

**SYNTHESIS OF PSEUDOINDOXYLS BY ASYMMETRIC AZA-HECK
CYCLIZATION**

by

Zeming Li

A thesis submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Master of Science in Chemistry and Biochemistry

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ABSTRACT

Pseudoindoxyl is a nitrogen-containing compound and a kind of the indole derivatives. Numerous natural alkaloids with versatile biological activity contain pseudoindoxyl carbon skeleton. The complex structure of pseudoindoxyl has motivated chemists, prompting the exploration and refinement of various synthetic methods. However, relatively narrow substrate scope extremely limits their application to total synthesis of natural products. Our group is dedicated to develop aza-Heck reaction into various circumstances and we found aza-Heck can be utilized in synthesizing pseudoindoxyls under excellent yield and ee to obtain desired chiral structure. In this document, I will first introduce some well-developed methodologies all over the world and then demonstrate our group and my contribution in the development of pseudoindoxyls syntheses via aza-Heck cyclization.

Chapter 1

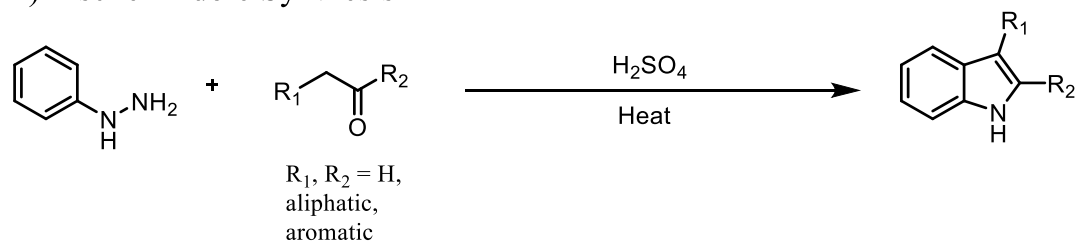
PRIOR ART OF SYNTHESIZING THE PSEUDOINDOXYL CORE

1.1 Introduction

Nitrogen heterocycles are one of the most common and crucial molecular motifs in pharmaceuticals. By 2012, 59% of the 1086 U.S. Food and Drug Administration (FDA) approved unique small-molecule drugs contained at least one nitrogen heterocycle.¹ This percentage has increased significantly to 88% from 2015 to 2022.²

Among the abundant existence of nitrogen-containing heterocycles, indoles and their derivatives are the core of numerous natural alkaloids and pharmaceuticals with significant biological activity.³ Significant approaches, including traditional methods like the Fisher indole synthesis (**Figure 1.1A**)⁴ and Bartoli indole synthesis (**Figure 1.1B**)⁵, have been used to achieve these nitrogen containing heterocycles efficiently and practically.⁶

A) Fischer Indole Synthesis



B) Bartoli Indole Synthesis

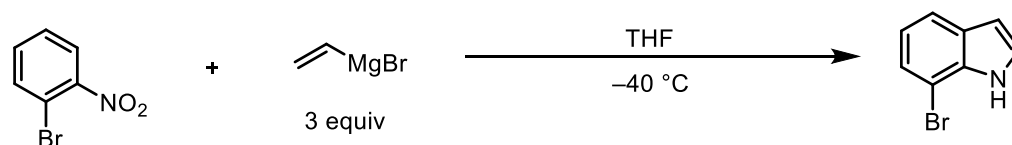
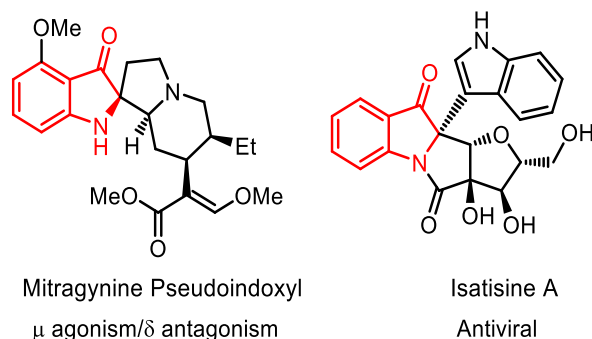


Figure 1.1: Traditional Methods of Synthesizing Indoles and their Derivatives

Among these natural products, molecules with the pseudoindoxyl scaffold, a stable ketonic structure generated from enolic form (3-hydroxyindole), draws attentions from researchers because of its unique structure. Since 1947, about 30 unique natural alkaloids containing the pseudoindoxyl core have been isolated and shown to exhibiting biological activity.⁷ For instance, mitragynine pseudoindoxyl acts as a μ -opioid receptor agonist and δ -opioid receptor antagonist, which leads to the separation of antinociception, body's response to potentially toxic stimuli, hindering negative side effects like addiction, which is commonly observed with traditional opioid drugs.⁸ Another example is isatisine A, an active ingredient separated from a plant that has been used in traditional Chinese medicine for the treatment of viral diseases such as influenza, viral pneumonia, mumps and hepatitis for hundreds of years.⁹ (**Figure 1.2A**)

A) Natural Products with Pseudoindoxyl Core



B) Biosynthetic Pathway

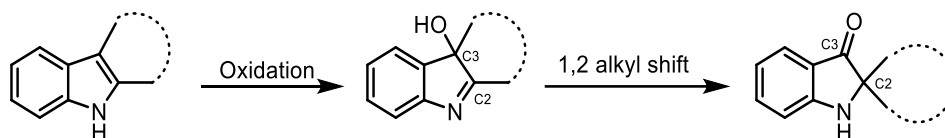


Figure 1.2: Pseudoindoxyl Core in Natural Product and its Biosynthetic Pathway

To date, 13 natural products with pseudoindoxyl core were successfully synthesized. The biosynthetic pathway is the most widely employed the method to establish this complicated core, beginning with the oxidation of a C2, C3 disubstituted indole to the 3-hydroxyindoxyl followed by 1,2 alkyl shift rearrangement to yield pseudoindoxyl (**Figure 1.2B**).⁶

In addition to this extensively applied method, there are also some well-developed methodologies.¹⁰ More details of the syntheses that mimic the biosynthetic pathway and novel methodologies will be discussed below. Although several pseudoindoxyl synthesis via various methods were published, there are still some challenges that need to be overcome. A major shortcoming is the lack of functional group tolerance on the new formed spiro pseudoindoxyl core. Our group is interested in developing a method that can synthesize pseudoindoxyl structure in good yield and *ee* that can also be employed in the total synthesis of natural products. This work was

inspired by our publication from 2019 (**Figure 1.3**)¹¹, which introduced a method to synthesize indoline from N-aryl-N-hydroxyl carbamates via aza-Heck cyclization.

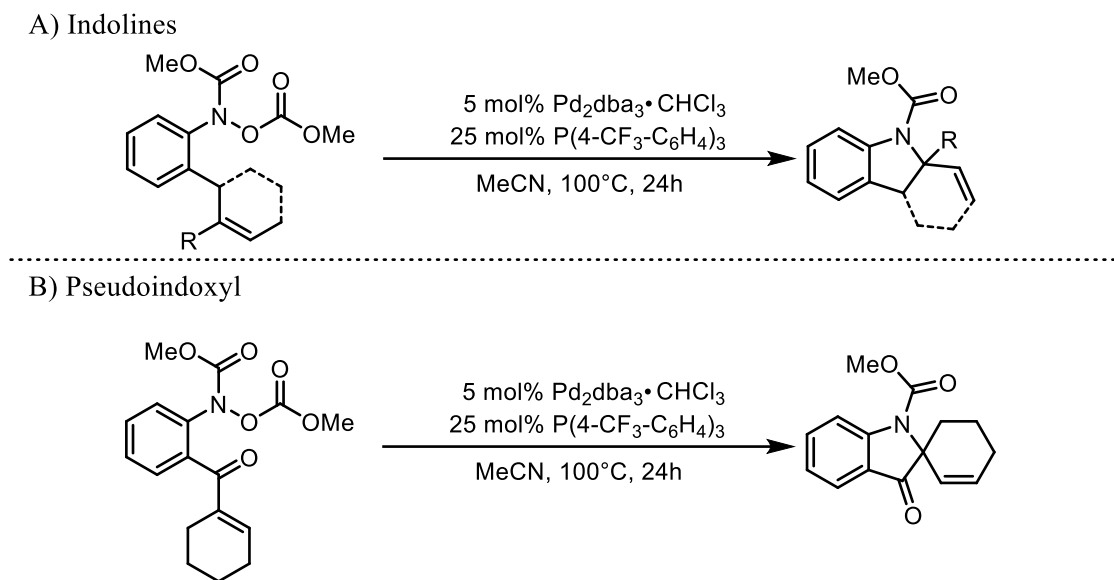


Figure 1.3: Indoline and Derivatives Synthesis via Aza-Heck Cyclization

In this document, the first chapter will conclude previous art of synthesizing the pseudoindoxyl skeleton, assorted by different symmetric or asymmetric methods. Methodologies and total syntheses precedent are both included. For the second chapter, I will show my efforts to demonstrate a method of solving the difficulties on establishing the chiral pseudoindoxyl by utilizing N-aryl-N-hydroxy carbamate with palladium catalyst.

1.2 Methods of Synthesizing Pseudoindoxyl Ring Systems

Upon the discovery and isolation of natural products containing a pseudoindoxyl core, the chirality of these compounds is essential (**Figure 1.4**). Therefore, asymmetric

construction of the pseudoindoxyl moiety becomes important and indispensable. Researchers from all over the world are dedicated to developing highly efficient and practical methods. These efforts will be discussed by reaction class.

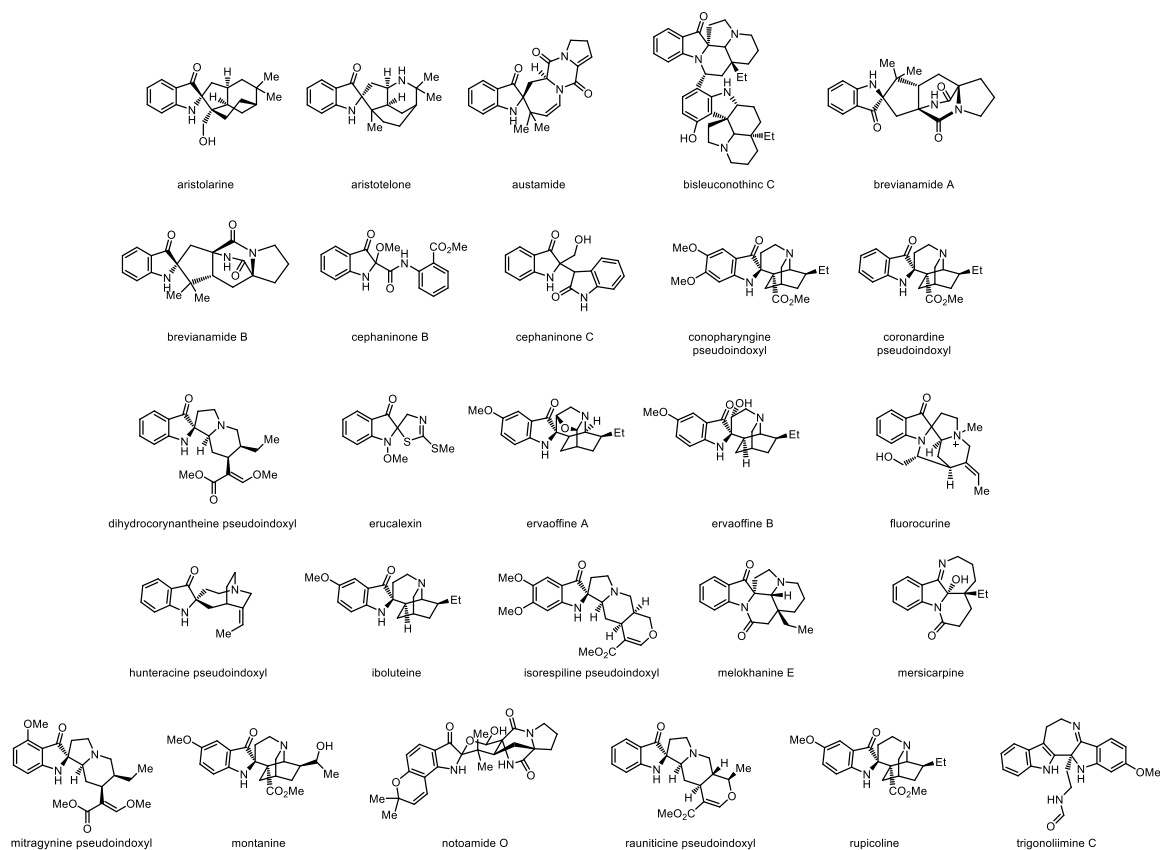


Figure 1.4: Selective Examples of Pseudoindoxyl-Contained Natural Products

1.2.1 Establish the Pseudoindoxyl Core Enantioselectively

1.2.1.1 Asymmetric Deprotonation

Grandilodines is a set of alkaloids isolated from genus *Kopsia*.¹² Its unique carbon skeleton, three quaternary carbon centers on indoline core furnished with

polycyclic ring system, and isolation scarcity, 16 mg per kilograms from leaves extracts, makes them remarkable synthetic targets. Nishida and co-workers proposed a novel synthetic route to complete the enantioselective total syntheses of grandilodine C **1.5.5**, a representative from the series alkaloids (**Figure 1.5**). Inspired from their past work, an essential chiral spirodiketone **1.5.4** was designed and could be applied for establishing the complex ring system. Starting from cyclohexanone derivative **1.5.1**, they synthesized the important precursor **1.5.2**. Then asymmetric deprotonation followed by Saegusa-Ito oxidation was proposed to generate the leading chiral center. They tried several chiral lithium amides under different temperature to achieve the desymmetrization of compound **1.5.2** and amine **1.5.3** was found the most efficient. After deprotonation under $-100\text{ }^{\circ}\text{C}$ for 5 minutes followed by trapping TMSCl and Saegusa-Ito oxidation, spirodiketone **1.5.4** was yielded 96% and 76% *ee*. Following synthesis smoothly transferred the chiral spirodiketone **1.5.4** to desired natural product **1.5.5** in 14 linear steps.

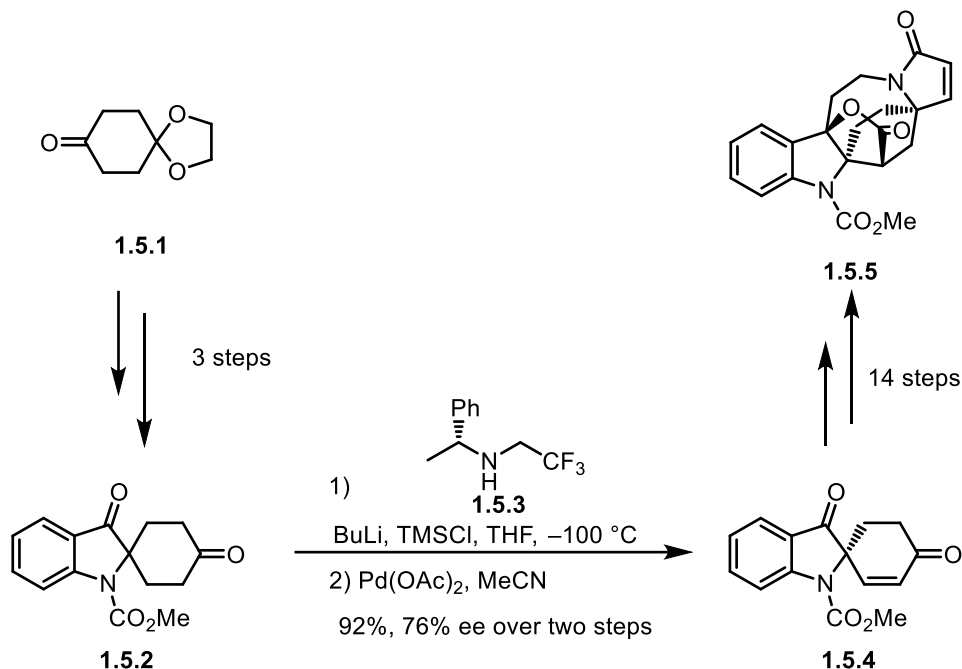


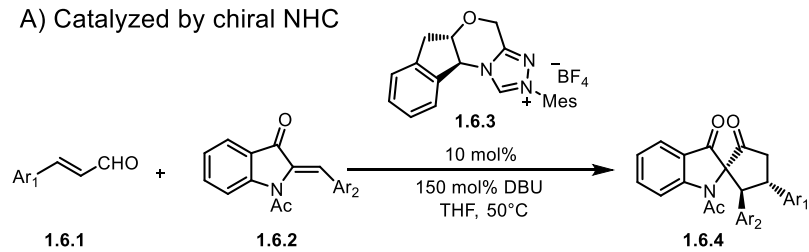
Figure 1.5: Total Synthesis of Grandilodine C

1.2.1.2 [3 + 2] Cycloaddition of Oxindole Derivatives

Another enantioselective establishment of pseudoindoxyl core utilizes [3+2] cycloaddition of oxindole derivatives. In 2014, Glorius and coworkers envisioned annulation reaction of unsaturated aldehyde with azaaurone-catalyzed chiral N-heterocyclic carbene (NHC) yielding valuable enantioenriched spiro pseudoindoxyl skeleton (**Figure 1.6A**).¹³ Optimized reaction condition evolved the combination of 10 mol % NHC catalyst **1.6.3**, 1.5 equivalent of DBU in THF under 50 °C for 24 h. To further explore the generality of this reaction, they investigated the electronic effect for both aldehyde **1.6.1** and azaaurone **1.6.2**. Whether the electron-rich or electron-poor, the annulation smoothly afforded desired spiro pseudoindoxyl product **1.6.4** under moderate yield (48%-82%) and excellent stereoselectivity (90%-95% ee and 3:1 to > 20:1 *dr*). Researchers also proposed a plausible mechanism (**Figure 1.6B**).

Starting from the deprotonation, the NHC is generated and undergo conjugate addition to receive NHC-homoenolate, which leads to 1,4-Michael addition from the back face directing by the hydrogen bond. After tautomerization to produce the acyl group, forming acyl azolium intermediate furnishes the final product via C-acylation and regenerate the NHC catalyst.

A) Catalyzed by chiral NHC



Ar₁ = Ph, 4-MePh, 4-FPh, 4-ClPh, 4-BrPh, 4-MeOPh, 4-Me₂NPh, 2-furyl, methyl, *n*-Pr

Ar₂ = Ph, 4-MePh, 4-ClPh, 3-ClPh, 4-MeOPh, 3-MeOPh, 2-furyl

48% - 82% yield
90% - 95% ee
3:1 to >20:1 dr

B) Proposed Mechanism

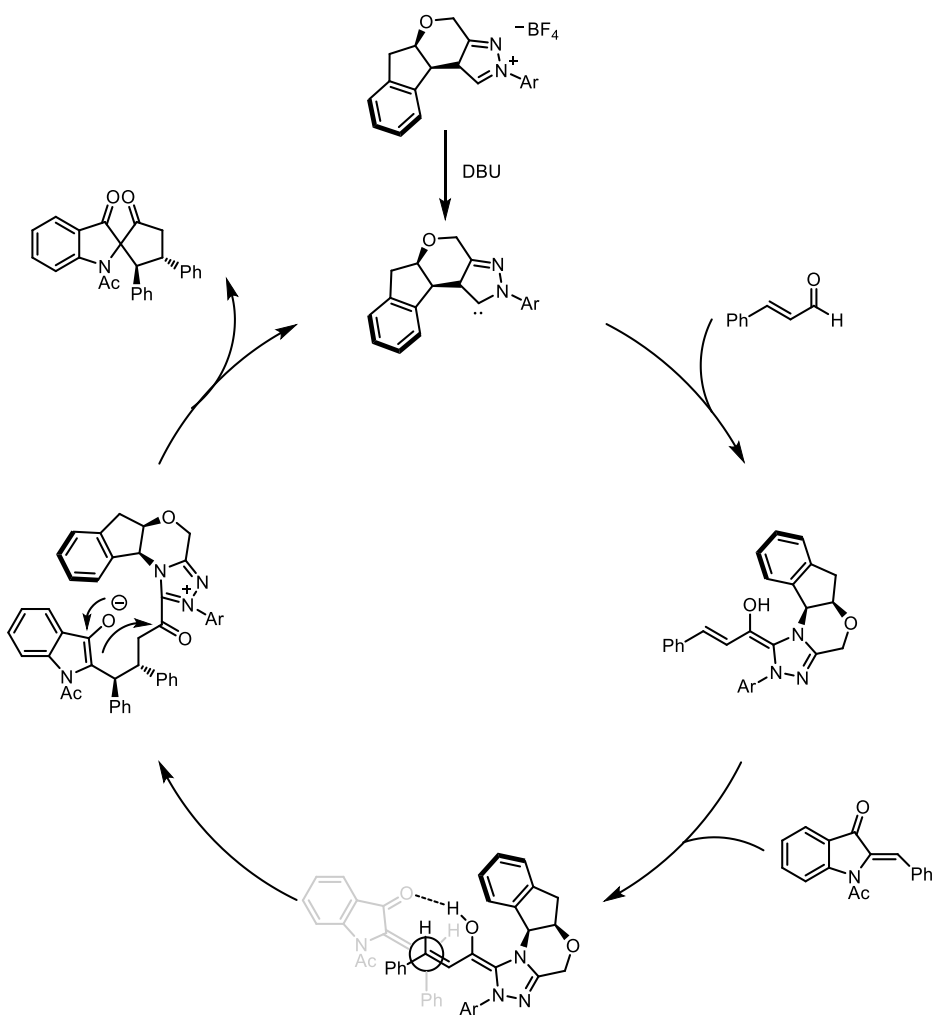


Figure 1.6: [3 + 2] Cycloaddition of Oxindole Derivatives

Similar to this method, Xu and coworker reported a thiourea catalyzed [3+2] cyclization of azomethine ylides **1.7.1** with azaaurone **1.7.2** to directly produce spiro-pseudoindoxyl-2,3'-pyrrolidine **1.7.4** (**Figure 1.7**).¹⁴ After screening several conditions, they found out the presence of catalyst **1.7.3** as the catalyst in DCE under room temperature was the most efficient combination. Various substitution groups, including electron-donating and electron-withdrawing group on different aromatic ring positions, were widely covered in their report. Good yield (64%-84%) and stereoselectivity (77%-95% ee and > 20:1 *dr*) revealed generality of this reaction for these substrates.

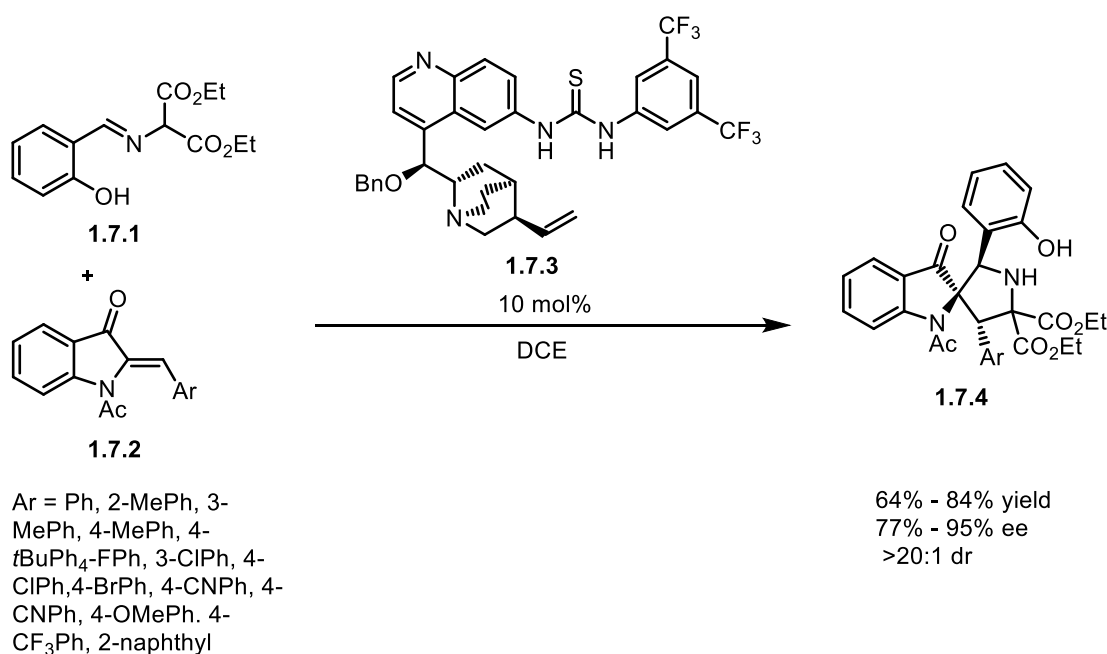


Figure 1.7: [3 + 2] Cycloaddition of Oxindole Derivatives

1.2.1.3 *O*-Phenyl Azide Acetylene Derivatives Cyclization

Recently, a freshly improved method of cyclization of *o*-phenyl azide acetylene by using dual catalyst: gold and proline was disclosed by Wu and coworkers in 2024 (**Figure 1.8**).¹⁵ They utilized 10 mol% of gold catalyst and 1 equiv of water to achieve the cyclization of *o*-phenyl azide acetylene derivatives **1.8.1**. With the leaving of nitrogen gas, the crucial intermediate 2-phenyl-3*H*-indol-3-one was formed. Directed by the hydrogen bond of the enamine product from proline and ketone **1.8.2**, the chiral center was generated in moderate yield (55% -97%) and excellent ee (87%-99%). This asymmetric Mannich reaction was conducted under mild condition and could tolerate various functional groups.

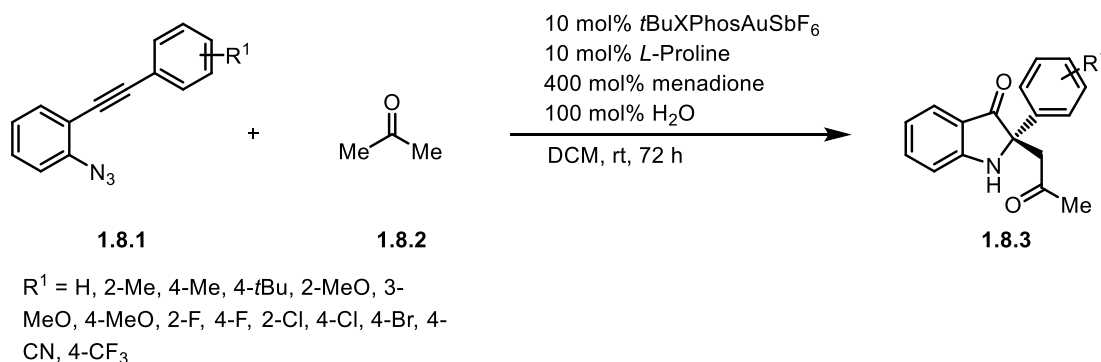


Figure 1.8: *O*-Phenyl Azide Acetylene Derivatives Cyclization

1.2.2 Prepare Diastereoselective Pseudoindoxyl Core

1.2.2.1 Biosynthetic Pathway Catalyzed by Base Condition

Diastereoselective construction of the pseudoindoxyl structure is an efficient way to synthesize this complex skeleton. The most widely applied method is to mimic the biosynthetic pathway, starting from the oxidation of C2, C3 disubstituted indole to

the 3-hydroxyindoxyl followed by 1,2-alkyl shift rearrangement to yield pseudoindoxyl. One of the representative examples is the accomplished enantioselective total synthesis of austamide by Baran and Corey utilized this approach to achieve the construction of chiral pseudoindoxyl (**Figure 1.9**).¹⁶ Austamide is a toxic natural product isolated from *Aspergillus ustus* CSIR 1128. Pentacyclic skeleton furnished with two tertiary carbon stereocenters through spiro quaternary connection. The synthesis commenced from (*S*)-tryptophan methyl ester and was successfully converted to diketopiperzine **1.9.2** in 6 steps. The treatment of compound **1.9.2** with *m*CPBA lead to epoxidation, which was followed by rearrangement using NaOMe produced intermediate **1.9.6** with all essential ring system in 54% yield over two steps. The synthesis was finished after the modification of functional groups in two linear steps.

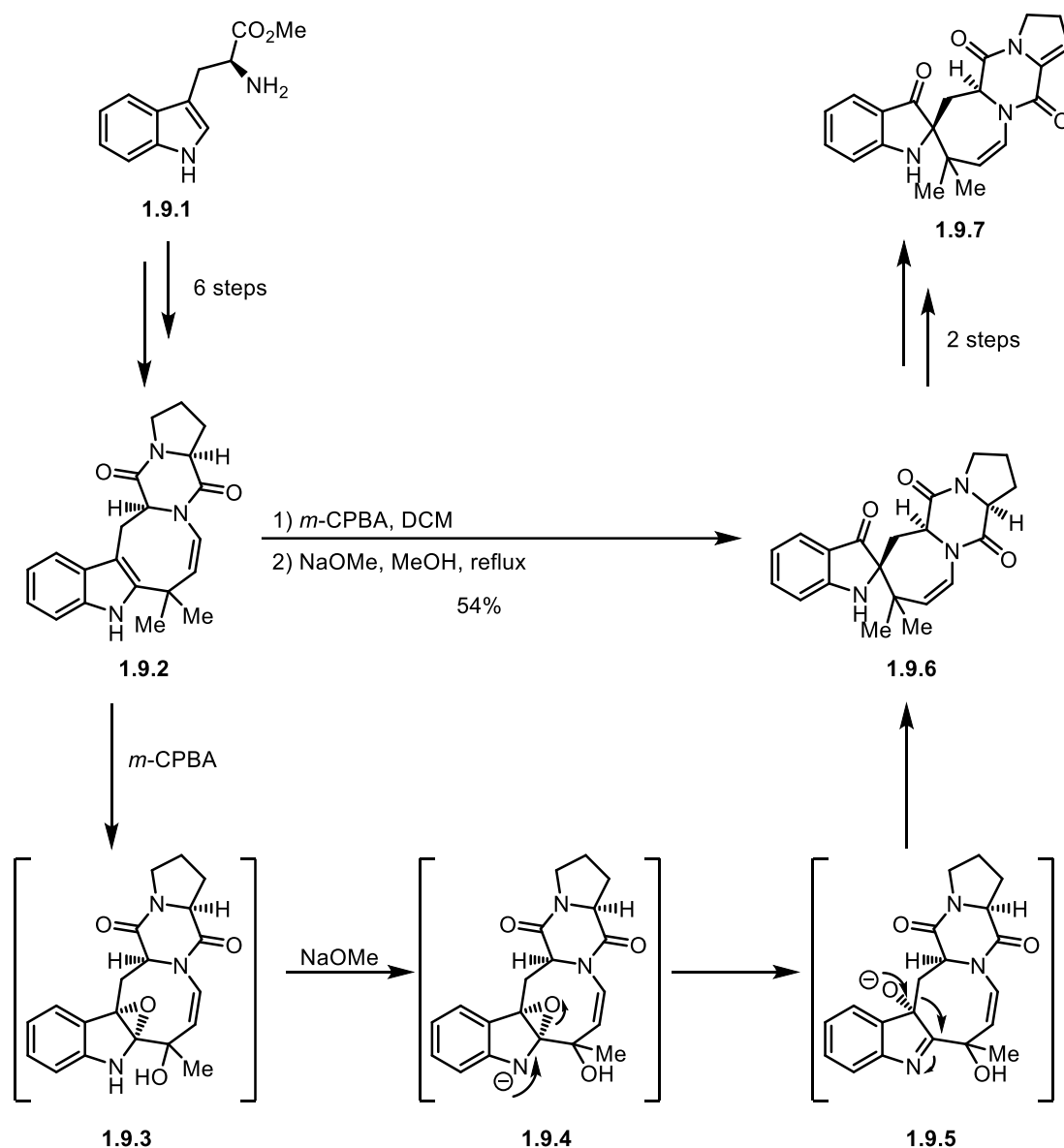
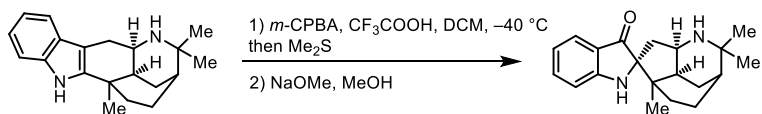


Figure 1.9: Total Synthesis of Austamide

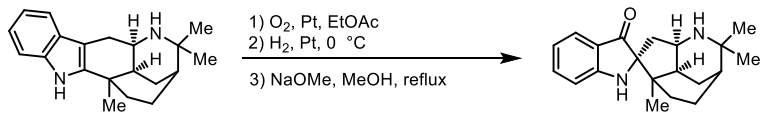
In addition to this pioneer work, there are also ten more total syntheses utilizing the biological pathway under base conditions: aristotelone by Borschberg¹⁷ in 3 steps and Heathcock¹⁸ in 8 steps, brevianamides A by Lawrence¹⁹ in 8 steps, brevianamides B by Williams²⁰ in 18 steps and Simpkins²¹ in 10 steps, iboluteine by She²² in 14 steps,

melokhanine E by Zhu²³ in 15 steps and mitragynine pseudoindoxyl by Sakai²⁴ in 3 steps. Key steps of the construction of pseudoindoxyl core for each synthesis were emphasized (**Figure 1.10A-1.10H**)

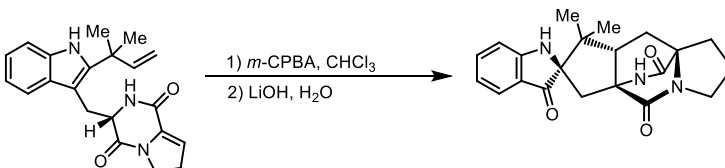
A) Synthesis of Aristotelone by Borschberg



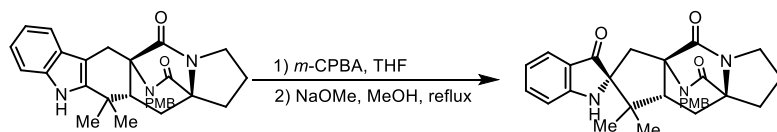
B) Synthesis of Aristotelone by Heathcock



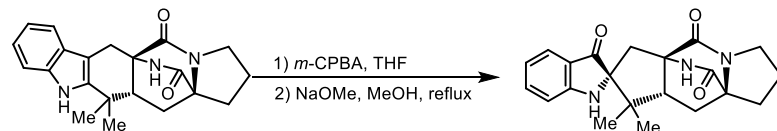
C) Synthesis of Brevianamide A by Lawrence



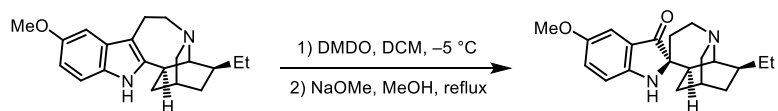
D) Synthesis of Brevianamide B by Williams



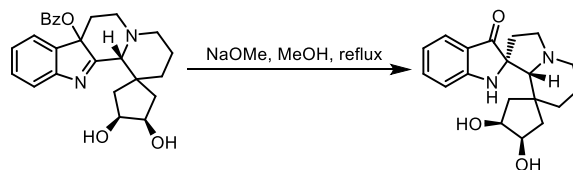
E) Synthesis of *ent*-Brevianamide B by Simpkins



F) Synthesis of Iboluteine by She



G) Synthesis of Melokhanine E by Zhu



H) Synthesis of Mitragynine Pseudoindoxyl by Sakai

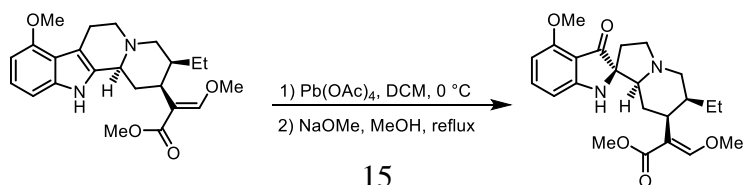


Figure 1.10: Key Steps of Synthesizing of Natural Products by Using Base-Catalyzed Biosynthetic Pathway

1.2.2.2 Biosynthetic Pathway Catalyzed by Acid Condition

The important rearrangement can also be catalyzed under acidic conditions. Majumdar and coworkers achieved the semi-synthesis of mitragynine pseudoindoxyl (**Figure 1.11**).⁸ Starting from mitragynine **1.11.1**, treatment of (bis(trifluoroacetoxy) iodo)benzene (PIFA) in water and acetonitrile resulted the oxidation of double bond and gave the hydroxylindolenine derivative in 57% yield. Catalyzed by Lewis acid $Zn(OTf)_2$, the rearrangement occurred under 110 °C in toluene and received the desired product in 39% yield with single isomer.

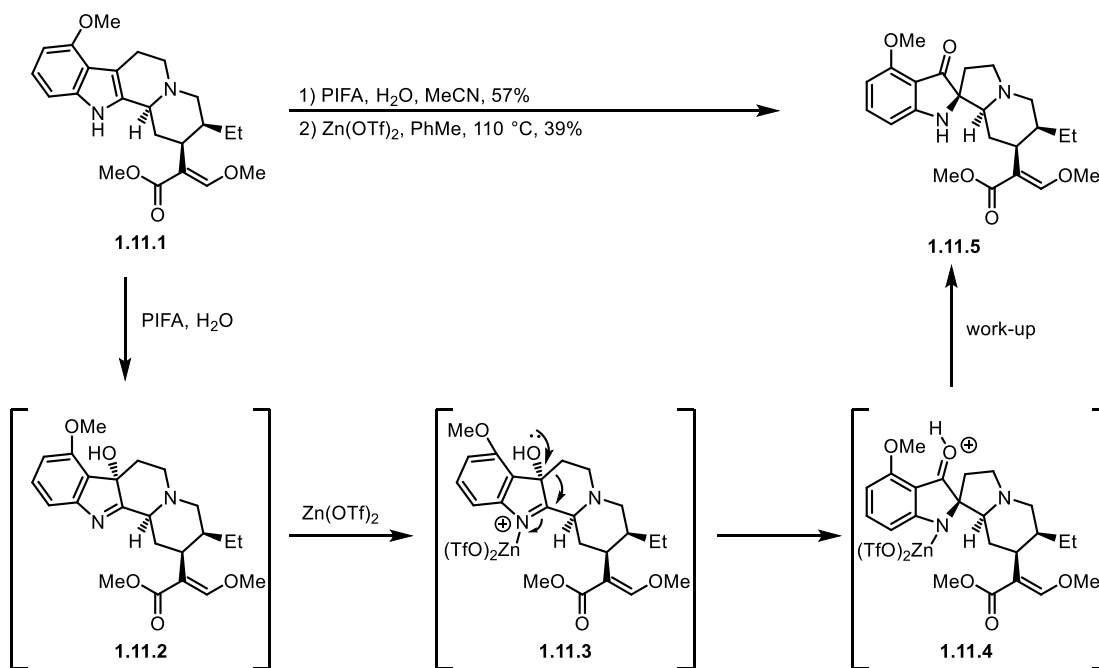
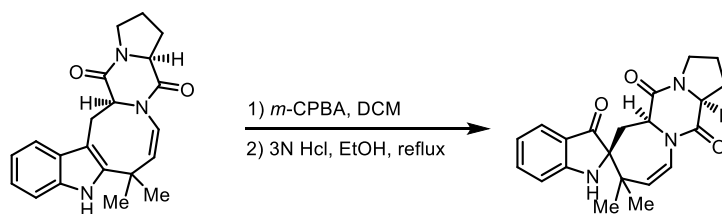


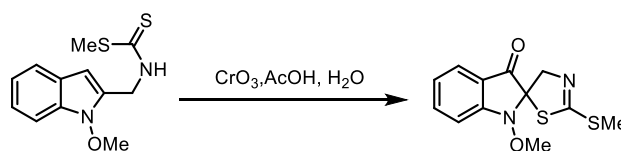
Figure 1.11: Semi Synthesis of Mitragynine Pseudoindoxyl

Except for this representative work, several reports also exhibit creative thoughts of synthesizing essential pseudoindoxyl core: austamide by Kishi²⁵ in 13 steps, erucalexin by Pedras²⁶ in 6 steps, isatisine A by Kerr²⁷ in 14 steps and Liang²⁸ in 11 steps (**Figure 1.12A-1.12D**).

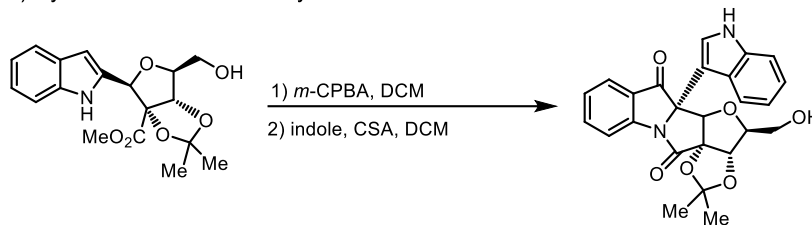
A) Synthesis of *trans*-Tetrahydroaustamide by Kishi



B) Synthesis of Erucalexin by Heathcock



C) Synthesis of Isatisine A by Kerr



D) Synthesis of Isatisine A by Liang

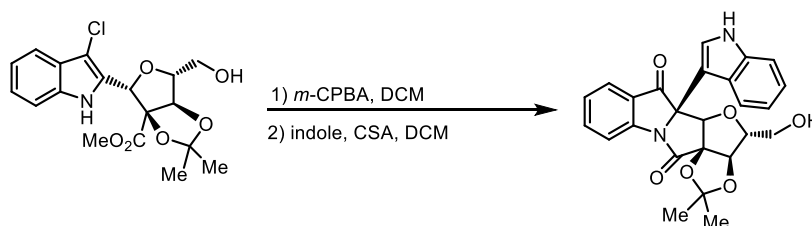


Figure 1.12: Key Steps of Synthesizing Natural Products by Using Acid-Catalyzed Biosynthetic Pathway

1.2.2.3 Buchwald Amidation

In addition to the widely applied and efficient method of making pseudoindoxyl skeleton, alternative ways were also well developed. Panek and coworkers reported a total synthesis of isatisine A, an alkaloid that exhibits cytotoxicity against C8166 and anti-HIV activity isolated from *I.Indigotica* (**Figure 1.13**).²⁹ Intriguing structure of isatisine A includes a tetracyclic pseudoindoxyl core fused with a fully substituted furan ring. The synthesis began with the construction of fully substituted furan ring by condensation of **1.13.1** and **1.13.2**, followed by building up other heteroatom rings to yield essential precursor **1.13.3** for modified Buchwald amidation. The key step of making pseudoindoxyl core **1.13.4** occurred under CuI-catalyzed coupling with the presence of potassium carbonate in 90% yield. Subsequent deprotection achieved the total synthesis of isatisine A **1.13.5**.

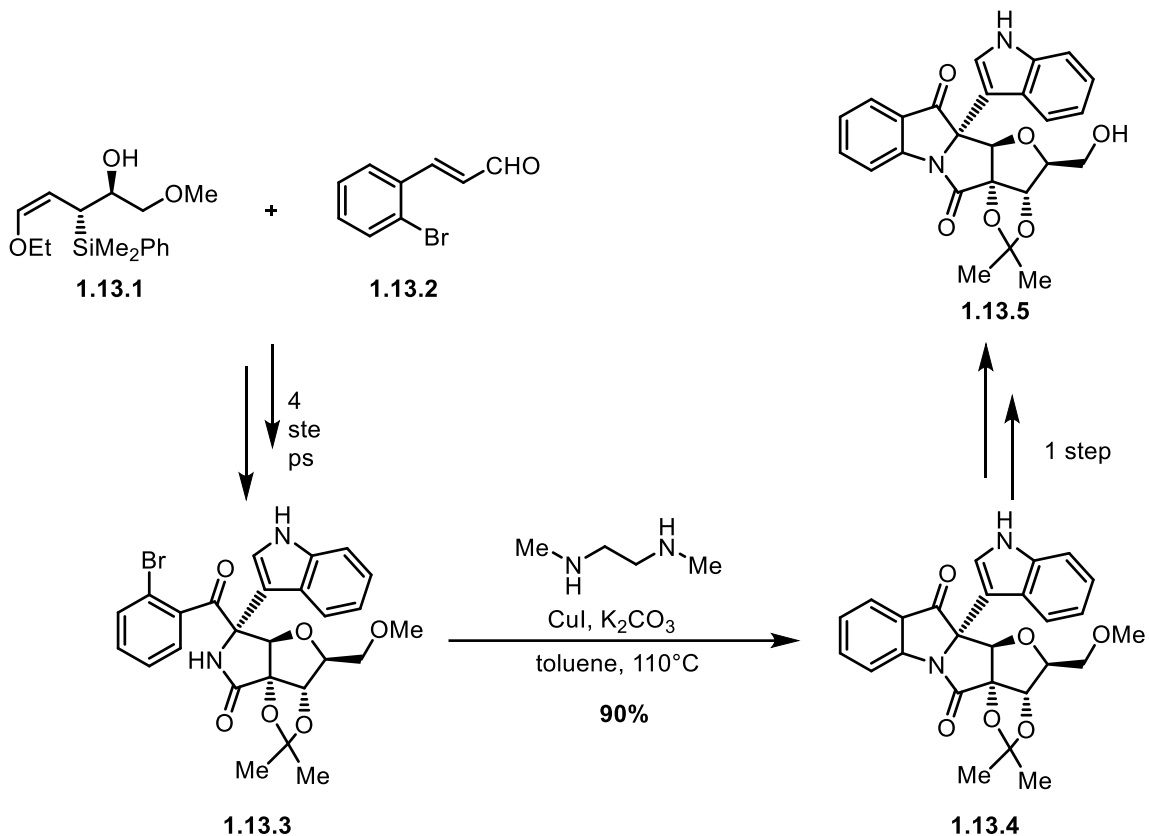


Figure 1.13: Total Synthesis of Isatisine A

1.2.2.4 Diels-Alder Reaction

Grandilodines are *Kopsia* alkaloids that received a lot of attention on their various structural complexity and abundant biological activity. Zu and coworkers reported grandilodine B as the target with the indoline core and bridge cycle furnished with 3 contiguous chiral centers (**Figure 1.14**).³⁰ The synthesis commenced from condensation of commercially available indoxyl **1.14.1** and ethyl glyoxylate to give the dienophile **1.14.2**. Following Diels-Alder reaction was successfully proceeded by combing dienophile **1.14.2** and diene **1.14.3** to establish the pseudoindoxyl core **1.14.4**

diastereoselectively in 72% yield. After building this important core, grandilodine B **1.14.5** was smoothly synthesized via 18 linear steps.

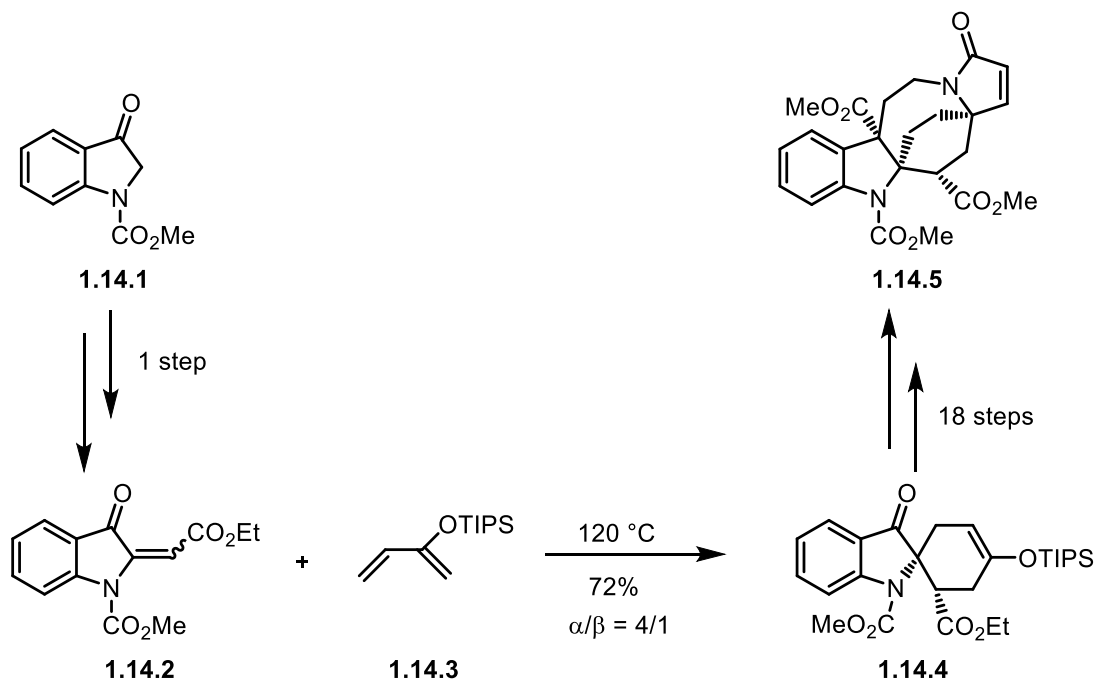


Figure 1.14: Total Synthesis of Grandilodine B

1.2.2.5 Ugi and Houben-Hoesch Reaction

Sorenson and coworkers reported a synthesis of 11-methoxy mitragynine pseudoindoxyl, a modified molecule from natural products, by utilizing an efficient combination of Ugi and Houben-Hoesch reaction (**Figure 1.15**).³¹ Starting from the Cbz-protected Geissman-Waiss lactone **1.15.1**, the ketone component **1.15.2** in Ugi reaction was synthesized. After mixing with 3,5-dimethoxyaniline, the imine was obtained and the exposure to isocyanide followed by hydrolysis resulted in the formation pseudoindoxyl core **1.15.6** in single isomer in 63% over 3 steps. Although

the structure is different from the natural product, the regioselectivity and reactivity exhibits significant improvements if 3,5-dimethoxyaniline is used instead of the 3-methoxyaniline. Later steps converted the pseudoindoxyl intermediate to the desired modified natural product **1.15.7** in 9 steps.

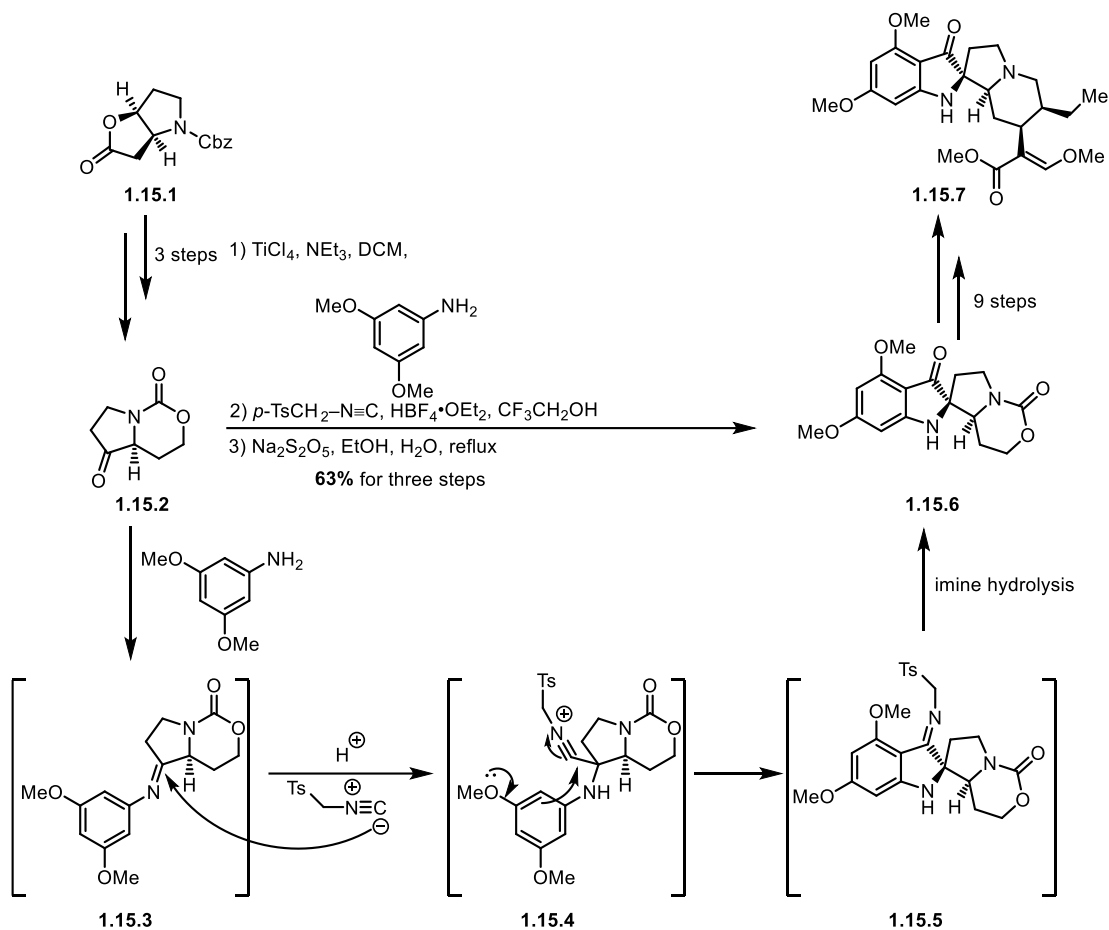


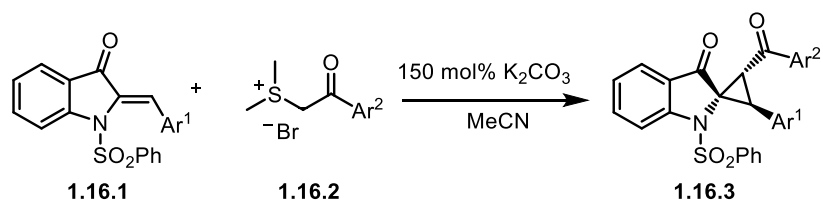
Figure 1.15: Total Synthesis of 11-Methoxy Mitragynine Pseudoindoxyl

1.2.2.6 [2 + 1] Cycloaddition of Oxindole Derivatives

[2 + 1] cycloaddition is also an alternative and efficient method to produce pseudoindoxyl core and cyclopropane ring. Huang and coworker developed a sulfur

ylide chemistry to react with 2-indenyl hydrazine (**Figure 1.16A**).³² The optimized conditions are the combination of hydrazine **1.16.1** and ylide **1.16.2** substrates with 150 mol % potassium carbonate in acetonitrile under 0 °C. The generality of this reaction was widely tested by various substituent groups with different electronic effect and spatial properties. Divergent substitution on aryl ring (Ar^1) and ylide (Ar^2) gives significant different yield with perfect selectivity (32%-88% yield and >20:1 *dr*). In addition to for ylide, tosylhydrazones can also participate this type of reaction. Rossi and coworkers reported another [2 + 1] annulation to receive fully substituted cyclopropane ring (**Figure 1.16B**).³³ After looking at several reagents, 10 mol % of catalyst benzyltriethylammonium chloride (BTEAC) was found the most efficient one with the presence of 200 mol % of cesium carbonate in toluene under 90 °C. Electronic effect was widely examined on aryl ring for both on olefin (R^1) and on hydrazone (R^2). Yield various from 46% to 99%, which was severely influenced by heteroatom ring system, but the stereoselectivity keeps the same, always > 20:1.

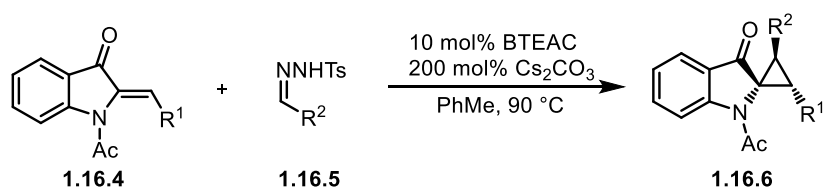
A) Catalyzed by Sulfur Ylide



Ar¹ = Ph, 2-MePh, 4-*i*PrPh, 3-ClPh, 4-ClPh, 3-BrPh, 4-BrPh, 2-MeOPh, 2-NO₂Ph, 4-NO₂Ph, 2-furyl, 2-thienyl
Ar² = Ph, 4-FPh, 4-BrPh, 2-NO₂Ph, 4-MeOPh, 2-naphthyl

32% - 88% yield
> 20:1 dr

B) Catalyzed by Tosylhydrazone



R¹ = Ph, 2-MePh, 4-MePh, 4-FPh, 4-ClPh, 4-CNPh, 3-MeOPh, 4-MeOPh
R² = Ph, 4-MePh, 4-FPh, 2-BrPh, 4-MeOPh, 2-naphthyl, cyclohexyl

46% - 99% yield
> 20:1 dr

Figure 1.16: [2 + 1] Cycloaddition of Oxindole Derivatives

1.2.3 Synthesize Racemic Pseudoindoxyl Core

1.2.3.1 Nucleophilic Attack

Highly enantioselective and diastereoselective methodologies could be developed and inspired from racemic reactions. For instance, Pierce group reported a total synthesis of melokhanine E, an alkaloid isolated from the twigs and leaves of *melodinus khasianus* exhibits biological activity (**Figure 1.17**).³⁴ The unique 6/5/5/6/6 pentacyclic structure with pseudoindoxyl ring system furnished with three contiguous stereocenters. The synthesis began with the C–N bond formation between anthranilic acid **1.17.1** and bromo-lactone, imperative amino acid precursor **1.17.2** was produced

in 72% yield. Then treatment of triethylamine and acetic anhydride gave spirocyclic pseudoindoxyl **1.17.3** in 61% yield. With necessary compound in hand, following synthesis achieved smoothly with 10 more convergent steps and finally obtained the melokhanine E in 11% overall yield.

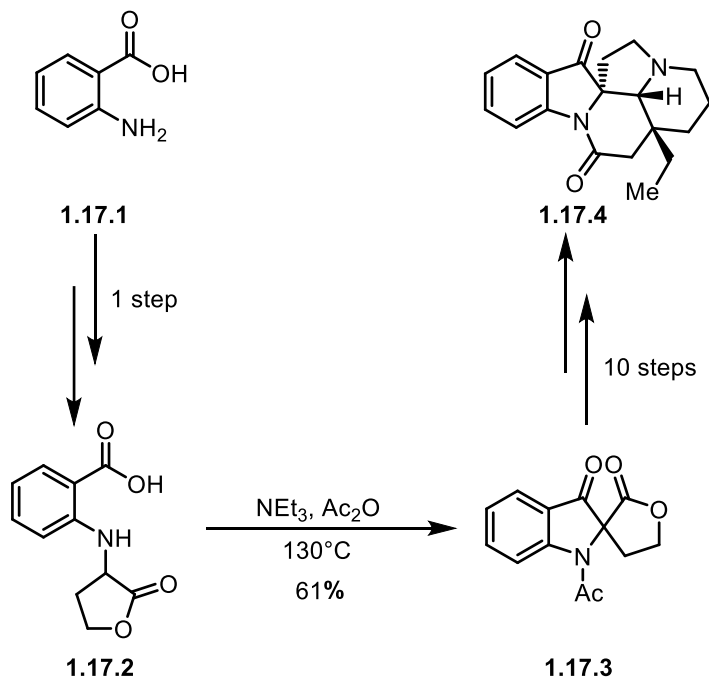


Figure 1.17: Total Synthesis of Melokhanine E

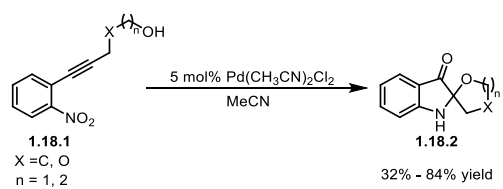
1.2.3.2 *O*-Nitro Phenyl Acetylene Derivatives Cyclization

In addition to the example appeared in the total synthesis paper, there are also several well-designed methodologies that show the great generality of reactions and excellent innovation from researchers. First general method is the cyclization of *o*-nitro phenyl acetylene derivatives. In 2011, Ramana and coworkers proposed a palladium catalyzed nitroalkynol cycloisomerizations to yield the desired spirocyclic

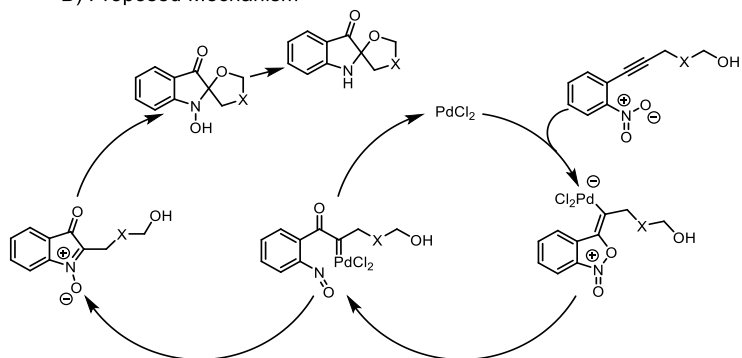
pseudoindoxyl (**Figure 1.18A**).³⁵ Extensive investigation for optimal reaction condition was proceeded and 10 mol % Pd(CH₃CN)₂Cl₂ as the catalyst in acetonitrile under room temperature for 4 h were the best combination. All the substrates that form the new tetrahydropyran ring or 1,4-diethylene dioxide ring were received in relatively high yield (78%-84%). However, the yield significantly dropped (32%-38%) if the new tetrahydrofuran ring was formed. A plausible mechanism was also proposed. Starting from the 5-*exo-dig* cyclization of nitroalkyne, intermediate was produced and transformed to metal carbene. After nitrogen addition to the metal carbene, isatogen was afforded and nucleophilic attack from OH group generated spirocyclic pseudoindoxyl skeleton followed by internal reduction of N–O bond to finally received the desired compound.

Another method that utilizes BF₃•Et₂O and phenyliodine diacetate (PIDA) as catalyst to generate 6/5/5/6 spiro pseudoindoxyl from diarylacetylene was disclosed by Du and coworkers in 2015 (**Figure 1.18B**).³⁶ After heating the mixture of starting material **1.18.3** and BF₃•Et₂O in DCE at 80 °C overnight, PIDA was added to the mixture under room temperature and stirred for 1 h to give the desired spiro pseudoindoxyl product **1.18.4**. Several substituents on both aryl ring with various electronic effect almost not impact the yield (77%-88%).

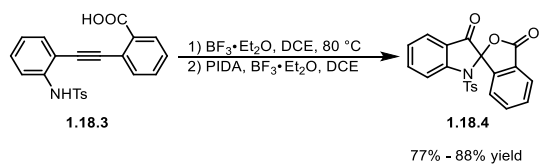
A) Catalyzed by Palladium



B) Proposed Mechanism



C) Catalyzed by PIDA



D) Proposed Mechanism

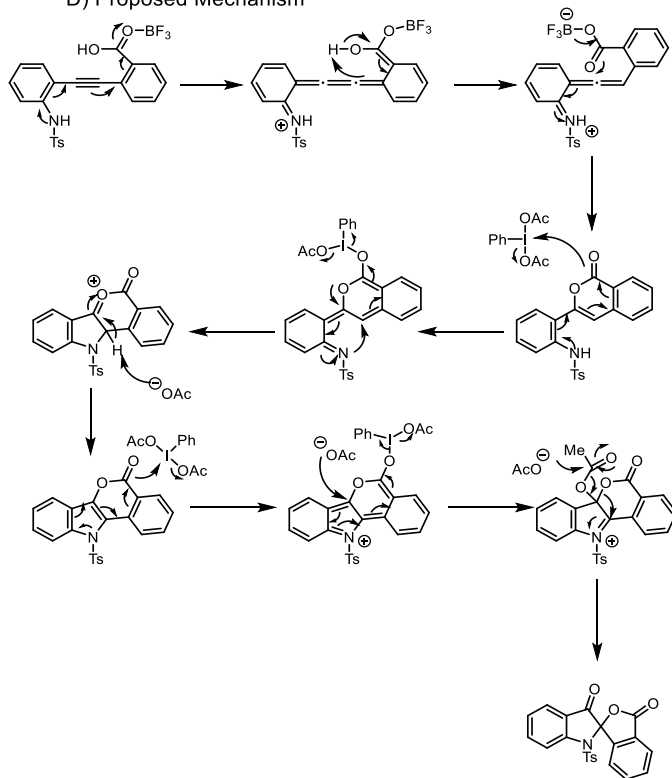
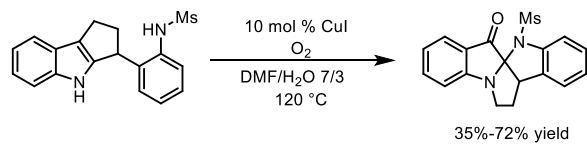


Figure 1.18: *O*-Nitro Phenyl Acetylene Derivatives Cyclization

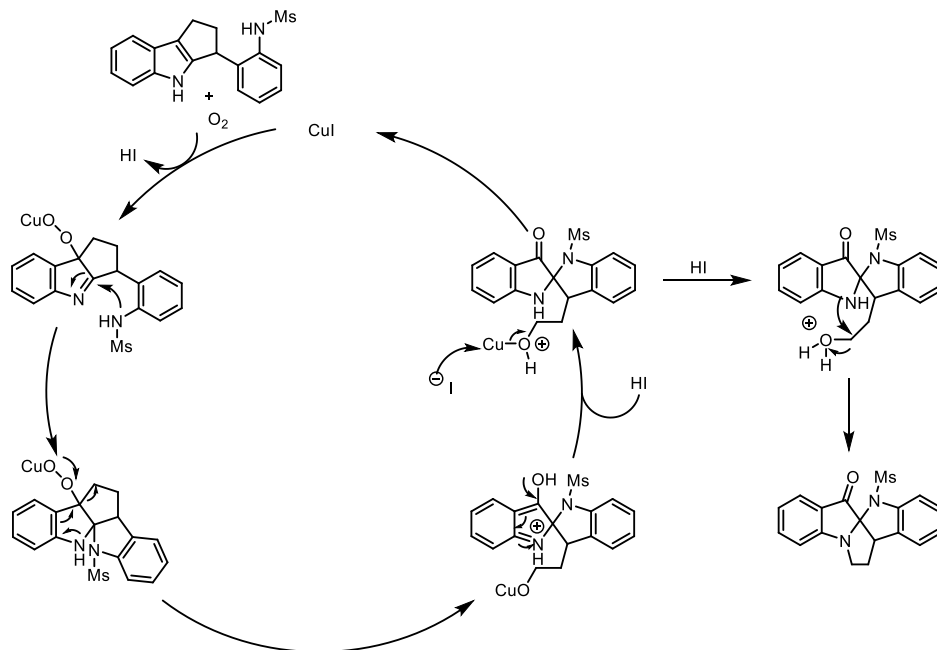
1.2.3.3 Indole derivative cycloaddition

Indole derivative cycloaddition is also an alternative method to obtain the pseudoindoxyl skeleton. In 2014, Pal and coworkers reported a copper-mediated cascade reaction of cyclopenta[b]indole to furnish the spiro pseudoindoxyl (**Figure 1.19A**).³⁷ Optimal conditions were found using 10 mol % of CuI as the catalyst in the mixture of DMF and water (7/3) under 120 °C for 2 h. Various substituent groups with different electronic effects could also produce corresponding product under optimal conditions in moderate yield (57%-72%). Compare to the result of performing reaction under nitrogen atmosphere or increasing the duration of the stirring, it was concluded that air played an essential role in this reaction. Another approach that using visible light to induce dearomative reaction of indole derivatives was described by Zhu and coworkers in 2016 (**Figure 1.19B**).³⁸ Provided optimal conditions were utilizing the 2 mol % Ru(bpy)₃Cl₂ as catalyst and DABCO as base in acetonitrile under room temperature and air with the irradiation of 36W CFL for 24 h. Toleration of methyl, methoxy and halogen on phenyl ring or adjacent carbon of alcohol made this reaction more persuasive. All reactions performed with moderate yield (61%-71%).

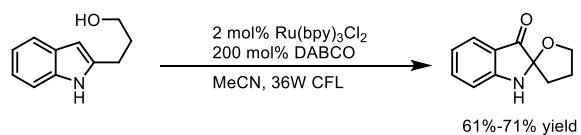
A) Copper Catalyzed Cascade



B) Proposed Mechanism



C) Photo redox



D) Proposed Mechanism

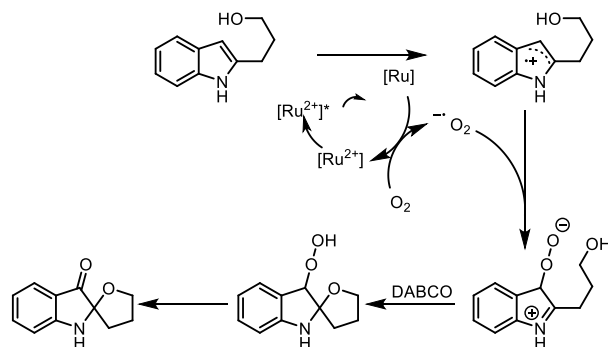


Figure 1.19: Indole Derivatives Cycloaddition

1.3 Conclusion

Synthesizing spirocyclic pseudoindoxyl draws tremendous attention for the researchers all over the world. Although several well-developed methodologies and widely used synthetic ways are utilized to resolve this problem, there are still some limitations. Firstly, four precedents synthesize pseudoindoxyl core enantioselectively but lead to products with narrow substrate scope due to mechanistic pathways. Then, all methodologies demonstrate excellent reactivity for proposed substrates. However, the new formed spiro ring must contain a heteroatom to achieve the nucleophilic attack to enol or enolate. Lastly, the new formed spiro ring is limited to each specific method and other ring size could result in low yield or poor selectivity. To overcome those shortages, we are dedicated to exploit a new method to synthesize spirocyclic pseudoindoxyls in an effective and comprehensive way.

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Chapter 2

ENANTIOSELECTIVE SYNTHESIS OF PSEUDOINDOXYL COMPOUNDS VIA AZA-HECK CYCLIZATION

2.1 Introduction

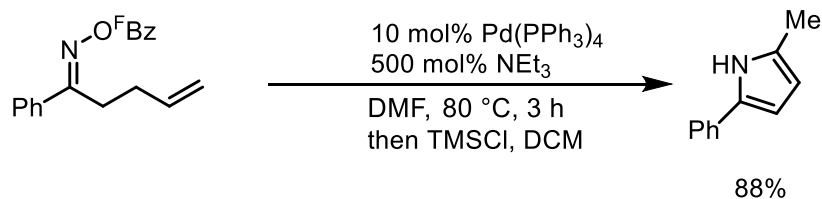
As described in chapter 1, there are various well-developed methods for synthesizing the spiro pseudoindoxyl scaffold. To overcome limitations mentioned in conclusion in chapter 1, our group is dedicated to developing a general method to expand the access to pseudoindoxyl motif. Encouraged by the previous success of indoline synthesis, we hypothesized that the aza-Heck cyclization is also available to synthesize the spiro pseudoindoxyl skeleton using nitrogen electrophile *N*-aryl-*N*-carbamate. The Heck-like cyclization exhibits some advantages such as high chemoselectivity, mild conditions, low toxicity. This chapter will highlight the early precedents of aza-Heck cyclization. There are several well-organized reviews by Narasaka¹, Bower² and Watson³. Additionally, a demonstration of our effort in developing the aza-Heck pathway to access to the spiro pseudoindoxyl products is also included.

2.2 Early Studies

2.2.1 First Example

Narasaka and co-workers first reported a cyclization reaction in 1998 synthesizing pyrrole (**Figure 2.1A**).⁴ They found that γ,δ -unsaturated *O*-pentafluorobenzoyloximes, treated with 10 mol % Pd(PPh₃)₄ and 5 equiv of triethylamine under 80 °C in DMF, yielded the cyclization product. Following exposure of TMSCl, they could obtain the isomerized pyrrole product. The proposed mechanism involves several elementary steps similar to conventional Heck reaction. Although the notable oxidative addition of Pd(0) into the N–O bond forming imine-like palladium species was not isolated by Narasaka, Hartwig and coworkers successfully obtained the key oxidative addition intermediate from the treatment of Pd(PCy₃)₂ with *O*-acyl ketoxime in toluene (**Figure 2.1B**).⁵ After Narasaka's pioneering work, a variety of related methodologies emerged to further develop the potential of aza-Heck reaction.

A) First Example of aza-Heck Cyclization



B) Isolation of Oxidative Addition Intermediate

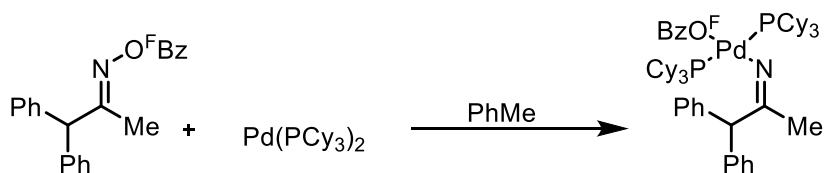


Figure 2.1: First Example of aza-Heck Cyclization and Isolation of Oxidative Addition Intermediate

2.2.2 Reactions with Oxime Ester Derivatives

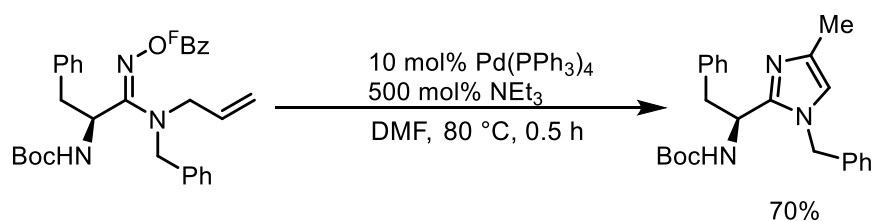
Various *N*-heterocycle compounds with different ring sizes were synthesized from oxime ester derivatives via distinguish modes. Abell and coworkers developed an intriguing method for the synthesis of trisubstituted imidazoles via *5-exo* cyclization and then utilized it to the application of amino acid mimetics with a C-terminal imidazole (**Figure 2.2A**).⁶ Same as Narasaka's condition, the *O*-pentafluorobenzoylamidoximes could be converted to the desired cyclization product in great yield (68%-88%) and chiral center could maintain the optical activity.

Compared to *5-exo* cyclization, *5-endo* cyclization could also work and Ito with coworkers reported the synthesis of 4-difluoromethylene-substituted 1-pyrrolines (**Figure 2.2B**).⁷ The reaction conditions was 1 mol % Pd(PPh₃)₄, 1 equiv of PPh₃ in dimethylacetamide (DMA) under 100 °C for 1 h. They also examined the importance

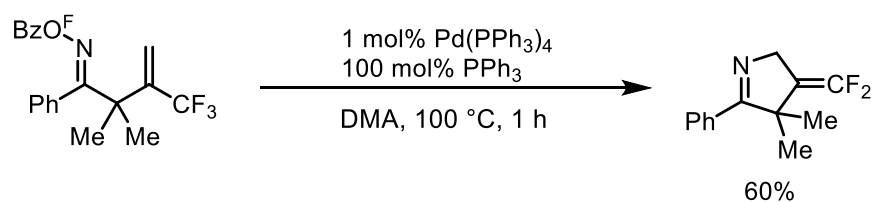
of trifluoromethyl group and it's proved that the *5-endo* cyclization only happened with the presence of trifluoromethyl group.

In addition to 5-membered ring, Narasaka and coworkers expanded the versatility to synthesize 6-membered pyridine ring. Based on the conditions they used in previous paper, the additive of 5 equiv $n\text{Bu}_4\text{NCl}$ was crucial to direct the *6-endo* cyclization of oxime with methoxy substitution on allylic position (**Figure 2.2C**).⁸ Under same condition, the *6-exo* cyclization can be smoothly performed from *o*-allylacetophenone derivatives in moderate yield to receive isoquinoline (**Figure 2.2D**).⁷

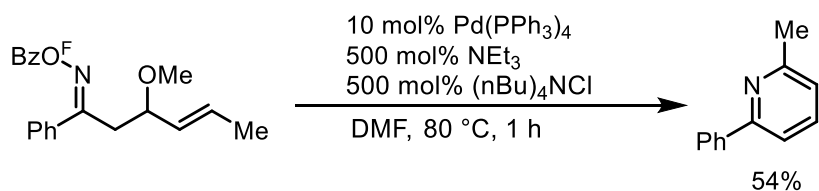
A) 5-Exo Cyclization: Making Imidazoles



B) 5-Endo Cyclization: Making Pyrrolines



C) 6-Endo Cyclization: Making Pyridines



D) 6-Exo Cyclization: Making Isoquinoline

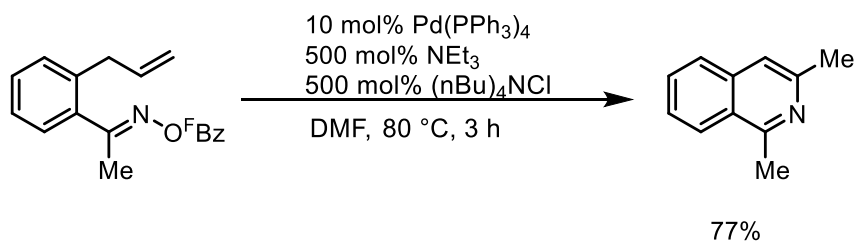


Figure 2.2: Aza-Heck Cyclization of Oxime Ester Derivatives

2.3 Recent Studies

2.3.1 Synthesis of steric hindered alkene from Oxime Esters

Recently, the reactivity of aza-Heck cyclization has been greatly studied. In 2013, Bower and coworker disclosed a palladium catalyzed 5-*exo* cyclization of 1,1-disubstituted alkenes to synthesize the α,α -disubstituted dihydropyrrole (**Figure 2.3**).⁹ The optimal conditions were 3.75 mol % Pd₂(dba)₃, 15 mol % P(3,5-(CF₃)₂C₆H₃)₃ as the ligand and 2 equiv of NEt₃ as additive in DMF for 120 °C. This protocol could tolerate various range of substitution groups of ketoxime esters and obtain corresponding products in good yield (61%-85%).

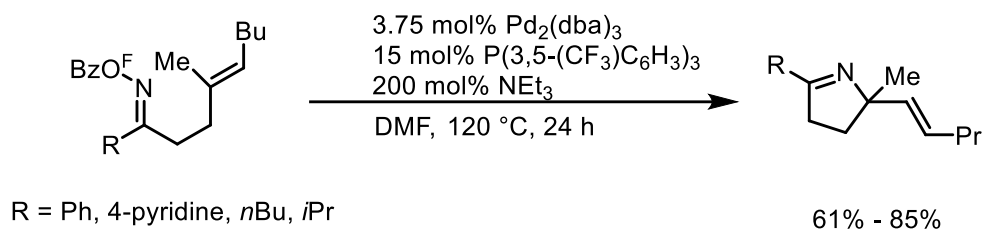


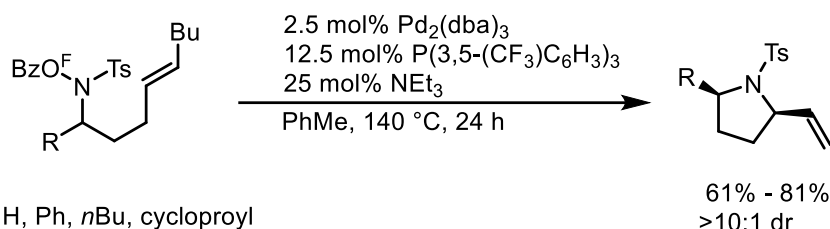
Figure 2.3: Synthesis of Steric Hindered Alkene

2.3.2 Synthesis of pyrrolidines from Sulfonamide

Except for oxime ester derivatives, palladium catalyzed cyclization of *N*-(pentafluorobenzyloxy)-sulfonamides, a new set of nitrogen electrophiles, was discovered by Bower and coworkers in 2016 (**Figure 2.4A**).¹⁰ This method overcome one of the major limitations of aza-Heck cyclization: nitrile formation of aldoxime substrates. (*E*)-imino-Pd(II) intermediate was favored compared to *Z*-isomer and the beta-hydride elimination underwent dominantly rather than the cyclization. *N*-(pentafluorobenzyloxy)-sulfonamide substrates force the palladium group staying at the

E position of hydrogen after oxidative addition and following cyclization was carried on rapidly to generate the heterocyclic ring systems (**Figure 2.4B**). The optimal conditions were 2.5 mol % Pd₂(dba)₃, 12.5 mol % P(3,5-(CF₃)₂C₆H₃)₃ as the ligand and 25 mol % of NEt₃ as additive in toluene under 140 °C for 24 h. Various multi-substituted alkenes and diverse electron effect substitutions could be tolerated under reaction conditions and corresponding desired cyclization products were obtained in good yield (61%-81%) and moderate diastereoselectivity (> 10:1 d.r).

A) Aza-Heck cyclization of *N*-(Pentafluorobenzoyloxy)sulfonamides



B) *E* and *Z* Isomers of Aldoxime Esters

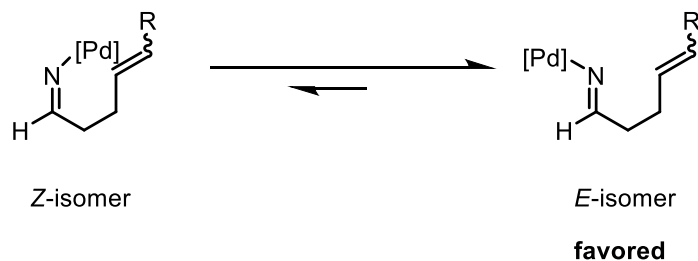


Figure 2.4: Aza-Heck Cyclization of *N*-(Pentafluorobenzoyloxy)sulfonamides

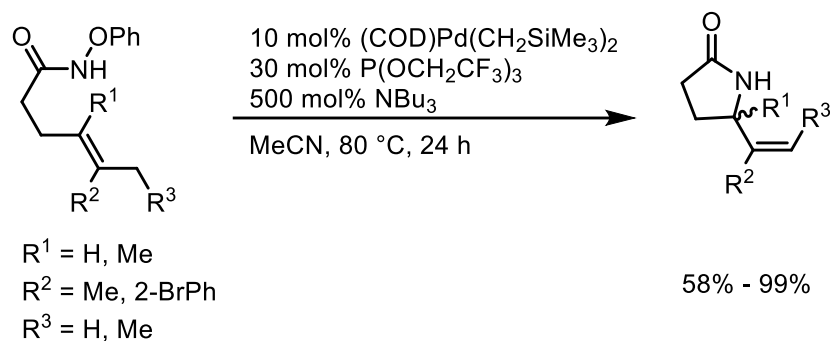
2.3.3 Aza-Heck Cyclization of *O*-Phenyl Hydroxamate

O-phenyl hydroxamate, another new class of nitrogen electrophile, and the direct synthesis of unprotected vinyl γ -lactams by the aza-Heck cyclization of *O*-phenyl

hydroxamate were developed by our group in 2016 (**Figure 2.5A**).¹¹ The choice of this type of nitrogen electrophile efficiently prevented the formation of urea derivatives through Lossen rearrangement. The optimal conditions were 10 mol % (COD)Pd(CH₂TMS)₂ as palladium source, 30 mol % electro-deficient P(OCH₂CF₃)₃ as the ligand with 5 equiv of NBu₃ in acetonitrile under 80 °C for 24 h. Utilizing this conditions, 5-*exo* aza-Heck cyclization involving various cycloalkenes, multi-substituted linear alkenes provided desired target with good yield (58%-99%). Reaction mechanism was confirmed to be aza-Heck pathway rather than aza-Wacker pathway, supported by the comparative experiment for the *N*-acyl sulfonamide substrates. There was no product obtained under original reaction conditions which states that palladium inserts to the N–O bond and undergoes aza-Heck pathway to achieve the cyclization.

Later in 2018, our group utilized the *N*-phenoxy urea substrates with *O*-Phenyl hydroxamate as electrophile to synthesize unsaturated and unprotected imidazolidinones by using aza-Heck cyclization (**Figure 2.5B**).¹² Investigation of reaction conditions began with the previous one in 2016 and was optimized to the combination of 2.5 mol % [(cinnamyl)PdCl]₂, 5 mol % P(OCH₂CF₃)₃, 2 equiv NEt₃, 5 mol % PhMgBr as the reducing agent and 10 mol % AgOTs as the inhibitor of alkene isomerization in acetonitrile under 50 °C for 24 h. A variety of substitution group on R₄ and R₅ allowed the formation of corresponding desired unprotected imidazolidinone products in moderate yield (47%-99%).

A) Synthesis of Lactam



B) Synthesis of imidazolidinones

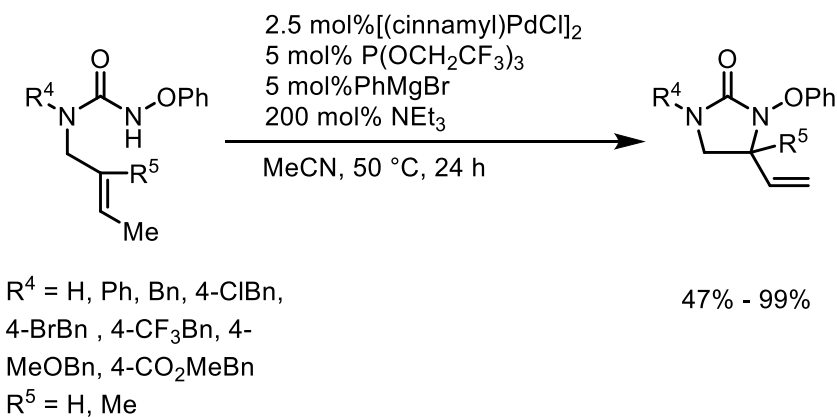


Figure 2.5: Aza-Heck Cyclization of *O*-Phenyl Hydroxamates

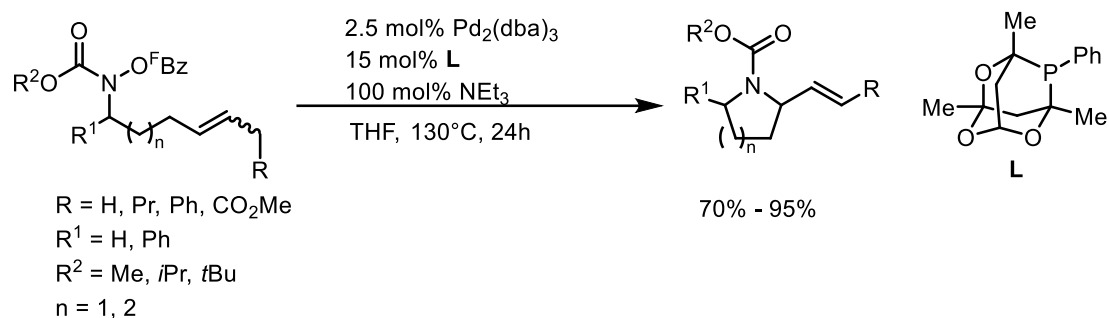
2.3.4 Aza-Heck Cyclization of Carbamates

Another creative development greatly expands the application range of aza-Heck cyclization: utilizing carbamate as nitrogen electrophile. Bower and coworkers disclosed an aza-Heck cyclization of *N*-pentafluorobenzoyl carbamates adapting to 5-*exo* and 6-*exo* cyclizations in 2018 (**Figure 2.6A**).¹³ Combination of 10 mol % of Pd₂(dba)₃ as Pd(0) source, 15 mol % of phosphadamantyl ligand and base 1 equiv NEt₃ in THF under 130 °C for 24 h was concluded after extensive investigation. Different

substitutional groups on aryl ring altered the electronic properties on the bulky phosphorus ligand and made it suitable for wide range of complex substrates, most of them were received in good yield (70%-95%).

Also, our group reported an efficient aza-Heck cyclization of *N*-aryl-*N*-hydroxy carbamates to synthesize indoline derivatives with the presence of low loading of 1.5 mol % Pd₂(dba)₃·CHCl₃ as palladium source and 7.5 mol % P(4-CF₃C₆H₄)₃ as triaryl phosphine ligand in acetonitrile under 80 °C for 24 h (**Figure 2.6B**).¹⁴ This was the first use of aniline electrophiles and carbonate as leaving groups in aza-Heck cyclization. Carbonate leaving groups greatly increased the reactivity of the substrates because of the irreversibility of oxidative addition. This reaction could tolerate various functional groups alkene substitution and complex ring systems in moderate yields (45%-89%).

A) Synthesis of Pyrrolidines and Piperidines



B) Synthesis of Indolines

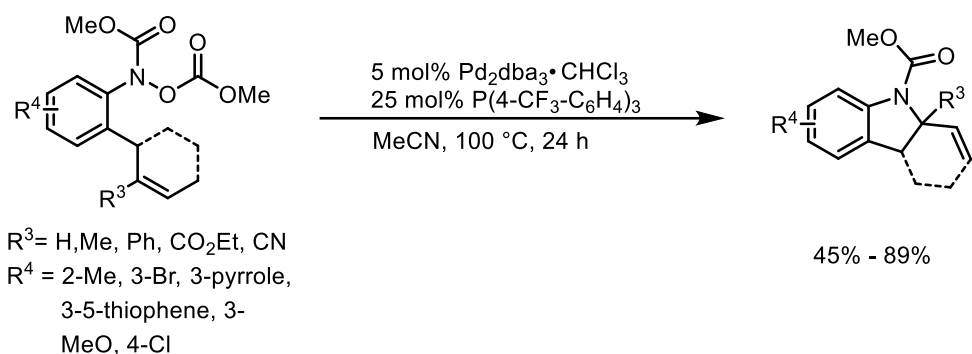


Figure 2.6: Aza-Heck Cyclization of Carbamates

2.3.5 Enantioselective Aza-Heck Cyclization

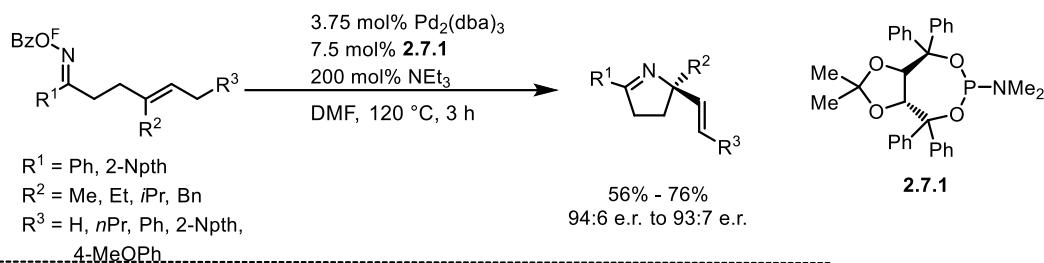
Promoting aza-Heck cyclization into enantioselective method was considered as an essential progress. Bower and coworker firstly identified the application of P-N ligand for highly enantioselective aza-Heck cyclization of oxime ester derivatives to generate quaternary chiral carbon center in 2017 (**Figure 2.7A**).¹⁵ Owing to their previous research on bidentate phosphorus ligand, they elaborately designed TADDOL-phosphoramidate compound, a chiral P-N bidentate ligand. By utilizing 7.5 mol % of this ligand, the aza-Heck cyclization operated the best with other components: 3.75 mol

% Pd₂(dba)₃, 2 equiv NEt₃ in DMF under 120 °C for 24 h. Moderate yield (56%-76%) and good enantioselectivity (93:7 er to 94:6 er) were received from aza-Heck cyclization from several substrates furnished with multiple substitution groups on imine carbon.

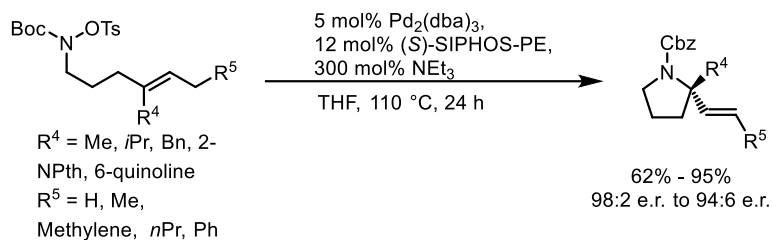
Later in 2019, Bower and coworker disclosed another *5-exo* and *6-exo* enantioselective aza-Heck cyclization of *N*-(tosyloxy) carbamates to synthesize pyrrolidines and piperidines (**Figure 2.7B**).¹⁶ An effective ligand system, SPINOL-derived phosphoramidate, was further investigated after they figured out that the application potential of chelating P,N and P,P ligand in this cyclization. Finally, 12 mol % SIPHOS-PE was proved to be the effective one and combined with 5 mol % Pd₂(dba)₃, 3 equiv NEt₃ in THF under 110 °C for 24 h. This reaction system proceeded well on *5-exo* cyclization in good yield (62%-95%) and high enantioselectivity (98:2 er to 94:6 er) with tolerance of various sterically trisubstituted alkenes.

A novel enantioselective method by utilizing nickel to catalyze desymmetrizing aza-Heck cyclization of oxime ester was published by Gong and coworker in 2021 (**Figure 2.7C**).¹⁷ Instead of traditional palladium catalyst, nickel has several advantages and may undergo single-electron transfer mechanism in oxidative addition of N-O bond. The optimal conditions were 10 mol % Ni(NTf₂)₂, 20 mol % chiral pybox ligand, 3 equiv Zn and 2 equiv iPr₂NEt in PhCN under 55 °C for 22 h. Wide range of aromatic substitution groups survived under this condition and received desired products in perfect yield (77%-98%) and moderate enantioselectivity (96.5:3.5 er to 87:13 er).

A) Reaction of Oxime Esters with TADDOL Ligand



B) Reaction of Carbamates with SIPHOS Ligand



C) Reaction of Oxime Esters with Nickel and Pybox Ligand

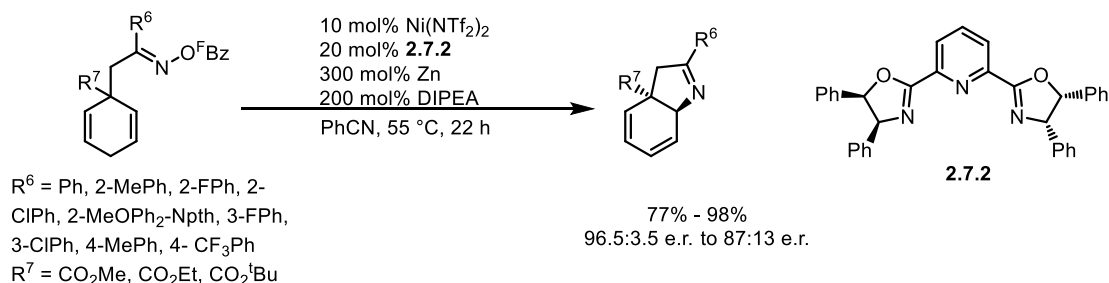


Figure 2.7: Enantioselective Aza-Heck Cyclization

2.4 Current Project

2.4.1 Introduction and Preliminary Studies

With several prior arts, our group was dedicated to develop a method by utilizing enantioselective aza-Heck cyclization to synthesize chiral spiro pseudoindoxyl compounds. Inspired from our paper from 2019, we decide to use *N*-aryl-*N*-hydroxy carbamates as the electrophile, which has been proved to be efficient from previous

result.¹⁴ Referring to previous synthetic route, the substrates could be easily synthesized from commercially available and simple starting materials (**Figure 2.8**). The model substrate synthesis commenced from the magnesium halogen exchange¹⁸, unsaturated cycloalkene carboxaldehyde was added subsequently to obtain alcohol and could be oxidized DMP reagent to harvest corresponding ketone **2.8.2**.¹⁹ *N*-aryl-*N*-hydroxy carbamate **2.8.3** could be obtained by a single step semi-reduction of converting nitro group to hydroxylamine and protect with methyl chloroformate in situ.²⁰ Following this protocol, the precursor was received, allowing a ready entry to asymmetric aza-Heck cyclization. After trying several bidentate phosphine ligands, Dr. Rout and Dr. Xu found that SEGPHOS works best. Subsequently, screening of solvent, reaction time and temperature were finished in series and Dr. Rout concluded the best combination of reaction conditions: 5 mol % Pd₂dba₃, 12.5 mol % SEGPHOS in CPME under 100 °C for 16 h. Under this condition, cyclization product **2.8.4** was obtained in 91% yield and 94% ee.

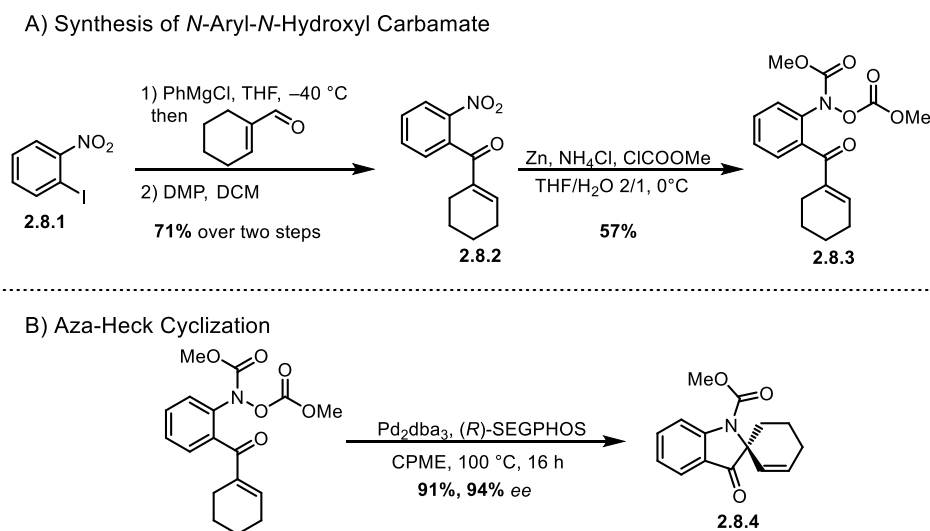


Figure 2.8: Synthesis of Model Substrate

2.4.2 Experimental

2.4.2.1 Synthesis of *N*-Aryl-*N*-Hydroxy Carbamates

2.4.2.1.1 Synthesis of 8-Membered Ring Substrate

To fully demonstrate universality and applicability of this method, several substrates were proposed and I'm currently working on their synthesizing. Firstly, I'd like to test if the ring size of cycloalkene matters and chose the 8-membered ring. The synthesis was commenced from cyclooctanone undergoing Wittig reaction. Enol ether **2.9.2** was obtained with the presence of phosphonium chloride salt and ^tBuOK. Then, traditional Sagusa oxidation conditions: 5 mol% Pd(OAc)₂, 1.2 equiv of benzoquinone and 4.0 equiv of acetic acid achieved the conversion of enol ether to unsaturated aldehyde **2.9.3** in 72% yield over two steps. 8-membered aldehyde replaced 6-membered aldehyde to undergo Grignard reaction with the intermediate of halogen exchange of 2-iodonitrobenzene and phenyl magnesium chloride. Then obtained alcohol was oxidized to corresponding ketone **2.9.4** by Dess-Martin Periodinane (DMP) in 60% over two steps. Following semi-reduction of the nitro group smoothly received the carbamate **2.9.5** in 34% yield.

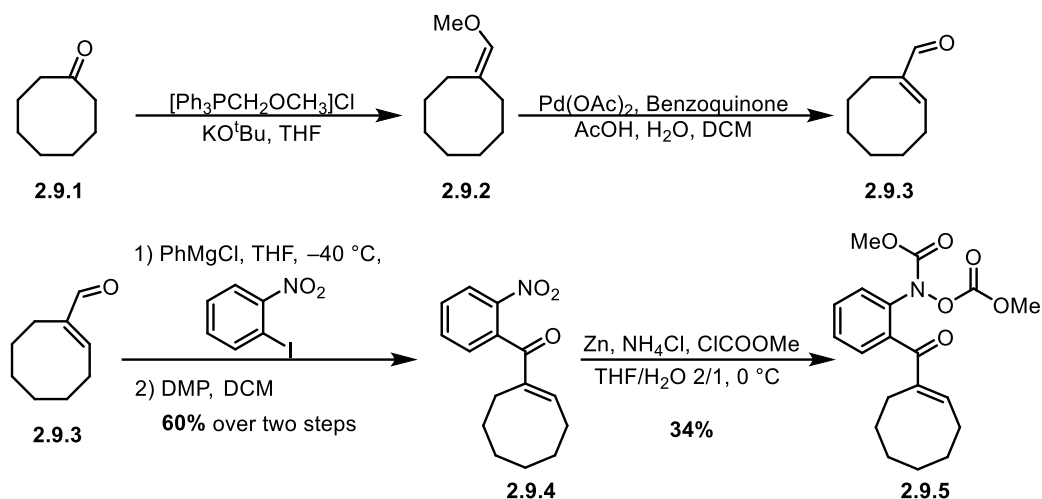


Figure 2.9: Synthesis of 8-Membered Ring Substrate

2.4.2.1.2 Synthesis of Methyl *Ortho* to Nitro Group Substrate

The steric effect is my next target so I'd like to add a methyl group ortho to the nitro group. The overall synthetic route of the corresponding carbamate mimicked the ordinary synthesis of the model substrate. Since the 1-iodo-3-methyl-2-nitrobenzene was not in hand, I proposed to utilize Sandmeyer reaction to convert 3-methyl-2-nitrobenzenamine **2.10.1** to the desired starting material of the Grignard reaction. Under modified conditions: hydrochloric acid and sodium nitrite followed by sodium iodide, 1-iodo-3-methyl-2-nitrobenzene **2.10.2** was received in 88% yield. Then the new formed nitrobenzene reacted with phenyl magnesium chloride and cyclohexene-1-carboxaldehyde followed by DMP oxidation to obtain ketone **2.10.3** in 72% yield over two steps. The yield of semi reduction of nitro group to desired carbamate **2.10.4** decreased to 26% compared to model substrate and probably because of the methyl blocked the nitro group and made it harder to react with reducing agent.

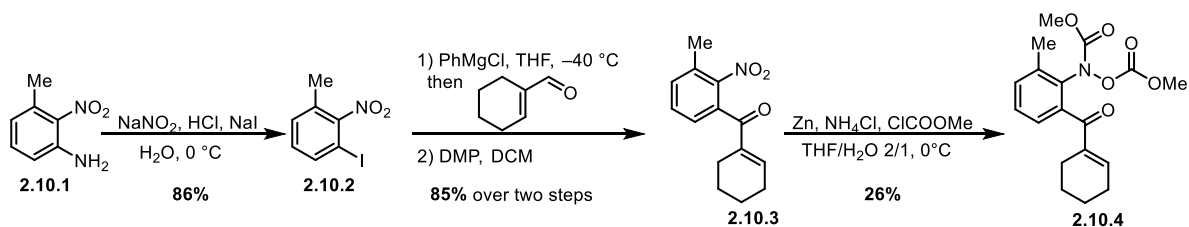


Figure 2.10: Synthesis of Methyl *Ortho* to Nitro Group Substrate

2.4.2.1.3 Synthesis of Methyl *Ortho* to Ketone Group Substrate

Continuing the test of steric effect, I moved to the methyl *ortho* to the ketone group substrate. The synthesis commenced from the magnesium halogen exchange of phenyl magnesium chloride and 2-iodo-1-methyl-3-nitrobenzene followed by Grignard reaction with cyclohex-1-ene-1-carboxaldehyde and DMP oxidation. Ketone **2.11.2** was observed in 68% over two steps. The semi reduction did not perform well: only 26% yield of desired carbamate **2.11.3** was obtained. Possible reason could be the configuration of the aromatic ring was influenced by the methyl group and change the reactivity of the nitro group.

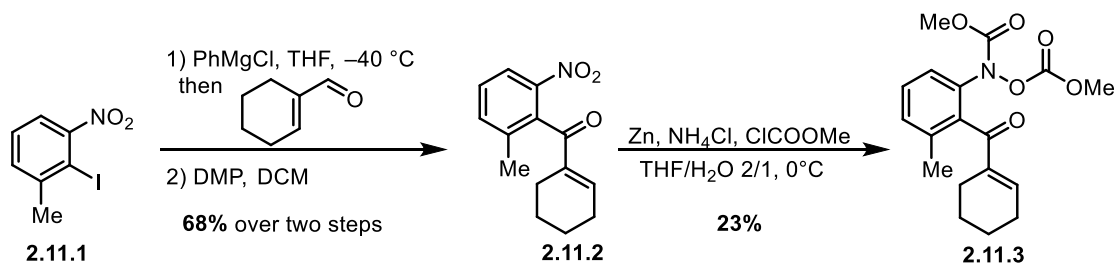


Figure 2.11: Synthesis of Methyl *Ortho* to Ketone Group Substrate

2.4.2.1.4 Synthesis of Thiophene Substituted on Phenyl Ring Substrate

Then biaryl systems with thiophene and pyrazole were selected. To introduce aromatic substitution group into original compound to obtain biaryl compound, the Suzuki coupling is one of the most widely used and efficient method. Therefore, I proposed to utilize 4-bromo-2-iodo-1-nitrobenzene to initiate the ketone side chain and leave the bromine to bring versatile functional groups via various types of hetero coupling reactions. The actual operation mostly followed predictions: ketone **2.12.2** was successfully synthesized by mixing nitrobenzene, phenyl magnesium chloride and aldehyde in order described above in 68% yield over two steps. With the ketone in hand, next step was the Suzuki coupling to introduce 5-acetothiophene group. Based on the literature precedent, I chose the PdCl₂(dppf)•CH₂Cl₂ as the palladium source, aryl bromide as electrophile, (5-acetylthiophen-2-yl)boronic acid as nucleophile and potassium carbonate as base and heat the mixture under 100 °C for 6 h. The corresponding biaryl compound **2.12.3** was received in 73% yield. Noticeably, the yield sharply decreased if heat the reaction mixture overnight. Then the semi reduction converted the nitro group to the protected carbamate **2.12.4** in 41% yield. By replacing the solvent THF to dioxane, the miscibility of organic solvent and water became better and the reaction received better yield.

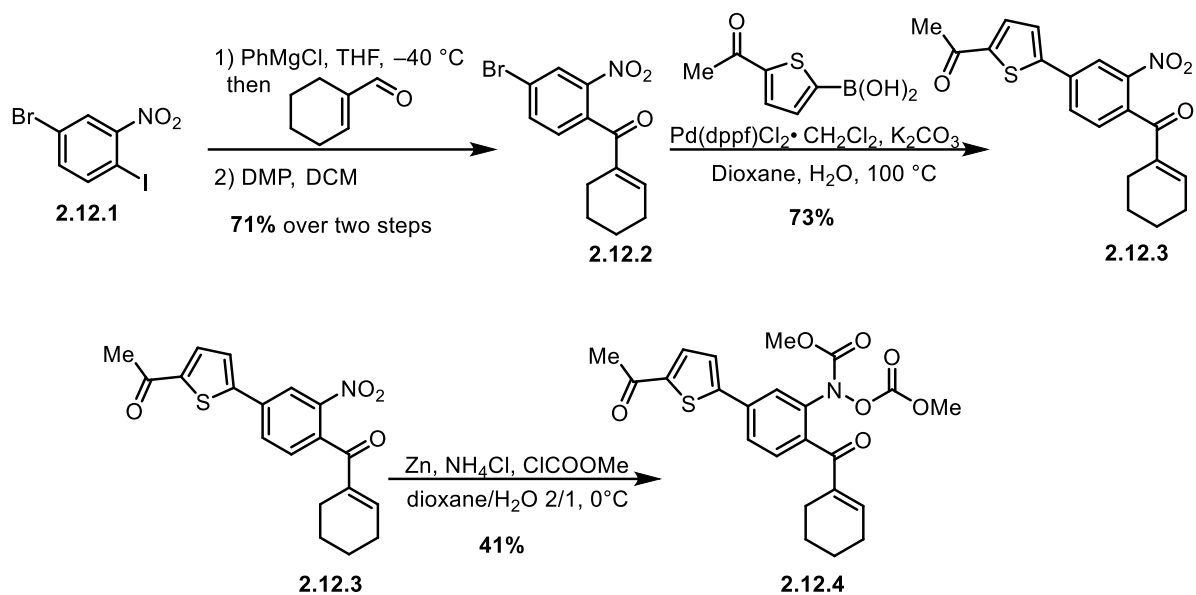


Figure 2.12: Synthesis of Thiophene Substituted on Phenyl Ring Substrate

2.4.2.1.5 Synthesis of Pyrazole Substituted on Phenyl Ring Substrate

The pyrazole substrate used the same aryl bromide as the thiophene substrate. But the Suzuki coupling conditions were completely different. Simply change the (5-acetylthiophen-2-yl)boronic acid to (1-methyl-1*H*-pyrazol-5-yl)boronic acid did not work. The major byproduct *N*-methyl pyrazole. Hence I adjusted some reagents of the previous conditions: Pd(PPh₃)₄ as the palladium source, ethanol, water and toluene as the solvent under 95 °C for overnight. The biaryl compound **2.13.3** was received in 43% yield. Under modified conditions, the nitro group smoothly reduced to carbamate **2.13.4** in 38% yield.

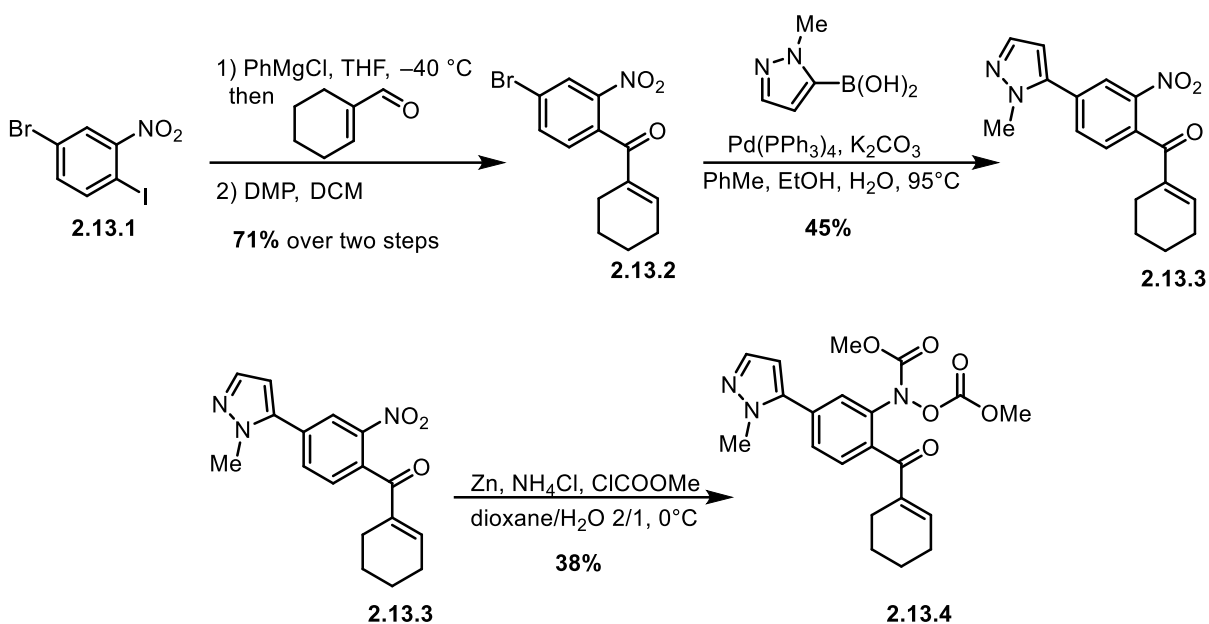


Figure 2.13: Synthesis of Pyrazole Substituted on Phenyl Ring Substrate

2.4.2.1.6 Synthesis of Phenyl Substitution on Alkene Ring Substrate

Then, I chose to test the substitution effect on the alkene ring. Similar to the ideas of making biaryl compound, I designed to leave bromide on the beta-position of the unsaturated ketone, which could easily carry out Suzuki coupling because of the excellent electrophilicity. The synthesis was commenced from cyclohexanone. Vilsmeier-Haack reaction conditions: phosphorus tribromide and dimethylformamide in chloroform was utilized and achieved the transformation of cyclohexanone to aldehyde **2.14.2**. Obtained aldehyde underwent Grignard reaction with the magnesium halogen exchange intermediate of 2-iodonitrobenzene and phenyl magnesium chloride and received corresponding ketone **2.14.3** after further oxidation by DMP in overall 47% yield for two steps. Suzuki coupling occurred with ketone **2.14.3** and phenyl boronic acid catalyzed by Pd(PPh₃)₄, sodium carbonate in ethanol, water and toluene. Cross coupling product **2.14.4** was received in 88% yield.

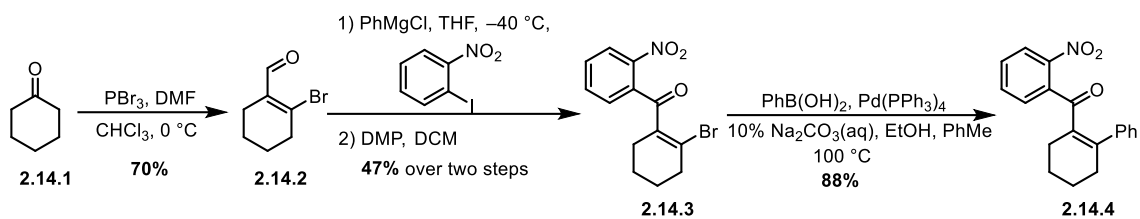


Figure 2.14: Synthesis of Phenyl Substitution on Alkene Ring Substrate

2.4.2.2 Aza-Heck Cyclization of Selected Substrates

With the electrophiles in hand, I used the conditions from Dr. Rout and Dr. Xu to obtain the desired aza-Heck cyclization products (**Figure 2.15**). All the reactions firstly occurred in glove box for 0.01 mmol scale and then run on bench for 0.05 mol scale. For ring size effects, the yield for 8-membered slightly decreased and ee remains the same. There was no significant difference between 6- and 8-membered alkene, which indicates the good compatibility of 8-membered alkene. Compare to almost no steric effect ortho to the ketone group, the steric bulky group ortho to carbamate lowered the yield but the ee remains. For heteroatom compatibility, competition between heteroatom and SEGPHOS ligand to coordinate with palladium could be a possible reason leading the yield and ee dramatically decreased apparently.

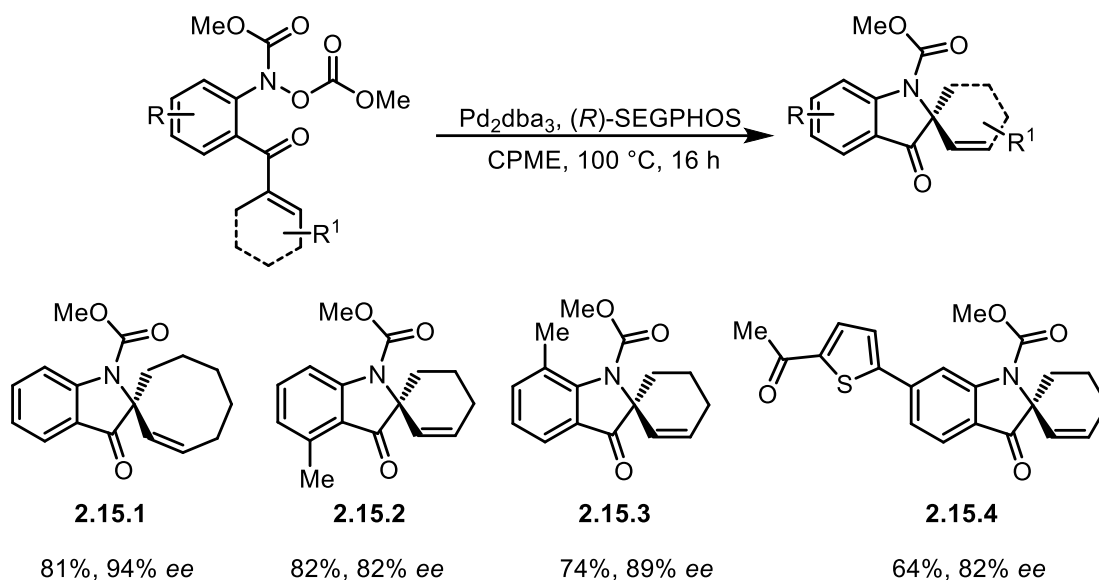
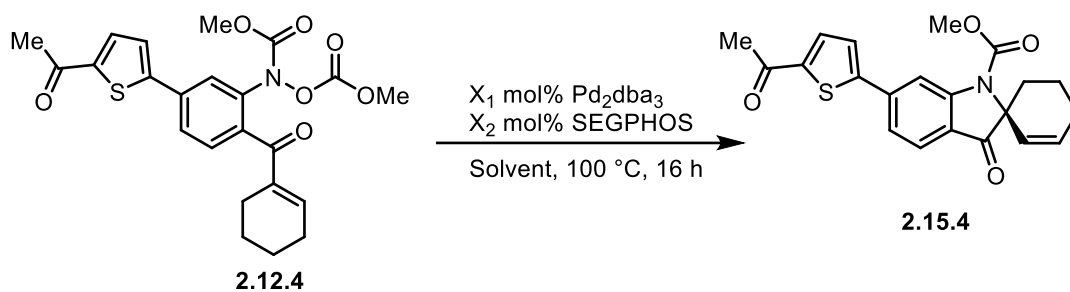


Figure 2.15: Synthesis of Pseudoindoxyls via Aza-Heck Cyclization

2.4.2.3 Optimization of Aza-Heck Cyclization of Selected Substrates

Due to the low yield and ee of the thiophene substrate, I decided to figure out if the current reaction conditions were the best. First, I tried to modify the amount of catalyst and ligand. Neither increased the loading of catalyst or ligand individually nor together affect yield and ee significantly (**Table 2.1** entry 2-5). Based on the results, the usage of palladium source and ligand are the best combination. Then I switched the CPME to other ethereal solvent (**Table 2.1** entry 6-8). Dioxane was found effective to increase the yield to 89% and the ee keeps the same. Although the yield was elevated, the ee still kept the same. Therefore, I also applied DTBM-SEGPHOS to reaction systems with CPME and dioxane but both received worse result (**Table 2.1** entry 9-10). In addition, I also attempted to lower the reaction temperature and shorten the reaction time to prevent the racemization by palladium but effect was not significant (**Table 2.1** entry 11-13).



Entry	X ₁	X ₂	Solvent	Yield of 2.10.4 [%]	ee of 2.10.4 [%]
1	5	12.5	CPME	64	82
2	7.5	12.5	CPME	65	77
3	10	12.5	CPME	59	78
4	5	17.5	CPME	52	77
5	7.5	17.5	CPME	57	78
6	5	12.5	DME	53	77
7	5	12.5	dioxane	89	82
8	5	12.5	THF	nd ^[b]	nd
9	5	12.5 ^[a]	CPME	53	33
10	5	12.5 ^[a]	dioxane	34	23
11	5	12.5	dioxane	80 ^[c]	79
12	5	12.5	dioxane	70 ^[d]	82
13	5	12.5	dioxane	65 ^[e]	85

[a] Use DTBM-SEGPHOS as the ligand

[b] Solvent evaporated

[c] Run at 90 °C

[d] Run for 12 h

[e] Run at 80 °C

Table 2.1: Modifications of Aza-Heck Cyclization Conditions

2.4.2.4 Optimization of Semi-Reductions

During substrate synthesis, a huge breach that I had to overcome was the low yield or no reaction of semi-reduction. The mechanism was proposed to undergo single electron transfer from zinc to nitro group. Including conversion from nitro to nitroso, hydroxylamine and amine.²¹ Desired reduction pathway would be aborted at

hydroxylamine because of the protection by methyl chloroformate. However, over reduction was one of the major problems. Hence, I bring forward three possible improvements to fix the issue.

Firstly, I tried different metal instead of zinc. Equivalence of metal was decided based on the provided amount of electrons. I supposed magnesium, cobalt and tin would offer two equivalences of electrons while iron would give three equivalences. Since the reduction potential of iron, cobalt and tin are relatively low compared to zinc, so there were almost no products generated. Manganese exhibited the best selectivity but the reaction rate was relatively low (**Table 2.2** entry 2-5).

Because of different miscibility of each organic solvent with water, screening of different solvent was also important. I chose dioxane, DMF, diethyl ether and acetonitrile. Among these solvents, usage of dioxane significantly increasing yield, while other three solvents performed poor reactivity (**Table 2.2** entry 6-9). I also replaced THF to dioxane to compare the semi-reduction yield for thiophene substrate. It was increased from 23% to 45%. Later I utilized the same conditions on pyrazole substrate and received good yield (38%).

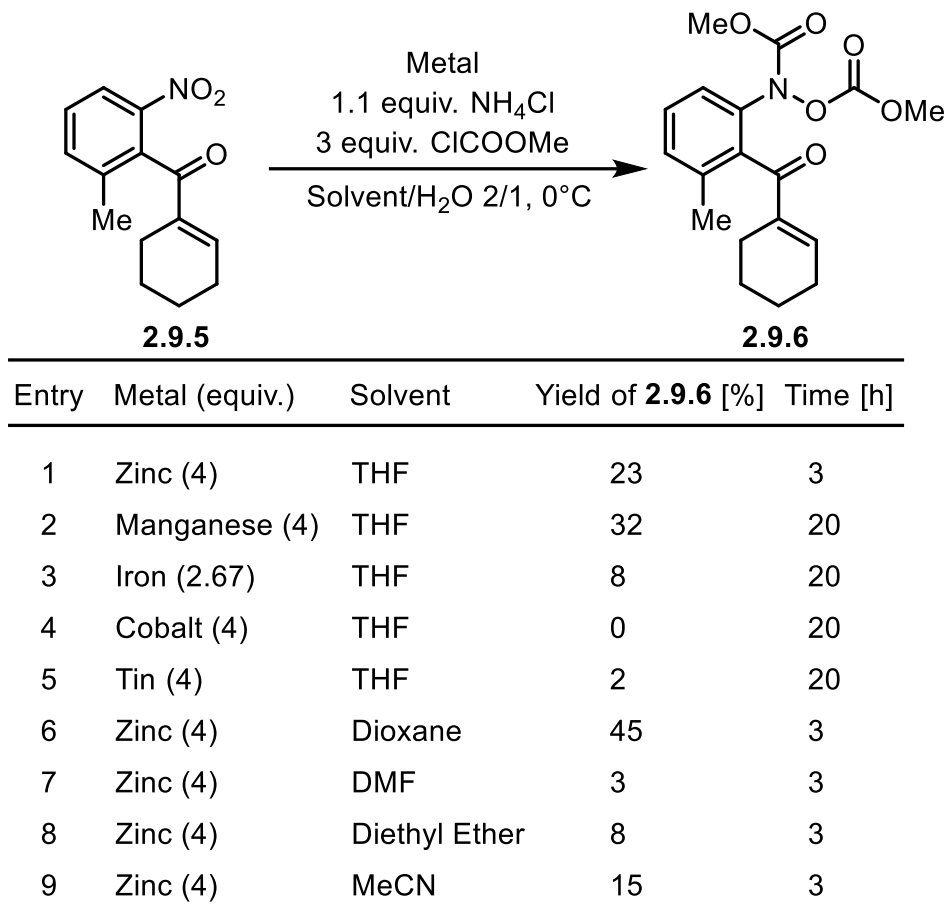


Table 2.2: Modifications of Aza-Heck Cyclization Conditions

Lastly, several methods of selective reduction from nitro group to hydroxylamine were developed by researchers.²²⁻²³ Therefore, I planned to execute on my substrates since the ketone group could be tolerated based on literature precedent. I tried the photo-redox condition with Hantzsch ester first (**Figure 2.16A**). After exposure to blue LED for 18 h, only few Hantzsch ester derivatives appeared and lots of starting material remained. The adjustment of distance between light source and the reaction flask didn't change the result. Another method I tried was utilizing the

ultrasound condition. Sonication of starting material and zinc followed by adding reducing agent ammonium formate would convert nitro group to hydroxylamine. But only over-reduction product aniline was synthesized by following the protocol (**Figure 2.16B**). Since the reaction time of two stages extremely depended on specific substrates, I have tried several combinations of time length but none of them received desired product. Only over-reduced aniline was yielded.

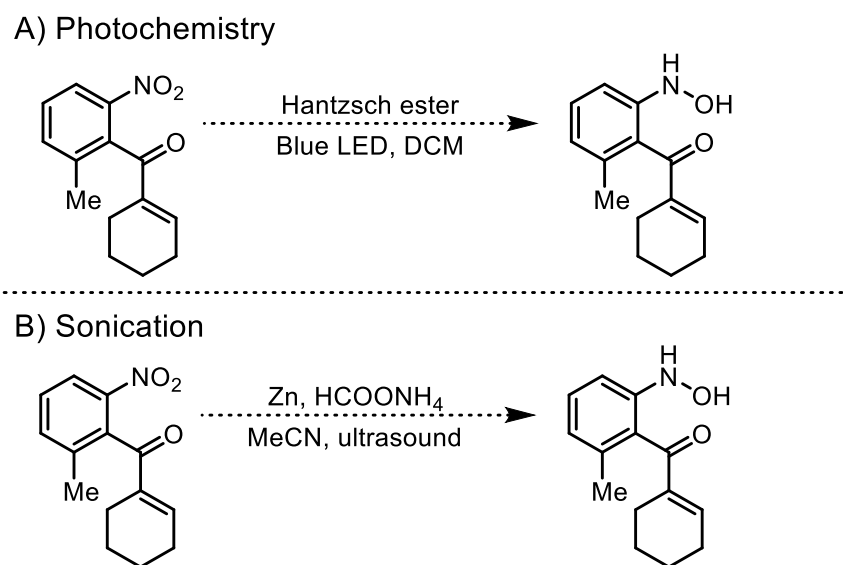


Figure 2.16: Potential Alternative Synthetic Methods of Hydroxylamine

2.5 Conclusion

This chapter provides a comprehensive overview of some well-designed reviews and explores the history of literature precedent of aza-Heck cyclization, ranging from early studies and recent works. Various classes of nitrogen electrophiles: oxime esters, sulfonamides, hydroxamates and carbamates greatly broaden the generality of aza-Heck

cyclization. Decent design of chiral bidentate or chelate ligand successfully enhanced the reaction's enantioselectivity. Also, I demonstrated my effort in synthesizing several substrates and optimizing key reactions to achieve better yield or ee, not only for aza-Heck but also for semi-reduction reaction. Future directions will likely expand the substrate scope more widely and carry out mechanism studies such as KIE and DFT analysis to elucidate the certain roles for each reagent in this reaction.

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