Investigation of Flavinium Salts as Catalysts for Intermolecular C(sp^3)-H Amination

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Abstract

For several decades, the synthesis of pharmaceutical drugs and biologically active compounds has advanced rapidly. The prevalence of nitrogen atoms in these drug compounds has led synthetic chemists to develop efficient and cost-effective methods to form carbon-nitrogen bonds in new ways. Among several methods, C-H amination has received a tremendous amount of attention due to its potential in efficiency and selectivity. Despite this, organocatalytic intermolecular C-H amination has been underexplored compared to the other catalytic systems. In this thesis, I have investigated flavinium salts as catalysts for intermolecular C-H amination. The flavinium salt catalyst **7.15** derived from flavin groups was capable of catalyzing intermolecular C(sp^3)-H amination using PhINTces as the nitrogen source. However, the reactivity was lower than that of the previous iminium salt catalyst **6.2**, and the scope was limited to substrates with highly activated benzylic C-H bonds. Despite this, the observed trend of scope indicated that the flavinium salt catalyst **7.15** might be going through the same mechanism as the iminium salt catalyst **6.2**, through the biradical intermediate.

Acknowledgements

Chapter 2 contains contributions from Dr. Johnathon Dooley who assisted in reaction development through screening and testing new substrates.

I would like to thank all my group members who have helped me. I have made many mistakes and all have given me advice and corrections that I needed.

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I would like to thank my parents for all the support you sent with food, prayers and encouraging words. I have to thank my brother as well as he has always been there for me. Also, my friends who have given me smiles when I needed them. Lastly, I would like to thank Heather who was always with me in both good and bad days. Thank you for supporting me when I doubted my ability to finish this race.

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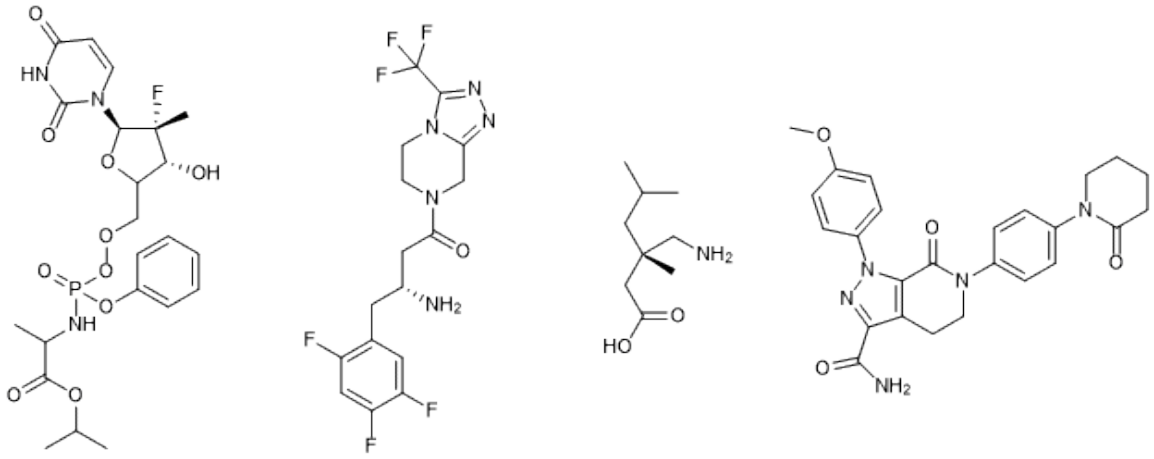
Chapter. I: A Review of Atom-Transfer Reactions

1.1 Advantages and Challenges in C-H Amination

Nitrogen atoms have been regarded by medicinal chemists as one of the most valuable atoms due to its ubiquity in FDA-approved drugs and bioactive natural products.[1] In comparison to carbon atoms, the non-bonding electron pair and electronegativity of nitrogen atoms have been known to impact molecular and physiochemical properties, offering more windows for pharmacological improvements.[2] This impact is suggested by an analysis of U.S FDA-approved pharmaceuticals, which showed that 59% of small molecule drugs contain at least one nitrogen heterocycle with an average of 3.1 nitrogen



1.1
Sofosbuvir
(antiviral)
1st most sold

1.2
Sitagliptin
(enzyme inhibitor)
2nd most sold

1.3
Pregabalin
(anticonvulsant)
3rd most sold

1.4
Apixaban
(anticoagulant)
4th most sold

Figure 1.1.1 Four of the US top five best-selling small molecule drugs that contain nitrogen atoms in 2018[2]

atoms per drug.[1] **Figure 1.1.1** lists four nitrogen containing compounds of the top five small molecule drugs in the U.S. based on retail sales in 2018.[3] As a result of their prevalence, synthetic chemists have endeavored to develop methods to access common nitrogen-containing functional groups that overcome limitations of current approaches.

Some of the most useful and robust methods known in the literature are reductive carbonyl amination,[4] Buchwald-Hartwig coupling,[5] hydroamination,[6] diamination of olefins,[7] and allylic amination (Figure 1.1.2).[8] One drawback of these transformations is the requirement for pre-installed functional groups, such as carbonyls, halides, olefins, and allylic alcohols,

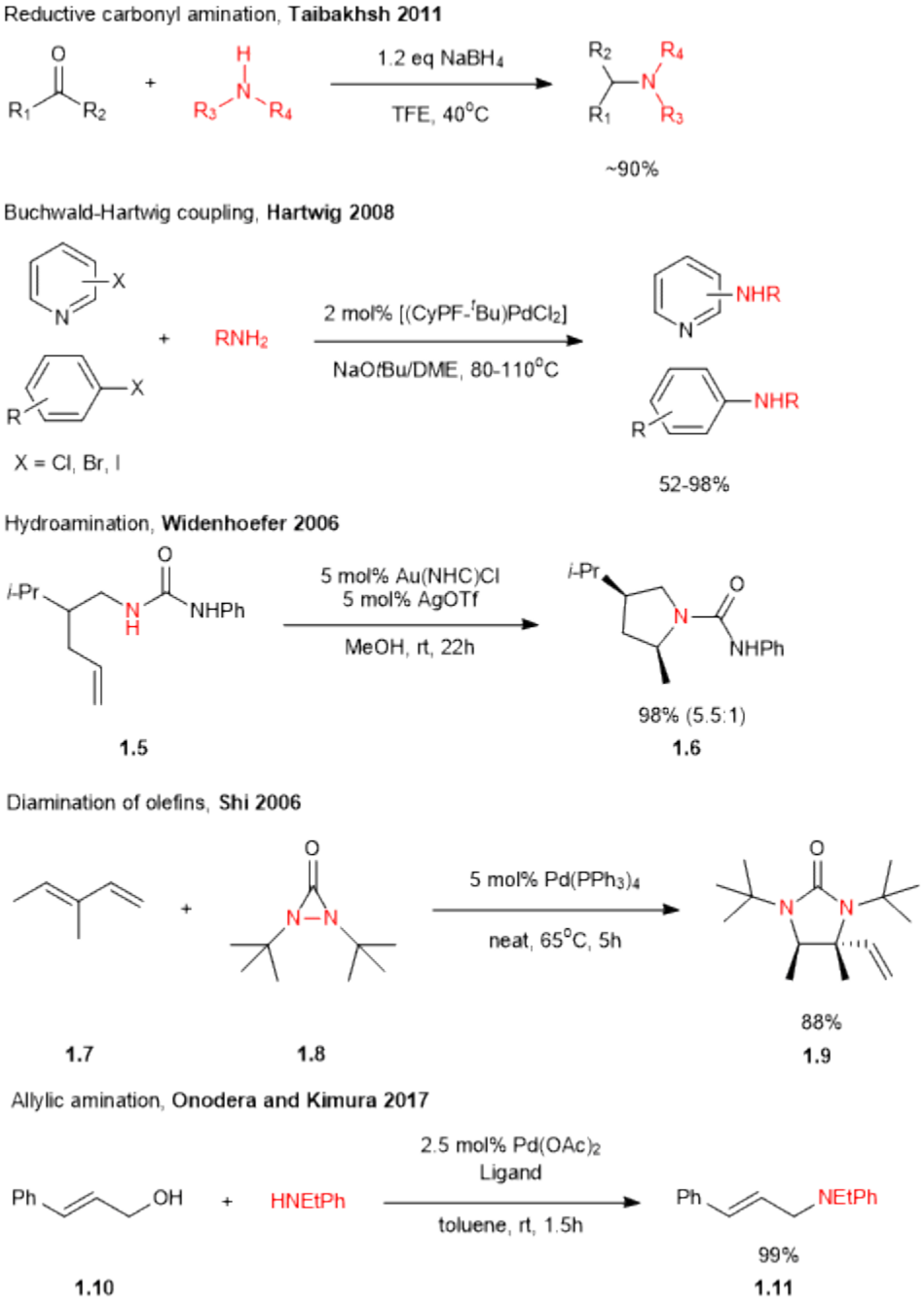


Figure 1.1.2 Traditional amination reactions

that are then converted into the desired nitrogen-containing product. This reduces synthetic efficiency by generally decreasing atom economy and increasing the number of synthetic steps required to access a particular product.[9,10,11] C-H amination offers a great potential advantage over the established methods. The direct functionalization of C-H bonds allows for simplification of synthetic strategies by avoiding prefunctionalization, thus increasing efficiency.

However, there exists numerous challenges to direct functionalization of C-H bonds. For instance, due to the abundant nature of C-H bond on any given molecules, it is difficult to achieve an absolute control over chemo- and site-selectivity. In many cases, the scope of the methods is largely limited by the intrinsic characteristics of the substrate, electronic and steric factors.[12-15] In order to address this challenge, we can envision developing new methods to target each and different C-H bonds found in any complex or natural compounds.

1.2 A Review of Transition metal-catalyzed CH amination

Over the past few decades, chemists have developed various effective transition metal-catalyzed C-H amination methods that proceed via nitrene transfer. In 1983, Breslow reported the first metal-catalyzed intramolecular C(sp^3)-H amination using a rhodium

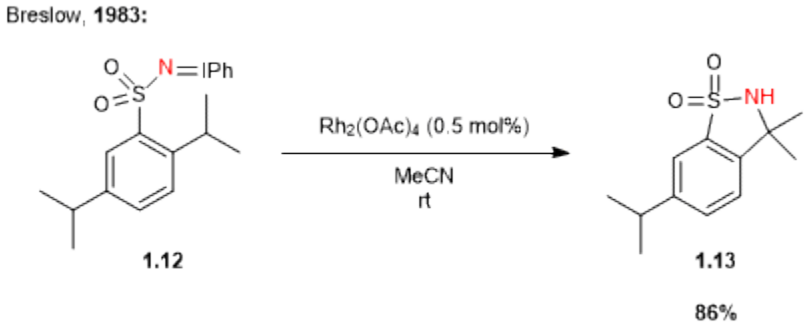


Figure 1.2.1. Pioneering intramolecular C-H amination work by Breslow

catalyst (**Figure 1.2.1**).[16] In 2001, Du Bois reported an improved rhodium catalytic system capable of performing intramolecular C(sp^3)-H amination, using diacetoxyiodobenzene ($PhI(OAc)_2$) as an oxidant to avoid pre-oxidation of the nitrogen atom (**Figure 1.2.2**).[17]

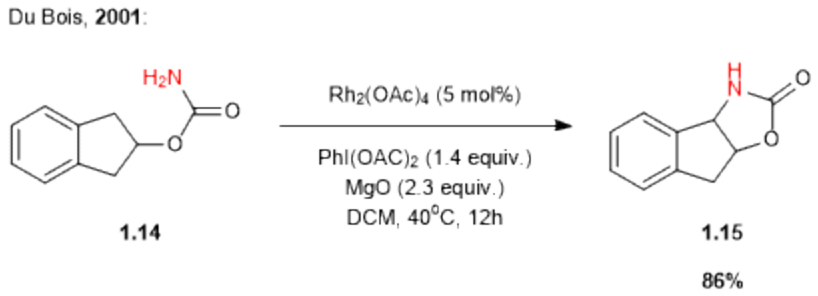


Figure 1.2.2. Pioneering intramolecular C-H amination work by Du bois

Following these two pioneering examples, others developed additional transition metal catalysts, such as manganese,[18] iron,[19,20] cobalt,[21] copper,[22,23] ruthenium,[24,25] rhodium,[26,27,28] silver,[29] iridium,[30] and gold.[31] In 2011, Du bois group reported ruthenium-catalyzed intramolecular allylic C(sp^3)-H amination (**Figure 1.2.3**).[25] This report examined

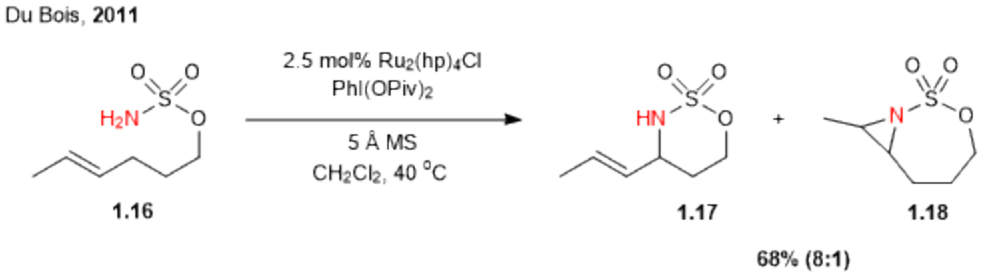


Figure 1.2.3. Ruthenium-catalyzed intramolecular C-H amination by Du Bois

for the first time the efficacy of the diruthenium complex for C-H amination. In the same year, Katsuki group reported iridium-catalyzed intramolecular C(sp3)-H amination (**Figure 1.2.4**).[30] In this system, formation of either a five-membered or a six-membered sultam was possible depending on the substituents. Moreover, the cyclization went with high enantioselectivity by choosing an appropriate catalyst. In 2012, the White group reported the use of an iron catalyst for intramolecular allylic C(sp3)-H amination which favored allylic CH amination over aziridination, as well as over amination of 3° and 2°

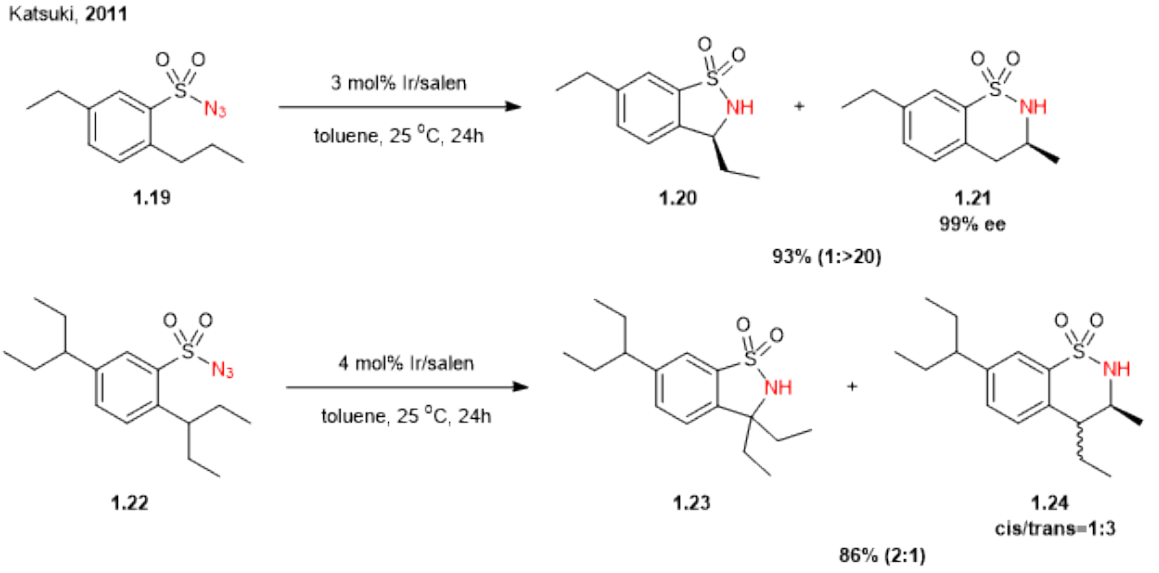


Figure 1.2.4. Iridium-catalyzed intramolecular C-H amination by Katsuki

aliphatic, ethereal, or benzylic C-H bonds (**Figure 1.2.5**).[19] In 2013, Schomaker group

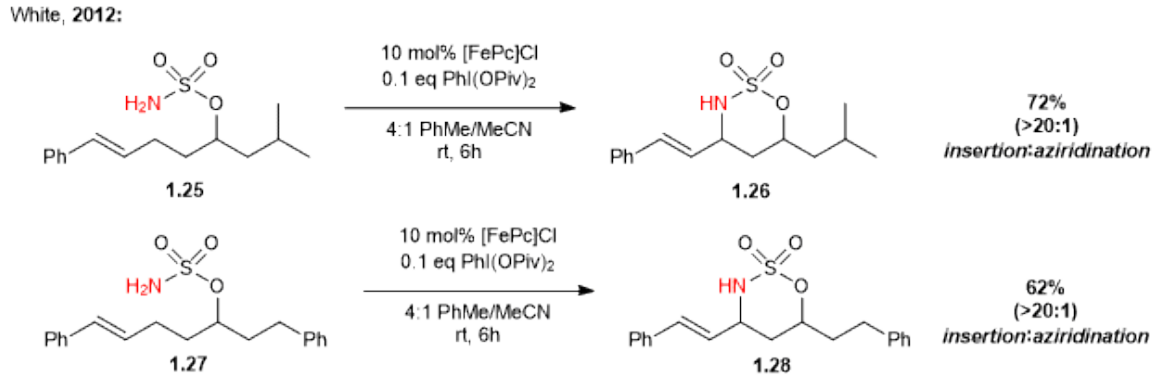


Figure 1.2.5. Iron-catalyzed intramolecular allylic C-H amination by White

reported ligand-controlled chemoselective C(sp^3)-H amination (**Figure 1.2.6**).[29] Notably, the chemoselectivity between aziridination and C(sp^3)-H amination was determined by the

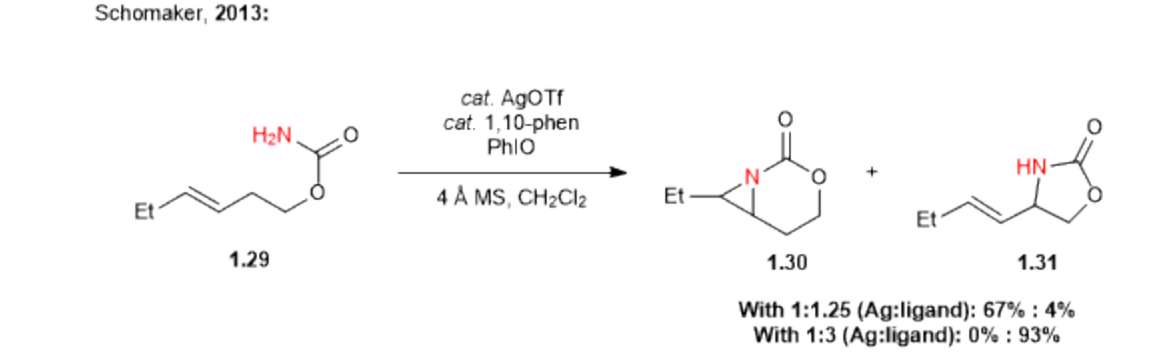


Figure 1.2.6. Silver-catalyzed intramolecular selective amination by Schomaker

silver salt and the ligand ratio. With 1:25 ratio (silver salt: ligand), aziridination was

favored whereas with 1:3 ratio, C-H insertion was favored. In 2015, the White group reported manganese-catalyzed intramolecular C(sp^3)-H amination (**Figure 1.2.7**).[18] This

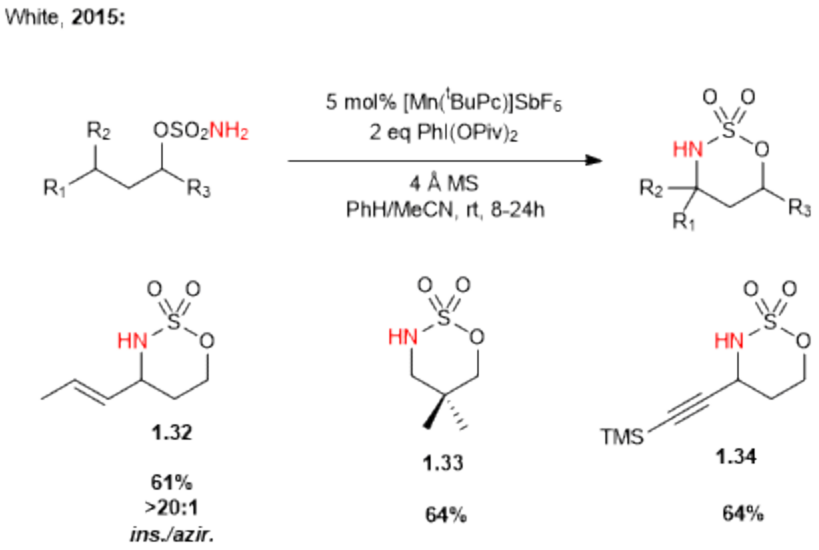


Figure 1.2.7. Manganese-catalyzed intramolecular C-H amination by White

system was capable of performing intramolecular amination of various types of C-H bonds, including 1°, 2°, and 3° aliphatic, allylic, and propargylic C-H bonds, while maintaining stereospecificity and broad functional group tolerance. In 2007, Du Bois reported intermolecular C-H amination using a dirhodium catalyst (**Figure 1.2.8**).[27] This catalyst showed a higher turnover number over traditional rhodium catalysts due to the use of a

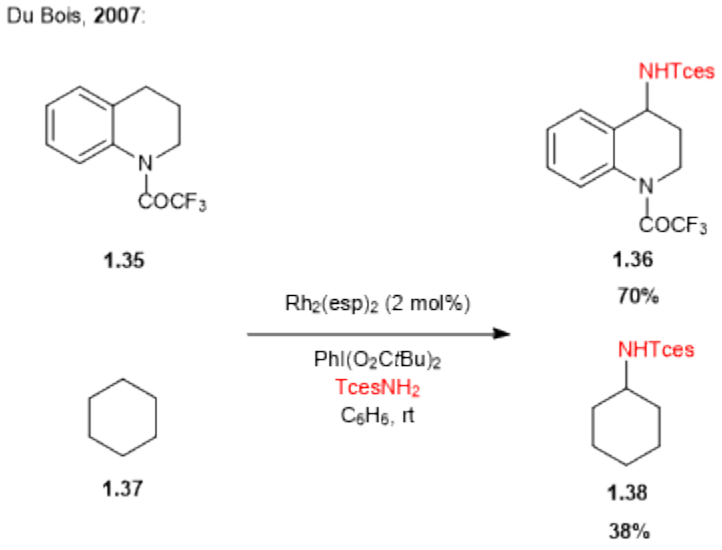


Figure 1.2.8. Rhodium-catalyzed C-H amination by Du Bois

strapped ligand. Studies revealed that during the reaction, previous unstrapped rhodium catalyst was subject to rapid ligand exchange which was believed to initiate catalyst decomposition.[32] Thus, the strapped ligand improved the stability of the catalyst by hindering the ligand exchange. In 2014, Stavropoulos group reported copper-catalyzed

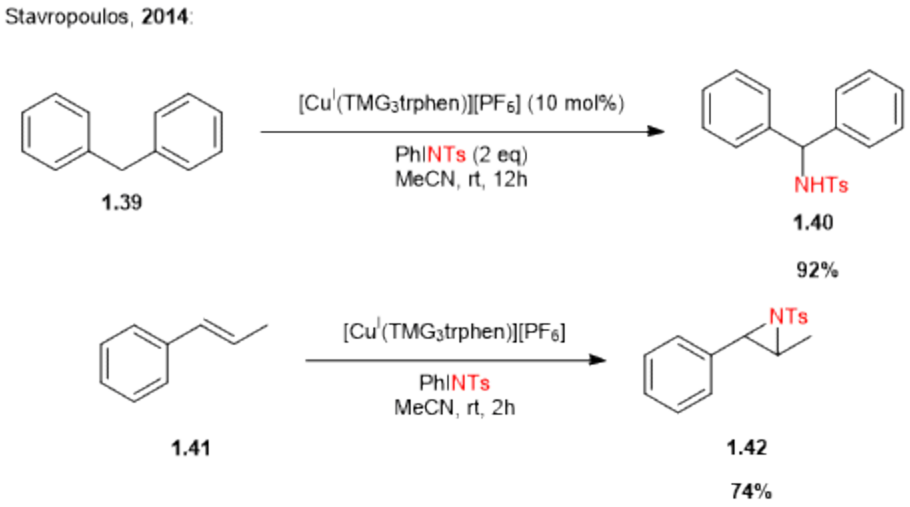


Figure 1.2.9. Copper-catalyzed amination by Stavropoulos

intermolecular C(sp^3)-H amination and aziridination (**Figure 1.2.9**).[23] 2º and 3º, benzylic, and ethereal C-H bonds aminated with ease.

There exist reports that examined C(sp^2)-H amination as well. Driver group pioneered the development of rhodium-catalyzed intramolecular C(sp^2)-H amination to obtain functionalized indoles using azides (**Figure 1.2.10**).[33-34] It was revealed in later

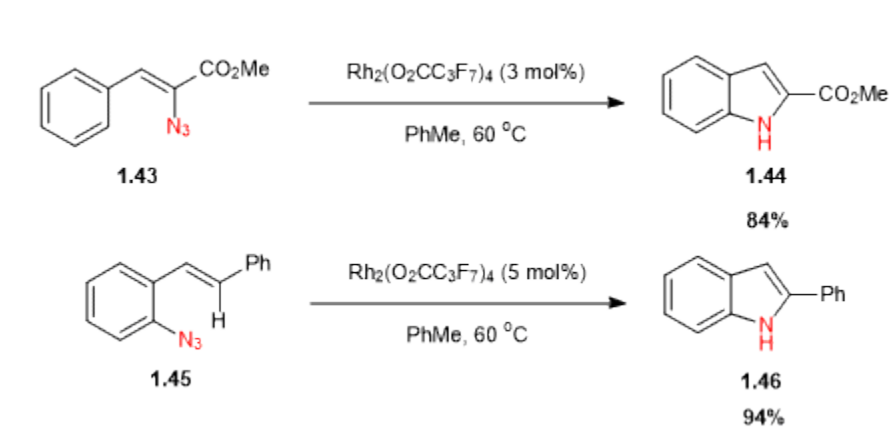


Figure 1.2.10. Rhodium-catalyzed intramolecular C(sp^2)-H amination by Driver

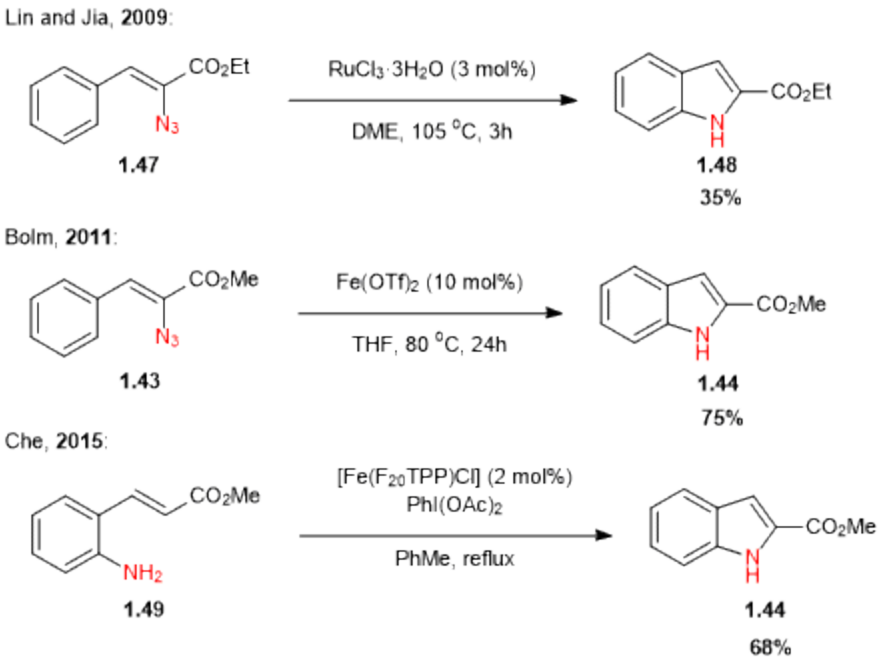


Figure 1.2.11. Transition metal-catalyzed intramolecular C(sp^2)-H amination

studies that the reactions underwent electrocyclization rather than concerted C-H insertion.[35] A few examples are known to employ other transition metal catalysts as well such as ruthenium and iron.[36-38] (**Figure 1.2.11**). For intermolecular C(sp^2)-H amination, Perez group reported a few examples of copper-catalyzed benzene C(sp^2)-H amination by

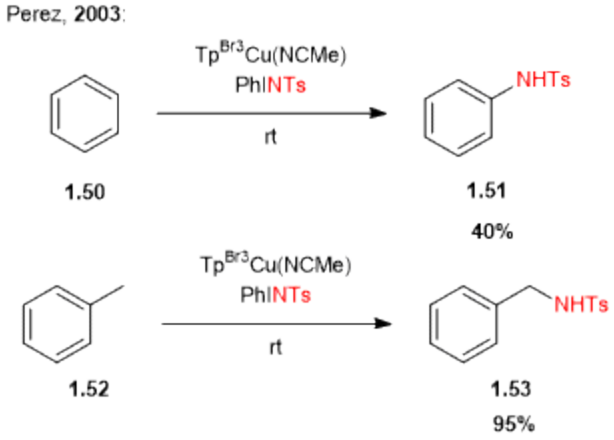


Figure 1.2.12. Copper-catalyzed intermolecular C(sp^2)-H amination by Perez

tosyliminoiodinanes under mild conditions (**Figure 1.2.12**).[39,22] However, alkylaromatic compounds underwent benzylic amination. In 2012, Jensen group reported iron-catalyzed C(sp^2)-H amination by tosyliminoiodinanes (**Figure 1.2.13**).[40] Reaction of toluene under

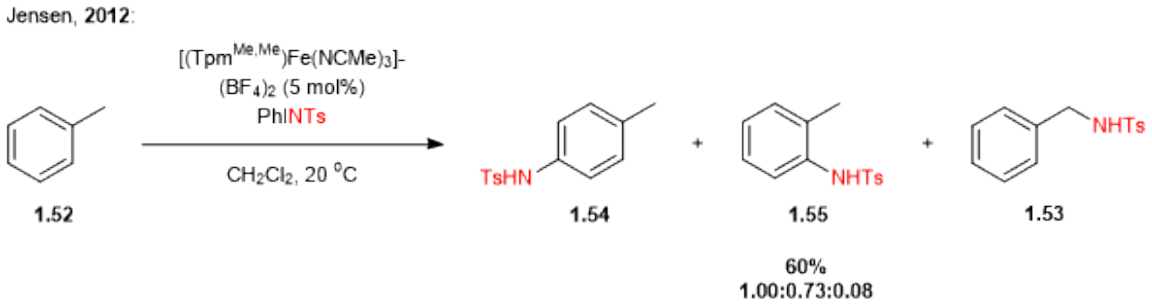


Figure 1.2.13. Iron-catalyzed intermolecular C(sp^2)-H amination by Jensen

the conditions showed a notable selectivity at C(sp^2)-H over the benzylic C-H bonds. In 2013, Nicholas group reported copper-catalyzed C(sp^2)-H amination of simple arenes by *N*-tosyloxycarbamates (**Figure 1.2.14**).[41] In comparison to the previous methods where

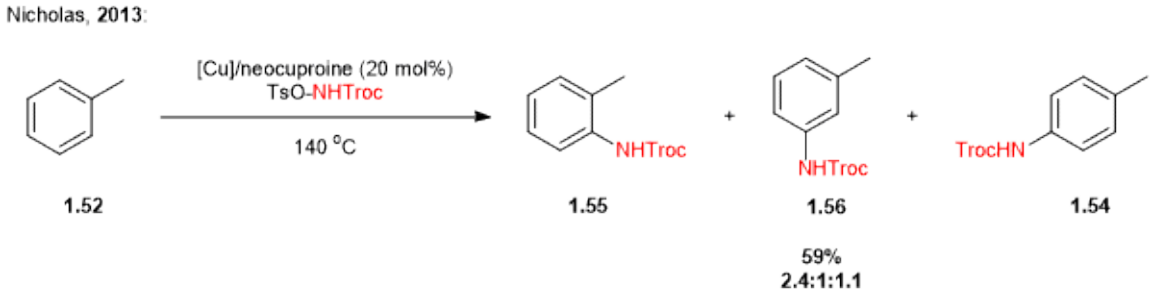


Figure 1.2.14. Copper-catalyzed intermolecular C(sp^2)-H amination by Nicholas

small amount of C(sp^3)-H amination products were observed, none of the benzylic amination was observed.

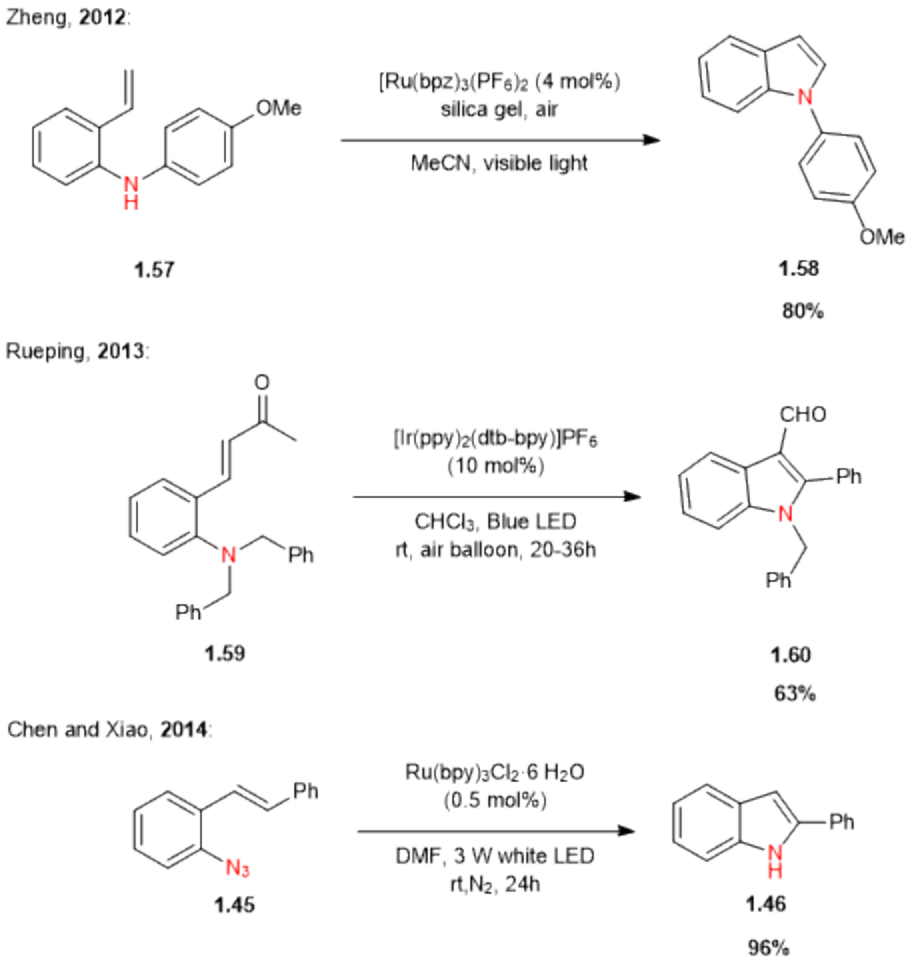


Figure 1.2.15. Transition metal-photocatalyzed intramolecular C(sp^2)-H amination

Photoredox catalysis has been studied as well. For intramolecular C(sp^2)-H amination, some have developed methods for synthesis of indoles (**Figure 1.2.15**).[42-44] In

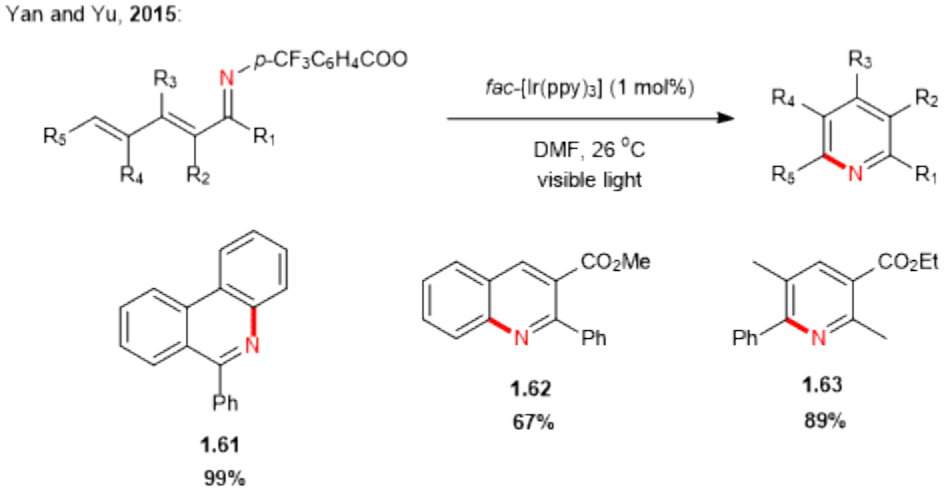


Figure 1.2.16. Iridium-photocatalyzed intramolecular C(sp^2)-H amination by Yan and Yu

2015, Yu and Zhang reported iridium-catalyzed C(sp^2)-H amination (**Figure 1.2.16**).[45] Compared to the previous reports, the scope of the substrates were extended to various heterocycles such as phenanthridines, quinolines, and pyridines. For intermolecular C(sp^2)-H amination, San ford reported iridium-catalyzed C(sp^2)-H amination of simple arenes and

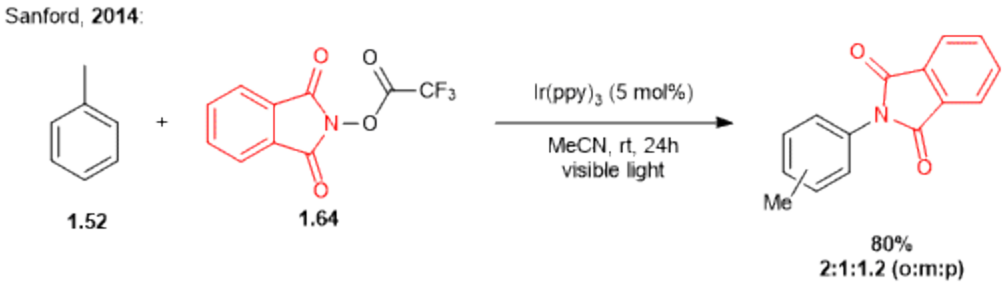


Figure 1.2.17. Iridium-photocatalyzed intermolecular C(sp^2)-H amination by Sanford

heteroarenes with trifluoromethylacyloxyphthalimide in 2014 (**Figure 1.2.17**).[46] In the same year, Yu reported iridium-catalyzed C(sp^2)-H amination of various heteroarenes with hydroxylamine derivatives (**Figure 1.2.18**).[47] The use of hydroxylamine derivatives

Figure 1.2.18. Iridium-photocatalyzed intermolecular C(sp^2)-H amination by Yu

afforded in high amination efficiency, thus increasing the product yields. Xue reported iridium-catalyzed C(sp^2)-H amination of benzoxazoles with morpholines and secondary amines as a nitrogen source (**Figure 1.2.19**).[48] Nonfunctionalized morpholines were

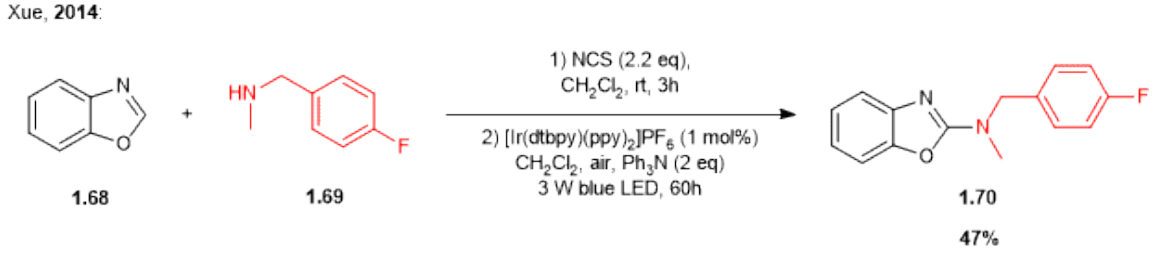


Figure 1.2.19. Iridium-photocatalyzed intermolecular C(sp^2)-H amination by Xue

converted to their chloroamines *in situ*, which then reacted with the substrate to produce the product. In 2015, Studer examined *N*-aminopyridinium salts as nitrogen sources to react with heteroarenes under a ruthenium photocatalytic system (**Figure 1.2.20**).[49] Electron-rich arenes were readily aminated whereas electron-deficient arenes were rather sluggish. In comparison to the progress of transition metal-catalyzed C-H amination, organocatalytic C-H amination has only recently started to be developed, showing notable potential. Direct amination of several types of C-H bonds have been explored, but most methods use either radical or photocatalytic pathways.[50,51,52] There exists one report of nitrene-transfer organocatalytic C(sp^3)-H amination from Hilinski group, which I will discuss in the next section. Thus, examination into new types of organocatalysts is necessary to further develop organocatalytic C-H amination chemistry.

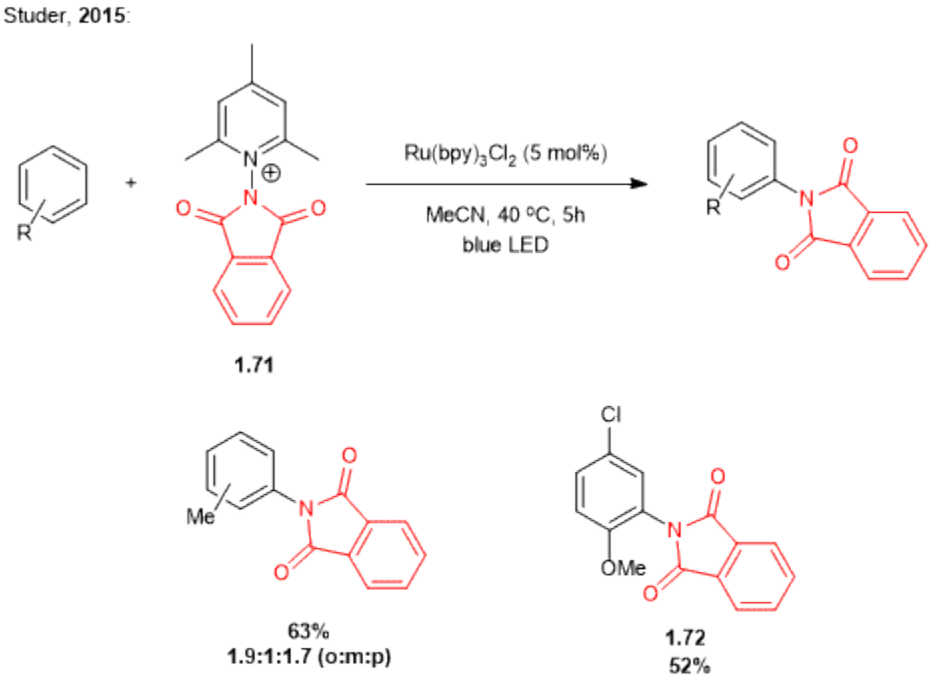


Figure 1.2.20. Ruthenium-photocatalyzed intermolecular C(sp^2)-H amination by Studer

1.3 Development of Three-Membered Heterocycles for Atom-Transfer Reactions

1.3.1 Introduction

In this section, I will discuss development of three-membered organo-heterocycles that has been studied for intermolecular atom transfer reactions. These heterocycles were found to be particularly interesting, as the strained three-membered ring and weak heteroatom-heteroatom single bond afforded high reactivity in atom transfer processes. Dioxiranes, oxaziridines, and oxaziridiniums were examined as either catalytic intermediates or catalysts for oxygen atom transfer reactions such as epoxidation and C-H hydroxylation. Its reactivity inspired many to consider nitrogen atom transfer reactions in a similar manner, leading to the development of diaziridiniums as catalytic intermediates for nitrene transfer reactions.

1.3.2 Dioxiranes

Dioxirane chemistry traces its roots back to 1979, when a synthetic route to dioxiranes using simple ketones and potassium carbonate was discovered.[53] In 1985, Murray successfully isolated dimethyldioxirane (DMDO) (**1.73**) and demonstrated its reactivity in epoxidation chemistry **(Figure 1.3.1**).[54] Various alkenes were converted to epoxides with retention of configuration. In 1984, Curci demonstrated the first *in-situ*

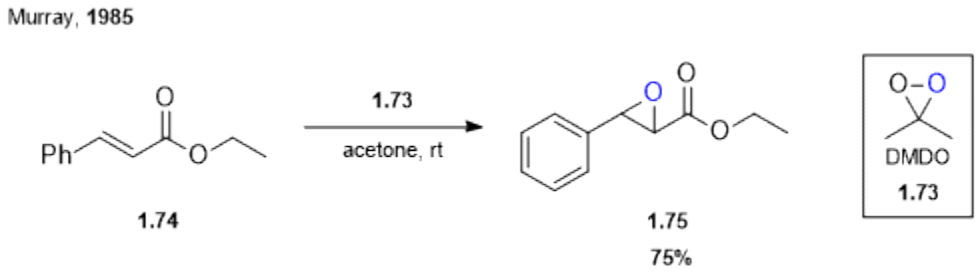


Figure 1.3.1. Epoxidation with dioxiranes by Murray

generation of dioxiranes with chiral ketones and oxone (**Figure 1.3.2**).[55] Chiral ketones produced the corresponding epoxides in moderate to good yields and poor enantiomeric

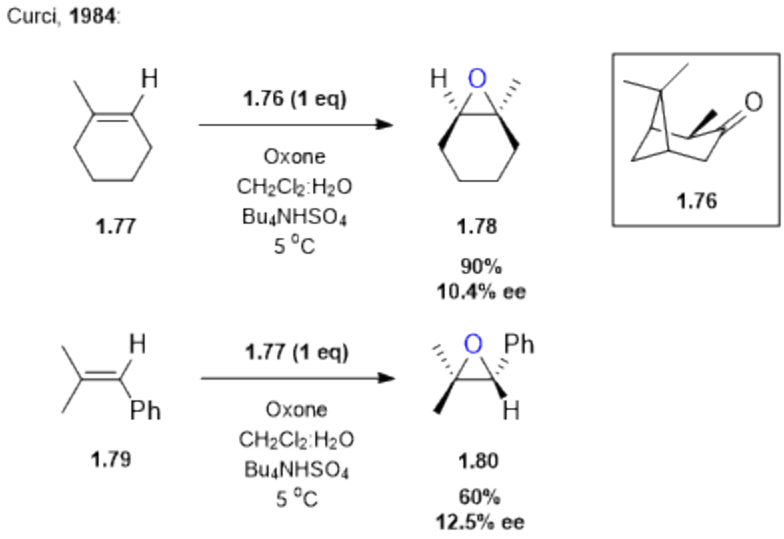


Figure 1.3.2. Epoxidation with chiral ketones by Curci

excesses were observed, where most cases were <15% ee. In 1994, Denmark reported a

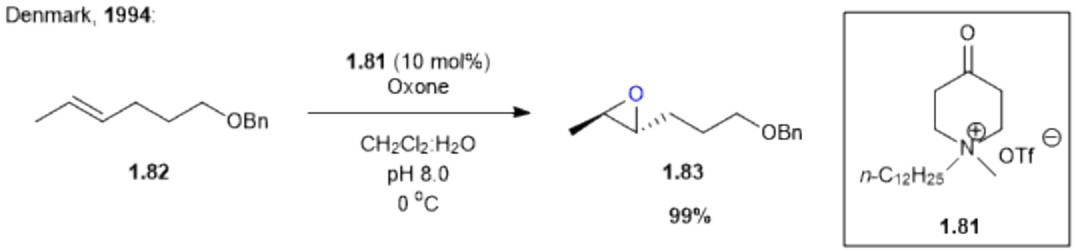


Figure 1.3.3. Epoxidation with piperidinium by Denmark

similar work, a study on catalytic epoxidation of alkenes with oxone (**Figure 1.3.3**).[56] The report examined multiple variables for the biphasic conditions with oxone and ketones, optimizing loadings of each reagents, addition rates, structures of ketones, and different pH environment. In 1996, Yang reported asymmetric epoxidation using C_2-symmetric chiral ketone (**1.84)** by oxone salt (**Figure 1.3.4**).[57] Notably, catalytic amount of chiral ketone effectively converted alkene to epoxide in high enantiomeric excess. In 1997, Shi reported a catalytic asymmetric epoxidation using a chiral ketone (**1.87)** derived from D-fructose (**Figure 1.3.5**).[58] Along with Yang's report, the high stereoselectivity demonstrated the effectiveness of dioxiranes in asymmetric chemistry.

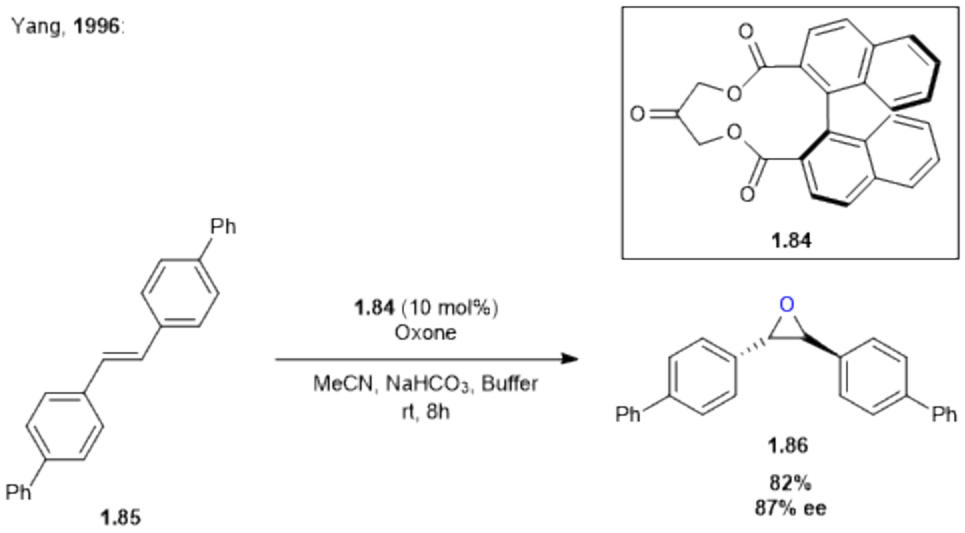


Figure 1.3.4. Asymmetric Epoxidation with C_2 Symmetric Chiral Ketone by Yang

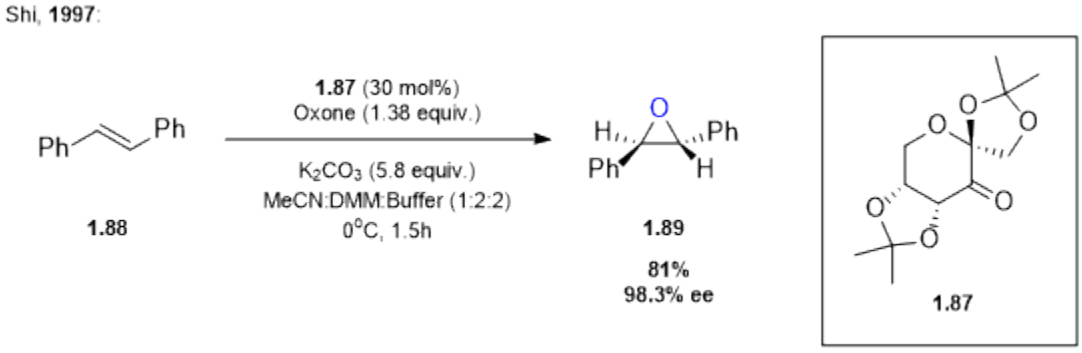


Figure 1.3.5. Asymmetric Epoxidation with Chiral Ketones by Shi

In 1986, Murray reported the first example of C-H hydroxylation using DMDO (**1.73**) as an oxidant.[59] He reported the conversion of various hydrocarbons, such as adamantane (**1.91**), to their corresponding tertiary alcohols. The mild and fast reactivity of dioxiranes in these chemical reactions demonstrated its potential for C-H functionalization. In 1988, Curci reported a new species of dioxirane - methyl(trifluoromethyl)dioxirane (TFDO) (**1.90**). He reported that TFDO (**1.90**) was 7000-fold more reactive than DMDO (**1.73**) in the hydroxylation of adamantane (**1.91**) (**Figure 1.3.6a**).[60] In these reactions, the dioxiranes were highly selective for tertiary over secondary and primary C-H bonds in aliphatic compounds. However, benzylic C-H bonds were selectively converted over

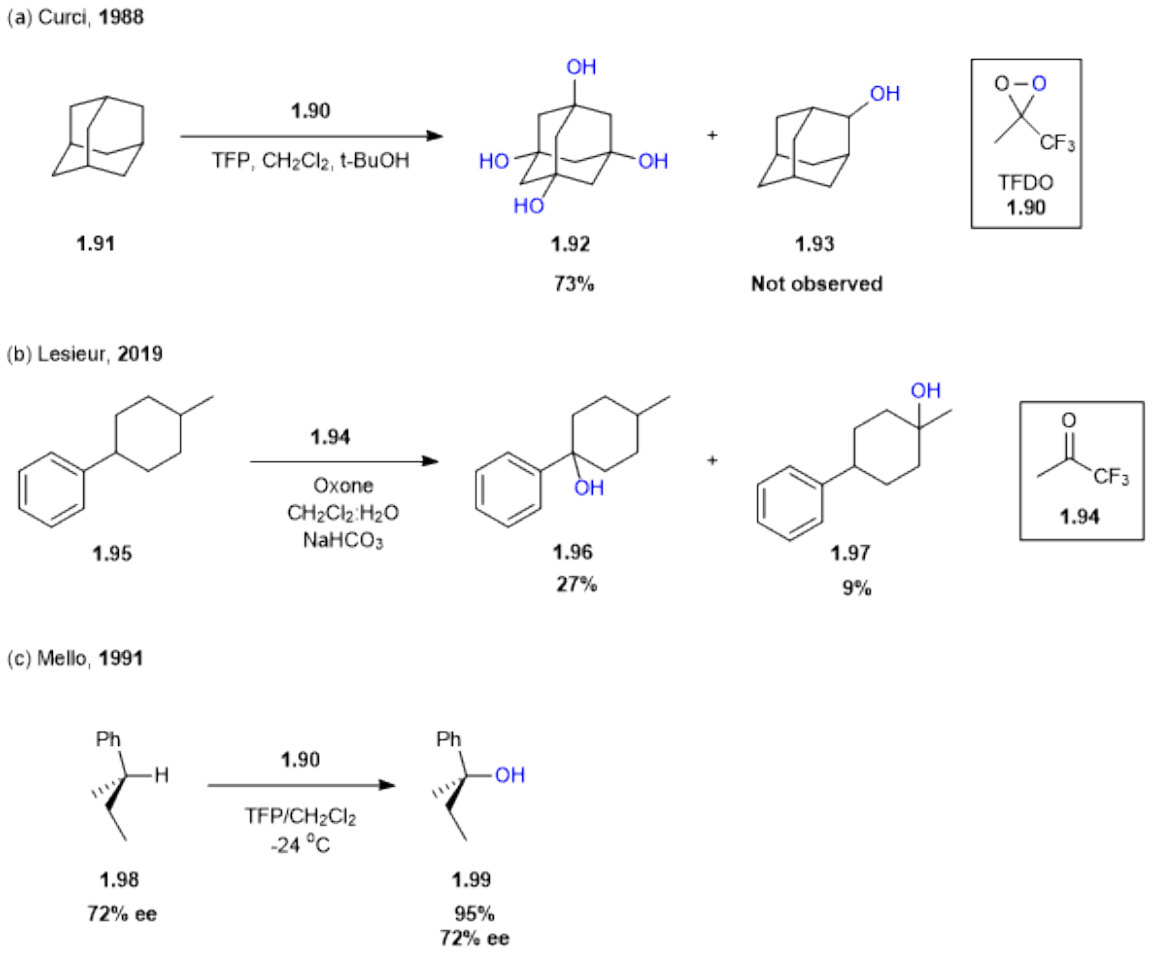


Figure 1.3.6. Selectivity and retention of configuration

aliphatic C-H bonds for aromatic compounds.[61] For instance, when adamantane (**1.91**) was reacted with TFDO (**1.90**), tetrahydroxyadamantane (**1.92**) was produced with no observation of 2-adamantanol (**1.93**) (**Figure 1.5a**). When **1.95** was reacted with trifluoroacetone (**1.94**), benzylic C-H hydroxylation was preferentially oxidized over tertiary C-H bond (**Figure 1.3.6b**). Complete retention of configuration was also observed when TFDO was reacted with optically pure 2-phenylbutane (**1.98**), producing optically pure 2-phenyl-2-butanol (**1.99**) (**Figure 1.3.6c**).[62]

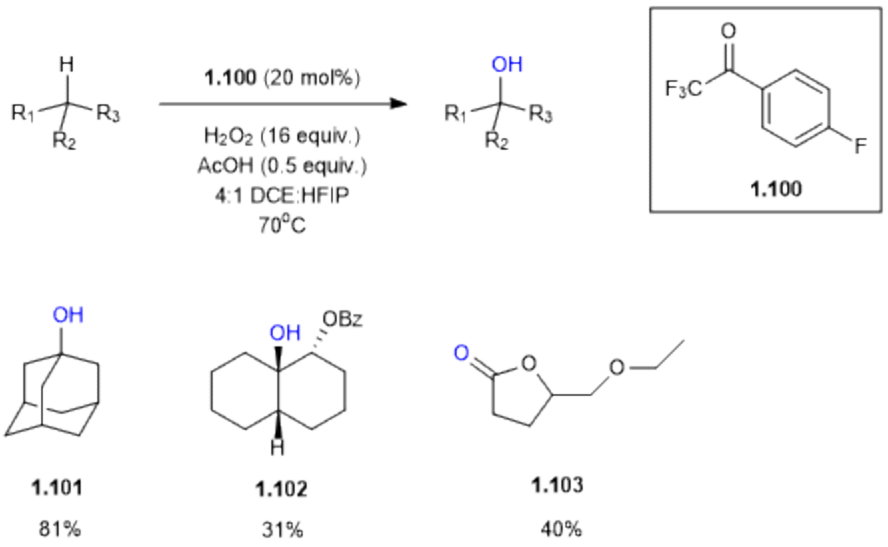


Figure 1.3.7. C-H hydroxylation using trifluoroacetophenone **1.100**

In 2014, the Hilinski group reported a chemoselective C-H hydroxylation using a trifluoromethylketone catalyst (**1.100**).[63] This report is the first example of the use of a ketone catalyst for C-H hydroxylation (**Figure 1.3.7**). The report demonstrated that hydrogen peroxide (H_2O_2) can replace oxone in ketone-catalyzed C-H hydroxylation reactions. Highly reactive substrates such as adamantane and *cis*-decalin were converted up to 81% yield.

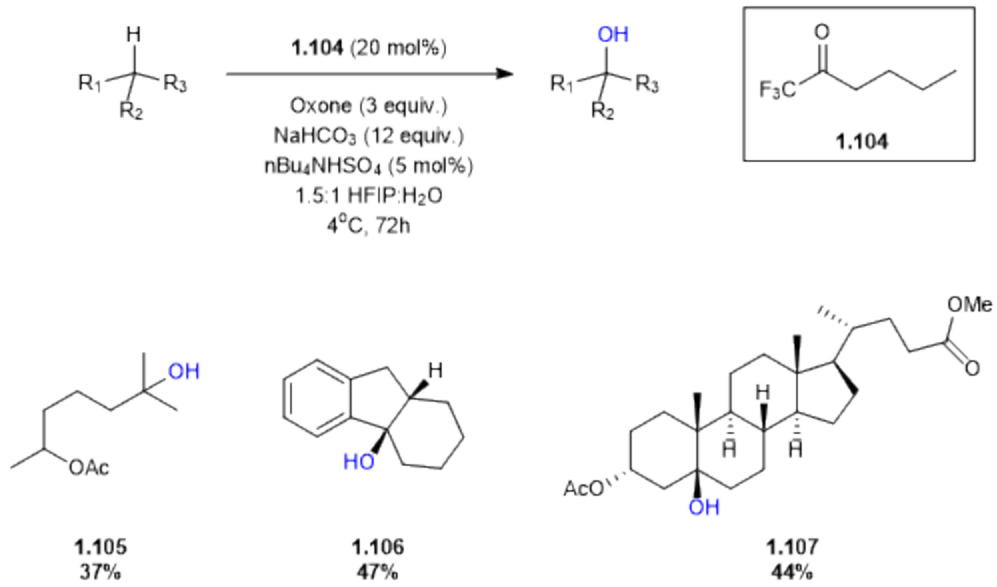


Figure 1.3.8. C-H hydroxylation using **1.104**

In 2017, the Hilinski group reported a second-generation dioxirane-mediated catalytic C-H hydroxylation using another ketone catalyst (**1.104**) (**Figure 1.3.8**).[64] Instead of H_2O_2, oxone was used as the terminal oxidant. The new catalytic system demonstrated improved reactivity over the previous system. The catalytic system favored benzylic positions and tertiary C-H bonds over aliphatic and secondary C-H bonds (**Figure 1.3.8**, **1.105** and **1.106)**. More complex compounds such as sterol derivatives were readily oxidized with impressive chemoselectivity (**Figure 1.3.8**, **3.33**).

1.3.2 Oxaziridines

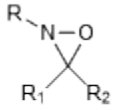


Figure 1.4.1. Oxaziridine

Oxaziridines are another class of three-membered heterocyclic compounds related to the dioxiranes (**Figure 1.4.1**). Instead of two oxygen atoms forming a single bond, oxaziridines have a nitrogen-oxygen single bond. Oxaziridines tend to be more stable than the dioxiranes and can be stored on benchtop without precautions against air or moisture.[65] Oxaziridines have been used in various oxidations such as epoxidation, sulfoxidation, enamine oxidation, and

enolate oxidation.[66] In 1977, Davis first synthesized *N*-sulfonyloxaziridines which quickly became the most utilized class of oxaziridines because of their stability, ease of synthesis, and ability to effectively transfer oxygen atoms to olefins[66a] In 1981, Davis demonstrated

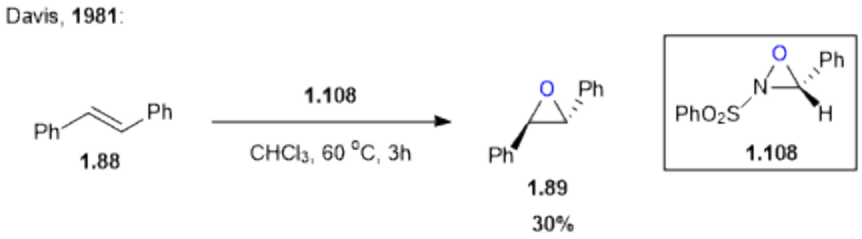


Figure 1.4.2. Epoxidation of olefins using oxaziridine **1.108** by Davis

stereospecific epoxidation of simple olefins using (*N*-benzenesulfonyl)-phenyloxaziridine (**Figure 1.4.2**).[67] A more reactive species of oxaziridines, perfluorinated oxaziridines, has been researched as well. In the mid-1970s, the first fluorinated oxaziridines were reported by DesMarteau.[68] Perfluorinated oxaziridines exhibited similar reactivity to the trifluorodioxiranes rather than to the hydrocarbon-substituted oxaziridines due to the electron withdrawing perfluoroalkyl groups.[69] In 1993, Resnati reported C-H hydroxylation of simple hydrocarbons using perfluorinated oxaziridines.[70] Similar to dioxirane chemistry, Resnati observed selective hydroxylation of tertiary C-H bonds.

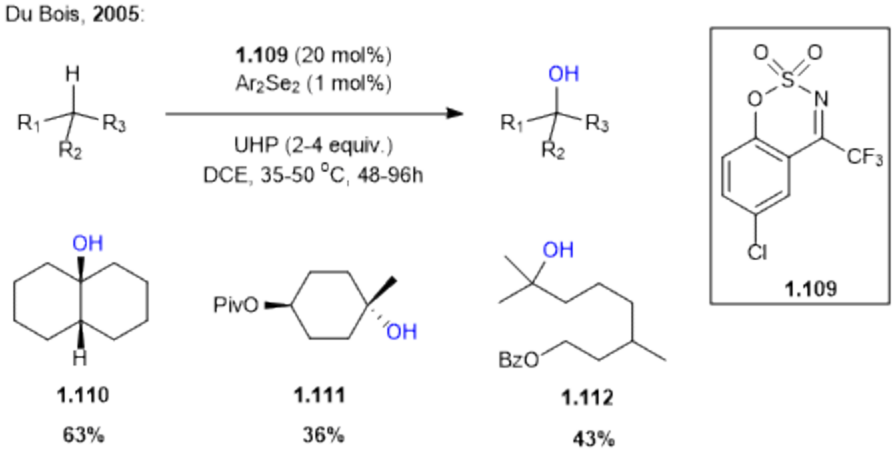


Figure 1.4.3. Intermolecular C(sp^3)-H hydroxylation using the benzoxathiazine catalyst **1.109**

In 2005, Du Bois reported C-H hydroxylation of tertiary C-H bonds using the benzoxathiazine catalyst (**1.109)** (**Figure 1.4.3**).[71] Du Bois was able to synthesize and

isolate the proposed oxaziridine intermediate and confirmed that it is the active species responsible for the C-H oxidation. As expected from the structural similarities to the perfluorinated oxaziridines, the catalytic system favored tertiary C-H bonds over other C-H bonds. Later, Du Bois was able to improve this catalytic system using two new methods. In 2009, use of modified catalyst, *p*-pentafluorophenyl-benzoxathiazine, enabled C-H hydroxylation of more complex substrates.[72a] In 2014, the use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a solvent with H_2O showed increase in yields and shortened reaction time.[72b] Du Bois proposed that the use of HFIP limits the accessibility of H_2O to the intermediate due to the hydrophobic solvation environment of the fluoroalcohol phase, which delays the decomposition of the intermediate.

1.3.3 Oxaziridinium salts

As indicated by the reactivity of electron deficient oxaziridines[67-70], positively charged oxaziridinium salts have been researched for oxygen atom transfer reactions as well. These salts are generally formed from corresponding iminium salts in the presence of

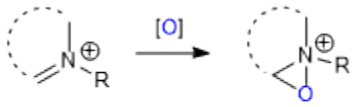


Figure 1.5.1. Generation of oxaziridinium salts from iminium salts

an oxidant such as oxone salt (**Figure 1.5.1**). Many have reported racemic epoxidation of olefins using iminium salt derivatives such as pyrrolidine-derived iminium salts and ketiminium salts, pioneering oxaziridinium-mediated reactions.[73] Asymmetric epoxidations have been extensively researched as well. In 1993, Bohé reported the first asymmetric epoxidation of alkenes using the iminium salt (**1.113)**.[74] With only 5 mol% loading of the catalyst, the reaction of alkene (**1.88)** produced 63% of the corresponding epoxide (**1.89**) with 42% ee (**Figure 1.5.2**). In 1996, Aggarwal reported catalytic

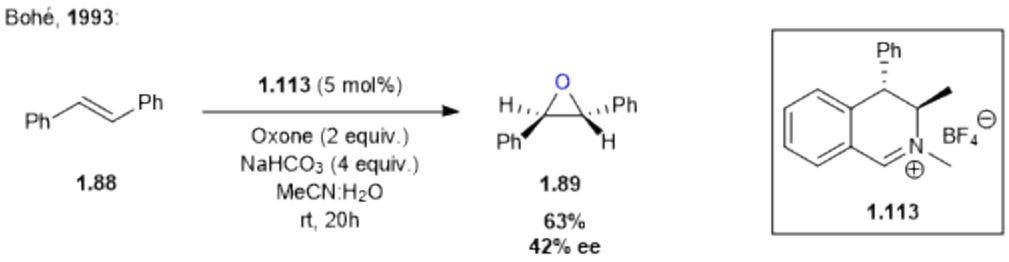


Figure 1.5.2. Oxaziridinium-mediated epoxidation of olefins by Bohe

asymmetric epoxidation using the chiral iminium salt (**1.114)**.[75] With only 5 mol% loading of the catalyst, the reaction of alkene produced 71% of the corresponding epoxide with 31% ee. The highest enantiomeric excess seen was 71% ee from the substrate 1-phenylcyclohexene (**1.115**) (**Figure 1.5.3**). Page reported a number of isoquinoline based

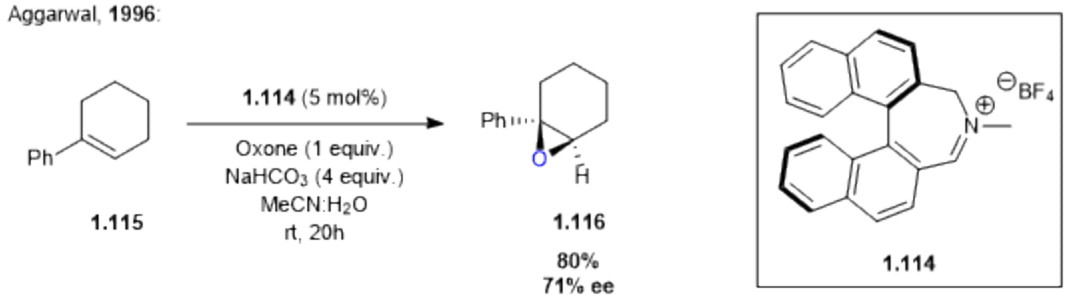


Figure 1.5.3. Oxaziridinium-mediated epoxidation of olefins by Aggarwal

chiral iminium salts for epoxidation of olefins.[76] The methods gave similar yields and enantiomeric excesses to Aggarwal's report. Binaphthylazepinium-based iminium salts were developed as well for asymmetric epoxidation of olefins.[77] Enhanced yields and

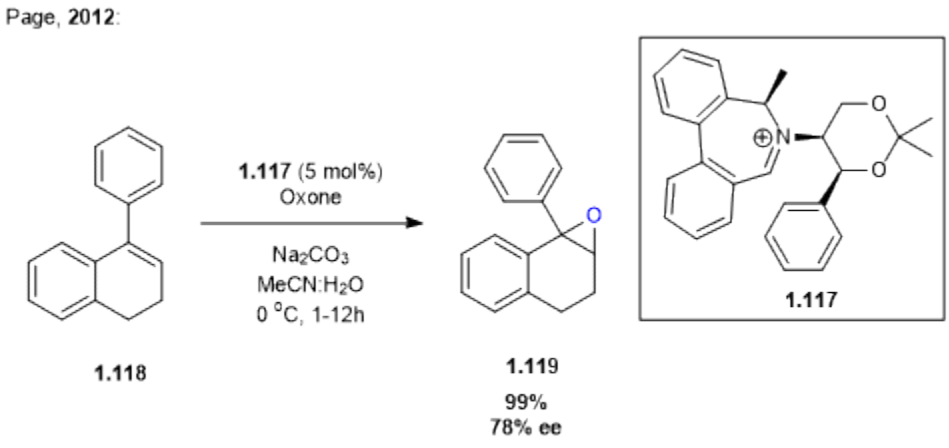
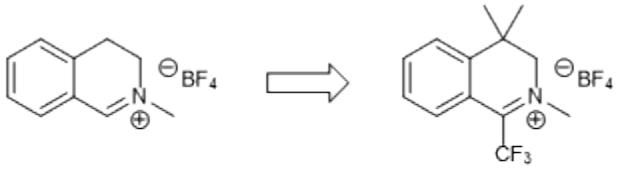


Figure 1.5.4. Oxaziridinium-mediated epoxidation of olefins using binaphthylazepium-based iminium salts **1.117** by Page

enantiomeric excesses were produced as shown by Page and coworkers in 2012 (**Figure 1.5.4**).[77f]

1.3.4 Hilinski catalyst

In 2016, the Hilinski group reported catalytic C-H hydroxylation using an iminium salt catalyst (**1.121**).[78] The initial structure of the catalyst (**1.120**) was inspired from the previously reported iminium salt catalysts.[79] However, initial studies showed that **1.120** was an ineffective catalyst. Two modifications were incorporated into the structure: trifluoromethyl group and gem-dimethyl group. As seen from the previous examples, installation of electron withdrawing group has shown an increase in the reactivity of the catalyst.[67-70] Thus, the trifluoromethyl group was installed. Moreover, installing gem-dimethyl group at the benzylic position to limit the catalyst aromatization greatly improved



1.120 **1.121**

Figure 1.6.1. Modifications of iminium salt catalyst **1.121**

the reactivity (**Figure 1.6.1**). The Hilinski catalyst (**1.121**) showed enhanced reactivity compared to the benzoxathiazine catalyst (**1.109**), where reactions were done in room temperature and in 20h compared to benzoxathiazine's 22-50 ºC and 48-96h.

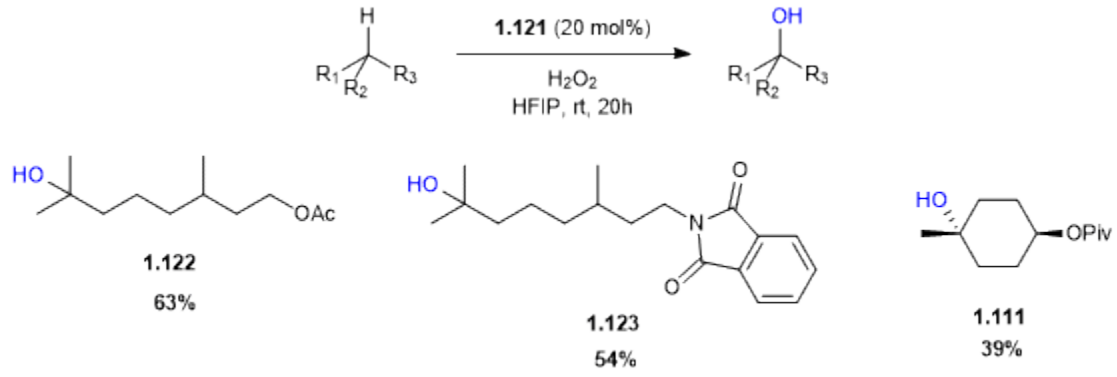


Figure 1.6.2. intermolecular C(sp^3)-H hydroxylation catalyzed by **1.121**

Hydroxylation of various tertiary C-H bonds yielded moderate to excellent yields. High site-selectivity was seen for the substrates with multiple tertiary positions, favoring the electron-rich positions (**Figure 1.6.2**). Hydroxylation of secondary C-H bonds, which has not been demonstrated before, was also possible. For instance, C-H hydroxylation of

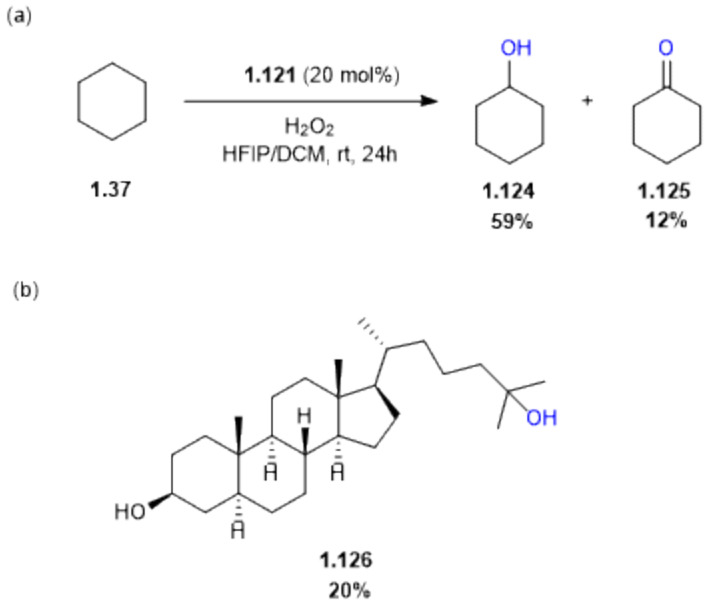


Figure 1.6.3. C-H hydroxylation of cyclohexane (**1.37**) and chemoselectivity by (**1.121**)

cyclohexane (**1.37**) yielded 59% of the alcohol (**1.124**) and 12% of the ketone (**1.125**) (**Figure 1.6.3a**). Remarkable chemoselectivity was observed as well. In addition to the tolerance to various protecting groups, unprotected alcohols were also well tolerated. For instance, a sterol derivative yielded 20% of the desired product (**1.126**) with no oxidation of alcohol (**Figure 1.6.3b**).

Mechanistic studies were performed in order to investigate the mechanism of the reaction. Although isolation of the oxaziridinium salt (**1.121a**) was not possible due to its instability, a species consistent with it was observed on an NMR experiment. A product (**1.121b**) resulting from the known decomposition pathway of oxaziridinium species was isolated, supporting the presence of oxaziridinium salt (**1.121a**). Moreover, in the same NMR experiment, after observation of the oxaziridinium salt (**1.121a**), addition of

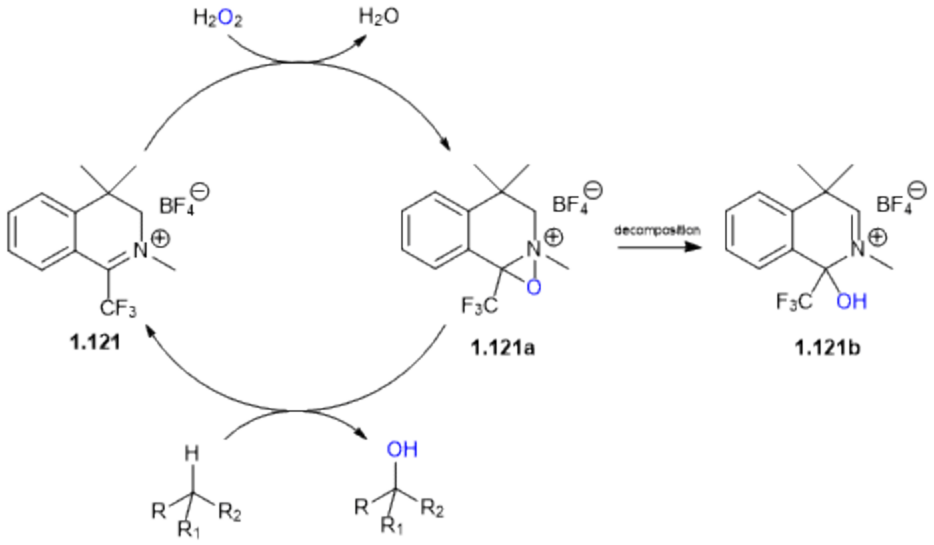


Figure 1.6.4. Mechanism of intermolecular C(sp^3)-H hydroxylation catalyzed by **1.121**

adamantane (**1.91**) to the NMR tube led to the formation of 1-adamantanol (**1.101**) with consumption of the oxaziridinium salt (**1.121a**). Thus, following mechanism was proposed (**Figure 1.6.4**). Hilinski catalyst (**1.121**) is reacted with H_2O_2, forming the oxaziridinium salt (**1.121a**). This can either decompose to **1.121b** or react with the substrate to form the desired product, reforming the catalyst (**1.121**).

Followed by the oxaziridinium-mediated C-H hydroxylation, the Hilinski group reported the first organocatalytic selective intermolecular C-H amination using the Hilinski catalyst (**1.121**).[80] The Hilinski group envisioned that the incorporation of nitrogen atom instead of oxygen atom could produce a new species, a diaziridinium salt, to transfer the nitrogen atom (**Figure 1.6.5**). For the nitrogen source, tosyliminoiodinane (PhINTs) was used as it is a common nitrenoid precursor (**Figure 1.6.6**).[81]

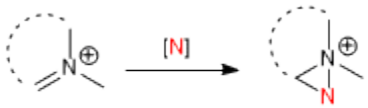
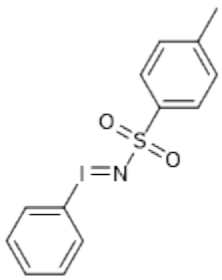


Figure 1.6.5. Diaziridinium salt



1.127

Figure 1.6.6. Tosyl iminoiodinane (PhINTs)

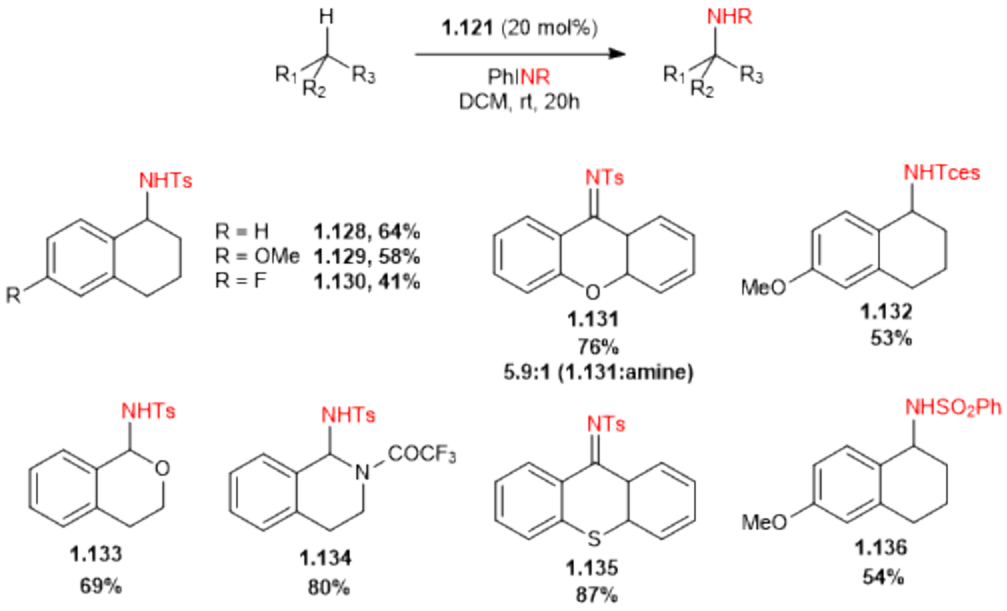
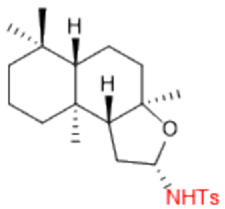


Figure 1.6.7. Intermolecular C(sp^3)-H amination catalyzed by **1.121**

The amination of benzylic C-H bonds in the presence of both electron withdrawing (**1.130**) and donating groups (**1.129**) were well tolerated. For the highly activated substrates only the overoxidation product (imine) was observed (**Figure 1.6.7**, **1.131, 1.135**). The amination of substrates with neighboring heteroatoms also proceeded well with high selectivity for electron-rich positions (**Figure 1.6.7**, **1.133, 1.134**). Nitrene precursors bearing different protecting groups were also tolerated, such as trichloroethylsulfonyl-iminoiodinane (PhINTces) and benzenesulfonyl-iminoiodinane (PhINSO$_2$Ph) (**Figure 1.6.7**, **1.132, 1.136**). In order to test the applicability of the iminium salt catalyst to the late-stage C-H amination, more complex molecules were investigated as well. The amination of ambroxide demonstrated site selectivity where ethereal secondary C-H bond was aminated producing 47% of the corresponding product (**1.137**) (**Figure 1.6.8**).



1.137
47%
dr = 1.5:1

Figure 1.6.8. Site selectivity of iminium salt catalyst **1.121**

In order to investigate the mechanism of the reaction, kinetic isotope effect (KIE) and Hammett analysis experiments were performed. A primary kinetic isotope effect of k_h/k_d = 2.5 was observed, suggesting that the C-H cleavage is occurring during the product-determining step. In comparison to the metal-catalyzed C-H amination, it was most in agreement with concerted mechanism. Hammett analysis experiment suggested that radical intermediates are unlikely to be involved. The mass of the diaziridinium salt was observable by LC-MS, supporting the formation of the diaziridinium intermediate (**1.121c**) (**Figure 1.6.9**).

1.121c

m/z = 411
observable by ESI-MS

Figure 1.6.9. LC-MS evidence in support of diaziridinium intermediate **1.121c**

Recently, the Hilinski group reported iminium salt catalyzed olefin aziridination.[82] Using Hilinski catalyst (**1.121**) and PhINTs (**1.127**), various styrene provided the corresponding aziridines in moderate to good yields. During the investigation, side products were seen which revealed key insights into the mechanism of the reaction. For example, reactions with both *trans*- and *cis*-*β*-methylstyrene (**1.138**, **1.139**) produced only the *trans*-aziridine product (**1.139**) (**Figure 1.6.10**). Due to the observed stereospecificity, the initial hypothesis suggested the presence of either a radical or a carbocation

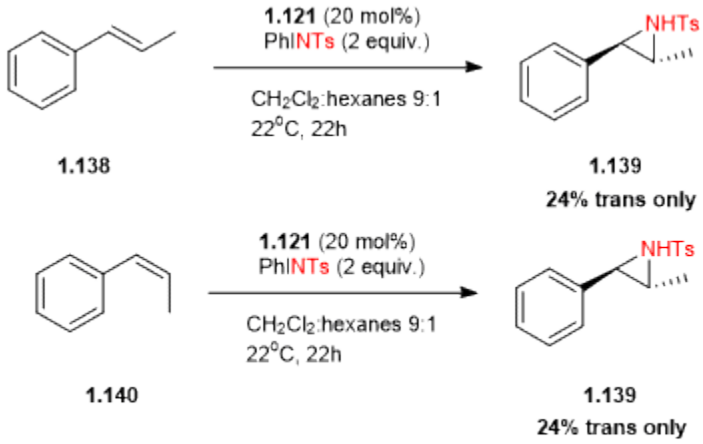


Figure 1.6.10. Stereospecificity observation

intermediate or a thermodynamically controlled reaction. By introducing cis-aziridine (**1.141**) to the reaction conditions, it was found that the reaction was under kinetic control

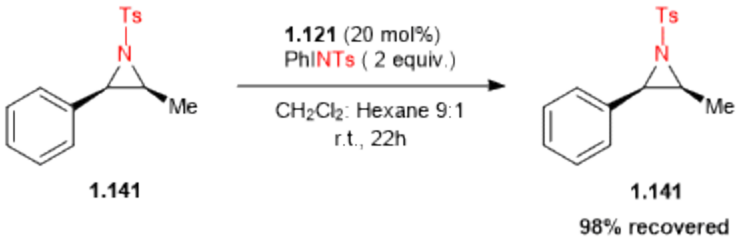


Figure 1.6.11. Kinetically controlled reaction

(**Figure 1.6.11**). In an experiment with trans-stilbene (**1.88**), *N*-tosyl enamine (**1.142**) was observed as the major product. This 1,2-rearrangement product (**1.142**) further supported the presence of either a radical or a carbocation (**Figure 1.6.12**). For styrene (**1.143**)

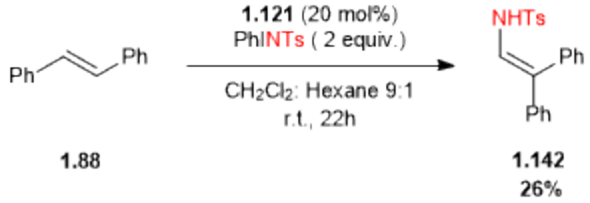


Figure 1.6.12. 1,2-rearrangement

aziridination, trace amounts of an imine byproduct (**1.145**) was observed along with the anticipated aziridine (**1.144**) (**Figure 1.6.13a**). It was hypothesized that the imine byproduct (**1.145**) may arise from the oxidative cleavage of the olefin. In order to confirm the hypothesis, *β*-cyclohexylstyrene (**1.146**) was subjected to the reaction conditions, and

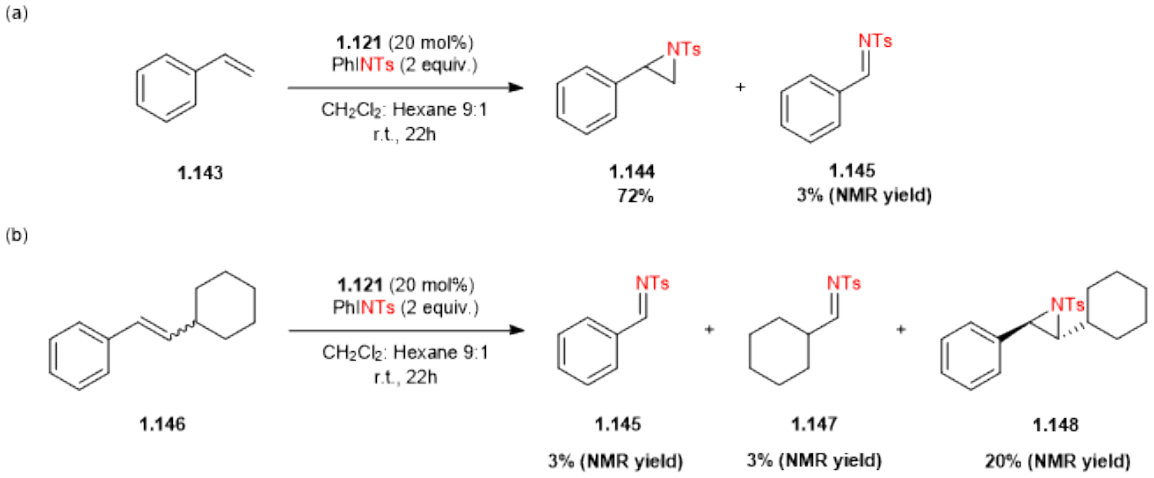


Figure 1.6.13. Oxidative cleavage of C-C bond

produced the expected imine byproducts (**1.145**, **1.147**) along with the aziridine (**1.148**) (**Figure 1.6.13b**).

The possibility of a radical mechanism was investigated by introducing radical inhibitors such as BHT and TEMPO to the reaction conditions. The inhibitors had no effect on the yield of products, providing evidence against the formation of long-lived free radicals. Thus, the following mechanism was proposed (**Figure 1.6.14**). Followed by the addition of PhINTs to the catalyst, a diaziridinium salt (**1.121c**) is formed following nucleophilic addition to the catalyst. The highly electrophilic diaziridinium salt (**1.121c**) then reacts with the olefin according to Markovnikov rules, producing the carbocation intermediate (**1.121d**). With the formation of the carbocation, three pathways are possible. Via path A, an aziridine can be formed from the ring closure. 1,2-rearrangement can happen via path B, and produce 1.142. Lastly via path C, following the nucleophilic attack of the second equivalence of iminoiodinane, **1.121e** can form, and oxidative cleavage of olefins can occur to produce the imine byproducts. This report not only broadened the potential of Hilinski catalyst (**1.121**) but also provided insights on the nature of diaziridinium salt chemistry.

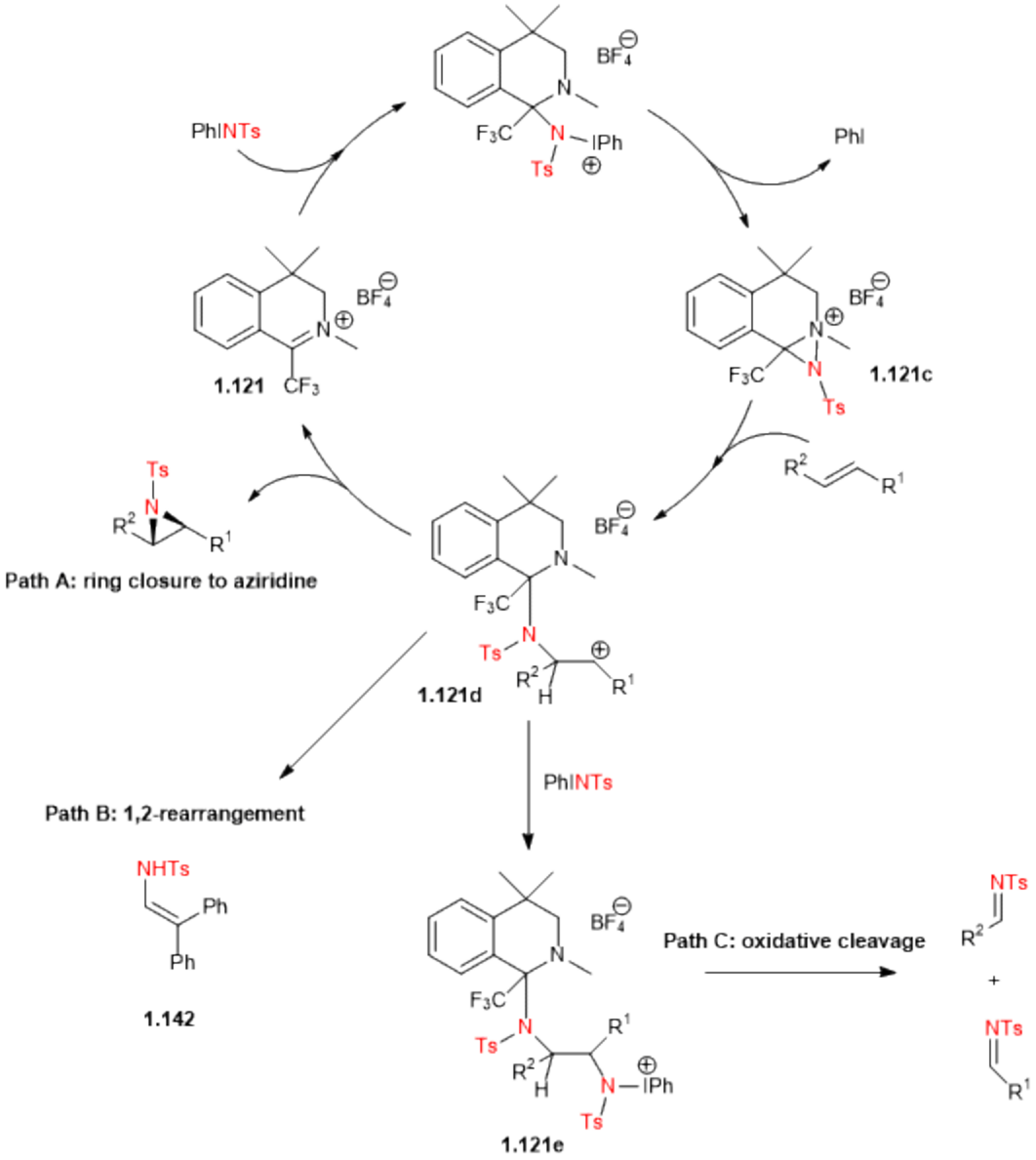


Figure 1.6.14. Proposed mechanism for aziridination

1.4 Conclusion

Much like the transition metal-catalyzed C-H amination, organocatalysis has been developed as well for related transformations. From dioxiranes to oxaziridinium salts, development of three-membered heterocycles as catalytic intermediates for oxygen-transfer reactions has shown remarkable advancements. However, in comparison, nitrogen-transfer reactions still remain underdeveloped. There still exist unanswered questions related to the scope of reactivity that might be achieved, which will be informed by a greater understanding of mechanism. Therefore, further investigations of organocatalytic C-H amination will be a critical new step with the potential to enable novel insights into this recently uncovered reactivity.

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Chapter. II: Flavinium Salt Catalyzed C(sp^3)-H Amination

2.1 Flavinium Salts as Catalysts for Atom-Transfer Reactions

Following the development and investigation of the Hilinski iminium salt catalyst (**1.121**) in C-H hydroxylation and C-H amination, we wanted to further investigate the potential of this catalytic system. In this system, the intermediates, oxaziridinium salt (**1.121a**) and diaziridinium salt (**1.121c**), are proposed to be the active oxidants engaging in atom-transfer reactions (**Figure 2.1.1**). As mentioned in the previous chapter,

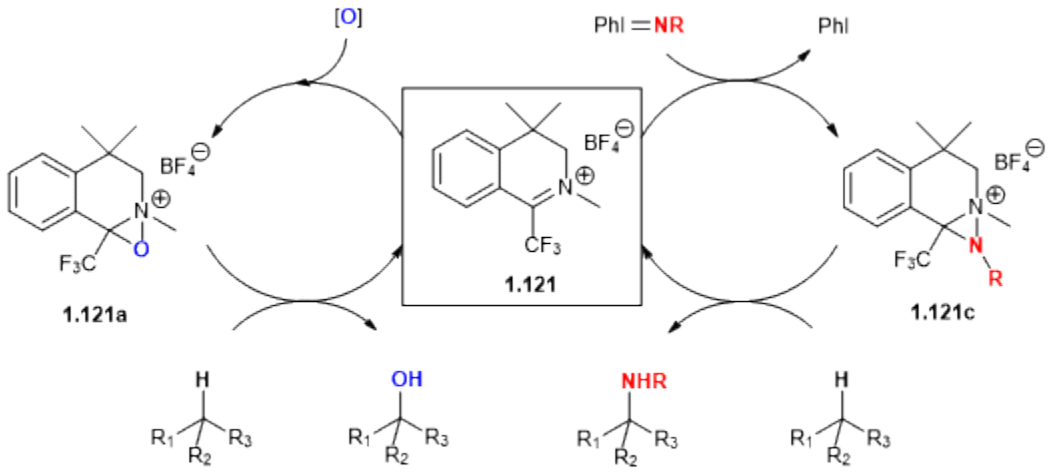


Figure 2.1.1. Catalytic cycle of Hilinski catalyst in atom-transfer reactions

oxaziridinium salts have been researched in epoxidation and C-H hydroxylation chemistries. However, iminium salt-catalyzed C-H hydroxylation by Hilinski group is the only report that has examined the reactivity of oxaziridinium salts in C-H hydroxylation. Similarly, the use of diaziridinium salts as oxidants in atom-transfer reactions is underdeveloped, with the exceptions of a report of synthesis and characterization published by Lambert in 2014[1] and iminium salt-catalyzed C-H amination by the Hilinski group.[2] Therefore, we envisioned to develop a new catalyst with a similar scaffold as the Hilinski catalyst for atom-transfer reactions in order to gain insights into oxaziridinium and diaziridinium intermediates.

Flavins are a class of compounds formed by the tricyclic heterocycle isoalloxazine that can exist in oxidized and reduced forms (**Figure 2.1.2**). Flavins are found commonly

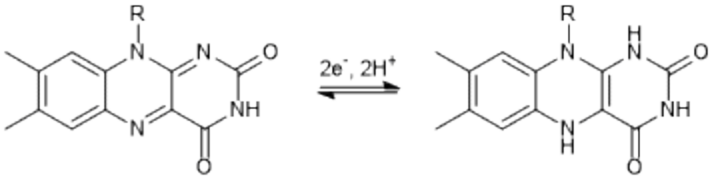


Figure 2.1.2. Equilibrium between the oxidized and reduced forms of flavin group

in nature as cofactors of various enzymatic redox processes. Flavin mononucleotide (FMN) (**2.1**) and flavin adenine dinucleotide (FAD) (**2.2**) are the two common flavin cofactors (**Figure 2.1.3**). These cofactors are commonly used by nature for oxidations and electron

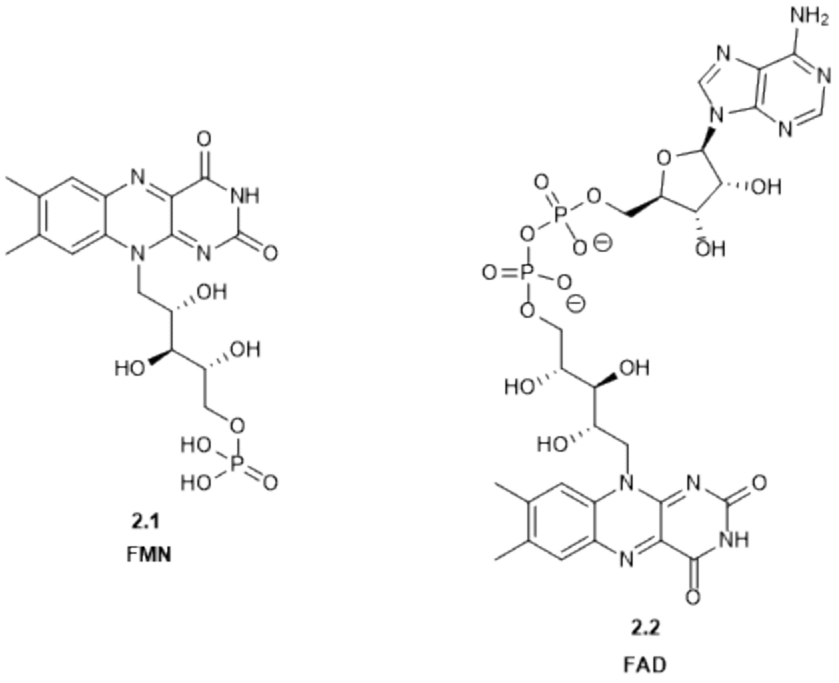


Figure 2.1.3. FMN and FAD

transfer reactions, such as hydroxylation,[3] epoxidaiton,[3] halogenation,[3] monooxygenation,[4,5] dehydrogenation,[4,5,6] thiol oxidaiton,[6] and oxygen activation.[4,5,6] Previous reports catalyzed by flavins and flavinium salts mostly involve the utilization of the redox chemistry to perform various oxidations, such as dakin oxidation,[7] photo-

activated cleavage of C-C bonds,[8] Baeyer-Villiger oxidation,[9] and sulfoxidation,[10] but no reports of C-H functionalization were seen (**Figure 2.1.4**).

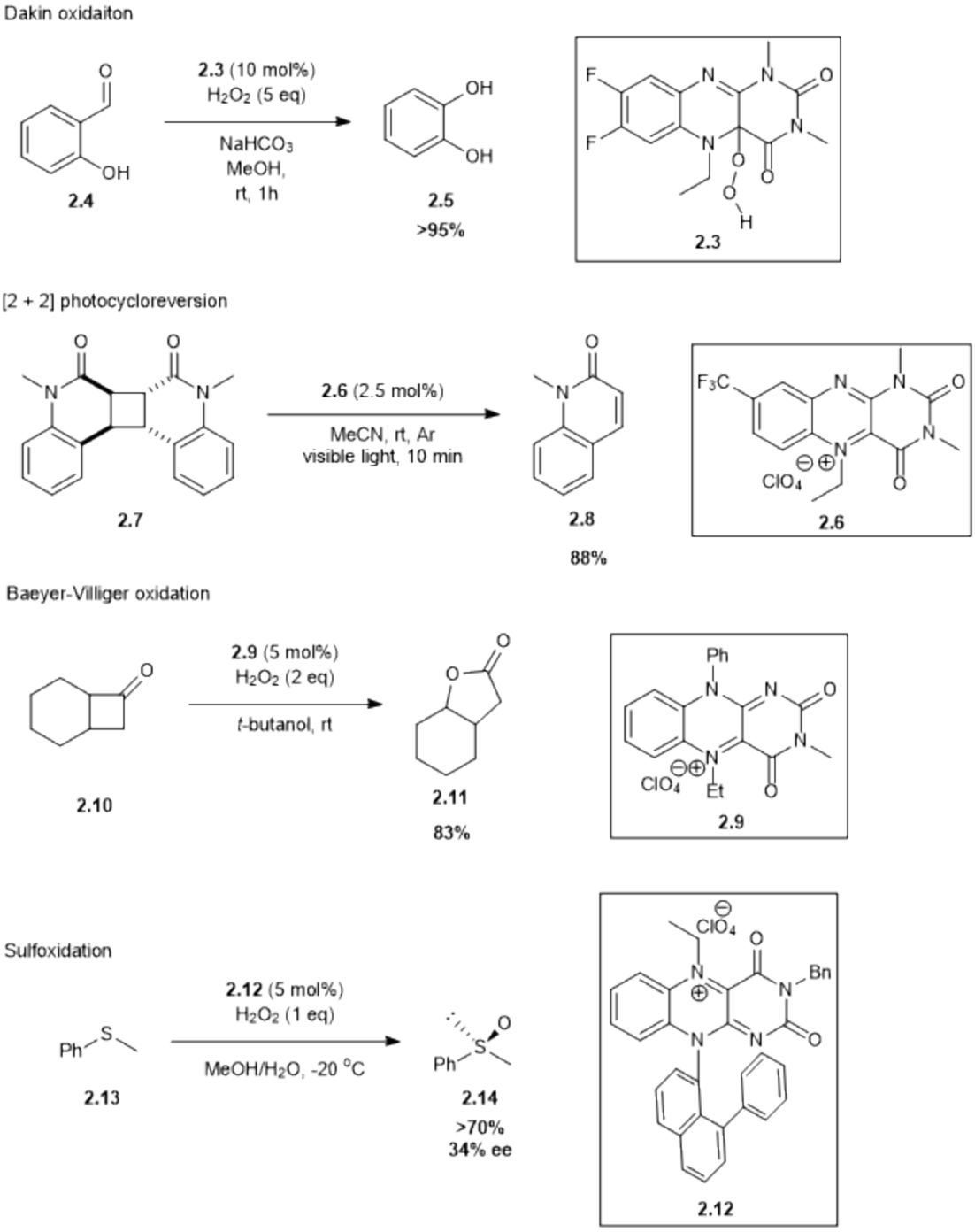


Figure 2.1.4. Flavin/flavinium salt catalyzed oxidation reactions

We envisioned of introducing the Hilinski catalytic system to the flavins as the flavins exhibited structural similarities to the iminium salt nitrogen atom (**Figure 2.1.5**).

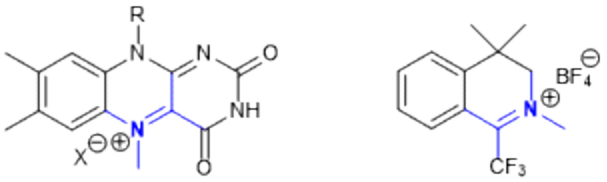


Figure 2.1.5. Structural similarity between flavinium salt and Hilinski catalyst **1.121**

As mentioned in the previous chapter, the installation of the trifluoromethyl group increased the reactivity of the Hilinski catalyst. Instead of the electron withdrawing group, flavins have an extensive aromaticity which could become the key driving force of the reaction. When the nitrogen atom is incorporated into the flavins, this aromaticity is broken. Thus, the reactivity of the formed intermediate would be driven by the catalyst's ability to restore the aromaticity. We hypothesized that the flavinium salt (2**.15**) would behave similarly to the Hilinski catalyst by forming the proposed intermediates, oxaziridinium and diaziridinium salts (**2.15a**, **2.15b**) (**Figure 2.1.6**). We envisioned that by investigating the flavinium salts in the iminium salt catalytic system, we could develop a new class of C-H functionalization catalysts, giving us an alternative scaffold that could be useful for manipulating stereoselectivity and chemoselectivity.

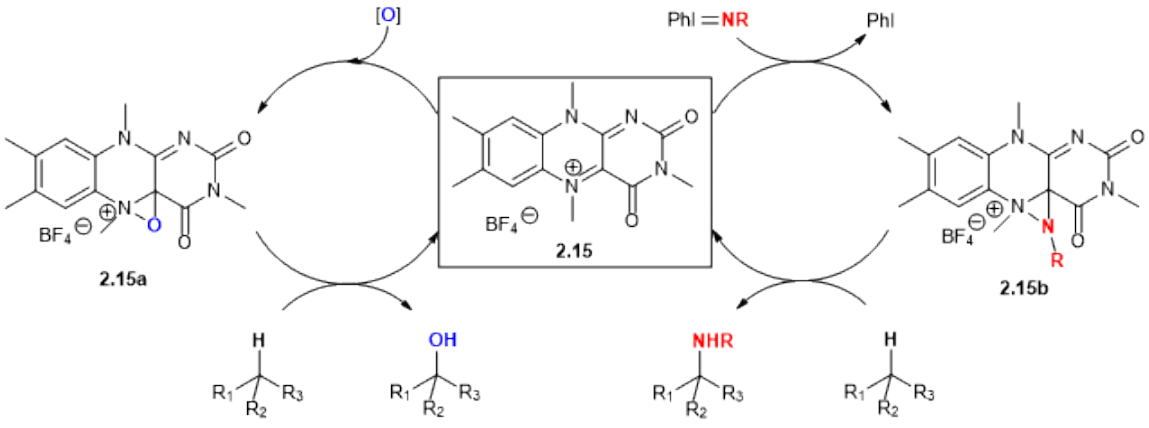


Figure 2.1.6. Proposed catalytic cycle of flavinium salt catalyzed atom-transfer reactions

2.2 Synthesis of Flavinium Tetrafluoroborate Salt

We first synthesized flavinium tetrafluoroborate salt (2**.15**) as the catalyst (**Figure 2.2.1**). Reductive amination of 2**.16** produced 97% of 2**.17**. sReduction of 2**.17** using palladium on carbon produced 90% of 2**.18**. Annulation of 2**.18** with alloxan monohydrate produced 40% of 2**.19**. Amine alkylation of **2.19** using iodomethane produced 38% of **2.20**. Finally, *N*-alkylation of **2.20** using Meerwein's salt produced 48% of **2.15**.

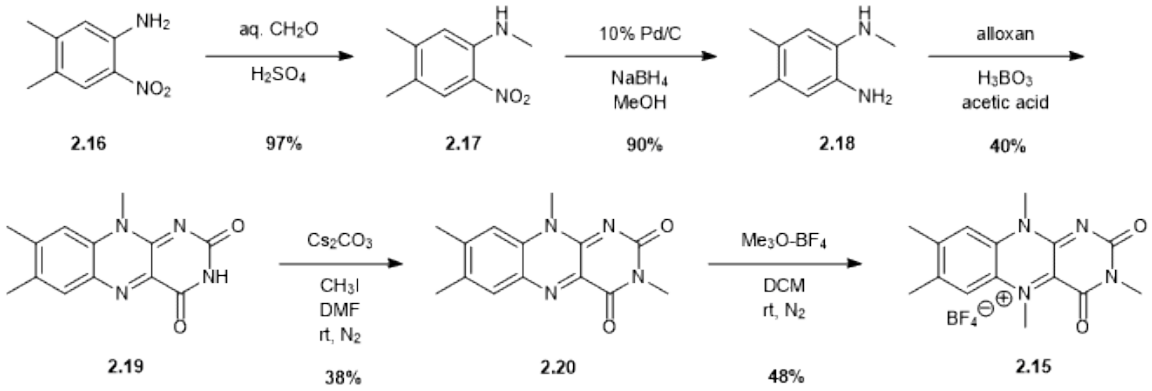


Figure 2.2.1. Synthesis scheme of flavinium tetrafluoroborate salt **2.15**

2.3 Investigation of Flavinium-Promoted *O*-Atom Transfer Reactions

Initial investigation of the flavinium salt (**2.15**) as a catalyst started with C-H hydroxylation. Various activated substrates were reacted with **2.15** using H_2O_2 or MCPBA as the terminal oxidant, but no hydroxylation products were observed, even at elevated temperatures (**Figure 2.3.1**). Since the Hilinski catalyst (**1.121**) is also capable of

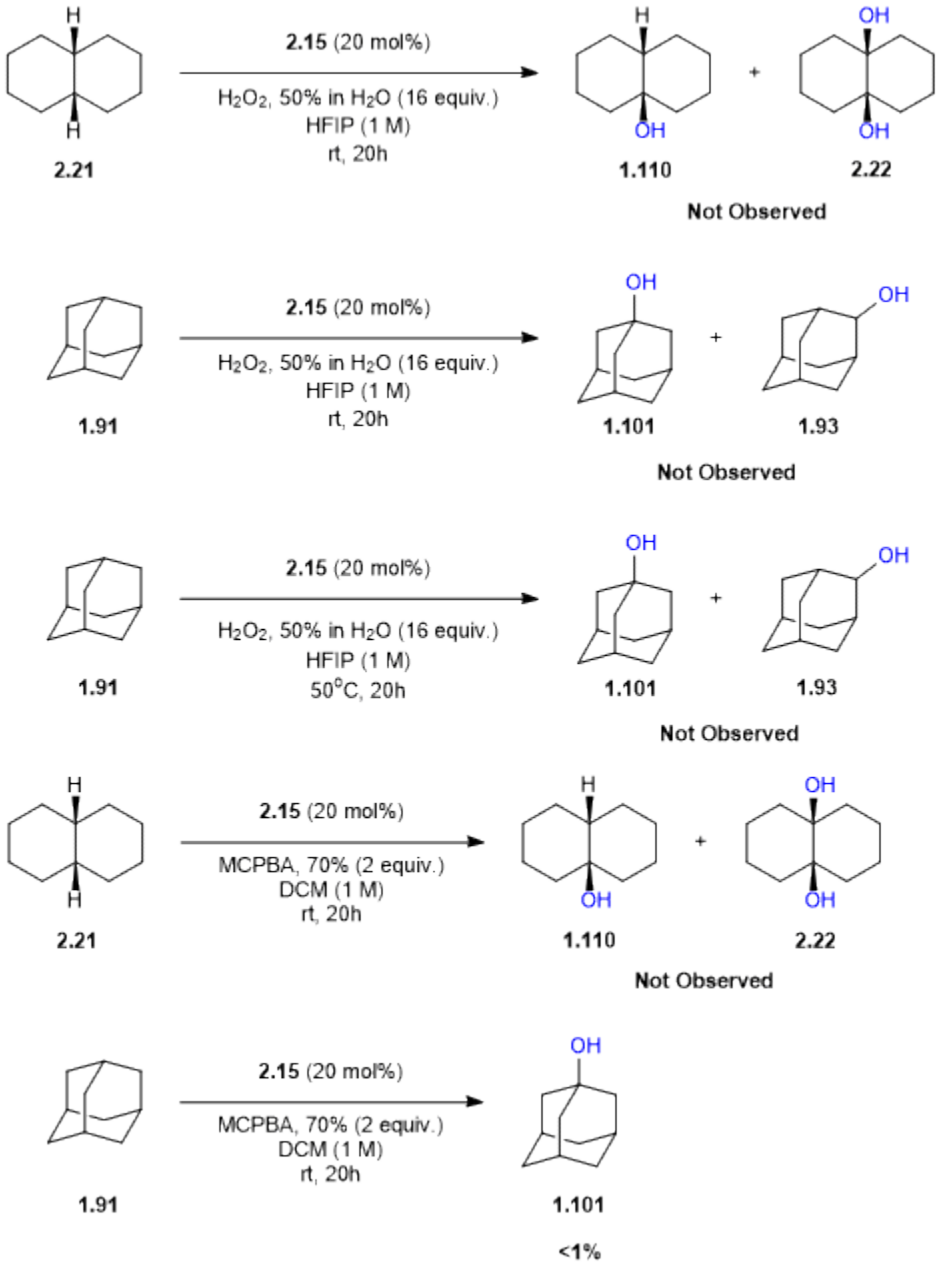


Figure 2.3.1. Initial investigation of flavinium salt **2.15** catalyzed C-H hydroxylation

performing epoxidation, we proceeded to examine this as well. Unfortunately, epoxidation

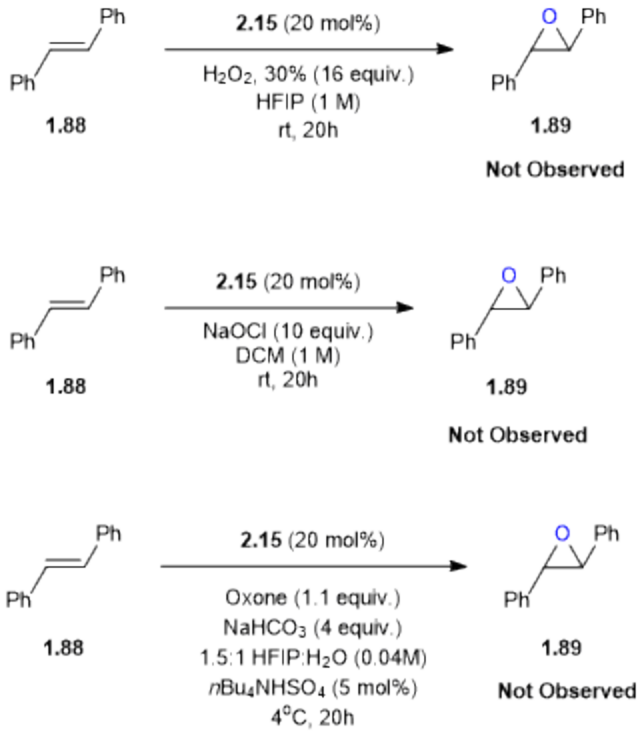


Figure 2.3.2. epoxidation catalyzed by flavinium salt **2.15**

of trans-stilbene (**1.88**) with 2**.15** did not produce the desired product (**Figure 2.3.2**). Initially, we hypothesized that the oxaziridinium intermediate (**2.15a)** is not forming, halting the reaction. As a control experiment, we evaluated the capability of **2.15** to catalyze the oxidation of benzaldehyde (**2.24**) by H_2O_2. In 2012, Murray reported a flavinium salt-catalyzed aryl aldehyde oxidation using H_2O_2 as the terminal oxidant.[11] Murray proposed that the formed hydroperoxy species of the catalyst will attack the aldehyde (**2.24**). After cleavage of the weak oxygen-oxygen bond, the final product is produced (**Figure 2.3.3**). Using similar reaction conditions, we observed 28% of the desired product (**Figure 2.3.4a**). This suggests that 2**.15** is forming the hydroperoxy species (**2.26**), but might be unable to form the oxaziridinium salt (**2.15a**), which is the proposed key intermediate for C-H hydroxylation (**Figure 2.3.4b**).

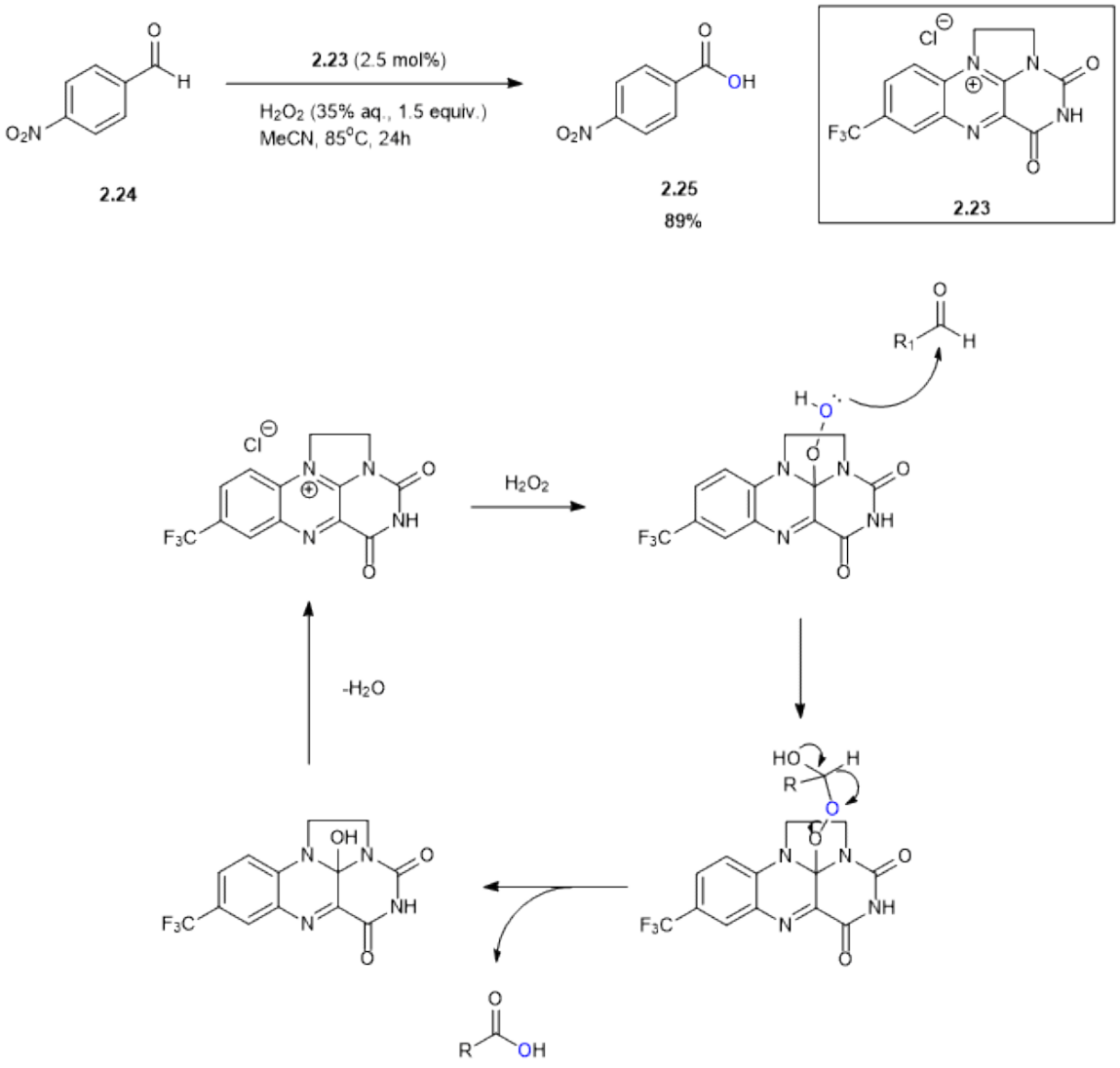


Figure 2.3.3. Murray's flavin-catalyzed aldehyde oxidation and its proposed mechanism

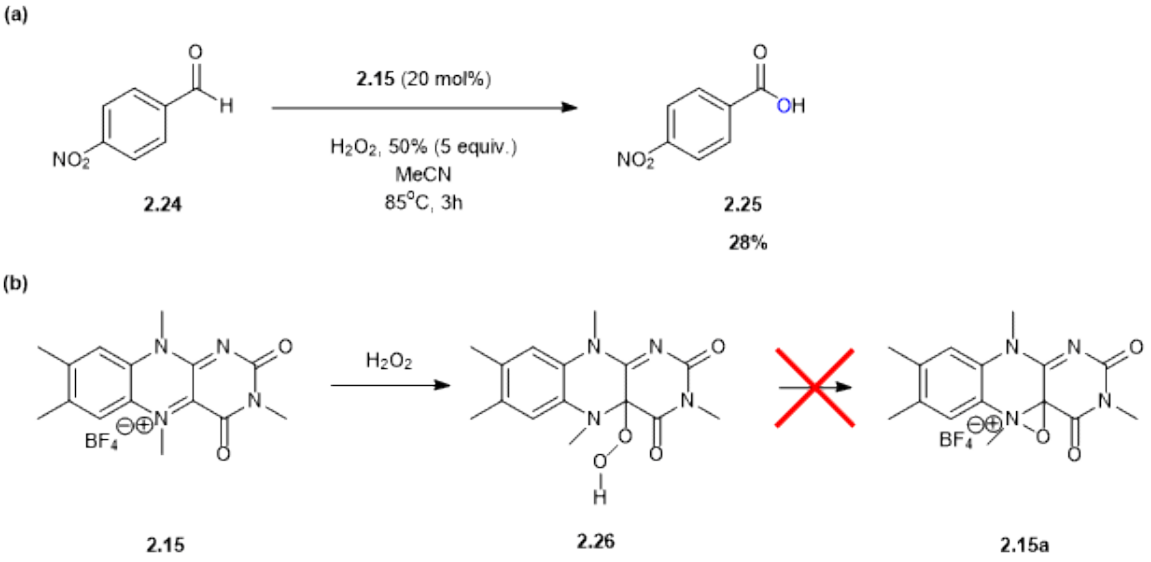


Figure 2.3.4. Aldehyde oxidation investigation using **2.15**

2.4 Investigation of Flavinium-Promoted *N*-Atom Transfer Reactions

Followed by the investigation on *O*-atom transfer reactions, we investigated *N*-atom transfer reactions as well. Using the conditions from the previously reported iminium salt catalyzed aziridination reactions,[12] **2.15** was able to produce 26% of the desired product (**1.144**) (**Figure 2.4.1**). Trace amounts of the imine byproduct (**1.145**) were observed as

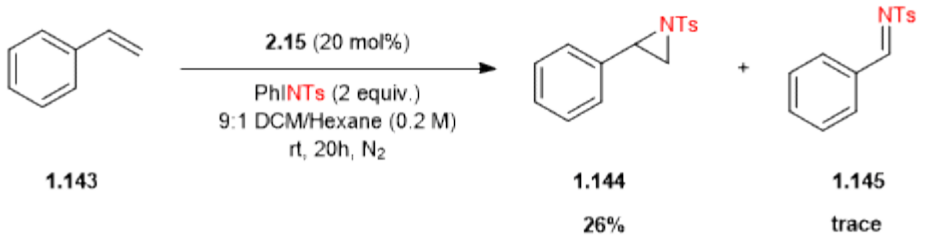


Figure 2.4.1. Aziridination of stilbene with **2.15**

well. These byproducts, which were also seen in the case of iminium salt-catalyzed aziridination, suggest that the mechanism of action might be similar to that class of catalysts, which are proposed to proceed through benzylic cation intermediates.

As mentioned previously, the iminium salt is also capable of catalyzing C-H amination of substrates such as tetralin (**2.27**). The reaction is proposed to proceed via a

diaziridinium salt (**2.15b**) as the active oxidant. In order to evaluate whether flavinium salt (**2.15**) is capable of catalyzing the same reaction, we attempted amination of tetralin (**2.27**) with PhINTs. No products of C–H amination were observed. Amination of substantially more reactive substrates (e.g. adamantane, xanthene) was observed, however at the extended reaction times that were required a non-trivial un-catalyzed background reaction was observed, which complicated the isolation of any catalyst-specific effects.

To address this, another iminoiodinane, PhINTces, which exhibits no uncatalyzed background reaction, was investigated as a potential nitrene precursor. The Hilinski catalyst (**1.121**) was capable of performing C-H amination by PhINTces as well but with limited substrate scope.[2] Initial experiments with tetralin (**2.27**) as the substrate showed no reactivity (**Figure 2.4.2a**). A more electron-rich substrate, *p*-methoxy-tetralin (2**.28**), was selected since the substrate showed the least amount of background activity with the most amount of catalyzed activity. Under the conditions shown, we were able to observe 9% of the desired product (**1.129**) (**Figure 2.4.2b**). By increasing the catalyst loading to 20 mol%,

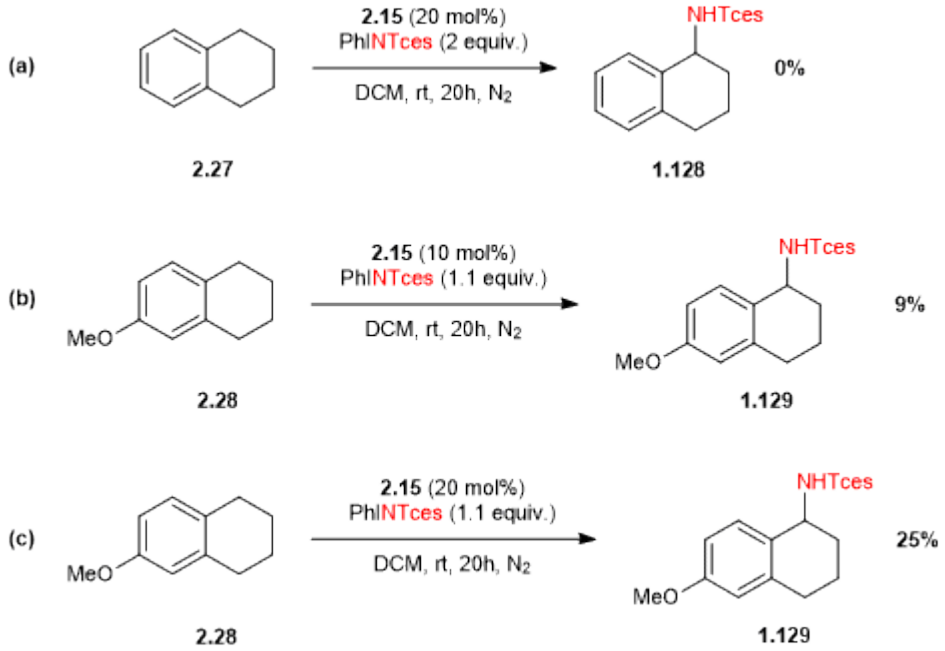
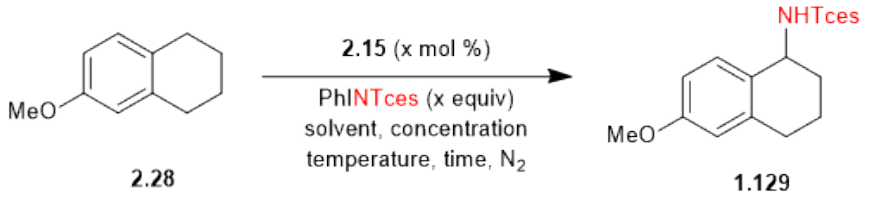


Figure 2.4.2. Initial investigation of flavinium salt **2.15**

we observed 25% of the desired product (**1.129**) (**Figure 2.4.2c)**. From here, we optimized the reaction conditions by examining each reaction parameter; reaction parameters included catalyst loading, equivalence of the iminoiodinane, solvent, concentration, temperature, and reaction time.

2.5 Optimization of Reaction Conditions

Table 1. Optimization of reaction conditions[a]



2.28 **1.129**

	2.15 loading (mol %)	PhINTces (equiv)	Solvent	Concentration (M)	Temperature (°C)	Time (h)	Yield (%)	RSM (%)
1	20	2	DCM	0.25	rt	20	4%	69%
2	0	1.1	DCM	0.25	rt	20	0%	95%
3	5	1.1	DCM	0.25	rt	20	0%	77%
4	30	1.1	DCM	0.25	rt	20	40%	32%
5	100	1.1	DCM	0.25	rt	20	36%	24%
6	30	2	DCM	0.25	rt	20	13%	79%
7	30	1.1	DCE	0.25	rt	20	8%	60%
8	30	1.1	C_6H_6	0.25	rt	20	0%	86%
9	30	1.1	$CHCl_3$	0.25	rt	20	0%	76%
10	30	1.1	DCM	0.025	rt	20	25%	31%
11	30	1.1	DCM	0.4	rt	20	34%	31%
12	30	1.1	DCM	0.25	0	20	0%	92%
13	30	1.1	DCM	0.25	40	20	38%	40%
14	30	2	DCM	0.25	40	20	40%	0%
15	30	1.1	DCE	0.25	80	20	16%	22%
16	30	1.1	DCM	0.25	rt	5	0%	99%
17	30	1.1	DCM	0.25	rt	10	5%	86%
18	30	1.1	DCM	0.25	rt	40	38%	0%

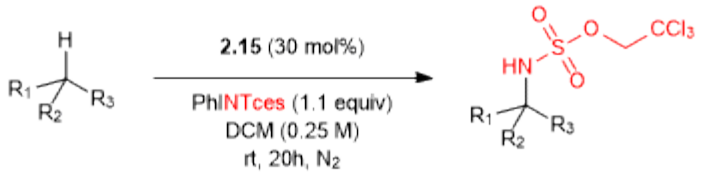
[a]0.1 mmol scale

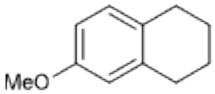
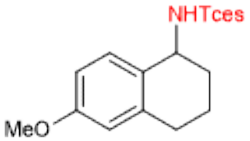
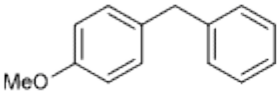
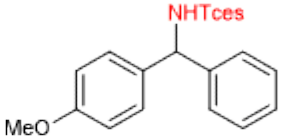
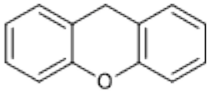
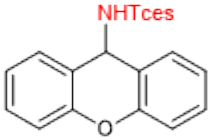
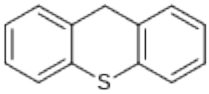
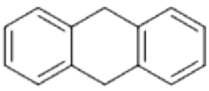
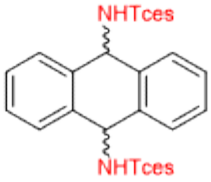
The optimized conditions resulted in 40% yield of **1.129** (**Table 1**, Entry 4). Increase in the catalyst loading to 30 mol% showed an increase in the yield, but more than 30 mol% showed no change in the yield (Entries 5). Decreased reactivity was observed

when solvents other than dichloromethane were used (Entries 7-9), which was also observed for the iminium salt catalyst. Decreasing the concentration of the reaction mixture slightly decreased the reactivity whereas increasing the concentration resulted in no change (Entries 10-11). Decreasing the reaction temperature resulted in a total shutdown of the reaction (Entry 12). An increase in the reaction temperature to 40 ^{o}C did not increase the product yield (Entry 13). When 2 equivalences of iminoiodinane was added to 40 ^{o}C condition, decomposition of remaining starting material was seen, and the product yield did not show a difference (Entry 14). When the temperature was further increased to 80 ^{o}C, decrease in the product yield was seen along with some decomposition of the remaining starting material (Entry 15). While investigating the scope of the reaction, we discovered that reactions with more reactive substrate such as xanthene (**2.31**) finished in 3 hours, producing 78% of the corresponding amine product (**2.32**). In order to investigate whether this applies to all substrates, the reaction was stopped at 5 and 10 hours. Incomplete reaction was observed (Entries 16-17). Increasing the reaction time to 40 hours resulted in decomposition of the remaining starting material without affecting the product yield (Entry 18). With the optimized conditions in hand, we next sought to examine the substrate scope of the reaction.

2.6 Scope of C-H amination

Table 2.: Scope of benzylic C-H amination



entry	substrates	products (yield[a])
1	 **2.28**	 **1.129**: 38%
2	 **2.29**	 **2.30**: 31%
3[b]	 **2.31**	 **2.32**: 78%
4	 **2.33**	 **2.34**: 50%
5	 **2.35**	 **2.36:** 20% dr = 1:1

[a] Isolated yield. [b]reaction was done after 3.3h.

Our substrate scope exploration revealed the capability of flavinium-catalyzed C(sp^3)-H amination on a variety of substrates. Benzylic C(sp^3)-H amination of substrates with electron donating substituents (**2.28**,**2.29)** proceeded well, yielding 38% (**1.129**) and 31% (**2.30**) (**Table 2**, Entry 1-2). Amination of xanthene (**2.31**) and thioxanthene (**2.33**) yielded 78% of **2.32** and 50% of **2.34 (Table 2**, Entry 3-4**)**. Interestingly, substrate **2.35** produced two diaminated diastereomer products (**2.36**), which was not observed for the similar reaction with the Hilinski catalyst.[2] The presence of diastereomers were confirmed by HRMS, which showed that the two isolated products had almost equal mass to charge ratio of 628.8511 and 628.8512. However, the characterization of each diastereomer was not possible using only the NMR data.

Some substrates failed to produce any products (**Figure 2.6.1**). Attempted amination of adamantane (**1.91**) using the flavinium catalyst (**2.15**) was unsuccessful, suggesting that the substrate scope is in this case limited to benzylic C-H bonds. Amination of unsubstituted substrates such as **2.27** and **2.37** was unsuccessful. Amination of substrates with electron withdrawing groups, **2.38**, **2.39**, and **2.41**, was unsuccessful as well. Interestingly, amination of isochroman (**2.40**) was unsuccessful, suggesting that benzylic ethereal C-H bonds are unreactive. Overall, the scope of the amination by the flavinium catalyst (**2.15**) is heavily limited to electron-rich benzylic C-H bonds. Heavy preferences for delocalization by resonance and π donation suggest that either a carbon radical or a carbocation could be involved during the reaction since these are factors that stabilize the two species.

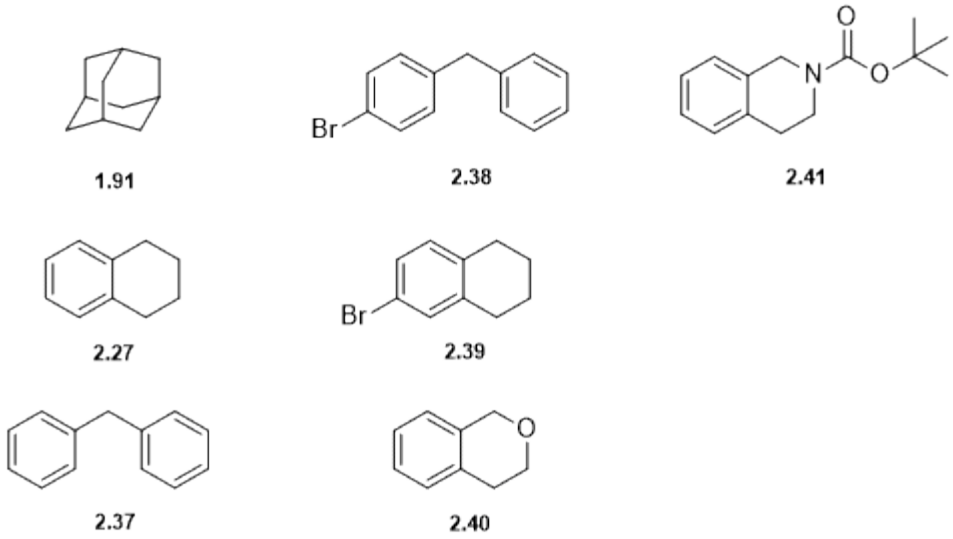


Figure 2.6.1. Unreacted substrates of the flavinium salt catalyzed condition

2.7 Further Discussion

A derivative of the flavinium salt catalyst, methoxy substituted flavinium salt, was synthesized and tested as well. We wanted to experiment whether increasing the electron density of the aromatic ring would enhance the reactivity of the catalyst. However, methoxy-substituted flavinium catalyst (**2.42**) showed a similar reactivity to the parent catalyst **2.15** producing 33% of **1.129** (**Figure 2.7.1**).

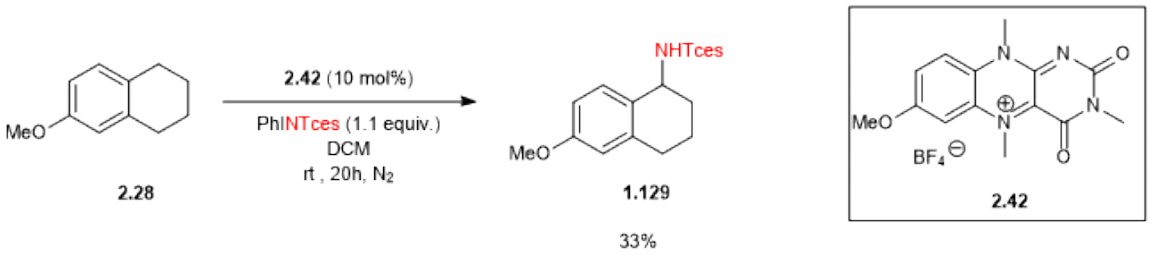


Figure 2.7.1. methoxy substituted flavinium salt investigation

In a recent study by the Hilinski group, the mechanism of C-H amination by the Hilinski catalyst (**1.121**) was investigated using quantum mechanical methods and molecular dynamics simulation (**Figure 2.7.2**).[14] In this investigation, it was found that the key intermediate responsible for C-H amination was not diaziridinium salts (**1.121c**) but long-lived biradical intermediates (**1.121f**, **1.121g**). In addition, the mechanism was

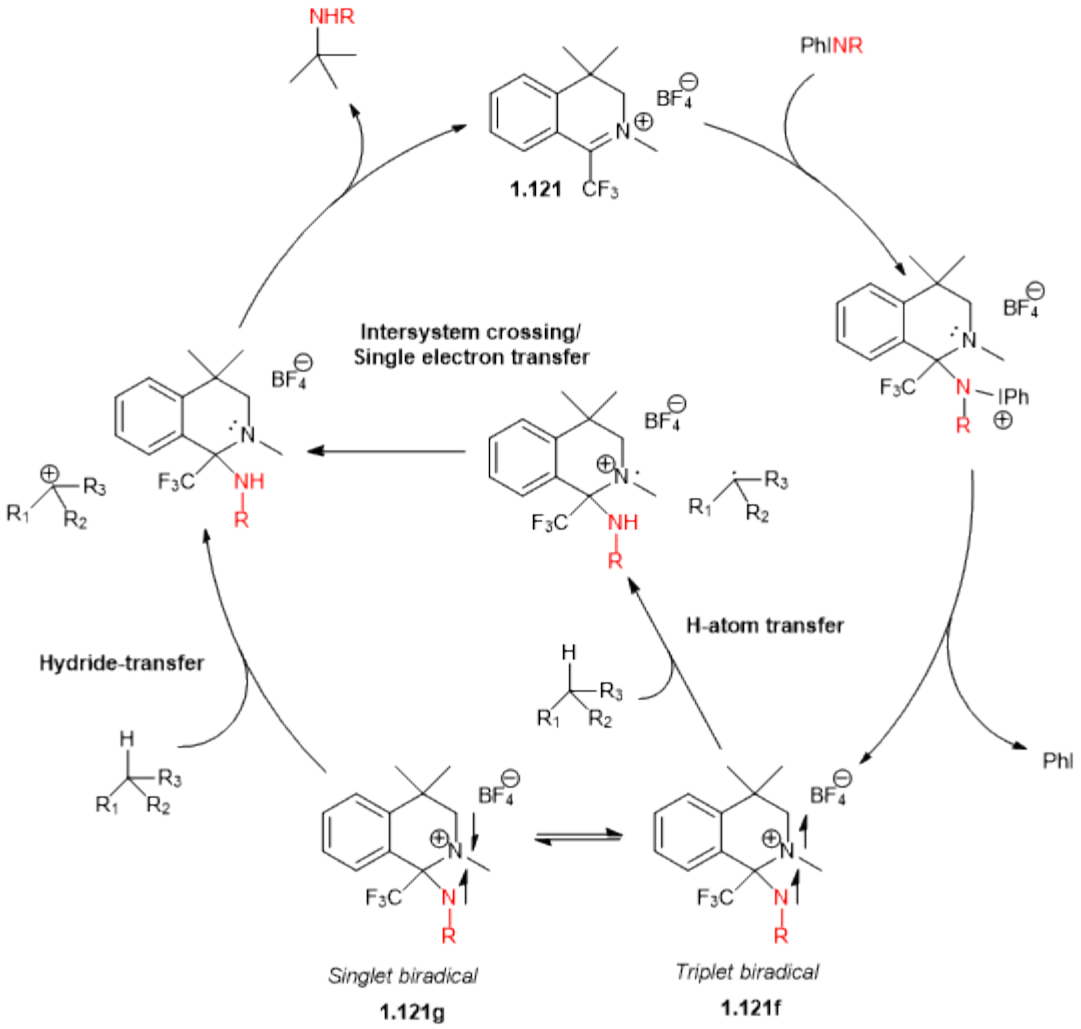


Figure 2.7.2. Recent proposal of mechanism for iminium-catalyzed C-H amination

varied by the quantum states of the biradical intermediates. When the amidyl-iminium biradical intermediate was in a triplet state (**1.121f**), regardless of the substrates, the reaction proceeded through a hydrogen atom transfer (HAT) mechanism, leading to the formation of a carbon radical. This radical then went through intersystem crossing and single electron transfer (SET) to form a carbocation, which proceeded to form products by nucleophilic addition. Alternatively, when the amidyl iminium biradical intermediate was in a single state (**1.121g**), the C-H cleavage step depended on the substrates. For unactivated substrates, such as methyl or 1°, similar to the triplet state (**1.121f**), HAT mechanism was favored. For activated substrates, such as 2°, 3°, or benzylic, both hydride

transfer and HAT mechanism were competitively in action. Since the trend of the limited scope of the flavinium catalyst (**2.15**) agrees well with that of the Hilinski catalyst (**1.121**), where substrates with substantially weakened C-H bonds are aminated successfully, we can imagine that a similar mechanism is at work for the flavinium catalyst (**2.15**) as well (**Figure 2.7.3**). After the addition of iminoiodinanes to the catalyst, the formed biradical intermediates (**2.15c**, **2.15d**) can proceed to perform C-H amination in a similar manner as the amidyl-iminium biradical intermediates (**1.121f**, **1.121g**). The

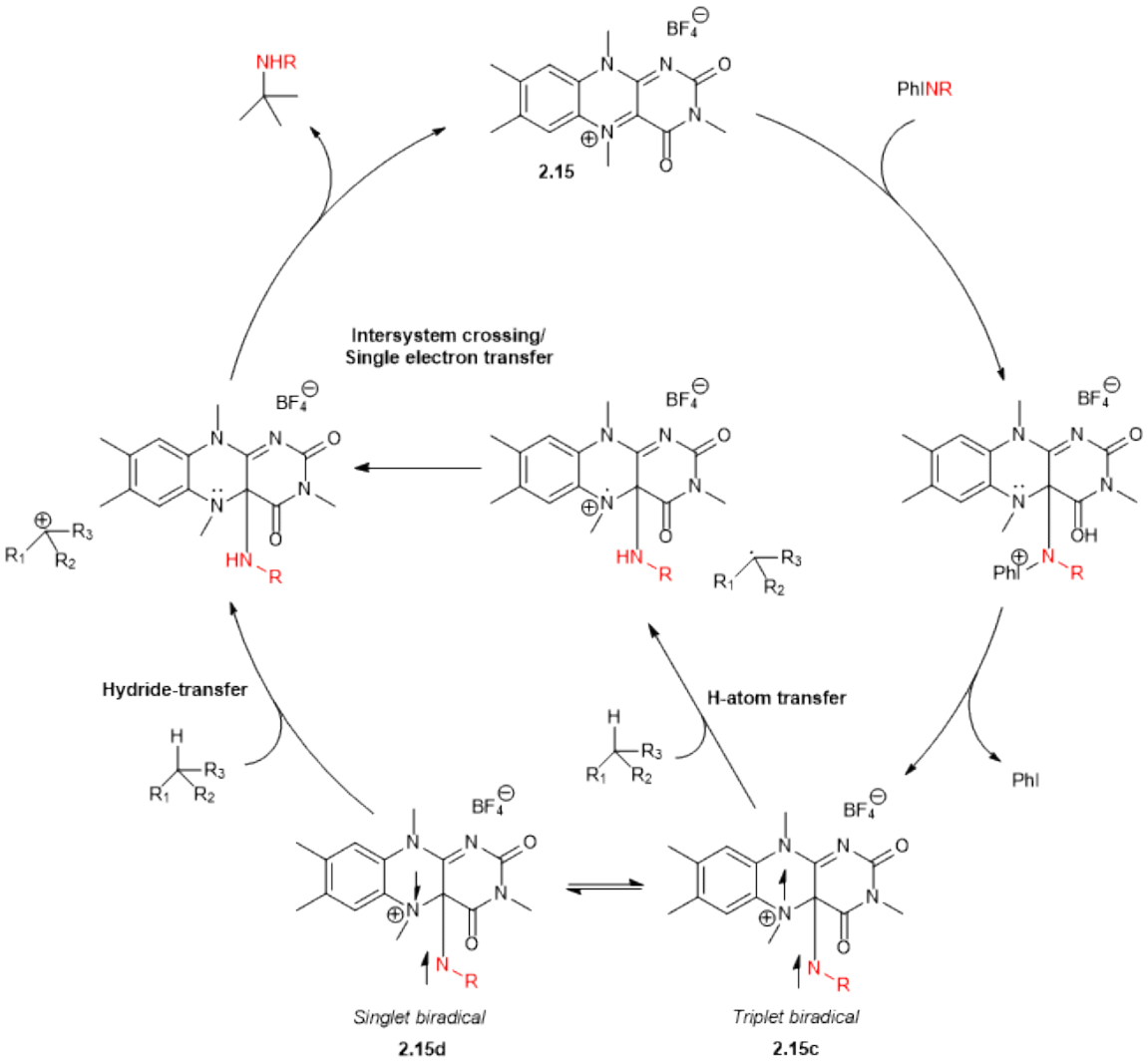


Figure 2.7.3. Proposed mechanism for C-H amination by **2.15**

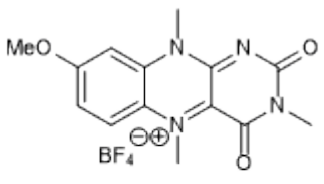
differences in inherent characteristics of the two catalysts can explain the observed dissimilarities in selectivity and reactivity.

2.8 Conclusion

In summary, we reported the first demonstration of flavinium salts as catalysts for intermolecular C(sp^3)-H amination. The method utilizes PhINTces as the nitrogen source for amination of substrates with electron-rich benzylic C-H bonds at room temperature. Although the scope is limited to highly activated substrates, the trend of the limited scope is mostly in agreement to the scope of the previously reported iminium-salt catalyzed C-H amination, indicating that the mechanism of action could be analogous.[2] Overall, this report offers an alternative catalyst for C-H amination, potentially guiding to further development of new catalysts with a similar scaffold.

2.9 Future Work

To further investigate the flavinium catalyst in C-H amination, the design of the catalyst could be explored more. The low reactivity of the catalyst limited the investigation to benzylic substrates only. As the flavin compounds have several places where different substituents can be installed, re-designing the catalyst to increase the reactivity would be beneficial. For example, installation of methoxy group on the C^8 atom could π donate to the reaction site, differing the reactivity. (**Figure 2.9.1**). More mechanistic studies can be explored as well to further confirm the proposed mechanism. Since only the intermolecular reaction was focused in this paper, it could be beneficial to investigate the activity of catalyst in intramolecular reactions.



2.43

Figure 2.9.1. New catalyst design

2.10 Reference

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12. Johnson, S. L.; Hilinski, M. K.; *J. Org. Chem.*, **2019**, *84*, 8589-8595.
13. See Appendix A for details
14. Michael Hilinski, personal communication

Appendix A

A.1 Methods, Reagents, and Instrumentation

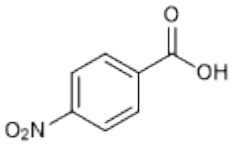
Unless otherwise noted, all substrates, reagents and solvents were obtained commercially in reagent grade or better quality and used without further purification. Anhydrous solvents were obtained from an aluminum oxide solvent purification system. Flash column chromatography was performed using silica gel (230 - 400 mesh) purchased from Silicycle. Elution of compounds was monitored by UV or PMA stain. ^{1} H and ^{13}C NMR spectra were measured on a Varian NMR (600 MHz) spectrometer and acquired at 300 K. Chemical shifts are reported in parts per million (ppm δ) referenced to the residual ^{1} H or ^{13}C resonance of the solvent. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet and br - broad. ^{1}H NMR yield analysis was performed using a Varian NMRs 600 (600 MHz) using methyl 3-nitrobenzoate as an internal standard. HRMS data were obtained from the School of Chemical Sciences Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign using Water Q-TOF ESI spectrometers.

A.2 Methods and Characterization for Flavinium Salt Catalyzed Aldehyde Oxidation

Hydrogen peroxide solution (85.2 μL, 1.5 mmol, 5 equiv., 50% w/w) was added to a mixture of 4-nitrobenzaldehyde **2.24** (0.3 mmol) and catalyst **2.15** (22.3 mg, 0.06 mmol, 20 mol %) in acetonitrile (1 mL). The mixture was stirred for 23 h in a vial at 85 ^{o}C. Upon cooling, saturated aqueous $NaHCO_3$ (5 mL) was added followed by CH_2Cl_2 (5 mL). The organics were then extracted three times with CH_2Cl_2 (3 x 5mL). The combined organic

extracts were dried over $MgSO_4$ and solvent removed in vacuo. The mixture was purified on silica gel with 1% AcOH and 5% MeOH in DCM.

4-nitrobenzoic acid (2.25)



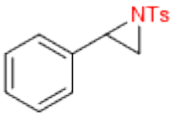
2.25

Yield: 14 mg (0.084 mmol, 28%) ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.0 Hz, 2H), 8.27 (d, *J* = 8.0 Hz, 2H) ppm. NMR spectra is consistent with literature report.[1]

A.3 Methods and Characterization for Flavinium Salt Catalyzed Aziridination

In a nitrogen glovebox, flavinium salt catalyst **2.15** (7.5 mg, 0.02 mmol, 20 mol%) and tosyl iminoiodinane (2 equiv.) was suspended in 9:1 anhydrous dichloromethane/hexane (0.5 µL, 0.2 M). Styrene (11.5 µL, 0.1 mmol) was added, and the reaction was stirred at room temperature. After 20h, the reaction was diluted with 2 mL of ethyl acetate and filtered through a short silica plug. The crude reaction mixture was concentrated on a rotary evaporator and purified on silica gel with 5-20% acetone in hexane.

2-phenyl-*N*-tosylaziridine (1.144)



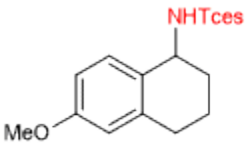
1.144

Yield: 7.1 mg (0.026 mmol, 26%) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.35−7.31 (m, 2H), 7.29 (d, J = 7.5 Hz, 3H), 7.22 (d, J = 2.1 Hz, 2H), 3.78 (dd, J = 7.2, 4.4 Hz, 1H), 2.99 (d, J = 7.2 Hz, 1H), 2.43 (s, 3H), 2.39 (d, J = 4.4 Hz, 1H) ppm. NMR spectra is consistent with literature report.[2]

A.4 Representative Procedure for flavinium catalyzed C-H amination

Unless otherwise noted, amination reactions were performed on a 0.1 mmol scale. In a nitrogen glovebox at room temperature, the substrate (0.1 mmol, 1 equiv), [N-(2,2,2-trichloroethyl)imino]phenyliodinane (47.4 mg, 0.11 mmol, 1.1 equiv) and flavinium tetrafluoroborate **2.15** (11.2 mg, 0.03 mmol, 0.3 equiv) were combined in a vial equipped with a stir bar. Anhydrous dichloromethane (0.4 mL) was then added and the reaction mixture was either left in the glovebox and stirred at room temperature for 20 hours or removed from the glovebox, place under positive pressure of nitrogen, and stirred at room temperature for 20 hours. The reaction mixture was then filtered through a silica gel plug, eluting with EtOAc. After removal of the solvent under reduced pressure, the crude reaction mixture was then purified by flash chromatography using the conditions noted.

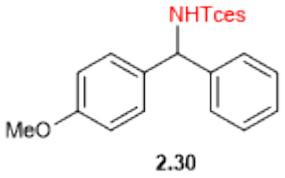
2,2,2-trichloroethyl (6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)sulfamate (1.129)



1.129

Purified on silica gel by gradient elution with 5-10% diethyl ether in hexanes. Yield: 14.77 mg (0.038 mmol, 38%) on 0.1 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, J = 8.5 Hz, 1H), 6.77 (ddd, J = 8.6, 2.8, 0.7 Hz, 1H), 6.63 - 6.60 (m, 1H), 4.80 - 4.73 (m, 2H), 4.68 (s, 2H) 3.78 (s, 3H), 2.80 (dt, J = 17.0, 5.4 Hz, 1H), 2.75 - 2.68 (m, 1H), 2.16 - 2.11 (m, 1H), 2.08 - 2.01 (m, 1H), 1.91 - 1.81 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.40, 139.24, 130.72, 126.75, 113.79, 113.16, 93.78, 78.21, 55.42, 53.22, 30.48, 29.33, 18.90 ppm. NMR spectra are consistent with literature reports.[3]

2,2,2-trichloroethyl ((4-methoxyphenyl)(phenyl)methyl)sulfamate (2.30)



2.30

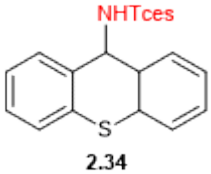
Purified on silica gel by gradient elution with 5-10% diethyl ether in hexanes. Yield: 13.17 mg (0.031 mmol, 31%) on 0.1 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 - 7.33 (m, 2H), 7.35 - 7.27 (m, 3H), 7.27 - 7.20 (m, 2H), 6.93 - 6.84 (m, 2H), 5.79 (d, J = 7.3 Hz, 1H), 5.25 (d, J= 7.3 Hz, 1H), 4.38 (d, J = 1.5 Hz, 2H), 3.80 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 132.11, 129.05, 128.92, 128.32, 127.49, 114.45, 97.57, 78.27, 61.96, 55.51 ppm. HRMS (ESI): *m/z* calcd for $C_{16}H_{16}NO_4SCl_3$ $[M-H]^+$: 422.9866, found 422.9860.

2,2,2-trichloroethyl (9H-xanthen-9-yl)sulfamate (2.32)

2.32

Purified on silica gel by gradient elution with 5-10% diethyl ether in hexanes. Yield: 31.88 mg (0.078 mmol, 78%) on 0.1 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 - 7.69 (m, 2H), 7.38 (ddd, J = 8.3, 7.4, 1.7 Hz, 2H), 7.23 - 7.13 (m, 4H), 6.02 (d, J = 8.2Hz, 1H), 5.05 (d, J = 8.2 Hz, 1H), 4.59 (s, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.57, 130.31, 130.08, 124.17, 119.43, 117.18, 97.65, 78.35, 51.16 ppm. HRMS (ESI): *m/z* calcd for $C_{15}H_{11}NO_4SCl_3$ $[M-H]^+$: 405.9474, found 405.9468.

2,2,2-trichloroethyl (9H-thioxanthen-9-yl)sulfamate (2.34)

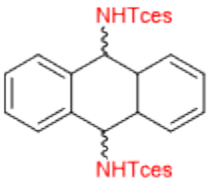


2.34

Purified on silica gel by gradient elution with 5-10% diethyl ether in hexanes. Yield: 21.24 mg (0.050 mmol, 50%) on 0.1 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 - 7.61 (m, 2H), 7.55 - 7.51 (m, 2H), 7.36 - 7.31 (m, 4H), 5.82 (d, J = 7.5 Hz, 1H), 5.30 (d, J = 7.5 Hz, 1H), 4.20 (s, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 133.26, 132.99, 129.93, 128.76, 127.60, 127.51, 97.43,

78.26, 59.56 ppm. HRMS (ESI): *m/z* calcd for $C_{15}H_{11}NO_3S_2Cl_3$ [M-H]$^+$: 628.8503, found 628.8511.

bis(2,2,2-trichloroethyl) (4a,9,9a,10-tetrahydroanthracene-9,10-diyl)bis(sulfamate) (2.36)



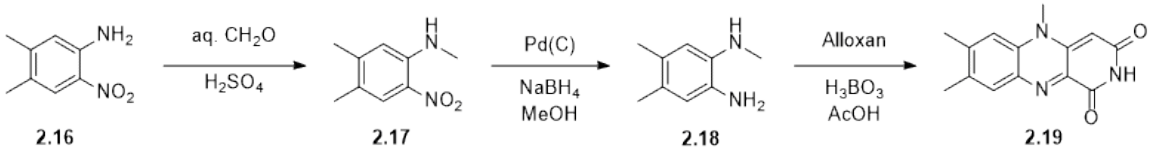
2.36

Purified on silica gel by elution with 5% diethyl ether in hexanes. Yield: 6.34 mg (0.010 mmol, 10%) on 0.1 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (dd, J = 5.6, 3.4 Hz, 4H), 7.43 (dd, J = 5.7, 3.2 Hz, 4H), 5.70 (d, J = 6.2 Hz, 2H), 5.59 (d, J = 6.2 Hz, 2H), 4.46 (s, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 135.65, 129.84, 129.59, 94.36, 78.29, 56.42 ppm. HRMS (ESI): *m/z* calcd for $C_{18}H_{15}N_2O_6S_2Cl_6$ [M-H]$^+$: 628.8503, found 628.8512. Yield: 6.33 mg (0.010 mmol, 10%) on 0.1 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (dd, J = 5.6, 3.3 Hz, 4H), 7.46 (dd, J = 5.7, 3.2 Hz, 4H), 5.86 (d, J = 7.3 Hz, 2H), 5.14 (d, J = 7.3 Hz, 2H), 4.53 (s, 4H) ppm. ^{13}C NMR (201 MHz, $CDCl_3$) δ 135.19, 129.28, 127.61, 94.41, 78.35, 56.10 ppm. HRMS (ESI): *m/z* calcd for $C_{18}H_{15}N_2O_6S_2Cl_6$ [M-H]$^+$: 628.8503, found 628.8511.

A.5 Synthesis of Flavinium Tetrafluoroborate Salt and Methoxy Substituted Flavinium Tetrafluoroborate Salt

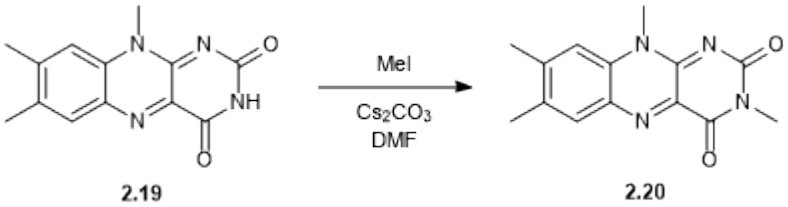
Lumiflavin (2.19):

Lumiflavin **2.19** was synthesized from 4,5-dimethyl-2-nitroaniline **2.16** according to previously reported methods.[4] After confirming the presence of the lumiflavin **2.19** using ^{1}H NMR, it was used for the next step without purification.



3,7,8,10-tetramethylbenzo[g]pteridine-2,4(3H,10H)-dione (2.20):

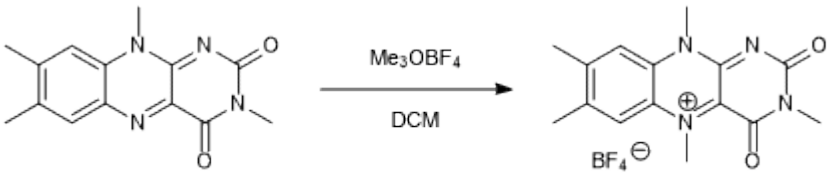
3,7,8,10-tetramethylbenzo[g]pteridine-2,4(3H,10H)-dione **2.20** was synthesized from lumiflavin **2.19** according to previously reported methods.[5] The crude mixture was then purified on basic alumina with 2% MeOH in DCM. ^{1}H NMR (600 MHz, D-DCM) δ 7.99 (s, 1H), 7.45 (s, 1H), 4.08 (s, 3H), 3.43 (s, 3H), 2.55 (s, 3H), 2.46 (s, 3H) ppm.



Flavinium tetrafluoroborate salt (2.15):

Flavinium tetrafluoroborate salt **2.15** was synthesized from 3,7,8,10-tetramethylbenzo[g]pteridine-2,4(3H,10H)-dione **2.20** according to previously reported methods.[6] ^{1}H NMR (600 MHz, D-acetone) δ 8.44 (s, 1H), 8.33 (s, 1H), 4.75 (s, 3H), 4.52 (s, 3H), 3.64 (s, 3H), 2.77 (s, 3H), 2.65 (s, 3H) ppm. ^{13}C NMR (201 MHz, D-acetone) δ

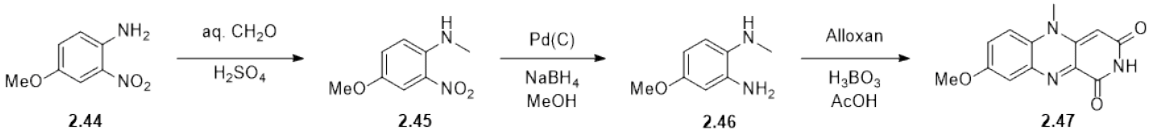
161.76, 158.90, 153.70, 146.95, 143.47, 140.81, 136.23, 133.06, 132.48, 118.87, 59.53, 21.87, 19.91 ppm. ^{19}F NMR (564 MHz, D-acetone) δ -152.18 ppm. HRMS (ESI): *m/z* calcd for $C_{15}H_{17}N_4O_2$ $[M\text{-}BF_4]^+$: 285.1352, found 285.1349.



2.20 2.15

MeO-lumiflavin (2.47):

MeO-lumiflavin **2.47** was synthesized from 4-methoxy-2-nitroaniline **2.44** according to previously reported methods.[4] After confirming the presence of each products using ^{1}H NMR, was moved to the next step without purification. After confirming the presence of the MeO-lumiflavin using ^{1}H NMR, it was used for the next step without purification.

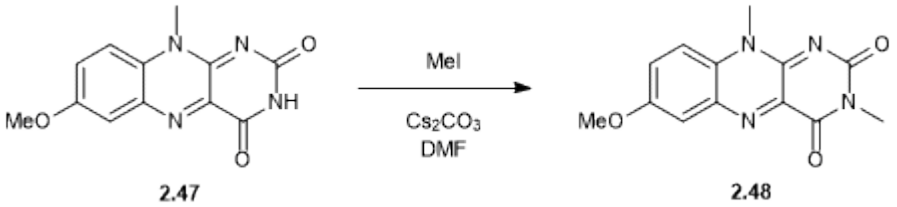


2.44 2.45 2.46 2.47

7-methoxy-3,10-dimethylbenzo[g]pteridine-2,4(3H,10H)-dione (2.48):

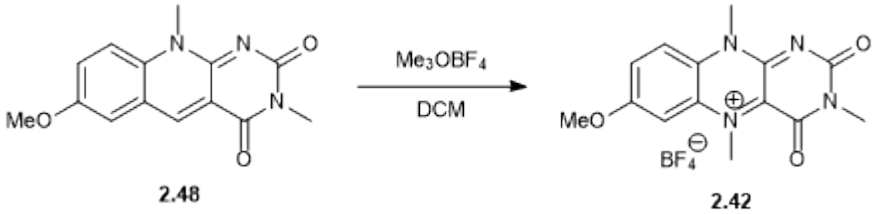
7-methoxy-3,10-dimethylbenzo[g]pteridine-2,4(3H,10H)-dione **2.48** was synthesized from MeO-lumiflavin **2.47** mixture according to previously recorded methods.[5] The crude mixture was then purified on basic alumina with 2% MeOH in DCM. ^{1}H NMR (600 MHz, D-DCM) δ 7.99 (s, 1H), 7.45 (s, 1H), 4.08 (s, 3H), 3.43 (s, 3H), 2.55 (s, 3H), 2.46 (s, 3H) ppm. ^{13}C NMR (201 MHz, D-acetone) δ 161.76, 158.90, 153.70, 146.95, 143.47, 140.81, 136.23, 133.06, 132.48, 118.87, 59.53, 21.87, 19.91 ppm. ^{19}F

NMR (564 MHz, D-acetone) δ -152.18 ppm. HRMS (ESI): m/z calcd for $C_{15}H_{17}N_4O_2$ [M-BF_4]$^+$: 285.1352, found 285.1349.



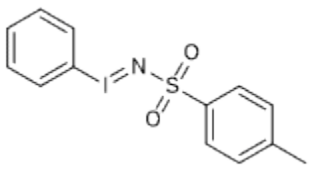
MeO-FlBF$_4$ (2.42):

MeO-FlBF$_4$ **2.42** was synthesized from 7-methoxy-3,10-dimethylbenzo[g]pteridine-2,4(3H,10H)-dione **2.48** according to previously recorded methods.[6]



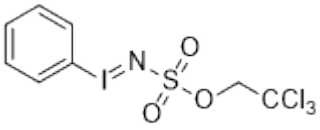
A.6 Synthesis of Iminoiodinane

[N-(p-toluenesulfonyl) imino]-phenyliodinane:



Prepare according to previously recorded methods.[2]

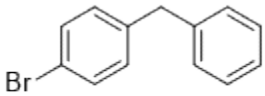
[N-(2,2,2-trichloroethoxysulfonyl) imino]-phenyliodinane:



Prepared according to previously recorded methods.[3]

A.7 Synthesis of Substrates

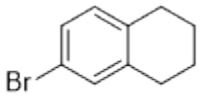
1-benzyl-4-bromobenzene (2.38):



2.38

Prepared according to previously recorded methods.[7]

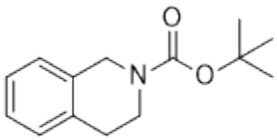
6-bromo-1,2,3,4-tetrahydronaphthalene (2.39):



2.39

Prepared according to previously recorded methods.[7]

tert-butyl 3,4-dihydroisoquinoline-2(1H)-carboxylate (2.41):



2.41

Prepared according to previously recorded methods.[8]

A.8 References

1. Murray, A. T..; Matton, P.; Fairhurst, N. W. G.; John, M. P.; Carbery, D. R.; *Org. Lett.*, **2012**, *14*, 3656-3659.

2. Johnson, S. L.; Hilinski, M. K.; *J. Org. Chem.*, **2019**, *84*, 8589-8595.

3. Combee, L. A.; Raya, B.; Wang, D.; Hilinski, M. K.; *Chem. Sci.*, **2018**, *9*(4), 935.

4. Jhulki, I.; Chananai, P. K.; Abdelwahed, S. H.; Begley, T. P.; *J. A. C. S.*, **2016**, *138* (27), 8324-8327.

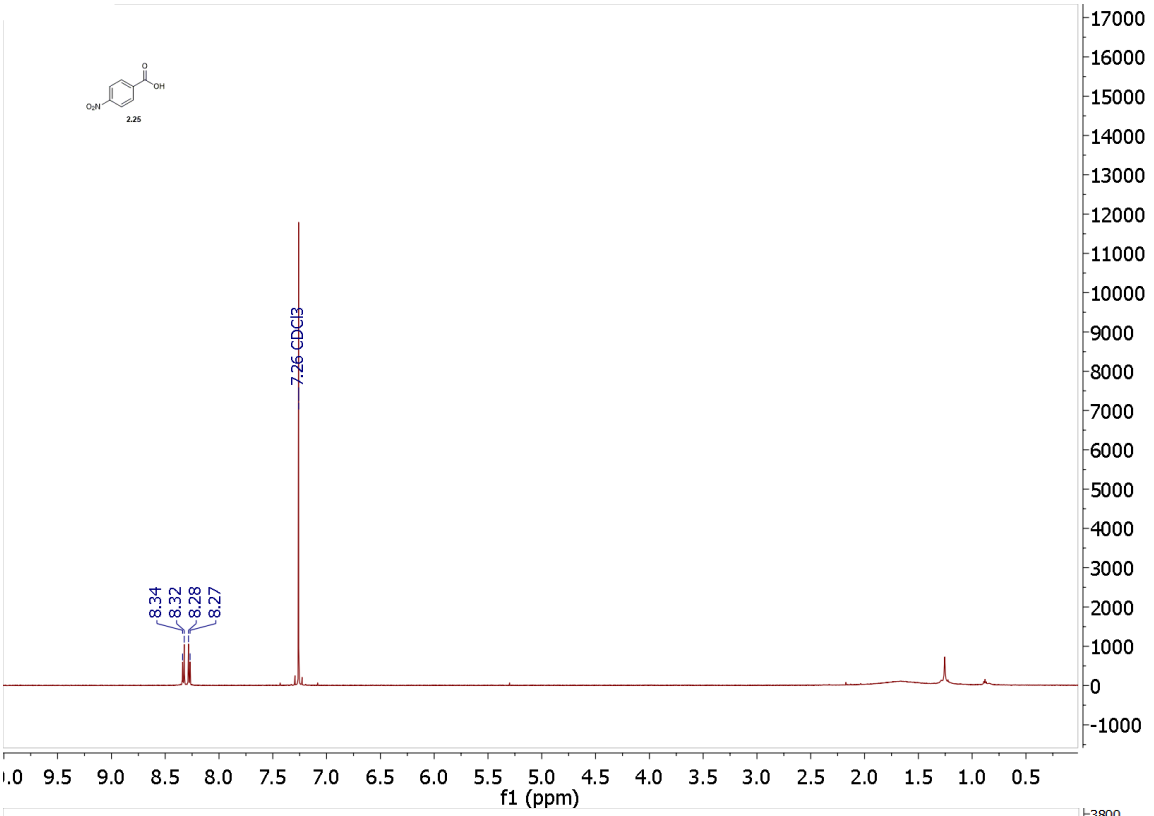
5. Pouy, M. J.; Milczek, E. M.; Figg, T. M.; Otten, B. M.; Prince, B. M.; Gunnoe, T. B.; Cundari, T. R.; Groves, J. T.; *J. Am. Chem. Soc.*, **2012**, *134* (31), 12920-12923.

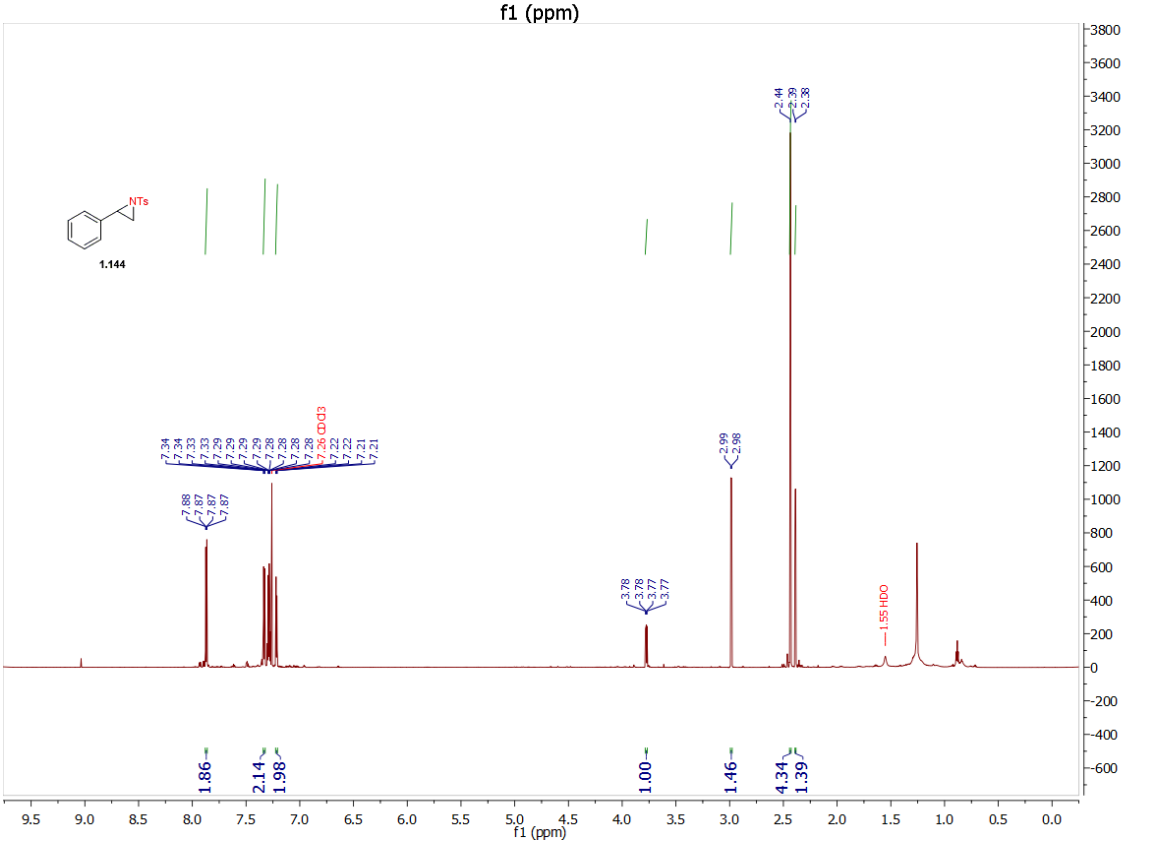
6. Wang, D.; Shuler, W. G.; Pierce, C. J.; Hilinski, M. K.; *Org. Lett.*, **2016**, *18* (15), 3826-2839.

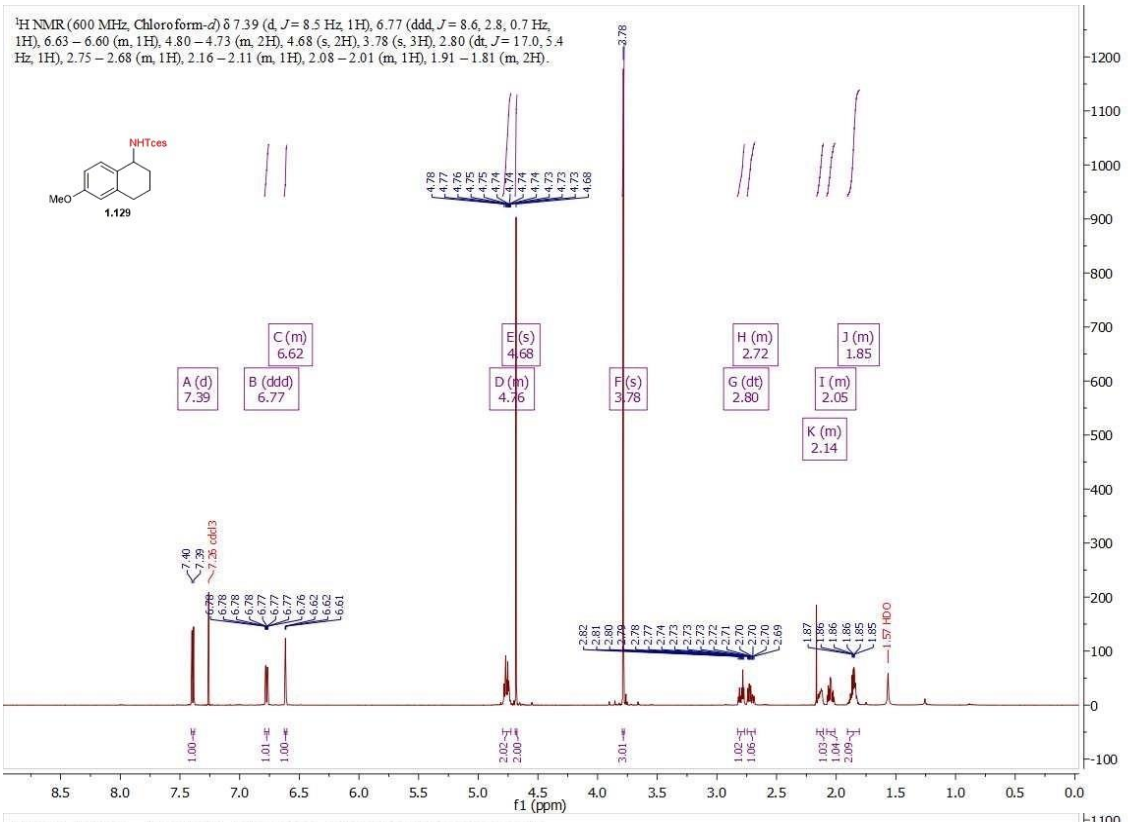
7. Boehm, J. C. (22013). *U.S. Patent No. WO2013006596A1*. Washington, DC: U.S. Patent and Trademark Office.

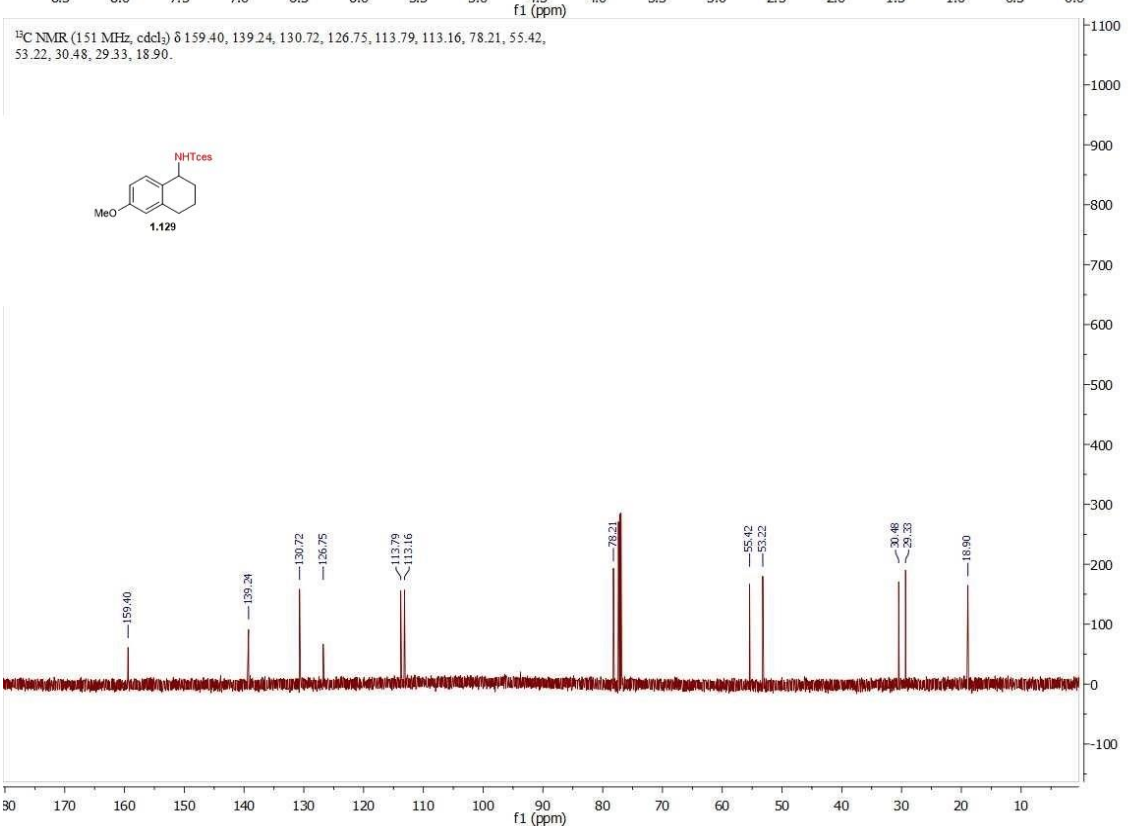
8. Yan, C.; Liu, Y.; Wang, Q.; *RSC Adv.*, **2014**, *4*, 60075-60078.

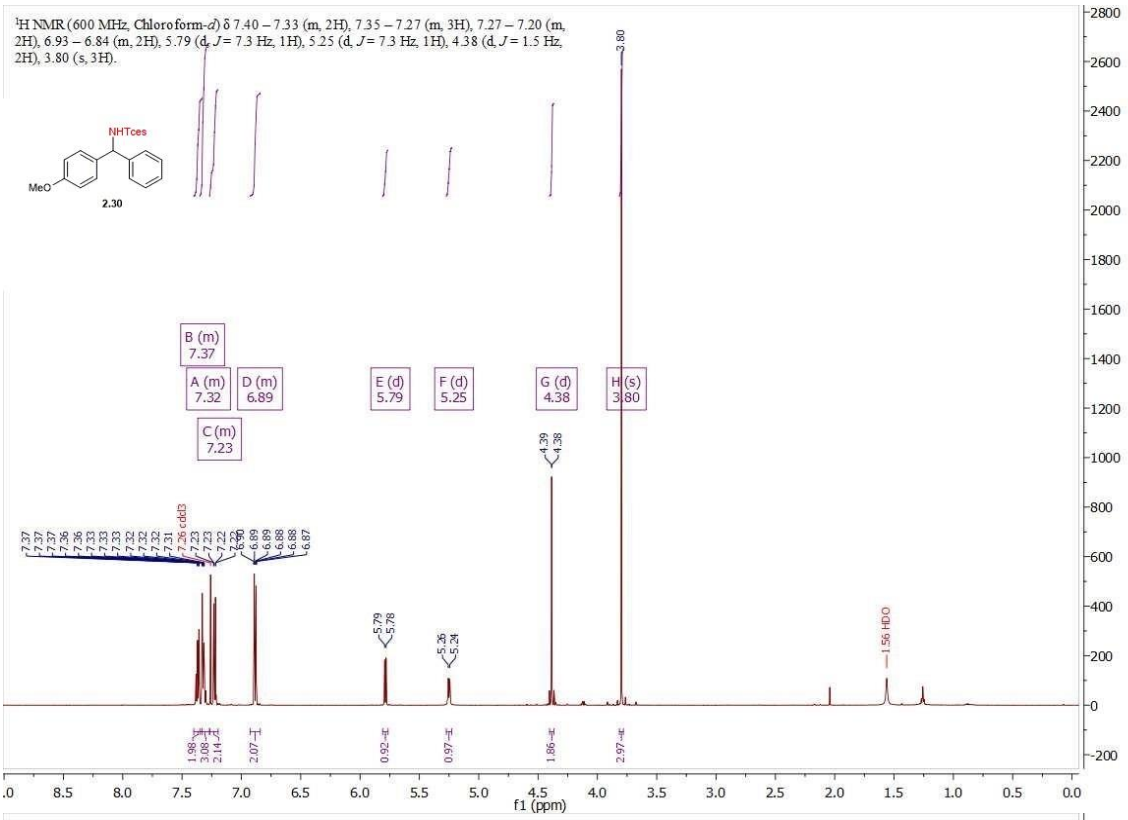
A.9 NMR spectra

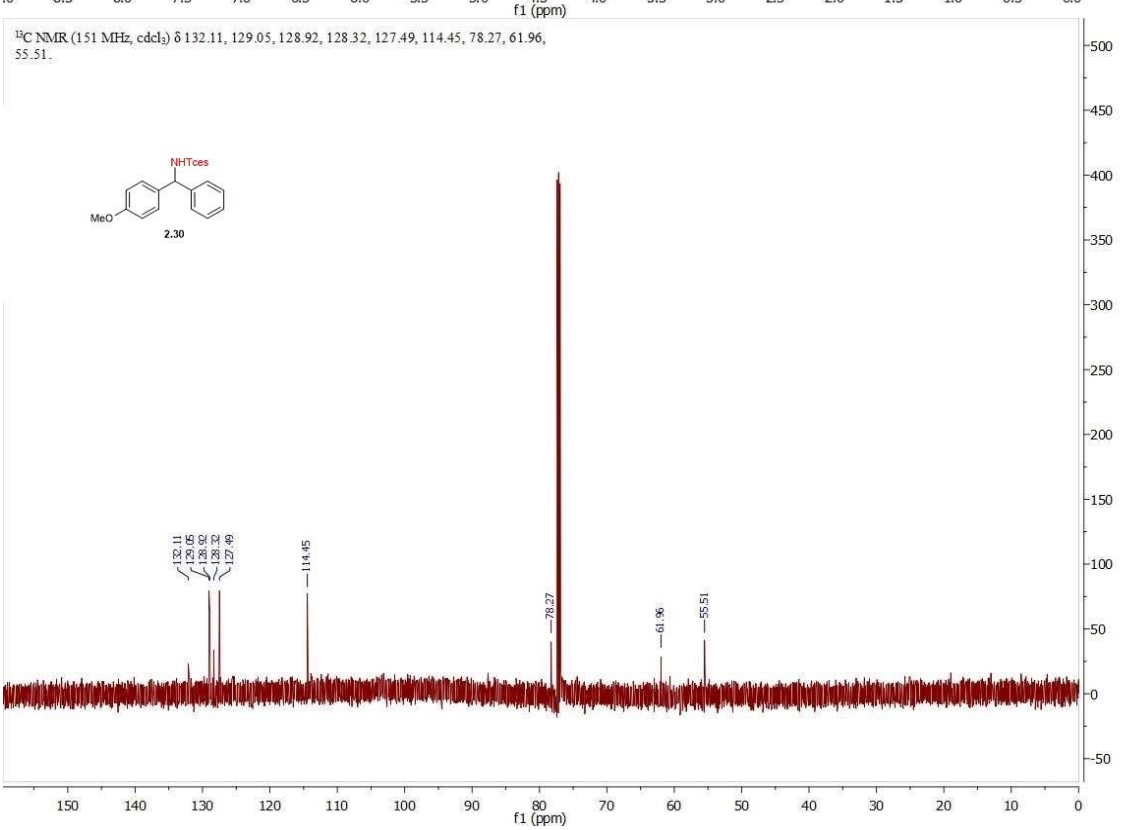


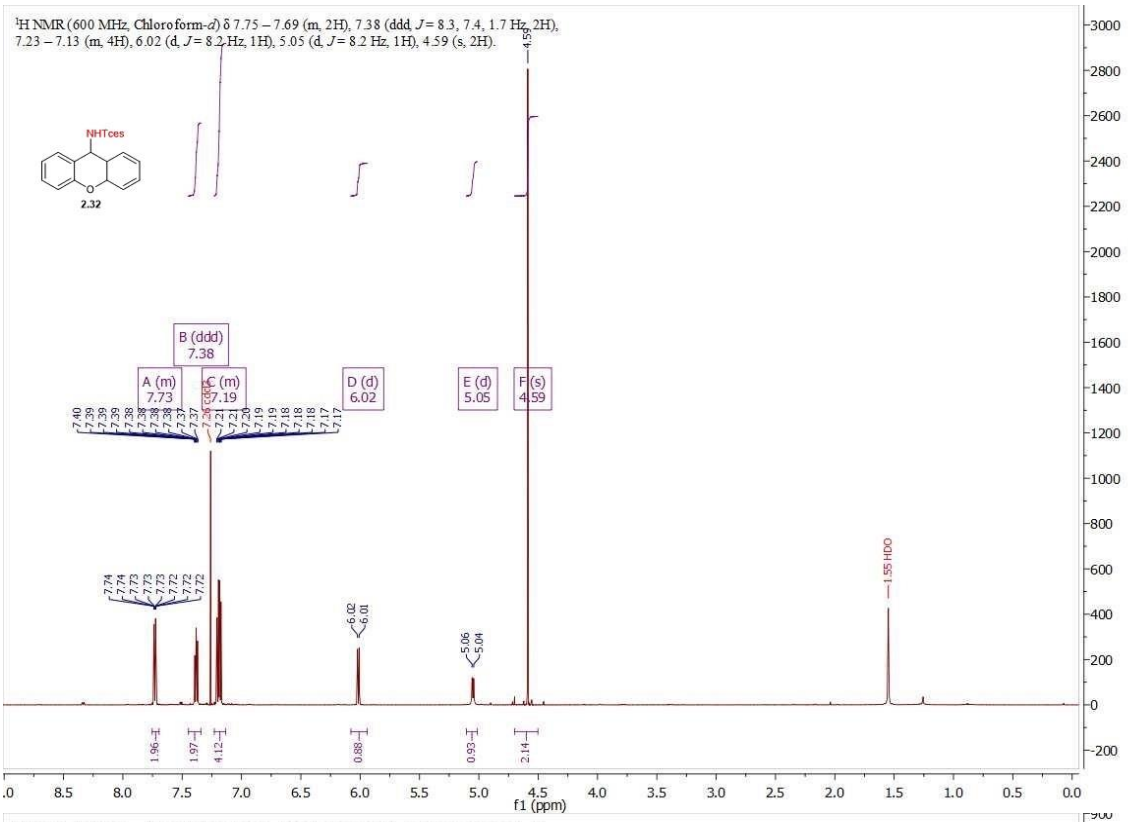


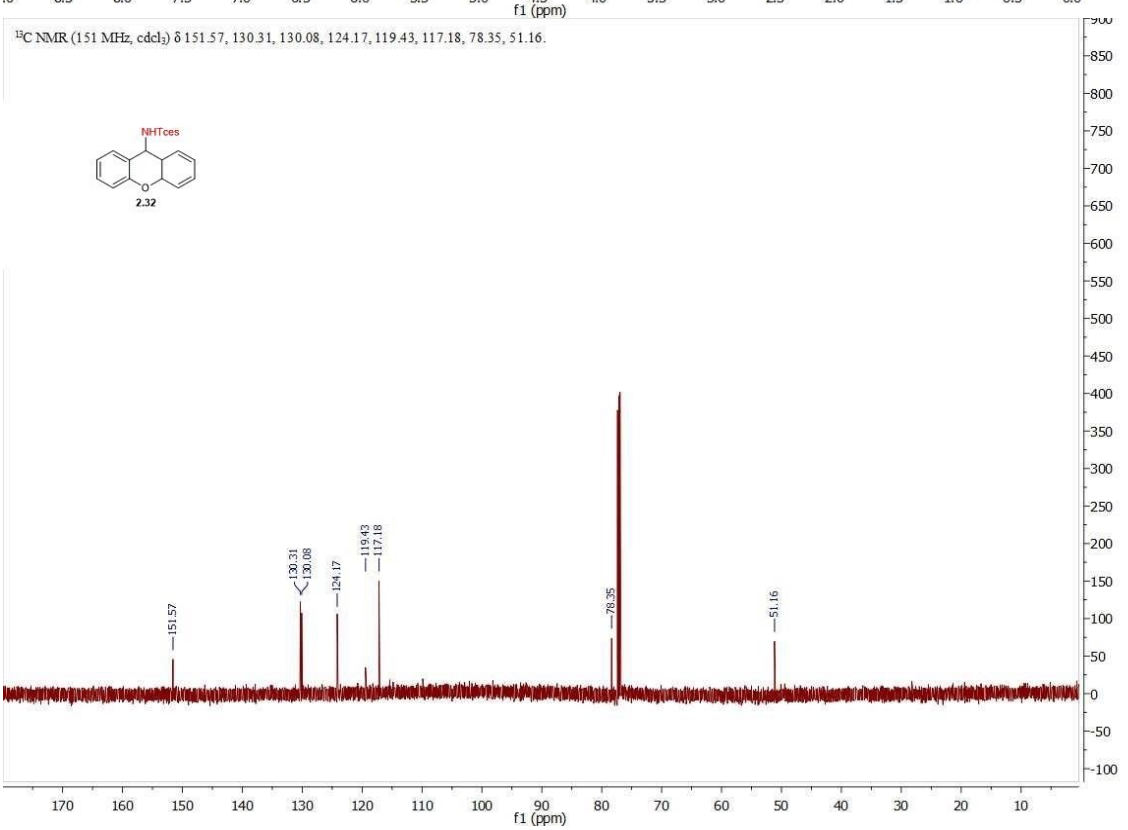

1H NMR (600 MHz, Chloroform-d) δ 7.39 (d, J = 8.5 Hz, 1H), 6.77 (ddd, J = 8.6, 2.8, 0.7 Hz, 1H), 6.63 – 6.60 (m, 1H), 4.80 – 4.73 (m, 2H), 4.68 (s, 2H), 3.78 (s, 3H), 2.80 (dt, J = 17.0, 5.4 Hz, 1H), 2.75 – 2.68 (m, 1H), 2.16 – 2.11 (m, 1H), 2.08 – 2.01 (m, 1H), 1.91 – 1.81 (m, 2H).
NHTces
MeO
1.129
A (d) 7.39
B (ddd) 6.77
C (m) 6.62
D (m) 4.76
E (s) 4.68
F (s) 3.78
G (dt) 2.80
H (m) 2.72
I (m) 2.05
J (m) 1.85
K (m) 2.14
f1 (ppm)

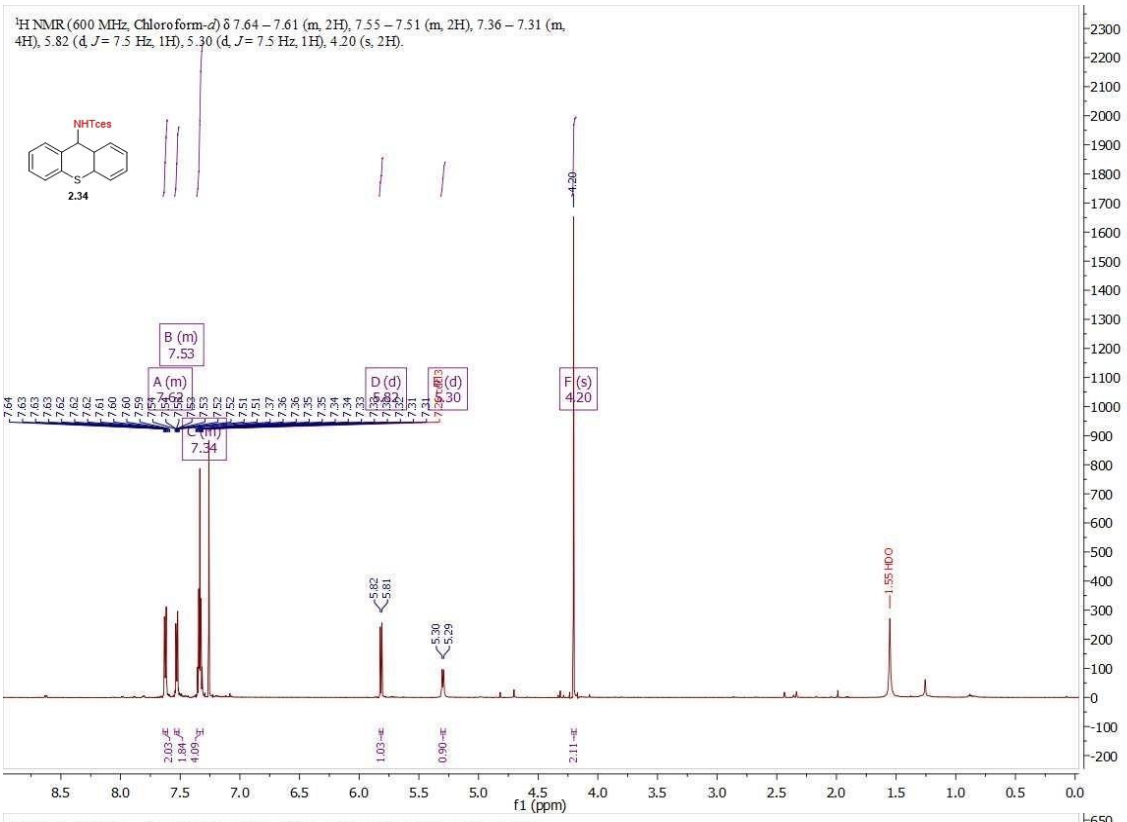

13C NMR (151 MHz, cdcl3) δ 159.40, 139.24, 130.72, 126.75, 113.79, 113.16, 78.21, 55.42, 53.22, 30.48, 29.33, 18.90.
NHTces
MeO
1.129
159.40
139.24
130.72
126.75
113.79
113.16
78.21
55.42
53.22
30.48
29.33
18.90
f1 (ppm)

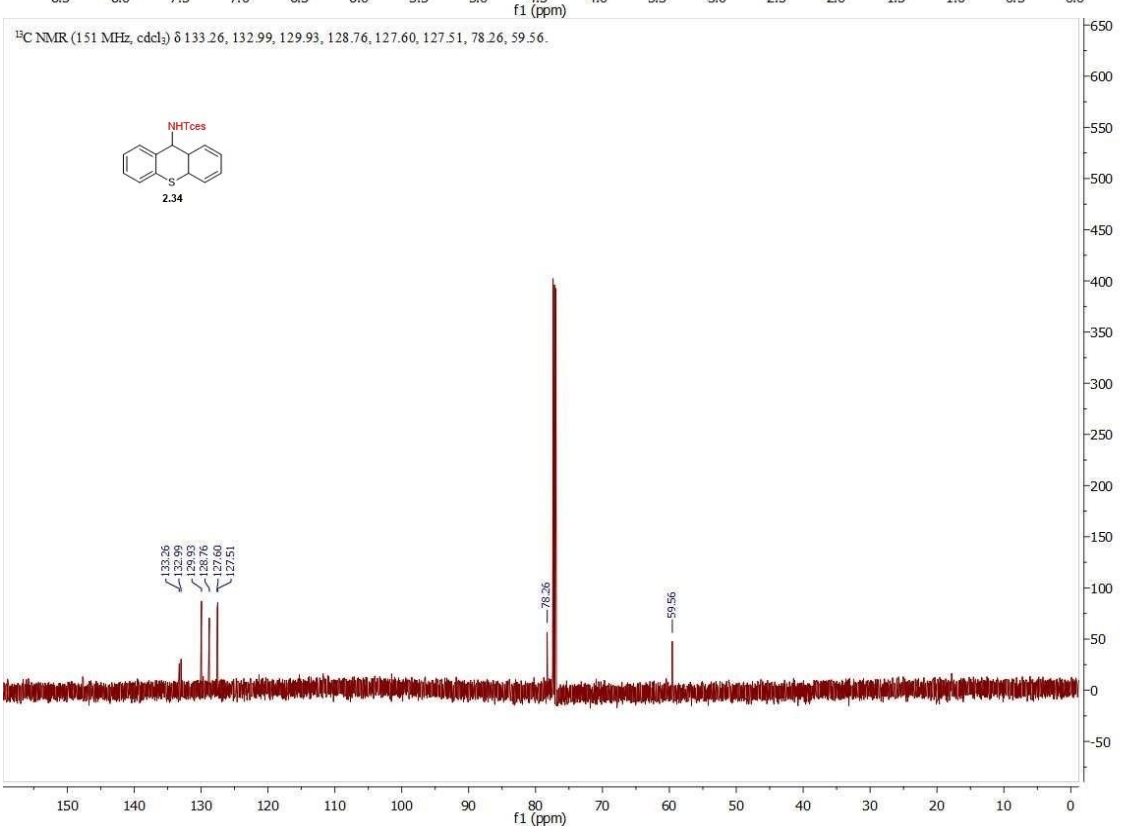

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.40 – 7.33 (m, 2H), 7.35 – 7.27 (m, 3H), 7.27 – 7.20 (m, 2H), 6.93 – 6.84 (m, 2H), 5.79 (d, *J* = 7.3 Hz, 1H), 5.25 (d, *J* = 7.3 Hz, 1H), 4.38 (d, *J* = 1.5 Hz, 2H), 3.80 (s, 3H).
NHTces
MeO
2.30
B (m) 7.37
A (m) 7.32
D (m) 6.89
C (m) 7.23
E (d) 5.79
F (d) 5.25
G (d) 4.38
H (s) 3.80
f1 (ppm)

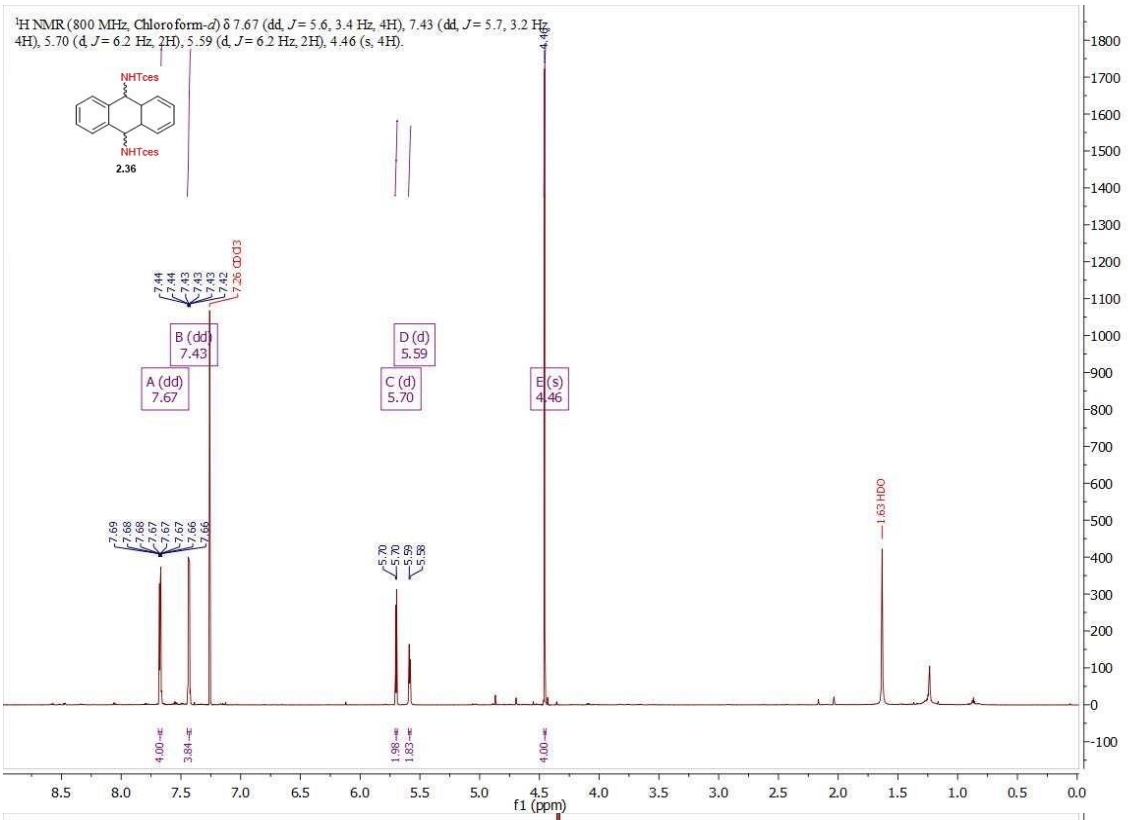

^{13}C NMR (151 MHz, cdcl$_3$) δ 132.11, 129.05, 128.92, 128.32, 127.49, 114.45, 78.27, 61.96, 55.51.
NHTces
MeO
2.30
f1 (ppm)

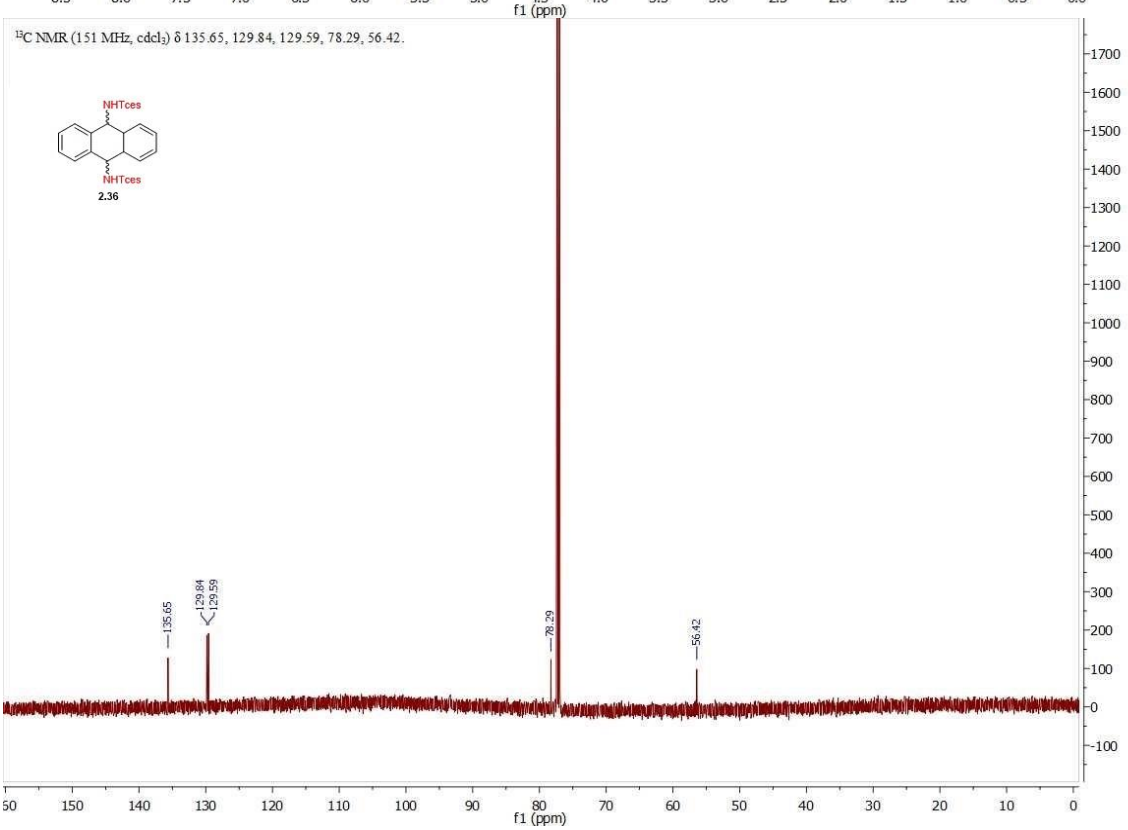

¹H NMR (600 MHz, Chloroform-d) δ 7.75 – 7.69 (m, 2H), 7.38 (ddd, J = 8.3, 7.4, 1.7 Hz, 2H), 7.23 – 7.13 (m, 4H), 6.02 (d, J = 8.2 Hz, 1H), 5.05 (d, J = 8.2 Hz, 1H), 4.59 (s, 2H).
NHTces
2.32
B (ddd) 7.38
A (m) 7.73
C (m) 7.19
D (d) 6.02
E (d) 5.05
F (s) 4.59
1.55 H2O
f1 (ppm)

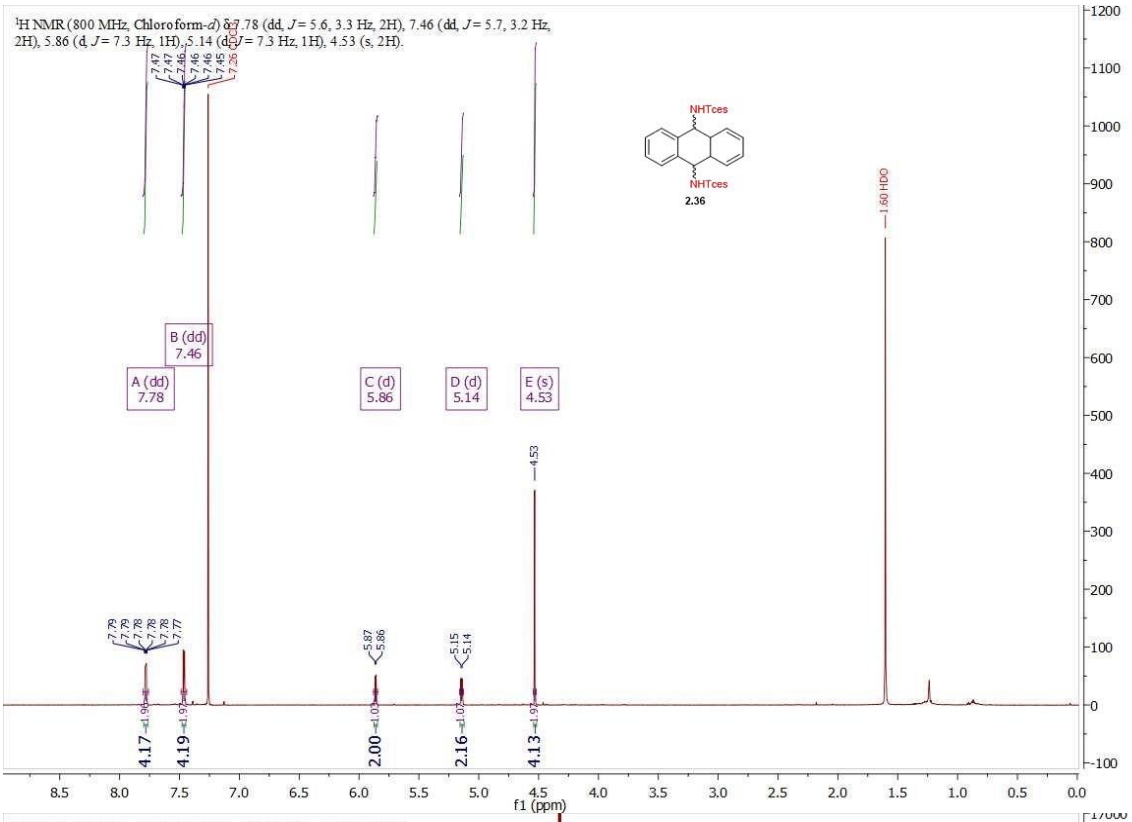

¹³C NMR (151 MHz, cdcl3) δ 151.57, 130.31, 130.08, 124.17, 119.43, 117.18, 78.35, 51.16.
NHTces
2.32
151.57
130.31
130.08
124.17
119.43
117.18
78.35
51.16
f1 (ppm)

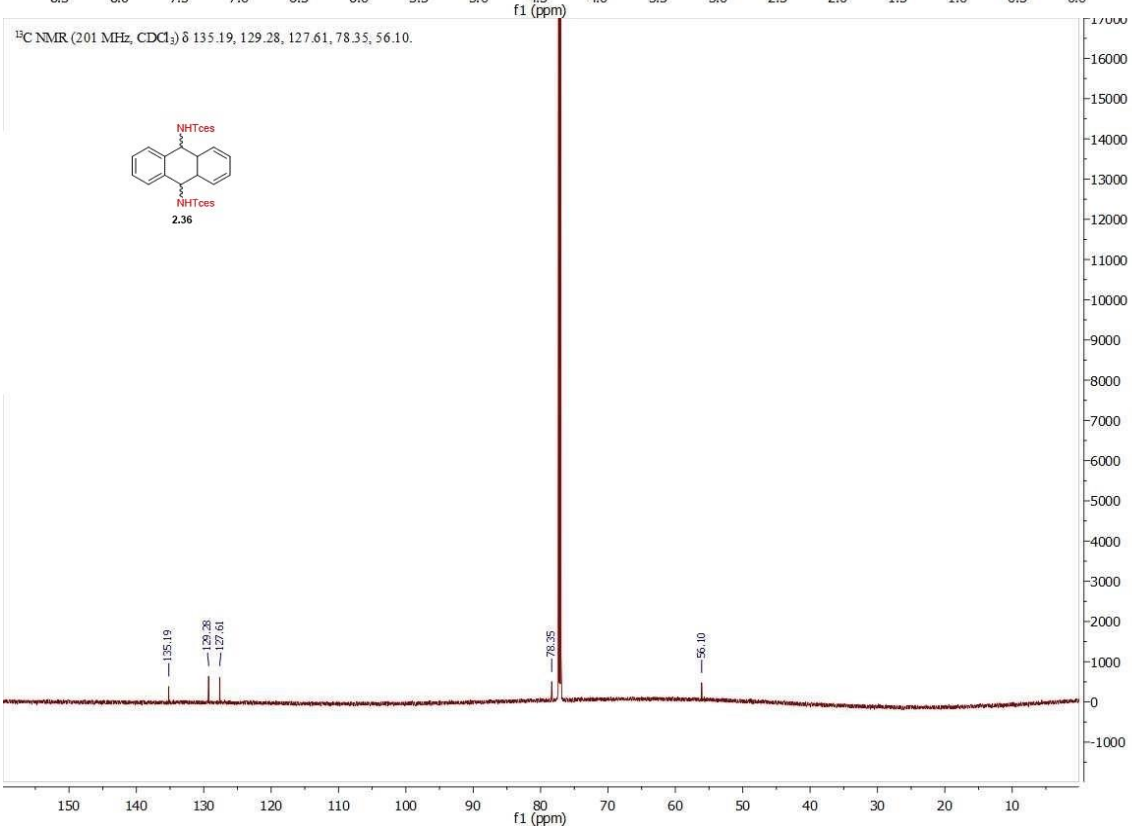

¹H NMR (600 MHz, Chloroform-d) δ 7.64 – 7.61 (m, 2H), 7.55 – 7.51 (m, 2H), 7.36 – 7.31 (m, 4H), 5.82 (d, J = 7.5 Hz, 1H), 5.30 (d, J = 7.5 Hz, 1H), 4.20 (s, 2H).
NHTces
2.34
B (m) 7.53
A (m) 7.62
C (m) 7.34
D (d) 5.82
E (d) 5.30
F (s) 4.20
1.55 HDO
f1 (ppm)

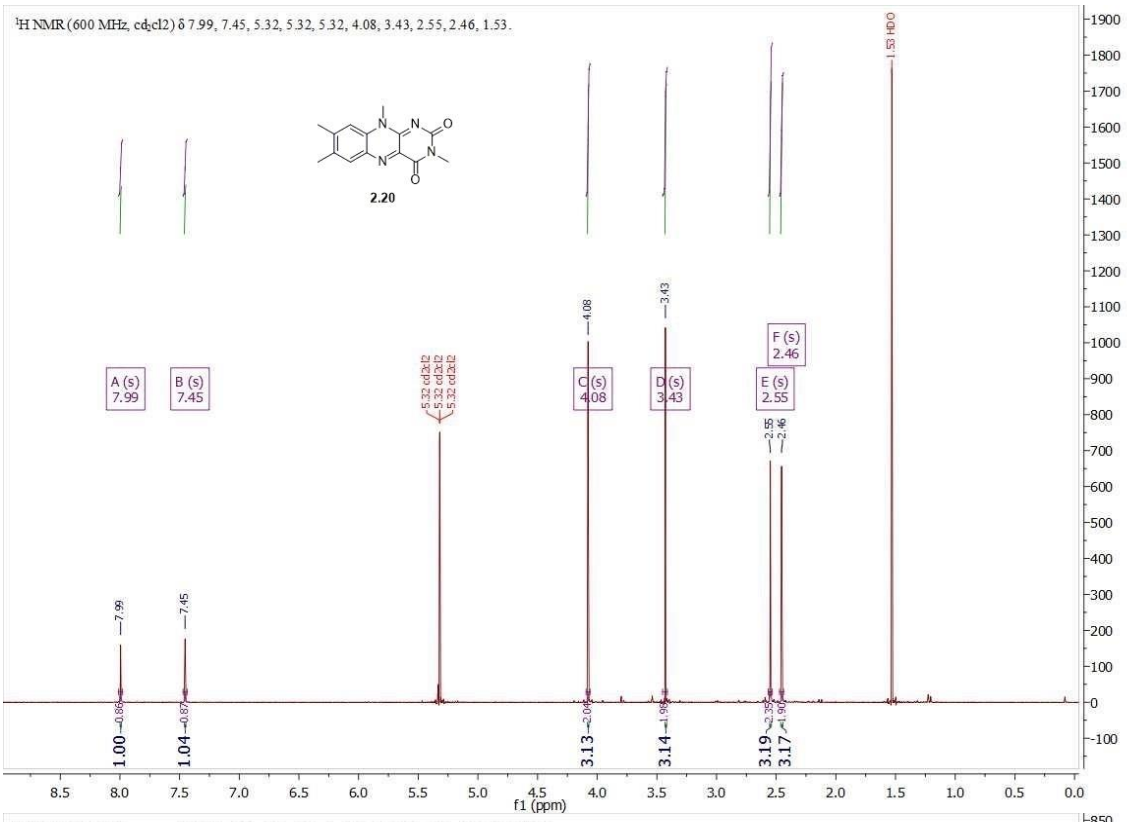

¹³C NMR (151 MHz, cdcl₃) δ 133.26, 132.99, 129.93, 128.76, 127.60, 127.51, 78.26, 59.56.
NHTces
2.34
133.26
132.99
129.93
128.76
127.60
127.51
78.26
59.56
f1 (ppm)

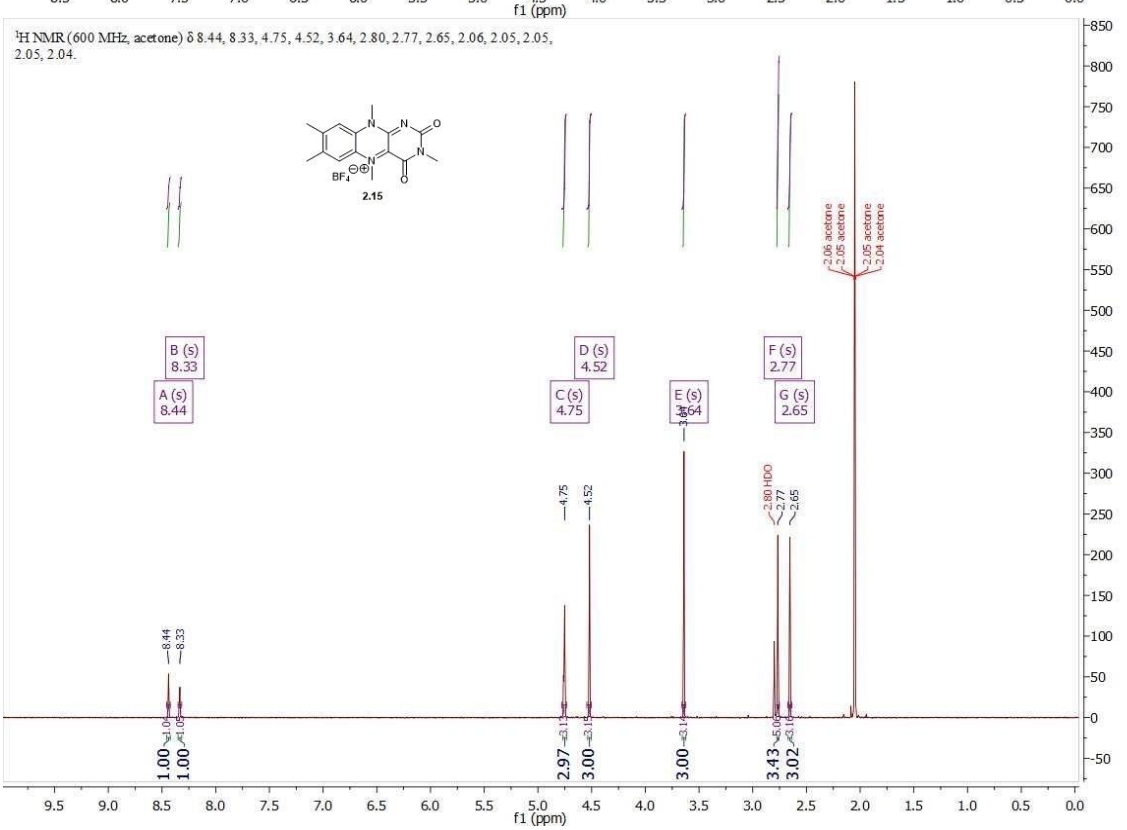

¹H NMR (800 MHz, Chloroform-d) δ 7.67 (dd, J = 5.6, 3.4 Hz, 4H), 7.43 (dd, J = 5.7, 3.2 Hz, 4H), 5.70 (d, J = 6.2 Hz, 2H), 5.59 (d, J = 6.2 Hz, 2H), 4.46 (s, 4H).
NHTces
NHTces
2.36
B (dd) 7.43
D (d) 5.59
A (dd) 7.67
C (d) 5.70
E (s) 4.46
1.63 HDO
f1 (ppm)

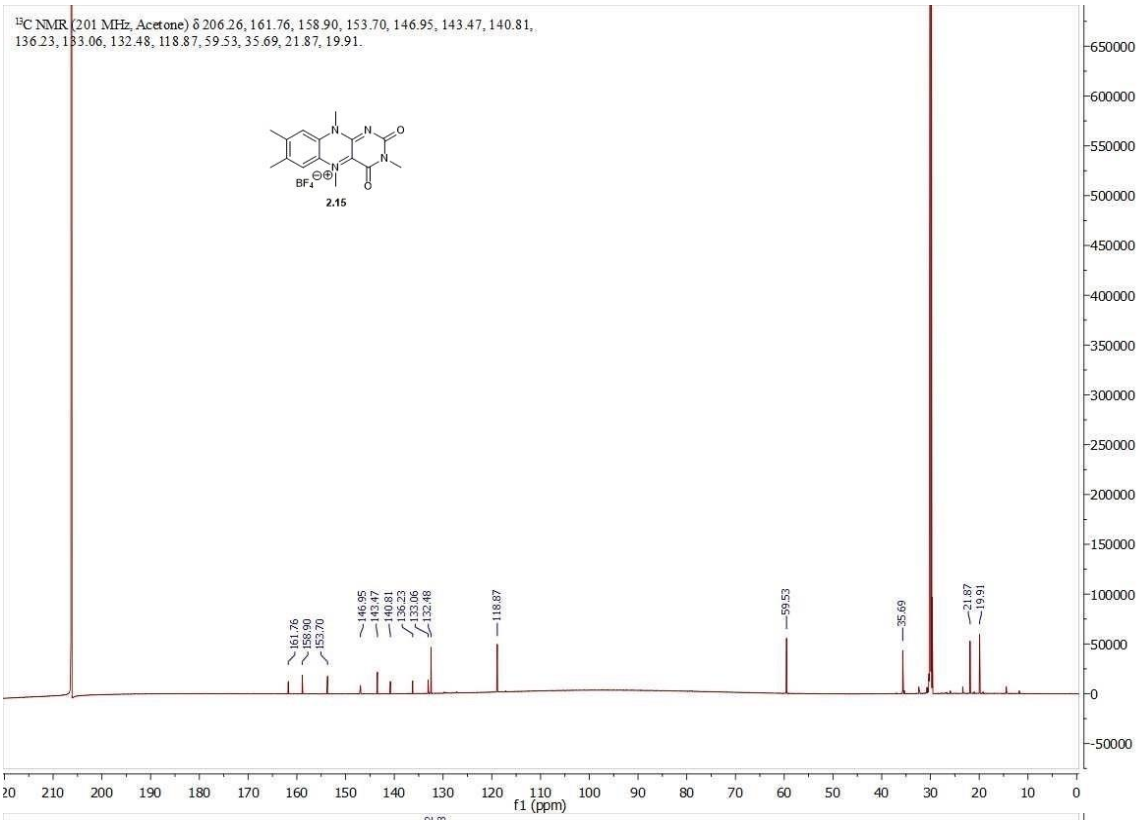

¹³C NMR (151 MHz, cdcl₃) δ 135.65, 129.84, 129.59, 78.29, 56.42.
NHTces
NHTces
2.36
135.65
129.84
129.59
78.29
56.42
f1 (ppm)

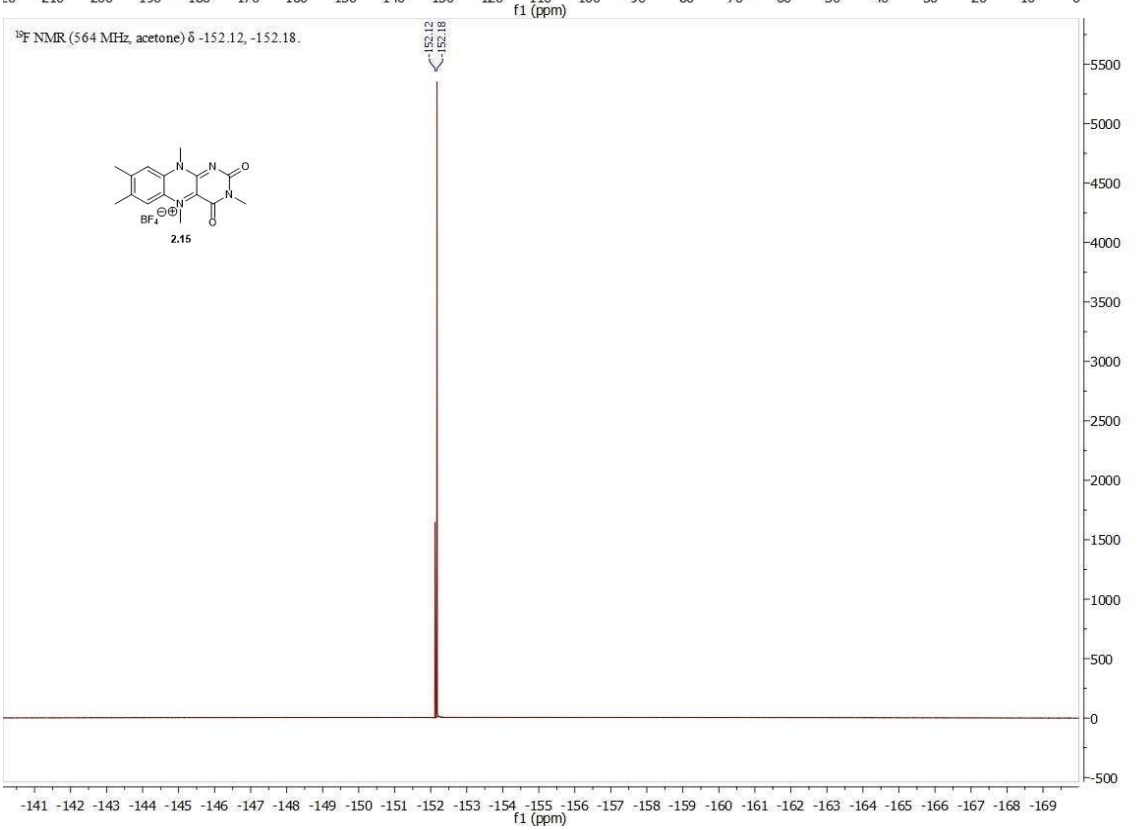

¹H NMR (800 MHz, Chloroform-d) δ 7.78 (dd, J = 5.6, 3.3 Hz, 2H), 7.46 (dd, J = 5.7, 3.2 Hz, 2H), 5.86 (d, J = 7.3 Hz, 1H), 5.14 (d, J = 7.3 Hz, 1H), 4.53 (s, 2H).
NHTces
NHTces
2.36
A (dd) 7.78
B (dd) 7.46
C (d) 5.86
D (d) 5.14
E (s) 4.53
1.60 HDO
4.17
4.19
2.00
2.16
4.13
f1 (ppm)

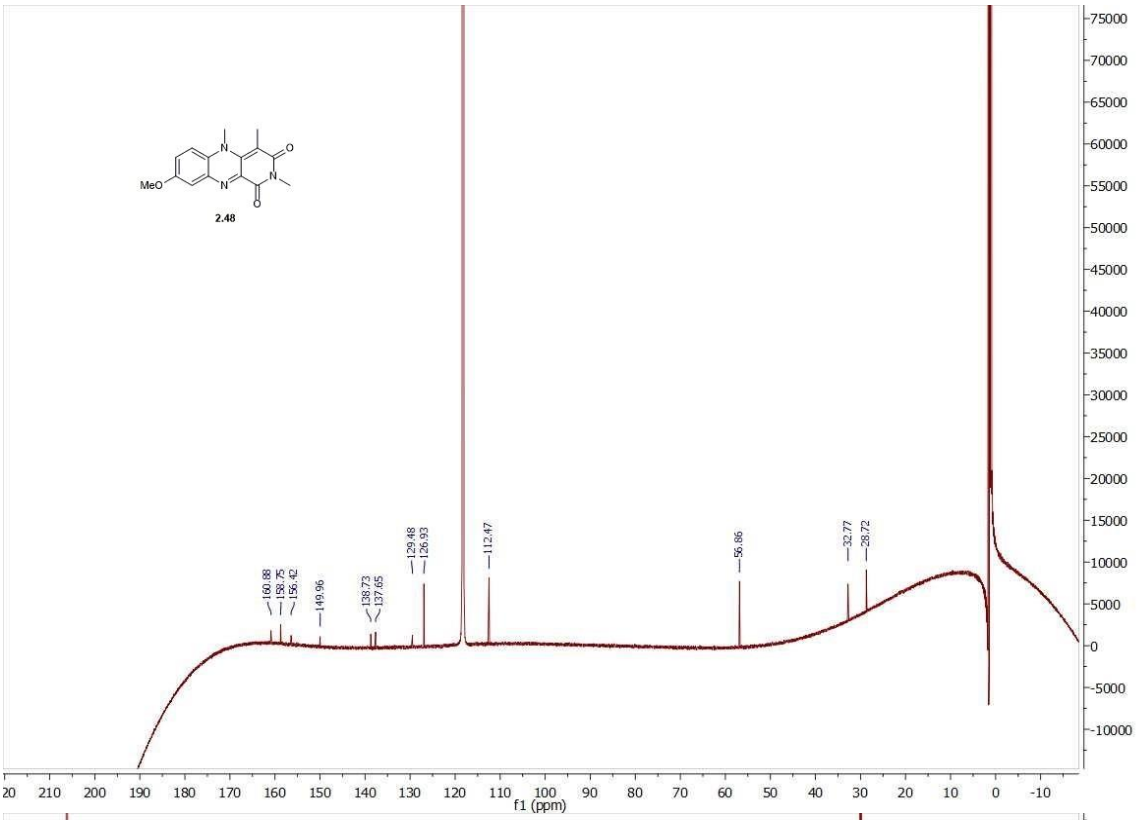

¹³C NMR (201 MHz, CDCl3) δ 135.19, 129.28, 127.61, 78.35, 56.10.
NHTces
NHTces
2.36
135.19
129.28
127.61
78.35
56.10
f1 (ppm)

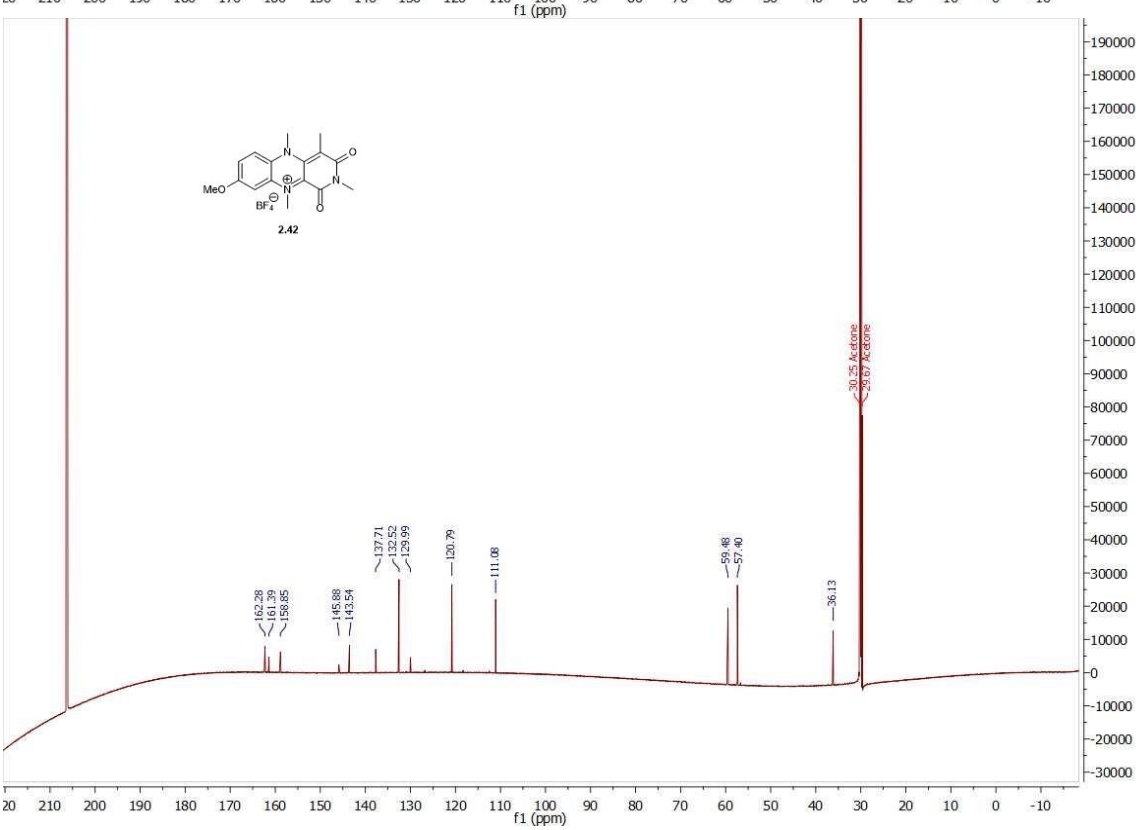

¹H NMR (600 MHz, cd2cl2) δ 7.99, 7.45, 5.32, 5.32, 5.32, 4.08, 3.43, 2.55, 2.46, 1.53.
2.20
A (s) 7.99
B (s) 7.45
C (s) 4.08
D (s) 3.43
E (s) 2.55
F (s) 2.46
1.53 HDO
1.00
1.04
3.13
3.14
3.19
3.17
f1 (ppm)


¹H NMR (600 MHz, acetone) δ 8.44, 8.33, 4.75, 4.52, 3.64, 2.80, 2.77, 2.65, 2.06, 2.05, 2.05, 2.05, 2.04.
2.15
A (s) 8.44
B (s) 8.33
C (s) 4.75
D (s) 4.52
E (s) 3.64
F (s) 2.77
G (s) 2.65
2.80 HDO
1.00
1.00
2.97
3.00
3.00
3.43
3.02
f1 (ppm)


13C NMR (201 MHz, Acetone) δ 206.26, 161.76, 158.90, 153.70, 146.95, 143.47, 140.81, 136.23, 133.06, 132.48, 118.87, 59.53, 35.69, 21.87, 19.91.
2.15
161.76
158.90
153.70
146.95
143.47
140.81
136.23
133.06
132.48
118.87
59.53
35.69
21.87
19.91
f1 (ppm)


19F NMR (564 MHz, acetone) δ -152.12, -152.18.
2.15
-152.12
-152.18
f1 (ppm)


MeO
2.48
160.88
158.75
156.42
149.96
138.73
137.65
129.48
126.93
112.47
56.86
32.77
28.72
f1 (ppm)


MeO
BF4
2.42
162.28
161.39
158.85
145.88
143.54
137.71
132.52
129.99
120.79
111.08
59.48
57.40
36.13
30.25 Acetone
29.67 Acetone
f1 (ppm)