides access to the ketal **44** derived from the corresponding ketone.[29] Feng proposes excited-state proton transfer from **5**$^*$ to **40** gives rise to a protonated carbonyl **48** which reacts with 2 equivalents of ROH regenerating the ground state photoacid catalyst **5** and affording acetal **49.**

In 2020, Kokotos and co-workers showed that Schreiner's thiourea **4** is a competent, photoacid catalyst for the formation of a diverse array of acetals **51** derived from alkyl and aryl aldehydes **50** (Scheme 12A).[30]

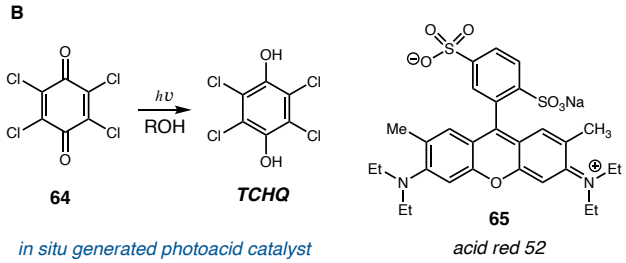
**Scheme 12A**: Acetalization using Schreiner's thiourea.




The aldehyde and thiourea **4** have a potent hydrogen bonding relationship, as demonstrated by a series of $^{19}F$ and $^{1}H$ NMR investigations. The authors suggest two potential mechanistic routes. Both start with excitation of the precoordinated thiourea-carbonyl complex **58**, to give excited state **58**$^{*}$. In pathway A, proton transfer results in an *in situ* generated acidic species **59** and **60**$^{*}$. Protonated **59** then reacts with 2 equivalents of ROH to give product **63** and regenerates the photogenerated acid. In pathway B, direct nucleophilic attack of ROH onto **58**$^{*}$ results in intermediate **61**. Deprotonation of **61** by another equivalent of aldehyde results in activated intermediates **59** and **62**, both of which afford the final product **63** after reaction with ROH and regeneration of the *in situ* generated acid.

Additional acetalization reactions involving a catalytically generated, photoacidic radical cation includes work done in 2004 by Lijser and co-workers, when chloranil (**64**) is irradiated with 350 or 420 nm light in protic media it forms an *in situ* photoacid catalyst **TCHQ** (2,3,5,6-tetrachloro-1,4-hydroquinone). Also, work by Chen and co-workers demonstrated success using the organophotoacid **65** (Scheme 12B).[31,32]

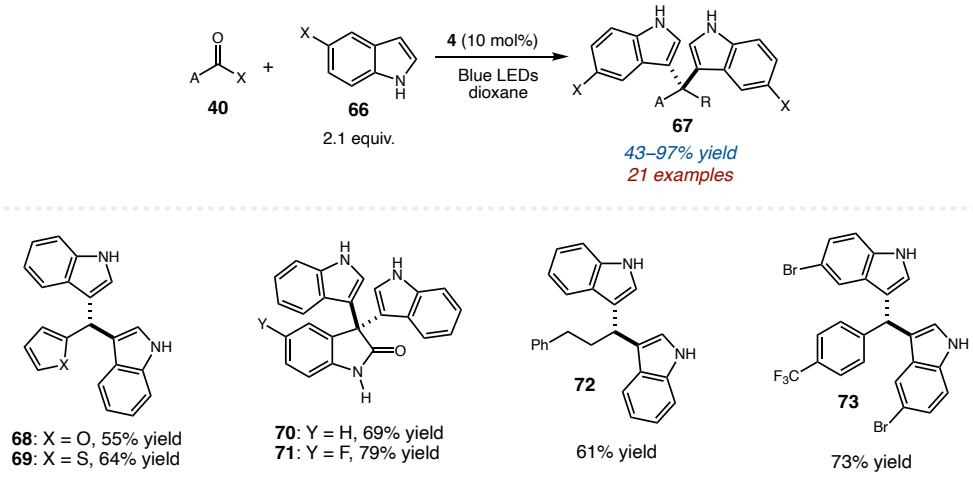
**Scheme 12B**: Acetylization photocatalysis **TCHQ** and **65.**




## V. Friedel-Crafts Arylation

An important field of study for organic synthesis is the creation of novel catalytic processes for the production of C–C bonds.[33] In 2019, the first instance of a thiourea photoacid catalyst enabling the production of C–C bonds was demonstrated by Badillo and colleagues. Photoirradiation of 10 mol% of **4** with 370 nm or Blue LEDs facilitated the double addition of indoles **66** with carbonyl compounds **40** to provide access to an array of triarylmethanes and 3,3'-diarylindolin-2-ones (**68**–**73**) (Scheme 13).[34]

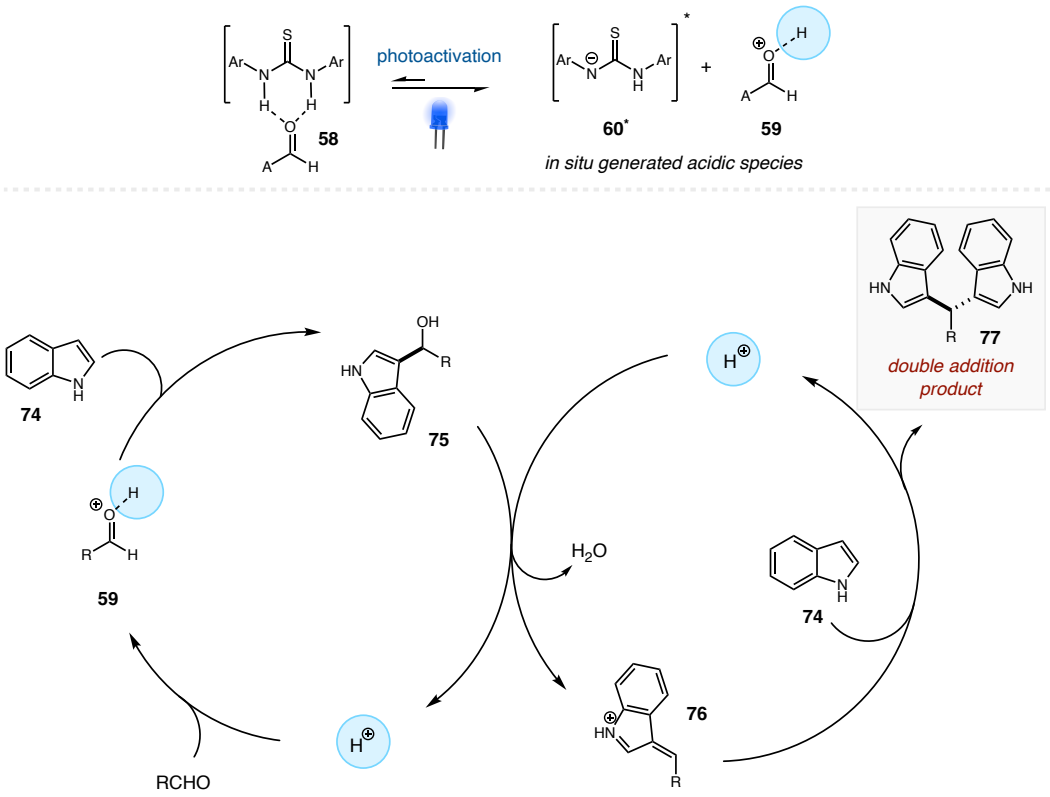
**Scheme 13**: Friedel-Crafts arylation of carbonyls using Schreiner's thiourea.




Studies on reaction initiation showed that a minimum of 30 minutes of photo-irradiation was necessary for reaction initiation. The reaction proceeded to completion in the absence of light

after being exposed to light for one hour and then being placed in the dark. Scheme 14 describes the suggested photoactivated catalytic cycle.

**Scheme 14**: Proposed mechanism for the Friedel-Crafts arylation using Schreiner's thiourea.

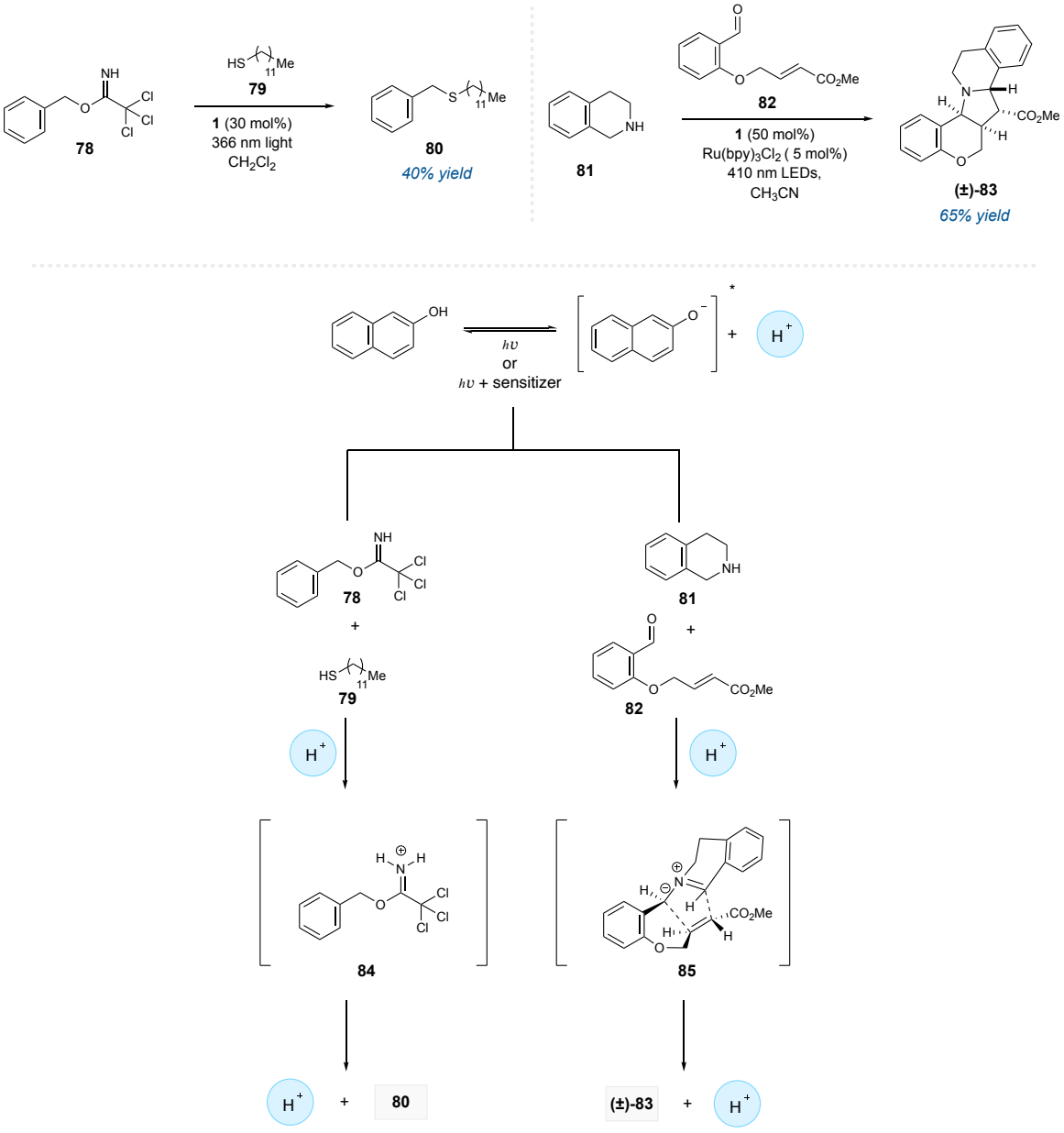



Photoactivation of hydrogen bonding complex **58** generates *in situ* acidic species **59**, which intercepts indole (**74**). After proton transfer and rearomatization, indole alcohol **75** and the regenerated *in situ* acid are formed. Dehydration of **75** gives rise to indolenium ion **76** which then intercepts a second equivalent of **74** to afford the double addition product **77** and regenerates the *in situ* formed acid.

## VI. Additional C-C & C-S bond forming reactions

Naphthol **1** can be employed as an organophotoacid to promote the formation of C–C and C–S bonds, as demonstrated by Protti and colleagues.[35] Photoirradiation of 30 mol% **1** with 366 nm light, activates benzyl trichloroacetimidate **78** for substitution with thiol **79** forming thiolation product **80** in 40% yield (Scheme 15).

**Scheme 15**: Naphthol photoacid catalyzed C–C and C–S bond-forming reactions.



The Protti Lab also showed that the energy transfer strategy developed by Hanson[10] could be applied to the synthesis of complex alkaloid **(±)-83**. Photoirradiation of 50 mol% naphthol catalyst **1** in the presence of 5 mol% $[Ru(bpy)_3]^{2+}$ results in the formation of polycyclic alkaloid **(±)-83** from **81** and **82**. The authors propose ESPT leads to intermediates **84** and **85** which afford **80** and **(±)-83**, respectively.

## VII. Conclusions

Only in recent years has the research on photoacid catalysis for organic synthesis started. The special reactivity of photoacids, their capacity to behave as potent acid catalysts only when light is absorbed, makes photoacid catalysis an intriguing field of study. Significant advancements in the field of photoacid catalysis will result from the construction of novel photoacid structures with relevant physical properties. New photoacid designs that absorb visible light and have longer excited-state lifetimes as well as chiral photoacid catalysts that may support asymmetric transformations may be among the next approaches in the field of photoacid catalysis.

## VIII. References


1. Reviews on photocatalysis: (a Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012,** *77*, 1617. (b) Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355. (c) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016,** *81*, 6898. (d) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017**, *1*, 0052.
2. (a) Shirai, M.; Tsunooka, M. *Prog. Polym. Sci.* **1996**, *21*, 1. (b) Fu, C.; Xu, J.; Boyer, C. *Chem. Commun.* **2016**, *52*, 7126. (c) Patel, P. K.; Arias, J. E.; Gongora, R. S.; Hernandez, F. E.; Moncomble, A.; Aloise, S.; Chumbimuni-Torres, K. Y. *Phys. Chem. Chem. Phys.* **2018**, *20*, 26804. (d) Kagel, H.; Frohme, M.; Glökler, J. *J. Cell. Biotechnol.* **2018**, *4*, 23.
3. Förster, T. *Naturwiss.* **1949**, *36*, 186.
4. Weller, A. *Naturwiss.* **1955**, *42*, 175.
5. Reviews on photoacids: (a) Ireland, J. F.; Wyatt, P. A. H. *Adv. Phys. Org. Chem.* **1976**, *12*, 131. (b) Arnaut, L. G.; Formosinho, S. J. *J. Photochem. Photobiol. A* **1993**, *75*, 1. *50*, 1956. (c) Shizuka, H. *Acc. Chem. Res.* **1985**, *18*, 141. (d) Tolbert, L. M.; Solntsev, K. M. *Acc. Chem. Res.* **2002**, *35*, 19. (e) Liao, Y. *Acc. Chem. Res.* **2017**, *50*, 1956. (f) Martin, C. J.; Rapenne, G.; Nakashima, T.; Kawai, T. *J. Photoch. PhotoBio. C.* **2018**, *34*, 41. (g) Zivic, N.; Kuroishi, P. K.; Dumur, F.; Gigmes, D.; Dove, A. P.; Sardon, H. *Angew. Chem. Int. Ed.* **2019**, *58*, 10410. (h) Kuznetsova, N. A.; Malkov, G. V.; Gribov, B. G. *Russ. Chem. Rev.* **2020**, *89*, 173.
6. Tolbert, L. M.; Haubrich, J. E. *J. Am. Chem. Soc.* **1994**, *116*, 10593.
7. Weller, A. Z. Z. *Elektrochem* **1960**, 64, 55.
8. Computational studies on photoacidity: (a) Acharya, A.; Chaudhuri, S.; Batista, V. S. *J. Chem. Theory Comput.* **2018**, *14*, 867. (b) Wang, Y.-F.; Cheng, Y.-C. *Phys. Chem. Chem. Phys.* **2018**, *20*, 4351.

9. Reviews on catalytic protonation strategies: (a) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359. (b) Oudeyer, S.; Brière, J.-F.; Levacher, V. *Eur. J. Org. Chem.* **2014**, 6103.
10. Das, A.; Banerjee, T.; Hanson, K. *Chem. Commun.* **2016**, *52*, 1350.
11. (a) McClure, D. S. *J. Chem. Phys.* **1949**, *17*, 665. (b) McClure, D. S.; Blake, N. W.; Hanst, P. L. *J. Chem. Phys.* **1954**, *22*, 255.
12. Das, A.; Ayad, S.; Hanson, K. *Org. Lett.* **2016**, *18*, 5416.
13. Solntsev, K. M.; Bartolo, E.-A.; Pan, G.; Muller, G.; Bommireddy, S.; Huppert, D.; Tolbert, L. M. *Isr. J. Chem.* **2009**, *49*, 227.
14. Ayad, S.; Posey, V.; Das, A.; Montgomery, J. M.; Hanson, K. *Chem. Commun.* **2019**, *55*, 1263.
15. Reviews on glycosylation: (a) Sangwan, R.; Mandal, P. K. *RSC Adv.* **2017**, *7*, 26256. (b) Nielsen, M. M.; Pedersen, C. M. *Chem. Rev.* **2018**, *118*, 8285. (c) Kulkarni, S. S.; Wang, C.-C.; Sabbavarapu, N. M.; Podilapu, A. R.; Liao, P.-H.; Hung, S.-C. *Chem. Rev.* **2018**, *118*, 8025.
16. Iwata, R.; Uda, K.; Takahashi, D.; Toshima, K. *Chem. Commun.* **2014**, *50*, 10695.
17. Kimura, T.; Eto, T.; Takahashi, D.; Toshima, K. *Org. Lett.* **2016**, *18*, 3190.
18. Reviews on hydrogen bond donor catalysis: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Nagorny, P.; Sun, Z. *Beilstein J. Org. Chem.* **2016**, *12*, 2834.
19. Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724.
20. This shift in acidity is based on glucosyl trichloroacetimidate activation, which requires a pKa value ≤ 5 at room temperature.
21. Liu, J.; Yin, S.; Wang, H.; Li, H.; Ni, G. *Carbohydr. Res.* **2020**, *490*, 107963.
22. Zhao, G.; Wang, T. *Angew. Chem., Int. Ed.* **2018**, *57*, 6120.
23. Wang, T.; Li, J.; Zhao, G. *Synlett* **2020**, *31*, 823.

24. Yan, D.-M.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2019**, *58*, 378.

25. Fukuzumi, S.; Kotani, H.; Ohkubo, K.; Ogo, S.; Tkachenko, N. V.; Lemmetyinen, H. *J. Am. Chem. Soc.* **2004**, *126*, 1600.

26. Iibuchi, N.; Eto, T.; Aoyagi, M.; Kurinami, R.; Sakai, H.; Hasobe, T.; Takahashi, D.; Toshima, K. *Org. Biomol. Chem.* **2020**, *18*, 851.

27. (a) Nishikubo, Y.; Kanzaki, S.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2006**, *47*, 8125. (b) Dharpure, P. D.; Bhowmick, A.; Warghude, P. K.; Bhat, R. G. *Tetrahedron Lett.* **2020**, *61*, 151407.

28. Yi, H.; Niu, L.; Wang, S.; Liu, T.; Singh, A. K.; Lei, A. *Org. Lett.* **2017**, *19*, 122.

29. Zhou, Q.; Jia, T.; Li, X.-X.; Zhou, L.; Li, C.-J.; Feng, Y.-S. *Synth. Commun.* **2018**, *48*, 1068.

30. Spiliopoulou, N.; Nikitas, N. F.; Kokotos, C. G. *Green Chem.* **2020**, *22*, 3539.

31. de Lijser, H. J. P.; Rangel, N. A. *J. Org. Chem.* **2004**, *69*, 8315.

32. Yu, L.; Lin, C.; Liao, C.; Zeng, X.; Chen, X.; Zhu, Z.; Huang, Y.; Li, Y.; Chen, L. *Environ. Chem. Lett.* **2020**, *18*, 1353.

33. Reviews on C–C bond formation: (a) Devdutt, C.; Nabin, C. B. *Curr. Org. Syn.* **2012**, *9*, 17. (b) Chen, F.; Wang, T.; Jiao, N. *Chemical Reviews* **2014**, *114*, 8613. (c) Brahmachari, G. *RSC Adv.* **2016**, *6*, 64676. (d) Ravelli, D.; Protti, S.; Fagnoni, M. *Chem. Rev.* **2016**, *116*, 9850.

34. Salem, Z. M.; Saway, J.; Badillo, J. J. *Org. Lett.* **2019**, *21*, 8528.

35. Strada, A.; Fredditori, M.; Zanoni, G.; Protti, S. *Molecules* **2019**, *24*, 1318.

## *Chapter 2: Photoacid Friedel-Crafts Arylation of Carbonyls*

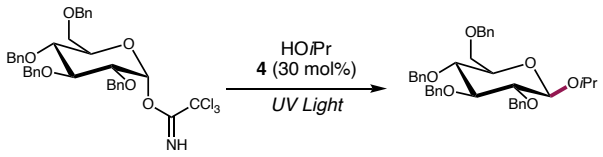
# I. Introduction

Chapter 2 describes the development of synthetic methodology using Schreiner's thiourea as a photoacid for the synthesis of triarylmethanes. The optimized conditions are elucidated for the model reaction. Presented in section four, the reactions of a variety of thiourea/urea derivatives are investigated. In sections five and six, the scope for the carbonyl and indole sources are also explored. A portion of the material presented in section chapter 2 is excerpted from a work that was published in *Organic Letters*, in collaboration with Zena Salem and Joseph J. Badillo 

# II. Previous Works with Schreiner's Thiourea

Toshima and co-workers showed that Schreiner's thiourea (**4**) functions as an organophotoacid, becoming up to $10^3$ times more acidic under long-wave UV (ultraviolet) irradiation to facilitate the glycosylation of alcohols (Figure 2).[8]

**Figure 2**: Photoinduced thiourea catalysis, Toshima Group.



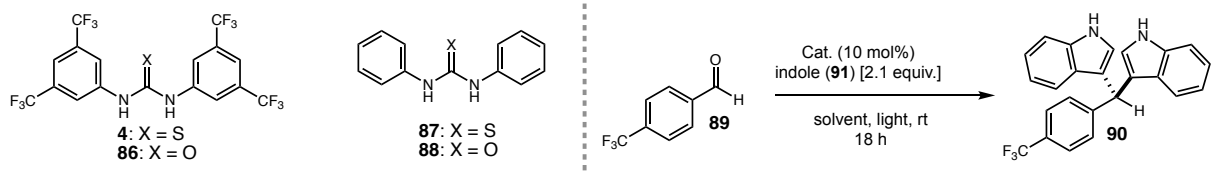

As part of our research on developing new photoacid catalysts, I considered if this photoinduced thiourea-catalyzed process could be used to facilitate C–C bond-forming reactions, specifically a Friedel-Crafts arylation.

## III. Optimization of Model Reaction

I began my investigation by finding optimal conditions. Starting by using 4-(trifluoromethyl) benzaldehyde (**89**) and 1*H*-indole (**91**) to form 3,3'-((4-(trifluoromethyl) phenyl)methylene)bis(1*H*-indole) (**90**) [Table 1]. In the absence of light and/or catalyst, no product was observed (Entries 1-10). Heating the reaction mixture to 65 °C in dioxane produced only trace product (<5%, Entry 11). Irradiation with 40 W Blue LEDs in the presence of 10 mol% **4** provided the desired product (Entries 12-16), with dioxane being the optimal solvent (85% yield of **90**, Entry 16).

Switching to a different light source, 370 nm LEDs also provided **90** in excellent yield (90%, Entry 17). It was determined that the reaction efficiency is effected by the catalyst loading; while lowering the catalyst loading to 5 mol% resulted in identical yield (90%, Entry 18), decreasing further to 1 mol% catalyst resulted in a significant drop off in reaction efficiency, 46% yield (Entry 19). I also discovered that the trifluoromethyl substituents on the photoacid are not strictly required for catalysis, as *N*,*N*′-diphenylthiourea (**87**) is also an efficient photocatalyst, providing **90** in 84% yield. Although both oxygen-containing urea catalysts **86** and **88** failed to induce catalysis, the increased acidity that the thiourea's sulfur imparts is essential for reactivity.[9]

**Table 1**: Optimization for the photoacid-catalyzed Friedel-Crafts arylation of carbonyls.




| entry | solvent | Cat. | light | % yield |
|---|---|---|---|---|
| 1 | DCM | -- | -- | 0 |
| 2 | 1,4-dioxane | -- | -- | 0 |
| 3 | DCM | -- | 40 W Blue LEDs | 0 |
| 4 | 1,4-dioxane | -- | 370 nm LEDs | 0 |
| 5 | 1,4-dioxane | -- | 40 W Blue LEDs | 0 |
| 6 | DCM | **4** | -- | 0 |
| 7 | DCE | **4** | -- | 0 |
| 8 | ACN | **4** | -- | 0 |
| 9 | THF | **4** | -- | 0 |
| 10 | 1,4-dioxane | **4** | -- | 0 |
| 11[b] | 1,4-dioxane | **4** | -- | <5 |
| 12 | DCM | **4** | 40 W Blue LEDs | 22 |
| 13 | DCE | **4** | 40 W Blue LEDs | 39 |
| 14 | ACN | **4** | 40 W Blue LEDs | 51 |
| 15 | THF | **4** | 40 W Blue LEDs | 75 |
| 16 | 1,4-dioxane | **4** | 40 W Blue LEDs | 85 |
| 17 | 1,4-dioxane | **4** | 370 nm LEDs | 90 |
| 18 | 1,4-dioxane | **4** | 370 nm LEDs | 90 |
| 19 | 1,4-dioxane | **4** | 370 nm LEDs | 46 |
| 20 | 1,4-dioxane | **86** | 370 nm LEDs | 84 |
| 21 | 1,4-dioxane | **87** | 370 nm LEDs | 0 |
| 22 | 1,4-dioxane | **88** | 370 nm LEDs | 0 |

## IV. Catalyst Evaluation

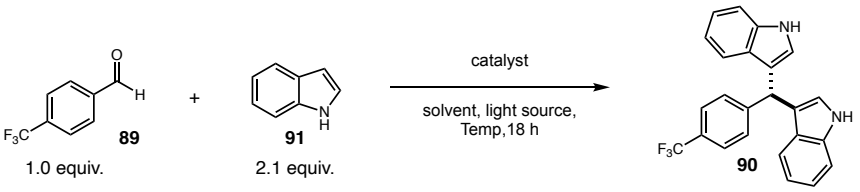
In addition to finding optimal conditions as mentioned before, I wanted to investigate and observe what was responsible for the catalysis. To do this a wide range of urea and thiourea catalysts were studied (Table 2). In the absence of catalyst with Blue LEDs no product was

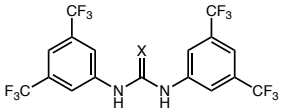
afforded (Entries 1 and 5). Using 10 mol% catalyst **4** with no light at ambient temperature or at elevated temperatures (40 °C in DCM or 65 °C in dioxane) produced only trace product in the case of dioxane (Entries 2, 3, 6 and 7). Using 10 mol% catalyst **4** in combination with Blue LEDs in DCM, provided double addition product **90** in 22% yield (Entry 4). Switching the solvent to 1,4-dioxane provided **90** in 85% yield with Blue LEDs and 90% yield with 370 nm LEDs (Entries 8 and 9). The presence of the trifluoromethyl groups on the thiourea were not required, photoexcited diphenyl thiourea **87** provided triarylmethane **90** in good yield (84%) when irradiated with 370 nm light and no product in the absence of light (Entries 12 and 13). Ureas **86** and **88** did not produce any reaction, both with and without light, indicating that the sulfur is necessary for reactivity (Entries 14, 15, 16, and 17). Thiourea **92** provided double addition product **90** in low yields, interestingly, light had little effect on the reaction efficiency (22%, no light and 30% with light). It is worth noting here that the ureas and thioureas (both from commercial sources and prepared in our laboratory) were recrystallized from EtOH or ACN.

There was evidence of trace acidic impurities in impure ureas and thioureas, which led to non-photoinduced catalysis resulting from the non-recrystalized catalysts. Chiral thiourea **94** with no light produced no product and elevating the temperature to 65 °C resulted in only 15% product formation (Entries 22 and 23). Chiral thiourea **94** provided **90** in 72% yield with 370 nm LEDs (Entry 24). Using a chiral photoacid opens the door for asymmetric photoinduced processes. Finally, we looked into benzoic acid (pKa = 11 in DMSO) and *p*-toluene sulfonic acid (*p*-TSA) (pKa 1.6 in DMSO) to determine the acidity required to catalyze the synthesis of **90**. No reaction was produced by benzoic acid, however >99% yield was produced by *p*-TSA. With a pKa of 8 in DMSO, Schreiner's thiourea **(4)** is insufficient to catalyze the production of **90** without

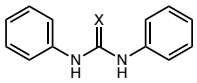
photoactivation. Under the reaction conditions, a photoinduced acidic species is anticipated to develop *in situ* and have a pKa between 8 and 1.6 in DMSO.

**Table 2**: Catalyst evaluations for the synthesis of **90.**

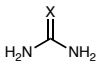


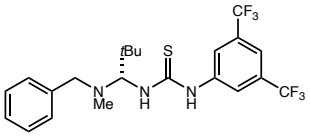
**4** (X = S)
**86** (X = O)



**87** (X = S)
**88** (X = O)



**92** (X = S)
**93** (X = O)



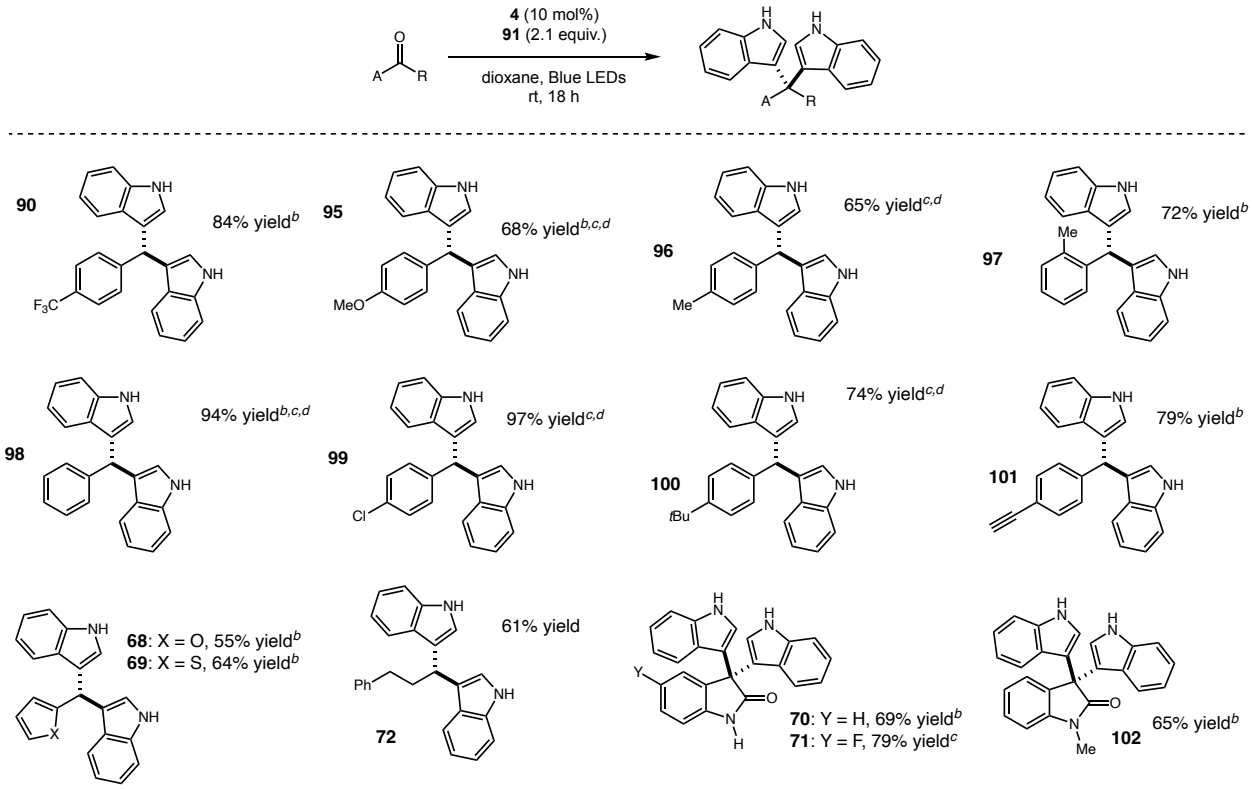
**94**

| entry | Cat. | mol% | Temp. (°C) | solvent | light | %yield |
|---|---|---|---|---|---|---|
| 1 | -- | -- | rt | DCM | 40 W blue LEDs | 0 |
| 2 | **4** | 10 | rt | DCM | -- | 0 |
| 3 | **4** | 10 | 40 | DCM | -- | 0 |
| 4 | **4** | 10 | rt | DCM | 40 W blue LEDs | 22 |
| 5 | -- | -- | rt | 1,4-dioxane | 40 W blue LEDs | 0 |
| 6 | **4** | 10 | rt | 1,4-dioxane | -- | 0 |
| 7 | **4** | 10 | 65 | 1,4-dioxane | -- | <5 |
| 8 | **4** | 10 | rt | 1,4-dioxane | 40 W blue LEDs | 85 |
| 9 | **4** | 10 | rt | 1,4-dioxane | 370 nm LEDs | 90 |
| 10 | **4** | 5 | rt | 1,4-dioxane | 370 nm LEDs | 90 |
| 11 | **4** | 1 | rt | 1,4-dioxane | 370 nm LEDs | 46 |
| 12 | **87** | 10 | rt | 1,4-dioxane | -- | 0 |
| 13 | **87** | 10 | rt | 1,4-dioxane | 370 nm LEDs | 84 |
| 14 | **86** | 10 | rt | 1,4-dioxane | -- | 0 |
| 15 | **86** | 10 | rt | 1,4-dioxane | 370 nm LEDs | 7 |
| 16 | **88** | 10 | rt | 1,4-dioxane | -- | 0 |
| 17 | **88** | 10 | rt | 1,4-dioxane | 370 nm LEDs | 0 |
| 18 | **92** | 10 | rt | 1,4-dioxane | -- | 22 |
| 19 | **92** | 10 | rt | 1,4-dioxane | 370 nm LEDs | 30 |
| 20 | **93** | 10 | rt | 1,4-dioxane | -- | 0 |
| 21 | **93** | 10 | rt | 1,4-dioxane | 370 nm LEDs | 0 |
| 22 | **94** | 10 | rt | 1,4-dioxane | -- | 0 |
| 23 | **94** | 10 | 65 | 1,4-dioxane | -- | 15 |
| 24 | **94** | 10 | rt | 1,4-dioxane | 370 nm LEDs | 72 |
| 25 | benzoic acid | 10 | rt | 1,4-dioxane | -- | 0 |
| 26 | *p*-TSA | 10 | rt | 1,4-dioxane | -- | >99 |

## V. Results of Carbonyl Scope

Afterwards the scope for this photoacid catalyzed process was investigated. It was found that a variety of substituted aryl aldehydes were tolerated (Table 3).

**Table 3**: Carbonyl Scope.




[a] Isolated yield. [b] Reaction run with 370 nm LEDs. [c] Reaction run with 4.2 equiv. **6**. [d] Run with dichloromethane as the solvent.

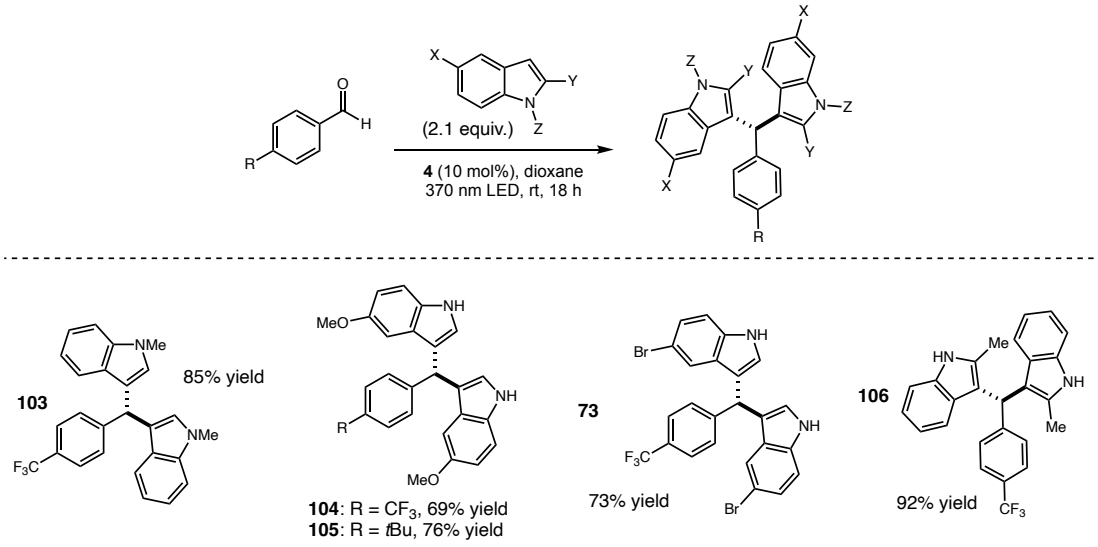
Unsubstituted benzaldehyde (**117**) provided double addition product **98** in an excellent 94% yield. Methyl-, *t*-butyl-, methoxy-, and chloro- groups that donate electrons in the *para*-position are well tolerated (**95**, **96**, **99**, **100**). It is interesting to note that while most substrates functioned better with either Blue LEDs or 370 nm LEDs, certain substrates performed slightly better with one or the other.[10] The efficiency of the reaction was found to be strongly dependent on the chosen solvent. For instance, 4-methoxybenzaldehyde produced 10% of product **95** in dioxane but 68% in DCM when illuminated by 370 nm LEDs. Sterically hindered *o*-tolualdehyde was doubly

arylated in good yield (72%, **97**), and an alkyne functional handle was well preserved in the course of the reaction (79% yield, **101**). Heteroaromatic aldehydes, furfural and thio-furfural, afforded triarylmethane products **68** and **69** in 74% and 64% yields, respectively. Significantly, 3-phenylpropanal, an aliphatic aldehyde, produced **72** in 61% yield, demonstrating that the aryl substitution on the aldehyde was not necessary. Isatins are capable electrophiles in this photoacid catalyzed reaction as well. The equivalent 3,3′-oxindoles were produced in excellent yields by both *N*-H and *N*-methyl isatins (**70-71**, **102**, 65-79% yields).

## VI. Results of Indole Scope

After investigating the versatility of the carbonyl source, the scope of indoles was examined using this photoinduced protocol (Table 4).

**Table 4**: Indole Scope.



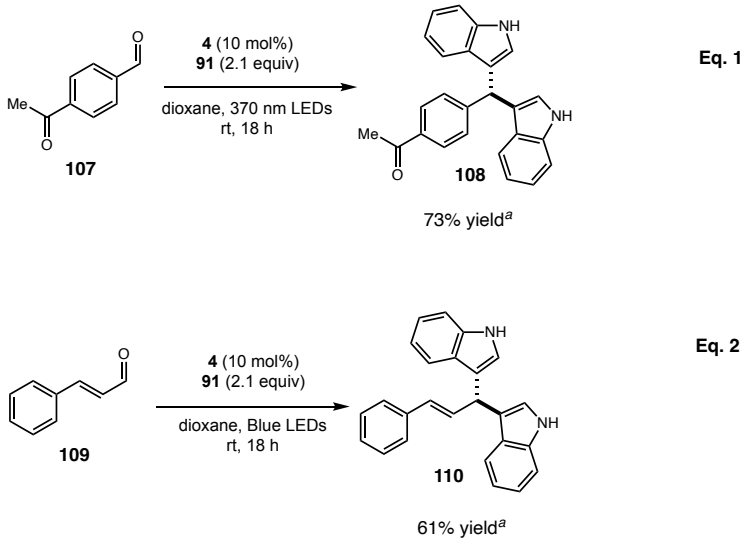

*N*-Methylindole provided triarylmethane product **103** in 85% yield. Varying the electronics on the indole was well tolerated. Acute myeloid leukemia (AML) inhibitors **104** and **105** were produced in good yields by 5-methylindole addition (69 and 76% yields, respectively).[11] Surprisingly, inductively deactivated 5-bromo indole provided **73** in good yield (73%). Sterically hindered 2-

methylindole was also a competent nucleophile, providing access to **106** in 92% yield. However, nucleophiles such allyltriisopropylsilane, skatole, and *N*,*N*-dimethyl-*m*-anisidine barely produced traces of products.

## VII. Competition Experiments for Carbonyl and Indole Sources

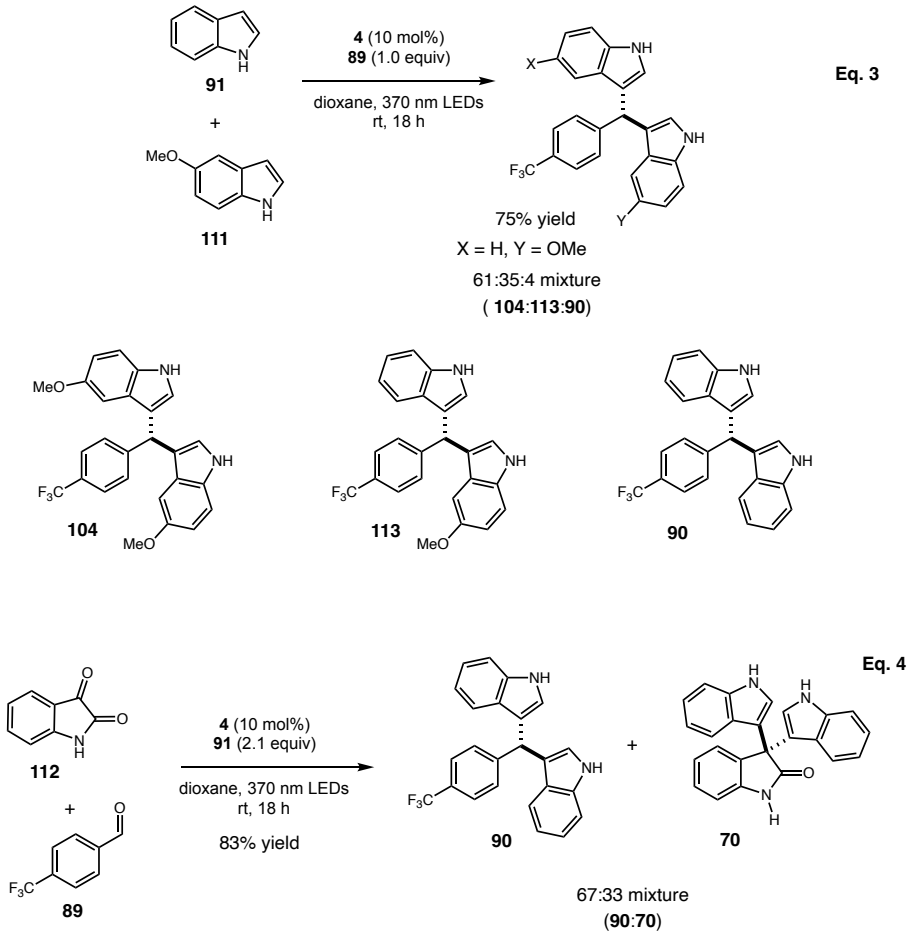
After investigating the scope of both the carbonyl and indole source, a series of competition experiments were run and they revealed that this photoactivated protocol is selective for addition to aldehydes as well as certain indoles (Figure 3).

**Figure 3**: Competition experiments.




Under typical circumstances, when 4-acetylbenzaldehyde (**107**) was used, only addition to the aldehyde was seen, resulting in compound **108** in 73% yield while leaving the ketone unaltered (Eq. 1). The reaction with cinnamaldehyde (**109**), solely produced **110**, albeit in a lower yield (43%, Eq. 2), revealed the reaction's preference for 1,2-addition to the aldehyde over 1,4-conjugate addition.[12]

**Figure 3**: Competition experiments (contd.).

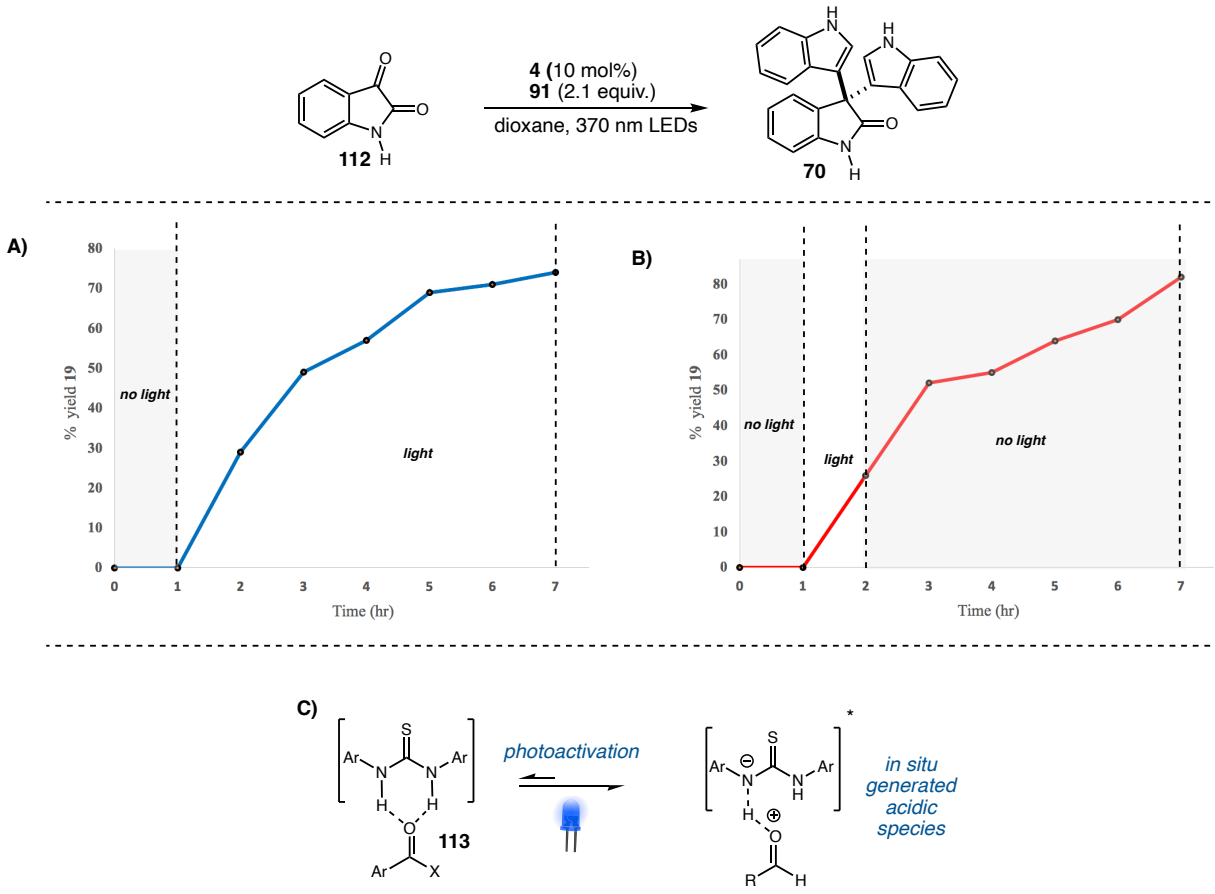



When aldehyde **89** was exposed to a 1:1 mixture of 1*H*-indole (**91**) and 5-methoxy-1*H*-indole (**111**), the more electron-rich 5-methoxyindole out competed **91** to form a 61:35:4 mixture of triarylmethane products with **104** and chiral cross product (±)-**113** as the major products (75% yield, Eq. 3). A competition between isatin **112** and **89** gave a 67:33 mixture of **90** to **70** in favor of addition to the aldehyde (83% yield, Eq. 4).

## VIII. Reaction Initiation and Time Studies

To understand more about the mechanism of action for this reaction, initiation and time studies were conducted. The results of these mechanistic studies demonstrate that light is required for reaction initiation, but that the reaction was not light dependent.

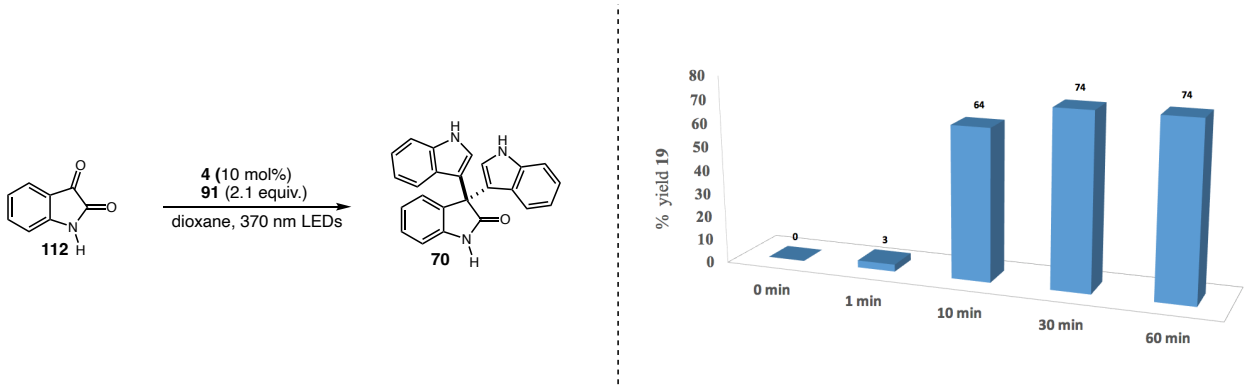
**Figure 4**: Reaction profile and photoacid activation.




Under constant irradiation with 370 nm LEDs the reaction between 1*H*-isatin (**112**) and 1*H*-indole (**91**) to form oxindole **70** reached 74% yield in 6 hours (Figure 4A). It's interesting to note that the reaction progressed at a similar rate even after being exposed to radiation for 1 hour and then left in the dark for 6 hours, yielding 81%. (Figure 4B). One possible explanation for this observation is the photogeneration of an *in situ* formed acidic species which then catalyzes the arylation reaction (Figure 4C).[5d,13-14]

In the absence of additional light exposure, the reaction only achieves a 35% yield after 5 hours when catalyst **4** alone is exposed to light for 1 hour, however it reaches a 71% yield when exposed constantly to light. In contrast, the reaction progresses to completion after 5 hours in the absence of additional light exposure if the combination of **4** and **112** or **4** and **91** is exposed to light for 1 hour.[15] Addition of 5 mol% $Na_2CO_3$ to the reaction under standard conditions for formation of **90**, reduced the yield to 32% and adding 5 mol% of a proton scavenger (2,6-di-*tert*-butyl-4-methylpyridine) had no effect on reaction efficiency (82% yield of **90**).[16] We found that the production of oxindole **70** required irradiation for at least 10 to 30 minutes before it could continue in the dark (Figure 5).

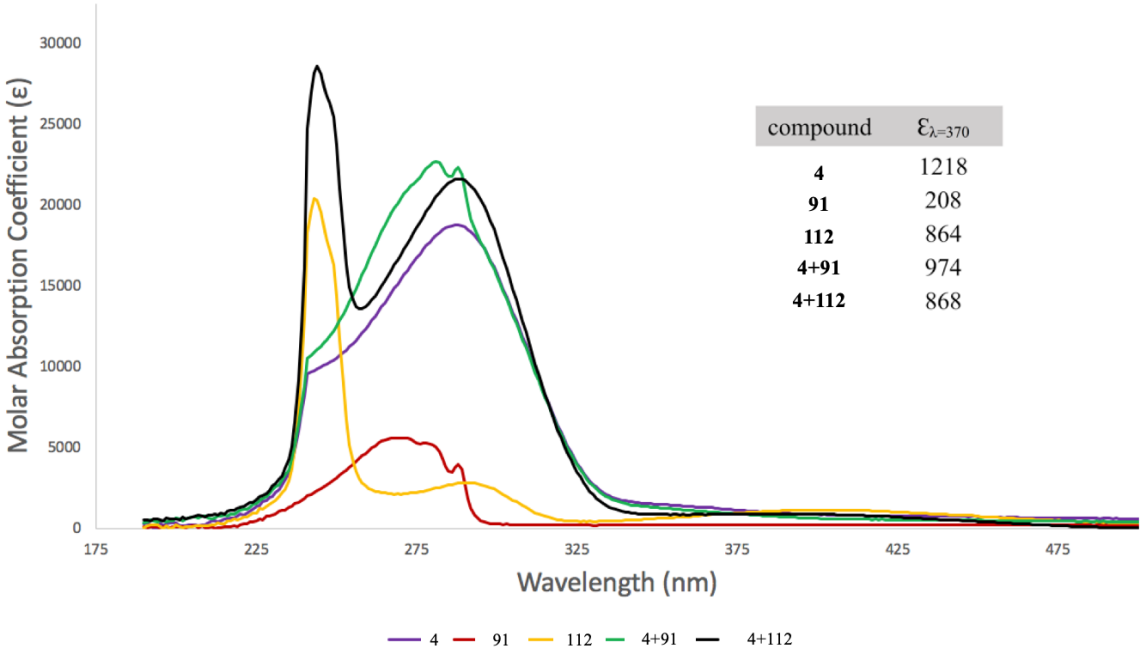
**Figure 5**: Time-dependent photoactivation.




## IX. Molar Absorption Spectra

The molar absorption spectra for for Schreiner's thiourea **4**, 1*H*-indole (**91**), isatin **112**, and a stochiometric 1:1 mixture of **4** and **91** (**4**+**91**) or **112** (**4**+**112**) are shown in Figure 6. All of the components absorb 370 nm light, with catalyst **4** having the strongest molar absorption coefficient ($\varepsilon_\lambda = 370$) of 1218.

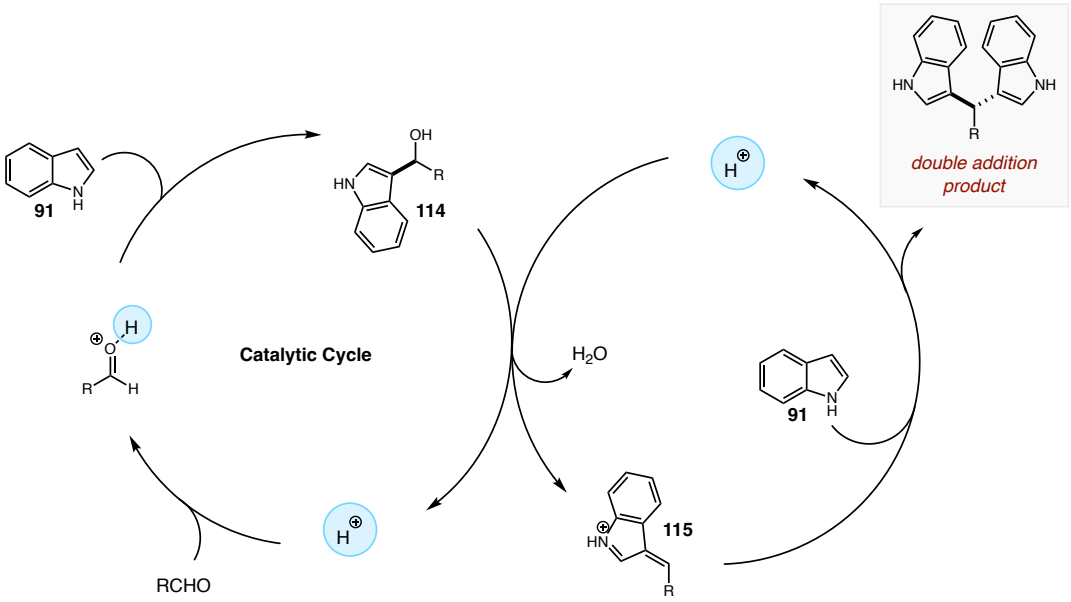
**Figure 6**: Molar absorption spectra in dioxane for **4**, **91**, **112**, and a 1:1 stochiometric mixture of **4**+**91** and **4**+**112**.




## X. Proposed Photoacid Catalyzed Mechanism

Finally, after the initiation, time and mechanistic studies were conducted, the following photoacid initiated catalytic cycle for this process is proposed as shown in Scheme 16.

**Scheme 16**: Proposed mechanism for Friedel-Crafts Arylation via Schreiner's thiourea.




A photogenerated *in situ* acidic species gives rise to a protonated carbonyl complex. Interception of indole (**91**) gives alcohol **114** which after proton transfer and loss of water gives rise to the resulting indolenium ion **115**. Finally, interception of a second equivalent of **91** provides the double addition product and regenerates the photogenerated acid.

## XI. Conclusions

In conclusion, the work I conducted in my first research project demonstrates that photoinduced thiourea catalysis facilitates a double Friedel-Crafts addition of indoles to aldehydes and isatins to form a wide-range of triarylmethanes and 3,3′-diarylindolin-2-ones. Competition experiments show that this light-facilitated protocol is selective for addition to aldehydes over ketones, isatins, and Michael acceptors. Mechanistic studies show that light irradiation is critical for reaction initiation.

# XII. Experimental

## A. General Information

Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on a Varian Inova (500 MHz) spectrometer. NMR samples were dissolved in $CDCl_3$ or DMSO-$d_6$, and chemical shifts were reported in ppm relative to tetramethylsilane (TMS). $^1$H NMR data are reported as follows: chemical shift, integration, multiplicity (s = singlet; d = doublet; dd = doublet of doublets; ddd = doublet of doublet of doublets; m = multiplet), coupling constant, and assignment. $^{13}$C NMR spectra were recorded on a Varian Inova (125 MHz) spectrometer. The samples were dissolved in $CDCl_3$ or DMSO-$d_6$, and chemical shifts are reported in ppm relative to the solvent ($CDCl_3$ as d = 77.2 ppm or DMSO-$d_6$ as d = 39.5). $^1$H and $^{13}$C NMR spectra were measured at room temperature and the chemical shifts are reported in parts per million, unless otherwise noted. High resolution mass spectra (HRMS) were obtained using a Waters Q-TOF Ultima ESI (electro-spray ionization) and are reported in m/z. Reactions were monitored by thin-layer chromatography (TLC) Silica gel 60 $F_{254}$. Compounds purified using Biotage® SNAP Ultra or Sfär silica columns. Rotary evaporation was performed using a Buchi R-300 rotary evaporator and Welch Model 2027 dry vacuum pump. Infrared spectra were recorded neat on a Nicolet 4700 spectrometer. UV-Vis spectra were obtained using a M&A Instruments Inc. UV-5500PC spectrophotometer. Aldehydes, indole-2,3-diones (isatins), and indoles were purchased from commercial sources. Thioureas **4** and **87** were prepared according to literature procedures. Urea **88** was prepared according to literature procedure. All other thioureas and ureas were purchased from commercial sources.

## B. General Procedures for Photoacid Catalyzed Indole Addition to Carbonyls

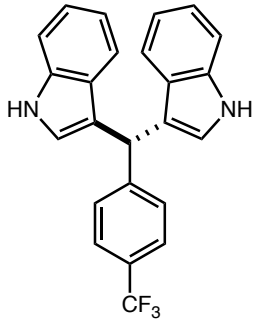
**Procedure A:**

To an 8 mL vial fitted with a magnetic stir bar was added **4** (0.02 g, 0.03 mmol, 0.1 equiv.) and the corresponding indole (0.6 mmol, 2.1 equiv.). Next, the carbonyl compound was added (0.297 mmol, 1.0 equiv.) followed by the solvent, either 1,4-dioxane or dichloromethane (0.2 M). The reaction mixture was then placed 4.0 cm from either a Kessil 370 nm or Tuna Blue LED light for 18 h. Fans were used to maintain room temperature throughout the duration of the reaction. The reaction was then dry-loaded onto silica gel (high-purity, pore size 60, particle size 40–63 μm, 230–400 mesh) and purified by flash chromatography (gradient 100% hexanes to 25% EtOAc/hexanes or 10-20% acetone/hexanes) to yield the aryl methane or oxindole products.

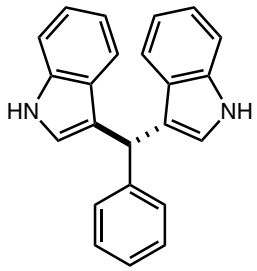
**Procedure B:** 1 mmol synthesis of **90.**

To an 8 mL vial fitted with a magnetic stir bar was added **4** (0.05 g, 0.1 mmol, 0.1 equiv.) and **91** (0.25 g, 2.1 mmol, 2.1 equiv.). Next, the carbonyl compound was added (137 μL, 1 mmol, 1.0 equiv.) followed by 1,4-dioxane (0.2 M). The reaction mixture was then placed 4.0 cm from a Kessil 370 nm LED light for 18 h. Fans were used to maintain room temperature throughout the duration of the reaction. The reaction was then dry-loaded onto silica gel (high-purity, pore size 60, particle size 40–63 μm, 230–400 mesh) and purified by flash chromatography (gradient 10-20% acetone/hexanes) to yield aryl methane **90** as a red powder, 0.328 g, 84% yield.

## C. Characterization Data

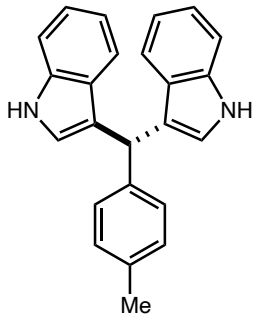



3,3'-((4-(trifluoromethyl)phenyl)methylene)bis(1*H*-indole) **90**: Compound **90** was prepared according to the general procedure A using 4-(trifluoromethyl)benzaldehyde (**89**), 1*H*-indole (**91**), 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 10-20% acetone/hexanes to give a red foam 0.097 g, 84% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 2H), 7.53 (d, $J$ = 8.1 Hz, 2H), 7.46 (d, $J$ = 8.1 Hz, 2H), 7.42 – 7.28 (m, 4H), 7.21 – 7.16 (m, 2H), 7.02 (ddd, $J$ = 8.1, 7.1, 0.8 Hz, 2H), 6.66 (dd, $J$ = 2.4, 0.9 Hz, 2H), 5.94 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 148.29, 136.83, 129.15, 128.59 (q, $J_{FCC}$ = 32.2 Hz), 126.98, 125.34 (q, $J_{FCCC}$ = 3.8 Hz), 124.50 (q, $J_{FC}$ = 272.2 Hz), 123.79, 122.32, 119.86, 119.59, 118.91, 111.31, 40.23. HRMS (ESI) m/z [M – H] calcd for $C_{24}H_{16}F_3N_2$, 389.1266; found 389.1267.

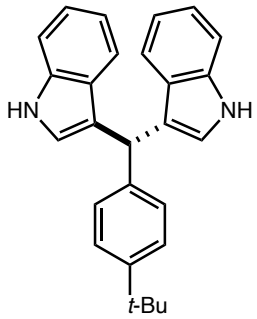



3,3'-(phenylmethylene)bis(1*H*-indole) **98**: Compound **98** was prepared according to the general procedure A with benzaldehyde, 4.2 equiv. 1*H*-indole (**91**), dichloromethane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a red

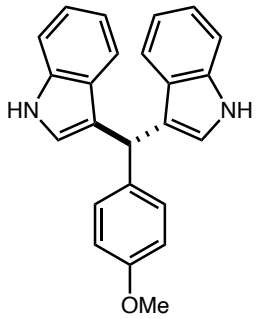
foam 0.090 g, 94% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.34 – 7.29 (m, 4H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.23 – 7.17 (m, 1H), 7.17 – 7.13 (m, 2H), 7.01 – 6.96 (m, 2H), 6.60 – 6.57 (m, 2H), 5.87 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 144.13, 136.79, 128.85, 128.35, 127.20, 126.26, 123.75, 122.05, 120.06, 119.81, 119.35, 111.16, 40.40, 40.23. IR (neat selected peaks) 3054, 2986, 1421, 1265, 896, 739 $cm^{-1}$. HRMS (ESI) m/z [M – H] calcd for $C_{23}H_{17}N_2$, 321.1392; found 321.1395.




3,3'-(*p*-tolylmethylene)bis(1*H*-indole) **96**: Compound **96** was prepared according to the general procedure A using 4-methylbenzaldehyde, 4.2 equiv. 1*H*-indole (**91**), dichloromethane, and Blue LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give an orange solid 0.065g, 65% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.23 – 7.20 (m, 2H), 7.16 – 7.12 (m, 2H), 7.07 (d, *J* = 7.7 Hz, 2H), 7.01 – 6.97 (m, 2H), 6.61 – 6.60 (m, 2H), 5.83 (s, 1H), 2.31 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 141.11, 136.81, 135.62, 129.05, 128.69, 127.23, 123.68, 122.00, 120.10, 120.02, 119.32, 111.14, 39.89, 21.20. HRMS (ESI) m/z [M – H] calcd for $C_{24}H_{19}N_2$, 335.1548; found 335.1548.

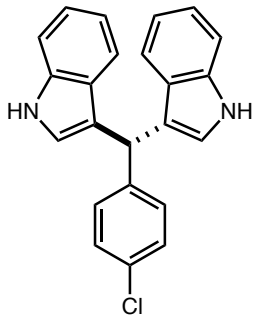



3,3'-((4-(*tert*-butyl)phenyl)methylene)bis(1*H*-indole) **100**: Compound **100** was prepared according to the general procedure A using 4-(*tert*-butyl)benzaldehyde, 4.2 equiv. 1*H*-indole (**91**), dichloromethane, and Blue LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give an orange foam 0.083 g, 74% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.23 (m, 4H), 7.17 – 7.12 (m, 2H), 6.99 (t, *J* = 7.5 Hz, 2H), 6.62 (d, *J* = 2.2 Hz, 2H), 5.84 (s, 1H), 1.29 (s, 9H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 148.84, 140.94, 136.78, 128.35, 127.27, 125.17, 123.68, 121.96, 120.12, 120.08, 119.25, 111.12, 39.74, 34.50, 31.58. HRMS (ESI) m/z [M – H] calcd for $C_{27}H_{25}N_2$, 377.2018; found 377.2018.

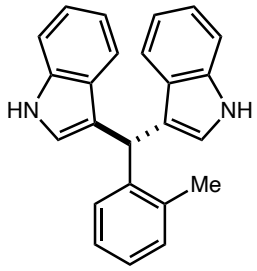



3,3'-((4-methoxyphenyl)methylene)bis(1*H*-indole) **95**: Compound **95** was prepared according to the general procedure A with 4-methoxybenzaldehyde, 4.2 equiv. 1*H*-indole (**91**), dichloromethane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give an orange foam (0.071 g, 68% yield). $^{1}$H NMR (500 MHz, $CDCl_3$) δ

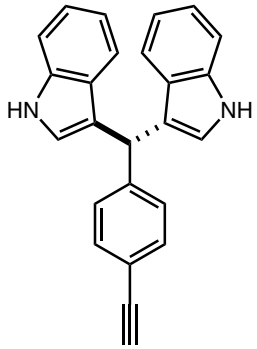
7.87 (s, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.26 – 7.19 (m, 2H), 7.18 – 7.13 (m, 2H), 7.03 – 6.96 (m, 2H), 6.83 – 6.79 (m, 2H), 6.64 – 6.62 (m, 2H), 5.83 (s, 1H), 3.77 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 158.05, 136.85, 136.36, 129.74, 127.21, 123.66, 122.04, 120.22, 120.13, 119.34, 113.71, 113.68, 111.14, 55.43, 55.27, 39.56, 39.39. HRMS (ESI) m/z [M – H] calcd for $C_{24}H_{19}N_2O$, 351.1497; found 351.1498.




3,3'-((4-chlorophenyl)methylene)bis(1*H*-indole) **99**: Compound **99** was prepared according to the general procedure A using 4-chlorobenzaldehyde, 4.2 equiv. 1*H*-indole (**91**), dichloromethane, and Blue LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give an orange solid 0.102g, 97% yield. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 2H), 7.37 – 7.31 (m, 4H), 7.28 – 7.20 (m, 4H), 7.19 – 7.13 (m, 2H), 7.03 – 6.97 (m, 2H), 6.60 (dd, *J* = 2.4, 1.1 Hz, 2H), 5.84 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 142.68, 136.81, 131.92, 130.20, 128.50, 127.01, 123.74, 122.21, 119.95, 119.49, 119.32, 111.25, 39.75. HRMS (ESI) m/z [M – H] calcd for $C_{23}H_{16}ClN_2$, 355.1002; found 355.1006.

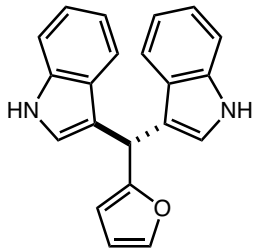



3,3'-(*o*-tolylmethylene)bis(1*H*-indole) **97**: Compound **97** was prepared according to the general procedure A using 2-methylbenzaldehyde, 1*H*-indole (**91**), 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give an orange solid 0.072 g, 72% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.16 – 7.07 (m, 3H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.00 – 6.94 (m, 3H), 6.36 (s, 2H), 5.97 (s, 1H), 2.33 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 142.19, 136.75, 136.17, 130.30, 128.49, 127.24, 126.19, 125.93, 124.01, 121.96, 119.84, 119.27, 119.08, 111.20, 36.27, 19.63. HRMS (ESI) m/z [M – H] calcd for $C_{24}H_{19}N_2$, 335.1548; found 335.1544.

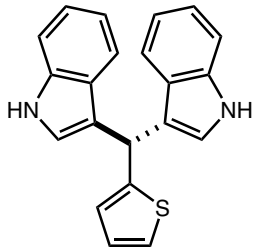



3,3'-((4-ethynylphenyl)methylene)bis(1*H*-indole) **101**: Compound **101** was prepared according procedure A to the general procedure using 4-ethynylbenzaldehyde, 1*H*-indole (**91**), 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give an orange solid 0.081 g, 79% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.84 (s,

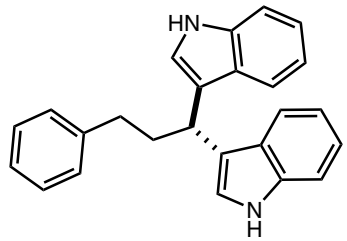
2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 2H), 6.57 (d, *J* = 2.2 Hz, 2H), 5.86 (s, 1H), 3.02 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 145.16, 136.74, 132.25, 128.85, 126.99, 123.78, 123.76, 122.17, 119.93, 119.86, 119.45, 119.11, 111.24, 84.03, 76.84, 76.83, 40.20. HRMS (ESI) m/z [M – H] calcd for $C_{25}H_{17}N_2$, 345.1392; found 345.1393.




3,3'-(furan-2-ylmethylene)bis(1*H*-indole) **68**: Compound **68** was prepared according to the general procedure A using furfural, 1*H*-indole (**91**), 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a dark red solid (0.051 g, 55% yield). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.44 (d, *J* = 1.0 Hz, 2H), 7.31 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.26 (dt, *J* = 8.2, 1.0 Hz, 2H), 7.16 – 7.11 (m, 2H), 7.04 – 6.99 (m, 2H), 6.74 (dd, *J* = 2.4, 1.0 Hz, 2H), 6.27 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.03 – 6.01 (m, 1H), 5.90 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 157.20, 141.34, 136.61, 126.86, 123.22, 122.05, 119.77, 119.46, 117.19, 111.29, 110.33, 110.29, 110.24, 106.79, 106.73, 106.68, 34.25, 34.20, 34.16. HRMS (ESI) m/z [M – H] calcd for $C_{21}H_{15}N_2O$, 311.1184; found 311.1182.

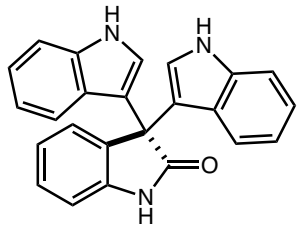



3,3'-(thiophen-2-ylmethylene)bis(1*H*-indole) **69**: Compound **69** was prepared according to the general procedure A using thioaldehyde, 1*H*-indole (**91**), 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 10-20% acetone/hexanes to give an orange solid (0.063 g, 64% yield). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 2H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.36 – 7.31 (m, 2H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.14 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.02 (td, *J* = 7.5, 7.0, 1.0 Hz, 2H), 6.92 – 6.88 (m, 2H), 6.82 (d, *J* = 2.2 Hz, 2H), 6.15 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 148.69, 148.64, 136.57, 126.76, 126.44, 125.16, 123.63, 123.19, 122.04, 119.78, 119.71, 119.38, 35.32. HRMS (ESI) m/z [M – H] calcd for $C_{21}H_{15}N_2S$, 327.0956; found 327.0960.

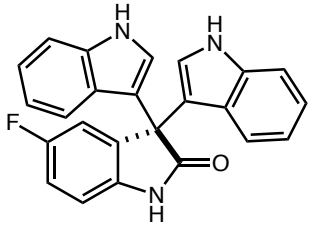



3,3'-(3-phenylpropane-1,1-diyl)bis(1*H*-indole) **72**: Compound **72** was prepared according to the general procedure A using 3-phenylpropanal, 1*H*-indole (**91**), 1,4-dioxane, and Blue LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give an orange solid (0.064 g, 61% yield). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.20 – 7.11 (m, 5H), 7.05 – 7.00 (m, 2H), 6.98 (d, *J* = 2.4 Hz, 2H), 4.49 (t, *J* = 7.4 Hz, 1H), 2.78 – 2.64 (m, 2H), 2.58 – 2.51 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 142.76, 136.73, 128.69, 128.41, 127.19, 125.81, 121.92, 121.64, 120.17,

119.77, 119.19, 111.21, 37.51, 34.58, 33.61. HRMS (ESI) m/z [M – H] calcd for $C_{25}H_{21}N_2$, 349.1705; found 349.1709.

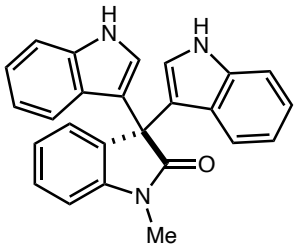


[3,3':3',3"-terindolin]-2'-one **70**: Compound **70** was prepared according to the general procedure A using 1*H*-isatin (**32**), 1*H*-indole (**91**), 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a tan solid 0.075 g, 69% yield. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.98 (d, $J$ = 2.6 Hz, 2H), 10.63 (s, 1H), 7.35 (d, $J$ = 8.2 Hz, 2H), 7.27 – 7.15 (m, 4H), 7.05 – 6.95 (m, 3H), 6.95 – 6.90 (m, 1H), 6.86 (s, 2H), 6.83 – 6.77 (m, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 178.78, 178.67, 141.35, 141.20, 136.94, 136.78, 134.63, 134.59, 127.88, 125.68, 124.95, 124.19, 124.11, 121.51, 120.97, 120.81, 118.26, 114.25, 111.58, 109.56, 52.56. HRMS (ESI) m/z [M – H] calcd for $C_{24}H_{16}N_3O$, 362.1293; found 362.1286.

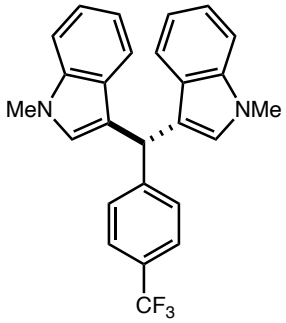


5'-fluoro-[3,3':3',3"-terindolin]-2'-one **71**: Compound **71** was prepared according to the general procedure A using 5-fluoro-1*H*-isatin, 4.2 equiv. 1*H*-indole (**91**), 1,4-dioxane, and Blue LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a yellow solid 0.063 g, 79% yield. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 11.02 (d, $J$ = 2.6 Hz, 2H), 10.66 (s,

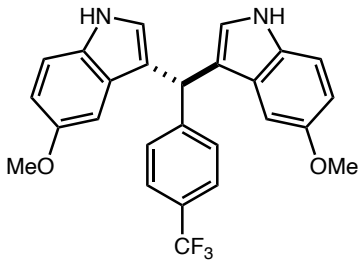
1H), 7.36 (d, $J$ = 8.3 Hz, 2H), 7.22 (d, $J$ = 8.0 Hz, 2H), 7.10 – 6.96 (m, 5H), 6.90 (d, $J$ = 2.6 Hz, 2H), 6.85 – 6.79 (m, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 178.68, 158.81, 156.92, 137.58, 137.57, 136.95, 136.37, 136.31, 125.55, 124.45, 121.04, 120.62, 118.38, 114.33, 114.14, 113.66, 112.54, 112.35, 111.71, 110.40, 110.34, 53.12. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{24}H_{17}FN_3O$, 382.1356; found 382.1357.




1'-methyl-[3,3':3',3''-terindolin]-2'-one **102**: Compound **102** was prepared according to the general procedure A using *N*-methyl isatin, 1*H*-indole (**91**), 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a tan solid (0.073 g, 65% yield). $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.98 (d, $J$ = 2.6 Hz, 2H), 7.37 – 7.31 (m, 3H), 7.28 (d, $J$ = 7.0 Hz, 1H), 7.19 – 7.14 (m, 3H), 7.01 (t, $J$ = 7.6 Hz, 3H), 6.85 (d, $J$ = 2.5 Hz, 2H), 6.79 (t, $J$ = 7.5 Hz, 2H), 3.26 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 176.91, 142.75, 136.95, 133.70, 128.01, 125.63, 124.60, 124.37, 124.33, 122.18, 120.99, 120.71, 118.32, 114.06, 111.65, 108.68, 52.16. HRMS (ESI) m/z [M] calcd for $C_{25}H_{19}N_3O$, 377.1528; found 377.1517.

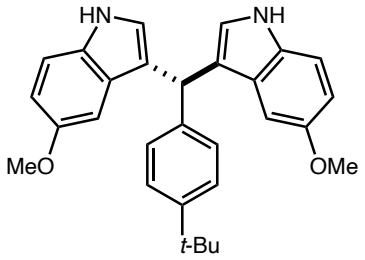



3,3'-((4-(trifluoromethyl)phenyl)methylene)bis(1-methyl-1*H*-indole) **103.** Compound **103** was prepared according to the general procedure A using 4-(trifluoromethyl)benzaldehyde (**89**), 1-methylindole, 1,4-dioxane, and 370 nm LEDs . Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a pink foam (0.105 g, 85% yield). $^{1}$H NMR (500 MHz, DMSO-*d*6) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.14 – 7.08 (m, 2H), 6.95 – 6.90 (m, 2H), 6.87 (s, 2H), 5.98 (s, 1H), 3.70 (s, 6H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 150.11, 137.44, 129.46, 128.54, 128.46, 127.19, 125.57, 121.67, 119.56, 119.00, 118.95, 116.84, 110.19, 66.83, 32.70. IR (neat selected peaks) 3054, 2987, 1422, 1266, 869, 746 cm$^{-1}$. HRMS (ESI) m/z [M – H] calcd for $C_{26}H_{20}F_3N_2$, 417.1579; found 417.1577.

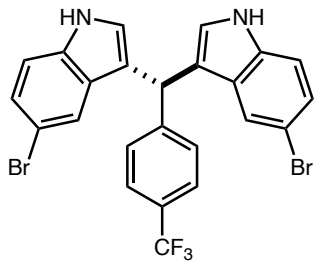



3,3'-((4-(trifluoromethyl)phenyl)methylene)bis(5-methoxy-1*H*-indole) **104**: Compound **104** was prepared according to the general procedure A using 4-(trifluoromethyl)benzaldehyde (**89**), 5-methoxy-1*H*-indole, 1,4-dioxane and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a red foam 0.092 g, 69% yield. $^{1}$H NMR (500 MHz,

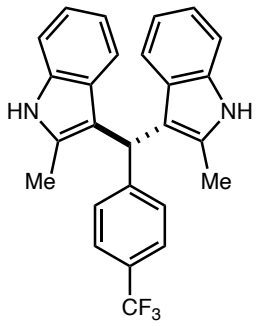
DMSO-$d_6$) δ 10.74 (s, 2H), 7.64 (d, $J$ = 8.1 Hz, 2H), 7.57 (d, $J$ = 8.1 Hz, 2H), 7.25 (d, $J$ = 8.7 Hz, 2H), 6.91 – 6.84 (m, 2H), 6.76 – 6.68 (m, 4H), 5.89 (s, 1H), 3.60 (s, 6H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 152.78, 149.98, 131.77, 129.04, 126.83, 126.58, 126.33, 125.60, 124.98, 124.46, 123.44, 116.77, 112.15, 110.73, 101.25, 101.21, 55.28. IR (neat selected peaks) 3054, 1421, 1266, 895, 738 cm$^{-1}$. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{26}H_{22}F_3N_2O_2$, 451.1633; found 451.1620.




3,3'-((4-(*tert*-butyl)phenyl)methylene)bis(5-methoxy-1*H*-indole) **105**: Compound **105** was prepared according to the general procedure A using 4-(*tert*-butyl)benzaldehyde, 4.2 equiv. 5-methoxy-1*H*-indole, dichloromethane, and Blue LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a brown foam (0.099 g, 76% yield). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.72 (m, 2H), 7.30 – 7.24 (m, 4H), 7.18 (d, $J$ = 8.6 Hz, 2H), 6.84 – 6.75 (m, 4H), 6.63 (d, $J$ = 2.5 Hz, 2H), 5.72 (s, 1H), 3.66 (s, 6H), 1.28 (s, 9H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.71, 148.84, 140.95, 131.96, 128.42, 127.67, 125.17, 124.49, 119.62, 111.93, 111.78, 102.13, 55.95, 39.89, 34.50. HRMS (ESI) m/z [M – H] calcd for $C_{29}H_{29}N_2O_2$, 437.2229; found 437.2224.



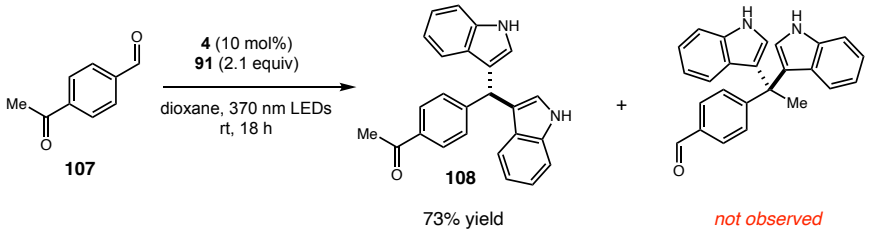

3,3'-((4-(trifluoromethyl)phenyl)methylene)bis(5-bromo-1*H*-indole) **73**: Compound **73** was prepared according to the general procedure A using 4-(trifluoromethyl)benzaldehyde (**89**), 4.2 equiv. 5-bromo-1*H*-indole, 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a dark red foam (0.119 g, 73% yield). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 1.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.21 (m, 4H), 6.61 (d, *J* = 2.5 Hz, 2H), 5.80 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 147.31, 135.44, 128.97, 128.51, 125.57, 125.32, 124.99, 124.97, 122.15, 122.13, 118.17, 112.97, 112.90, 39.83. HRMS (ESI) m/z [M – H] calcd for $C_{24}H_{14}Br_2F_3N_2$, 544.9476; found 544.9479.



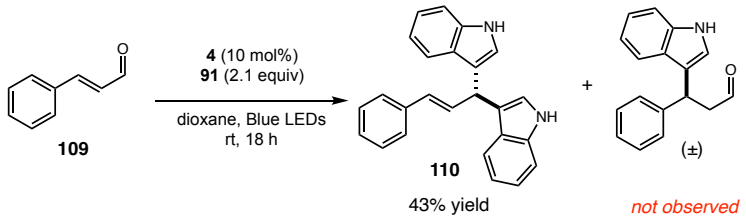

3,3'-((4-(trifluoromethyl)phenyl)methylene)bis(2-methyl-1*H*-indole) **106**: Compound **106** was prepared according to the general procedure A using 4-(trifluoromethyl)benzaldehyde (**89**), 4.2 equiv. 2-methyl-1*H*-indole, 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a pink foam (0.114 g, 92% yield). $^{1}$H NMR (500 MHz, DMSO-$d_6$) δ 10.85 (s, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.24 (d,

$J$ = 8.0 Hz, 2H), 6.93 – 6.89 (m, 2H), 6.81 (d, $J$ = 7.8 Hz, 2H), 6.72 – 6.68 (m, 2H), 6.03 (s, 1H), 2.10 (s, 6H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 149.37, 135.13, 132.40, 129.41, 128.02, 126.97 (q, $J_{FCC}$ = 31.5 Hz), 125.00 (q, $J_{FC}$ = 271.7 Hz), 125.31 (q, $J_{FCCC}$ = 3.7 Hz), 119.70, 118.32, 118.12, 111.27, 110.48, 38.57, 38.47, 11.94. HRMS (ESI) m/z [M – H] calcd for $C_{26}H_{20}F_3N_2$, 417.1579; found 417.1573.

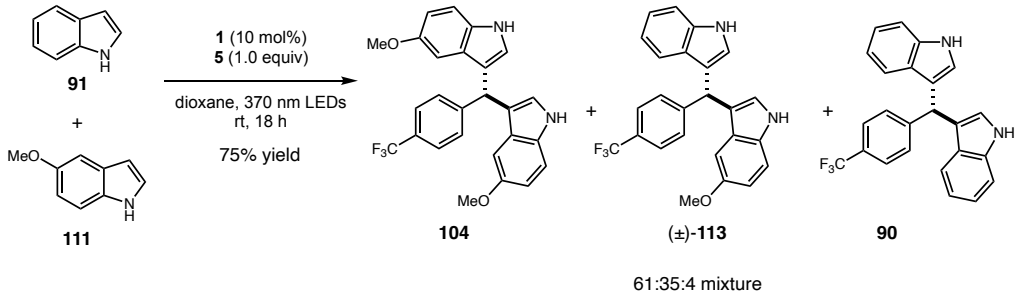
## D. Competition Experiments & Characterization for Compounds 108, 110, 113




1-(4-(di(1*H*-indol-3-yl)methyl)phenyl)ethan-1-one **108**: Compound **108** was prepared according to the general procedure A using 4-acetylbenzaldehyde (**107**), 1*H*-indole (**91**), 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a brown solid 0.079g, 73% yield. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, $J$ = 2.6 Hz, 2H), 7.80 (d, $J$ = 8.4 Hz, 2H), 7.36 (d, $J$ = 8.3 Hz, 2H), 7.32 (d, $J$ = 8.0 Hz, 2H), 7.26 (d, $J$ = 8.2 Hz, 2H), 7.13 (ddd, $J$ = 8.2, 7.0, 1.1 Hz, 2H), 6.98 (ddd, $J$ = 8.0, 7.0, 1.0 Hz, 2H), 6.57 – 6.43 (m, 2H), 5.88 (s, 1H), 2.51 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 198.57, 150.03, 136.71, 135.29, 129.00, 128.58, 126.87, 123.80, 122.13, 119.75, 119.40, 118.58, 111.33, 40.30, 26.72. HRMS (ESI) m/z [M – H] calcd for $C_{25}H_{19}N_2O$, 363.1497; found 363.1492.




(*E*)-3,3'-(3-phenylprop-2-ene-1,1-diyl)bis(1*H*-indole) **110**: Compound **110** was prepared according to the general procedure A using cinnamaldehyde, (**109**) 4.2 equiv. 1*H*-indole (**91**), 1,4-dioxane, and Blue LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a red solid (0.044 g, 43% yield). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 2H), 7.57 (d, *J* = 7.9 Hz, 2H), 7.34 – 7.28 (m, 4H), 7.24 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.18 – 7.13 (m, 3H), 7.05 – 7.01 (m, 2H), 6.81 (d, *J* = 2.5 Hz, 2H), 6.76 (dd, *J* = 15.8, 7.1 Hz, 1H), 6.53 – 6.47 (m, 1H), 5.37 (d, *J* = 7.1 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 137.79, 136.72, 132.46, 130.02, 128.57, 127.12, 127.04, 126.44, 122.74, 122.71, 122.03, 120.08, 119.36, 118.40, 111.25, 37.56, 37.52. HRMS (ESI) m/z [M – H] calcd for $C_{25}H_{19}N_2$, 347.1548; found 347.1555.



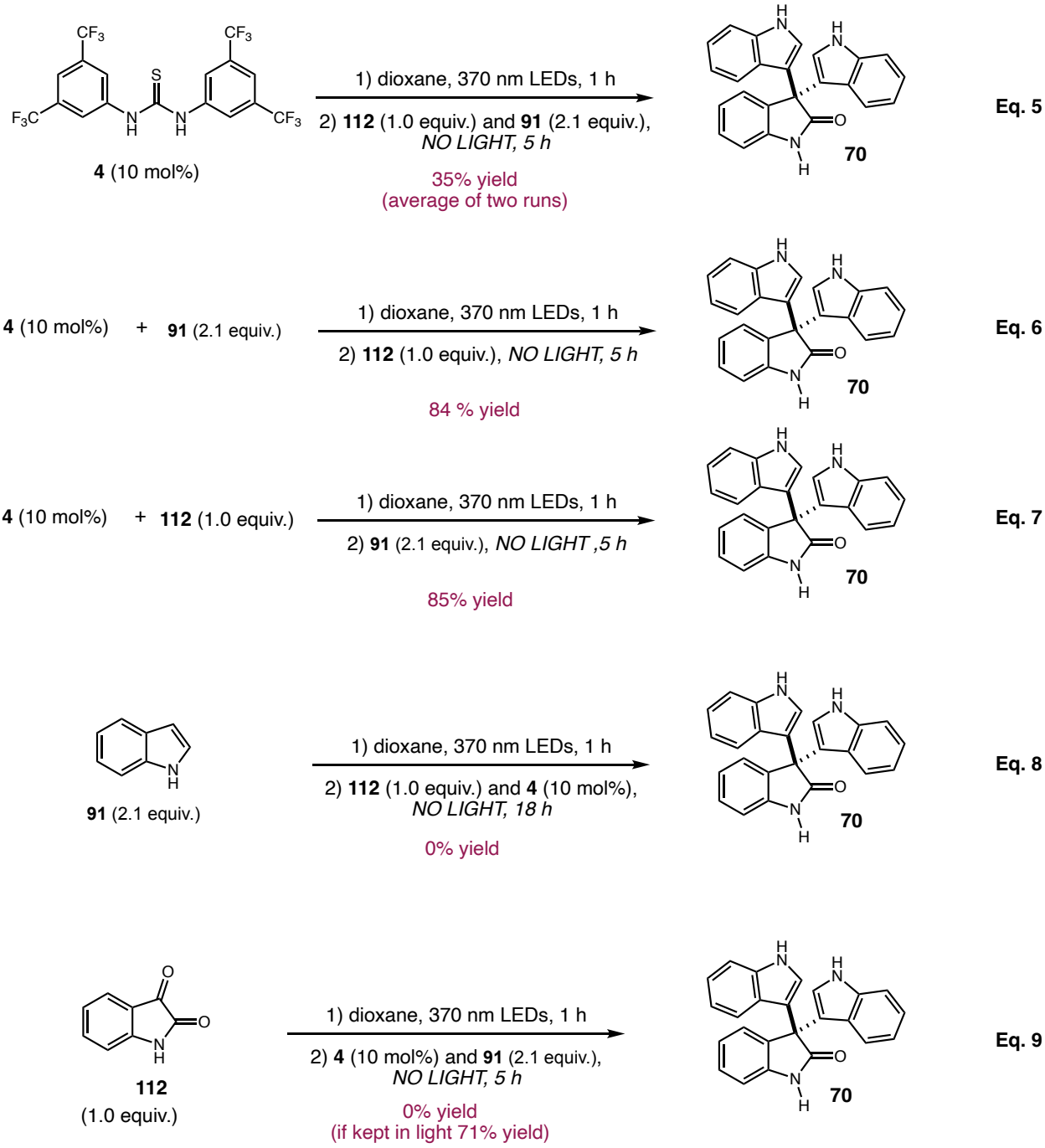

Competition run using the general procedure A with 4-(trifluoromethyl)benzaldehyde (**89**), 2.1 equiv. 1*H*-indole (**91**), 2.1 equiv. 5-methoxy indole (**111**), 1,4-dioxane, and 370 nm LEDs. 75% yield based on NMR mixture using 5,6-dibromobenzo[*d*][1,3]dioxole as an internal standard. 3-((1*H*-indol-3-yl)(4-(trifluoromethyl)phenyl)methyl)-6-methoxy-1*H*-indole (±)-**113**: Isolated by

flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a red solid (the isolated yield was not determined). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.87 (s, 1H), 7.56 (d, $J$ = 8.1 Hz, 2H), 7.48 (d, $J$ = 8.1 Hz, 2H), 7.39 (d, $J$ = 8.6 Hz, 2H), 7.27 (d, $J$ = 8.8 Hz, 1H), 7.22 (t, $J$ = 7.2 Hz, 1H), 7.07 (d, $J$ = 8.1 Hz, 1H), 6.89 (dd, $J$ = 8.8, 2.5 Hz, 1H), 6.82 (d, $J$ = 2.5 Hz, 1H), 6.65 (ddd, $J$ = 15.6, 2.5, 1.1 Hz, 2H), 5.92 (s, 1H), 3.74 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.98, 148.27, 136.86, 131.96, 129.14, 127.39, 126.96, 124.61, 124.53 (q, $J_{FC}$ = 272.0 Hz), 123.84, 128.56 (q, $J_{FCC}$ = 32.1 Hz), 125.33 (q, $J_{FCCC}$ = 3.7 Hz), 122.28, 119.88, 119.55, 118.74, 118.56, 112.25, 111.99, 111.32, 101.88, 56.05, 55.98, 40.28, 40.22. HRMS (ESI) m/z [M – H] calcd for $C_{25}H_{18}F_3N_2O$, 419.1371; found 419.1363.

## E. Initiation Studies with Isatin & 4-Trifluoromethyl Benzaldehyde

Initiation studies with isatin are shown in Scheme 17. If catalyst **4** is irradiated with 370 nm LEDs for 1 h, followed by the addition of isatin and indole, the reaction only reaches 32% yield after 5 h in the absence of further light irradiation (Eq. 5). Interestingly if either isatin or indole is initiated in the presence of catalyst **4**, the reactions go to completion (Eq. 6 and 7). These results suggest that substrate is required for reaction initiation. If only indole or isatin is irradiated there is no reaction (Eq. 8 and 9).

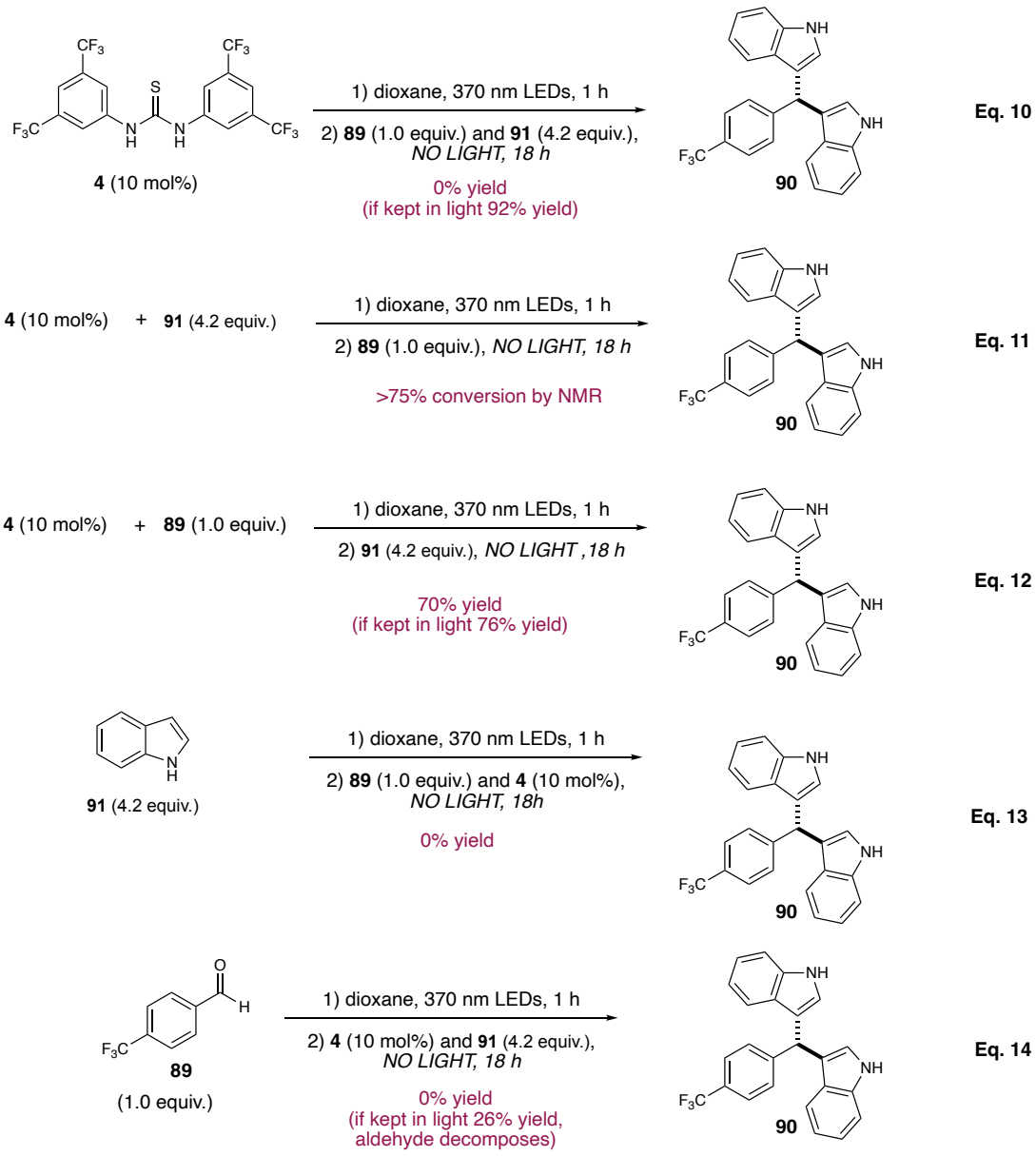
**Scheme 17:** Initiation studies with isatin.




Initiation studies with aldehyde **89** are shown in Scheme 18. In contrast to the isatin reaction, if catalyst **4** is irradiated with 370 nm LEDs for 1 h, followed by the addition of **89** and indole, there is no reaction after 18 h in the absence of further light irradiation (Eq. 10). If either

**89** or indole is irradiated in the presence of catalyst **4**, the reactions go to completion (Eq. 11 and 12). Again, these results suggest that substrate is required for reaction initiation. If only indole or **89** is irradiated alone there is no reaction (Eq. 13 and 14).

**Scheme 18:** Initiation studies with 4-trifluoromethyl benzaldehyde.



## XIII. References


1) Reviews on photocatalysis: (a) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (b) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (c) Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355. (d) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898. (e) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017**, 1, 1052

2) (a) Anastas, P. T.; Kirchhoff, M. M.; Williamson, T. C. *Appl. Catal., A* **2001**, *221*, 3. (b) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (c) Ivankovic, A.; Dronjic, A.; Bevanda, A. M.; Talic, S. *Int. J. Sustainable Green Energy* **2017**, *6*, 39.

3) (a) Tolbert, L. M.; Haubrich, J. E. *J. Am. Chem. Soc.* **1994**, *116*, 10593. (b) Maus, D.; Grandjean, A.; Jung, G. *J. Phys. Chem. A* **2018**, *122*, 9025.

4) (a) Shirai, M.; Tsunooka, M. *Prog. Polym. Sci.* **1996**, *21*, 1. (b) Fu, C.; Xu, J.; Boyer, C. *Chem. Commun.* **2016**, *52*, 7126. (c) Patel, P. K.; Arias, J. E.; Gongora, R. S.; Hernandez, F. E.; Moncomble, A.; Aloise, S.; Chumbimuni-Torres, K. Y. *Phys. Chem. Chem. Phys.* **2018**, *20*, 26804. (d) Zivic, N.; Kuroishi, P. K.; Dumur, F.; Gigmes, D.; Dove, A. P.; Sardon, H. *Angew. Chem. Int. Ed.* **2019**, 58, 10410.

5) Examples of photoacid catalysis: (a) Iwata, R.; Uda, K.; Takahashi, D.; Toshima, K. *Chem. Commun.* **2014**, *50*, 10695. (b) Das, A.; Banerjee, T.; Hanson, K. *Chem. Commun.* **2016**, *52*, 1350. (c) Das, A.; Ayad, S.; Hanson, K. *Org. Lett.* **2016**, *18*, 5416. (d) Yi, H.; Niu, L.; Wang, S.; Liu, T.; Singh, A. K.; Lei, A. *Org. Lett.* **2017**, *19*, 122. (e) Zhao, G.; Wang, T. *Angew. Chem., Int. Ed.* **2018**, *57*, 6120. (f) Yan, D.-M.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2019**, *58*, 378. (g) Strada, A.; Fredditori, M.; Zanoni, G.; Protti, S. *Molecules* **2019**, *24*, 1318.

6) Reviews on hydrogen bond donor catalysis: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Nagorny, P.; Sun, Z. *Beilstein J. Org. Chem.* **2016**, *12*, 2834.

7) (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Samet, M.; Kass, S. R. *J. Org. Chem.* **2015**, *80*, 7727. (c) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277.

8) Kimura, T.; Eto, T.; Takahashi, D.; Toshima, K. *Org. Lett.* **2016**, *18*, 3190.

9) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724.

10) Anywhere between 5-10% boost in efficiency depending on the substrate.

11) Contractor, R.; Samudio, I. J.; Estrov, Z.; Harris, D.; McCubrey, J. A.; Safe, S. H.; Andreeff, M.; Konopleva, M. *Cancer Res.* **2005**, *65*, 2890.

12) No 1,4-addition product was observed.

13) (a) de Lijser, H. J. P.; Rangel, N. A. *J. Org. Chem.* **2004**, *69*, 8315. (b) Martin, C. J.; Rapenne, G.; Nakashima, T.; Kawai, T. *C* **2018**, *34*, 41.

14) 10 mol% HF provided no product.

15) Irradiation of **6** or **32** in the absence of catalyst produces no product.

16) 10 mol% $Na_2CO_3$ resulted in <5% yield.

## *Chapter 3: Acetalization of Carbonyls*

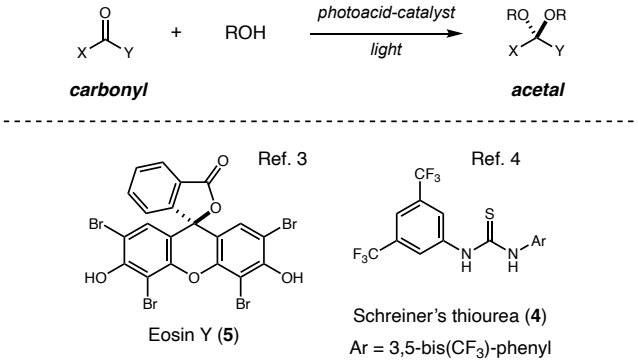
# I. Introduction

The development of a synthetic approach for the production of acetals employing 6-bromo-2-naphthol as a photoacid is covered in Chapter 3. The optimal conditions are explained in section three. Section five further explains how the $S_1$ excited-state pKa for 6-bromo-2-naphthol was determined and illustrates how this compound exhibits increased excited-state acidity in comparison to 2-naphthol in water. A portion of the material presented in section chapter 3 is excerpted from a work that was published in *Organic & Biomolecular Chemistry*, in collaboration with Abigail F. Pierre and Joseph J. Badillo  after peer review. To access the final edited and published work see DOI: 10.1039/D2OB00435F

# II. Previous Acetalization Reactions

Reports by Lei and Kokotos have shown that the direct excitation of photoacids **5** and **4** provide access to acetylated materials from aldehydes and ketones (Figure 7).[3-5]

**Figure 7**: Previous examples of photoacid-catalyzed acetalization of carbonyls.



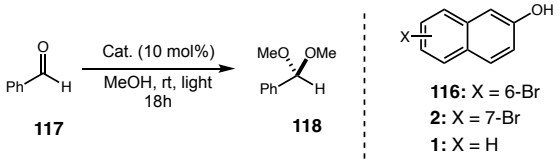

With their previous work in mind, I started to question if a cheaper, more commercially available photoacid could facilitate acetalization as well. In my second research project, I

demonstrate how 6-bromo-2-naphthol (**116**) works as a photoacid catalyst for the production of acetals when exposed to visible light irradiation.[6,7] I also show that the acetalization of electron-deficient aldehydes is facilitated by the photosensitization of 2-naphthol in the presence of a photosensitizer.

## III. Optimization

I began my research by synthesizing acetal **118** in 90% yield by irradiating benzaldehyde (**117**) and 10 mol% 6-bromo-2-naphthol (**116**) with 40 W Blue LEDs in methanol (Table 5, Entry 4). No product is seen in the absence of a catalyst and/or light (Entries 1-3). By employing 5 mol% **116**, the yield reduces to 36%, and when using 1 mol% **116**, just trace product is seen (Entries 6-7). The bromine atom is essential for catalyst activation, 7-bromo-2-naphthol (**2**) provides **118** in 84% yield and unsubstituted 2-naphthol (**1**) is inactive (Entries 8-9). It is worth noting that in the case of benzaldehyde (**117**) aerobic photoirradiation (reaction run open to air) in the absence of catalyst, provides **118** in 90% efficiency.[8] In addition, a methodology where catalyst **116** can be recovered up to 96% without the need for column chromatography was developed. This recovered catalyst can be used in subsequent reactions without loss of efficiency.

**Table 5**: Optimization for the photoacid-catalyzed acetalization of carbonyls.




**117** **118**

**116:** X = 6-Br
**2:** X = 7-Br
**1:** X = H

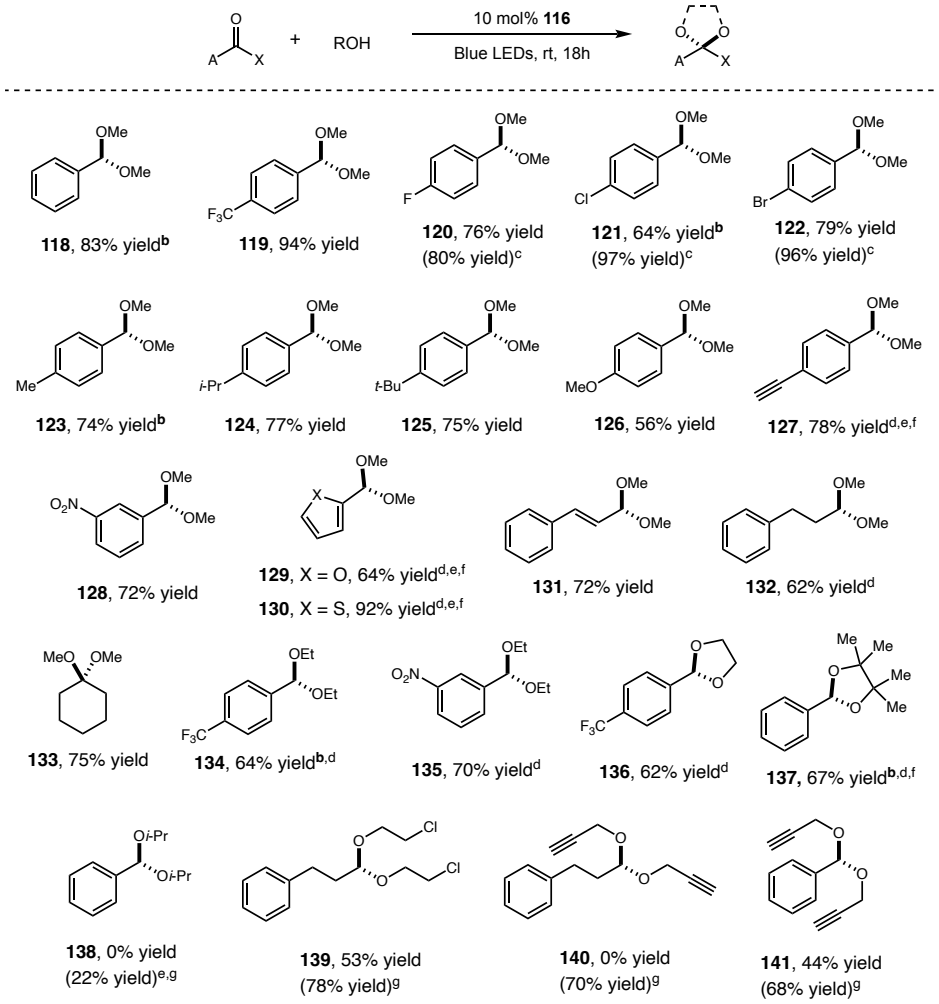
a) Conditions: 6 (0.5 mmol) in MeOH (0.5 M), under argon atmosphere. b) % yields based on 1H NMR using an internal standard: 5,6-dibromo-1,3-benzodioxole. c) Run with 5 mol% 3. d) Run with 1 mol% 3. e) No catalyst, reaction run open to air. f) Based on conversion by 1H NMR.

| entry | catalyst | light | % yield[b] |
|---|---|---|---|
| 1 | -- | -- | 0 |
| 2 | -- | 40 W Blue LEDs | 0 |
| 3 | 116 | -- | 0 |
| 4 | 116 | 40 W Blue LEDs | 90 |
| 5 | 116 | 370 nm LEDs | 44 |
| 6[c] | 116 | 40 W Blue LEDs | 36 |
| 7[d] | 116 | 40 W Blue LEDs | <5 |
| 8 | 2 | 40 W Blue LEDs | 84 |
| 9 | 1 | 40 W Blue LEDs | 0 |
| 10[e] | -- | 40 W Blue LEDs | 90[f] |

## IV. Results of Carbonyl & Alcohol Scope

With optimized conditions in hand, I proceeded to elucidate the scope of this photoacid catalyzed protocol (Table 6).

**Table 6**: Scope for the photoacid-catalyzed acetalization of carbonyls.




a) Conditions: carbonyl compound (0.5 mmol) in the corresponding alcohol (0.5 M), under argon atmosphere, b)% yields based on 1H NMR using an internal standard: 5,6-dibromo-1,3-benzodioxole. c) Based on conversion by 1H NMR and run with no catalyst. d) Run with 20 mol% 3. e) Run with 370 nm LEDs. f) Run in 0.33 M MeOH:dioxane (2:1). g) Run with 10 mol% 2.

Aromatic aldehydes **119-126** containing both electron-donating and electron-withdrawing groups work well (56-94% yield). Interestingly, photoirradiation of halogenated aldehydes provided acetals **120-122** with or without catalyst **116** (80-97% yield). A possible explanation for this observation is the formation of trace amounts of halogen acids during the reaction. Acetal **127**, containing an alkyne functional handle forms in 78% yield. Both heteroaromatics **129** and **130**,

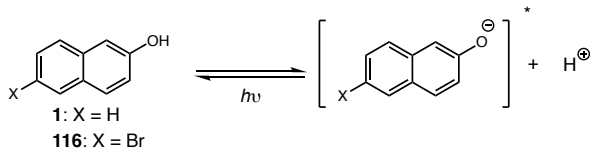
and α,β-unsaturated system **131** form acetals in good yields (64-92% yield). Importantly, aliphatic acetal **132** and cyclohexanone-derived acetal **133** form in 62 and 75% yield, respectively.

We also investigated a range of alcohols for this photoacid-catalyzed protocol. Ethoxy acetals **134** and **135** formed in 64 and 70%, respectively. Pinacol **137** and ethylene glycol **136** derived cyclic acetals were produced with good yields of 62 and 67%, respectively. In general, this photoacid catalyzed approach performed poorly with more intricate and sterically hindered alcohols. Acetal **138** generated from isopropyl alcohol was not produced while using **116**. Acetals produced from aliphatic and aromatic propargyl alcohols (**140** and **141**) formed in 0 and 44% yield, respectively, whereas acetals derived from 2-chloroethanol (**139**) formed in 53% yield. Thiourea photoacid catalyst **2** was examined for comparison and offered **138-141** from 22-78% yield.

## V. pKa Studies

It is noted that the bromine atom of **116** is critical for photoacid catalysis to occur, unsubstituted 2-naphthol (**1**) is completely inactive. To compare their reactivity I determined both the ground state acidity (pKa) and excited-state acidity ($pKa^*$) for both **116** and **1** (Figure 8A).[9]

**Figure 8A**: Excited-state pKa and lifetime determination for catalysts **116** and **1**.



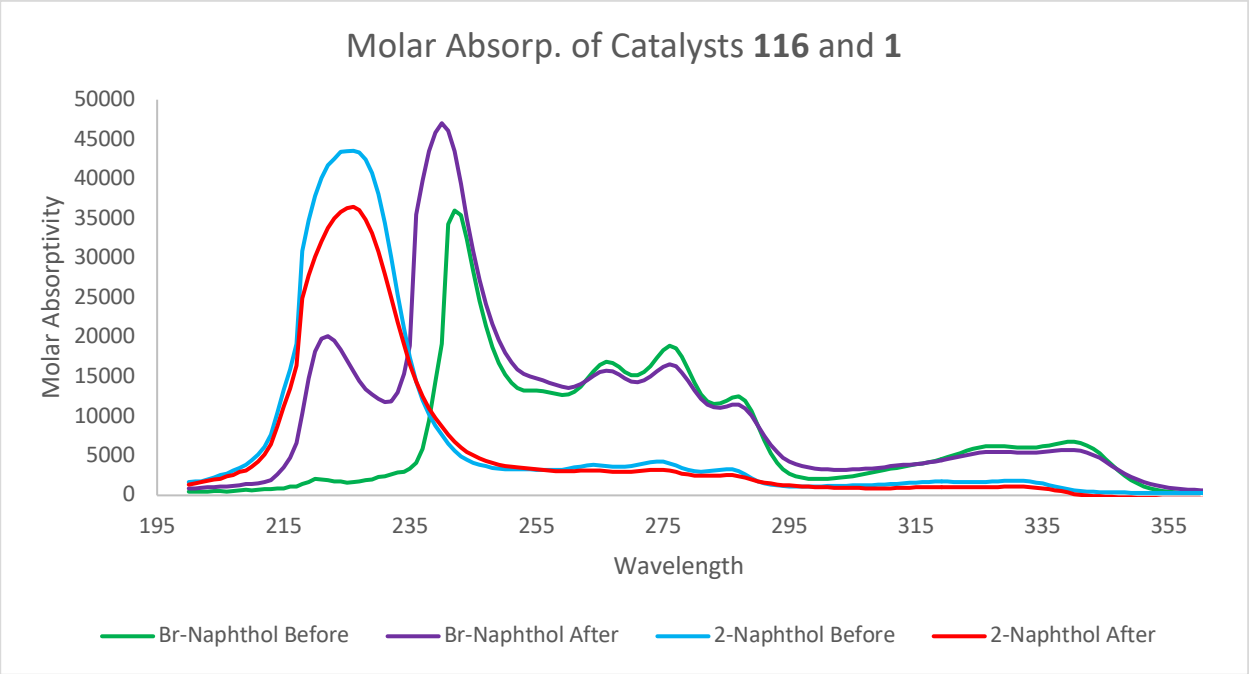

**1**: X = H
**116**: X = Br

| X | $\lambda_{max}$ (nm) | $\tau_{S1}$ (ns) | $pK_a$ ($H_2O$) | $pK_a^*$ ($H_2O$) |
|---|---|---|---|---|
| H | 330 | 8.6[ref. 10] | 9.75 (9.45)[ref. 12] | 3.26 (2.8)[ref. 12] |
| Br | 340 | 0.061 | 9.84 | 1.98 |

The pKa of **1** was determined to be 9.75 and the pKa of **116** was determined to be 9.84, to the best of our knowledge this represents the first time the pKa for **116** has been determined in water.[10] The $pKa^*$ of **116** and **1** was determined to be 1.98 and 3.26, respectively. Interestingly, although the ground state pKa of **116** and **1** differ by only 0.09 pKa units, the $pKa^*$ of **116** was found to be $10^{1.4}$ times more acidic than the $pKa^*$ of **1**.

It was also determined that the excited state ($S_1$) lifetimes for both **116** and **1** were 0.061 ns (4.9 ps) and 8.6 ns, respectively. The quick intersystem crossover (ISC) caused by the bromine's heavy atom effect into a triplet excited state is thought to be the cause of **116**'s significantly shorter siglet lifespan.[11] It is worth noting that the pKa, $pKa^*$, and $S_1$ lifetime values determined for **1** are in good agreement with Tolbert and Haubrich.[12] Significantly, photoacid catalyst **116** is activated by the direct stimulation with visible light (Blue LEDs) to promote acetalization. We examined the UV-Vis spectra for both **116** and **1** before and after the 18-hour exposure to better understand this (Figure 8B).

**Figure 8B**: UV-vis spectra for **116** and **1** before & after 18 h irradiation with blue LEDs.

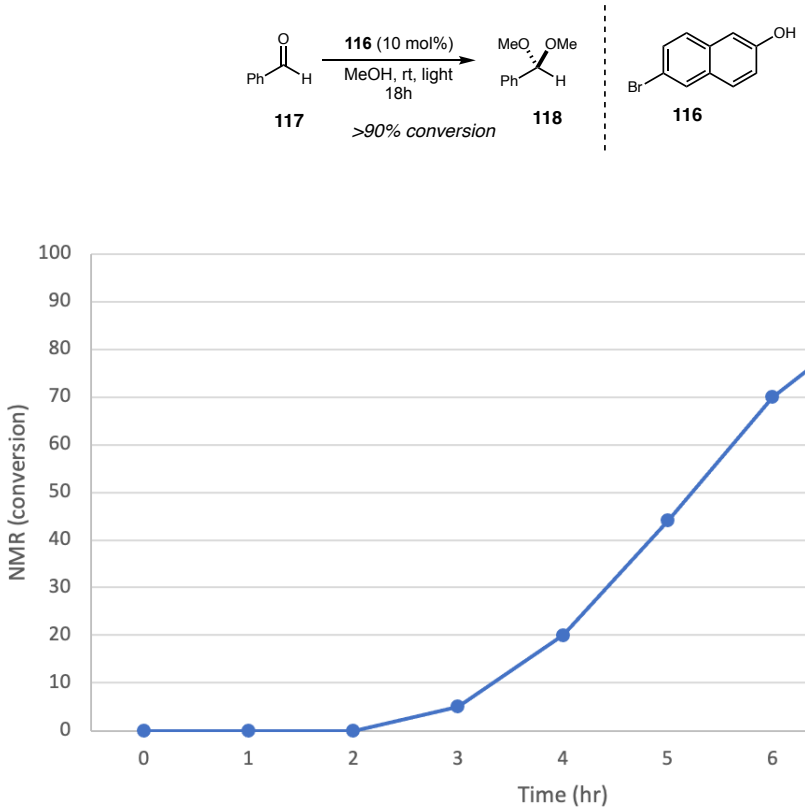



Catalyst **116** develops a prominent new feature at ~220 nm after irradiation, **1** remains largely unchanged. Catalyst **116** absorbs lower-energy light (340-360 nm) and with higher efficiency when compared to **1**, however, neither **116** nor **1** significantly absorbs light in the blue region of the electromagnetic spectrum (450-485).[14]

## VI. Initiation Studies

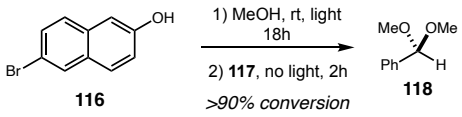
After determining the ground state (pKa) and excited-state acidity (pKa*), initiation studies were conducted to determine how long it would take for the reaction to go to completion. According to the investigations, the reactions require a 2 h induction time before they can start, and if enough photoactivation is accomplished, the acetalization process may still occur in the dark, indicating that the catalysis is provided by a persistent acidic species that is created *in situ*. The standard reaction was monitored under constant irradiation with Blue LEDs (Figure 9). A 2 h induction period was observed, after which the reaction reached 90% conversion after 6 h.

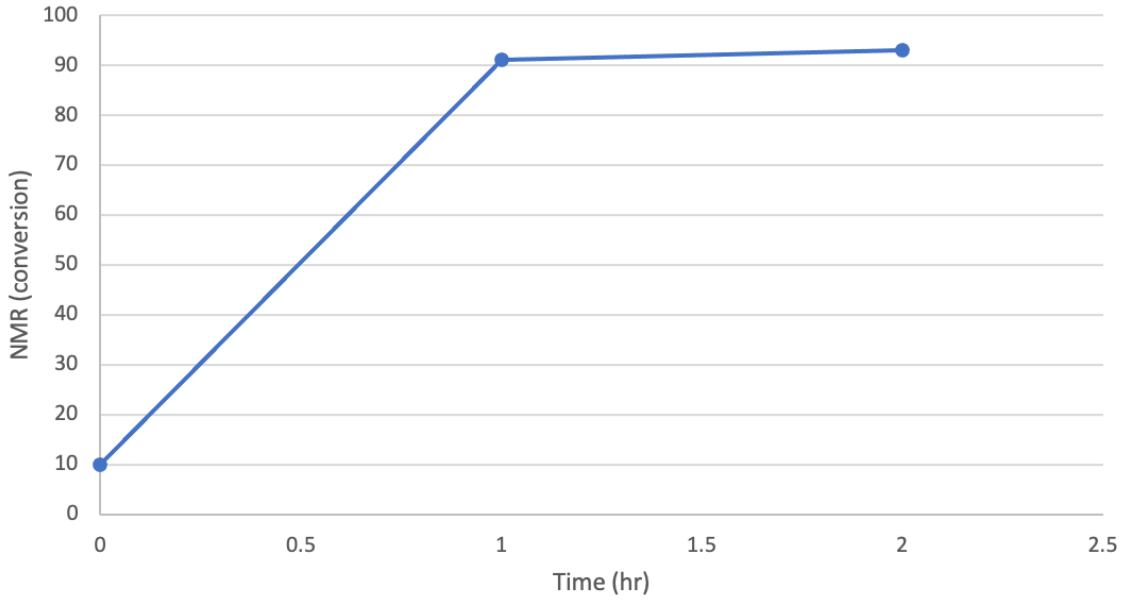
**Figure 9:** Reaction run according to standard procedure A. Aliquots were taken every 1 h using a BD spinal needle and %conversion of **117** to **118** was determined by NMR spectroscopy.




To further probe the initiation kinetics, catalyst **116** in methanol was irradiated with Blue LEDs for 17 h (Figure 10). Next, aldehyde **117** was added and the reaction was placed in the dark. The reaction reached completion in less than 2 h. This suggests that a strongly acidic species is generated and persists in the absence of further irradiation.

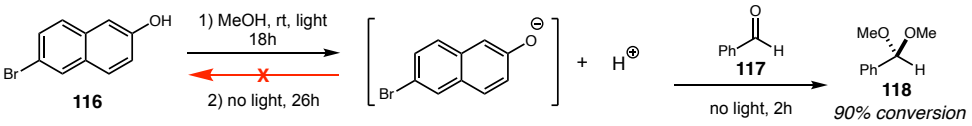
**Figure 10:** Reaction run with 0.05 mmol **116** and 0.5 mmol **117** in methanol (0.5 M) under argon atmosphere. Aliquots were taken using a BD spinal needle and %conversion of **117** to **118** was determined by NMR spectroscopy.

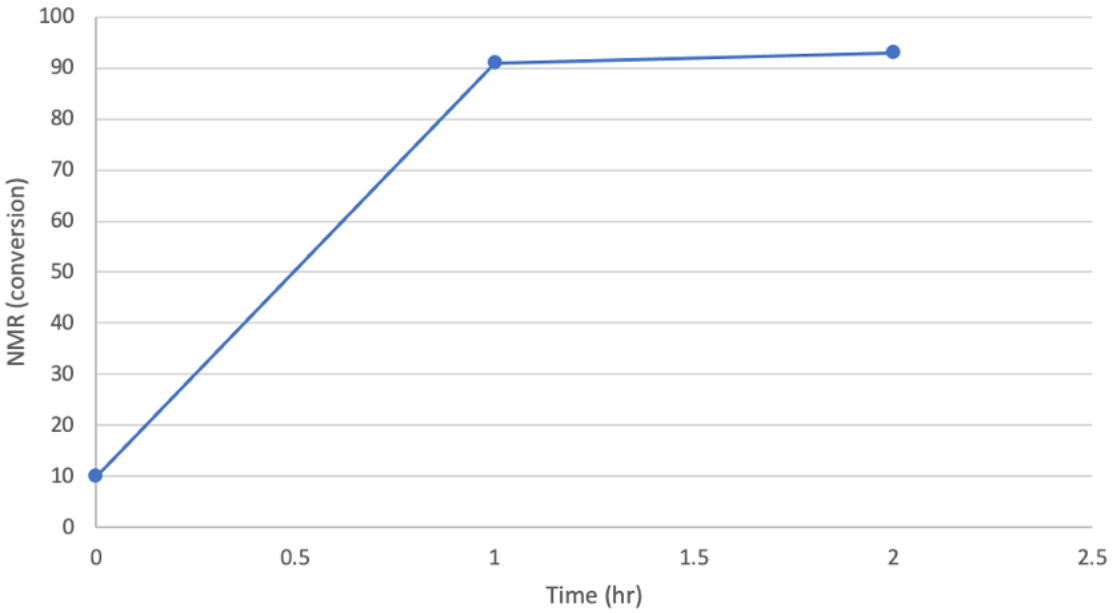



Catalyst **116** was exposed to light radiation for 24 hours in order to assess the reversibility of strong acid production (Figure 11). Then the reaction was placed in the dark for 26 h. Next, **117** was added, and the reaction was left to stir in the dark until complete. Despite having stirred in the dark for 26 h, the reaction still finished in less than 2 h, indicating the formation of a persistent strongly acidic species is not reversible. It was discovered that the usual reaction of **117** to **118** in the presence of 10 mol% **116** was entirely stopped by the addition of 5 mol% triethylamine or sodium bicarbonate.

**Figure 11:** Reaction run with 0.05 mmol **116** and 0.5 mmol **117** in methanol (0.5 M) under argon atmosphere. Aliquots were taken using a BD spinal needle and % conversion of **117** to **118** was determined by NMR spectroscopy.

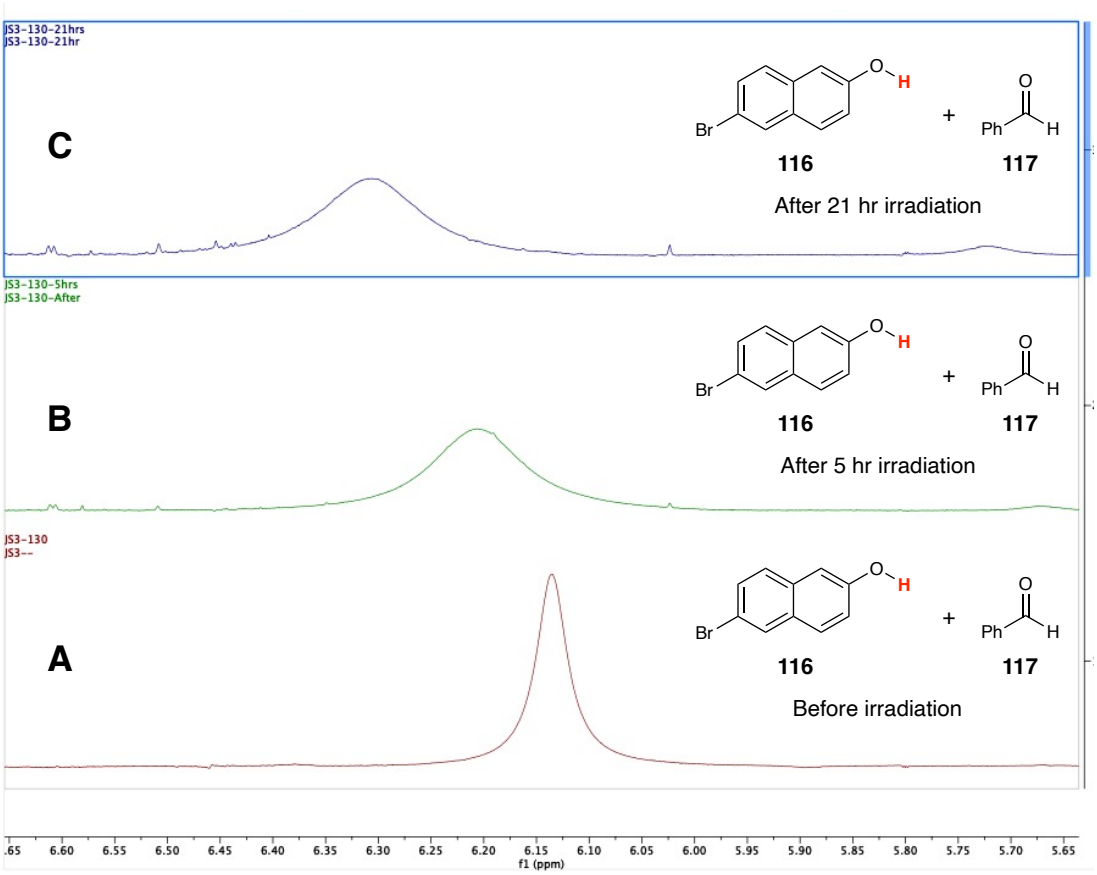



I also performed an NMR experiment to see if there was hydrogen-bonding between the catalyst and reagent that resulted in a highly acidic species being generated. To start an aliquot of of **116** and **117** was taken and an NMR was run. The OH-peak was observed to be broadened at 6.13 ppm, indicating the creation of an H-bonding complex between **116** and **117**, Figure 12A. After 5 h irradiation with Blue LEDs, the OH-peak of **116** significantly broadens and shifts from 6.13 to 6.20 ppm, suggesting enhanced hydrogen bonding upon irradiation, Figure 12B.

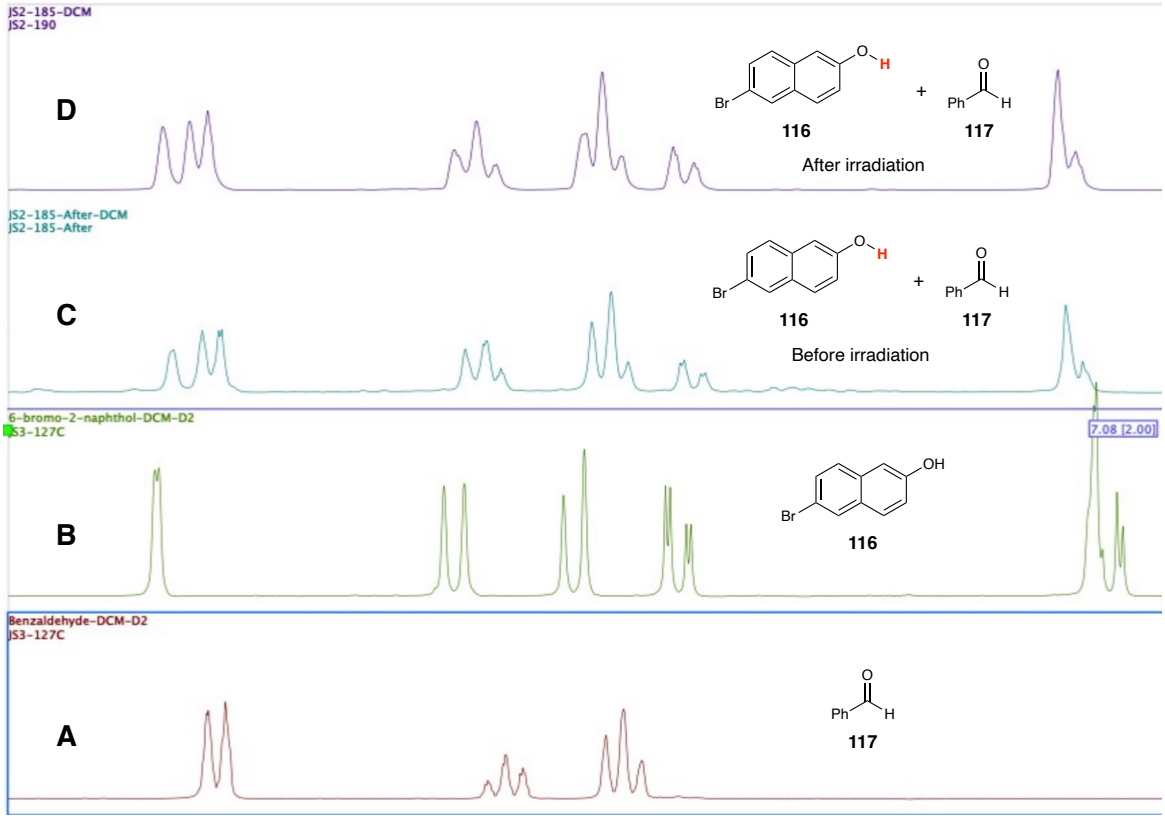
Ultimately, the OH-peak moves to 6.31 ppm after 21 hours of exposure, Figure 12C. This demonstrates that persistent radiation causes the formation of a strongly acidic species.

**Figure 12:** NMR spectra showing the hydroxy chemical shift of **116** compared to a 1:1 mixture of **116** and **117** before and after 5 h and 21 h irradiation with Blue LEDs (0.25 M in $CD_2Cl_2$).




The aromatic region for catalyst **116** and aldehyde **117** is shown in Figure 13A and B. Upon mixing of **116** and **117**, the peaks broaden, suggesting formation of an H-bonding complex (Figure 13C). Notably, the catalyst peaks at 7.11 ppm shift downfield by ~0.05 ppm. After 18 h irradiation with Blue LEDs, the aromatic region shows little change (Figure 13D).

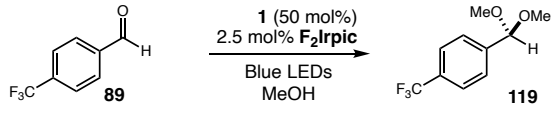
**Figure 13:** NMR spectra showing the aromatic region of **116** and **117** compared to of a 1:1 mixture of **116** and **117** before and after 18 h irradiation with Blue LEDs (0.25 M in $CD_2Cl_2$).




## VII. Photosensitizer & 2-Naphthol Complex

Interestingly, even though 2-naphthol (**1**) was unable to catalyze the reaction it was found that 2-naphthol in the presence of {**$F_2$Irpic**,bis[2-(4,6-difluorophenyl)pyridinato-C2,N](picolinato)iridium(III)} facilitates the reaction of aldehyde **89** to form acetal **119** in 74% yield (Figure 14A).

**Figure 14A**: Photosensitization of 2-naphthol

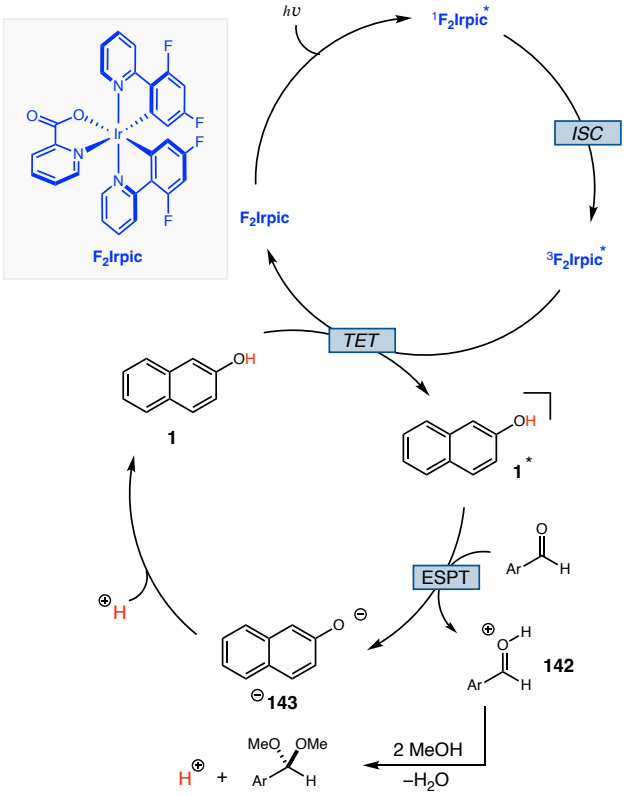



| 1 | $F_2$Irpic | *yield* |
|---|---|---|
| × | × | — |
| √ | × | 0 |
| × | √ | 25 |
| √ | √ | ***74*** |

When the sensitizer **$F_2$Irpic** alone is used the reaction only reaches 25% yield. However, the reaction yield increases to 74% when both **$F_2$Irpic** (2.5 mol%) and **1** (50 mol%) are used. Emission quenching studies showed that **$F_2$Irpic** emission was 66% quenched in the presence of 2-naphthol (**1**) with and without **89**, suggesting efficient energy transfer between **$F_2$Irpic** and **1**. No **$F_2$Irpic** emission quenching was observed in the presence of **89** in the absence of **1**. Based on independent reports by Hanson and Protti, a possible mechanism for the formation of **119** is shown in Figure 14B.[15,16]

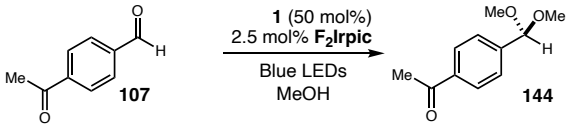
Photoexcitation of **$F_2$Irpic** results in formation of singlet $^1$**$F_2$Irpic**$^*$, intersystem crossing (ISC), and metal to ligand charge transfer (MLCT) gives rise to triplet excited state $^3$**$F_2$Irpic**$^*$. Triplet energy transfer from $^3$**$F_2$Irpic**$^*$ to **1**, gives rise to **1**$^*$ which is sufficiently acidic to protonate the aldehyde to afford oxonium ion **142**. Subsequent reaction of **142** with 2 equivalents of methanol results in acetal formation and regenerates a proton. The *in situ* produced proton that follows can either protonate another equivalent of aldehyde or protonate **143** to recombine with **1**. In the presence of **$F_2$Irpic** with and without **1**, the addition of 5 mol% sodium bicarbonate prevented acetal synthesis, indicating that the reaction includes the production of a Brønsted acid. It was found that the sensitization reaction requires electron-withdrawing groups and that light irradiation is necessary for the reaction to continue.

**Figure 14B**: Possible mechanism for the formation of **119**



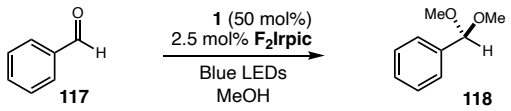

I noticed that the sensitization reaction occurs primarily in the presence of electron-withdrawing groups. In the instance of 4-acetylbenzaldehyde (**107**), acetal **144** was produced in 12% yield in the absence of **1**. (Scheme 19). However, a 40% yield of **144** was generated after adding both **$F_2$Irpic** and **1**. When benzaldehyde (**117**) was investigated only 6% product **118** was observed in the presence of **$F_2$Irpic**, with and without **1** (Scheme 20). For the reaction of electron-rich *p*-tolualdehyde **145** in the presence of **$F_2$Irpic**, with or without **1**, 57 and 54% yield of **123** was observed, respectively (Scheme 21). Importantly, overnight irradiation of **$F_2$Irpic** and **1**, followed by the addition of **89**, and placement in the dark did not result in the production of any product, in contrast to the situation of 6-bromo-2-naphthol (**116**). A permanent *in situ* produced acidic species does not seem to be developing.

**Scheme 19:** Photosensitizer and 2-naphthol with 4-acetylbenzaldehyde.



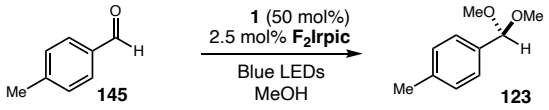

| **1** | **$F_2$Irpic** | ***yield*** |
|---|---|---|
| × | √ | 12 |
| √ | √ | ***40*** |

**Scheme 20:** Photosensitizer and 2-naphthol with benzaldehyde.




| **1** | **$F_2$Irpic** | ***yield*** |
|---|---|---|
| × | √ | 6 |
| √ | √ | ***6*** |

**Scheme 21:** Photosensitizer and 2-naphthol with *p*-tolualdehyde.




| **1** | **$F_2$Irpic** | ***yield*** |
|---|---|---|
| × | √ | 54 |
| √ | √ | ***57*** |

## VIII. Conclusions

In conclusion, I have demonstrated that visible light irradiation of 6-bromo-2-naphthol (**116**) facilitates the photoacid-catalyzed synthesis of acetals. I also found that 2-naphthol in the presence of a photosensitizer facilitates the acetalization of electron-deficient aldehydes. In addition, the pKa, $pKa^*$, and $S_1$ lifetime for 6-bromo-2-naphthol were determined. Catalyst **116** was shown to exhibit enhanced excited-state acidity relative to 2-naphthol in water.

# IX. Experimental

## A. General Information

$^{1}$H NMR spectra were recorded on a Varian Inova (500 MHz) spectrometer, and chemical shifts were reported in ppm relative to tetramethylsilane (TMS). Data for $^{1}$H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet; d = doublet; dd = doublet of doublets; ddd = doublet of doublet of doublets; m = multiplet), coupling constant (Hz), and integration. Data for $^{13}$C NMR spectra were recorded on a Varian Inova (125 MHz) spectrometer, chemical shifts are reported in ppm relative to the solvent ($CDCl_3$ as δ = 77.2 ppm). High-resolution mass spectra (HRMS) were obtained using a Waters Q-TOF Ultima ESI (electrospray ionization) and are reported in m/z. Silica gel high-purity, pore size 60, particle size 40–63 μm, 230–400 mesh was used for flash column chromatography. Rotary evaporation was performed using a Buchi R-300 rotary evaporator and Welch Model 2027 dry vacuum pump. Carbonyl reagents and catalysts **3**, **4**, and **5** were purchased from commercial sources and used without further purification. Thiourea **2** was prepared according to literature.

## B. General procedures for the photoacid catalyzed acetalization of carbonyls:

Procedure **A**:

To an 8 mL vial fitted with a magnetic stir bar was added 6-bromo-2-naphthol (0.011g, 0.05 mmol, 0.1 equiv.) and the corresponding alcohol (1 mL). Next, the carbonyl compound was added (0.5 mmol, 1.0 equiv.) The reaction mixture was then sparged for 5 min, sealed under inert atmosphere, and placed 4.0 cm from a 40 W Blue LED light (Kessil Tuna Blue) for 18 h. Cooling fans were used to maintain room temperature. To the reaction was then added 5,6-dibromo-1,2-benzodioxole (0.5. mmol) and 250 μL of dioxane. An aliquot was then taken up, dissolved in $CDCl_3$, and analyzed by $^{1}$H NMR.

**Column Free Acetal Isolation and Catalyst Recovery:**

Procedure **B**:

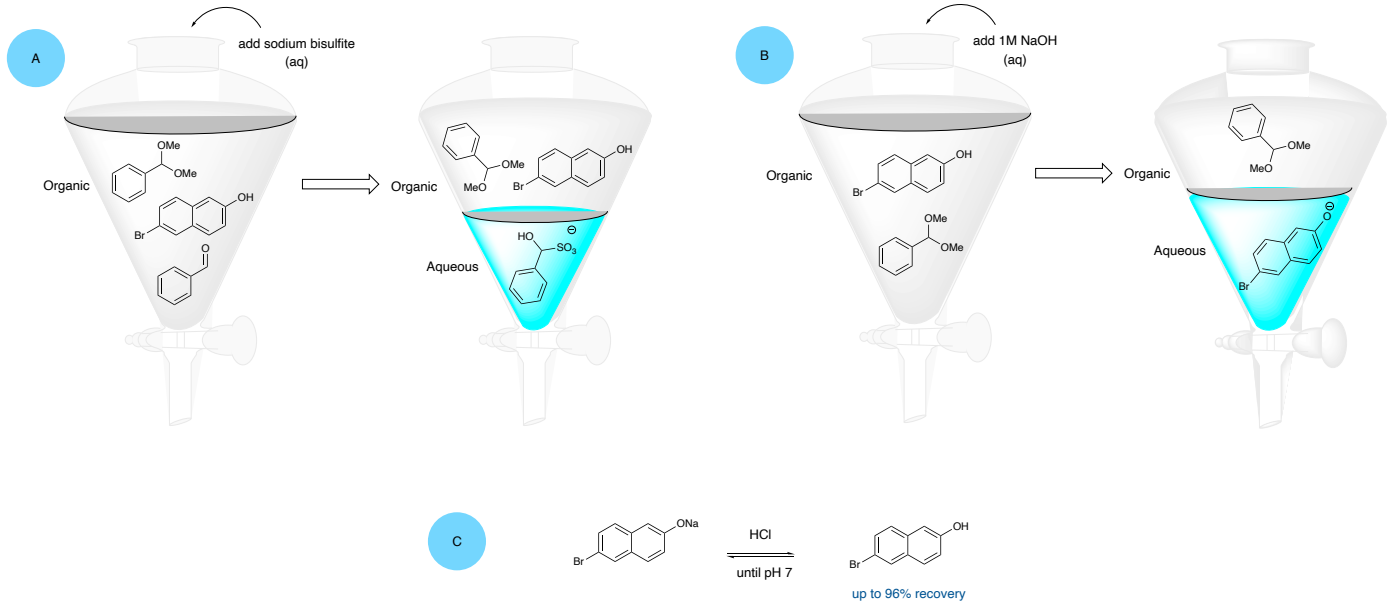
Acetal isolation:

The reaction mixture was transferred into a separatory funnel using 5 mL of diethyl ether. Saturated, aqueous sodium bisulfite (10 mL) was added, and the mixture was shaken vigorously for approximately 1 min (Scheme 22A). The organic layer was washed with (3 X 10 mL) 1 M NaOH, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the acetal (Scheme 22B).

Recovery of catalyst **116**:

Concentrated HCl was added to the NaOH(aq) layer (from Scheme 22B) until pH 7 (Scheme 22C). Afterward, 2 X 10 mL of diethyl ether was added. Then the organic layer was collected and dried over MgSO4, filtered, and concentrated *in vacuo* to give **116** as a white solid in up to 96% yield. Note: If needed **116** can be run through a $SiO_2$ plug with hexanes/ethyl acetate to remove trace impurities.

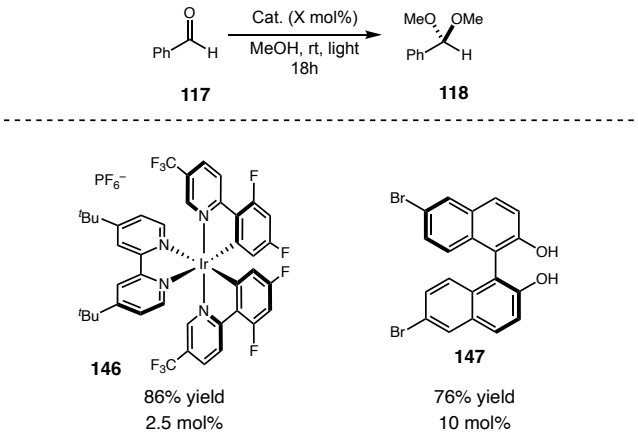
**Scheme 22:** Column free isolation of acetals and recovery of catalyst **116**.



## C. Additional Catalyst, Substrate, and Control Reactions:

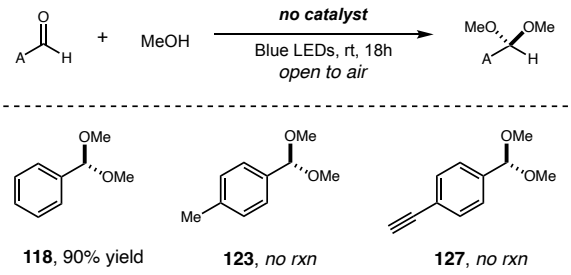
Iridium catalyst **146** provides **118** in 86% yield and dibromo-BINOL **147** gives **118** in 76% yield Scheme 23.

**Scheme 23:** Reactions run according to modified procedure **A**, using either **146** or **147**.




In the case of benzaldehyde (**117**), aerobic (reaction run open to air) photoirradiation in the absence of a catalyst provides **118** in 90% efficiency (Scheme 24). This phenomenon is only observed for benzaldehyde. Acetals **123** and **127** are not formed in the absence of catalyst.

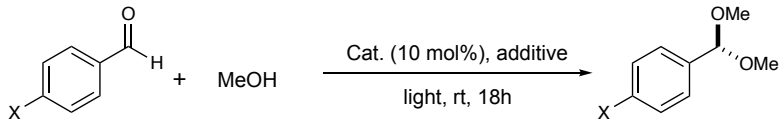
**Scheme 24:** Reactions run according to modified procedure **A**, no sparge, and left open to air.




It is possible that benzoic acid is being generated under the reaction conditions, however, when 10 mol% benzoic acid was used with and without light only 40 and 50% yield was observed, respectively (Table 7, Entries 1 and 2). The addition of 5 mol% triethylamine shut down the standard reaction (with 10 mol% **116**), however 4-chlorobenzaldehyde proceeds in 68% yield in

the absence of a catalyst (Entries 3 and 4). The addition of 15 mol% triethylamine shut down the reaction with 4-chlorobenzaldehyde in the absence of **116**, suggesting that the mechanism is indeed acid-catalyzed (Entry 5). Finally, the addition of 5 mol% sodium bicarbonate shut down the standard reaction and the reaction with 4-chlorobenzaldehyde (Entries 6 and 7).

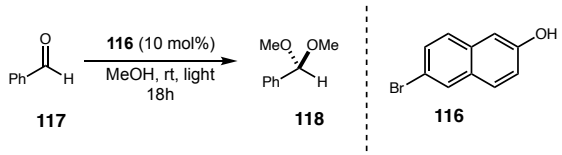
**Table 7:** Reactions run with 0.5 mmol aldehyde in MeOH (0.5 M), under argon atmosphere, % yields based on $^1$H NMR using an internal standard: 5,6-dibromo-1,3-benzodioxole.




| Entry | X | Cat. | additive | light | %yield |
|---|---|---|---|---|---|
| 1 | H | — | 10 mol% benzoic acid | Blue LEDs | 40 |
| 2 | H | — | 10 mol% benzoic acid | — | 50 |
| 3 | H | **116** | 5 mol% $NEt_3$ | Blue LEDs | 0 |
| 4 | Cl | — | 5 mol% $NEt_3$ | Blue LEDs | 68 |
| 5 | Cl | — | 15 mol% $NEt_3$ | Blue LEDs | 0 |
| 6 | H | **116** | 5 mol% $NaHCO_3$ | Blue LEDs | 0 |
| 7 | Cl | — | 5 mol% $NaHCO_3$ | Blue LEDs | 0 |

It is worth noting that we observed inconsistent results depending on the batch of methanol used (Table 8). Several "dry" bottles of AcroSeal® methanol were shipped from the vendor leaking, and thus were assumed not to be dry, and provided no product (Entries 1 and 2). Others appeared to be sealed, however, no reaction was observed, even after subsequent drying with activated 5 Å mol sieves (Entries 3 and 4). Ultimately, it was determined that methanol dried over activated 5 Å MS and subsequent bulb-to-bulb distillation under argon via a short path condenser provided consistent results, Entry 7.

**Table 8:** [a]Conditions: Carbonyl compound (0.5 mmol) in the corresponding alcohol (0.5 M), under argon atmosphere, % yields based on $^1$H NMR using an internal standard: 5,6-dibromo-1,3-benzodioxole.

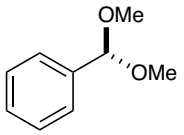



| Entry | MeOH Source | Part - Lot # | % yield | Comments |
|---|---|---|---|---|
| 1 | AcroSeal® | 36439-B0539396A[b] | 0 | Shipped from vendor leaking |
| 2 | AcroSeal® | 36439-B0538002A[b] | 0 | Shipped from vendor leaking |
| 3 | AcroSeal® | 36439-B0539396A[b] | 0 | Not leaking |
| 4 | AcroSeal® | 61098-B0535263 | 0 | Dried over 5 Å mol sieves |
| 5 | AcroSeal® | 61098-B0542325C | 91 | Not leaking |
| 6 | Macron | 3016-16-0000178672 | 13 | Dried over 5 Å mol sieves |
| 7 | Macron | 3016-16-0000178672 | 90 | Distilled over 5 Å mol sieves |

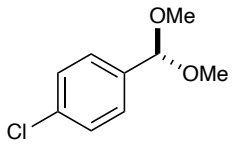
[b]LOT #s: B0539396A and B0538002A shipped over mol sieves from vendor.

## D. Characterization Data

Data for compounds **118**, **121**, **122**, **126**, **132**, **133**, **134**, **135**, **136**, **139**, **140**, were all consistent with the reported literature.[1,2,3,4,5,6,7,8,9]

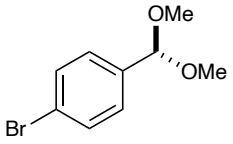



(dimethoxymethyl)benzene **118**: Compound **118** was prepared according to the general procedure **A** and purified according to procedure **B** to give a pale-yellow oil, (0.067g, 83% yield). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H), 7.39 – 7.29 (m, 3H), 5.39 (s, 1H), 3.33 (s, 6H).

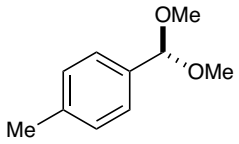



1-chloro-4-(dimethoxymethyl)benzene **121**: Compound **121** was prepared according to the general procedure **A** and purified according to procedure **B** to give a pale-yellow oil, 0.060g, 64% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, $J$ = 8.3 Hz, 2H), 7.33 (d, $J$ = 8.5 Hz, 2H), 5.37 (s, 1H), 3.30 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 136.73, 134.32, 128.45, 128.26, 102.34, 52.60. HRMS (ESI) m/z [M + H] calcd for $C_9H_{12}ClO_2$, 186.0451 found 186.0448.

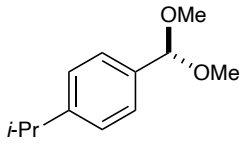
[1] Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679.
[2] Fujioka, H.; Goto, A.; Otake, K.; Kubo, O.; Sawama, Y.; Maegawa, T. *Chem. Commun.* **2011**, *47*, 9894.
[3] Knauber, T.; Arikan, F.; Roeschenthaler, G.-V.; Goossen, L. J. *Chem. - Eur. J.* **2011**, *17*, 2689.
[4] Li, G.-Q.; Shan, W.-G.; Su, W.-K.; Yao, Z.-J. *Chin. J. Chem.* **2007**, *25*, 90.
[5] Loft, K. J.; Bojarova, P.; Slamova, K.; Kren, V.; Williams, S. J. *ChemBioChem* **2009**, *10*, 565.
[6] Sakai, N.; Moritaka, K.; Konakahara, T. *Eur. J. Org. Chem.* **2009**, 4123.
[7] Zhao, Y.-J.; Chng, S.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129*, 492.
[8] Spiliopoulou, N.; Nikitas, N. F.; Kokotos, C. G. *Green Chem.* **2020**, *22*, 3539.
[9] De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2004**, *45*, 8141.




1-bromo-4-(dimethoxymethyl)benzene **122**: Compound **122** was prepared according to the general procedure **A**, and purified by column chromatography (98% hexanes/2% triethylamine), the isolated yield was not determined. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, $J$ = 8.5 Hz, 2H), 7.32 (d, $J$ = 8.5 Hz, 2H), 5.35 (s, 1H), 3.30 (s, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 137.25, 131.45, 128.63, 122.61, 102.40, 52.67. HRMS (ESI) m/z [M + H] calcd for $C_9H_{11}BrO_2$, 229.9942; found 229.9932.

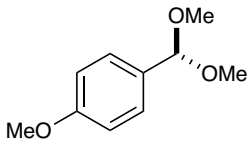



1-(dimethoxymethyl)-4-methylbenzene **123**: Compound **123** was prepared according to the general procedure **A** and purified according to procedure **B** to give a pale-yellow oil, 0.065g, 74% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, $J$ = 7.4 Hz, 2H), 7.17 (d, $J$ = 7.7 Hz, 2H), 5.36 (s, 1H), 3.32 (s, 6H), 2.35 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 138.27, 135.25, 128.99, 126.72, 103.33, 52.75, 21.32. HRMS (ESI) m/z [M + H] calcd for $C_{10}H_{15}O_2$, 166.0994 found 166.0994.

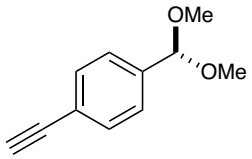



1-(dimethoxymethyl)-4-isopropylbenzene **124**: Compound **124** was prepared according to the general procedure **A** and purified by column (98% hexanes/2% triethylamine), the isolated yield was not determined. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, $J$ = 6.9 Hz, 2H), 7.22 (d, $J$ = 8.5 Hz,

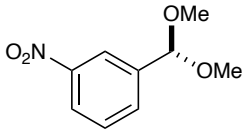
2H), 5.35 (s, 1H), 3.33 (s, 6H), 3.00 – 2.80 (m, 1H), 1.25 (d, $J$ = 6.9 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 149.31, 135.65, 126.76, 126.40, 103.53, 52.95, 34.03, 24.11. HRMS (ESI) m/z [M + H] calcd for $C_{12}H_{19}O_2$, 194.1307 found 194.1303.



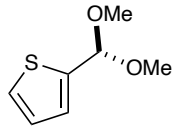

1-(dimethoxymethyl)-4-methoxybenzene **126**: Compound **126** was prepared according to the general procedure **A** and purified by column chromatography (98% hexanes/2% triethylamine), the isolated yield was not determined. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, $J$ = 8.3 Hz, 2H), 6.89 (d, $J$ = 8.3 Hz, 2H), 5.35 (s, 1H), 3.81 (s, 3H), 3.31 (s, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.79, 130.49, 128.04, 113.65, 103.18, 55.37, 52.72. HRMS (ESI) m/z [M + H] calcd for $C_{10}H_{15}O_3$, 182.0943 found 182.0948.



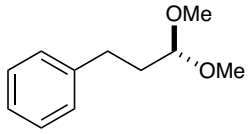

1-(dimethoxymethyl)-4-ethynylbenzene **127**: Compound **127** was prepared according to modified general procedure **A**, using 20 mol% **116**, 370 nm LEDs, and 0.33 M MeOH:dioxane (2:1). Compound **127** was purified by column chromatography (98% hexanes/2% triethylamine), the isolated yield was not determined. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, $J$ = 7.9 Hz, 2H), 7.41 (d, $J$ = 7.9 Hz, 2H), 5.39 (s, 1H), 3.32 (s, 6H), 3.08 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 138.87, 132.14, 126.87, 122.31, 102.61, 83.56, 77.59, 52.75. HRMS (ESI) m/z [M + H] calcd for $C_{11}H_{13}O_2$, 176.0837 found 176.0835.



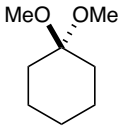

1-(dimethoxymethyl)-3-nitrobenzene **128**: Compound **128** was prepared according to the general procedure **A** and purified by column chromatography (98% hexanes/2% triethylamine), the isolated yield was not determined. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.22 – 8.16 (m, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 5.48 (s, 1H), 3.35 (s, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 148.32, 140.40, 132.91, 129.26, 123.44, 122.07, 101.44, 52.72. HRMS (ESI) m/z [M + H] calcd for $C_9H_{12}NO_4$, 197.0688 found 197.0691.



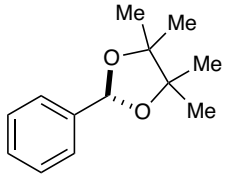

2-(dimethoxymethyl)thiophene **130**: Compound **130** was prepared according to modified general procedure **A**, using 20 mol% **116**, 370 nm LEDs, and 0.33 M MeOH:dioxane (2:1). Compound **130** was purified by column chromatography (98% hexanes/2% triethylamine), the isolated yield was not determined. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 5.1 Hz, 1H), 7.07 (dd, *J* = 2.8, 1.7 Hz, 1H), 7.00 (dd, *J* = 5.0, 3.5 Hz, 1H), 5.64 (s, 1H), 3.36 (s, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 141.61, 126.76, 125.78, 125.52, 100.18, 52.64. HRMS (ESI) m/z [M + H] calcd for $C_7H_{11}O_2S$, 159.0474 found 159.0475.




(3,3-dimethoxypropyl)benzene **132**: Compound **132** was prepared according to modified general procedure **A**, using 20 mol% **116**. Compound **132** was purified by column chromatography (98% hexanes/2% triethylamine), the isolated yield was not determined. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.09 (m, 5H), 4.37 (t, 1H), 3.33 (s, 6H), 2.68 (t, *J* = 8.0 Hz, 2H), 1.97 – 1.89 (m, 2H). $^{13}$C NMR (125 MHz, cdcl$_3$) δ 141.77, 128.74, 128.54, 126.02, 103.90, 52.87, 34.23, 31.01. HRMS (ESI) m/z [M + H] calcd for $C_{11}H_{17}O_2$, 181.1229 found 181.1184

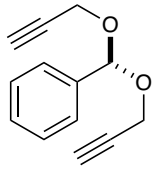



1,1-dimethoxycyclohexane **133**: Compound **133** was prepared according to the general procedure **A** and purified by column chromatography (98% hexanes/2% triethylamine), the isolated yield was not determined. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 3.17 (s, 6H), 1.91 – 1.30 (m, 11H). $^{13}$C NMR (125 MHz) δ 100.09, 47.43, 32.81, 25.72, 22.95. HRMS (ESI) m/z [M + H] calcd for $C_8H_{17}O_2$, 145.1229 found 145.1184.




4,4,5,5-tetramethyl-2-phenyl-1,3-dioxolane **137**: Compound **137** was prepared was prepared according to modified general procedure **A**, using 20 mol% **116** and 0.33 M MeOH:dioxane (2:1). Compound **137** was purified according to procedure **B** to give a pale-yellow oil, 0.069g, 67% yield.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.38 – 7.27 (m, 3H), 5.98 (s, 1H), 1.32 (s, 6H), 1.27 (s, 6H). $^{13}$C NMR (125 MHz) δ 139.76, 128.70, 128.34, 126.36, 100.00, 82.73, 24.43, 22.29.



bis(prop-2-yn-1-yloxy)methyl)benzene **141**: Compound **141** was prepared according to the general procedure **A** and purified according to procedure **B** to give a pale-yellow oil, 0.025g, 25% yield (44% NMR yield). $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 2H), 7.46 – 7.34 (m, 3H), 5.90 (s, 1H), 4.34 (dd, *J* = 15.7, 2.4 Hz, 2H), 4.20 (dd, *J* = 15.7, 2.4 Hz, 2H), 2.46 (t, *J* = 2.4 Hz, 2H).$^{13}$C NMR (125 MHz, $CDCl_3$) δ 136.95, 129.08, 128.52, 126.94, 99.74, 79.56, 74.54, 53.23.

## E. Photosensitizer procedure and mechanistic studies:

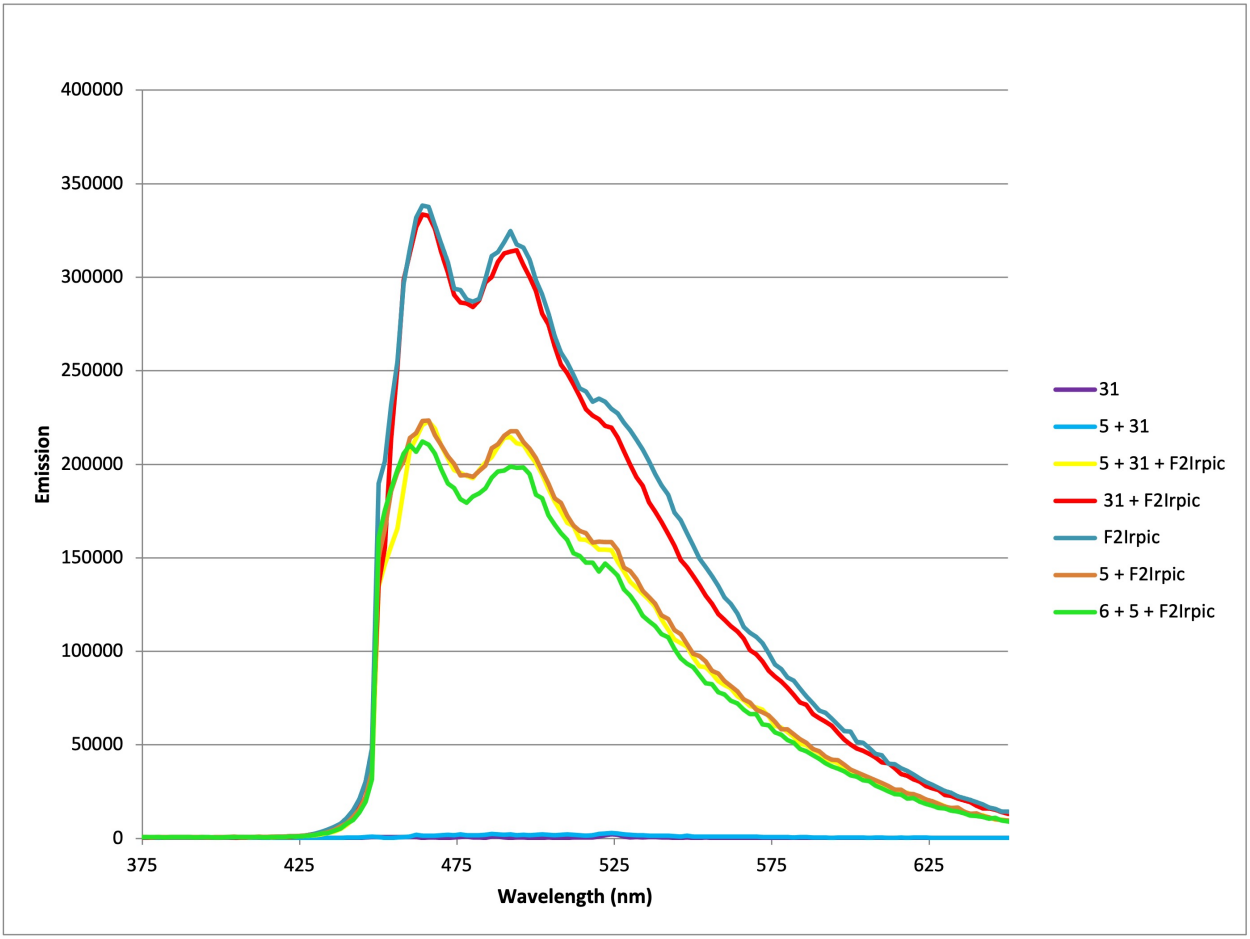
**General procedure for sensitizer reaction:**

To an 8 mL vial fitted with a magnetic stir bar was added bis[2-(4,6-difluorophenyl)pyridinato-C2,N](picolinato)iridium(III) (0.005g, 0.0065 mmol, 0.025 equiv.), 2-naphthol (0.018g, 0.125 mmol, 0.5 equiv.), and methanol (1 mL). Next, the carbonyl compound was added (0.25 mmol, 1.0 equiv.). The reaction mixture was then sparged for 5 min, sealed, and placed 4.0 cm from a 40 W Blue LED light (Kessil Tuna Blue) for 18 h. Cooling fans were used to maintain room temperature. To the reaction was then added 5,6-dibromo-1,2-benzodioxole (0.5. mmol) and 250 μL of dioxane. An aliquot was then taken up, dissolved in $CDCl_3$, and analyzed by $^{1}$H NMR.

**Photosensitizer mechanistic studies:**

Emission quenching studies showed that **$F_2$Irpic** emission was 34% quenched in the presence of 2-naphthol (**1**) with and without benzaldehyde (**117**) and 4-trifluoromethyl benzaldehyde (**89**), suggesting efficient energy transfer between **$F_2$Irpic** and **1** (Figure 15). No **$F_2$Irpic** emission quenching was observed in the presence of **117** and **89** in the absence of **1**.

**Figure 15:** Emission spectra of **$F_2$Irpic** [bis(4,6-difluorophenyl-pyridine)(picolinate) iridium(III)] (0.8 mM in methanol) with and without 25 equivalents of the corresponding aldehydes (**117** or **89**) and/or 2-naphthol (**1**).



## F. Determination of the excited state pKas and excited state lifetimes for catalysts

2-naphthol (**1**):

The following aqueous stock solutions were prepared:

- 1 mg in 50 mL; 2-naphthol (2-Nap) solution
- 0.10 M HCl
- 0.10 M NaOH
- 0.20 M 1:1 $NH_3$-$NH_4Cl$ buffer solution

Afterward, the solutions being analyzed were prepared in the following ratio:

- Acidic Solution: 10 mL of HCl solution, 5 mL of (2-Nap) solution diluted up to 50 mL with DI water
- Basic Solution: 10 mL of NaOH solution, 5 mL of (2-Nap) solution diluted up to 50 mL with DI water
- Buffer Solution: 10 mL of Buffer solution, 5 mL of (2-Nap) solution diluted up to 50 mL with DI water

The pH for those solutions were as follows (measured by Vernier Go Direct™ Electrode Amplifier):

- Acidic: 1.7
- Basic: 12.33
- Buffer: 9.48

The three solutions were analyzed using UV-Vis (Figure 16) and fluorometer (Figure 17).

**Figure 16:** UV-Vis for the acidic, basic, and buffer solutions of **1**.

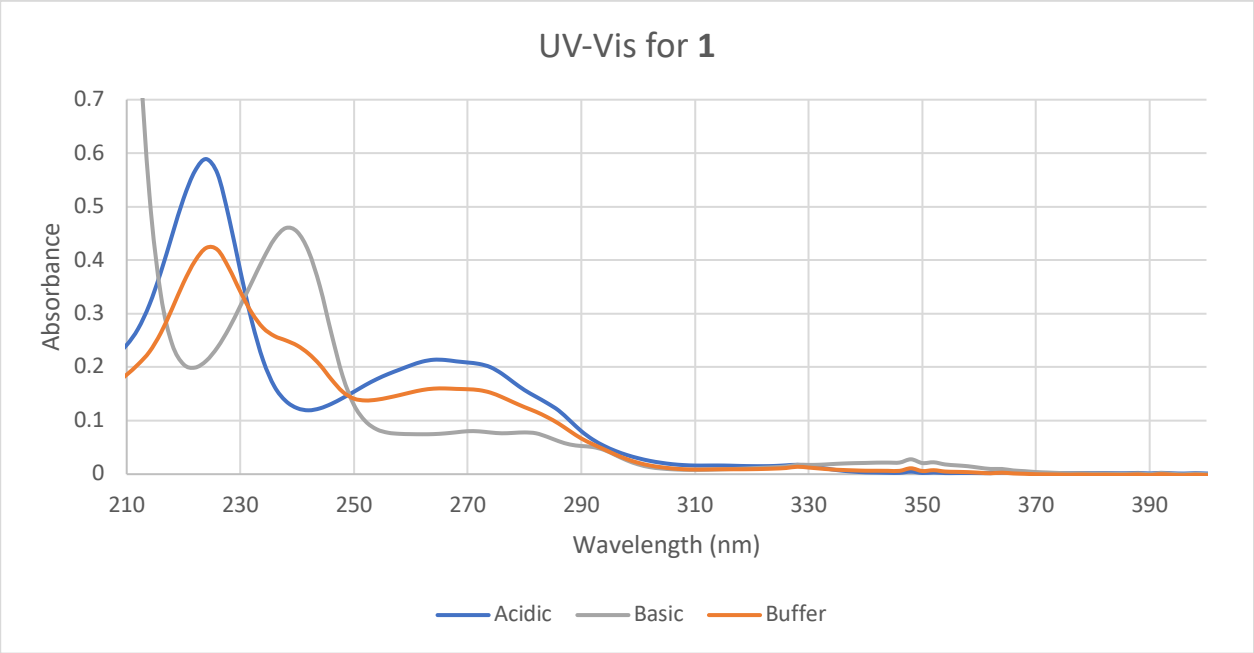
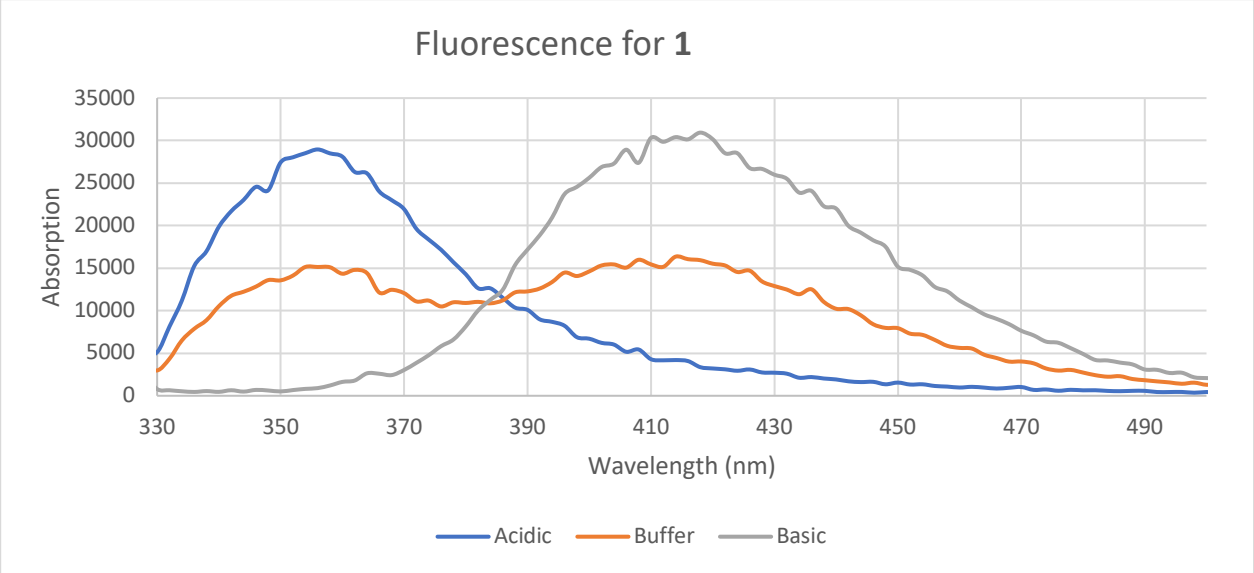



**Figure 17:** Fluorescence spectra for the acidic, basic, and buffer solutions of **1**




From the acidic and basic solutions, the 0-0 energy was able to be calculated by overlaying the UV-Vis and fluorometer graphs (Figures 18 and 19).

**Figure 18:** Fluorescence and UV-Vis overlay of the acidic solution for **1**.

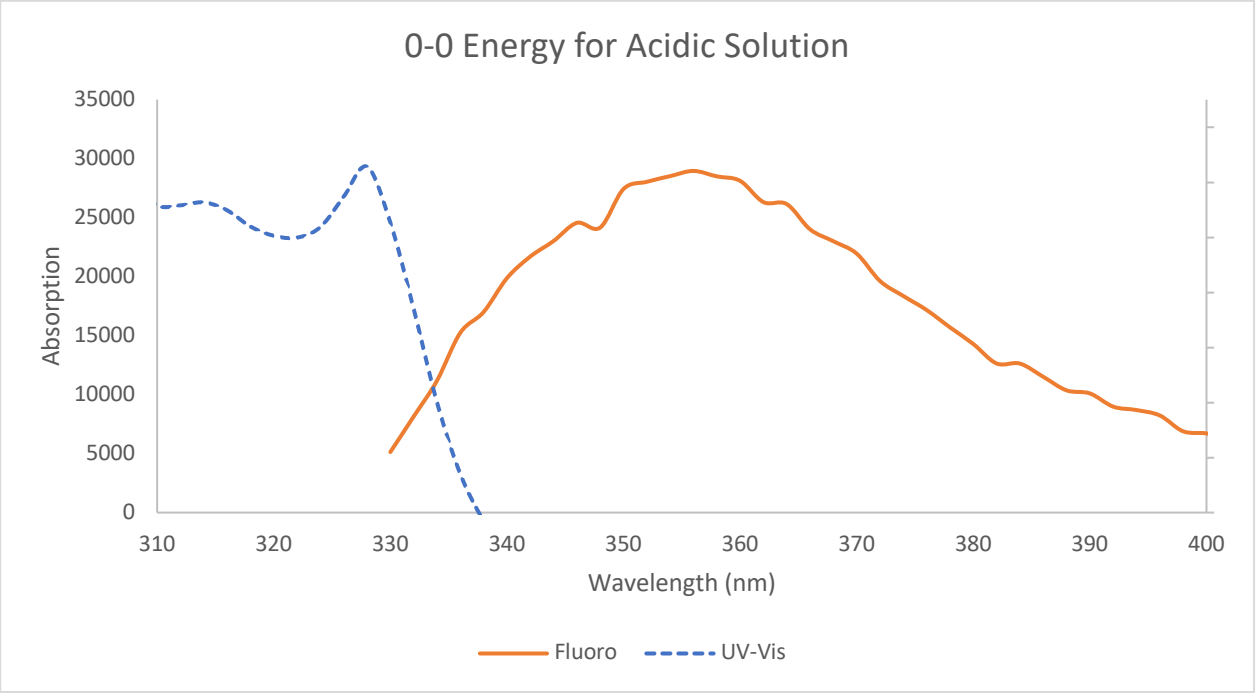
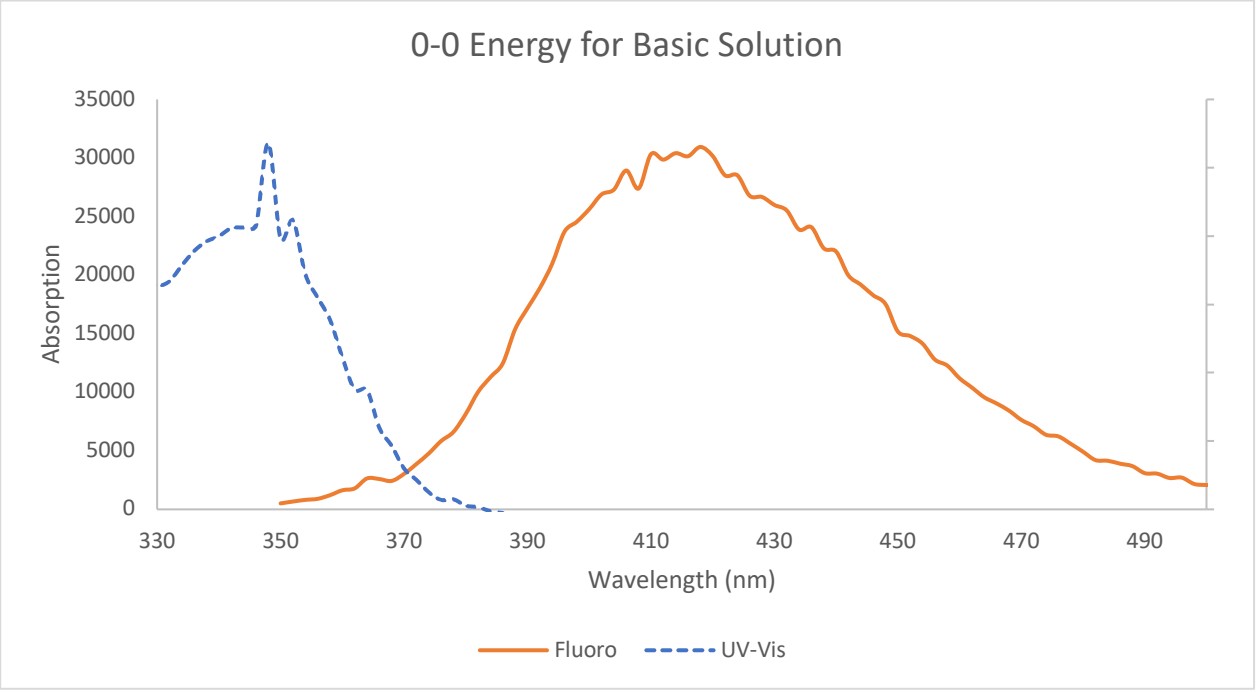



**Figure 19:** Fluorescence and UV-Vis spectra overlay of the basic solution for **1**.




The following calculations were performed to determine pKa and pKa*:

To begin we must figure out the concentration of the analyte in the three solutions being tested;

$$M_1V_1=M_2V_2$$

$$(1.388x10^{-4}M)(5\ mL)=M_2(50\ mL)$$

$$M_2= 1.388x10^{-5}M=c_o$$

We must also calculate the molar absorptivity (ε) of the acidic and basic forms of 2-naphthol at the wavelength of maximum absorbance for the **conjugate base** form from UV-Vis graphs:

$$A=\varepsilon bc_o$$

$c_o= 1.388x10^{-5}M$

b = 1 cm

$A_{238(NOH)}=.137$

$A_{238(NO^-)}=.460$

$$\varepsilon_{(NOH)}= \frac{.137}{(1.388x10^{-5})} = 9876.317$$

$$\varepsilon_{(NO^-)}= \frac{.460}{(1.388x10^{-5})} = 33141.21$$

Afterward, we can calculate the concentration of the (NOH) and ($NO^-$) in the buffer using the absorbance at the wavelength used previously and the following equations:

$$A = (\varepsilon_{NOH} - \varepsilon_{NO^-})[NOH] + (\varepsilon_{NO^-})c_o$$

and

$$c_o = [NOH] + [NO^-]$$

$A_{238(Buffer)}$=.250

$\varepsilon_{(NOH)}$= 9876.317

$\varepsilon_{(NO^-)}$= 33141.21

$c_o = 1.388x10^{-5}M$

$$[NOH] = \frac{A-((\varepsilon NO-)co)}{(\varepsilon NOH - \varepsilon NO-)}$$

$$[NOH] = \frac{.25-((33141.21)(1.388x10^{-5}))}{(9876.317-33141.21)}$$

$$[NOH] = (9.026x10^{-6}M)$$

$$c_o - [NOH] = [NO^-]$$

$$(1.388x10^{-5}M) - (9.026x10^{-6}M) = (4.854x10^{-6}M)$$

$pK_a$ for the buffered solution was determined using the following equation:

$$pK_a = pH + \log\left(\frac{[NOH]}{[NO^-]}\right)$$

$$pK_a = 9.48 + \log\left(\frac{[9.026x10^{-6}M]}{[4.854x10^{-6}M]}\right)$$

$$pK_a = 9.75$$

Next you must first determine the wavelength at which the two graphs intersect in the overlay for both the acidic and basic solutions:

0-0 energy of acidic solution: 332 nm

0-0 energy of basic solution: 370 nm

Afterward, use this equation to determine the corresponding wavenumbers ($\vartheta_{OH}$ & $\vartheta_{NO^-}$):

$$\vartheta = \left(\frac{10^7}{wavelength\ (nm)}\right)$$

$\vartheta_{OH}$ = 30120 $cm^{-1}$

$\vartheta_{NO^-}$ = 27027 $cm^{-1}$

To calculate the $pK_a^*$ the following förster equation was used:

$$pK_a^* = pK_a - \left(\frac{[N_o hc]}{[2.303RT]}\right)(\vartheta_{OH} - \vartheta_{NO^-})$$

$\vartheta$ = wavenumber based on 0-0 energy for acidic and basic solutions

$N_o$ = Avagadro's number = $(6.022x10^{23})$

$h$ = Planck's constant = $(6.626x10^{-34})$ J/Hz

$c$ = speed of light = $(3x10^{10})$ cm/s

R = Gas Constant = 8.3145 J/mol*K

T = Room Temp = 298 K

$$pK_a^* = 9.75 - \left(\frac{[(6.022x10^{23})(6.626x10^{-34})(3x10^{10})]}{[2.303(8.3145)(298)]}\right)(30120 - 27027\ )$$

$$pK_a^* = 3.26$$

6-bromo-2-naphthol (**116**):

The following aqueous stock solutions were prepared:

- 1 mg in 50 mL; 6-Bromo-2-Naphthol (6-Bromo) solution
- 0.10 M HCl
- 0.10 M NaOH
- 0.20 M 1:1 $NH_3$-$NH_4Cl$ buffer solution

Afterward, the solutions being analyzed were prepared in the following ratio:

- Acidic Solution: 10 mL of HCl solution, 5 mL of (6-Bromo) solution diluted up to 50 mL with DI water
- Basic Solution: 10 mL of NaOH solution, 5 mL of (6-Bromo) solution diluted up to 50 mL with DI water
- Buffer Solution: 10 mL of Buffer solution, 5 mL of (6-Bromo) solution diluted up to 50 mL with DI water

The pH for those solutions were as follows:

- Acidic: 1.73
- Basic: 12.45
- Buffer: 9.51

The three solutions were analyzed using UV-Vis and Fluorometer (Figures 20 and 21):

**Figure 20:** UV-Vis for the Acidic, Basic, and Buffer solutions of **116**.

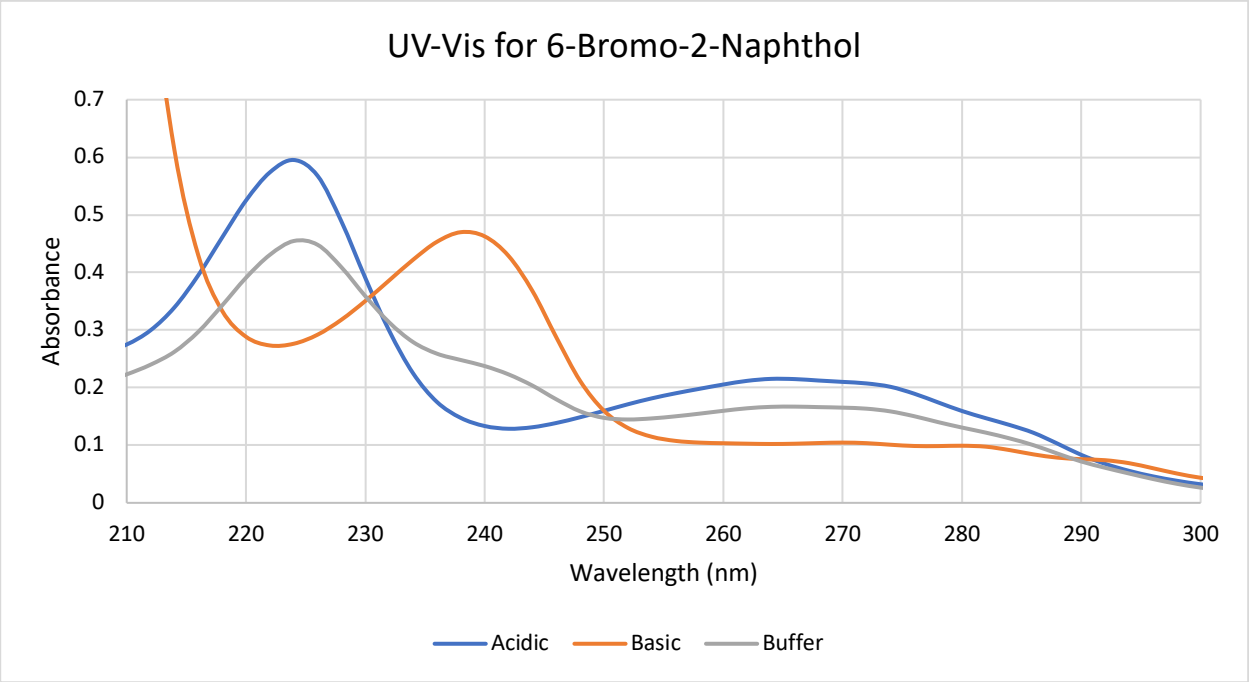
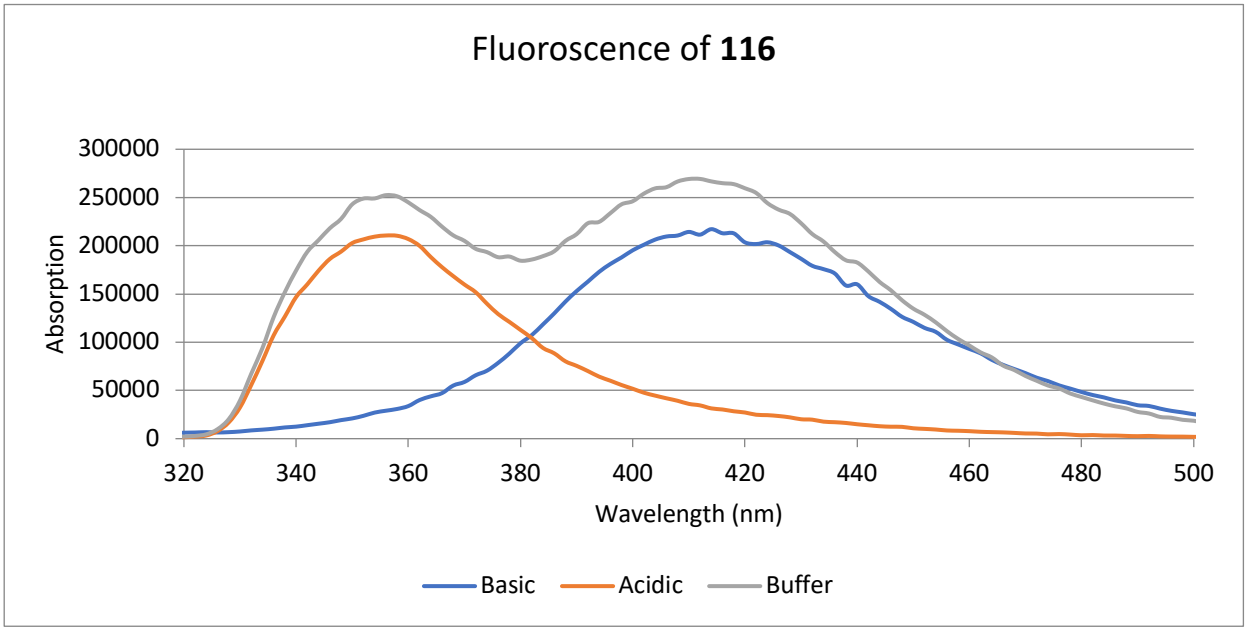



**Figure 21:** Fluorescence spectra for the acidic, basic, and buffer solutions of **116**.




The 0-0 energy was calculated by overlaying the UV-Vis and fluorometer graphs for the acidic (Figure 22) and basic (Figure 23) solutions:

**Figure 22:** Fluorescence and UV-Vis overlay of the acidic solution for **116**.

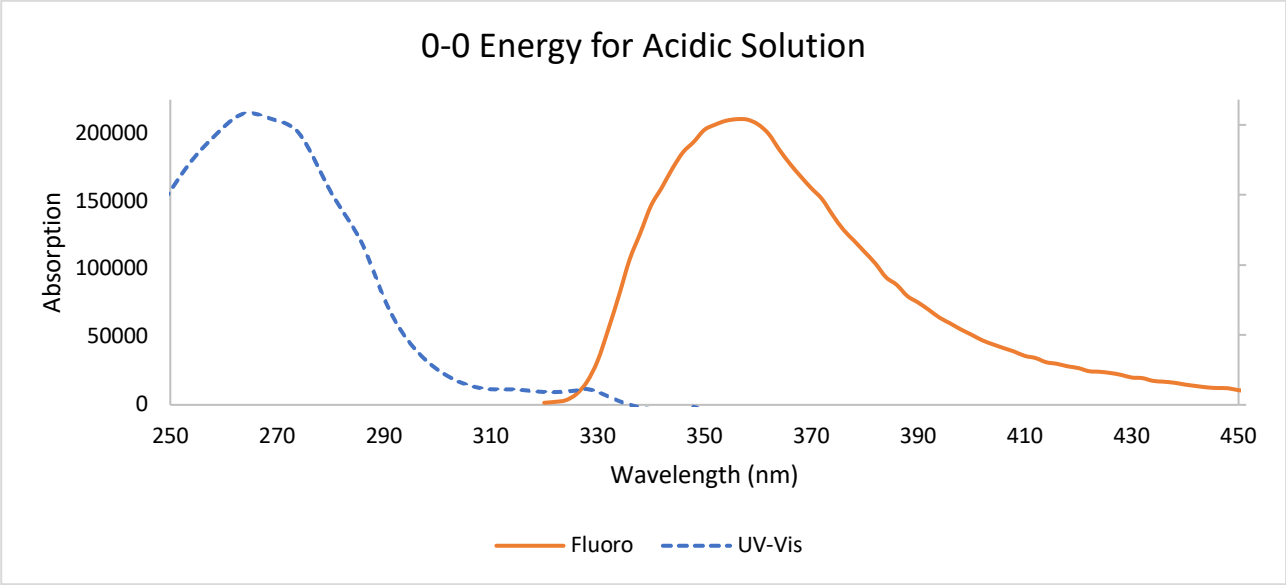
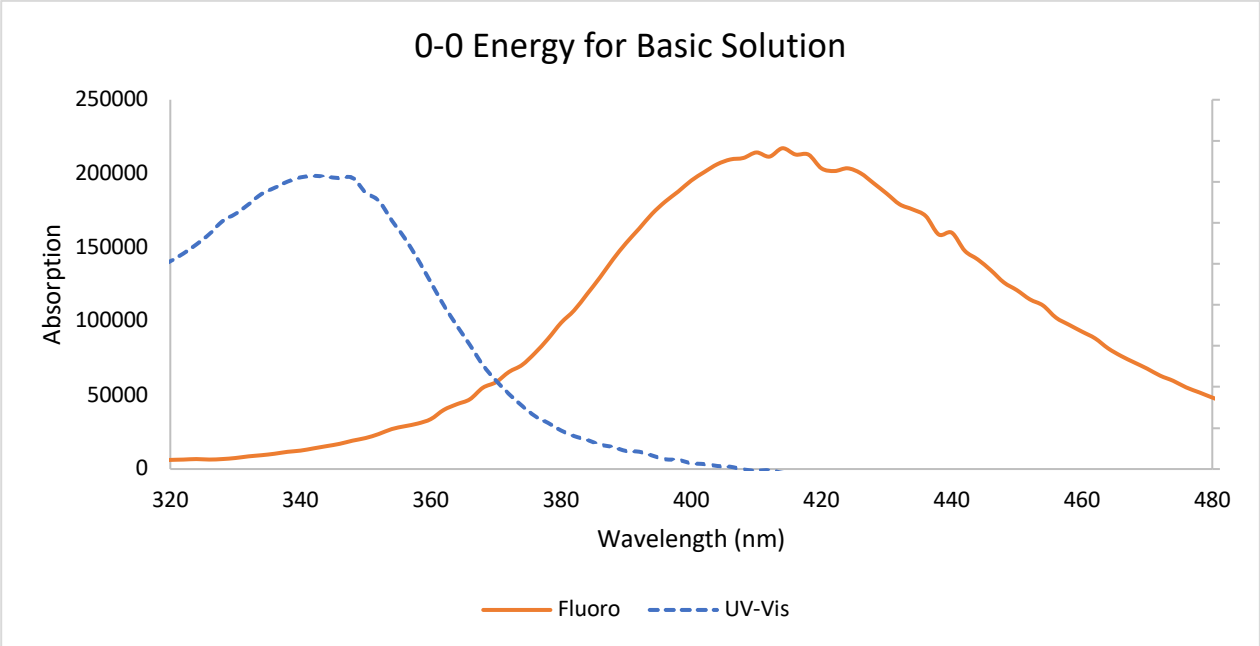



**Figure 23:** Fluorescence and UV-Vis spectra overlay of the basic solution for **116**.



The following calculations were performed to determine pKa and pKa*:

To begin we must figure out the concentration of the analyte in the three solutions being tested;

$$M_1V_1=M_2V_2$$

$$(8.97x10^{-4}M)(5\ mL)=M_2(50\ mL)$$

$$M_2= 8.97x10^{-5}M=c_o$$

We must also calculate the molar absorptivity (ε) of the acidic and basic forms of 6-Bromo-2-naphthol at the wavelength of maximum absorbance for the **conjugate base** form from UV-Vis graphs:

$$A=\varepsilon bc_o$$

$c_o= 8.97x10^{-5}M$

b = 1 cm

$A_{238(NOH)}=.147$

$A_{238(NO^-)}=.469$

$$\varepsilon_{(NOH)}= \frac{.147}{(8.97x10^{-5})} = 1638.796$$

$$\varepsilon_{(NO^-)}= \frac{.469}{(8.97x10^{-5})} = 5228.539$$

Afterwards we can calculate the concentration of the (NOH) and ($NO^-$) in the buffer using the absorbance at the wavelength used previously and the following equations:

$$A = (\varepsilon_{NOH} - \varepsilon_{NO^-})[NOH] + (\varepsilon_{NO^-})c_o$$

and

$$c_o = [NOH] + [NO^-]$$

$A_{238(Buffer)}$=.250

$\varepsilon_{(NOH)}$= 1638.796

$\varepsilon_{(NO-)}$= 5228.539

$c_o$= $8.97x10^{-5}M$

$$[NOH] = \frac{A-((\varepsilon NO-)co)}{(\varepsilon NOH - \varepsilon NO-)}$$

$$[NOH] = \frac{.25-((5228.539)(8.97x10^{-5}))}{(1638.796-5228.539)}$$

$$[NOH] = (6.101x10^{-5}M)$$

$$c_o - [NOH] = [NO^-]$$

$$(8.97x10^{-5}M) - (6.101x10^{-5}M) = (2.87x10^{-5}M)$$

$pK_a$ for the buffered solution was determined using the following equation:

$$pK_a = pH + \log\left(\frac{[NOH]}{[NO^-]}\right)$$

$$pK_a = 9.51 + \log\left(\frac{[6.101x10^{-5}M]}{[2.87x10^{-5}M]}\right)$$

$$pK_a = 9.84$$

Next, you must first determine the wavelength at which the two graphs intersect in the overlay for both the acidic and basic solutions:

1-0 energy of acidic solution: 328 nm

1-0 energy of basic solution: 374 nm

Afterwards use this equation to determine the corresponding wavenumbers ($\vartheta_{OH}$ & $\vartheta_{NO^-}$):

$$\vartheta = \left(\frac{10^7}{wavelength\ (nm)}\right)$$

$\vartheta_{OH}$ = 30487.8 $cm^{-1}$

$\vartheta_{NO^-}$ = 26737.97 $cm^{-1}$

To calculate the $pK_a^*$ the following förster equation was used:

$$pK_a^* = pK_a - \left(\frac{[N_o hc]}{[2.303RT]}\right)(\vartheta_{OH} - \vartheta_{NO^-})$$

$\vartheta$ = wavenumber based on 0-0 energy for acidic and basic solutions

$N_o$ = Avagrado's number = $(6.022x10^{23})$

$h$ = Planck's constant = $(6.626x10^{-34})$ J/Hz

$c$ = speed of light = $(3x10^{10})$ cm/s

R = Gas Constant = 8.3145 J/mol*K

T = Room Temp = 298 K

$$pK_a^* = 9.84 - \left(\frac{[(6.022x10^{23})(6.626x10^{-34})(3x10^{10})]}{[2.303(8.3145)(298)]}\right)(30487.8 - 26737.97\ )$$

$$pK_a^* = 1.976$$

The singlet excited-state lifetimes for 2-naphthol (**1**, τ = 6.8 ns) and 6-bromo-2-naphthol (**116**, τ = 0.049 ns) were measurements in 80% ethanol (Figures 24 and 25). The short-lived $S_1$ excited state for **116** is attributed to rapid intersystem crossing into a triplet excited state (not measured) due to the heavy atom effect (bromine).

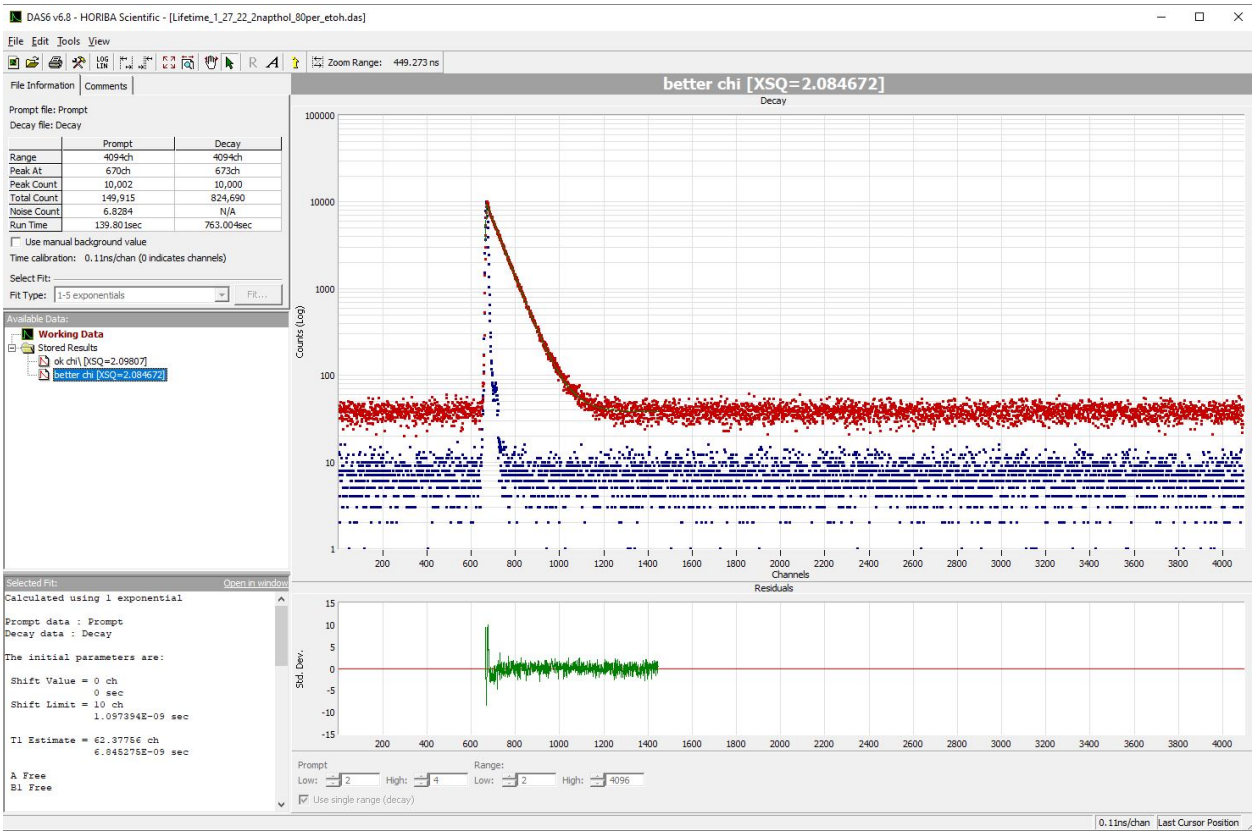



**Figure 24:** Singlet excited-state spectrum for 2-naphthol (**1**) in 80% ethanol.

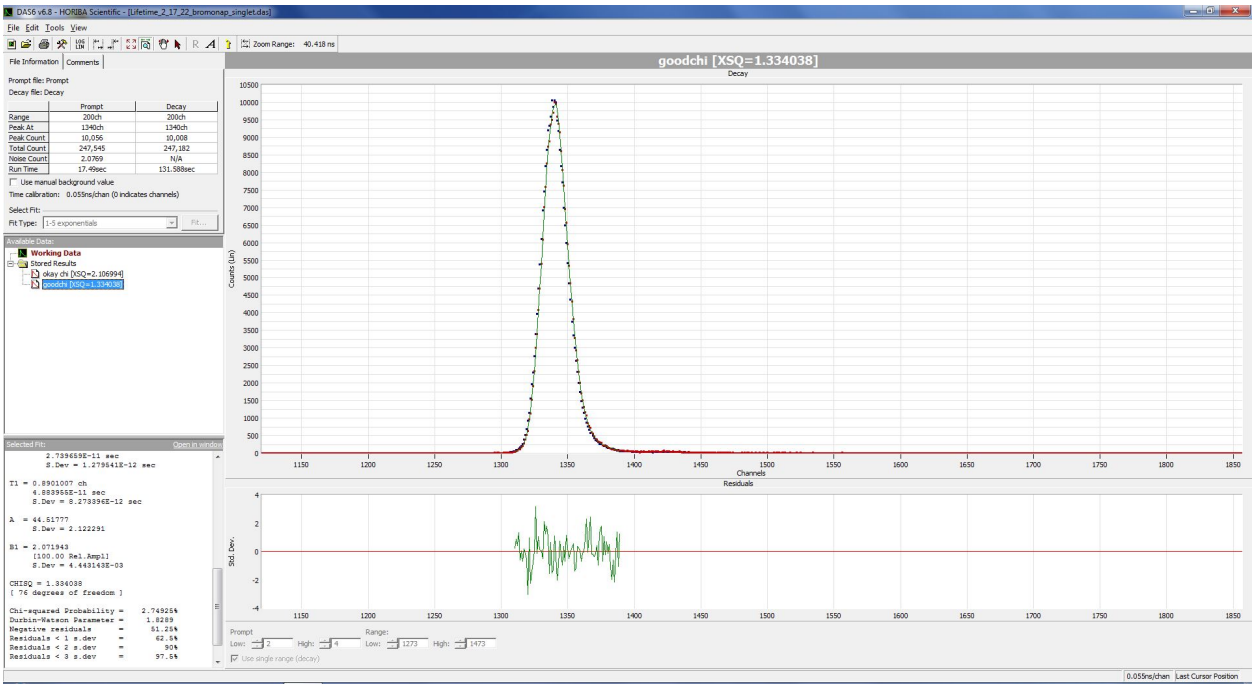



**Figure 25:** Singlet excited-state spectrum for 6-bromo-2-naphthol (**116**) in 80% ethanol.

## X. References


1. For a review on the recent advances in photoacid catalysis see: Saway, J.; Salem, Z. M.; Badillo, J. J. *Synthesis* **2021**, *53*, 489.
2. a) Ott, J.; Ramos Tombo, G. M.; Schmid, B.; Venanzi, L. M.; Wang, G.; Ward, T. R. *Tetrahedron Lett.* **1989**, *30*, 6151. b) Ranu, B. C.; Jana, R.; Samanta, S. *Adv. Syn. Catal.* **2004**, *346*, 446. c) Kumar, R.; Chakraborti, A. K. *Tetrahedron Lett.* **2005**, *46*, 8319. d) Wu, S.; Dai, W.; Yin, S.; Li, W.; Au, C.-T. *Catal. Lett.* **2008**, *124*, 127. e) Zhao, S.; Jia, Y.; Song, Y.-F. *Catal. Sci. Technol.* **2014**, *4*, 2618. f) Zong, Y.; Yang, L.; Tang, S.; Li, L.; Wang, W.; Yuan, B.; Yang, G. *Catalysts* **2018**, 8. g) Poly, S. S.; Jamil, M. A. R.; Touchy, A. S.; Yasumura, S.; Siddiki, S. M. A. H.; Toyao, T.; Maeno, Z.; Shimizu, K.-i. *Mol. Catal.* **2019**, *479*, 110608. h) Hall, J. N.; Bollini, P. *ACS Catal.* **2020**, *10*, 3750.
3. Yi, H.; Niu, L.; Wang, S.; Liu, T.; Singh, A. K.; Lei, A. *Org. Lett.* **2017**, *19*, 122.
4. Spiliopoulou, N.; Nikitas, N. F.; Kokotos, C. G. *Green Chem.* **2020**, *22*, 3539.
5. Additional examples of photoacid catalyzed acetalizations: a) de Lijser, H. J. P.; Rangel, N. A. *J. Org. Chem.* **2004**, *69*, 8315. b) Yu, L.; Lin, C.; Liao, C.; Zeng, X.; Chen, X.; Zhu, Z.; Huang, Y.; Li, Y.; Chen, L. *Environ. Chem. Lett.* **2020**, *18*, 1353.
6. For an example of naphthols as photoacid catalysts for glycosylation see: Iwata, R.; Uda, K.; Takahashi, D.; Toshima, K. *Chem. Commun.* **2014**, *50*, 10695.
7. For an example of 2-naphthol as a photoacid for the deprotection of alcohols see: Nishikubo, Y.; Kanzaki, S.; Matsumura, S.; Toshima, K. *Tetrahedron Letters* **2006**, *47*, 8125.
8. This is not observed for other aldehydes, see supporting information.
9. Marciniak, B.; Kozubek, H.; Paszyc, S. *J. Chem. Ed.* **1992**, *69*, 247.
10. For the excited state acidity and lifetime of **3** in acetonitrile see: Dempsey, J. L.; Winkler, J. R.; Gray, H. B. *J. Am. Chem. Soc.* **2010**, *132*, 16774.

11. a) McClure, D. S. *J. Chem. Phys.* **1949**, *17*, 665. b) McClure, D. S.; Blake, N. W.; Hanst, P. L. J. Chem. Phys. 1954, 22, 255.
12. Tolbert, L. M.; Haubrich, J. E. *J. Am. Chem. Soc.* **1994**, *116*, 10593.
13. Salem, Z. M.; Saway, J.; Badillo, J. J. *Org. Lett.* **2019**, *21*, 8528.
14. See supporting information for LED emission spectra.
15. a) Das, A.; Banerjee, T.; Hanson, K. *Chem. Commun.* **2016**, 52, 1350. b) Das, A.; Ayad, S.; Hanson, K. *Org. Lett.* **2016**, *18*, 5416.
16. Strada, A.; Fredditori, M.; Zanoni, G.; Protti, S. *Molecules* **2019**, *24*, 1318.

## *Chapter 4: Triazole Synthesis*

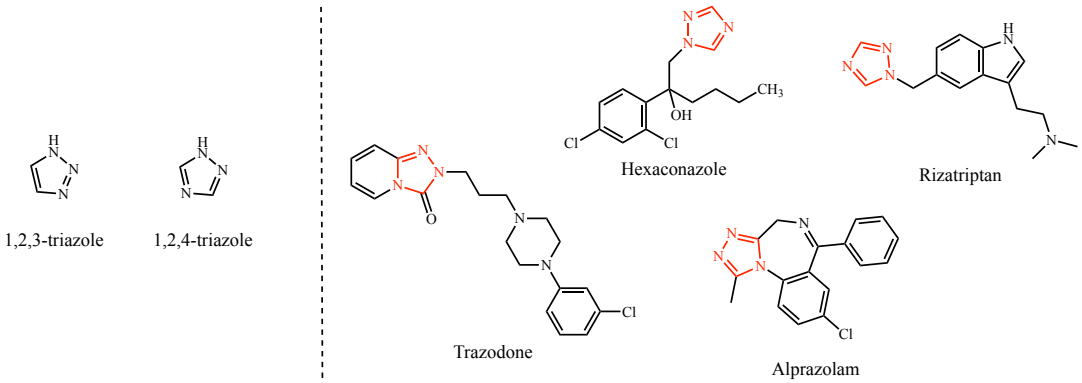
# I. Introduction

Chapter 4 describes the development of photoacid-catalyzed methodology, a greener approach, to synthesize alkyne containing bis(indolyl)methanes (BIMs). Afterwards, the BIMs were subsequently subjected to a copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction (click chemistry) to afford a variety of triazoles. The preliminary biological activity of both the parent alkynes and triazole functionalized compounds were evaluated using a sulforhodamine (SRB) assay. Finally, different methodologies were investigated, providing a one-pot synthesis approach which makes these triazoles more easily accessible.

# II. Methodologies for triazole synthesis

There are two different classes of triazoles (1,2,3)-triazoles and the (1,2,4)-triazoles shown below in Figure 26. The (1,2,3)-triazole is very stable under thermal and acidic conditions, and not reactive to redox and hydrolysis reactions.[1,2] The (1,2,4)-triazole is the more common variety seen in medicinal applications such as anticancer, anti-HIV, and antifungal drugs as seen in Figure 26. Previous strategies to access these triazoles involve the use of sodium azide or hydrazine and were investigated by the Tseng, Li, and Tian groups.[3,4,5]

**Figure 26:** Different kinds of triazoles, and medicines that contain them.



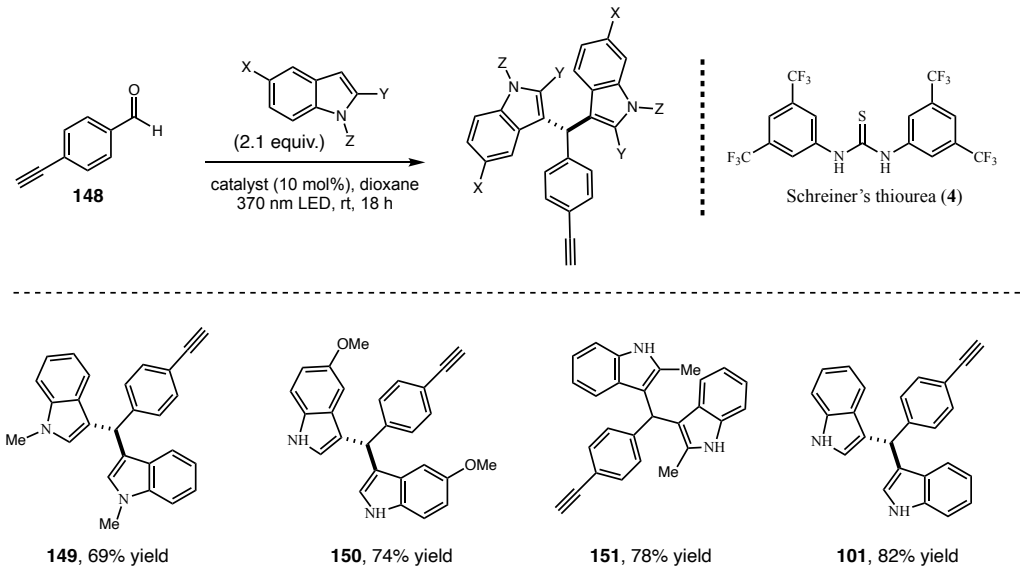

In addition to these syntheses, other methods include microwave synthesis to provide a greener and faster approach. The more common one however, has become copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction (click chemistry), which recently won the Nobel Prize in 2022.[6]

## III. Photoacid Synthesis of Parent Library

Building of the work described in Chapter 1, I wondered if I could use the bis(indolyl)methanes (BIMs) as a core and build upon them. To do this I would need a functional handle that I could further functionalize to grow my structure. The functional handle I settled on was an alkyne-functional handle due to the variety of reactions that could occur depending on what it was reacted with. I set out to synthesize an alkyne containing library of compounds, that I would use as a parent library. Due to me wanting to use BIMs as a core moiety, I first started by testing conditions in our first publication. I started with 4-ethynyl benzaldehyde (**148**) and a variety of indoles to access parent compounds with one alkyne functional handle, Scheme 25. The results showed that this reaction proceeded in good to high yields using 1H-indole (82% yield) and *N*-

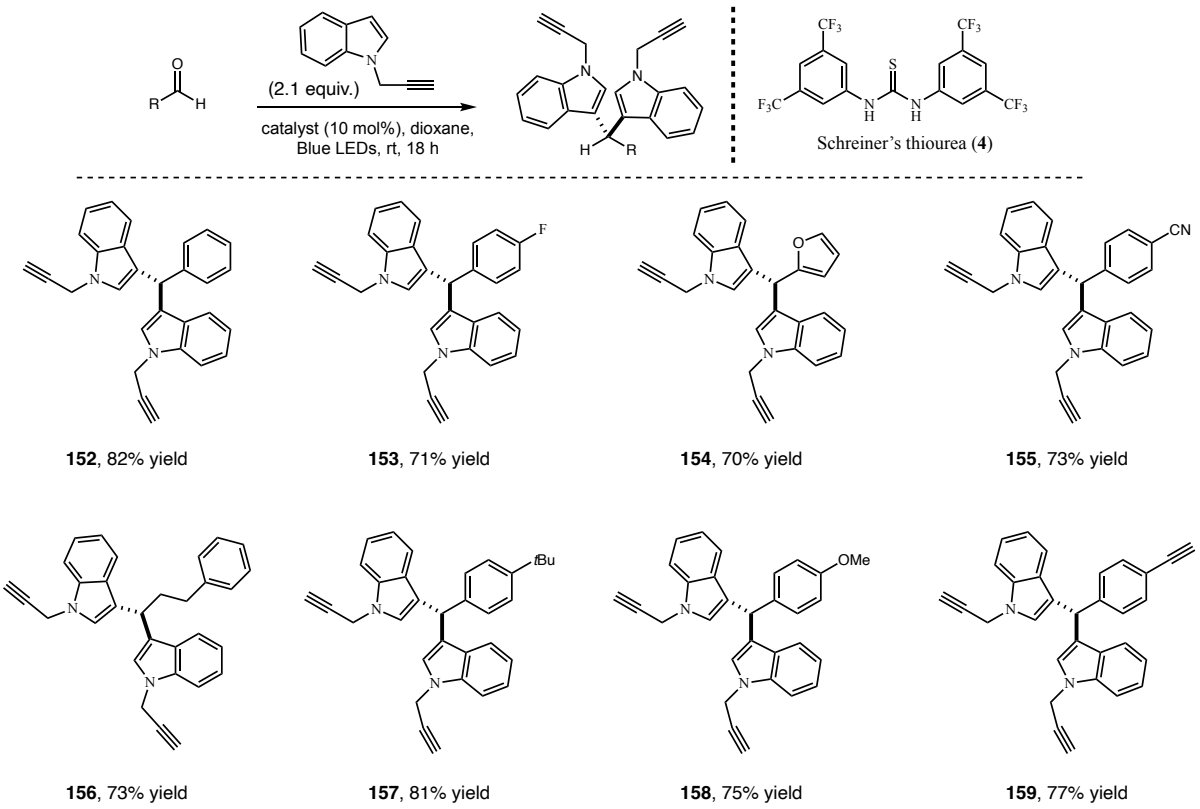
methylindole (69% yield). In addition, 5-methoxyindole, a more electron-donating nucleophile gave (74% yield) and the sterically hindered 2-methylindole gave (78% yield).

**Scheme 25:** 4-Ethynyl benzaldehyde (**148**) and various indoles.




After seeing these promising results, I moved on to adding more alkyne-handles to the core moiety. My goal would be to ultimately add an alkyne handle to every end of the BIM compounds. To investigate this, 1-(prop-2-yn-1-yl)-1*H*-indole was reacted with a variety of aldehydes, including 4-ethynyl benzaldehyde, Scheme 26. During these reactions, the alkyne functional handles were well preserved. It was seen that these conditions worked well when using benzaldehyde and its *para* substituted derivatives. The heteroaromatic aldehyde, fufural derived **154** was produced in 70% yield, while aliphatic aldehyde 3-phenylpropanal provided **156** in 73% yield. Lastly, I was able to synthesize a tris-funcitonalized parent compound **159** in 77% yield.

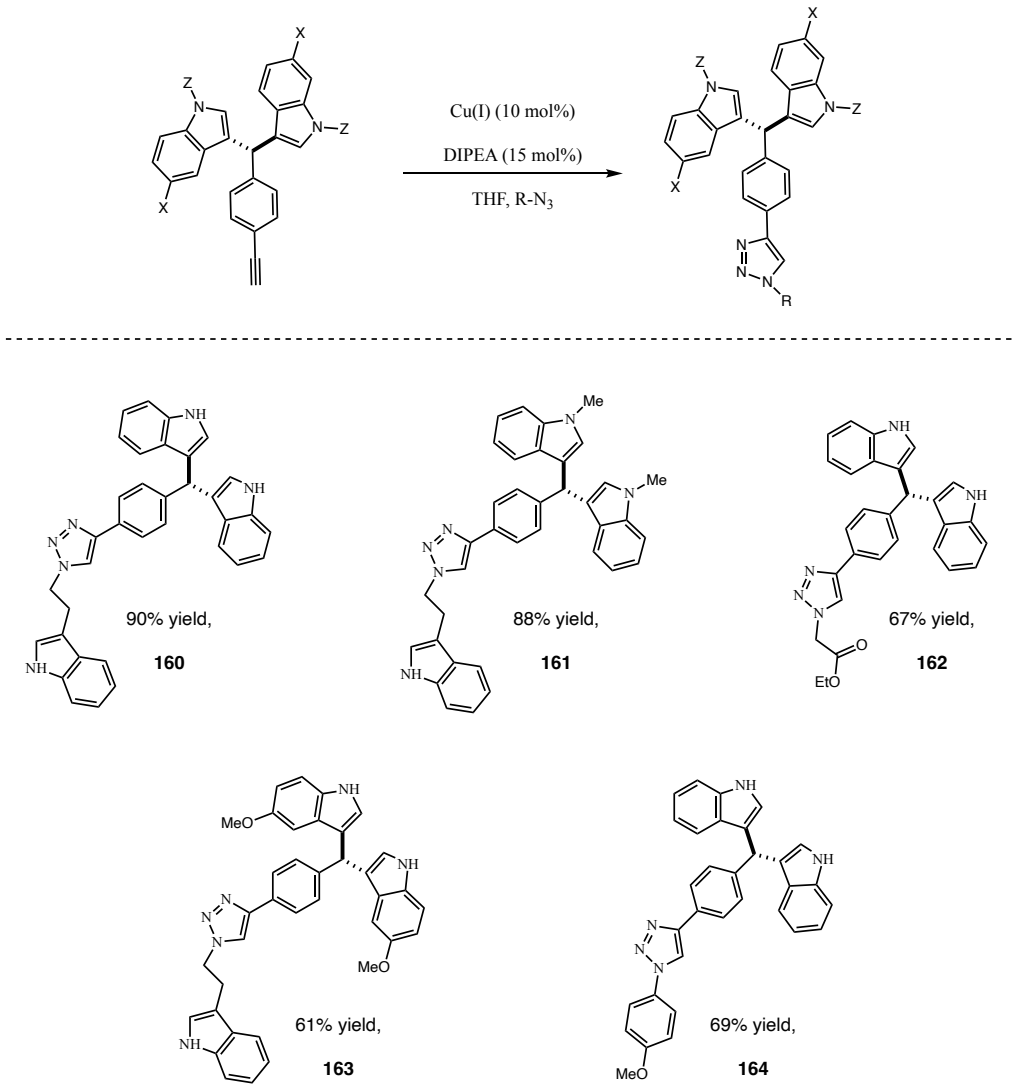
**Scheme 26:** Bis- and tris-alkyne functionalized BIMs.




## IV. Click Chemistry and Triazole Library

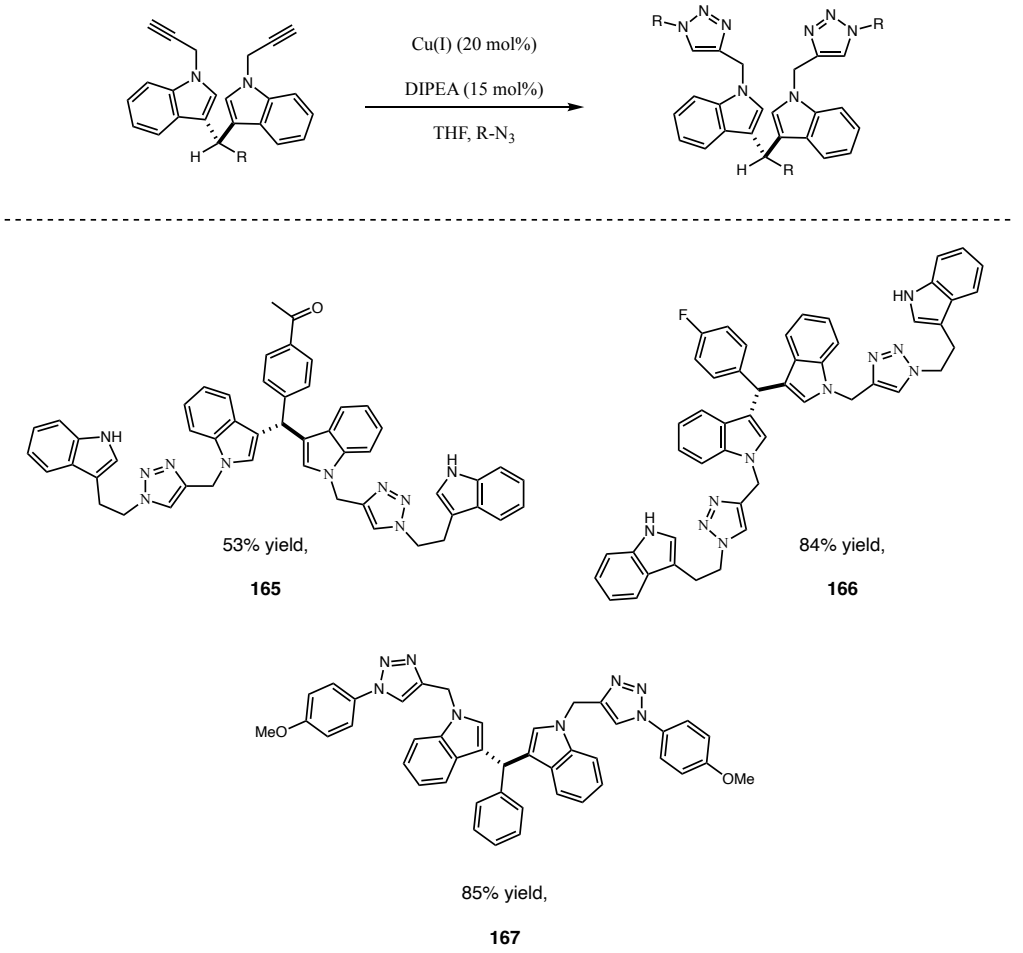
After the parent compounds were synthesized, they served as a core for the next class of molecules, triazoles. I decided to use click chemistry which involves an alkyne source and an azide to synthesize triazoles. Having the alkyne compounds in hand the azides were synthesized using a procedure outlined by Stick and coworkers.[7] Using this procedure, I was able to synthesize three different azides which I then used to access mono-substituted triazoles, Scheme 27. The reactions proceeded in good to high yields, all occurring under an inert atmosphere.

**Scheme 27:** Mono-substituted triazoles.



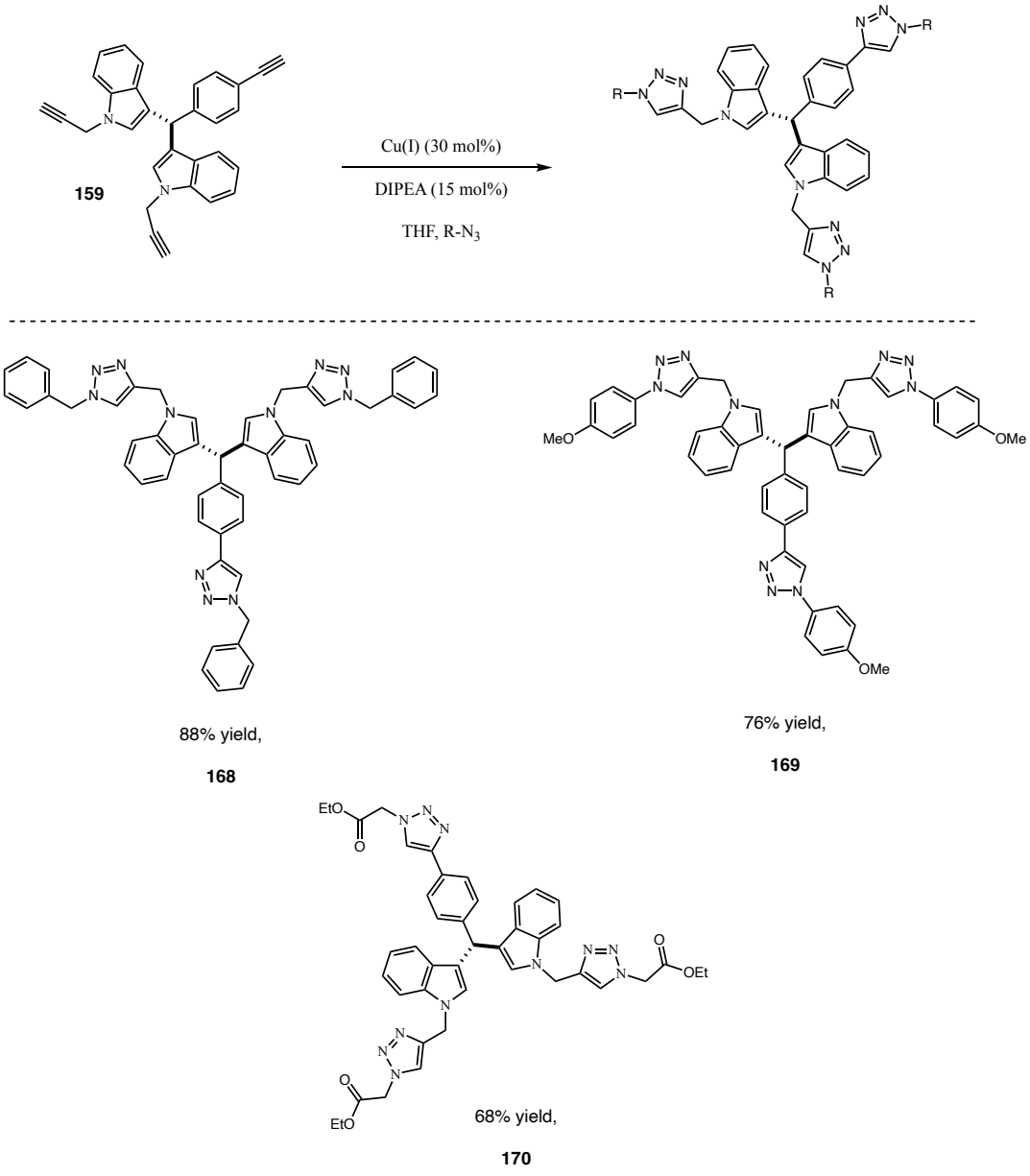

After the mono-compounds were synthesized, I moved on to the bis- and tris-substituted alkyne substituted BIMs. To successfully synthesize these triazoles, the amount of catalyst, Cu(I) had to be adjusted according to the number of triazoles that were to be synthesized. For the *bis*-substituted triazoles, the amount was 20 mol% of Cu(I) and this produced good to high yields of products, Scheme 28.

**Scheme 28:** Bis-substituted triazoles.




Likewise, for the tris-substituted triazoles, 30 mol% of Cu(I) was required, due to there being three triazoles being formed. However, it was seen for aromatic azides that the catalyst amount would have to be increased to 50 mol% to achieve good yields, using 30% mol only gives 30% yield for compound **167**, Scheme 29. In addition to this for the tris-substituted triazoles, higher dilution was required to ensure a homogenous mixture was achieved.

**Scheme 29:** Tris-substituted Triazoles.

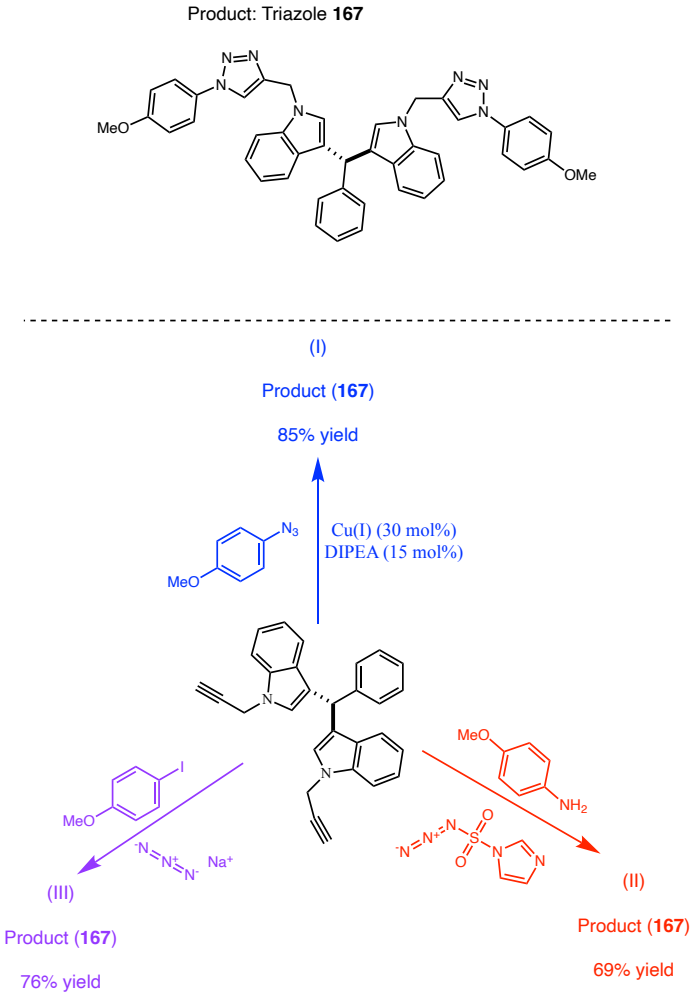



## V. Different methodologies for Triazole Synthesis

In addition to synthesizing this library, another component of the project was to see if these triazoles could be accessible using one-pot methodologies. Various one-pot and *in-situ* azide generation strategies were investigated. I started by choosing to investigate if these procedures

provide access to bis-triazole (**167**), seen in Scheme 30. The first process involved using diazotransfer reagent 1H-imidazole-1-sulfonyl azide in conjunction with the corresponding aniline, shown in red (II).[8] It was found that this procedure gave 69% yield. The second process utilized aryl iodides with sodium azide in the presence of copper iodide, shown in purple (III).[9] For this process, the bis-triazole was synthesized in 76% yield after optimization which involved stirring for two days and adding 30 mol% of copper iodide.

**Scheme 30:** Different methods for bis-triazole synthesis.



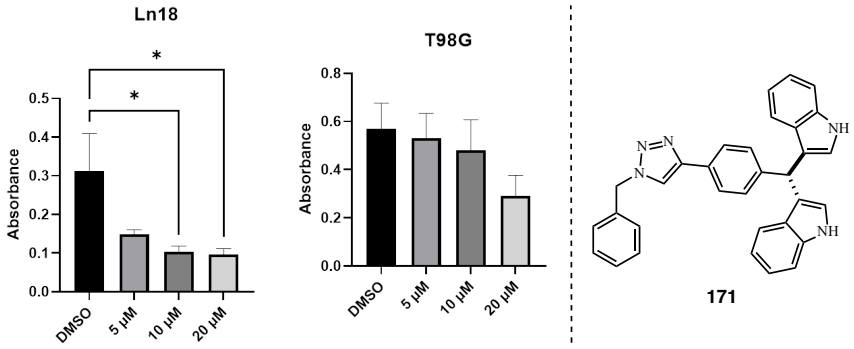
All three processes afforded high yields for the desired bis-triazole and were isolated using similar conditions. The triazole was purified by a flash chromatography gradient (100% DCM to 20% EtOAc/DCM) to remove starting material, then flushed with 50% EtOAc/DCM.

## VI. Preliminary Biological activity of triazoles and parent compounds

After the parent compounds and their correspondng triazoles were synthesized, their biological activity was investigated. To do this we collaborated with the Department of Biological Sciences at Seton Hall. To prepare the sample, they would take the parent compound or triazole and prepare a 20 mM concentration solution. When that was accomplished, they would prepare the cell cultures for testing, the cell lines that was studied were the T98G glioblastoma multiforme cell line and the Ln18 cell line. After deciding what cell lines to test, a sulforhodamine (SRB) Assay was run to determine if these parent compounds and triazoles reduced cell growth within these cell lines. Finally, the results were quantified using the GraphPad Prism software. This software was used to calculate $EC_{50}$ values from the SRB absorbance data that was previously collected.

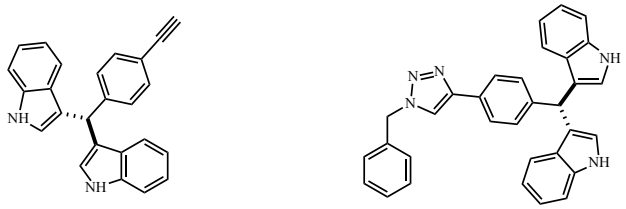
We started by evaluating mono-triazole **171** cellular growth inhibition within these two cell lines. It was found that at doses of 10 and 20 μM **171** inhibited growth when compared to the standard in DMSO, Figure 27.

**Figure 27:** Triazole **171** effect on Ln18 and T98G cell lines.




Another comparison that was looked at was the effect that the parent compound had on the T98G cell line vs. its triazole counterpart. For this the $EC_{50}$ values were observed for both compounds. It was found that triazole **171** had a lower $EC_{50}$ value than its parent alkyne containing BIM **101**, meaning that it is a more potent inhibitor of proliferation for the T98G cell line, Figure 28.

**Figure 28:** Structures and $EC_{50}$ values for parent compound and triazole.




**101**

$EC_{50}$ value: 17 µM

**171**

$EC_{50}$ value: 12 µM

## VII. Conclusions

In conclusion, I have been able to synthesize a library of alkyne functionalized compounds using the photoacid chemistry developed in our lab. I have also been able to take those alkyne functionalized parent compounds and using click chemistry transform them into triazole containing compounds. Afterwards, their biological activity was evaluated which led to the discovery that the triazoles are a more potent inhibitor of proliferation of the Ln18 cell line vs. the parent compounds.

## VIII. Experimental

### I. General Information:

Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on a Varian Inova (500 MHz) spectrometer. NMR samples were dissolved in $CDCl_3$ or DMSO-$d_6$, and chemical shifts were reported in ppm relative to tetramethylsilane (TMS). $^1$H NMR data are reported as follows: chemical shift, integration, multiplicity (s = singlet; d = doublet; dd = doublet of doublets; ddd = doublet of doublet of doublets; m = multiplet), coupling constant, and assignment. $^{13}$C NMR spectra were recorded on a Varian Inova (125 MHz) spectrometer. The samples were dissolved in $CDCl_3$ or DMSO-$d_6$, and chemical shifts are reported in ppm relative to the solvent ($CDCl_3$ as d = 77.2 ppm or DMSO-$d_6$ as d = 39.5). $^1$H and $^{13}$C NMR spectra were measured at room temperature and the chemical shifts are reported in parts per million, unless otherwise noted. High resolution mass spectra (HRMS) were obtained using a Waters Q-TOF Ultima ESI (electro-spray ionization) and are reported in m/z. Reactions were monitored by thin-layer chromatography (TLC) Silica gel 60 $F_{254}$. Compounds purified using Biotage® SNAP Ultra or Sfär silica columns. Rotary evaporation was performed using a Buchi R-300 rotary evaporator and Welch Model 2027 dry

vacuum pump. Infrared spectra were recorded neat on a Nicolet 4700 spectrometer. UV-Vis spectra were obtained using a M&A Instruments Inc. UV-5500PC spectrophotometer. Aldehydes, indole-2,3-diones (isatins), and indoles were purchased from commercial sources. Thioureas **1** and **2** were prepared according to literature procedures.

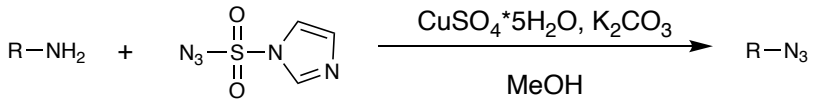
## II. General Procedures:

### Procedure for synthesis of Parent Compounds (A):

To an 8 mL vial fitted with a magnetic stir bar was added **1** (0.015 g, 0.0297 mmol, 0.1 equiv.) and the corresponding indole (0.624 mmol, 2.1 equiv.). Next, the carbonyl compound was added (0.297 mmol, 1.0 equiv.) followed by the solvent, either 1,4-dioxane or dichloromethane (0.2 M). The reaction mixture was then placed 4.0 cm from either a Kessil 370 nm or Tuna Blue LED light for 18 h. Fans were used to maintain room temperature throughout the duration of the reaction. The reaction was then dry-loaded onto silica gel (high-purity, pore size 60, particle size 40–63 μm, 230–400 mesh) and purified by flash chromatography (gradient 100% hexanes to 25% EtOAc/hexanes or 10-20% acetone/hexanes) to yield the aryl methane products.

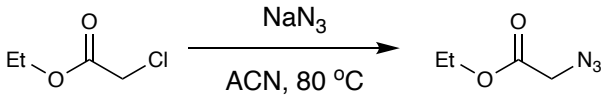
**Procedures for Azide synthesis:**

**Method 1:**




Using a modified version of the procedure outlined by Stick and coworkers[7], the appropriate amine (1.00 mmol) and 5 mL of methanol was added to a 20 mL scintillation vial containing a magnetic stir bar, followed by the addition of $CuSO_4$•$5H_2O$ (0.01 mmol), $K_2CO_3$ (1.7 mmol), and imidazole-1- sulfonyl azide hydrochloride (1.2 mmol). The reaction was stirred at room temperature until complete (as judged by TLC, 10% EtOAc/DCM). The reaction mixture was concentrated *in vacuo*, diluted with $H_2O$ (10 mL), and acidified with concentrated HCl (5-10 drops). The aqueous layer was extracted with 3 × 20 mL of EtOAc and brine. Then the combined organic layers were dried with MgSO4, filtered and concentrated *in vacuo*. The compound was then purified by flash chromatography using pure hexanes to give the corresponding azide.

**Method 2:**




To a dry 250 mL round-bottom flask with magnetic stir bar, acetonitrile (75 mL) was added, followed by ethyl chloroacetate (1.6 mL, 0.015 mol), and sodium azide (1.17 g, 0.018 mol). The mixture was refluxed at 80 °C for 4 h under argon, than cooled to room temperature and stirred for 18 h under argon atmosphere. The reaction mixture was then filtered over diatomaceous earth (Celite®) and concentrated in *vacuo*. The crude product was purified by flash chromatography

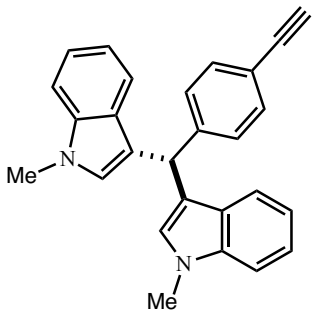
(gradient from 100% DCM to 10:90 EtOAc/DCM) to afford the ethyl azidoacetate as a colorless oil (1.50 g, 82%). Spectral data matches reports in the literature.

**Procedure of Triazole synthesis (B):**

A solution of azide (0.16 mmol) in THF (0.24 M) was prepared in a 4 mL vial containing a magnetic stir bar at room temperature that had been dried under vacuum and flushed with argon. To this solution was added copper(I) iodide (0.016 mmol, *N,N*-diisopropylethylamine (0.024 mmol), and the alkyne (0.18 mmol). The reaction was stirred at room temperature until complete as judged by TLC. The crude mixture was concentrated *in vacuo* and the resulting residue was loaded onto a flash silica gel column and was eluted with a gradient of DCM/EtOAc.

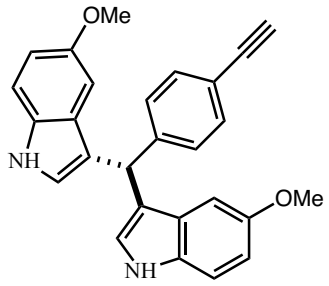
## III. Characterization Data

### a. Characterization Data for Parent Compounds

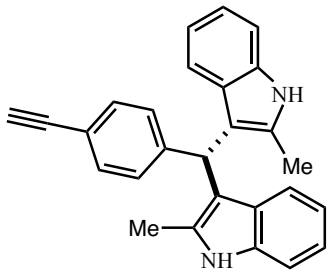



3,3'-((4-ethynylphenyl)methylene)bis(1-methyl-1*H*-indole): Compound **149** was prepared according procedure A using 4-ethynylbenzaldehyde, 1-methylindole, 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a red solid 0.076 g, 69% yield. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H), 7.37 – 7.32 (m, 2H), 7.29 (dd, *J* = 8.4, 2.1 Hz, 4H), 7.20 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 2H), 6.99 (t, *J* = 8.1, 6.9, 1.1

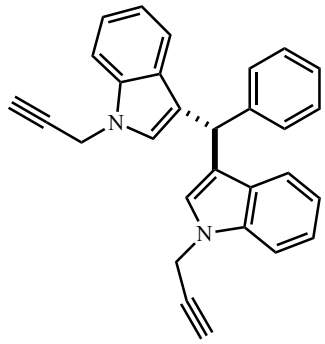
Hz, 2H), 6.50 (s, 2H), 5.86 (s, 1H), 3.67 (d, $J$ = 1.5 Hz, 6H), 3.01 (d, $J$ = 1.5 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 145.65, 137.53, 132.24, 128.83, 128.42, 127.43, 121.67, 120.05, 118.89, 117.73, 109.26, 84.08, 76.72, 40.14, 32.82. HRMS (ESI) m/z [M + H] calcd for $C_{27}H_{23}N_2$, 375.1824; found 375.1807




3,3'-((4-ethynylphenyl)methylene)bis(5-methoxy-1*H*-indole): Compound **150** was prepared according procedure A using 4-ethynylbenzaldehyde, 5-methoxy-1*H*-indole, 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 20% acetone/hexanes to give a red solid 0.090 g, 74% yield. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.40 (d, $J$ = 8.2 Hz, 3H), 7.28 (d, $J$ = 8.3 Hz, 3H), 7.21 (d, $J$ = 8.7 Hz, 3H), 6.82 (dd, $J$ = 8.7, 2.4 Hz, 4H), 6.76 (d, $J$ = 2.5 Hz, 4H), 6.59 (d, $J$ = 2.4 Hz, 4H), 5.75 (s, 2H), 3.68 (s, 10H), 3.03 (s, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.9, 145.1, 145.1, 132.3, 131.9, 128.9, 127.5, 124.6, 124.6, 119.9, 118.7, 118.7, 112.1, 111.9, 111.9, 101.9, 84.1, 84.0, 76.8, 76.8, 56.0, 40.3. HRMS (ESI) m/z [M + H] calcd for $C_{27}H_{23}N_2O_2$, 407.1786; found 407.1712

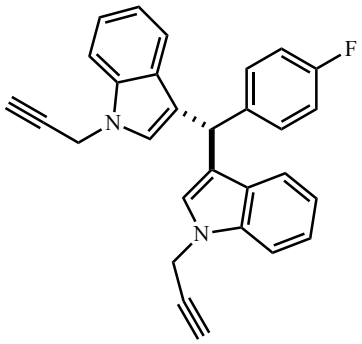



3,3'-((4-ethynylphenyl)methylene)bis(2-methyl-1*H*-indole): Compound **151** was prepared according procedure A using 4-ethynylbenzaldehyde, 2-methyl-1*H*-indole, 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 30% EtOAc/hexanes to give a red solid 0.086 g, 78% yield. $^{1}$H NMR (500 MHz, acetone-$D_6$) δ 9.95 (s, 1H), 7.40 (dt, *J* = 8.3, 1.4 Hz, 2H), 7.27 (ddt, *J* = 7.6, 4.3, 1.5 Hz, 4H), 6.94 (dt, *J* = 7.6, 1.4 Hz, 4H), 6.93 – 6.91 (m, 1H), 6.74 (tq, *J* = 7.1, 1.2 Hz, 2H), 6.07 (s, 1H), 3.82 – 3.45 (m, 1H), 2.35 – 2.07 (m, 6H). $^{13}$C NMR (125 MHz,acetone-$D_6$) δ 146.76, 136.48, 136.33, 133.10, 132.96, 132.41, 130.07, 129.64, 129.60, 120.88, 120.52, 119.70, 119.20, 113.08, 113.03, 111.14, 111.09, 84.54, 78.52, 40.06, 12.33, 12.28. HRMS (ESI) m/z [M + H] calcd for $C_{27}H_{23}N_2$, 375.1758; found 375.1808

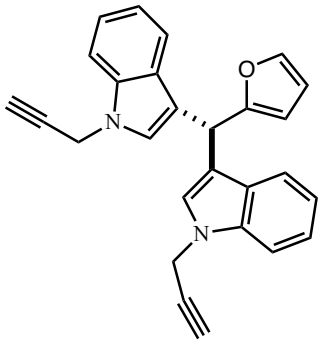



3,3'-(phenylmethylene)bis(1-(prop-2-yn-1-yl)-1*H*-indole): Compound **152** was prepared according procedure A using benzaldehyde, 1-(prop-2-yn-1-yl)-1*H*-indole, 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 20% acetone/hexanes to give ared solid 0.097 g, 82% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 4H), 7.35 – 7.31

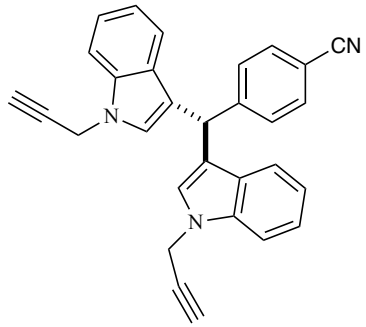
(m, 2H), 7.29 – 7.23 (m, 2H), 7.19 (tdd, *J* = 7.5, 3.2, 1.5 Hz, 3H), 7.02 – 6.97 (m, 2H), 6.62 (t, *J* = 1.4 Hz, 2H), 5.85 (s, 1H), 4.69 (t, *J* = 2.2 Hz, 4H), 2.34 – 2.22 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 143.97, 136.67, 128.82, 128.38, 128.07, 127.01, 126.30, 122.01, 120.39, 119.49, 119.18, 109.52, 78.17, 73.33, 40.25, 35.84. HRMS (ESI) m/z [M + H] calcd for $C_{29}H_{23}N_2$, 399.1839; found 399.1799




3,3'-((4-fluorophenyl)methylene)bis(1-(prop-2-yn-1-yl)-1*H*-indole): Compound **153** was prepared according procedure A using 4-Fluorobenzaldehyde, 4.2 equiv. 1-(prop-2-yn-1-yl)-1*H*-indole, 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a red solid 0.085 g, 71% yield. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41 (dt, *J* = 8.2, 0.9 Hz, 2H), 7.36 (dt, *J* = 8.0, 1.0 Hz, 2H), 7.33 – 7.27 (m, 2H), 7.25 – 7.21 (m, 2H), 7.03 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 1.1 Hz, 2H), 5.85 (s, 1H), 4.77 (d, *J* = 2.5 Hz, 4H), 2.34 – 2.32 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 162.49, 160.55, 139.66, 139.64, 136.69, 130.21, 130.14, 127.91, 126.93, 122.12, 120.31, 119.56, 119.03, 115.21, 115.04, 109.57, 78.09, 73.41, 39.52, 35.85. HRMS (ESI) m/z [M + H] calcd for $C_{29}H_{22}N_2F$, 417.1893; found 417.1703

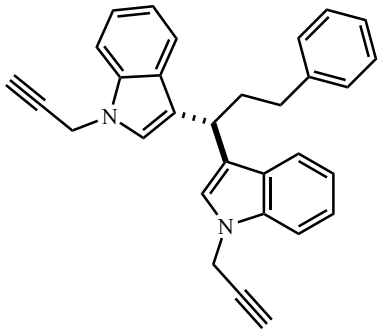


3,3'-(furan-2-ylmethylene)bis(1-(prop-2-yn-1-yl)-1*H*-indole): Compound **154** was prepared according procedure A using furfural, 4.2 equiv. 1-(prop-2-yn-1-yl)-1*H*-indole, 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 30% DCM/hexanes to give a brown solid 0.080 g, 70% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.56 (dt, *J* = 8.1, 1.0 Hz, 4H), 7.48 – 7.42 (m, 6H), 7.31 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 4H), 7.14 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 4H), 6.94 (d, *J* = 1.0 Hz, 4H), 6.38 (dd, *J* = 3.2, 1.9 Hz, 2H), 6.15 (dt, *J* = 3.1, 0.8 Hz, 2H), 6.00 (d, *J* = 1.1 Hz, 2H), 4.81 (d, *J* = 2.7 Hz, 8H), 2.40 (t, *J* = 0.6 Hz, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 156.98, 141.39, 136.50, 127.77, 126.41, 122.03, 120.12, 119.61, 116.62, 110.25, 109.56, 106.79, 78.04, 73.47, 35.91, 34.10, 29.83. HRMS (ESI) m/z [M + H] calcd for $C_{27}H_{21}N_2O$, 389.1674; found 389.1592

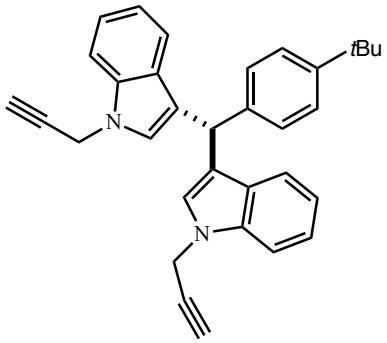


4-(bis(1-(prop-2-yn-1-yl)-1*H*-indol-3-yl)methyl)benzonitrile: Compound **155** was prepared according procedure A using 4-Formylbenzonitrile, 4.2 equiv. 1-(prop-2-yn-1-yl)-1*H*-indole, 1,4-

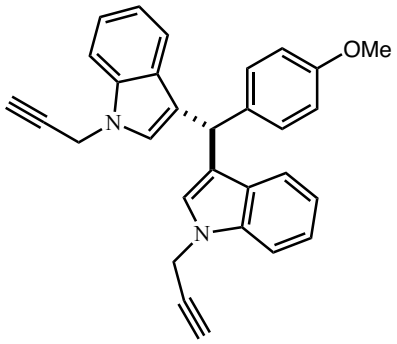
dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 30% acetone/hexanes to give a purple solid 0.092 g, 73% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1 Hz, 1H), 7.27 (dd, *J* = 13.3, 8.1 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.52 (s, 1H), 5.76 (s, 1H), 4.56 (d, *J* = 2.6 Hz, 2H), 2.18 (t, *J* = 2.5 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 149.55, 136.58, 132.22, 129.48, 127.57, 126.90, 126.87, 122.29, 119.94, 119.73, 119.17, 117.56, 110.05, 109.68, 77.85, 73.57, 73.56, 40.30, 35.76. HRMS (ESI) m/z [M + H] calcd for $C_{30}H_{22}N_3$, 424.1745; found 424.1750



3,3'-(3-phenylpropane-1,1-diyl)bis(1-(prop-2-yn-1-yl)-1*H*-indole): Compound **156** was prepared according procedure A using 3-phenylpropanal, 4.2 equiv. 1-(prop-2-yn-1-yl)-1*H*-indole, 1,4-dioxane, and 456 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 10% EtOAc/hexanes to give a red solid 0.092 g, 73% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 3H), 7.18 – 7.10 (m, 6H), 7.02 (t, *J* = 7.5 Hz, 2H), 6.95 (s, 2H), 4.64 (q, *J* = 1.8, 1.0 Hz, 4H), 4.45 (t, *J* = 7.3 Hz, 1H), 2.68 (dd, *J* = 9.1, 6.4 Hz, 2H), 2.51 (q, *J* = 7.5 Hz, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 142.58, 136.48, 128.63, 128.33, 128.01, 125.74, 124.85, 121.82, 119.98, 119.50, 119.25, 109.43, 78.16, 73.40, 37.65, 35.64, 34.47, 33.40. HRMS (ESI) m/z [M + H] calcd for $C_{31}H_{27}N_2$, 427.1965; found 427.2112

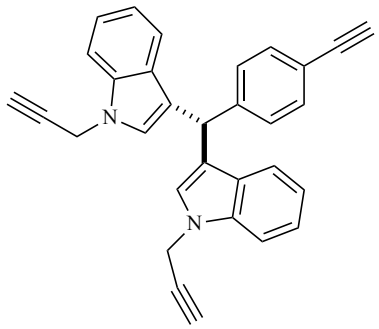



3,3'-((4-(*tert*-butyl)phenyl)methylene)bis(1-(prop-2-yn-1-yl)-1*H*-indole): Compound **157** was prepared according procedure A using 4-(*tert*-butyl)benzaldehyde, 4.2 equiv. 1-(prop-2-yn-1-yl)-1*H*-indole, 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 30% acetone/hexanes to give a red solid 0.109 g, 81% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 4H), 7.28 – 7.24 (m, 4H), 7.21 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.08 – 6.94 (m, 2H), 6.66 (d, *J* = 1.2 Hz, 2H), 5.83 (s, 1H), 4.76 (dd, *J* = 2.5, 1.3 Hz, 4H), 2.33 – 2.29 (m, 2H), 1.29 (d, *J* = 1.5 Hz, 9H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 148.88, 140.79, 136.67, 128.33, 128.16, 126.95, 125.22, 121.94, 120.46, 119.45, 119.39, 109.49, 78.25, 73.27, 39.70, 35.87, 34.50, 31.58, 29.83. HRMS (ESI) m/z [M + H] calcd for $C_{33}H_{31}N_2$, 455.2642; found 455.2411

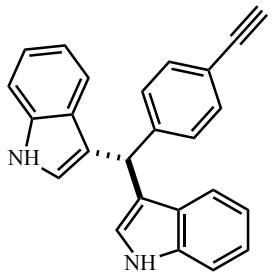



3,3'-((4-methoxyphenyl)methylene)bis(1-(prop-2-yn-1-yl)-1*H*-indole): Compound **158** was prepared according procedure A using 4-methoxybenzaldehyde, 4.2 equiv. 1-(prop-2-yn-1-yl)-1*H*-indole, 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes

to 30% EtOAc/hexanes to give a red solid 0.095 g, 75% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.38 (ddt, *J* = 8.1, 5.2, 0.9 Hz, 3H), 7.29 – 7.18 (m, 3H), 7.02 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.62 (d, *J* = 1.0 Hz, 1H), 5.81 (s, 1H), 4.74 (d, *J* = 2.5 Hz, 3H), 3.77 (s, 2H), 2.31 (t, *J* = 2.5 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 158.04, 136.69, 136.69, 136.17, 129.72, 128.06, 126.96, 121.98, 120.45, 119.54, 119.45, 113.72, 109.50, 78.19, 73.31, 55.32, 39.39, 35.88. HRMS (ESI) m/z [M + H] calcd for $C_{30}H_{24}N_2O$, 429.4159; found 429.1904



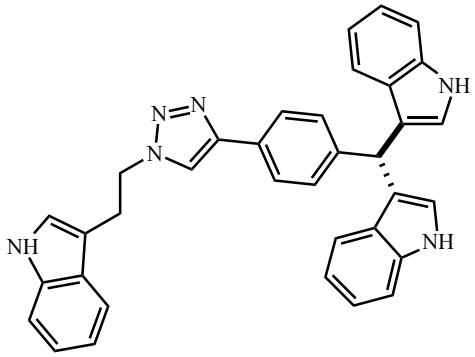
3,3'-((4-ethynylphenyl)methylene)bis(1-(prop-2-yn-1-yl)-1*H*-indole): Compound **159** was prepared according procedure A using 4-ethynylbenzaldehyde, 4.2 equiv. 1-(prop-2-yn-1-yl)-1*H*-indole, 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give a red solid 0.095 g, 77% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 12.3, 8.1 Hz, 4H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.21 (t, *J* = 7.7 Hz, 2H), 7.01 (t, *J* = 7.5 Hz, 2H), 6.62 (s, 2H), 5.85 (s, 1H), 4.72 (d, *J* = 2.5 Hz, 4H), 3.01 (s, 1H), 2.30 (d, *J* = 2.6 Hz, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 145.01, 136.67, 132.29, 128.84, 127.90, 127.01, 122.14, 120.28, 119.94, 119.60, 118.54, 109.57, 84.01, 78.06, 73.45, 40.17, 35.88. HRMS (ESI) m/z [M + H] calcd for $C_{31}H_{23}N_2$, 423.3185; found 423.1800




3,3'-((4-ethynylphenyl)methylene)bis(1*H*-indole): Compound **101** was prepared according procedure A using 4-ethynylbenzaldehyde, 1*H*-indole, 1,4-dioxane, and 370 nm LEDs. Purified by flash chromatography gradient 100% hexanes to 25% EtOAc/hexanes to give an orange solid 0.081 g, 79% yield. $^{1}$H NMR (500 MHz, CDCl3) δ 7.84 (s, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 2H), 6.57 (d, *J* = 2.2 Hz, 2H), 5.86 (s, 1H), 3.02 (s, 1H). $^{13}$C NMR (125 MHz, CDCl3) δ 145.16, 136.74, 132.25, 128.85, 126.99, 123.78, 123.76, 122.17, 119.93, 119.86, 119.45, 119.11, 111.24, 84.03, 76.84, 76.83, 40.20. HRMS (ESI) m/z [M – H] calcd for $C_{25}H_{17}N_2$, 345.1392; found 345.1393.

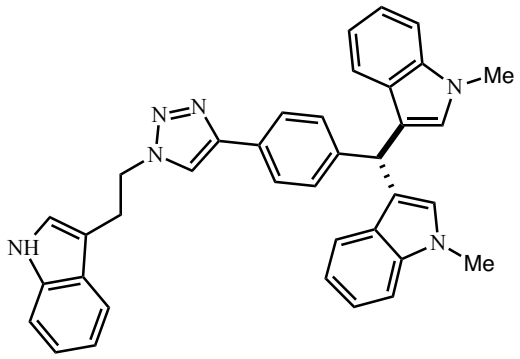
## III. Characterization Data

### b. Characterization Data for Triazoles



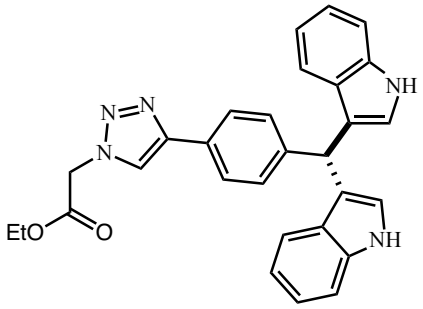

3,3'-((4-(1-(2-(1*H*-indol-3-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)phenyl)methylene)bis(1*H*-indole): Compound **160** was prepared according procedure B using parent compound (**101**). Purification

by flash chromatography gradient 100% DCM to 10% EtOAc/DCM to remove starting material then flushed with 40% EtOAc/DCM to give a red solid 0.030 g, 90% yield. $^{1}$H NMR (500 MHz, acetone-$D_6$) δ 10.03 (d, *J* = 9.7 Hz, 3H), 8.18 – 8.11 (m, 1H), 7.80 – 7.72 (m, 2H), 7.62 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.45 (t, *J* = 8.3, 1.7 Hz, 2H), 7.39 (td, *J* = 8.1, 2.2 Hz, 5H), 7.16 – 6.99 (m, 5H), 6.95 – 6.88 (m, 2H), 6.85 (td, *J* = 2.5, 1.2 Hz, 2H), 5.95 (d, *J* = 2.4 Hz, 1H), 4.72 (ddd, *J* = 8.8, 5.3, 1.6 Hz, 2H), 3.45 – 3.38 (m, 2H). $^{13}$C NMR (125 MHz, acetone-$D_6$) δ 147.74, 145.55, 138.11, 137.64, 130.18, 129.89, 128.18, 128.08, 126.00, 124.63, 123.97, 122.30, 122.10, 121.16, 121.14, 120.31, 119.68, 119.67, 119.35, 119.05, 112.29, 112.19, 112.14, 111.61, 51.33, 40.93, 27.19. HRMS (ESI) m/z [M + H] calcd for $C_{35}H_{29}N_6$, 533.5246; found 533.2449

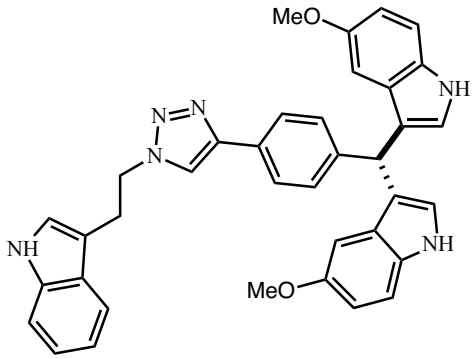



3,3'-((4-(1-(2-(1*H*-indol-3-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)phenyl)methylene)bis(1-methyl-1*H*-indole): Compound **161** was prepared according procedure B using parent compound (**149**). Purification by flash chromatography using a gradient of 100% DCM to 5% EtOAc/DCM to remove starting material then flushed with 20% EtOAc/DCM to give a red solid 0.020 g, 88% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.43 – 7.31 (m, 6H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.22 – 7.16 (m, 3H), 7.16 – 7.10 (m, 1H), 7.03 – 6.94 (m, 2H), 6.75 (d, *J* = 2.3 Hz, 1H), 6.52 (s, 2H), 5.87 (s, 1H), 4.63 (t, *J* = 6.9 Hz, 2H), 3.64 (s, 6H), 3.35 (t, *J* = 6.9 Hz, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 147.58, 144.60, 137.52, 136.37,

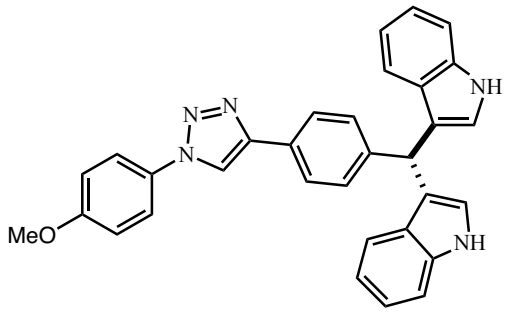
129.21, 128.62, 128.43, 127.50, 126.86, 125.77, 122.87, 122.41, 121.58, 120.11, 120.02, 119.79, 118.79, 118.33, 118.05, 111.58, 111.19, 109.22, 50.80, 40.01, 32.78, 29.83, 26.72. HRMS (ESI) m/z [M + H] calcd for $C_{37}H_{33}N_6$, 561.2771; found 561.2756




Ethyl 2-(4-(4-(di(1*H*-indol-3-yl)methyl)phenyl)-1*H*-1,2,3-triazol-1-yl)acetate: Compound **162** was prepared according procedure B using parent compound (**101**). Purification by flash chromatography using a gradient of 100% DCM to 20% EtOAc/DCM to remove starting material then flushed with 40% EtOAc/DCM to give a red solid 0.033 g, 67% yield.$^1$H NMR (500 MHz, acetone-$D_6$) δ 10.02 (s, 2H), 8.30 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.51 – 7.45 (m, 2H), 7.45 – 7.35 (m, 4H), 7.07 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 2H), 6.94 – 6.82 (m, 4H), 5.97 (s, 1H), 5.36 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, acetone-$D_6$) δ 167.77, 148.18, 145.81, 138.09, 129.98, 129.77, 128.06, 126.09, 124.64, 122.51, 122.11, 120.29, 119.62, 119.36, 112.19, 62.43, 51.40, 40.93, 14.37. HRMS (ESI) m/z [M + H] calcd for $C_{29}H_{26}N_5O_2$, 476.1824; found 476.2082

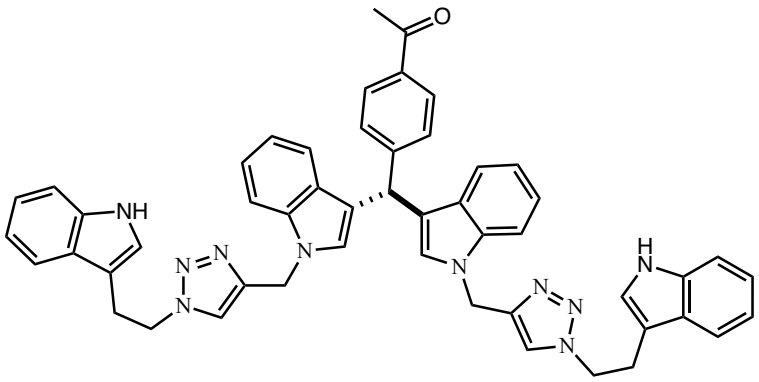



3,3'-((4-(1-(2-(1*H*-indol-3-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)phenyl)methylene)bis(5-methoxy-1*H*-indole): Compound **163** was prepared according procedure B using parent compound (**150**). Purification by flash chromatography gradient 100% DCM to 10% EtOAc/DCM to remove starting material then flushed with 40% EtOAc/DCM to give a red solid 0.038 g, 61% yield. $^{1}$H NMR (500 MHz, acetone-$D_6$ / MeOH-$D_4$) δ 7.99 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.48 – 7.39 (m, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.26 – 7.18 (m, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.97 (t, *J* = 7.8 Hz, 1H), 6.92 – 6.84 (m, 2H), 6.70 (d, *J* = 2.5 Hz, 2H), 6.66 (s, 2H), 6.62 (d, *J* = 2.5 Hz, 1H), 6.60 (d, *J* = 2.5 Hz, 1H), 5.70 (s, 1H), 4.29 (s, 6H), 3.50 (s, 5H), 2.01 (s, 2H). $^{13}$C NMR (125 MHz, acetone-$D_6$ / MeOH-$D_4$) δ 154.47, 148.23, 146.24, 137.75, 133.40, 130.15, 129.47, 128.50, 128.21, 126.19, 125.37, 125.35, 123.98, 123.95, 122.36, 121.89, 119.73, 119.21, 118.98, 112.76, 112.28, 112.12, 111.39, 102.49, 55.88, 51.90, 41.21, 27.25. HRMS (ESI) m/z [M + H] calcd for $C_{37}H_{33}N_6O_2$, 593.2670; found 593.2653

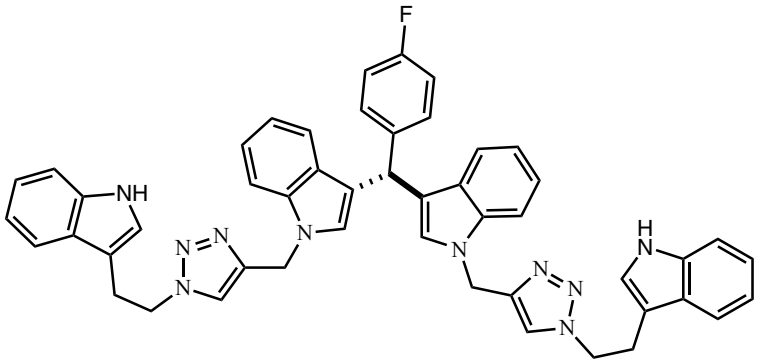



3,3'-((4-(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)phenyl)methylene)bis(1*H*-indole):

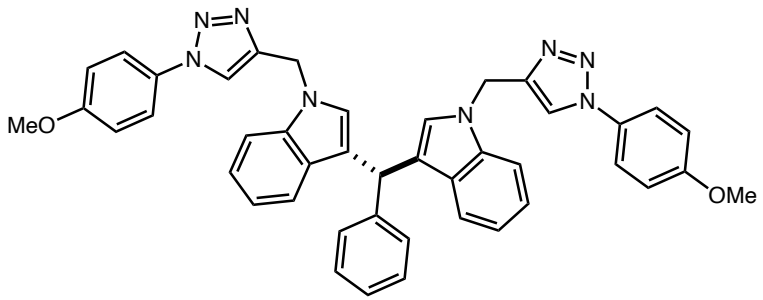
Compound **164** was prepared according procedure B using parent compound (**101**). Purification by flash chromatography gradient 100% DCM to 10% EtOAc/DCM to remove starting material then flushed with 40% EtOAc/DCM to give a red solid 0.037 g, 71% yield. $^{1}$H NMR (500 MHz, acetone-$D_6$) δ 10.05 (s, 2H), 8.78 (d, *J* = 0.8 Hz, 1H), 7.94 – 7.88 (m, 2H), 7.83 (dd, *J* = 9.1, 0.8 Hz, 2H), 7.53 – 7.49 (m, 2H), 7.40 (ddt, *J* = 8.1, 5.0, 0.9 Hz, 4H), 7.13 (dd, *J* = 9.2, 0.8 Hz, 2H), 7.08 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 2H), 6.92 (ddd, *J* = 8.1, 7.0, 0.9 Hz, 2H), 6.89 – 6.86 (m, 2H), 5.98 (s, 1H), 3.87 (d, *J* = 0.8 Hz, 3H). $^{13}$C NMR (125 MHz, acetone-$D_6$) δ 160.65, 148.68, 146.01, 138.08, 131.59, 129.99, 129.57, 128.04, 126.18, 124.63, 122.56, 122.10, 120.28, 119.58, 119.35, 119.20, 115.60, 112.19, 55.98, 40.96. HRMS (ESI) m/z [M + H] calcd for $C_{32}H_{26}N_5O$, 496.2159; found 496.2136



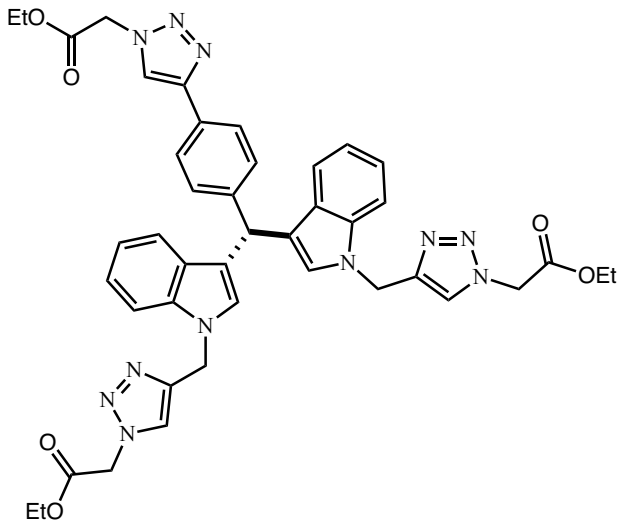
1-(4-(bis(1-((1-(2-(1*H*-indol-3-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)methyl)phenyl)ethan-1-one: Compound **165** was prepared according procedure B using the parent compound. Purification by flash chromatography gradient 100% DCM to 10% EtOAc/DCM to remove starting material then flushed with 40% EtOAc/DCM to give a red solid 0.020 g, 53% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.66 – 7.63 (m, 2H), 7.42 (d, *J* = 7.9 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.13 (m, 10H), 7.11 – 7.04 (m, 2H), 6.98 (t, *J* = 7.4 Hz, 2H), 6.48 (d, *J* = 5.5 Hz, 4H), 6.16 (d, *J* = 2.5 Hz, 2H), 5.83 (s, 1H), 5.39 – 4.99 (m, 4H), 4.45 (tt, *J* = 13.5, 7.0 Hz, 4H), 3.15 (td, *J* = 6.4, 3.6 Hz, 4H), 2.54 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 198.24, 149.49, 143.89, 136.71, 136.22, 135.59, 128.86, 128.68, 127.79, 127.48, 126.47, 123.20, 122.59, 122.27, 122.09, 119.88, 119.63, 119.36, 118.11, 118.06, 111.58, 110.39, 110.12, 50.90, 42.03, 40.13, 26.75, 26.62. HRMS (ESI) m/z [M + H] calcd for $C_{51}H_{45}N_{10}O$, 813.3798; found 813.3773



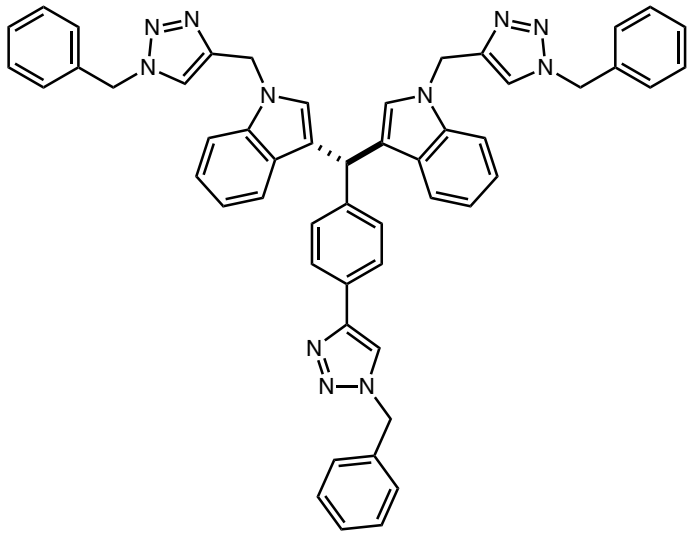
3,3'-((4-fluorophenyl)methylene)bis(1-((1-(2-(1*H*-indol-3-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole): Compound **166** was prepared according procedure B using parent compound (**153**). Purification by flash chromatography gradient 100% DCM to 10% EtOAc/DCM to remove starting material then flushed with 40% EtOAc/DCM to give a red solid 0.014 g, 84% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.42 (t, *J* = 6.2 Hz, 4H), 7.24 (s, 1H), 7.21 (d, *J* = 8.6 Hz, 3H), 7.16 (t, *J* = 7.7 Hz, 7H), 7.08 (t, *J* = 7.4 Hz, 2H), 6.99 (t, *J* = 7.5 Hz, 2H), 6.89 (t, *J* = 8.4 Hz, 2H), 6.48 (s, 2H), 6.42 (s, 2H), 6.11 (s, 2H), 5.76 (s, 1H), 5.19 (q, *J* = 16.1 Hz, 4H), 4.46 (qt, *J* = 13.4, 6.4 Hz, 4H), 3.15 (q, *J* = 6.1 Hz, 4H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 162.49, 160.55, 144.02, 139.46, 139.43, 136.74, 136.21, 130.04, 129.98, 127.90, 127.47, 126.45, 123.27, 122.67, 122.30, 122.01, 120.00, 119.67, 119.27, 118.95, 118.07, 115.33, 115.17, 111.59, 110.37, 110.14, 50.93, 42.10, 39.36, 29.84, 26.65. HRMS (ESI) m/z [M + H] calcd for $C_{49}H_{42}N_{10}F$, 789.3594; found 789.3569



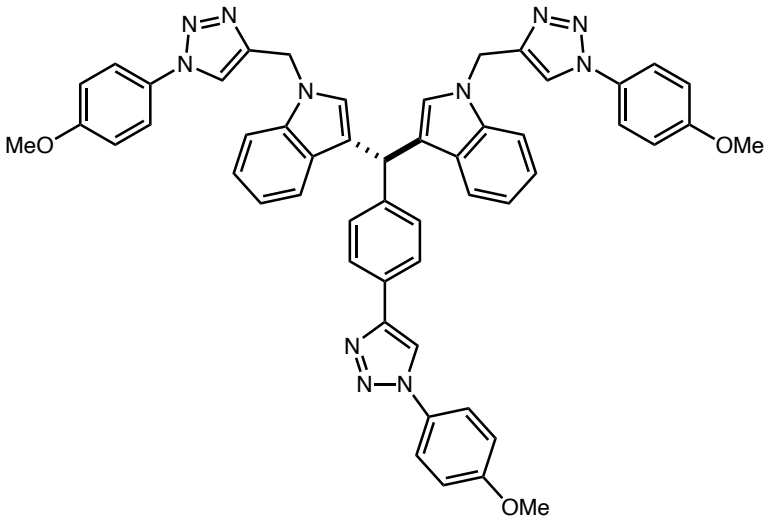

3,3'-(phenylmethylene)bis(1-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole): Compound **167** was prepared according procedure B using parent compound (**152**). Purification by flash chromatography gradient 100% DCM to 20% EtOAc/DCM to remove starting material then flushed with 50% EtOAc/DCM to give a red solid 0.029 g, 85% yield. $^{1}$H NMR (500 MHz, acetone-$D_6$) δ 8.18 (d, *J* = 3.5 Hz, 2H), 7.63 (dd, *J* = 9.5, 3.1 Hz, 4H), 7.57 (dd, *J* = 8.3, 3.5 Hz, 2H), 7.44 – 7.32 (m, 4H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.19 – 7.13 (m, 1H), 7.10 (t, *J* = 8.9, 6.4 Hz, 2H), 7.04 (dd, *J* = 9.5, 3.1 Hz, 4H), 6.98 (d, *J* = 3.5 Hz, 2H), 6.89 (td, *J* = 7.6, 3.4 Hz, 2H), 5.91 (d, *J* = 3.5 Hz, 1H), 5.44 (d, *J* = 3.4 Hz, 4H), 3.83 (d, *J* = 3.5 Hz, 6H). $^{13}$C NMR (125 MHz, acetone-$D_6$) δ 160.70, 145.95, 145.51, 137.82, 131.39, 129.51, 128.95, 128.76, 128.17, 126.83, 122.72, 122.31, 121.57, 121.53, 120.62, 119.65, 119.61, 115.56, 110.82, 55.98, 55.97, 41.97, 41.05. HRMS (ESI) m/z [M + H] calcd for $C_{43}H_{36}N_8O_2$, 697.3028; found 697.2796



Diethyl 2,2'-(((((4-(1-(2-ethoxy-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)phenyl)methylene)bis(1*H*-indole-3,1-diyl))bis(methylene))bis(1*H*-1,2,3-triazole-4,1-diyl))diacetate: Compound **170** was prepared according procedure B using parent compound (**159**). Purification by flash chromatography gradient 100% DCM to 20% EtOAc/DCM to remove starting material then flushed with 40% EtOAc/DCM to give a red solid 0.026 g, 68% yield. $^{1}$H NMR (500 MHz, acetone-$D_6$) δ 8.32 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.77 (s, 2H), 7.53 (dt, *J* = 8.3, 0.9 Hz, 2H), 7.46 – 7.42 (m, 2H), 7.37 (dt, *J* = 8.0, 1.0 Hz, 2H), 7.11 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 2H), 6.96 – 6.90 (m, 4H), 5.93 (s, 1H), 5.44 (s, 4H), 5.37 (s, 2H), 5.26 (s, 4H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 4H), 1.26 (dd, *J* = 7.4, 6.9 Hz, 3H), 1.21 (t, *J* = 7.3, 6.9 Hz, 6H). $^{13}$C NMR (125 MHz, acetone-$D_6$) δ 167.80, 167.73, 148.12, 145.45, 145.42, 137.77, 129.92, 129.88, 128.72, 128.16, 126.16, 124.78, 122.52, 122.29, 120.53, 119.66, 119.35, 110.83, 62.42, 62.38, 51.41, 51.29, 42.06, 40.67, 14.33. HRMS (ESI) m/z [M + H] calcd for $C_{43}H_{44}N_{11}O_6$, 810.3498; found 810.3466



3,3'-((4-(1-benzyl-1*H*-1,2,3-triazol-4-yl)phenyl)methylene)bis(1-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole): Compound **168** was prepared according procedure B using parent compound (**159**). Purification by flash chromatography gradient 100% DCM to 30% EtOAc/DCM to give a red solid 0.034 g, 88% yield. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.7 Hz, 2H), 7.52 (s, 1H), 7.38 – 7.19 (m, 17H), 7.16 – 6.99 (m, 8H), 6.88 (t, *J* = 7.6 Hz, 2H), 6.63 (s, 2H), 5.80 (s, 1H), 5.48 (s, 2H), 5.27 (d, *J* = 22.6 Hz, 8H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 148.21, 144.06, 136.68, 134.83, 134.45, 129.18, 129.11, 128.76, 128.51, 128.04, 127.99, 127.70, 127.38, 125.83, 121.96, 120.01, 119.56, 119.22, 118.78, 109.75, 54.19, 42.08, 39.95. HRMS (ESI) m/z [M + H] calcd for $C_{52}H_{44}N_{11}$, 822.3979; found 822.3766




3,3'-((4-(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)phenyl)methylene)bis(1-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole): Compound **169** was prepared according procedure B using parent compound (**159**). Purification by flash chromatography using a gradient of 100% DCM to 20% EtOAc/DCM to remove starting material then flushed with 40% EtOAc/DCM to give a red solid 0.031 g, 76% yield. $^{1}$H NMR (500 MHz, DCM-$D_2$) δ 8.12 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 2H), 7.68 (dd, *J* = 9.0, 1.7 Hz, 2H), 7.59 (s, 2H), 7.53 – 7.44 (m, 8H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.12 (m, 2H), 7.05 (dd, *J* = 8.9, 1.7 Hz, 2H), 7.00 – 6.94 (m, 6H), 6.84 (s, 2H), 5.95 (s, 1H), 5.40 (s, 4H), 3.90 – 3.85 (m, 3H), 3.83 (s, 6H). $^{13}$C NMR (125 MHz, DCM-$D_2$) δ 160.45, 148.49, 145.71, 144.98, 137.40, 131.12, 130.88, 129.72, 129.16, 128.31, 127.87, 126.31, 122.67, 122.44, 120.43, 119.71, 119.33, 115.29, 115.20, 110.30, 56.18, 42.47, 40.62. HRMS (ESI) m/z [M + H] calcd for $C_{52}H_{44}N_{11}O_3$, 870.3699; found 870.3569

# IX. References


1. Seregin, I.V.; Ryabova, V.; Gevorgyan. V. *J. Am. Chem. Soc.* **2007**, 129, 7742-7743. b) Chuprakov, S.; Gevorgyan. V. Regiodivergent metal-catalyzed rearrangement of 3-iminocyclopropenes into N-fused heterocycles. *Org. Lett*. **2007**, 9, 4463-4466.
2. Motornov, V. A., Tabolin, A. A., NoviKOV, R. A., Shepel, N. E., Nenajdenko, V. G., and Ioffe, S. L. *Tetrahedron.* **2018,** 74, 3897–3903.
3. Tseng, W.C., Wang, L.Y., Wu, T.S., and Wong, F. F. *Tetrahedron,* **2011**, 67, 5339–5345.
4. Li, Y. J., Li, X., Zhang, S. X., Zhao, Y. L., and Liu, Q. *Chem. Commun*., **2015**, *51*, 11564–11567.
5. Tian, Y. T., Zhang, F. G., Nie, J., Cheung, C. W., & Ma, J. A. *Adv. Synth. Catal.*, **2021,** *363*(1).
6. Kolb, H. C., Finn, M. G., & Sharpless, K. B. *Angew Chem Int Ed.* **2001**, 40, 11
7. Goddard-Borger, E. D., & Stick, R. V. *Org. Lett.*, **2007**, *9*(19), 3797–3800.
8. Conrad, W. E.; Fukazawa, R.; Haddadin, M. J.; Kurth, M. J. *Org. Lett*. **2011**, 13, 3138– 3141
9. Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett*. **2008**, 10, 3081– 3084