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SYNTHESIS AND MECHANISTIC EXPERIMENTS OF PHOTOELECTROCYCLIZATION REACTIONS OF PYRIDINE CONTAINING BIS-ARYL CYCLOHEXENONES

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ABSTRACT

Electrocyclization reactions are commonly found in synthetic chemistry as a means to access cyclic systems and to define stereocenters. Rules for electrocyclization were developed by Woodward and Hoffman, and these rules allow chemists to predict the stereochemical outcome of potential electrocyclization reactions, as well as whether or not such reactions are likely to proceed under given conditions. While electrocyclization reactions are well understood from the singlet excited state, investigations into the stereochemical outcome of electrocyclizations taking place from the triplet excited state is lacking, as well as study into factors that may make the triplet excited state more likely. Previous work in the Rainier group showed evidence that the nature of the excited state in the electrocyclization of bis-aryl cycloalkenones was in some way dependent on the aromatic substitution. Additionally, previous work in the Rainier group has shown that the presence of TFA leads to a different stereochemical outcome for the reaction. This work discusses the synthesis of several pyridine-containing bis-aryl cyclohexenones and further investigates the impact of aromatic substation on the nature of the excited state, namely the effect of electron poor heteroaromatics. Additionally, this work seeks to better understand the stereochemical outcomes of the photoelectrocyclization of pyridine containing bis-aryl cyclohexenones in the presence of TFA.

ACKNOWLEDGEMENT

I would like to start off by saying the idea of writing a thesis terrified me from the beginning of my undergraduate career. Starting as a freshman with little chemistry experience, but knowing I was going to be writing a document that detailed chemistry research I had performed seemed impossible. To be honest, it would have been impossible if not for the help of a lot of people along the way. I'm deeply indebted to Dr. Jon Rainier for allowing me to join his research group without any prior experience, and also mentoring me frequently along the way. The nearly two years I've spent in his lab have made me confident that I want to pursue a PhD, and that I'll be able to obtain one if I keep up the hard work. Jon's outlook on what it means to be a synthetic chemist has become my own, and he has always been adept at pushing me to become as great a chemist as I want to be. I'm also extremely grateful to Dr. Xuchen Zhao, who at the time I met him was simply Xuchen Zhao. Xuchen brought me on to his project, and taught me nearly everything I know regarding lab technique (or lack thereof). If it hadn't been for his patience in mentoring me, or his willingness to allow me on to his project this thesis would not have been possible. I also thank all the other members of the Rainier group who I have come to know as my friends. Alex Wade, Skylar Blank, Hannah Johansson, Jinya Yin, Colin Campbell, Ian Merski, and more who have come through the group. These were the people who I have been the closest with throughout my undergraduate degree, and who I could always rely on to blow off some steam and have a good laugh. I also would not have been able to complete this thesis without the support of my family, especially my mom Calli Payne who has supported me both emotionally and financially throughout my entire life. Whenever things have been hard, I've always been able to complain about it to my mom - including when I was writing this thesis. She has always believed in my ability to succeed as a scientist, even when I was doubting myself. I also want to give special thanks to my grandmother Rita Stevenson who has always fostered my interest in science. From her demonstrations in my youth as "Professor Scatterbrain" to her insistence on me always competing in the science fair, she has been a driving factor in my life and career.

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Introduction:

A pericyclic reaction can be defined as a reaction in which the transition state is cyclic in nature, and bonds are being made and broken in a simultaneous concerted fashion, as opposed to the more common linear and stepwise reactions. Some examples of pericyclic reactions include cycloadditions, such as the famous Diels-Alder reaction which could be more formally described as a [4+2] cycloaddition of a diene and an alkene, sigmatropic rearrangements such as the Cope and Claisen rearrangements, ene reactions, and electrocyclizations. Electrocyclic reactions are pericyclic in nature and occur intramolecularly. Through the course of an electrocyclization one pi bond is converted to a sigma bond, or vice versa. These are known as electrocyclic ring closing or electrocyclic ring opening reactions, respectively.

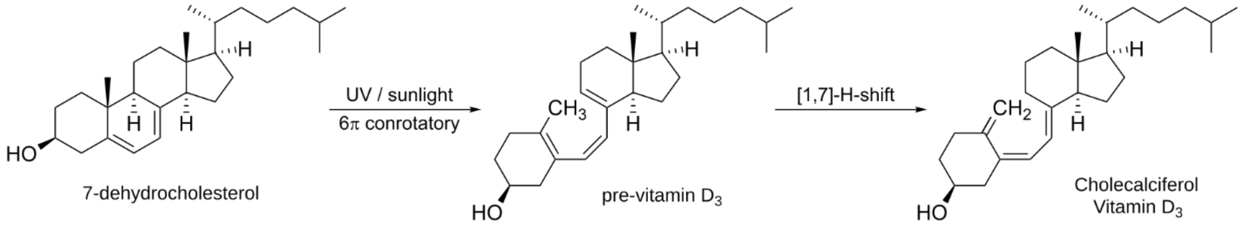


Figure 1: The biosynthesis of Vitamin D_3 from 7-dehydrocholesterol featuring a 6π conrotatory electrocyclic ring opening[1]

Electrocyclization reactions are commonly seen with 4, 6, or 8 π electron systems such as the simple examples shown below. As can be seen in the examples, for each substrate the number of pi bonds decreased by one while a new sigma bond was formed.

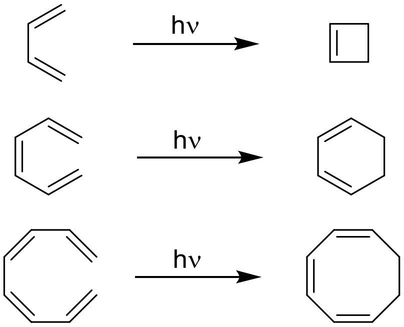


Figure 2: From top to bottom, photochemical electrocyclic ring closing reactions of 4π, 6π, and 8π electrons.

While electrocyclization reactions are fairly well understood today, their discovery and development occurred recently. The first electrocyclization reaction was discovered by accident Willstätter and his coworker von Schmaedel in 1905 in the attempted synthesis of cyclobutene at elevated temperatures. While they successfully synthesized cyclobutene, they also found large amount of 1,3-butadiene in the solution.[2] Willstätter did not offer an explanation to the mysterious formation of 1,3-butadiene, and would not go on to do so. Still, in the next few decades the reaction was investigated in greater detail culminating in the formulation of what is known today as the Woodward-Hoffman rules. Professors R.B. Woodward and Roald Hoffmann laid out a series of selection rules for electrocyclization reactions based on experimental and computational findings and defined the terms conrotatory and disrotatory for the transition states of electrocyclic reactions.[3] Woodward and Hoffman found that electrocyclization reactions are stereospecific in nature, and laid out a means of predicting the stereochemistry of a reaction based on the number of pi electrons in the system. The basis of this stereospecificity lies in orbital symmetry, that is, in order for the reaction to occur, the orbital symmetry of the starting material must be conserved in the transition state.

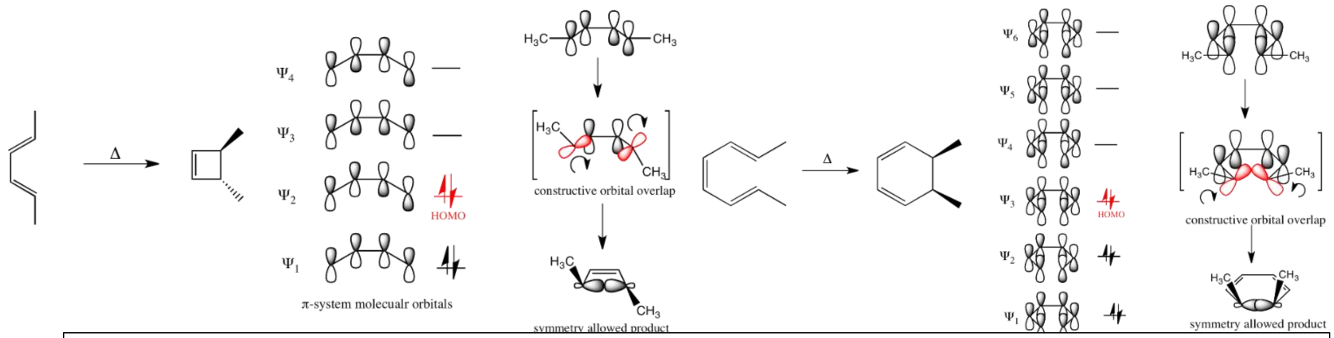
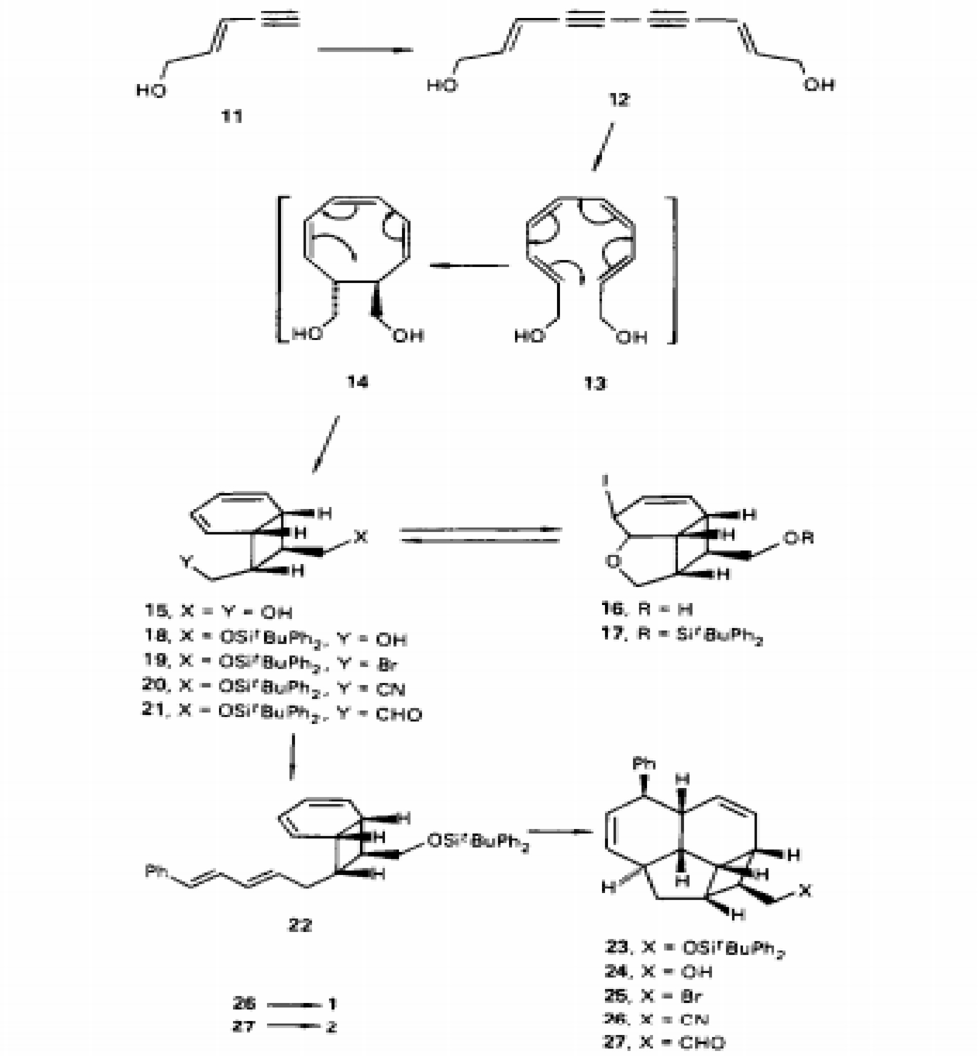


Figure 3: On the left, the conrotatory thermal electrocyclization of a substituted butadiene. On the right, the disrotatory thermal electrocyclization of hexa-1,3,5-triene. Images of the pi orbitals and the constructive overlap in the transition state are depicted for both reactions.

Woodward and Hoffman note that, for the 4π thermal electrocyclic ring opening of cyclobutene, the stereochemistry clearly depicts a conrotatory reaction. The thermal electrocyclic ring closing reaction of hexatrienes is indicative of a disrotatory process. Furthermore, the opposite holds true in the case of photochemical electrocyclizations, that is, the 4π photochemical electrocyclization is disrotatory, while the 6π is conrotatory. This fact is attributed to the inversion of orbital symmetry in the excited state, as can be seen in the orbital symmetry diagrams of *Figure* 3. Hoffman would go on to receive a Nobel prize in chemistry for his work in the field of electrocyclizations. Woodward had unfortunately died two years before Hoffman was awarded, and thus was not eligible to receive what would have been his second Nobel prize.

The formulation of the Woodward-Hoffman rules made electrocyclic reactions a powerful tool for synthetic chemists. The ability to quickly build cyclic structures in a stereospecific fashion attracted interest in the field of total synthesis, and electrocyclic reactions have been featured in the synthesis of many natural products.[4, 5, 6, 7] Among the more famous synthesis utilizing electrocyclic reactions is Nicolau's 1982 synthesis of several different Endiandric acids. The Nicolau synthesis starts with building a polyene system which undergoes a series of electrocyclic ring closures to quickly build complexity in a stereospecific manner.[7] The precursors to electrocyclization were built by first dimerizing compound **11** through an acetylene coupling reaction, and then treating the resulting compound **12** with Lindlar's catalyst. The resulting compound **13** very readily underwent a series of electrocyclic ring closing reactions. So readily, that after the mild reduction of **12,** compound **15** was isolated. The suspected intermediates **13** and **14** were not observed. As can be seen in **Scheme 1**, intermediate **13** undergoes an 8π conrotatory thermal electrocyclic ring closure to give compound **14**, which subsequently undergoes a 6π disrotatory thermal electrocyclic ring closure affording compound **15** in stereospecific manner.



Scheme 1: Nicolau's synthesis of Endiandric acids A and B. Synthetic route involves an electrocyclic ring closing cascade reaction from a conjugated tetraene to furnish a fused 6 membered and 4 membered ring system.[7]

Compound **15** was then transformed into **22**, which underwent an intramolecular Diels-Alder reaction to complete the carbon skeleton for Endiandric acids A and B. The Nicolau synthesis highlights the power of electrocyclization reactions as a means to develop complex ring systems in a stereospecific manner.

While electrocyclizations in general have had much use in total synthesis, investigation into the electrocyclization of bis-aryl alkene systems to synthesize dihydrophenanthrenes is still in the early stages of development,[9] both in terms of scope and towards the synthesis of more complex molecules. Previous work in our group by Xuchen Zhao and Changqing Song expanded on the initial reporting of the photoelectrocyclization of biaryl alkenes by Horgan and Morgan.[10] Morgan and coworkers found that electrocyclic ring closing reactions of biaryl alkenes proceeded through a conrotatory mechanism followed by a thermal 1,5-hydride shift to restore aromaticity. Interestingly, it was also found that the reactions generally proceeded through a singlet state and do not proceed from thermal excitation, likely due to the large activation energy required to disrupt the aromaticity in the biaryl system. The work in our group further developed these ideas, and mechanistic studies supported the hypothesis of a conrotatory ring closure followed by a 1,5-hydride shift. Interestingly, our group also found that the intermediate following the conrotatory electrocyclic ring closure could be intercepted by a proton source if the 1,5-hydride shift was relatively slow to afford the *cis*-fused dihydrophenanthrene.[9]

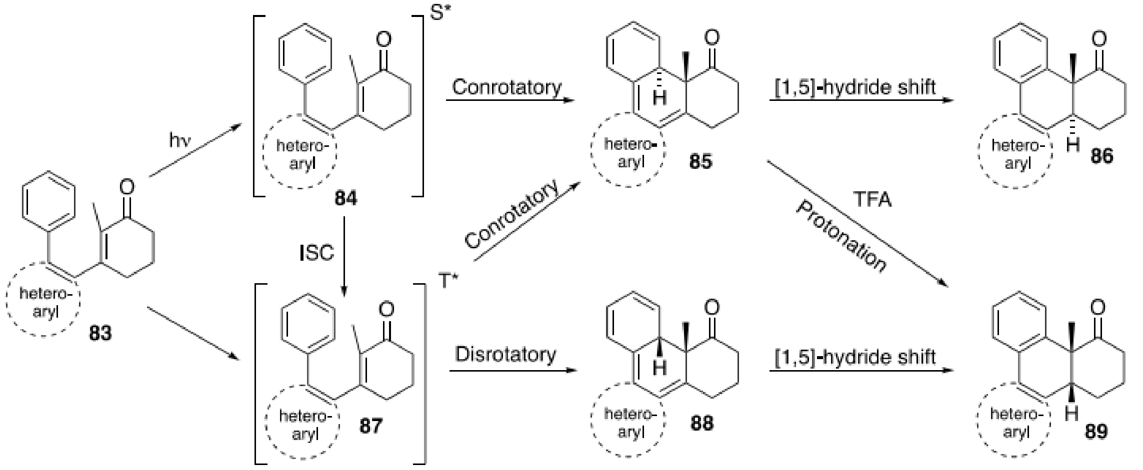


Figure 4: General mechanism of photoelectrocyclization reaction of a bis-aryl cyclohexenones showing the singlet excited state pathway (top) as well as the triplet excited state pathway (bottom) including the potential interception of the non-aromatic intermediate with acid to afford the *cis*-diastereomer.[8]

Our group also found that the photoelectrocyclization of bis-aryl cyclohexenones was possible when a heteroaromatic ring was incorporated. Experiments involving several different pyrazines with variable substitution on the benzene ring gave results consistent with non-heteroaromatic systems. Namely, electrocyclizations without the presence of an acid predominantly formed the *trans*-diastereomer, while the presence of TFA afforded predominantly the *cis*-diastereomer (**Table** 1, entries 1-4, compounds **26, 28, 30**). Unpredictably, pyridine containing substrates gave

$$\text{bis-arylcyclohexenone} \xrightarrow[\text{conditions}]{\text{350 nm}} \text{dihydrophenanthrene(s)}$$

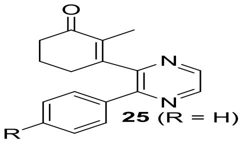
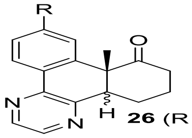
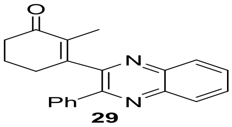
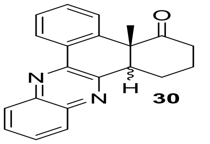
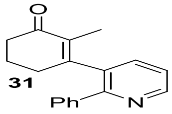
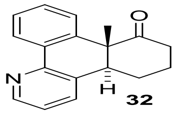
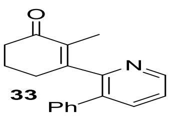
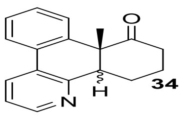
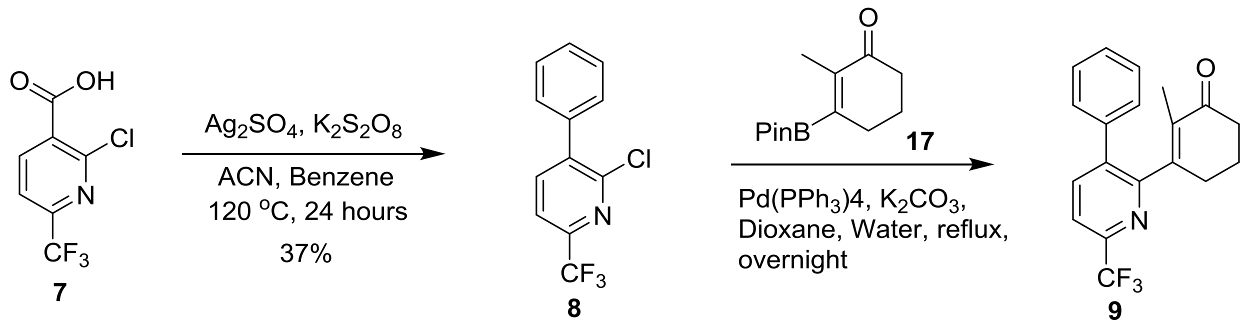
entry	heteroarenes	conditions	products	yield	*cis:trans*
1	 **25** (R = H)	$CHCl_3$, TFA (1 equiv)	 **26** (R = H)	85%	>95:5
2	**25** (R = H)	CH_3CN	**26** (R = H)	95%	<5:95
3	**27** (R = OCH_3)	$CHCl_3$, TFA (1 equiv)	**28** (R = OCH_3)	85%	>95:5
4	**27** (R = OCH_3)	CH_3CN	**28** (R = OCH_3)	95%	<5:95
5	 **29**	$CHCl_3$, TFA (1 equiv.)	 **30**	82%	>95:5
6	**29**	CH_3CN	**30**	92%	<5:95
7	 **31**	$CHCl_3$, TFA (1 equiv.)	 **32**	95%	<5:95
8	**31**	CH_3CN	**32**	95%	<5:95
9	 **33**	$CHCl_3$, TFA (1 equiv.)	 **34**	86%	1.6:1
10	**33**	CH_3CN	**34**	91%	<5:95

Table 1: Photoelectrocyclization reactions of several bis-aryl cyclohexenones containing heteroaromatics. The presence of TFA is believe to intercept the cyclized intermediate before a [1,5]-hydride shift is able to occur.[9]

unusual results when subjected to the same conditions. Compound **33** gave a mixture of diastereomers when subjected to light in the presence of TFA, while the isomeric compound **31** gave nearly exclusively the *trans*-diastereomer in the presence of TFA. These findings intrigued us, as we first believed that the electron deficient nature of the pyridine would slow down the 1,5-hydride shift and allow easier interception of the intermediate by a proton source, and so we wished to conduct studies on a broader range of pyridine containing bis-aryl cyclohexenones. Thus, we set out to investigate the reactions of pyridine containing substrates under several different reaction conditions. Namely, we wished to see the results of reactions under standard UV light, through the triplet excited state, in the presence of TFA, and in the presence of a triplet quencher. We believe these experiments will help us understand the mechanism of the photoelectrocyclization of pyridine containing substrates by allowing us to understand the impact of the triplet excited state on the reaction as well as the effect of the presence of TFA. The synthesis of several pyridine containing bis-aryl cyclohexenones, and the subsequent photoelectrocyclization experiments are described in this thesis.

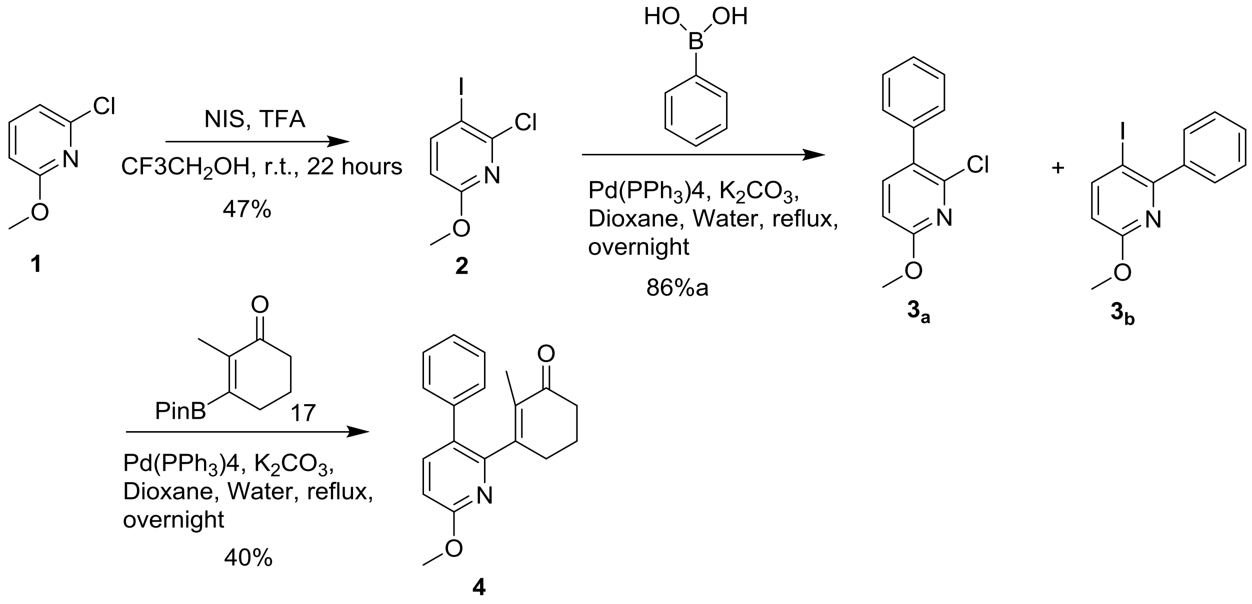
Results and Discussion:

With an interest in the effect of electron deficiency on the pyridine ring on the electrocyclization reaction, we set out to synthesize a trifluoromethyl containing pyridine system. Starting with commercially available nicotinic acid **7**, a Minisci-like radical decarboxylative coupling reaction[16] installed a phenyl group at the 3 position in 37% yield. With compound **8** in hand, cyclization precursor **9** was generated from a Suzuki-Miyaura coupling with pinacol borane **17**.



Scheme 2: Synthesis of a 2-trifluoromethyl pyridine substrate for electrocylization experiments. Carried out from a Minisci like decarboxylative radical coupling followed by a Suzuki coupling.

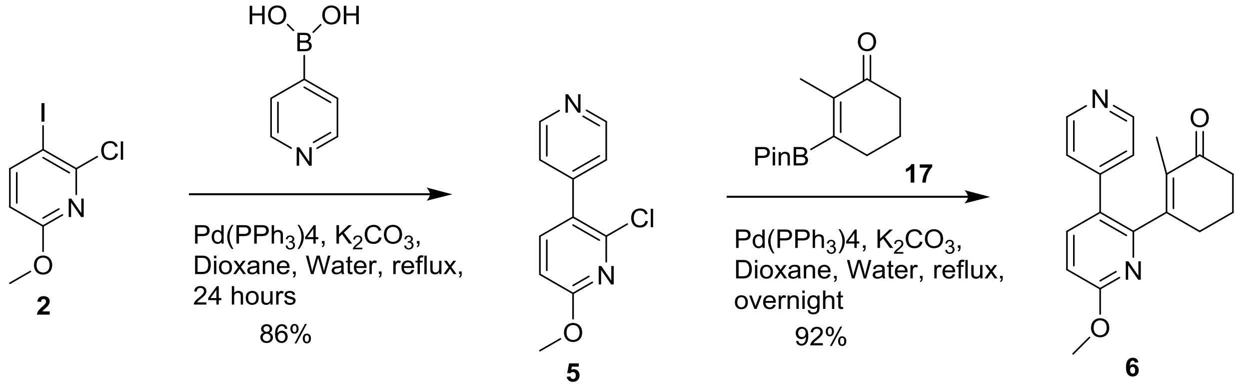
We were unable to improve the yield of the Minisci-like reaction beyond around 50%. In addition, while further attempts at optimization of this reaction might be possible this reaction came with concerns as it was carried out at elevated pressure, and involved gas evolution over the course of the reaction resulting in a potentially explosive mixture on large scale. Another limitation of this synthetic pathway was the inability to selectively add different functionality to the aryl group. If we desired to investigate substitution, the decarboxylative coupling would likely afford a mixture of regioisomers. Due to the low yield, the dangerous reaction conditions, and the inability to selectively add different functionality to the aryl group, we decided to pursue a synthetic route involving sequential Suzuki couplings. Our group had previously synthesized many bis-aryl cyclohexenones via sequential Suzuki coupling reactions[7], and we envisioned the synthesis of pyridine substrates could also take place in the same manner. Commercially available 2-chloro-3-iodo-6-methoxypyridine (compound **1**) was iodinated at the position para to the methoxy group following a procedure from Tang, Milcent, and Crousse[8] to afford compound



Scheme 3: Synthesis of 2-methoxy pyridine electrocyclization precursor carried out via sequential Suzuki couplings. [a]isolated a 4:1 ratio of 3-benzyl:2-benzyl regioisomers.

2 in 47% yield. By-products of this reaction included iodination ortho to the methoxy group and a small amount of the di-iodinated compound. While we had hoped that the reaction would be regioselective due to coordination with the trifluoroethanol solvent[8], we did not see much selectivity. Fortunately, the regioisomers were able to be separated using column chromatography to afford **2** as a white solid. A Suzuki-Miyaura coupling was then performed between **2** and commercially available phenyl-boronic acid to afford **3$_a$** and **3$_b$** in 86% combined yield. We had hoped that the iodine would undergo a more facile oxidative addition than the chlorine. Unfortunately, this Suzuki-Miyaura coupling actually gave a 4:1 ratio of **3$_a$** and **3$_b$** as an inseparable mixture. Still attracted by the convenience of a modular synthetic approach, this mixture was used in the next Suzuki coupling with **17**. To our delight, the conversion of **3** to **4** gave a separable mixture of regioisomers in 40% yield to allow for a pure sample of compound **4** to be used for the electrocyclization experiments. While the yield of the Suzuki-Miyaura coupling left something to be desired, the reaction can definitely be improved, and optimization efforts are underway. While we are interested in the impact of electron deficiency on the electrocyclization reactions, we are also interested in the use of this reaction towards the synthesis of natural products containing a similar carbon core that have shown biological activity.[11] While the methoxy substitution adds some electron density back into the system, we hope to use the group as a functional handle for the de-aromatization of the heterocycle in later studies.[12]

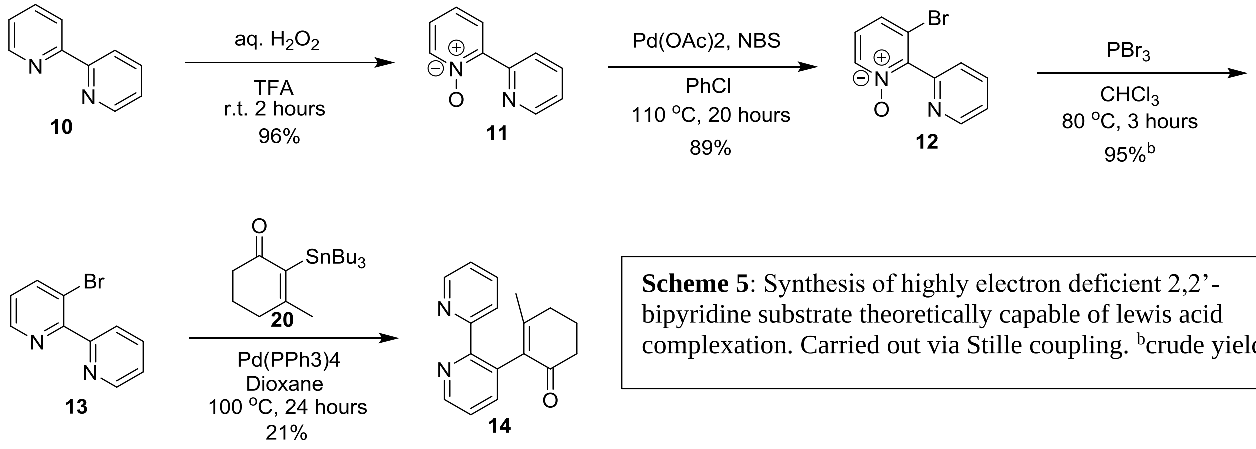
We were also interested in the effects of a second pyridine ring rather than a benzyl ring on the electrocyclization reaction, and so set out to synthesize compound **6** using the same approach involving sequential Suzuki couplings.



Scheme 4: Synthesis of a highly electron deficient bi-pyridine substrate for electrocyclization experiments. Carried out via sequential Suzuki coupling reactions.

Compound **2** was coupled to pyridine-4-boronic acid to afford compound **5** in 86% yield. Unlike the coupling to form compound **3**, **5** was isolated as a single isomer. This difference is perhaps due to the slower transmetallation of the electron deficient pyridine boronic acid as opposed to the phenyl boronic acid, but a more rigorous study would be required to make definitive claims. With compound **5** in hand, **6** was generated from a second Suzuki-Miyaura coupling in 93% yield.

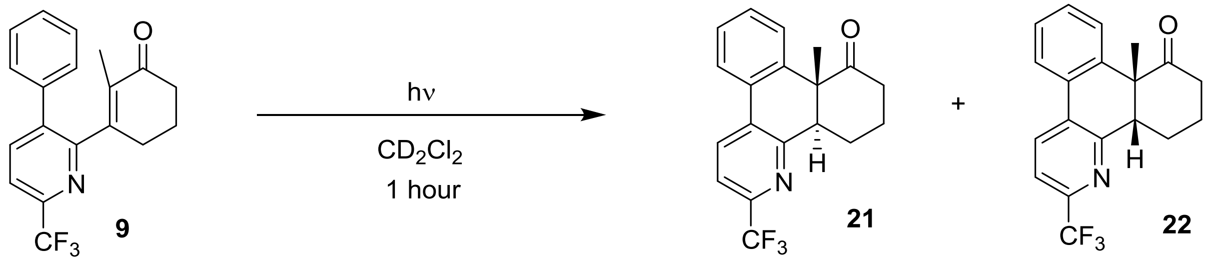
We were also interested in the possibility of a 2,2'-bipyridyl system, both for the electron withdrawing effects as well as the possibility of a coordination of such a system to a Lewis acid. A previous report by Takahashi, Hirose, Kusama, and Iwasawa[13] had shown that such systems, when coordinated to a Lewis acid, undergo a bathochromic shift. We speculate it may also be possible to coordinate the bi-pyridine system to a chiral Lewis acid in order to affect an enantioselective cyclization, although we have yet to begin such experiments.



Scheme 5: Synthesis of highly electron deficient 2,2'-bipyridine substrate theoretically capable of lewis acid complexation. Carried out via Stille coupling. ^{b}crude yield

Following the procedure of Zucker, Wossidlo, Weber, Lentz, and Tzschucke, compound **13** was synthesized from a regioselective, palladium catalyzed bromination.[14] 2,2'-Bipyridine was oxidized from 30% aqueous hydrogen peroxide in TFA to afford **11** in 96% yield. The n-oxide allowed for a regioselective bromination to take place using a palladium catalyst[14] to afford compound **12** in 89% yield. The N-oxide was reduced using PBr_3 in $CHCl_3$ at elevated pressure, and the resulting white solid was used without further purification in a Stille coupling with **20** to afford **14** in 21% yield.[13] We had many concerns about the coupling of **13** to **20** as we envisioned the bipyridine may coordinate to the palladium and inadvertently poison the catalyst. Consistent with this, attempts at a Suzuki coupling between **13** and **17** were unsuccessful. Still wishing to investigate this interesting moiety, we decided to try some alternate conditions in an effort to optimize the Stille coupling. It was reported by Mee, Lee, and Baldwin that the addition of CuI as a co-catalyst and CsF improved the results of difficult Stille couplings when run in polar solvents.[15] Copper iodide was theorized to help coordinate to the solvent, thus removing it from coordination with the palladium catalyst. In polar solvents the copper iodide was also theorized to undergo transmetallation with the stannane to form an organocopper reagent that would rapidly react with the palladium catalyst. The CsF was added to form tin fluorides with the stannanes left over from the reaction, as other tin halides could potentially slow or inhibit the Stille coupling.[15] Despite our great optimism with these modifications, the product was not isolated when these conditions were used. We believe that this may also be due to the bi-pyridine moiety coordinating to the copper(I), and thus either inhibiting the copper from its intended role of transmetallation with the stannane, or potentially effecting unwanted transformations. Regardless, the synthesis of a bi-pyridine moiety for electocyclization experiments is still of great interest to us, and thus further efforts will be made to improve the synthesis of **14**.

With the precursors for the electrocyclizations in hand, we set out to carry out the variety of experiments that were outline above. As was mentioned, previous reports[9,10] had shown that bis-aryl systems primarily undergo electrocyclic ring closure through the singlet excited state, although previous work in our group suggested it was also possible that the singlet excited state undergoes inter system crossing to the triplet before ring closure. Pyridine containing substrates showed unique results, and differed from several other substrates when irradiated in the presence of TFA. While other heteroaromatic substrates gave nearly exclusively *cis*-fused dihydrophenanthrenes in the presence of TFA, those with pyridines were not nearly as selective or did not give the *cis* compound at all[9]. With these curious results in mind, we set out to investigate the role of the triplet excited state in the electrocyclization, as well as the results when the reaction was run in the presence of TFA.



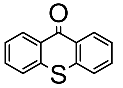
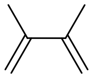
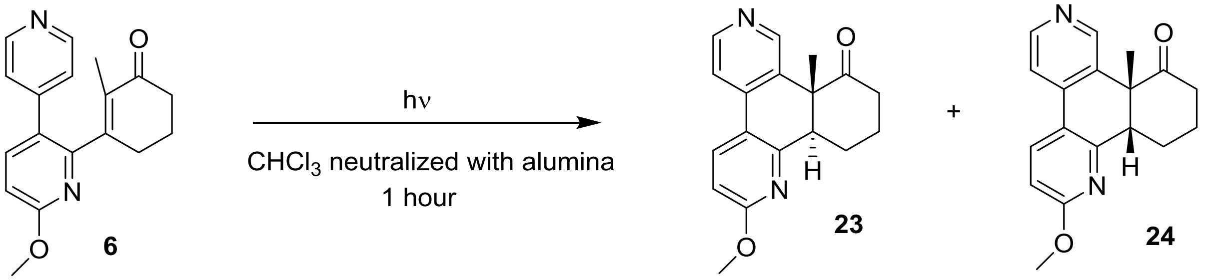
Entry	Wavelength	Additives	trans:cis	Yield
1	350nm	--	>20:1	88%
2	419nm	--	No reaction	No reaction
3	419nm	 3 eq.	9.1:1	Not isolated[a]
4	350nm	 5 eq.	>20:1	89%[b]
5	350nm	TFA	1:4.5	70%[c]

Table 2: Electrocyclization reaction results for compound **7** under a variety of conditions. [a] reaction time 48 hours, [b] reaction time 80 minutes, [c] reaction run in neutralized $CDCl_3$

Direct irradiation of compound **9** at 350 nm (entry 1) gave exclusively the *trans*-diastereomer **21** by ^{1}H NMR, and was isolated in 88% yield. While the lack of *cis*-diastereomer formation points to a reaction pathway involving the singlet excited state, we investigated the results of the reaction at 419 nm light both with and without the triplet sensitizer thioxanthone. In the absence of thioxanthone (entry 2), only starting material is recovered after irradiation for 48 hours. In the presence of thioxanthone (entry 3), a 9.1:1 ratio of *trans*-**21** to *cis*-**22** was observed via ^{1}H NMR. This shows that even when the reaction proceeds exclusively through the triplet excited state, the *trans*-diastereomer was heavily preferred. An isolated yield was unable to be obtained due to difficulties separating thioxanthone from **21** and **22** via silica gel chromatography. Additional efforts using different solvent systems and reverse phase may prove useful to overcome this issue. Pyridine **9** was also irradiated at 350 nm in the presence of 1,3-dimethyl butadiene (entry 4) as a triplet quencher in order to observe the results of the reaction through the singlet excited state exclusively. As we expected, the results showed the exclusive formation of the *trans*-diastereomer. Lastly, we also examined the irradiation of **7** at 350 nm in the presence of TFA (entry 5). While pyrazine and quinoxaline compounds would give nearly exclusively the *cis*-diastereomer, **7** gives a 1:4.5 mixture of *trans* **21** to *cis* **22**. These results show that **7** has a greater preference for the *cis*-diastereomer than the other pyridine containing substrates (entries 7 and 9 of **Table 1**). We next investigated the electrocyclization reaction of the bi-pyridyl substrate **6**. We were primarily interested in this substrate due to its highly electron deficient nature, as well as a point of comparison against the results of the 2,2'-bipyridine substrate **14**. Additionally,



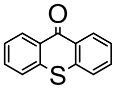
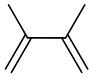
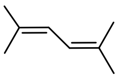
Entry	Wavelength	Additives	trans:cis	Yield
1	350nm	--	2:1	86%^{a}
2	419nm	--	No reaction	No reaction
3	419nm	 3 eq.	3:1	83%^{b}
3	350nm	 5 eq.	2:1	Not isolated
4	350nm	 5 eq.	2:1	Not isolated
5	350nm	TFA	1:3.5	86%

Table 3: Electrocyclization of **6** under a variety of conditions ^{a} reaction run in CD_2Cl_2, ^{b} reaction time 24 hours

to the best of our knowledge, substrate **6** is the first bis-heteroaromatic system to undergo examination of the electrocyclic ring closing reaction. Unlike the results from the irradiation of **9** at 350 nm which gave exclusively the *trans*-diastereomer, the irradiation of **6** at 350 nm (entry 1) afforded a mixture of *trans*-**23** and *cis*-**24** in a 2:1 ratio. The large amount of *cis*-diastereomer found in the product led us to believe there was a substantial amount of **6** which was proceeding through a triplet excited state. In order to test this theory, we irradiated **6** at 419 nm both in the presence and absence of thioxanthone. In the absence of thioxanthone (entry 2) we observed only starting material after 24 hours. In the presence of thioxanthone (entry 3) we observed a 3:1 mixture of *trans*-**23** to *cis*-**24**. These results were unexpected and perplexing. If the singlet excited state only affords the *trans*-fused dihydrophenanthrene due to Woodward-Hoffman rules, then any *cis*-fused isomer found from the irradiation would be a result of the triplet excited state. Yet, when we examined the reaction through the triplet excited state alone, we found a greater amount of *trans*-**23** than irradiation at 350 nm in the absence of additives. In an effort to better understand the reaction, we irradiated **6** at 350 nm in the presence of 1,3-butadiene and 2,4-hexadiene (entries 4 and 5 respectively). To our dismay, we found a ratio of diastereomers in each reaction that was the same as irradiation at 350 nm in the absence additives, leading us to believe the triplet quenchers did not match the energy of the triplet excited state and thus were unable to relax the triplet excited state of **6** back to the ground state. Going forward, we are interested in examining other triplet quenchers such as piperylene in order to further investigate the effect of quenchers on the reaction. Finally, we irradiated **6** at 350 nm in the presence of TFA observing a 1:3.5 ratio of *trans*-**23** to *cis*-**24**. Like the other pyridine containing substrates, irradiation in the presence of TFA does not provide exclusive formation of the *cis* product. Interestingly, the addition of a second pyridine ring slightly decreased the amount of *cis* product formed when compared to **9** (**Table 2**), but still was more selective than **33** (**Table 1**) which showed a 1:1.6 ratio of *trans*-**34** to *cis*-**34** as a substrate with a single pyridine ring.

Conclusion:

Previous studies from our group have shown that the electrocyclization of pyridine containing bis-aryl cyclohexenones offer varied results when compared to their non-heteroaromatic counterparts.[9] The work described in this thesis is a more thorough investigation of pyridine containing substrates in an effort to understand and explain their varied results. Thus far the results from these studies have yielded more questions than answers. The selectivity for the *cis*-fused dihydrophenanthrene derivatives over the *trans*-fused derivatives when the substrate was irradiated at 350 nm in the presence of TFA is not well understood, and the varied selectivity observed with pyridine containing systems even less so. Additionally, the perplexing result of the photoelectrocyclization of **6** giving a higher ratio of *trans*-fused to *cis*-fused products when going through the triplet excited state alone vs. a combination of singlet and triplet excited states requires a more thorough examination. At the present moment, it is premature to draw conclusions on the reasons behind the why a particular substrate may proceed preferentially through the singlet or triplet excited state when both are possible, or why certain substrates form the *cis*-fused product selectively in the presence of TFA. More pyridine-containing substrates need to be examined through their singlet and triplet excited states as well as in the presence of TFA in order for clearer trends to emerge. Currently we plan to expand the scope of this project to include the following substrates, some of which have already been synthesized and only require electrocyclization experiments, while for others the synthesis is currently underway.

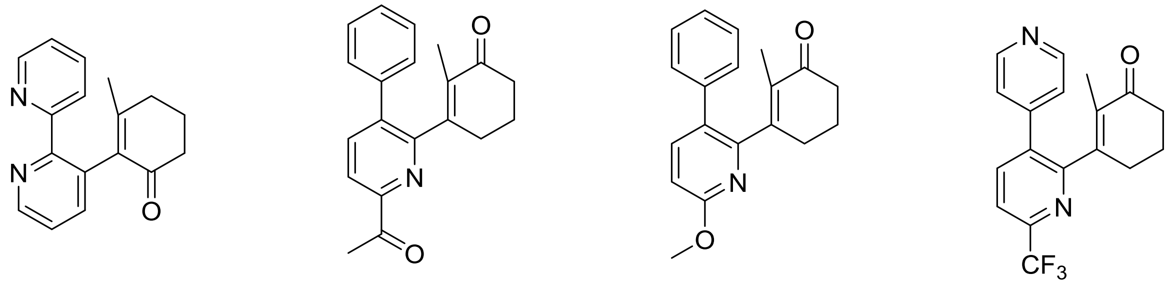


Figure 5: Substrates planned for future electrocyclization experiments

Experimental Section:

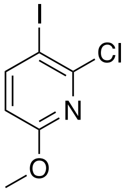
General Procedure A for the Suzuki-Miyaura Coupling of Bis-Aryls Halides and Cyclohexenone Boronic Ester. To a solution of bis-aryl halide (1 eq.) in dioxane and water (v/v = 4/1, 0.1M), 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-en-1-one (**17**) (1.2 eq.) and K_2CO_3 (3 eq.) were added. The solution was purged with nitrogen for 5 minutes before addition of $Pd(PPh_3)_4$ (5.0 mol%). The resulting mixture was heated to reflux under nitrogen atmosphere until the starting material was no longer observed via TLC. The reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2, and filtered through a pad of celite. The solution was then diluted with water, and the aqueous phase was extracted 3 times with CH_2Cl_2. The combined organic layer was dried with $MgSO_4$, and then concentrated under reduced pressure. The resulting residue was purified via flash chromatography.

General Procedure B for the Electrocyclization Reaction of Bis-Aryl Cyclohexenones at 350nm. A solution of the bis-aryl cyclohexenone in CD_2Cl_2 (10mM) was purged with N_2 for 1 minute. The solution was then transferred to Pyrex reaction tubes, sealed, and irradiated at 350nm in a Rayonet photoreactor until the starting material was consumed by ^1H NMR (1-2 hours). The reaction mixture was concentrated under reduced pressure and the resulting residue was purified via flash chromatography.

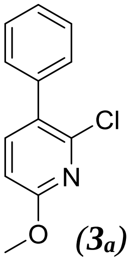
General Procedure C for the Electrocyclization of Bis-Aryl Cyclohexenones at 419nm. A solution of the bis-aryl cyclohexenone in $CHCl_3$ (10mM) neutralized by passing the solvent through a pad of neutral alumina was purged with nitrogen for 1 minute. The solution was then transferred to a scintillation vial equipped with a stir bar. Thioxanthone (3 eq.) was added and the resulting mixture irradiated at 419nm with constant stirring for 24-48 hours. When the starting material had been consumed by TLC, the solution was concentrated under reduced pressure and the resulting residue purified via flash chromatography.

General Procedure D for the Electrocyclization of Bis-Aryl Cyclohexenones at 350nm with Triplet Quencher. A solution of the bis-aryl cyclohexenone in CD_2Cl_2 (10mM) was purged with N_2 for 1 minute. 5 eq. of 1,3-butadiene was added to the solution before transferring to Pyrex reaction tubes. The reaction tubes were then sealed and irradiated at 350nm in a Rayonet photoreactor until the starting material was consumed by ^1H NMR (1-2 hours). The reaction mixture was concentrated under reduced pressure and the resulting residue was purified via flash chromatography.

General Procedure E for the Electrocyclization of Bis-Aryl Cyclohexenones at 350nm in the presence of TFA. A solution of the bis-aryl cyclohexenone in $CHCl_3$ (10mM) neutralized by passing the solvent through a pad of neutral alumina was purged with nitrogen for 1 minute. 5 equivalence of TFA was added to the solution and stirred thoroughly. The solution was then transferred to Pyrex reaction tubes, sealed, and irradiated at 350nm in a Rayonet photoreactor for 1 hour. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified via flash chromatography.

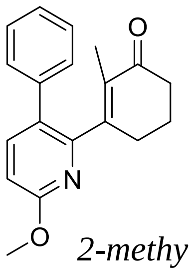


*2-chloro-3-iodo-6-methoxypyridine (**2**):* To a solution of 2-chloro-6-methoxypyridine (6.25g, 43.53mmol) in trifluoroethanol (174mL, 0.25M), TFA (5.02g, 44.03mmol) and N-iodosuccinimide (10.79g, 47.96mmol) were added. This mixture was stirred for 22 hours, at which point the starting material was consumed by TLC. The mixture was washed with saturated sodium thiosulfate and diluted with water. The aqueous layer was extracted 3 times with CH_2Cl_2, and the combine organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash chromatography (hexane) to afford the title compound as a white solid (5.4994g, 46.8% yield). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.89 (d, J=8.5Hz, 1H), 6.45 (d, J=8.5Hz, 1H), 3.92 (s, 3H).

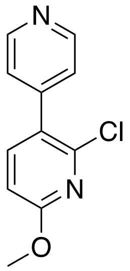


2-chloro-6-methoxy-3-phenylpyridine *(**3**$_a$)*: To a solution of **2** (1g, 3.71mmol) in dioxane and water (v/v= 4:1, 0.1M) Phenyl-boronic acid (542.8mg, 4.45mmol) and K_2CO_3 (1.538g, 11.13mmol) were added. The solution was flushed with nitrogen for 5 minutes before adding $Pd(PPh_3)_4$ (128.6mg, 3 mol%). The solution was then heated to reflux under a nitrogen atmosphere overnight. Upon completion, the solution was cooled to room temperature, diluted with CH_2Cl_2 and water, and then filtered over a pad of celite. The aqueous layer was extracted 3 times with CH_2Cl_2 and the combined organic layer was dried with $MgSO_4$. The solvent was removed under reduced pressure and the resulting residue was purified via flash chromatography (49:1 hexane/ethyl acetate) to yield the title compound as a white solid (704.5mg, 86.5% yield).

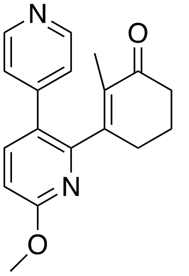
^{1}H NMR (500MHz, CDCl$_3$) δ 7.57 (d, J=8.2 Hz,1H), 7.46-7.36 (m, 5H), 6.75 (d, J=8.3 Hz, 1H), 3.99 (s, 3H).



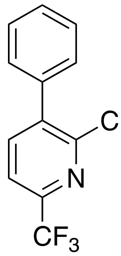
*3-(6-methoxy-3-phenylpyridin-2-yl)-2-methylcyclohex-2-en-1-one (**4**)*: Compound **4** was synthesized following general procedure A using **3** (117.8mg, 0.536mmol). Purification via flash chromatography (49:1 hexane/ethyl acetate) yielded the title compound as a white solid (63.2mg, 40.2% yield). ^{1}H NMR (500MHz, CDCl$_3$) δ 7.61 (d, J=8.4 Hz, 1H), 7.37-7.28 (m, 3H), 7.26-7.22 (m, 2H), 6.78 (d, J= 8.4 Hz, 1H), 3.96 (s, 3H), 2.70-2.44 (m, 2H), 2.42 (t, J=6.7 Hz, 2H), 1.91 (s, 2H), 1.48 (t, J=1.9 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 200.2, 162.9, 155.2, 154.3, 140.9, 138.8, 133.7, 128.8, 128.6, 128.6, 127.7, 110.1, 53.9, 38.0, 31.4, 23.0, 12.7



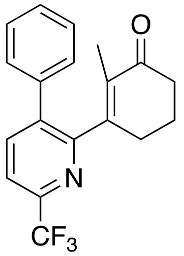
*2-chloro-6-methoxy-3,4'-bipyridine (**5**):* To a solution of **2** (1g, 3.71mmol) in dioxane/water (4:1, 37.1mL, 0.1M), pyridin-4-ylboronic acid (547.2mg, 4.45mmol) and K$_2$CO$_3$ (1.538g, 11.13mmol) were added. The solution was purged with N$_2$ for 5 minutes before the addition of Pd(PPh$_3$)$_4$ (214.3mg, 0.185mmol). The mixture was then heated to reflux under nitrogen atmosphere for 24 hours, or until the starting material was consumed by TLC. The solution was cooled to room temperature, diluted with CH$_2$Cl$_2$, and filtered over a pad of celite. The solution was then diluted with water, and the aqueous layer was extracted with CH$_2$Cl$_2$ 3 times. The combined organic layer was dried with $MgSO_4$, and then concentrated under reduced pressure. The resulting residue was purified via flash chromatography (4:1 hexane/ethyl acetate, then 2:1 hexane/ethyl acetate) to afford the title compound as a white solid (552.8mg, 67.5% yield). ^{1}H NMR (500MHz, $CDCl_3$) δ 8.66 (d, J=5.3Hz, 2H), 7.55 (d, J=8.3Hz, 1H), 7.36 (d, J=5.5Hz, 2H), 6.77 (d, J=8.3Hz, 1H), 3.98 (s, 3H); ^{13}C{^{1}H} (126MHz, $CDCl_3$) δ 163.6, 150.0, 146.1, 145.5, 141.8, 126.4, 124.4, 110.1, 54.5; HRMS (ESI) *m/z*:



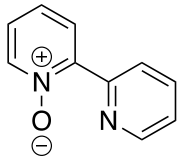
*3-(6-methoxy-[3,4'-bipyridin]-2-yl)-2-methylcyclohex-2-en-1-one (**6**)*: Following general procedure A, compound **6** was synthesized using **5** (500mg, 2.266mmol). Purification of the concentrated residue via flash chromatography (4:1 hexane/acetone) afforded the title compound as a white solid (454.8 mg, 68.2% yield). MP; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.51 (d, J=5.0Hz, 2H), 7.55 (d, J=8.5Hz, 1H), 7.13 (d, J=4.9Hz, 2H), 6.74 (d, J=8.5Hz, 1H), 3.88 (s, 3H), 2.79-2.41 (m, 2H), 2.36 (t, J=6.8Hz, 2H), 1.89 (s broad, 2H), 1.37 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 199.7, 163.8, 154.7, 154.0, 150.1, 146.8, 140.4, 134.1, 126.0, 123.3, 110.6, 54.1, 37.9, 31.4, 23.0, 12.7.



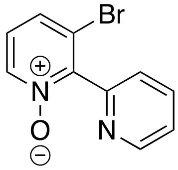
*2-chloro-3-phenyl-6-(trifluoromethyl)pyridine (**8**)*: To a solution of 2-chloro-6-(trifluoromethyl)nicotinic acid (100mg, 0.443mmol) in acetonitrile (0.886mL, 0.5M), benzene (0.888mL), $K_2S_2O_8$ (359.3mg, 1.329mmol), and Ag_2SO_4 (3.45mg, 2.5mol%) were added. The pressure vial was evacuated and refilled with nitrogen 3 times before sealing and heating to 120°C. This mixture was stirred for 24 hours and then cooled to 0°C before breaking the seal on the pressure vial. The solution was diluted with water, and then quenched with 2M NaOH (20mL). The aqueous layer was extracted 3 times with CH_2Cl_2, and the combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash chromatography (4:1 hexane/ethyl acetate) to afford the title compound as a white solid (42.6mg, 37% yield).



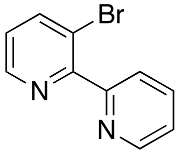
*2-methyl-3-(3-phenyl-6-(trifluoromethyl)pyridin-2-yl)cyclohex-2-en-1-one (**9**)*: Following general procedure A, compound **9** was synthesized using **8** (257.6mg, 1mmol). Purification of the concentrated residue via flash chromatography (9:1 hexane/ethyl acetate) afforded the title compound as a white solid (749mg, 75% yield).



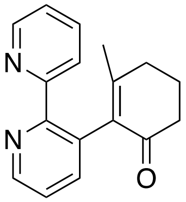
*[2,2'-bipyridine] 1-oxide (**11**):* 2,2’-bipyridine (2g, 12.81mmol) was added to a round bottom flask equipped with a stir bar and dissolved in trifluoro acetic acid (9.63mL, 1.33M). After cooling the solution to room temperature, 30% hydrogen peroxide in water (2.15mL, 19.22mmol) was added dropwise via syringe. This mixture was allowed to stir at room temperature for 3.5 hours. The solution was then diluted with CH_2Cl_2 (25mL) and washed with 6M sodium hydroxide solution 3 times. The aqueous phase was extracted 3 times with CH_2Cl_2 and the combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the resulting residue via flash chromatography (2:3 hexane/acetone) afforded the title compound as a white solid (2.119g, 96.1% yield). ^{1}H NMR (500MHz, $CDCl_3$) δ 8.90 (d, J=8.1Hz, 1H), 8.72 (d, J=3.9Hz, 1H), 8.31 (d, J=5.9Hz, 1H), 8.18 (dd, J=8.1, 2.1Hz, 1H), 7.82 (td, J=7.8, 1.8Hz, 1H), 7.38-7.32 (m, 2H), 7.30-7.23 (m, 1H).



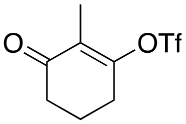
*3-bromo-[2,2'-bipyridine] 1-oxide (**12**):* To a solution of Compound **11** (716.8mg, 4.16mmol) in chlorobenzene (41.6mL, 0.1M) in a pressure vial, N-bromosuccinimide (886.7mg, 4.98mmol), and palladium(II) acetate (92.6mg, 5mol%) were added. The reaction vessel was sealed and the solution was stirred at 110°C for 20 hours. After completion, the solution was cooled to room temperature and filtered over a pad of celite. The solution was then washed with 3M HCl 3 times, and the aqueous layer was extracted 3 times with CH_2Cl_2. The aqueous layer was then neutralized with potassium carbonate, and then extracted 6 times with CH_2Cl_2. The organic layers extracted from the neutralized aqueous layer were combined and dried with $MgSO_4$ and concentrated under reduced pressure to yield compound **6** as a yellow solid (927.7mg, 88.8% yield). ^{1}H NMR (500MHz, $CDCl_3$) δ 8.80 (d, J=4.8 Hz, 1H), 8.29 (d, J=6.6 Hz, 1H), 7.88 (td, J=7.8, 1.7 Hz, 1H), 7.53 (d, J=7.8 Hz, 1H), 7.41 (dd, J=7.6, 4.9 Hz, 1H), 7.18 (dd, J=8.2, 6.6 Hz, 1H).



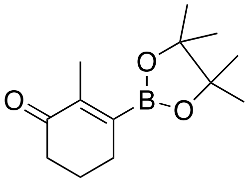
*3-bromo-2,2'-bipyridine (**13**):* Compound **12** (145mg, 0.578mmol), was added to a pressure vial and dissolved in chloroform (5.78mL, 0.1M). The solution was cooled to 0^{o}C before adding phosphorous tribromide (625.8mg, 2.312mmol). The reaction vessel was sealed and the mixture was stirred at 80^{o}C for 3 hours. Upon completion, the mixture was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted 3 times with CH_2Cl_2, and the combine organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The resulting off white solid was used without further purification (129.1mg 95.1% yield).



*2-([2,2'-bipyridin]-3-yl)-3-methylcyclohex-2-en-1-one (**14**)*: To a solution of **13** (49.7mg, 0.211mmol) in dioxane (0.05M), **20** (102.8mg, 0.258mmol) was added. Nitrogen was bubbled through the solution for 5 minutes before adding $Pd(PPh_3)_4$ (12.7mg, 5 mol%). This solution was heated to reflux under a nitrogen atmosphere for 24 hours. After the reaction was complete, the solution was cooled to room temperature, diluted with CH_2Cl_2, and quenched with saturated aq. KF. This solution was filtered over a pad of celite, and then the aqueous layer was extracted 3 times with CH_2Cl_2. The combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash chromatography (19:1 hexane/ethyl acetate) to afford the title compound as a white solid (11.7mg, 20.8% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.74-7.69 (m, 3H), 7.45-7.36 (m, 4H), 2.35 (t, J=6.7 Hz, 1H), 2.28 (t, J= 6.3 Hz, 1H), 2.03-1.97 (m, 1H), 1.63 (q, J=7.7 Hz, 1H), 1.36 (q, J=7.4 Hz, 1H), 1.25 (s, 3H), 0.92 (t, J= 7.3 Hz, 1H).

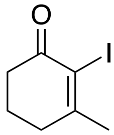


*2-methyl-3-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (**16**):* To a flame dried round bottom flask, 2-methylcyclohexane-1,3-dione (2.933g, 23.25mmol) was dissolved in dichloromethane (116.25mL, 0.2M). Pyridine (3.761mL, 46.5mmol) was added and the mixture was stirred for 10 minutes at -78°C before trifluoromethanesulfonic anhydride (4.694mL, 27.9mmol) was added dropwise. This solution was stirred at -78°C for 20 minutes, warmed to 0°C and stirred for 20 minutes, then warmed to room temperature and allowed to stir for an additional 30 minutes. Upon completion by TLC, the solution was quenched with 1M HCl and the aqueous layer was extracted 3 times with diethyl ether. The combined organic fractions were washed with a saturated solution of sodium carbonate, dried with magnesium sulfate, and concentrated under reduced pressure. Purification of the resulting residue via flash chromatography (50:1 hexane/ethyl acetate) afforded compound **1** as a yellow oil (5.686g, 94.7% yield). ^{1}H NMR (500MHz, CDCl$_3$) δ 2.73 (ddt, J=6.2, 4.0, 2.1 Hz, 2H), 2.47 (t, J=7.5 Hz, 2H), 2.07 (p, J=6.4 Hz, 2H), 1.84 (s, 3H)

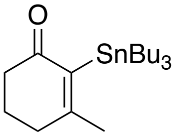


*2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-en-1-one (**17**):*

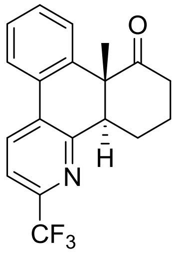
Bis(pinacolato)diboron (2.877g, 11.33mmol), triphenylphosphine (160.44mg, 0.612mmol), potassium carbonate (2.113g, 15.29mmol), and bis(triphenylphosphine)palladium(II) dichloride (214.7mg, 3 mol%) were added to a round bottom flask and flushed with nitrogen before being dissolved in dioxane (121.4mL, 0.167M). Compound **16** (5.266g, 20.39mmol) was added and the solution was stirred at 80^{o}C for 5 hours, at which time the reaction mixture was cooled to room temperature and filtered over a pad of celite. The organic layer was concentrated under reduced pressure, and the resulting residue was purified via flash chromatography (9:1 hexane/ethyl acetate) to afford the title compound as a viscous colorless oil (1.4418g, 30.0% yield, remaining mass balance is unreacted starting materials). ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.45-2.35 (m, 4H), 1.99-1.89 (m, 5H), 1.30 (s, 12H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 200.0, 143.6, 92.4, 84.2, 38.7, 28.8, 25.0, 23.6, 15.1.



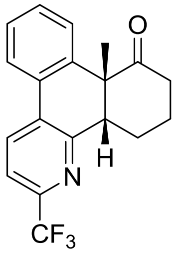
*2-iodo-3-methylcyclohex-2-en-1-one (**19**):* To a solution of iodine (1.3766g, 5.42mmol) and pyridine (880.2mg, 11.13mmol) in dichloromethane (10.21mL, 0.9075M), (bis(trifluoroacetoxy)iodo)benzene (2.3445g, 5.45mmol) was added. The solution was stirred for one hour at room temperature, at which point the coloration of the iodine had largely subsided. Then, 3-methylcyclohex-2-en-1-one (1.0206g, 9.26mmol) was added and the mixture was stirred at room temperature overnight. The reaction was quenched with a saturated solution of sodium thiosulfate, and the aqueous layer was extracted with CH_2Cl_2 3 times. The combined organic fractions were dried with $MgSO_4$ and concentrated under reduced pressure. Purification via flash chromatography (9:1 hexane/ethyl acetate) afforded the title compound as an orange oil (2.0242g, 92.6% yield). ^1H NMR (500MHz, $CDCl_3$) d 2.58 (t, J=7 Hz, 2H), 2.54 (t, J=6.1 Hz, 2H), 2.24 (s, 3H), 1.97 (p, J=6.3 Hz, 2H).



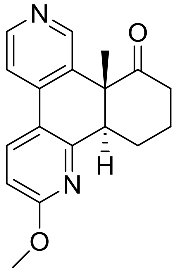
*3-methyl-2-(tributylstannyl)cyclohex-2-en-1-one (**20**):* Compound **19** (493.9mg, 2.09mmol) and bis(tributyltin) (3.1964g, 5.51mmol) were added to a pressure tube equipped with a stir bar and dissolved in dioxane (20.92mL, 0.1M). The solution was flushed with nitrogen for several minutes before adding bis(triphenylphosphine)palladium(II) dichloride (372.01mg, 0.53mmol) and sealing the reaction vessel. The solution was then stirred at 100°C for 24 hours. Upon reaction completion, the solution was cooled to room temperature, and washed with a saturated aqueous solution of KF. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified via silica chromatography (9:1 hexanes/ethyl acetate) to afford the title compound as a colorless oil (444.9mg, 53.3% yield).



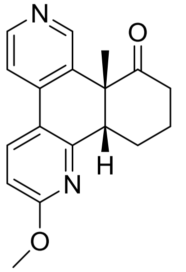
*(8bR,12aR)-8b-methyl-2-(trifluoromethyl)-10,11,12,12a-tetrahydrodibenzo[f,h]quinolin-9(8bH)-one (**21**)*: **21** was synthesized from **9** following general procedures B, C, D, and E. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (d, J=8.0 Hz, 1H), 7.96 (d, J=7.7 Hz, 1H), 7.81 (d, J=7.3 Hz, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.42 (dt, J=19.2, 7.5 Hz, 2H), 3.42 (dd, J=12.5, 3.9 Hz, 1H), 2.90 (dt, J=12.7, 6.1 Hz, 1H), 2.87-2.81 (m, 1H), 2.55 (dt, J=13.0, 5.1 Hz, 1H), 2.30-2.21 (m, 1H), 2.21-2.09 (m, 1H), 2.00-1.89 (m, 1H), 1.23 (s, 3H).



*(8bR,12aS)-8b-methyl-2-(trifluoromethyl)-10,11,12,12a-tetrahydrodibenzo[f,h]quinolin-9(8bH)-one (**22**)*: **22** was synthesized from **9** following the general procedures B, C, D, and E. ^{1}H NMR (500MHz, CDCl$_3$) δ 8.21 (d, J=8.1 Hz, 1H), 7.89-7.84 (m, 1H), 7.66 (d, J=8.1 Hz, 1H), 7.45-7.37 (m, 2H), 6.98-6.93 (m, 1H), 3.27 (dd, J=12.7, 4.0 Hz, 1H), 2.61 (td, J=13.9, 6.1 Hz, 1H), 2.51 (ddt, J=13.8, 4.3, 2.3 Hz, 1H), 2.04-1.98 (m, 1H), 1.98-1.92 (m, 1H), 1.92-1.81 (m, 1H), 1.67-1.58 (m, 1H), 1.19 (s, 3H).



*(8bR,12aR)-2-methoxy-8b-methyl-10,11,12,12a-tetrahydrobenzo[f][3,7]phenanthrolin-9(8bH)-one (**23**)*: **23** was synthesized from **6** following the general procedures B, C, D, and E. ^{1}H NMR (500MHz, CDCl$_3$) δ 9.17 (s, 1H), 8.53 (d, J=5.2 Hz, 1H), 7.92 (d, J= 8.6 Hz, 1H), 7.50 (d, J=5.2 Hz, 1H), 6.74 (d, J= 8.5 Hz, 1H), 4.01 (s, 3H), 3.31 (dd, J= 12.5, 3.8 Hz, 1H), 2.96 (td, J= 13.0, 6.5 Hz, 1H), 2.83 (dt, J= 14.4, 1.4 Hz, 1H), 2.52 (dddd, J= 13.1, 4.9, 3.3, 1.3 Hz, 1H) 2.33-2.24 (m, 1H), 2.12 (dtd, J= 14.6, 12.7, 4.9, Hz, 1H), 1.95-1.84 (m, 1H), 1.31 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 212.5, 164.7, 154.1, 150.2, 148.4, 138.9, 134.5, 119.5, 117.1, 110.2, 109.3, 53.8, 51.8, 48.8, 38.9, 25.9, 21.7, 20.



*(8bR,12aS)-2-methoxy-8b-methyl-10,11,12,12a-tetrahydrobenzo[f][3,7]phenanthrolin-9(8bH)-one (**24**)*: **24** was synthesized from **6** following the general procedures B, C, D, and E. ^{1}H NMR (500MHz, CDCl$_3$) δ 8.56 (d, J=5.1 Hz, 1H), 8.11 (s, 1H), 8.00 (d, J=8.6 Hz, 1H), 7.55 (d, J=5.2 Hz, 1H), 6.76 (d, J=8.6Hz, 1H), 3.99 (s, 3H), 3.03 (dd, J=12.7, 4.1 Hz, 1H), 2.65 (td, J=13.9, 6.0 Hz, 1H), 2.55 (ddt, J=13.8, 4.3, 2.2, 1H), 2.02 (ddt, J=12.5, 6.2, 3.1 Hz, 1H), 1.96 (dp, J=16.5, 3.5 Hz, 1H), 1.84 (qt, J=13.5, 3.8 Hz, 1H), 1.51 (qd, J=13.1, 3.6 Hz, 1H), 1.23 (s,

3H); $^{13}C\{^1H\}$ (126MHz, $CDCl_3$) δ 212.1, 165.2, 157.6, 149.2, 148.2, 139.0, 134.9, 132.1, 117.7, 117.2, 110.1, 54.1, 53.0, 52.8, 39.6, 29.4, 26.0, 22.9

Compounds **25** – **34** were synthesized by Xuchen Zhao and described in a previous publication[9], and so their synthesis is not described here.

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