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# Development of Palladium Catalyzed Alkene Difunctionalization on Vinyl-Quinoline Type Substrate and Isolation of Pd-Alkyl Intermediate

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# Development of Palladium-Catalyzed Alkene Difunctionalization on Vinyl-Quinoline Type Substrate and Isolation of Pd-Alkyl Intermediate

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## ABSTRACT

The synthesis of quinoline derivatives is a continuing issue facing organic chemists in both academia and industry. To address this problem, palladium-catalyzed alkene difunctionalization was developed to be a powerful and straightforward strategy of synthetic transformations for adding diversity to organic molecules. In this thesis, Pd-catalyzed olefin difunctionalization reactions of vinyl-quinoline type substrate via generating Pd-alkyl intermediates were mainly described. The reactions described herein are pursuing three significant goals: 1) to isolate and recrystallize Pd-alkyl complexes; 2) to achieve oxidation reactions on Pd-alkyl intermediate; and 3) to investigate stereochemistry of nucleopalladation step on vinyl-quinoline starting materials.

ACKNOWLEDGEMENTS

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My sincere thanks also goes to Flo Bachrach, Stephen Moss, who work with me, and who gave me help to the laboratory and research facilities. Without their support it would not be possible to conduct this research.

I owe my deepest gratitude to my parents for providing immense support and inspiring me to make it here and beyond.

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LIST OF ABBREVIATIONS

BHE…..……β-hydride elimination

Bn……..……..benzyl

DCM……...……dichloromethane

DIAD……..….diisopropyl azodicarboxylate

DMAP……...……N,N-4-dimethylaminopyridine

DMF……..…….N,N-dimethylformamide

DMSO……...……dimethylsulfoxide

Dppe……...1,2-Bis(diphenylphosphino)ethane

$Et_2O$……...diethyl ether

EtOAc……ethyl acetate

equiv……....equivalents

g……...……..gram(s)

GC……...……..gas chromatography

h……..hour(s)

HPLC…….. High performance liquid chromatography

J…….…..NMR spectra coupling constant

M…….…….molar

Me……...methyl

MeCN……...acetonitrile

MeOH……..methanol

Mg……..milligram(s)

min……..minute(s)

mL……...…….millilitre(s)

mmol……millimole(s)

mol…….mol(es)

m/z…….……mass to charge ratio

NFSI……N-fluorobenzenesulfonimide

NMR……..……nuclear magnetic resonance

NBS…….N-bromosuccinimide

Nu……..……..nucleophile

OAc…….acetate

OTf…….…….....trifluoromethanesulfonate

Pd…….……..palladium

Ph……...…….phenyl

$Ph_3P$……..……...triphenylphosphine

RT……..room temperature

sat.……...…….saturated

TEA……..triethylamine

THF……...tetrahydrofuran

TBDPS……...……tert-butyldiphenylsilyl

TLC……..….thin layer chromatography

# CHAPTER ONE: DEVELOPMENT OF PALLADIUM-CATALYZED ALKENE DIFUNCTIONALIZATION

## 1.1 Introduction

The development of alkene transformations is of great importance for organic synthesis as alkene compounds are readily available and taking part in many organic transformations. In the mid-20$^{th}$ century, some catalytic transformations of alkenes included hydrogenation, and hydroformylation have been developed and applied to the chemical industry. In 1959, researchers at Wacker Chemie developed a Pd-catalyzed method for the aerobic oxidative coupling of ethylene and water to produce acetaldehyde as shown in Fig. 1.[1] This reaction is considered to be the starting point of Pd-catalyzed alkene functionalization. After that, various Pd-catalyzed reactions have been achieved in the broad scope of alkene functionalization.

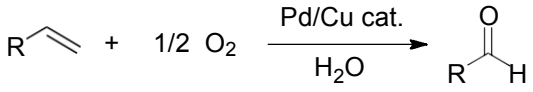



Figure.1. Wacker Oxidation

Difunctionalization of unactivated alkene is achieved by adding two functional groups on each side of carbon carbon double bond, difunctionalized product is formed in one step. Therefore, alkene difunctionalization reactions have been a significant area of research in organic chemistry. In particular, Pd-catalyzed alkene difunctionalizations provide an abundance of possibilities of C-X bond formation. Typically, the first step of alkene difunctionalization is to form a Pd-alkyl intermediate, which either reacts with another reactant or undergoes rapid **β**-hydride elimination to yield Wacker-type products. To pursue alkene difunctionalization, the rate of Pd alkyl functionalization must be faster compared to the rate of **β**-hydride elimination (Fig. 2)

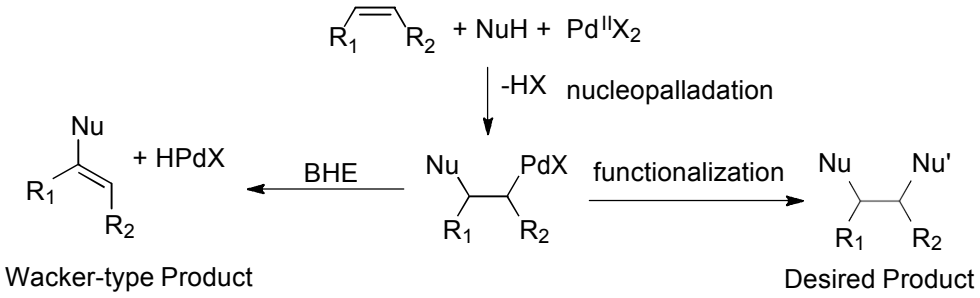



Fig. 2. Mechanism of Alkene Difunctionalization

## 1.2 Stereochemical Pathways of Nucleopalladation

A new stereogenic center is often generated in an alkene nucleopalladation. A mechanism of nucleopalladation in achieving efficient enantioselective catalysis is that nucleopalladation reactions are capable of proceeding by two stereochemically different but competitive pathways[2]: *cis*- or *trans*-nucleopalladation (Fig.3). In the $S_N2$ type *trans*-nucleopalladation, the Pd catalyst first coordinates to the alkene before it has nucleophilic attack from the opposite face to the $Pd^{II}$. In the case of *cis*-nucleopalladation, the nucleophile coordinates to the Pd catalyst, which then Pd complex undergoes the addition to form the alkyl-Pd species.

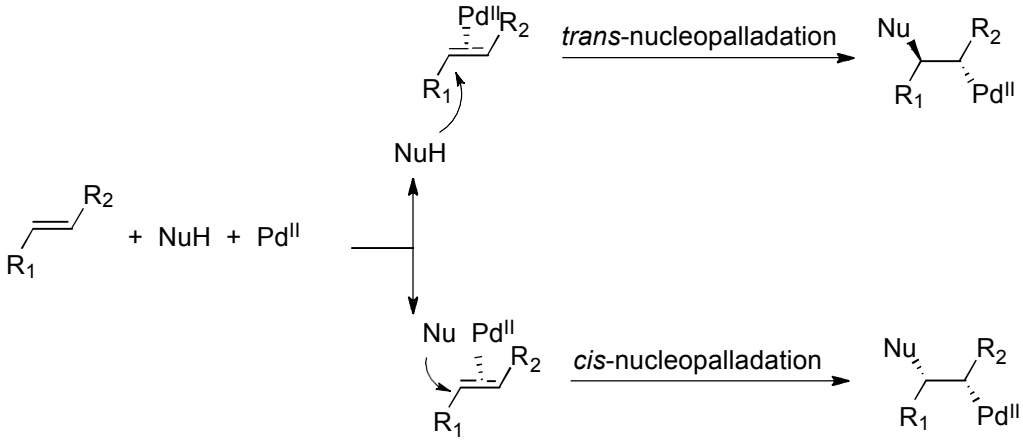



Fig. 3. Model for Palladium Promoted Addition of Nucleophile to an Alkene

If the Pd-alkyl compounds are stable and react with a second nucleophile, then the process can be described in the following figure 4 from cis-nucleopalladated intermediate. Pd(II) intermediate can be oxidized to Pd(IV) intermediate[3], which then undergoes

reductive elimination to form new bond and Pd(II) species. Trans-nucleopalladated intermediate can also follow trans- and cis- process to give different isomers compared to cis-nucleopalladated intermediate. These transformations provide a broad scope for stereochemistry of alkene difunctionalization.

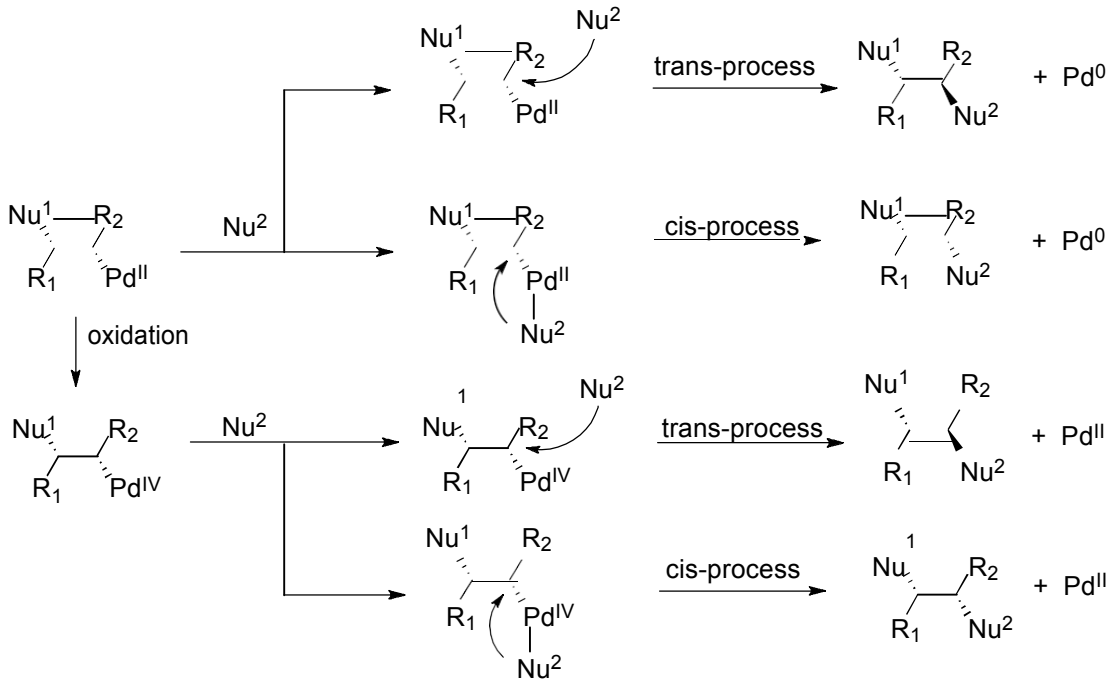



Fig. 4. Representative Pathways for Nucleophilic Addition to Pd(II)-Alkyl and Pd(IV)-Alkyl Compounds

## 1.3 Examples of Pd-catalyzed Alkene Difunctionalization

### 1.3.1. Hydroxychlorination and Dibromination of Olefins

Early studies found that the Wacker process always involved the by-product from carbon and bromide bond formation. In general, an aldehyde is the product of Wacker process under the usual Wacker conditions; Wacker process generated the chlorohydrin product when using excess amounts of [$CuCl_2$] (>2.5 M) and [Cl] (>2 M). The research of Henry and coworkers reported Wacker process also gave the chlorohydrin product in the $PdCl_3(py)^-$ system.[4]

In 1998, Henry and coworkers developed the asymmetric hydroxychlorination of alkenes.[5] This literature reported that highest enantioselectivity was achieved by employing a bimetallic or a monomeric palladium(II) complex bearing chelating diphosphines such as BINAPs catalyst. This reaction condition is suitable for unfuntionalized alkenes, enol ethers, and allyl acetates to achieve relative high enantioselectivity, but not for alkene substrates containing hydroxyl, carboxylic acid and aldehyde groups.

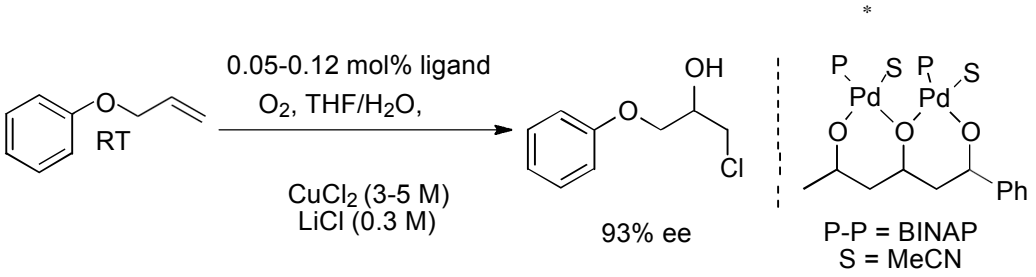



Fig. 5. Pd-Catalyzed Enantioselective Chlorohydrin Reaction

In 2003, Henry and coworkers investigated this dibromination reactions using superstoichiometric quantities of $CuBr_2$ instead of $CuCl_2$ as the bromide source in aqueous-THF solvent mixtures, olefins were transformed to dibromides.[6] Importantly, production of the aldehyde and ketone products are inhibited and the oxidation of olefins did not produce the bromohydrin. Instead, the products were the 1,2-dibromides achieving in high enantioselectivities as the bromide is a much better nucleophile than chloride.

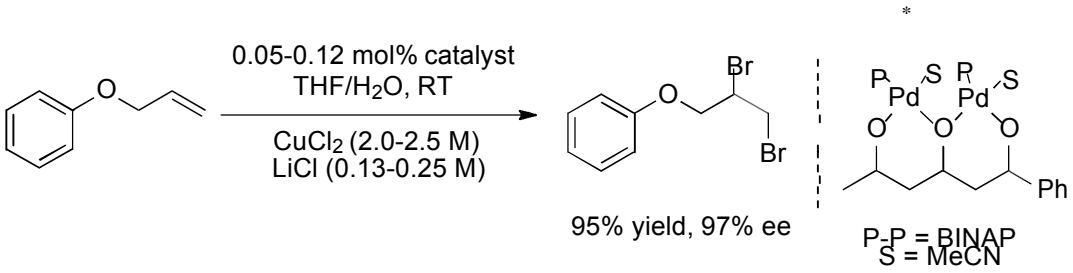



Fig. 6. Pd-Catalyzed Enantioselective Dibromination Reaction

Anti bromide attack forming a carbon-bromine bond generates the trans configuration dibromocyclopentane from cyclopentene as Pd catalyst have a large coordinated complex. The mechanism is shown in Fig.7.

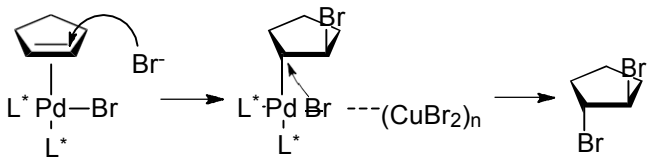



Fig. 7. Proposed Mechanism for the Oxidation of Cyclopentene

### 1.3.2. Dioxygenation of Olefins

Compared to other difunctionalization of olefins, research of alkene dioxygenation reactions have long been developed, and widely used. For example, the sharpless asymmetric dihydroxylation have been developed and applied to the industry.[7] Sharpless asymmetric dihydroxylation converted an alkene with osmium tetroxide to a vicinal diol in the Fig. 8. However, olefin difunctionalizations catalyzed by palladium via dioxygenation are less reported.

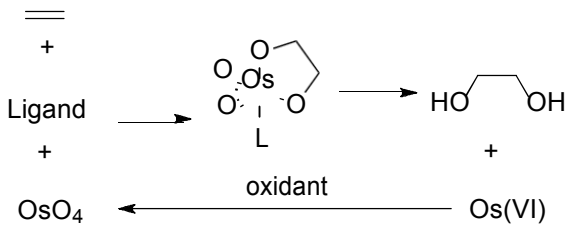



Fig. 8. Pathway for Sharpless Asymmetric Dihydroxylation

In 2005, Le Bras, Muzart and coworkers reported the dioxygenation of *ortho*-vinyl phenols using $Pd(TFA)_2$ as catalyst.[8] This reaction proceeded in the presence of hydrogen peroxide, water, and methanol allowed the direct transformation to resulting product which gave the low enantioselectivity. The mechanism starts via Pd-catalyzed epoxidation, followed by nucleophilic attack at the benzylic postion to yield different difunctionalized products.

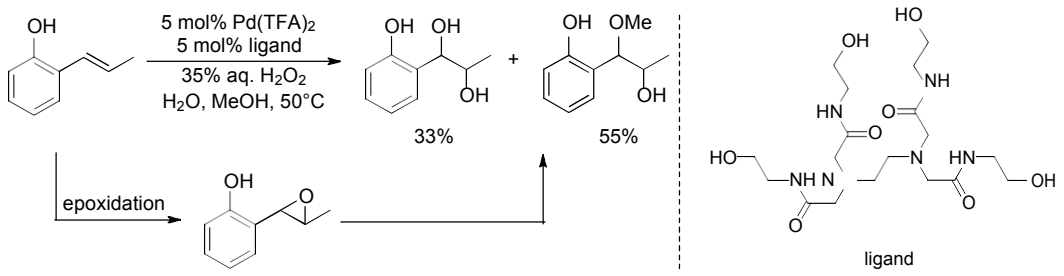



Fig. 9. Pd-catalyzed Dioxygenation of *O*-vinylphenols

In 2006, the Sigman group investigated a dialkoxylation reaction of styrenes containing an *o*-phenol using $Pd(CH_3CN)_2Cl_2$ as the catalyst.[9] Good to high enantioselectivity and diastereoselectivity are observed in this dialkoxylation process. This report proposed the mechanism that addition to the α carbon of the styrene generate a regioselective nucleopalladation, followed by formation of complex which a quinone methide intermediate coordinated with Pd(0). Evidence for this mechanism was provided by the later mechanistic experiments.[10]

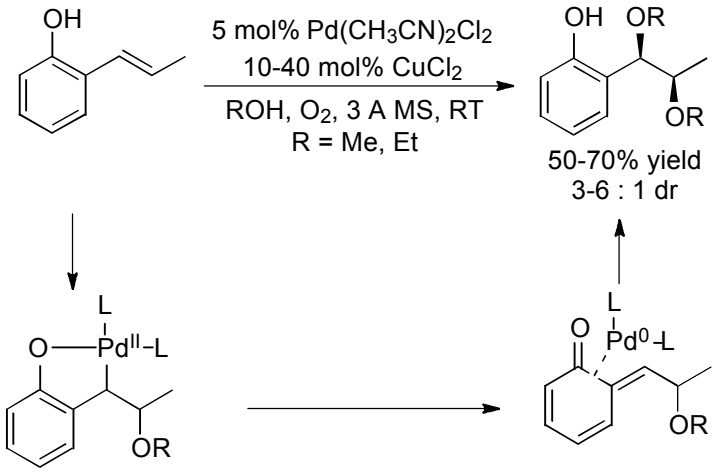



Fig. 10. Pd-Catalyzed Dioxygenation Reaction of Styrenes Containing an *o*-phenol

Sigman and coworkers developed this dioxygenation to asymmetric enantioselective dialkoxylation of 2-propenylphenols in 2007.[11] This report evaluated a variety of ligands, low enantiomeric excess found using (-)- sparteine and bisoxazoline whereas excellent asymmetric catalysis is observed in the presence of $C_1$-symmetric quinoline derived oxazolines. Importantly, no enantioselectivity was found using bis-substituted terminal olefin substrate. Based on this observation, the authors hypothesized that **β**-nucleopalladation is the enantio-determining step, followed by rapid reduction of palladium leaving from intermediate, even it is faster than the nucleophilic attack rate of second alkoxy nucleophile. Therefore, enantioselectivity cannot be controlled by second alkoxy group nucleophilic attack.

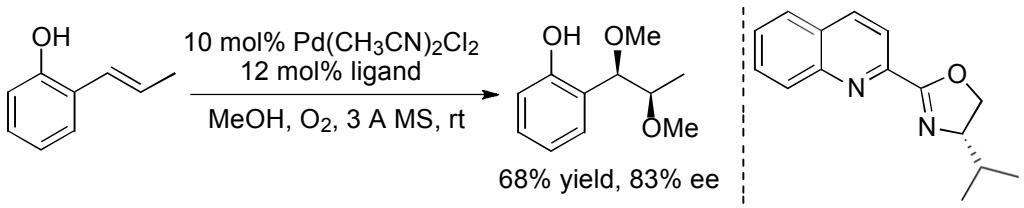



Fig. 11. Pd-Catalyzed Asymmetric Enantioselective Dialkoxylation

In 2008, Dong and coworkers reported a new method for the vicinal dioxygenation of olefins by using cationic Pd diphosphine complexes as the catalysts.[12] This catalyst has two significant structural features: non-coordinating counterion and electron-deficient bisphosphine ligand. Compared to the previous reports, this way is suitable for a broad range of olefins in both inter- and intramolecular reactions. Importantly, Pd-catalyzed intermolecular olefin 1,2-dioxygenation reactions were first

reported. In this report, they proposed the mechanism that cationic Pd catalyst undergoes *trans*-acetoxypalladation with olefin to yield organopalladium intermediate, oxidation of Pd(II) intermediate with $PhI(OAc)_2$ to generate Pd(IV) intermediate. The formation of acetoxonium is achieved via intramolecular cyclization and the catalyst is generated via an $S_N2$-type reductive elimination. Hydrolysis of intermediate delivers the hydroxyacetate product.

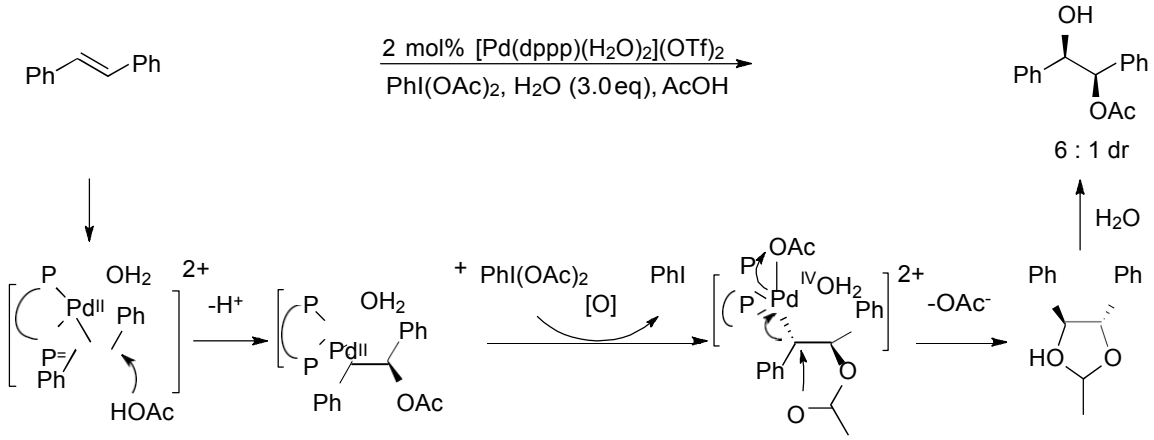



Fig. 12. Pd-Catalyzed Vicinal Dioxygenation of Alkenes

A novel method of olefin diacetoxylation in presence of peracetic acid and acetic anhydride was reported by Jung group in 2010.[13] Due to the mild conditions, a broad range of substrates was achieved in high diastereoselectivity. In the proposed mechanism of this paper, $Pd(OAc)_2$ was oxidized to Pd(IV) species which undergo *syn*-addition onto the alkene to generate Pd(IV) intermediate. The new C-O bond was afforded by reductive elimination.

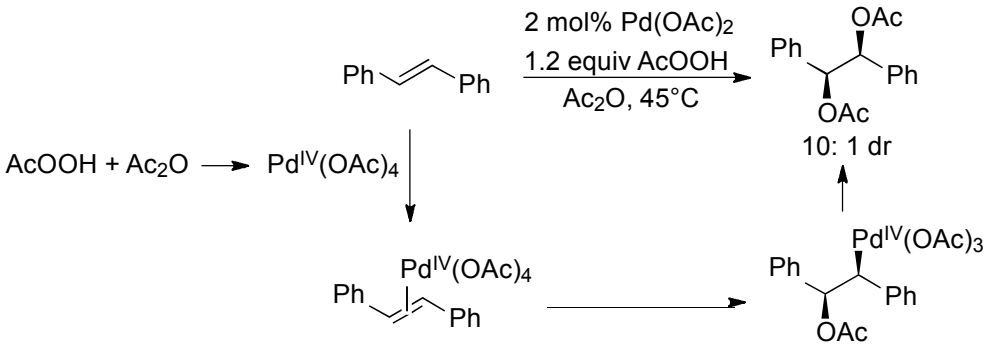



Fig. 13. Pd-Catalyzed Diacetoxylation of Olefins

In 2010, Shi's group developed a novel Bis(NHC)-Pd(II) complexes derived from 1,1′-binaphthyl-2,2′-diamine (BINAM) catalyzed the dioxygenation of alkenes in simple way under mild conditions tolerant of air and moisture in good *syn*-diastereoselectivity.[14]

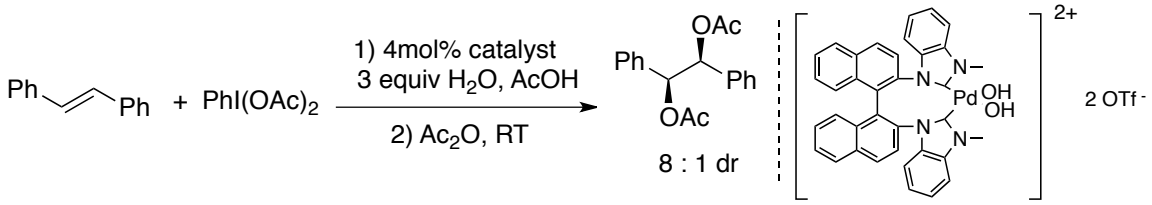



Fig. 14. Dioxygenation of Alkenes Using Bis(NHC)-Pd(II) as Catalyst

Recently, Sanford and coworks developed a Pd-catalyzed asymmetric alkene 1,2-dioxygenation reaction, and the high enantioselectivity was achieved by using a chiral oxime ether directing group.[15] The diastereoselectivity of the reaction controlled by tethering a chiral directing group to the alkene substrate was first described by this literature.

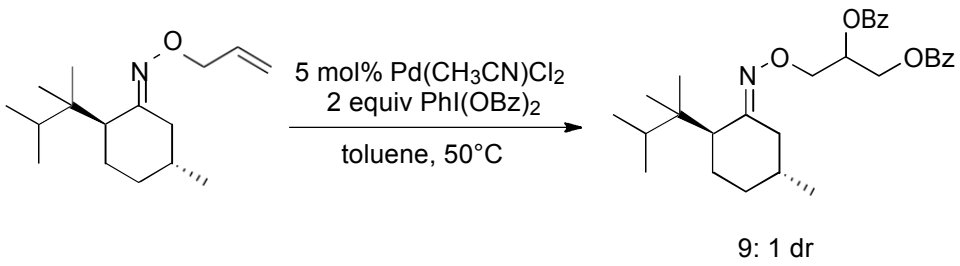



Fig. 15. Pd-Catalyzed Asymmetric Dioxygenation Reaction

1.3.3. Oxydative Amination of Olefins

The development of the oxidative olefin amination is early, but Pd-catalyzed oxidative olefin amination is less reported. In 2005, Sorensen group first reported Pd-catalyzed intramolecular aminoacetoxylation of alkenes by using $PhI(OAc)_2$ as an oxidant.[16] Shortly after, Stahl and coworkers published an intermolecular Pd-catalyzed aminoacetoxylation of alkenes.[17] The substrates are containing an ether functional group increasing selectivity and reactivity, included allylic ethers, vinylic and homoallylic ethers. Highly regio- and diastereoselectivity can be achieved through this aminoacetoxylation reaction, different configurations of the olefins are obtained which correspond to the configurations of the products. Through the mechanistic experiments, the authors proposed a *cis*-aminopalladation mechanism followed by oxidation to Pd(IV) intermediate. Hydrogen of Pd(II) intermediate should be rotated to the same face to Pd(II) which then undergo β-hydride elimination that is why give the configuration of product as described in Fig.16.

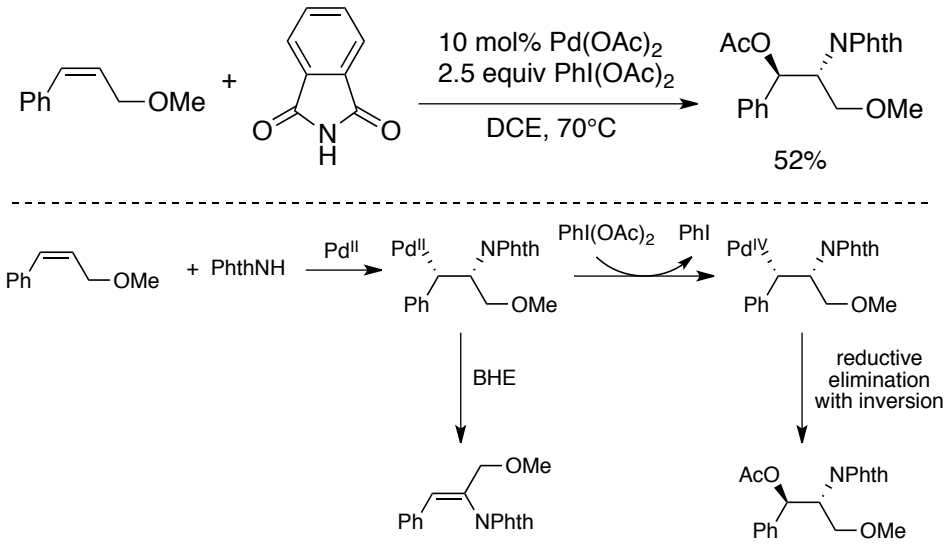



Fig. 16. Pd-Catalyzed Aminoacetoxylation Reaction and Mechanism

In 2007, Sanford and Desai's report of Pd-catalyzed intramolecular aminooxygenation reaction employed homoallylic alcohols as substrates and phthalimide as the nitrogen source to synthesize substituted tetrahydrofurans.[18] Based on *trans*-product from (Z)-olefins, they proposed the *cis*-nucleopalladation of the olefin followed by direct reductive elimination with retention of the stereochemistry. Due to the alcohol as substrate, the authors hypothesized the formation of a six-membered Pd(IV)-alkyl-alkoxide intermediate in the mechanism which favored to undergo direct *cis*-reductive elimination with retention of the stereochemistry, yielding the *trans*-configuration product.

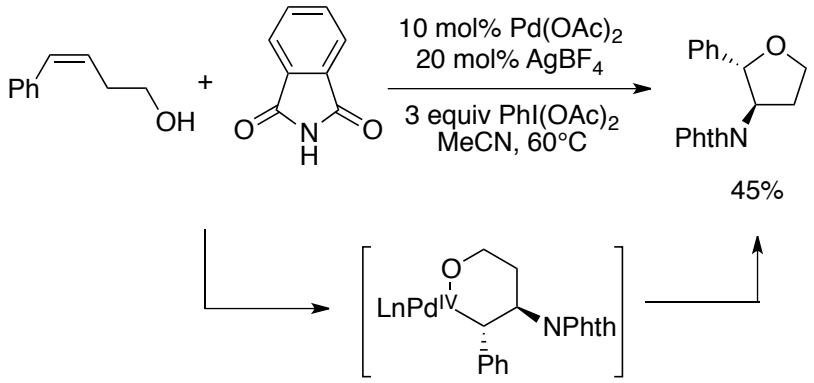



Fig. 17. Pd-Catalyzed Aminoacetoxylation Reaction

In 2010, Michael and coworkers described a Pd-catalyzed intramolecular/intermolecular aminoacetoxylation of the olefins utilizing $Pd(CH_3CN)_2Cl_2$ as catalysts and NFSI as oxidants.[19] Under this condition, protected aminoalkenes was cyclized and oxidized to the resulting product, and by changing co-solvent, a switch from exo to endo selectivity was found.

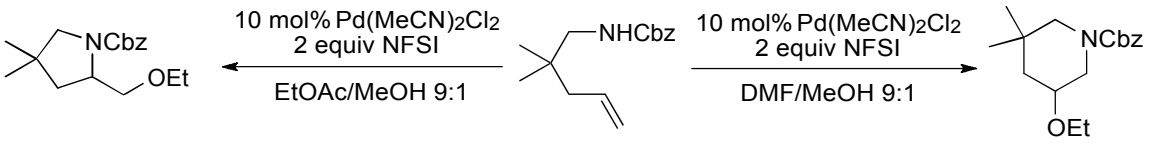



Fig. 18. Pd-Catalyzed Alkoxyamination of Protected Aminoalkenes

## 1.4 Palladium(IV) Chemistry

The key issue of alkene difunctionalization is to increase the rate of Pd-alkyl functionalization compared to the rate of **β-**hydride elimination. Recently, a powerful strategy to avoid **β-**hydride elimination is to proceed through a Pd(II)-Pd(IV) cycle due to higher reactivity of higher oxidation state. Also, due to the nonavailability of Pd(IV) open coordination site, Pd(IV) complexes are resistant to **β-**hydride elimination. Mechanistically, this Pd(II)-Pd(IV) cycle is proceed with alkene coordination, nucleopalladation to generate the Pd-alkyl intermediate which then oxidized by an oxidant to generate a Pd(IV) intermediate before **β-**hydride elimination occurs. Finally the difunctionalized products were formed through reductive elimination. Herein we describe the oxidation of the Pd(II) complexes to Pd(IV) complexes by hypervalent iodine(III) reagents $PhI(OAc)_2$.

In the dioxygenation of olefins section, we had presented Dong and coworkers reported dioxygenation of alkenes using the hypervalent iodine reagent $PhI(OAc)_2$ as oxidant to control **β-**hydride elimination.

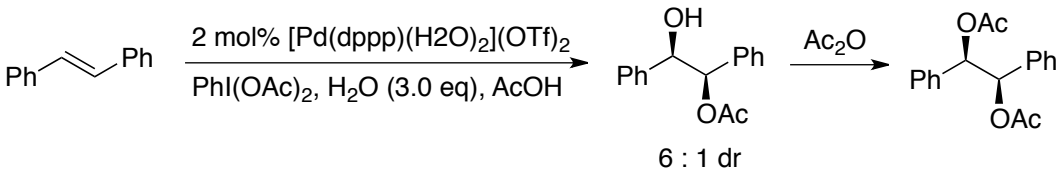



Fig. 19. Pd-Catalyzed Vicinal Dioxygenation of Alkenes

# CHAPTER TWO: USING 8-VINYLQUINOLINE AS A MODEL

## 2.1 Background

In 1994, the Dupont group developed the synthesis of cyclopalladated 8-substituted quinoline derivatives via a nucleophilic addition to terminal vinyl-quinoline substrate.[20] 8-bromoquinoline was treated with $Pd(CH_3CN)_2Cl_2$ in THF at room temperature followed by sodium dimetheylmalonate to yield a yellow solid which can be determined by $^1H$ NMR. It seems plausible that Palladium coordinated both the nitrogen and the double bond of 8-vinylquinoline that is proceed nucleophilic additions. However the crystal structure and type of nucleopalladation were still unknown.

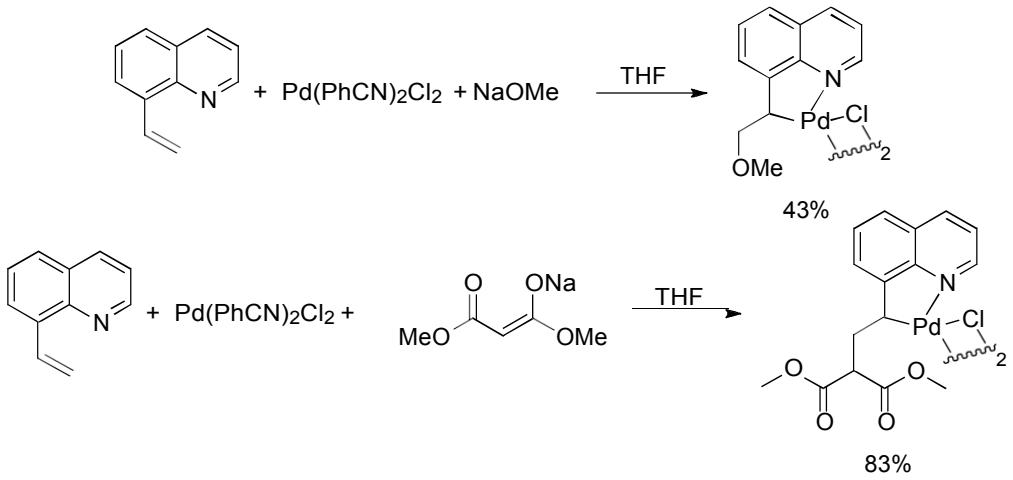



Fig. 20. Nucleophilic Addition to Terminal Vinyl-Quinoline Substrate

## 2.2 Isolation of Pd-alkyl Complex

### 2.2.1. Substrate Synthesis

Initial studies began with 8-vinylquinoline, which was derived from quinolin-8-ol via formation of the triflate and Stille cross-coupling..[21]

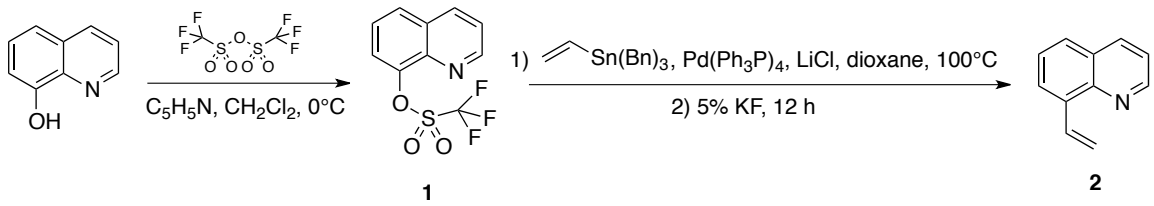



Fig. 21. Previously Reported Synthesis of 8-Vinylquinoline

Treatment of quinolin-8-ol with pyridine in DCM and a solution of trifluoromethanesulfonic anhydride in DCM was dropwise at 0°C. The mixture was stirred at room temperature for 1 h. The crude mixture was purified by 10% EtOAc/Hexanes flash chromatography giving a yellow oil in 90% yield. Following the procedure reported by Vittorio and coworkers, the resulting product was treated with lithium chloride under $N_2$ atmosphere, which then added $Pd(Ph_3P)_4$, dioxane, tributyl(vinyl)tin. The mixture was reacted at 100°C for over night to yield 8-vinylquinoline in 63% yield. Following this procedure provided product contaminated with tin byproducts, and overall yield is 57% over two steps.

Herein we developed an alternate synthetic approach of Kumada reaction to synthesize 8-vinylquinoline that was isolated in 80% yield. In this way, the procedure of

reaction is simple and the reagents are cheap. Therefore, the Kumada reaction from 8-bromoquinoline proved to be a powerful strategy to synthesize 8-vinylquinoline.

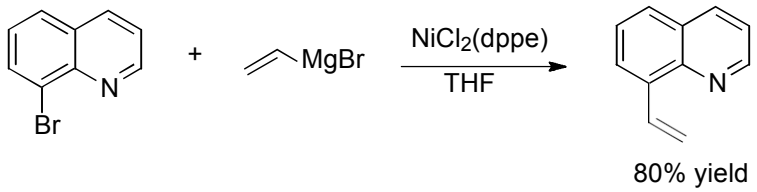
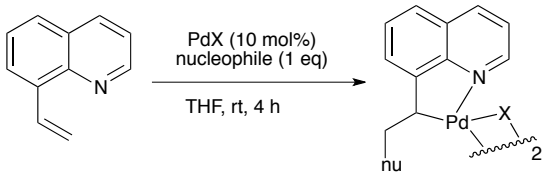



Fig. 22. Synthesis of 8-Vinylquinoline via Kumada Coupling Reaction

2.2.2. Nucleopalladation of Olefins

Next, based on the report of Dupont and coworkers, we examined different nucleophiles and Pd catalysts to undergo nucleopalladation with 8-vinylquinoline. 8-Vinylquinoline was solved in the THF solvent which was then treated with Pd catalyst. In another round bottom flask, nucleophile was dissolved in THF. Next two solvent mixtures were combined. THF as less coordinated solvent gave the best yield, and as illustrated in Fig. 23, a number of nucleophiles were converted 8-vinylquinoline to Pd-alkyls that can be isolated in moderate yields. The nucleopalladation of 8-vinylquinoline with malonate and bis(acetonitrile)dichloropalladium as the catalyst gave the Pd-alkyl complex in 96% yield, when changing catalyst to palladium acetate decrease the yield to 86%. Then we examined morpholine nucleophile with bis(acetonitrile)dichloropalladium and palladium acetate giving product in 45% and 35% yield, respectively. However, efforts to transform nucleophilic addition with potassium phthalimide have been successful in low yield.



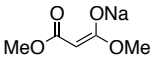
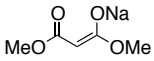
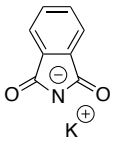

| entry | nucleophile | X | yield | entry | nucleophile | X | yield |
|---|---|---|---|---|---|---|---|
| 1 |  | $(CH_3CN)_2Cl_2$ | 96% | 4 |  | $(OAc)_2$ | 35% |
| 2 |  | $(OAc)_2$ | 86% | | | | |
| 3 |  | $(CH_3CN)_2Cl_2$ | 45% | 5 |  | $(CH_3CN)_2Cl_2$ | 15% |

Fig. 23. Formation of Pd-Alkyl Compounds

2.2.3. Recrystallization of Pd-alkyls

Although we can isolate Pd-alkyl intermediate, which can be determined by $^1H$ NMR, the crystal structure of Pd-alkyl intermediate is still unknown. Herein we developed the recrystallization procedure of Pd-alkyls. As shown in Fig. 24, recrystallization technique of Pd-alkyls is to find a suitable solvent for the Pd-alkyl complex at first, dissolve the Pd-alkyl solid in a minimum volume of solvent with a small vial 1, then put antisolvent in the vial 2, slowly transfer the vial 1 to the vial 2, move the vial with cap to the dark, stable environment., we used the recrystallization technique to examine the Pd-alkyl complex crystal structure of 8-vinylquinoline with malonate and bis(acetonitrile)dichloropalladium in Fig. 24.

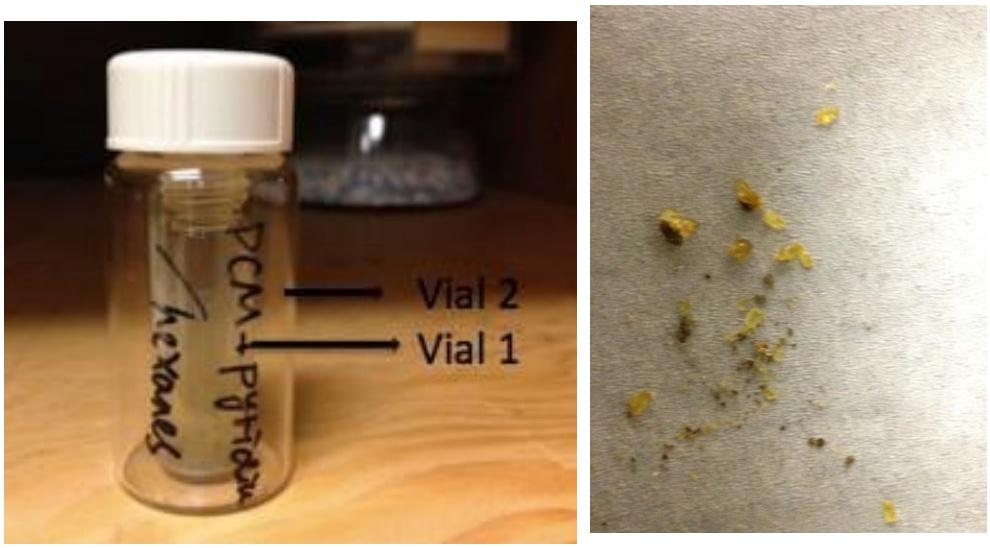



Fig. 24. Recrystallization of Pd-alkyl Complex

When solvent is dichloromethane and one drop of pyridine and antisolvent is hexane, after 3 days, the yellow crystal was formed as the right part of Fig.24. The pyridine can break the palladium-chloride dimer and coordinate to palladium. As expected, the nucleopalladation mechanism was confirmed by X-ray crystallography.

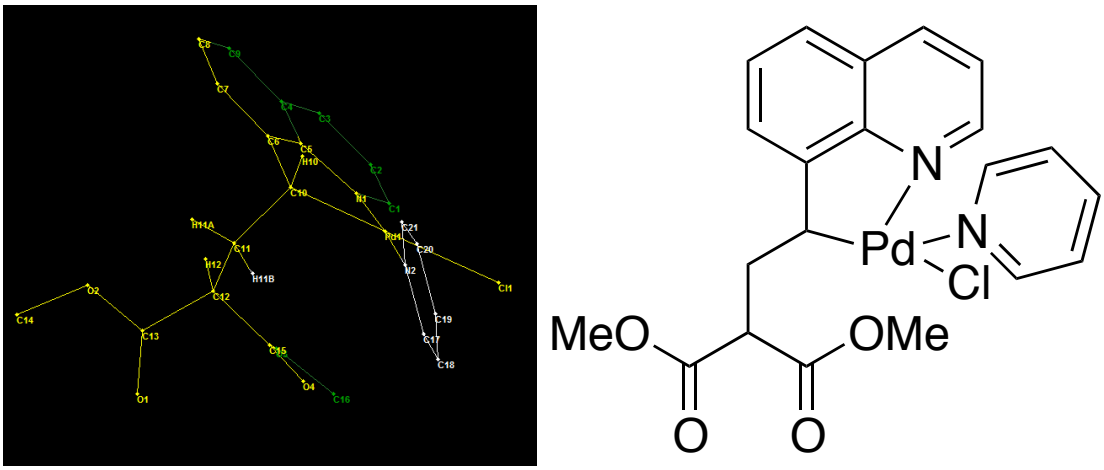



Fig. 25. Structure of Pd-Alkyl

2.3 Oxidation of Pd-alkyl Complex

With Pd-alkyl intermediates in hand, we aim to form difunctionalized products via functionalization with oxidants. At first, The palladium chloride dimer as substrate developed functionalization, whereas the desired difunctionalized product was not formed. Next, we examined iodobenzene diacetate as oxidant to undergo oxidation with palladium acetate dimer. As illustrated in Fig. 26, the difunctionalized product was formed. We hypothesized that the 3-dimensional structure of palladium acetate dimer is easier attacked by the nucleophile than square planar structure of palladium chloride dimer.

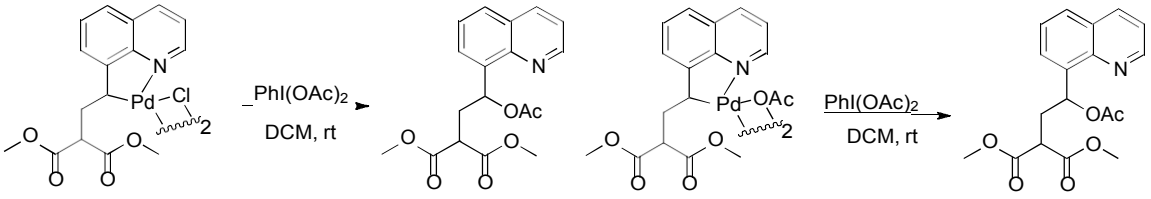



Fig. 26. Functionalization of Pd-Alkyl Complex

As the oxidation of Pd-alkyl intermediate is successful, we examined difunctionalization of 8-vinylquinoline with different nucleophiles and oxidants. Different solvents were examined, dichloromethane yield the desired product. Next we examined different nucleophiles and oxidants. However, difunctionalized product was only formed in the condition of malonate and iodobenzene diacetate. When changing

oxidant to selectfluor, nucleophile to morpholine and potassium phthalimide, the desired products were not formed as shown in Fig.27.

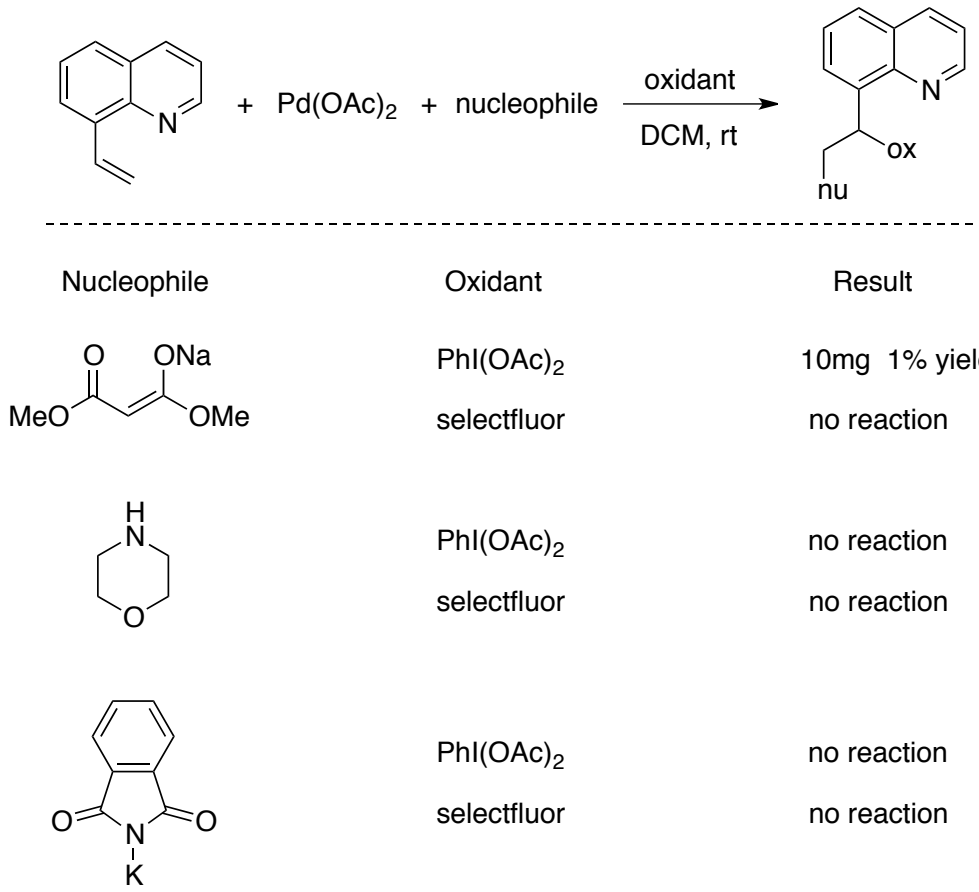



Fig. 27. Difunctionalization of 8-Vinylquinoline

This reaction was also examined at elevated temperatures, and no obvious result was showed. In the future work, we will examine more nucleophiles and oxidants to develop further difunctionalization.

2.4 Stereochemical Study

To further demonstrate the nucleopalladation step of 8-vinylquinoline, we sought to do the stereochemical study to identify the trans- or cis- nucleopalladation. The investigation of stereometric study was from 8-propenylquinoline[22] and deuterated 8- inylquinoline[23]. The preparation of substrates was as described below.

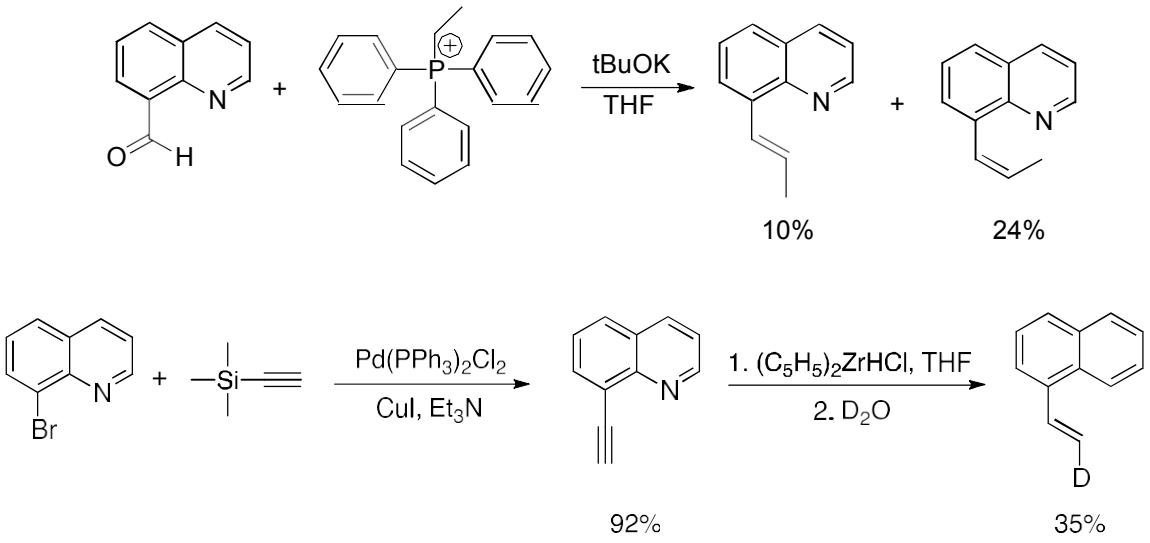
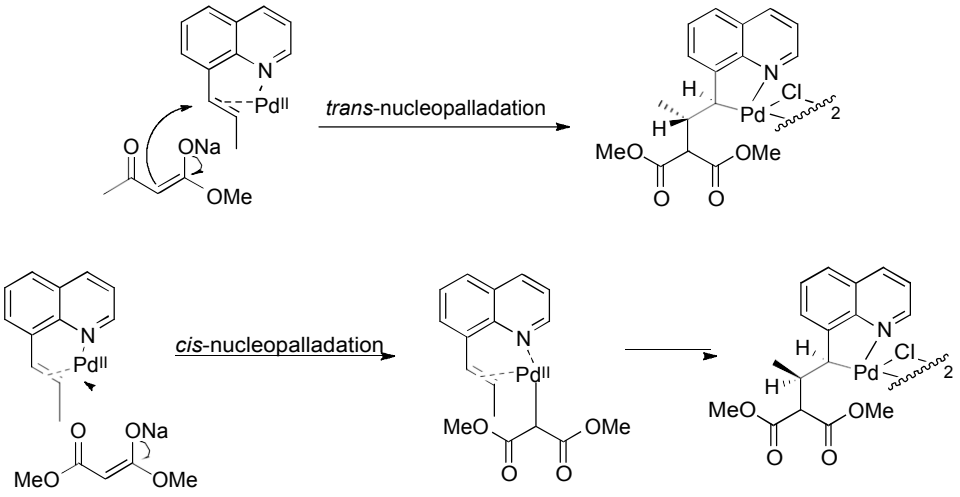



Fig. 28. Substrate Synthesis of Stereochemical Study

These substrates were followed the reaction condtion as Dupont's report to proceed nucleopalladation which was identified by $^1$H NMR. As shown in Fig.29, in the trans-nucleopalladation mechanism, the Pd catalyst first coordinates to the deuterated-8-vinylquinoline before dimethyl malonate has nucleophilic attack from the opposite face to the $Pd^{II}$. In the *cis*-nucleopalladation mechanism, dimethyl malonate first coordinates to the Pd catalyst, which then Pd complex undergoes the addition to form the

cis-nucleopalladated alkyl-Pd species. Compared to two different isomers, hydrogens showed trans configuration for the trans-nucleopalladation pathway; the trans geometry of hydrogens support a cis-nucleopalladation mechanism. Therefore, deuterium labeling experiment support the stereochemistry of the nucleopalladation step. 8-Propenylquinoline as substrate can be also used for stereochemical study of the nucleopalladation mechanism as described in the Fig.29.



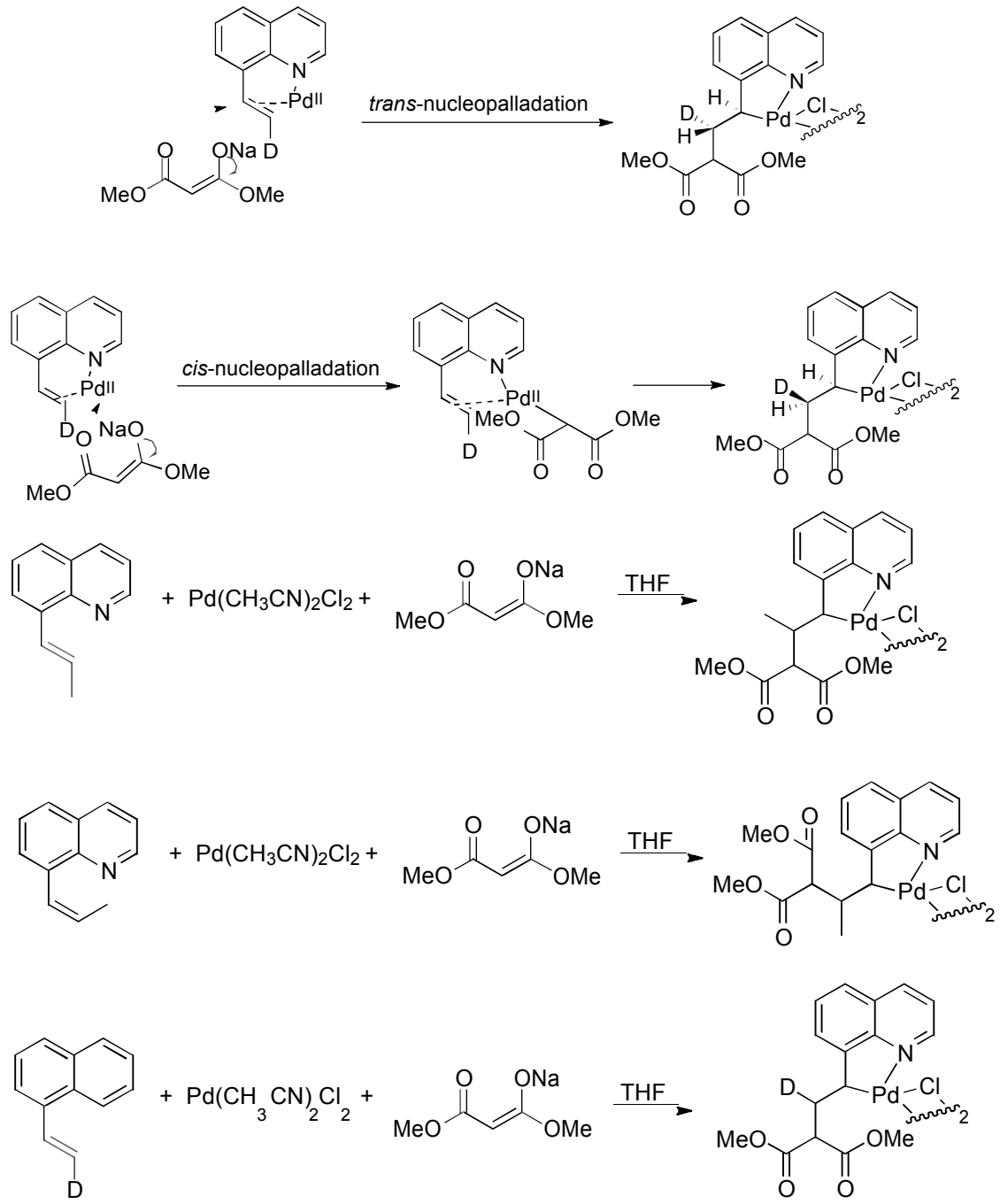



Fig. 29. Stereochemical Study

According to the $^{1}$H NMR spectra of Pd-alkyl complex, although the product was formed as we expected, the NMR spectrometry is not so clear that can give us J coupling

data to identify the cis- or trans- nucleopalladation. In the future work, we need to purify the Pd-alkyl complex to get a clear spectra to identify stereochemistry of the nucleopalladation step. Another strategy to examine the stereochemistry of nucleopalladation is to recrystallize the Pd-alkyl complex from 8- propenylquinoline.

## 2.5 Conclusion

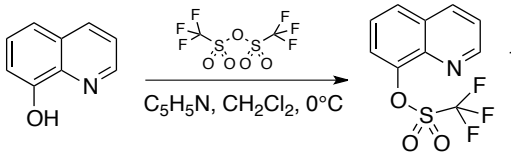
In conclusion, we developed the difunctionalization reaction on vinylquinoline type substrate. Herein we divided alkene difunctionalization to two parts. In the first part, we isolate many Pd-alkyl intermediates. Importantly, we utilized the recrystallization technique to discover the crystal structure of Pd-alkyl compound. The mechanism of nucleopalladation was demonstrated by the crystal structure of Pd-alkyl. Secondly, Pd-alkyl intermediates for further functionalization was described in this part. The advantage of separating alkene difunctionalization to nucleopalladation and oxidation is to better explore the mechanism and simplify the reaction procedure. Furthermore, we synthesized two substrates to undergo the nucleopalladation reaction and used for further stereochemistry study. In addition, we are also trying to synthesize the desired product from other pathways.

Future work is focusing on recrystallizing deuterated Pd-alkyl intermediate to further identify the nucleopalladation step. Besides, optimizing the reaction condition is to increase the yield of alkene difunctionalization. To examine the substrate scope, this strategy can be a powerful way to synthesize the quinoline derivatives.

2.6 Experimental

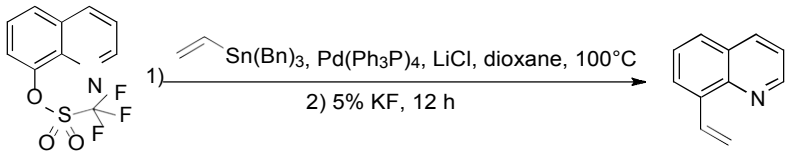
**General:** All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. All catalysts and reagents were obtained from commercial sources and were used without further purification. THF, dichloromethane were dried in the solvent system.

**Preparation of Substrates**



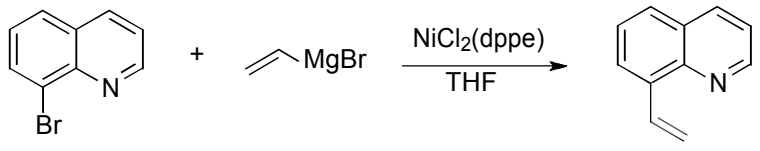

1

**Quinolin-8-yl trifluoromethanesulfonate (1).** Pyridine (4.4 mL, 55.24 mmol) was added to a stirred solution of quinolin-8-ol (4 g, 27.66 mmol) in $CH_2Cl_2$, and a solution of trifluoromethanesulfonic anhydride (5.6 mL, 33.08 mmol) in $CH_2Cl_2$ was added dropwise at 0°C. The mixture was stirred at room temperature for 1 h then washed with water and the organic layer was dried over $MgSO_4$. The solvent was removed under pressure and the residue was purified by flash chromatography (EtOAc/Hexane, 10%). Yield: 90%, Yellow solid. $^1$H NMR ($CDCl_3$): δ 9.06 (dd, J = 4.1 Hz, J = 1.7 Hz, 1H), 8.24 (dd, J = 8.5 Hz, J = 1.7 Hz, 1H), 7.87 (dd, J = 8.0 Hz, J = 1.7 Hz, 1H), 7.64-7.52 (m, 3H). MS: 278.2 ($M^+$).



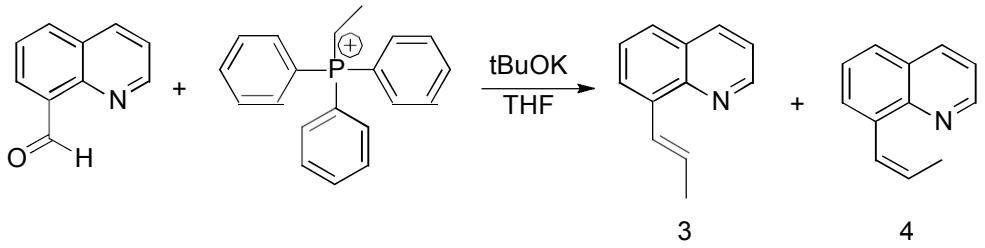

**1** **2**

**8-vinylquinoline (2).** A dried 2-neck round bottom flask equipped with a stir bar was charged with quinolin-8-yl trifluoromethanesulfonate (5 g, 18 mmol) and suspended in 80 mL of dioxane. Lithium chloride (2.29 g, 54 mmol), tributyl(vinyl)tin (5.5 mL, 18.72 mmol), tetrakis(triphenylphosphine)palladium(0) (0.416 g, 0.36 mmol) were added and the reaction mixture was heated to 100 °C over night. The resulting mixture was cooled to room temperature, diluted with $Et_2O$, added 150 ml 5% KF solution and the stirring was continued over night at rt. The solid was removed by celite and the mixture was transferred to a separatory funnel, the organic layers was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (EtOAc/Hexane, 7.5%) to afford 1.77 g (63%) of 8-vinylquinoline. $^1$H NMR ($CDCl_3$): δ 5.53 (dd, J = 11.07, J = 1.49 Hz, 1H), 5.94 (dd, J = 1.65, J = 17.65 Hz, 1H), 7.39-8.15 (m, 6H), 8.95 (s, 1H). MS: 156.2 ($M^+$).

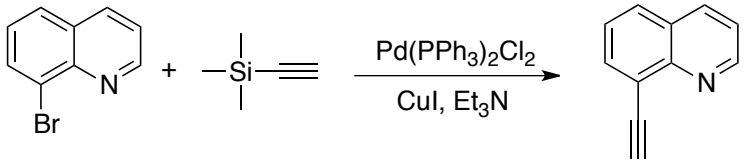



**2**

**8-vinylquinoline (2).** 8-Bromoquinoline (12.07g, 58 mmol) was added to a solution of $NiCl_2$(dppe) (2.66g, 5.05 mmol) with a stir bar in dry THF (210 mL). The reaction mixture was stirred at room temperature under $N_2$ atmosphere for 5 min and then a solution of vinyl magnesium bromide solution in THF (70 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography (EtOAc/Hexane, 7.5%) to afford 2.94 g (65%) of the desired compound as a yellow oil. H NMR ($CDCl_3$): δ 5.53 (dd, J = 11.07, J = 1.49 Hz, 1H), 5.94 (dd, J = 1.65, J = 17.65 Hz, 1H), 7.39-8.15 (m, 6H), 8.95 (s, 1H). MS: 156.2 ($M^+$).

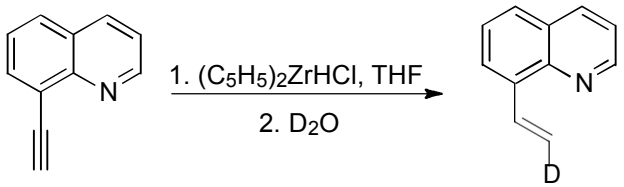



**8-Propenylquinoline (3 or 4).** Potassium tert-butylate (1.0 g, 6.4 mmol) was added to a mixture of triphenylethyl phosphonium bromide (2.4 g, 6.4 mmol) in dry THF (24 mL) at room temperature. The color of the mixture became orange. After 5 min 1 eq. of the corresponding aldehyde (6.4 mmol) was added. The reaction instantly changed color. The reaction course was monitored by thin layer chromotography. *Cis*-8-propenylquinoline (3): major product, *trans*-8-propenylquinoline (4): minor product, E/Z ratio: 1: 2.6.




5

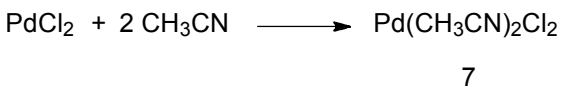
**8-Quinolinyl-acetylene (5).** A mixture of 8-bromoquinoline (3.00 g, 14.4 mmol), trimethylsilyl-acetylene (1.86 g, 19.0 mmol), $Pd(PPh_3)_2Cl_2$ (20 mg), cuprous iodide (20 mg), and triphenylphosphine (70 mg) was suspended in triethylamine (20 mL), and the resulting suspension was stirred and heated at 90 °C for 1.5 h. The reaction mixture was quenched with aqueous sodium carbonate solution (10%, 20 mL) and was extracted with ether (2 x 15 mL). The solvent of the combined organic extract was evaporated under reduced pressure, and the resulting oily residue, redissolved in methanol (20 mL), was treated with potassium fluoride (1.74 g, 30 mmol) and stirred at room temperature for 1.5 h. Evaporation of the solvent and chromatographic purification (EtOAc/Hexane, 20%) afforded a brown oil (2.02 g, 92% yield), that solidified in the refrigerator. $^1$H NMR ($CDCl_3$): δ 9.06 (dd, 1H, J = 4.3 Hz, J = 1.7 Hz); 8.15 (dd, 1H, J = 8.3 Hz, J = 1.7 Hz); 7.96 (dd, 1H, J = 7.2 Hz, J = 1.5 Hz); 7.81 (dd, 1H, J = 8.3 Hz, J = 1.5 Hz); 7.49 (dd, 1H, J = 8.3 Hz, J = 7.2 Hz); 7.44 (dd, 1H, J = 4.3 Hz, J = 8.3 Hz); 3.62 (s, 1H). MS: 154.2 ($M^+$).




6

**(E)-deutero-8-vinyl-quinoline (6).** Alkyne (0.63 g, 4.14 mmol) was treated with $(C_5H_5)_2ZrHCl$ (1.34 g, 5.18 mmol) in THF (20 mL, 0.2 M). After 10 min, the solution turned black, and the reaction was then quenched with $D_2O$ (2 mL, 2.0 M) and the mixture was stirred over night. The mixture was then diluted with $Et_2O$, dried over $MgSO_4$, filtered and concentrated. The mixture was purified by flash chromatography (EtOAc/Hexane, 10%-20%) giving 0.22 g (35% yield) of the product **6** as a brown oil. $^1H$ NMR ($CDCl_3$) δ 8.98 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.03 (d, *J* = 17.7 Hz, 1H), 7.95 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.78 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.1 Hz, 1H). MS: 156.2 ($M^+$).

**Preparation of the Palladium Catalysts**




7

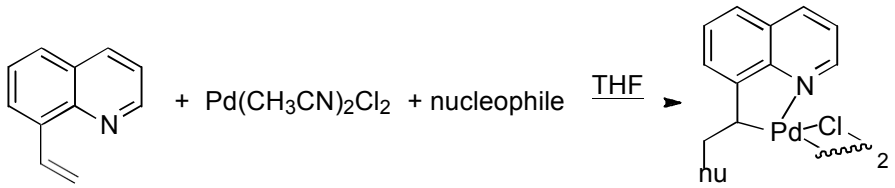
**Bis(acetonitrile)dichloropalladium(II) (7).** A suspension of $PdCl_2$ (2.00 g, 11.28 mmol) was heated to reflux in $CH_3CN$ (112.8 mL, 10 mL/mmol) over night under N2. Hot filtration of the resultant wine-red colored solution through a celite pad then cooled down to room temperature afforded a yellow-orange solid. Recrystallisation from $CH_3CN$ (100 mL), DCM (150 mL) and hexane (50 mL) gave 2.34 g (80% yield) of the product as a bright yellow solid.


8

**Bis(triphenylphosphine)palladium(II) dichloride (8).** A suspension of $PdCl_2$ (0.13 g, 0.7 mmol) and triphenylphosphine (0.375 g, 1.4 mmol) was heated to reflux in DMF (20 mL) over night under N2. Hot filtration of the resultant orange colored solution through a celite pad then cooled down to room temperature afforded a yellow solid. Recrystallisation from DCM (150 mL) and hexane (50 mL) gave 0.32 g (66% yield) of the product as a yellow solid.

**Synthesis of Pd-alkyl intermediates**

**General Procedure:**




9

Bis(acetonitrile)dichloropalladium(II) (77.8 mg, 0.3 mmol) was placed in an oven-dried 100 ml round bottom flask, THF (30 mL) was added to dissolve the solid. Then 8-vinylquinoline (51.2 mg, 0.33 mmol) was added, the mixture was stirred at room temperature for 5 min. Nucleophile (0.33 mmol) was added to another 50 mL round bottom flask charged with 20 mL THF. The THF mixtures were combined, stirred for 5 h. The solvents were then removed under reduced pressure to around 5 mL, 40 mL hexane was added to the flask. The solid was collected by vacuum filtration. The product can be characterized by HNMR.

When the nucleophile is dimethyl malonate. $^1$H NMR ($CDCl_3$) δ 8.99 (s, 1H), 8.31 (dd, *J* = 8.3 Hz, 1H), 7.68 (dd, *J* = 7.7 Hz, 2H), 7.53 (dd, *J* = 7.6 Hz, 1H), 7.45 (dd, *J* = 8.4, 5.0 Hz, 1H), 4.65 (s, 1H), 4.05 (d, *J* = 26.1 Hz, 1H), 3.82 (s, 3H), 3.27 (s, 3H), 2.61 (s, 1H), 1.95 (s, 1H). The Pd-alkyl complex cannot be completely solved in $CDCl_3$, one drop of pyridine can be added to solve solid. The pyridine was then coordinated to Pd to form a Pd pyridine complex which can be identified by $^1$H NMR. $^1$H NMR ($CDCl_3$) δ 9.59 (dd, *J* = 5.1, 1.6 Hz, 1H), 8.57 (s, 1H), 8.23 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.59 – 7.54 (m, 1H), 7.49 (dd, *J* = 8.7, 6.4 Hz, 1H), 7.38 (dd, *J* = 8.3, 5.0 Hz, 1H), 7.23 (s, 2H), 3.95 (t, *J* = 4.8 Hz, 1H), 3.77 (s, 3H), 3.31 (d, *J* = 3.3 Hz, 3H), 3.05 (s, 3H), 2.05 (ddd, *J* = 15.1, 8.2, 5.3 Hz, 1H), 1.89 – 1.72 (m, 1H).

When the nucleophile is morpholine. $^1$H NMR ($CDCl_3$) δ 9.83 – 9.54 (dd, 1H), 8.26 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.67 (t, *J* = 6.7 Hz, 2H), 7.56 (dd, *J* = 7.6 Hz, 1H), 7.43 (dd, *J* = 8.3, 5.1 Hz, 1H), 6.82 (s, 1H), 4.00 – 2.50 (m, 6H).

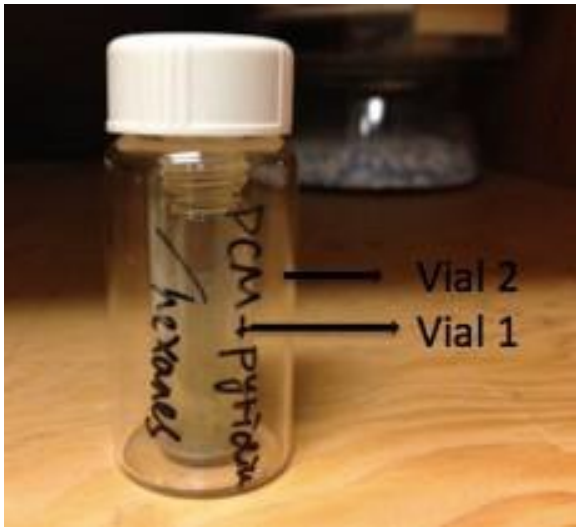
When the nucleophile is potassium phthalimide. $^1$H NMR ($CDCl_3$) δ 9.96 (d, *J* = 5.2 Hz, 1H), 9.70 (d, *J* = 5.1 Hz, 1H), 8.40 (q, *J* = 9.5, 8.5 Hz, 2H), 8.30 (s, 1H), 8.08 (d, *J* = 7.3 Hz, 1H), 8.00 – 7.38 (m, 4H), 5.55 (t, 1H), 4.22 (d, 2H).

**Preparation for the crystals**

**General Procedure:**

Palladium complexes (~ 10 mg) were placed in an oven-dried 5 ml vial. Then solvent (1 mL) was added with a syringe. In a 20 mL scintillation vial, antisolvent (2 mL~ 3 mL)

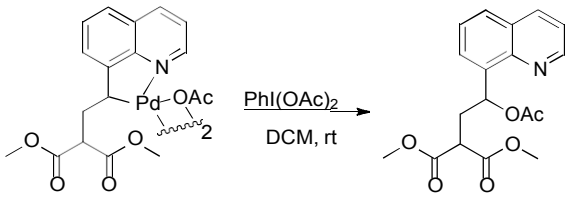
was charged. The 5 mL vial was removed to a 20 mL scintillation vial, and the whole vial with cap was placed to a dark, stable environment followed as the below figure.




When solvent is 1 mL dichloromethane and one drop of pyridine and antisolvent is hexane, the crystal was formed. Followed are the crystal data.

**Oxidation of Pd-alkyl intermediates**

**General Procedure:**




Palladium acetate dimer(50 mg) was weighted into a 18 mL test tube, which then charged 1-2 mL DCM to dissolve all Palladium acetate dimer. 1.5 eq $PhI(OAc)_2$ was then tranferred to the test tube. The solvent mixture was react under $N_2$ atmosphere for over 4

h. The reaction was monitored by TLC, the crude material was purified by flash chromatography (EtOAc/Hexane, 10-50%) to afford the product. The product can be characterized by $^{1}H$ NMR.

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APPENDIX X-RAY CRYSTAL DATA

Pd1 0.03543(9) 0.03386(9) 0.03758(9) 0.00017(5) 0.01333(6) 0.00075(5)

Cl1 0.0573(3) 0.0503(3) 0.0506(3) -0.0066(2) 0.0241(2) 0.0042(2)

O1 0.0490(8) 0.0963(13) 0.0617(9) -0.0052(9) 0.0057(7) -0.0031(8)

O2 0.0595(8) 0.0856(11) 0.0475(8) -0.0165(8) 0.0191(7) -0.0220(8)

O3 0.0852(11) 0.0493(8) 0.0609(9) 0.0069(7) 0.0186(8) 0.0145(8)

O4 0.0538(9) 0.0751(11) 0.0601(10) 0.0059(7) 0.0235(8) 0.0029(7)

N1 0.0469(8) 0.0369(8) 0.0404(8) -0.0002(6) 0.0120(6) -0.0026(6)

N2 0.0345(7) 0.0440(8) 0.0427(8) 0.0020(6) 0.0113(6) -0.0026(6)

C1 0.0716(13) 0.0404(10) 0.0501(11) -0.0027(8) 0.0187(10) -0.0043(9)

C2 0.0993(18) 0.0396(11) 0.0633(13) -0.0002(10) 0.0200(13) -0.0179(12)

C3 0.0770(15) 0.0588(13) 0.0608(13) 0.0051(11) 0.0202(11) -0.0280(12)

C4 0.0493(10) 0.0579(12) 0.0445(10) 0.0022(9) 0.0111(8) -0.0157(9)

C5 0.0388(9) 0.0458(10) 0.0364(8) 0.0001(7) 0.0084(7) -0.0055(7)

C6 0.0384(9) 0.0464(10) 0.0412(9) -0.0030(7) 0.0103(8) -0.0026(7)

C7 0.0510(11) 0.0584(13) 0.0622(12) -0.0122(10) 0.0251(9) -0.0023(10)

C8 0.0561(14) 0.0854(18) 0.0693(15) -0.0127(12) 0.0354(12) -0.0082(12)

C9 0.0546(12) 0.0817(17) 0.0589(13) -0.0014(11) 0.0274(10) -0.0211(11)

C10 0.0402(9) 0.0359(9) 0.0424(9) -0.0011(7) 0.0148(7) 0.0011(7)

C11 0.0474(10) 0.0375(9) 0.0466(10) -0.0046(8) 0.0149(8) -0.0053(8)

C12 0.0448(10) 0.0464(11) 0.0427(10) 0.0004(8) 0.0138(8) -0.0090(8)

C13 0.0510(11) 0.0495(11) 0.0451(10) 0.0055(8) 0.0118(8) -0.0089(9)

C14 0.0834(16) 0.0911(19) 0.0493(12) -0.0179(12) 0.0157(11) -0.0211(14)

C15 0.0459(10) 0.0547(11) 0.0445(10) 0.0034(9) 0.0068(8) 0.0037(9)

C16 0.115(2) 0.0666(17) 0.093(2) -0.0025(15) 0.0286(18) 0.0367(16)

C17 0.0386(10) 0.0739(14) 0.0584(12) 0.0133(10) 0.0171(9) 0.0040(9)

C18 0.0426(11) 0.111(2) 0.0725(15) 0.0220(15) 0.0187(10) -0.0162(13)

C19 0.0676(15) 0.0770(17) 0.0716(15) 0.0211(13) 0.0070(12) -0.0318(13)

C20 0.0688(13) 0.0449(11) 0.0586(12) 0.0067(9) 0.0065(10) -0.0110(10)

C21 0.0454(10) 0.0418(10) 0.0458(10) 0.0009(8) 0.0098(8) -0.0010(8)

checkCIF/PLATON report

**Datablock: xls1224**

---

| | | | |
|---|---|---|---|
| Bond precision: C-C = 0.0033 A | | Wavelength=0.71073 | |
| Cell: | a=10.1275(1) | b=9.1222(1) | c=22.8758(3) |
| | alpha=90 | beta=99.980(1) | gamma=90 |
| Temperature: | 296 K | | |
| | Calculated | Reported | |
| Volume | 2081.40(4) | 2081.40(4) | |
| Space group | P 21/c | P2(1)/c | |
| Hall group | -P 2ybc | ? | |
| Moiety formula | C21 H21 Cl N2 O4 Pd | C21 H21 Cl N2 O4 Pd | |
| Sum formula | C21 H21 Cl N2 O4 Pd | C21 H21 Cl N2 O4 Pd | |
| Mr | 507.25 | 507.25 | |
| Dx,g cm-3 | 1.619 | 1.619 | |
| Z | 4 | 4 | |
| Mu (mm-1) | 1.050 | 1.050 | |
| F000 | 1024.0 | 1024.0 | |
| F000’ | 1020.99 | | |
| h,k,lmax | 12,10,27 | 12,10,27 | |

| | | |
|---|---|---|
| Nref | 3681 | 3681 |
| Tmin,Tmax | 0.493,0.794 | 0.519, 0.802 |
| Tmin’ | 0.465 | |

Correction method= # Reported T Limits: Tmin=0.519 Tmax=0.802

AbsCorr = MULTI-SCAN

Data completeness= 1.000 Theta(max)= 25.030

R(reflections)= 0.0181( 3587) wR2(reflections)= 0.0536( 3681)

S = 0.895 Npar= 268

The following ALERTS were generated. Each ALERT has the format **test-name_ALERT_alert-type_alert-level**.

Click on the hyperlinks for more details of the test.

[IMAGE] **Alert level C**

ABSTY02_ALERT_1_C An _exptl_absorpt_correction_type has been given without a literature citation. This should be contained in the _exptl_absorpt_process_details field.

Absorption correction given as multi-scan

PLAT232_ALERT_2_C Hirshfeld Test Diff (M-X) Pd1 -- N1 .. 5.3 s.u.

PLAT232_ALERT_2_C Hirshfeld Test Diff (M-X) Pd1 -- N2 .. 5.4 s.u.

**Alert level G**

PLAT005_ALERT_5_G No Embedded Refinement Details found in the CIF Please Do !

PLAT063_ALERT_4_G Crystal Size Likely too Large for Beam Size .... 0.72 mm

PLAT164_ALERT_4_G Nr. of Refined C-H H-Atoms in Heavy-Atom Struct. 1 Note

PLAT232_ALERT_2_G Hirshfeld Test Diff (M-X) Pd1 -- Cl1 .. 9.3 s.u.

PLAT793_ALERT_4_G The Model has Chirality at C10 (Centro SPGR) R Verify

PLAT899_ALERT_4_G SHELXL97 is Deprecated and Succeeded by SHELXL 2014 Note

PLAT909_ALERT_3_G Percentage of Observed Data at Theta(Max) Still 95 %

PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density 5 Note

0 **ALERT level A** = Most likely a serious problem - resolve or explain

0 **ALERT level B** = A potentially serious problem, consider carefully

3 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight

8 **ALERT level G** = General information/check it is not something unexpected

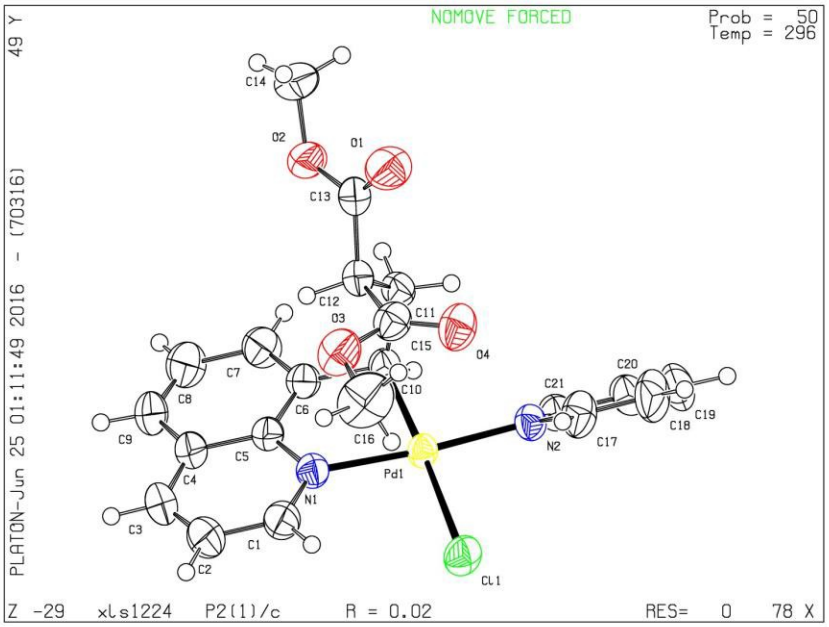
1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data

4 ALERT type 2 Indicator that the structure model may be wrong or deficient

1 ALERT type 3 Indicator that the structure quality may be low

4 ALERT type 4 Improvement, methodology, query or suggestion

1 ALERT type 5 Informative message, check


NOMOVE FORCED
Prob = 50
Temp = 296
49 Y
PLATON-Jun 25 01:11:49 2016 - (70316)
C14
O2
O1
C13
C12
O3
C11
C15
O4
C7
C8
C6
C10
C21
C20
C9
C5
C16
N2
C17
C18
C19
C4
Pd1
N1
C3
C1
C2
CL1
Z -29 xls1224 P2(1)/c R = 0.02 RES= 0 78 X