EXPLORATION OF PALLADIUM COMPLEXES OF 2-ARYLQUINOLINES FOR CATALYTIC NON-CHELATION-ASSISTED DIRECT ARENE C-H AMINATION WITH PHTHALIMIDE AND IODINATION USING INORGANIC IODIDE AS REAGENTS

LI CHUN KIT

MPhil

The Hong Kong Polytechnic University

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The Hong Kong Polytechnic University

Department of Applied Biology and Chemical Technology

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Li Chun Kit

A thesis submitted in partial fulfilment

of the requirements for the degree of

Master of Philosophy

June 2019

CERTIFICATE OF ORIGINALITY

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Li Chun Kit

ABSTRACT

Abstract of the thesis entitled

EXPLORATION OF PALLADIUM COMPLEXES OF 2-ARYLQUINOLINES FOR CATALYTIC NON-CHELATION-ASSISTED DIRECT ARENE C-H AMINATION WITH PHTHALIMIDE AND IODINATION USING INORGANIC IODIDE AS REAGENTS

Submitted by Li Chun Kit

for the degree of Master of Philosophy

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The concept of step-economical and environmentally friendly synthesis has aroused great interest in recent years. Diminishing functional group manipulations typically required to afford pre-oxidized compounds is one of the unsophisticated ways to reduce numbers of steps of a certain synthetic route via direct functionalization from targeted C-H bond to desired carbon-carbon (C-C) or carbon-heteroatom bond (C-X). Meanwhile, the selectivity issue always remains an essential obstacle in this chemistry. Generally, several types of unique C-H bonds can be found even in a moderately simple organic compound. Therefore, selective functionalization of a targeted robust

C-H bond is challenging when dealing with a direct C-H bond activation based synthesis.

Aryl amine is an important scaffold in medicine, agroscience and material science that makes them valuable synthetic targets, therefore, synthetic reactions that constructing C-N bonds are extensively investigated. In this thesis, we have successfully demonstrated the non-chelation-assisted arene C-H amidation with phthalimide employing palladium complexes. We began by treating simple non-directing arene (1 ml) with phthalimide (0.2 mmol) with diacetoxy iodobenzene (6.0 equiv) as the oxidant in the presence of palladium(II) acetate (5 mol%). Under the optimized reaction conditions, a wide scope of simple non-directing arenes can be amidated in good yields (50-80%) while showing good functional group tolerance. In addition, single-crystal X-ray crystallography of the $[Pd(qin)(OAc)]_2$ complex was established.

Aryl halides are essential and versatile starting materials for Grignard reaction and also numerous cross-coupling reactions that are employed for synthesizing various pharmaceuticals, natural products and functional compounds. In this thesis, we have also established the non-chelation-assisted arene C-H iodination using inorganic

iodide as the coupling reagent by employing palladium complexes. By treating simple arene(1 ml) with potassium iodide (0.2 mmol) and $PhI(TFA)_2$ (2.0 equiv) as the oxidant in the presence of $[Pd(qin)(OAc)]_2$ complex (5 mol%) and pyridine (10 mol%), a wide scope of simple non-directing arenes can be halogenated in good yields.

SYMPOSIUMS

Li, C.-K.; Ling, C.-H.; Yu, W.-Y. "Ligand-Enabled Pd-Catalyzed Site-Selective Non-Chelation-Assosted Direct Amidation of Unactivated Arenes", The 25th Symposium on Chemistry Postgraduate Research in Hong Kong, 28 April 2018.

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TABLE OF CONTENTS

LIST OF FIGURES

Chapter 1 Introduction

Chapter 2 Synthesis and Characterization of Cyclopalladated Complexes and Exploration of their Catalytic Activities Towards Direct Arene C-H Activation

Chapter 3 Ligand enabled Pd-catalyzed site selective nondirected iodination of unactivated arenes with inorganic iodide

LIST OF TABLES

Chapter 1 Introduction

Chapter 2 Synthesis and Characterization of Cyclopalladated Complexes and Exploration of their Catalytic Activities Towards Direct Arene C-H Activation

Chapter 3 Ligand enabled Pd-catalyzed site selective nondirected iodination of unactivated arenes with inorganic iodide

LIST OF SCHEMES

Chapter 1 Introduction

Chapter 3 Ligand enabled Pd-catalyzed site selective nondirected iodination of unactivated arenes with inorganic iodide

Chapter 1

Introduction

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Introduction

1.1. General background

The concept of step-economical and environmentally friendly synthesis has aroused great interest in recent years. Functional group manipulations to afford pre-oxidized compounds are commonly required in multi-step organic synthesis. It is conceivable that direct transformation of non-acidic C-H bonds to common functional groups such as halides, carbonyls and alcohols, allows the elaboration of more complex organic molecules through employing the feedstock that are of lower price and higher abundance.

In general, there are two fundamental obstacles limiting direct C-H functionalization reactions, namely the intrinsic properties of the carbon-hydrogen bonds and control of site-selectivity as one molecule contain diverse carbon-hydrogen bond. The first limitation has been addressed through extensive studies on transition metal-mediated “C-H bond activation”. C-H bond activation refers to the process of generating metal-carbon bonds via interaction of transition metals with C-H bonds. The resultant reactive C-M bonds can therefore be transformed to other desired functional groups under mild conditions.

Site-selectivity issue control remains a formidable challenge since several types of C-H bonds are commonly found in any moderately simple organic compounds. Therefore, selective functionalization of a particular C-H bond is challenging when directed towards synthesis of a specific target. The most popular strategy employs substrates containing coordinating donor groups that bind to the metal centers for regioselective C-H activation through the formation of a metallocycle.

1.2. Reactivity of an isolated C-H bond

Owing to the large kinetic barrier associated with the C-H bond cleavage that in turn in correlation with the apolar nature of such bond, an isolated, *i.e.* non acidic, C-H bond in a molecule has a very low reactivity generally.

The acidities and the bond dissociation energies (BDEs) of typical C-H bonds in seven simple hydrocarbons are depicted in Table 1.1. The BDE drops from C(sp)-H to C(sp^2)-H and then C(sp^3)-H, and also along the series 1^o , 2^o ,3^o and allylic C(sp^3)-H bond. The decrease of the BDE parallels with the concept that the BDE value has the inverse proportional to the stability of the radicals generated from homolytic cleavage of the bond. On the other hand, the pK_a values have a roughly opposite trend since acidity is proportional to the stability of the corresponding deprotonated species, except for the allyl C-H bond.[1]

Though simple correlations between either homolytic or heterolytic C-H bond cleavages and the C-H bond reactivity may not be readily established, one can see that the interaction between these strictly inter-laced forces drives and explains this chemistry.

In this context, transition metals therefore have a key role in C-H bond activation / functionalization chemistry.

Table 1.1 BDE and pK_a values of several C-H bonds

Type of C-H	C(sp)	$C(sp^2)_{arom}$	$C(sp^2)_{vinyl}$	$C(sp^3)_{1°}$	$C(sp^3)_{2°}$	$C(sp^3)_{3°}$	$C(sp^3)_{allylic}$
structure							
BDE (kJ/mol)	552.2	473.0	460.2	410.8	397.9	389.9	361.1
pK_a	~25	43	44	~50	~50	~50	43

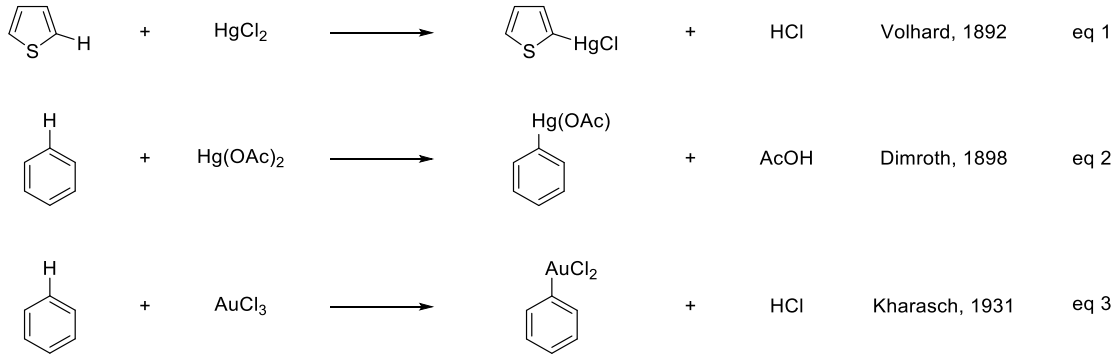
1.3. History

Volhard and co-workers reported the first example of metal assisted C-H activation in 1892.[2] By reaction between thiophene and mercury(II) chloride (Scheme 1.1, eq 1), 2-thiophenylmercury(II) chloride was initiated. Later, Dimroth and co-workers demonstrated the reaction of $Hg(OAc)_2$ with several aromatic hydrocarbons to afford a number of arylmercury(II) acetate products (Scheme 1.1, eq 2).[3] Afterwards, Kharasch and Isbell showed that reacted $AuCl_3$ with benzene to yield PhCl and AuCl after isolating $PhAuCl_2$ as intermediate (Scheme 1.1, eq 3).[4]

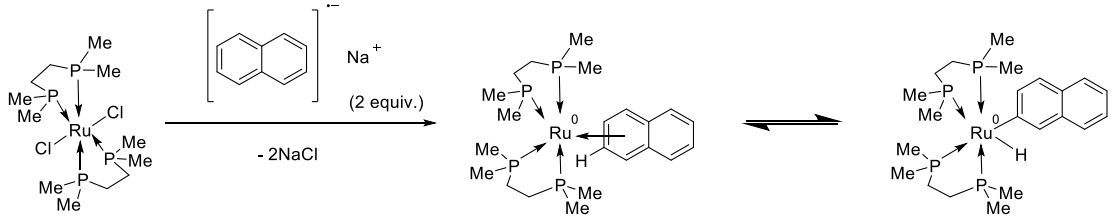
However, Chatt and co-workers has reported the insertion of a ruthenium(0) complex into the C-H bond of naphthalene in 1965 and was probably regarded as the pioneer of the metal-assisted C-H bond activation (Scheme 1.2).[5]

These pioneering works were the first examples that helped initiate the development of metal assisted C-H bond functionalization chemistry to present days.

Scheme 1.1. Pioneering examples of electrophilic C-H metalations



Scheme 1.2. Chatt's pioneer C-H activation on naphthalene



1.4. Site selectivity

Regio-, chemo- and stereoselective activation of a desired C-H bond for transformation among other C-H bonds in a substrate is always a major obstacle in C-H bond functionalization chemistry.

Conceptually, the site-selectivity can be achieved by either (i) substrate-, or (ii) reagent-controlled approaches. For *substrate-control*, it is a more classical strategy relying on the intrinsic properties of the substrate for functionalizing at one particular spot. For *reagent-control*, the site-selectivity is determined by the special characteristics of the reagent that can overwhelm the inherent properties of the substrate ideally.[6]

1.4.1. Directed C-H activations

The most common *substrate-control* scheme is to induce the metal approaching the desired, unactivated C-H bond at a certain position by employing the directing Lewis bases that covalently bonded onto the substrate. Both heteroatom-based groups and alkenes are known to be effective directing groups.[7, 8] Though stable σ-adducts will not be formed between the C-H bonds and the transition metals, metal-to-C-H bond pre-coordination is a compulsory step before the cleavage of the C-H bond in a C-H bond activation process.

Directing group-assisted Pd(II) C-H activations has been extensively investigated, particularly for arene C-H activation. *Ortho*-selectivity through cyclometallation is the most successful for arene C-H activation. Notably, specially designed directing groups allowing *meta*-selectivity has also been explored and demonstrated in recent years.

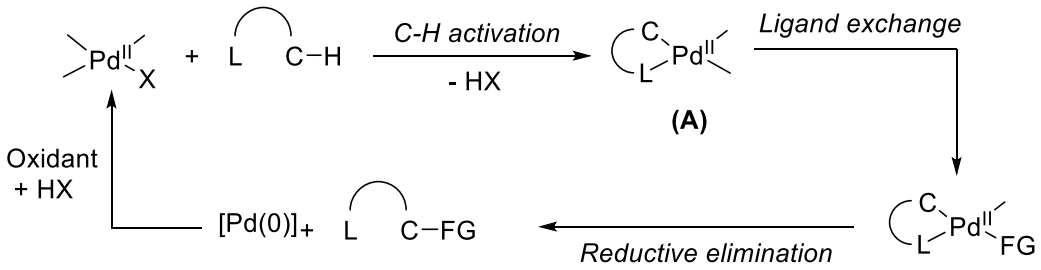
1.4.2. Introduction to Pd-Catalyzed Directed C-H Functionalization

There are several reasons for palladium complexes to be attractive catalysts for ligand-directed C-H functionalization. First, organopalladium complexes are known to mediate C-O bond, C-S bond, C-X bond (X= halogens), C-N bond and also C-C bonds formation. Such high versatility stems from the high compatibility of many Pd(II) complexes with oxidants and also high capability for selective functionalization of cyclopalladated intermediates. Second, palladium(II) readily promotes C-H activation at both sp^2 and sp^3 C-H bonds with a wide variety of directing groups. Lastly, most of the palladium-catalyzed reactions allow mild reaction conditions, making it practical in organic synthetic applications.

1.4.3. Mechanistic Manifolds

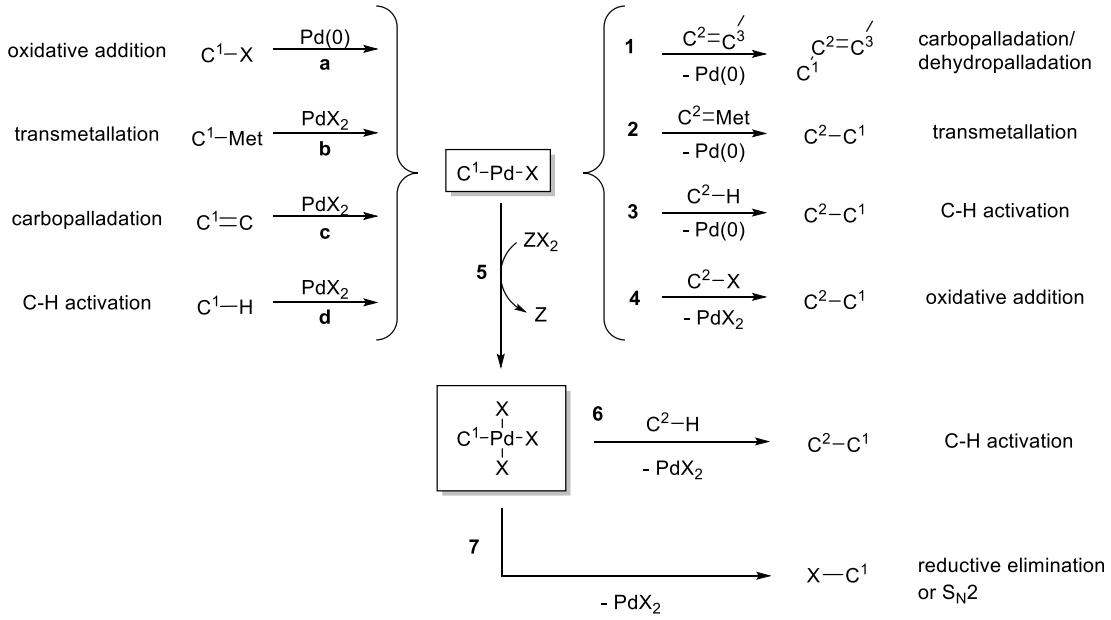
Generally, most of the palladium catalyzed ligand-directed C-H activation reactions occur at the Pd(II) center, affording in general a cyclopalladated complex structure **A**. Complex **A** can then undergo functionalization involving a Pd(II/0) pathway and afford the desired product through reductive elimination or beta-hydride elimination/deprotonation. The active Pd(II) intermediate will then be regenerated through oxidizing the resulting Pd(0) species. (Scheme 1.3)

Scheme 1.3. Reductive functionalization pathway: Pd(II/0) catalytic cycle



Yet, an organopalladium(II) complex can undergo a $2e^-$ oxidation to form an organopalladium(IV) complex[9] or an organopalladium(III) dimer[10] in the presence of suitable oxidant (path 5, Scheme 1.4). Such high valent species can again react with a C-H bond (path 6, Scheme 1.4) or yield a carbon-heteroatom bond (path 7, Scheme 1.4) through reductive elimination or Walden inversion (S_N2 reaction).

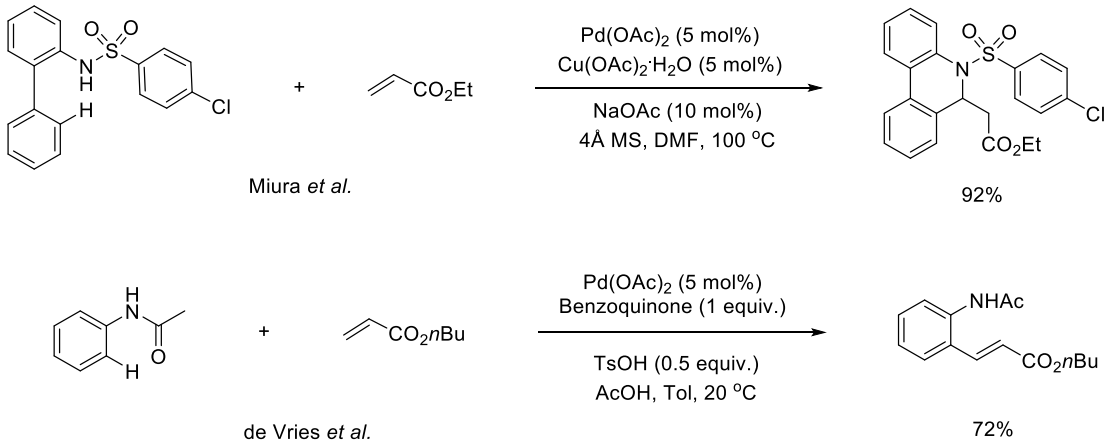
Scheme 1.4. The pivotal role of the C-Pd-X moiety



1.4.4. Ortho C-H activation

With the inspiration from the Ru(0) catalyzed reaction[11], Miura and soon after deVries, discovered that the first step of an oxidative catalytic cycle could be the well-known cyclometallation of arenes by electrophilic PdX_2 salts (Scheme 1.5).[12, 13]

Scheme 1.5. Pioneering examples of the directed Fujiwara-Moritani reaction



The scope of the *ortho*-directing method has been broadened to multiply functionalize numerous aromatic compounds that containing directing groups after the above refined reactions.

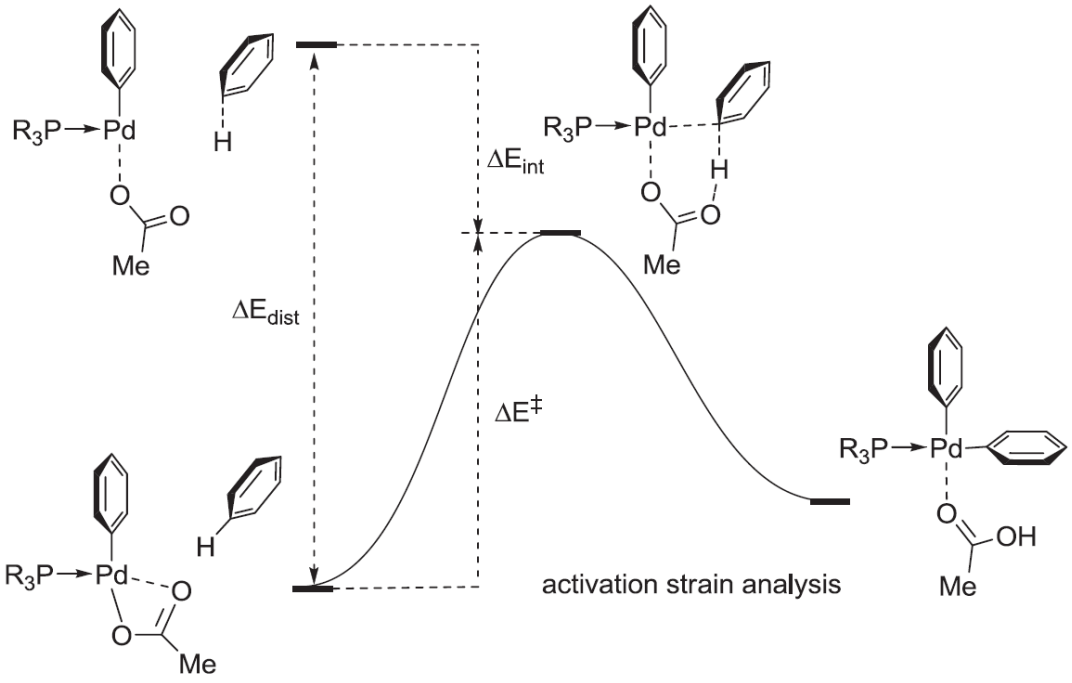
A more thorough and clear understanding of the underlying physical parameters determining selectivity and reactivity across the diverse scope of substrates is required in order to predict the product region-selectivity. In the case of palladium catalyzed *ortho*-directing reactions, several reaction pathways such as oxidative C-H insertion,[14]

electrophilic aromatic substitution (S_EAr),[15] Heck-like,[16] anionic cross-coupling and concerted metalation-deprotonation (CMD),[17] are being proposed.

1.4.4.1. Analysis of Concerted Metalation Deprotonation Mechanism (CMD)

Fagnou and Gorelsky demonstrated the CMD pathway to predict the regioselectivity observed in the palladium-catalyzed direct arylation across a broad range of aromatic substrates in 2008.[18, 19] In this study, an activation-strain analysis was constructed with the activation barrier was divided into two components: (1) *energetic gain* (electronic interaction energy, E_{int}), owing to the interaction of the substrates at the transition state and (2) *energetic cost* (distortion energy, Edist) accompanied the distortion of the substrates to achieve the transition state (Scheme 1.6). Such analysis illustrated that π-electron rich arenes possessed the most favorable energetic gain while it was counterbalanced by the greatest energetic cost for distorting the metal complex and arene from the ground state to the transition state geometry. For electron deficient arenes, though the energetic gain became less favorable, the accessibility to the transition state was still available owing to an easier arene distortion. Shortly conclude, both the electron-rich and electron deficient arenes tend to undergo electrophilic metal-catalyzed C-H activation via CMD mechanism.

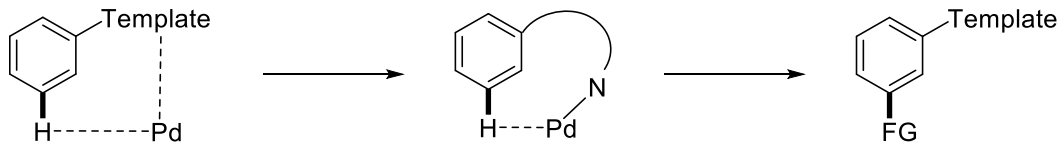
Scheme 1.6. Activation-Strain Analysis for the Lowest Free Energy CMD TS



1.4.5. Meta C-H activation

Selective *ortho*-substitution of aromatic arenes has been fully investigated by the aid of chelation-assisted C-H functionalizations in the past few decades. Yet, the extension of such strategy for performing *meta* C-H transformations remained a challenge due to the difficulty of a cyclic metallacycle formation of the distal location of the target bond. A leap in this regard was performed by introducing a palladium(II) catalyzed directing group to activate *meta* C-H bonds that are at a distal location relative to the existing functional groups and meanwhile overcome any possible steric and electronic bias (Scheme 1).

Scheme 1.7. Template directed *meta* C-H activation



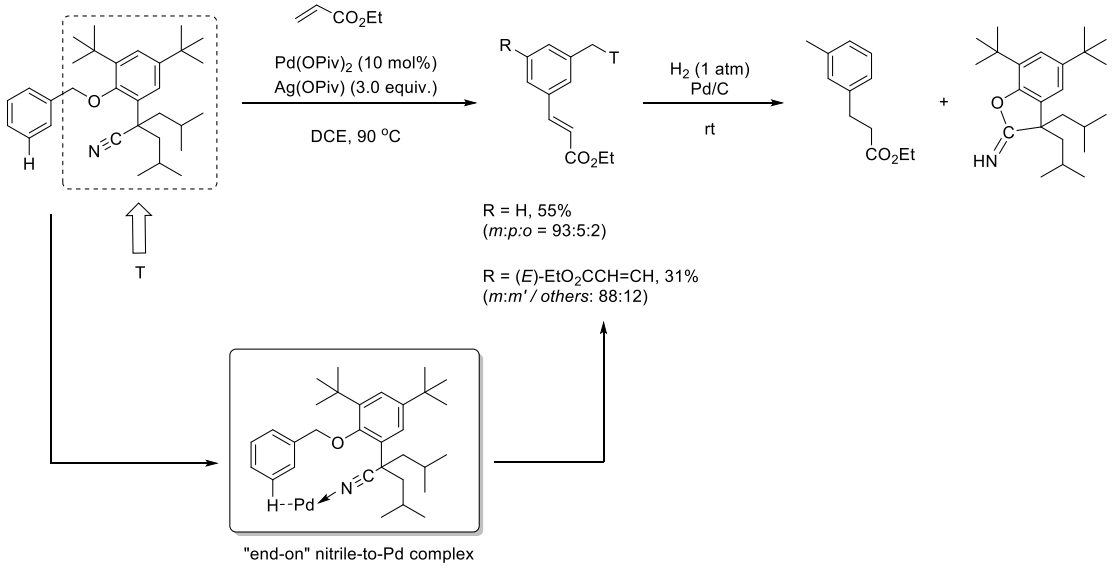
Yu group in this regard established a successful breakthrough in 2012 by reporting the first template assisted *meta* C-H functionalizations through the formation of a 12-membered metallacyclic transition state by using a palladium(II) catalyst and *N*-acetyl glycine ligand (Scheme 1.8).[20] Such nitrile-based templates override both the intrinsic steric and electronic properties of several categories of substituted aromatic

compounds like phenols, phenylacetic acids, benzylic amines, toluene derivatives, anilines and hydrocin-namic acids, as well as their *ortho*-directing property. Among these functionalization reactions, it is believed that the *meta* directing effect stems from an "end-on" nitrile-to-Pd complex with the formation of a cyclophane-like 12-membered pre-transition state involving in the C-H activation step.

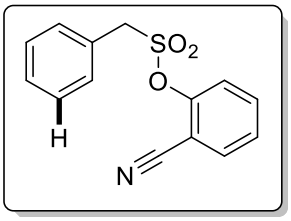
Later, Maiti reported a new strategy for achieving meta-selective homo-diolefination and sequential hetero-diolefination of benzylsulphonylester derivatives in 2015 (Scheme 1.9).[21-23] Such sulphonyl tether provided certain flexibility for the directing group and therefore helped to locate the distal *meta* C-H bond.

Such selective chelation-assisted *meta* C-H functionalizations was further applied on other transformations such as acetoxylation,[24] hydroxylation[25], arylation[26] and iodination.[27] Selected examples are depicted in Scheme 1.10.

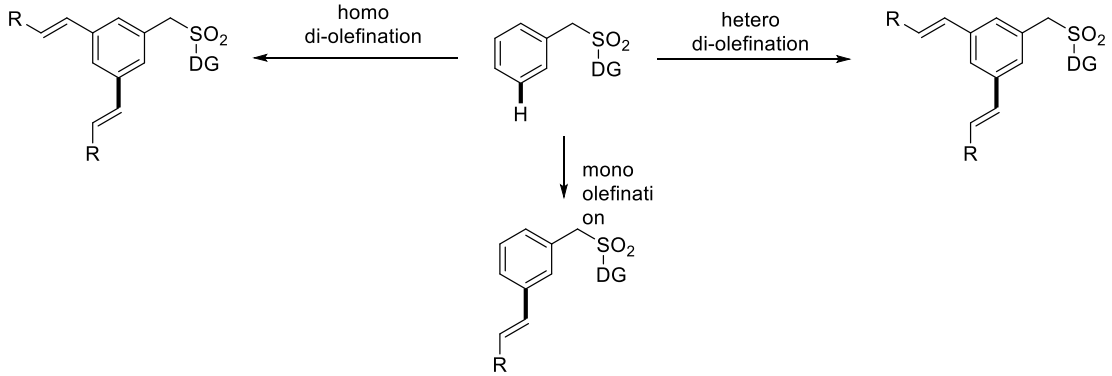
Scheme 1.8. Pioneering example of *meta*-directing C-H activation



Scheme 1.9. Advantages of Maiti's template and the *meta*-selective olefination

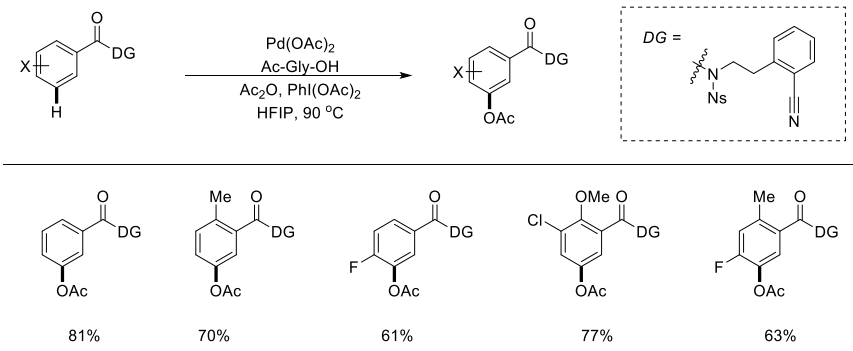


1.DG is simple and commercially available
2.Mono vs di-selectivity is very high
3.Two different robust conditions developed for mono-olefination
4.The -SO_2-X unit (DG) can be converted to other FG

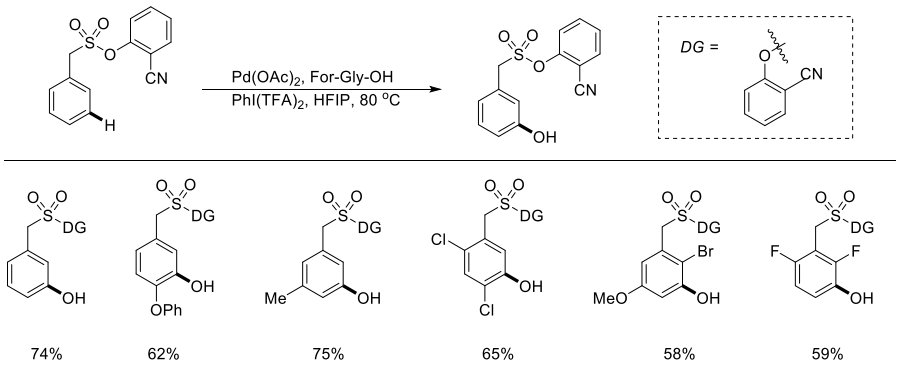


Scheme 1.10. Examples of chelation-assisted *meta* C-H functionalizations

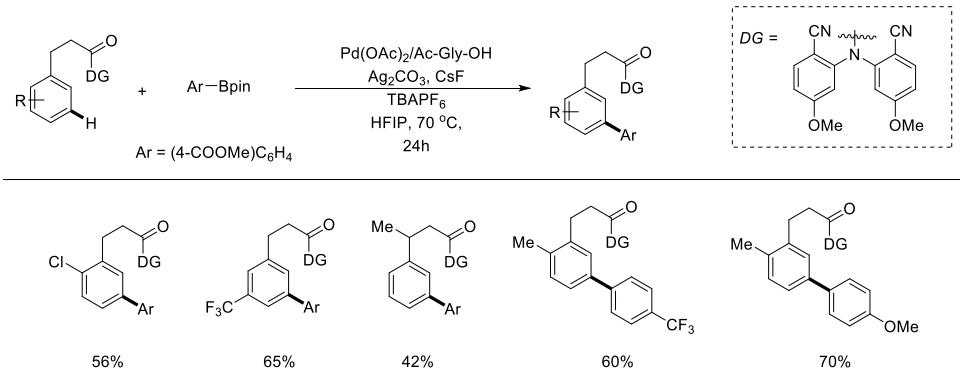
(a) Acetoxylation



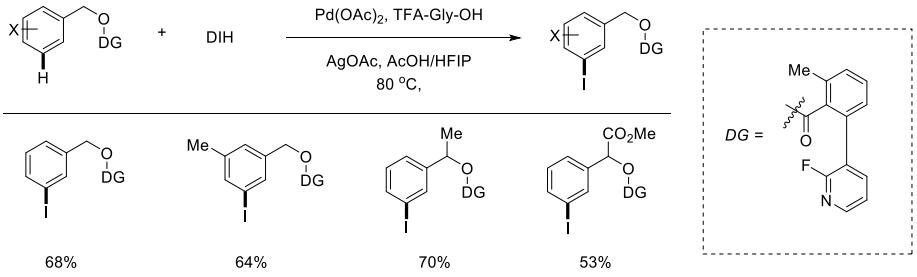
(b) Hydroxylation



(c) Arylation



(d) Iodination



1.5. High-Oxidation-State Palladium Catalysis

Reductive elimination from defined organo-palladium(II) complexes is a principal route to forge carbon(sp^2)-carbon(sp^2) and carbon(sp^2)-heteroatom bonds.[28-29] Compared to Pd(0)/Pd(II) catalytic cycle, Pd(IV) intermediates possess a great potential for developing new transition-metal-catalyzed reactions beyond C-C bond formations due to the intrinsic nature of the Pd(IV) to hold up to four different functional groups at the same time for subsequent reductive elimination processes.

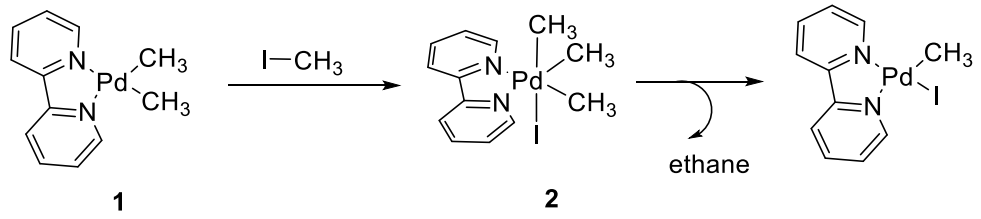
The accessibility of achieving high oxidation states of the palladium at certain stage of the catalytic cycle and within particular reaction conditions is one of the key challenge for such catalytic reactions involving aryl and alkyl palladium(IV) complexes, having lower redox potential than that of simple Pd(II) salts. As a result, unprecedented organic functionalizations that are not possible under the traditional Pd(II) catalysis become accessible with Pd(IV)-mediated transformations. Moreover, the dominating beta-hydride elimination as well as palladium black deposition from Pd(II) species were no longer expected for Pd(IV)-mediated transformations. Most importantly, facile reductive elimination from Pd(IV) intermediates is expected to stabilize the metal, and this avoids fine-tuning of the ligands for reaction optimizations that is normally required for Pd(II) catalysis.[30]

1.5.1. C-C Coupling

In general, reductive elimination to form a C-C bond represents the classical transformation for Pd(IV). Canty and co-workers demonstrated the first example of C-C coupling reactions with the dimethylpalladium(II) complex **1** which readily undergoes oxidative addition with methyl iodide, to form the trimethylpalladium(IV) complex **2**. Complex **2** was subsequently isolated and characterized by X-ray crystallography as shown in Scheme 1.11.[31-33]

With the presence of neutral dinitrogen bidentate ligands such as bipyridine and also with the assistance of a large number of carbon-based ligands, the structural chemistry of such Pd(IV) complexes was able to characterized.

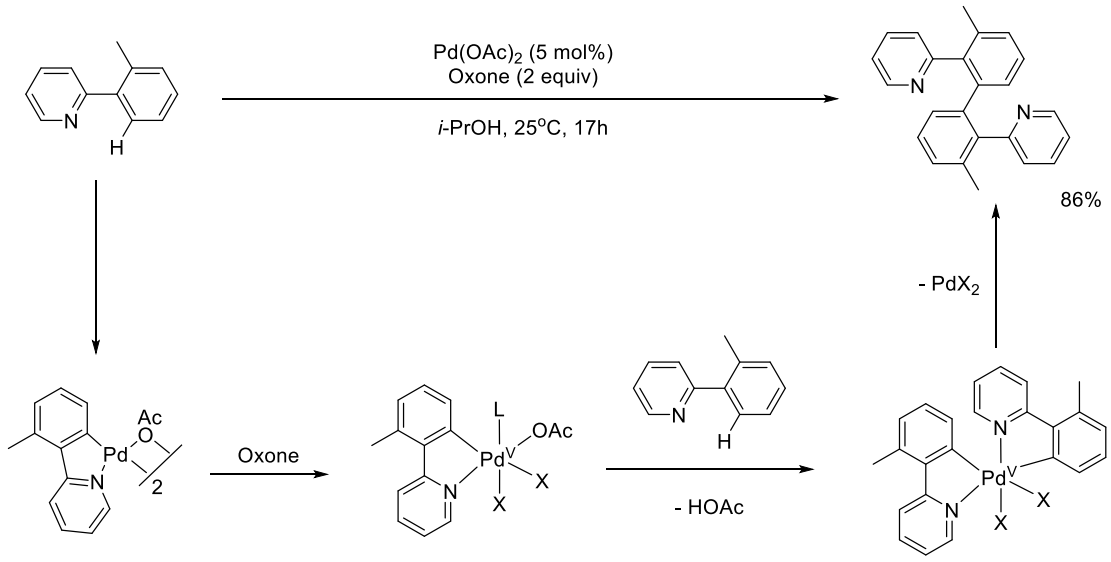
Scheme 1.11. Pioneering synthesis of Pd(IV) complexes



1 **2**

In 2006, Sanford's group has reported the oxidative dimerization of 2-arylpyridines by employing Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as the oxidant (Scheme 1.12).[34] A series of mechanistic experiments was conducted, and two discrete C-H activation processes were involved in the oxidative dimerization reaction. It was proposed that one C-H activation step occurred at the Pd(II) center while the second step occurred at the Pd(IV) center, which was generated by the oxidation of the Pd(II) species. Lastly, the C-C oxidative coupling product was formed via reductive elimination (Scheme 1.12). This finding prompted the synthetic potential of electrophilic palladium catalysis as well as the possibility of investigating further catalysis mediated by Pd(IV) species.

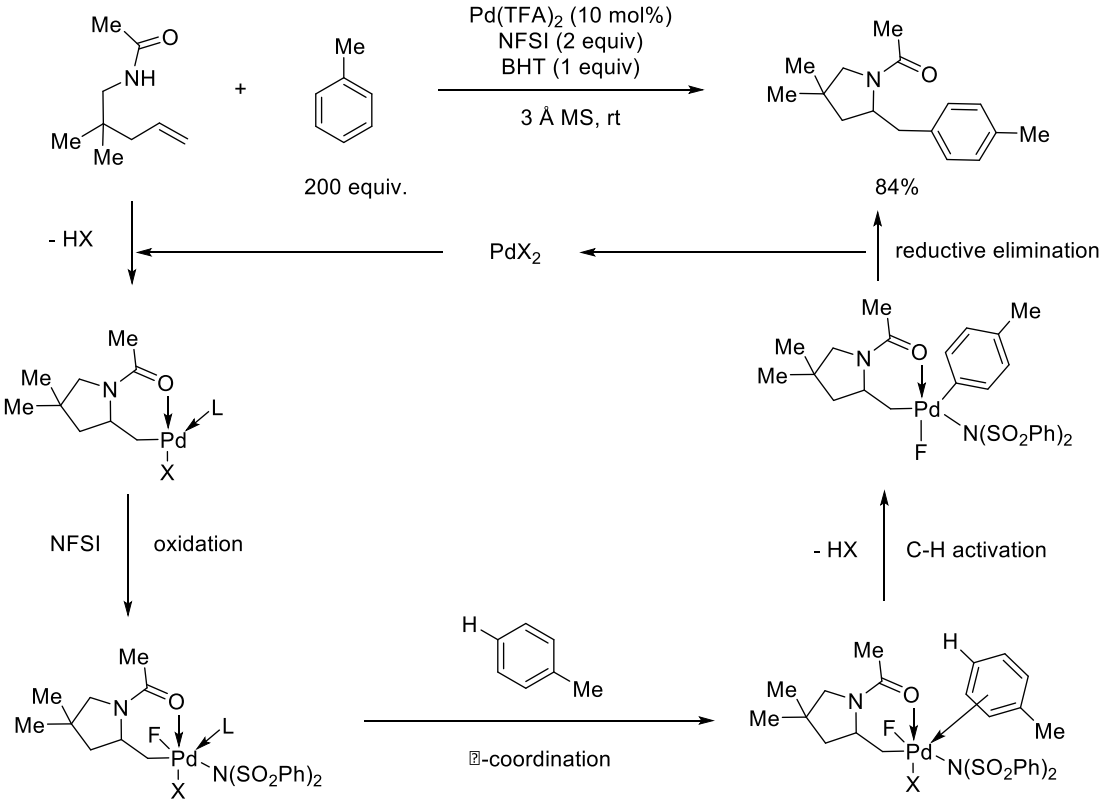
Scheme 1.12. Mechanism of Pd-catalyzed dimerization of 2-aryl pyridines



Later, Michael's group established the Pd(II)/Pd(IV) catalyzed carboamination of terminal alkenes, using neat arene solvent and N-fluorobenzenesulfonamide (NFSI) as the oxidizing agent and the carboaminated arenes was formed in high *para*-selectivity.[35] A series of experiments have been conducted like arene competition experiments and inter- and intra-isotopic effect (IE) studies to reveal the mechanism in depth.

The carboamination reaction starts with an intramolecular *anti*-aminopalladation step and then undergo oxidation by employing NFSI to generate the corresponding Pd(IV) complex. Afterwards, the arene coordinates on to the metal center in the form of π-coordination and undergo C-H activation, forming the Pd(IV) aryl intermediate and affording the carboaminated arene through reductive elimination (Scheme 1.13).

Scheme 1.13. Mechanism of Pd-catalyzed carboamination of alkenes

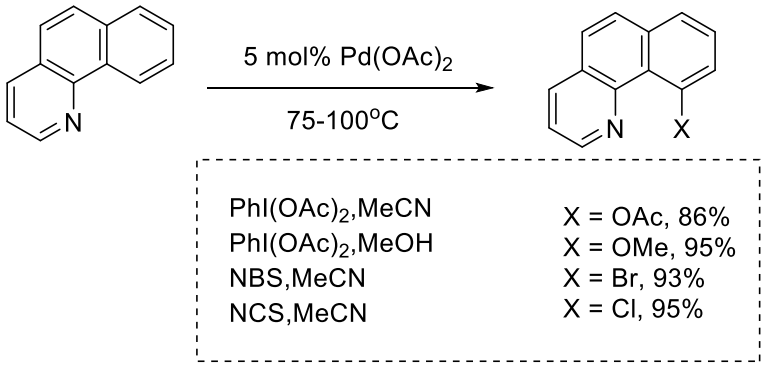


1.5.2. C-O and C-X Bond Formation

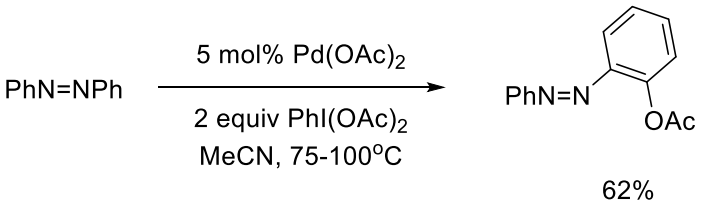
Crabtree and Yoneyama developed the acetoxylation of arenes through catalytic C-H activation by employing a palladium(II) catalyst and iodosobenzene as the oxidant.[36] Such observation inspired Sanford and co-workers developing sets of novel catalytic functionalizations of simple arenes with high selectivity for the *ortho*-position (Scheme 1.14a and b).[37-39] The underlying theory lies on the formation of palladacycles via chelation control strategy, followed by oxidizing the metal center with a strong oxidizing agent to effect a carbon-heteroatom bond formation through the reductive elimination from a Pd(IV) intermediate. Oxidants apart from PhI(OAc)2 like combination of oxone and acetic acid and also NBS also perform similarly with high *ortho*-selectivity on acetoxylation of acetophenone and aniline derivatives as depicted in scheme 1.14c, d, e.[40-44]

Scheme 1.14. Catalytic C-O and C-X bond formation via Pd(IV) intermediate

a)

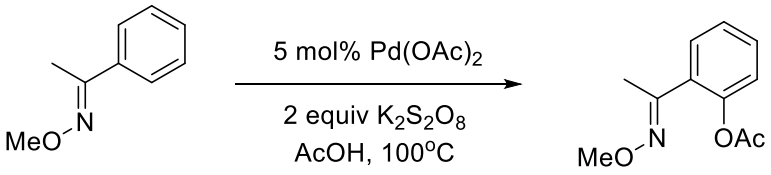


b)



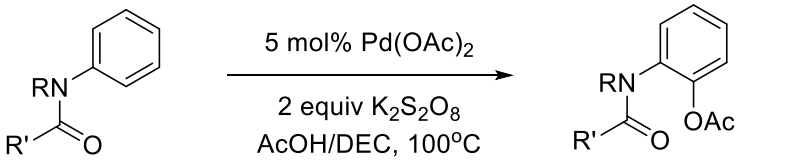
62%

c)



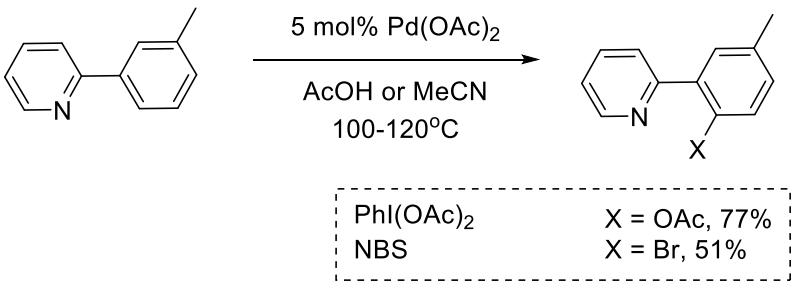
53%

d)



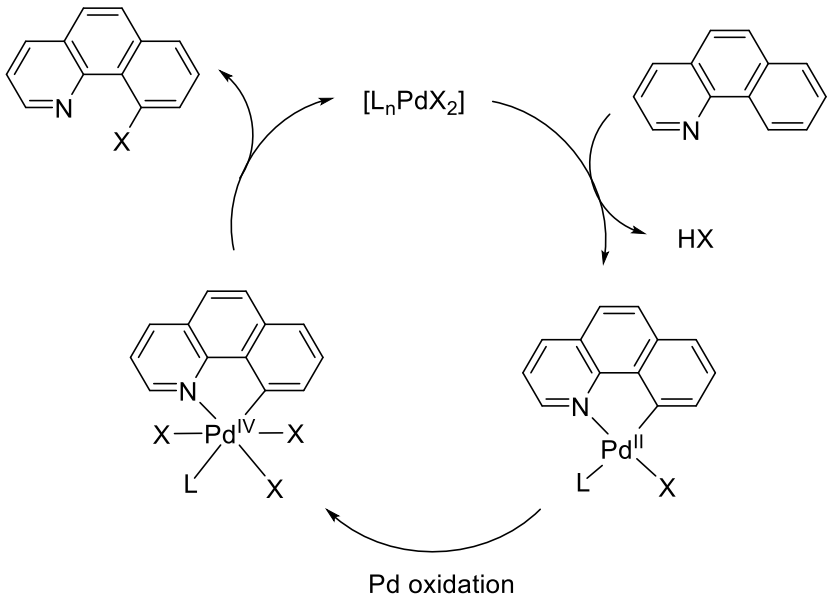
12 examples, 22-93%

e)



A plausible catalytic cycle for the Pd(IV) mediated arene C-H functionalization is illustrated in scheme 1.15. The chelated palladacyle is oxidized by a strong oxidizing agent forming a Pd(IV) intermediate followed by reductive elimination to effect the carbon-heteroatom bond formation.

Scheme 1.15. Plausible mechanism for Pd(IV) mediated arene C-H functionalization

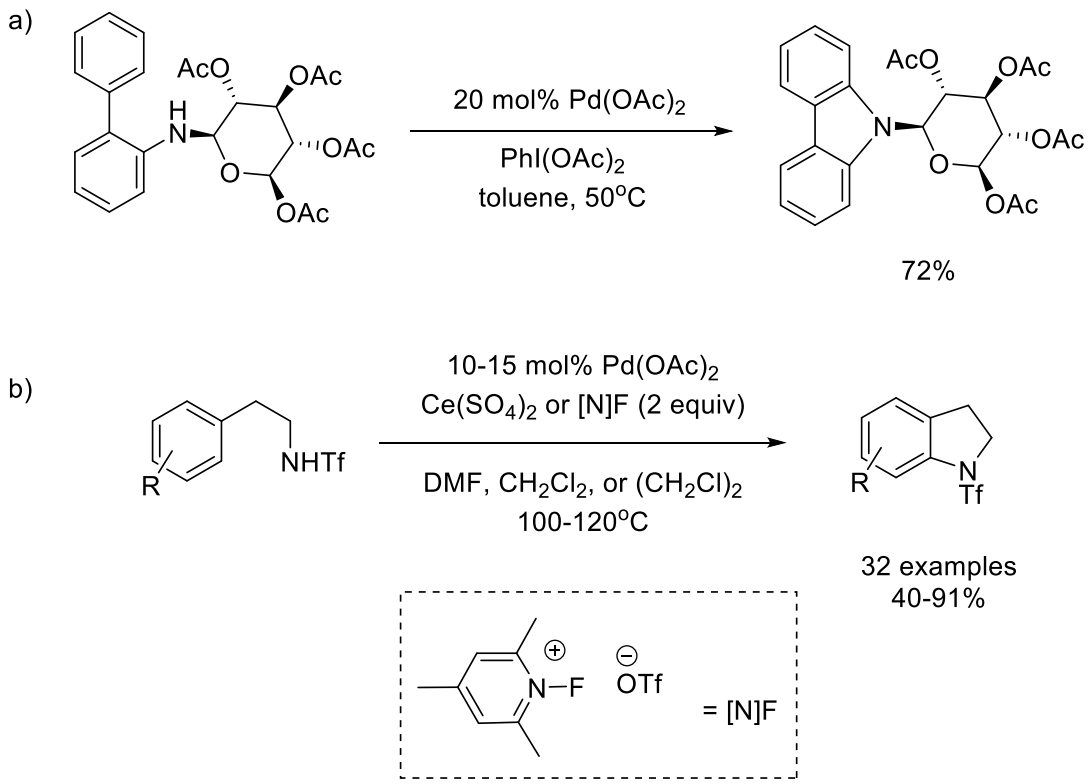


1.5.3.C-N bond formation

Gaunt and co-workers reported an intramolecular C-N bond formation from different 2-amino-biphenyls for carbozole synthesis.[45] Again, the underlying principle lies on the region-control C-H activation on Pd(II) center with the aniline functional group acts as a tether forming a trinuclear Pd(II) complex, followed by the oxidation of the metal center and subsequent reductive elimination allows the C-N bond formation readily even at room temperature (Scheme 1.16a).

Recently, Yu and co-workers also developed indolines synthesis through the oxidative cyclization of the *N*-trifluoro-methanesulfonyl 2-aryl ethylamines from the high valent palladium center (Scheme 1.16b). Here, a cationic fluoro-organic reagent is employed as the oxidizing agent.[46]

Scheme 1.16. Examples of C-N bond formation through Pd(IV) intermediate

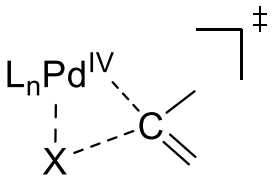


1.6. Mechanisms of Reductive Elimination from σ–Aryl Palladium(IV) catalysts

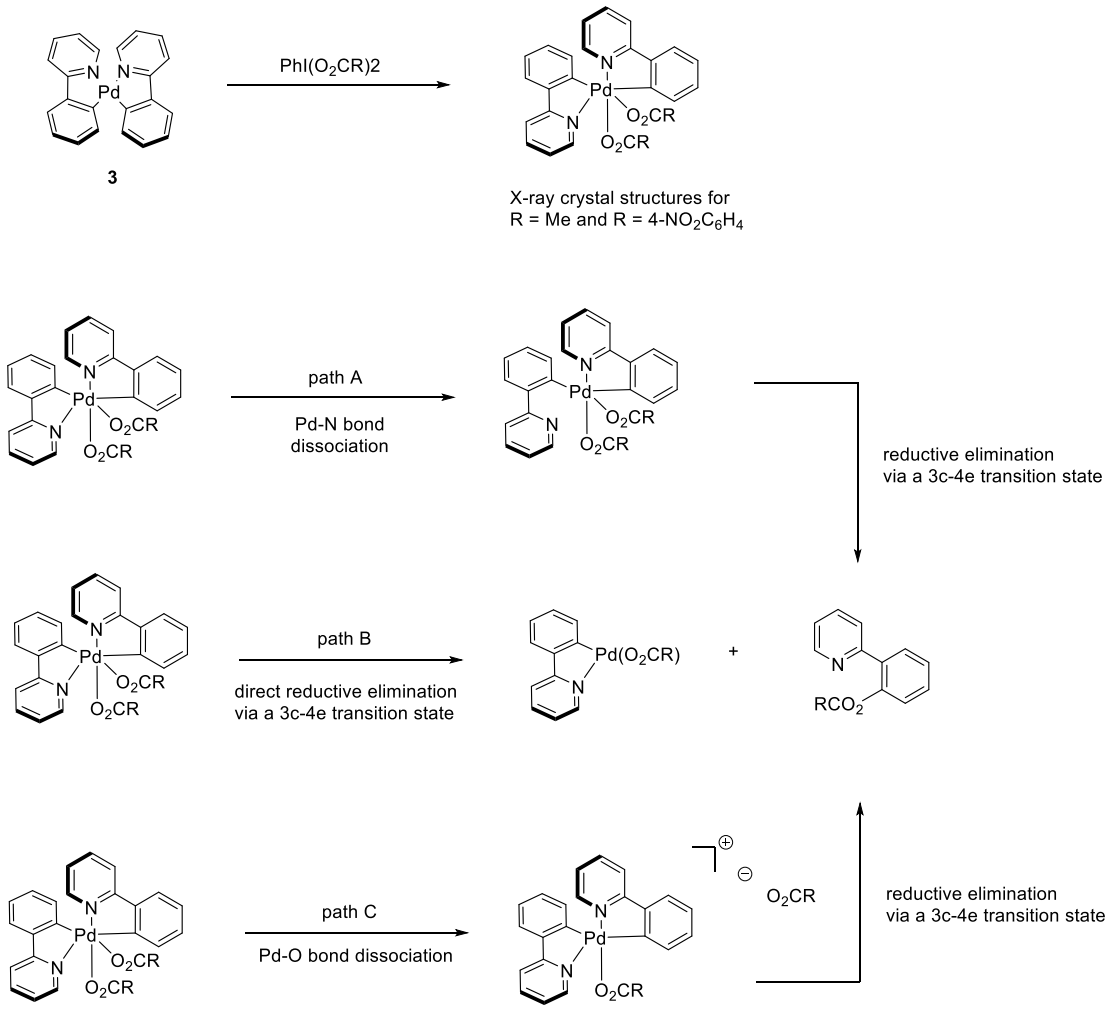
In theory, the formation of aryl-aryl and aryl-heteroatom bonds is believed to proceed through the reductive elimination from σ–aryl palladium(IV) intermediates with a three center-four electrons (3c-4e) transition state (Figure 1.1).

The precise mechanistic pathway involving palladium(IV) intermediates is not yet completely established and may still contains mechanistic surprises. This limitation primarily stems from the low stability of palladium(IV) complexes to be isolated for further structure characterization and advanced mechanistic investigations. In spite of such limitation, Pd(IV) mediated arene oxygenation is exceptional. Sanford and co-workers successfully isolated monomeric palladium(IV) complexes responsible for arene oxygenation as shown in scheme 1.17.[47,48] By treating the hypervalent iodosobenzene oxidant with the chelated bisaryl palladium(II) complex **3**, a stable corresponding palladium(IV) complex was successfully isolated and was fully characterized with X-ray crystallography.

Figure 1.1. Three center-four electrons (3c-4e) transition state



Scheme 1.17. Pd(IV) complexes synthesis and mechanistic studies for C-O bond formation

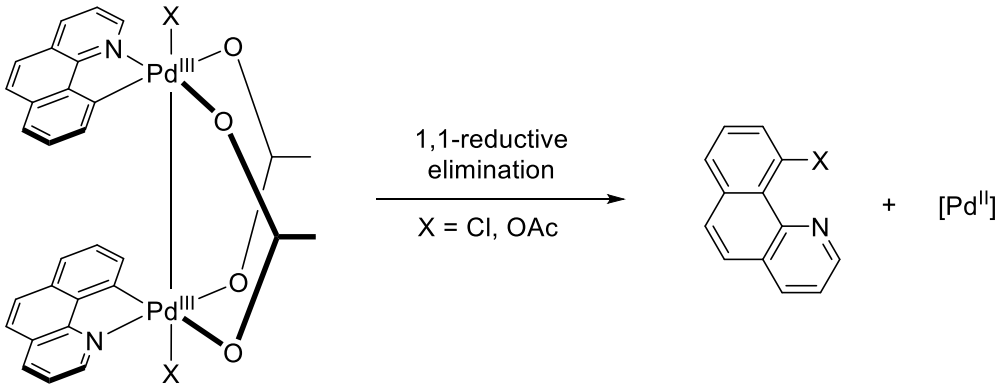


There are three possible pathways that may proceed for the following reductive elimination process (Scheme 1.17): (A) Chelate dissociation in a pre-equilibrium was initially suggested with subsequent reductive elimination from a neutral, penta-coordinating palladium(IV) complex.[47] (B) Contrastingly, the initial ocatahedral palladium(IV) complex directly proceed reductive elimination for oxygenation was proposed by theoretical study.[49] (C) Recently, Sanford and co-workers conducted a detailed investigation and observed the involvement of positive-selective anion cleavage in the realistic mechanistic pathway.[48] Such observation also explains the resulting chemo-selectivity of the oxygenation reaction as the competing carbon-carbon bond formation that is likely to happen directly from the original palladium(IV) complex without a pre-equilibrium would become dominant with the presence of excess amount of anion.

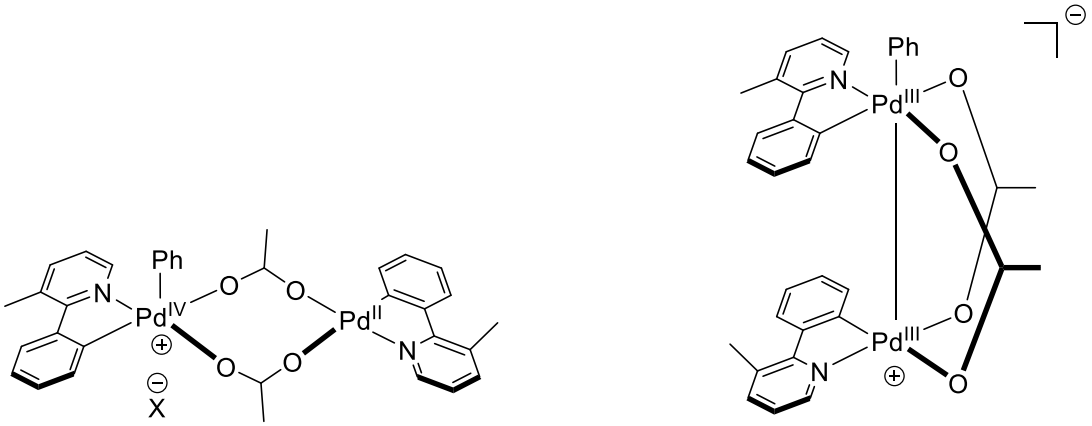
Apart from the monomeric palladium(IV) intermediates, neutral dimeric palladium(III) complexes was recently suggested to possibly allow high oxidation state palladium mediated catalysis by Ritter and Powers (Scheme 1.18).[50] A concerted 3c-4e reductive elimination from one of the two palladium(III) metal centers was suggested with the support of both orbital geometry and kinetic data and such process produced a mixture of palladium(II) complex with unknown structure. The dimer **4**

could be regenerated from such mixture and by treating with NCS, the catalytic chlorination reaction was achieved. The reaction order of 1.0 with respect to the related bimetallic palladium complex with the bridging dicarboxylate group was observed for the above catalytic chlorination reaction, indicated the possibility of the presence of aggregated palladium(III) species.[50-51] In addition, Deprez and Sanford conducted further investigation on the biaryl coupling reactions of 2-aryl pyridines with hypervalent iodine oxidant[52] and suggested that such bimetallic high valent palladium complex was generated as an intermediate. The actual catalytic form of the palladium complex prior to the reductive elimination has two possibilities: (A) a mixed valent Pd(IV)/Pd(II) species and (B) a symmetrical Pd(III)/Pd(III) dimer, depends on the actual bonding environment between the two palladium centers.[53]

Scheme 1.18. Dimeric Pd complexes for aryl-aryl and C-X bond generation



4



A **B**

1.7. Aim and objective

Functionalizations of C-H bond are of great significance in organic chemistry. In this research, we aim to establish the synthesis and characterization of cyclopalladated complexes and exploration of their catalytic activities towards non-directed arene C-H activation and ligand enabled Palladium-catalyzed site selective non-directed iodination of unactivated arenes by employing potassium iodide as the inorganic iodide reagent.

Traditional C-N bond construction methods are Buchwald-Hartwig amination, Ullmann-Goldberg coupling reaction and Chan-Evans-Lam oxidative coupling reaction. These amination reactions have been thoroughly investigated and applied for pharmaceutical usage. However, several limitations such as harsh reaction conditions, expensive transition metal / reagents being used and poor functional group diversity have limited their synthetic values.

In Chapter 2, we developed the 2-phenylquinoline ligand-enabled Pd-catalyzed regioselective nondirected amidation of unactivated arenes. Preliminary mechanistic study suggested a Pd(II)/Pd(IV) reaction manifold involving arene C-H activation by Pd(IV), This work demonstrates that it is plausible to manipulate the reactivity and

selectivity of organopalladium(IV) species by ligand modification.

Aryl iodides are essential and versatile starting materials for cross-coupling reactions that are employed for synthesizing various pharmaceuticals, natural products and functional compounds. Conventionally, aryl iodides can be prepared by Sandmeyer-type reactions of diazonium salts, direct lithiation/halogenation and Friedel-Crafts-type electrophilic halogenation. However, these traditional routes suffer from several limitations such as low functional group tolerance, poor regio-control, limited substrate scope, stoichiometric metal salts byproducts and over halogenation.

In Chapter 3, we achieved the 2-phenylquinoline ligand-enabled Pd-catalyzed nondirected iodination of unactivated arenes with moderate yields by employing the inorganic potassium iodide as the iodination reagent.

Chapter 2

Synthesis and Characterization of Cyclopalladated Complexes and Exploration of their Catalytic Activities Towards Direct Arene C-H Activation

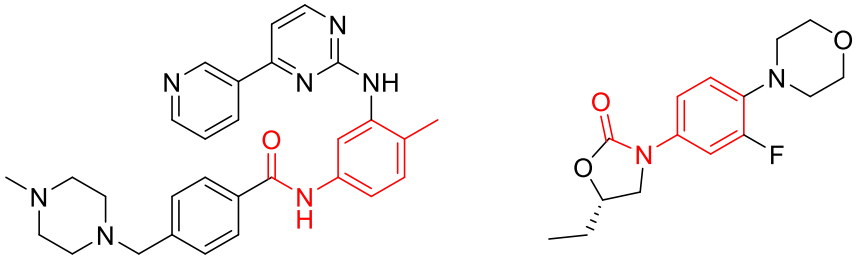
Chapter 2

Synthesis and Characterization of Cyclopalladated Complexes and Exploration of their Catalytic Activities Towards Direct Arene C-H Activation

2.1 Introduction

Aryl amine is an important scaffold in medicine,[54] agroscience and material science that makes them valuable synthetic targets (Figure 2.1). Synthetic reactions constructing C-N bonds are extensively investigated. Traditionally, aryl amine synthesis involves electrophilic aromatic nitration, followed by nitro group reduction and nucleophilic aminations on electron-poor arenes (Scheme 2.1). Limitations exist particularly in the functional group tolerance, harsh reaction conditions, poor regioselectivity controlled by the electronic properties of the substitutents and overalkylation of amine nucleophiles.

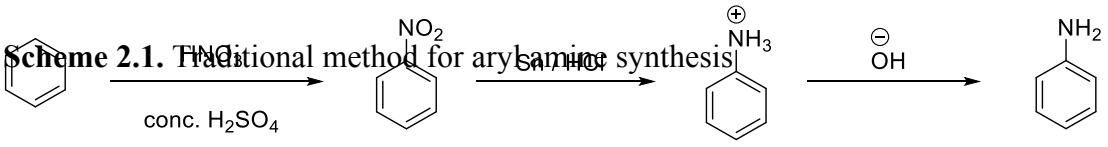
Figure 2.1. Examples of essential pharmaceutical compounds



Imatinib
Kinase inhibitor

Linezolid
Antibiotics

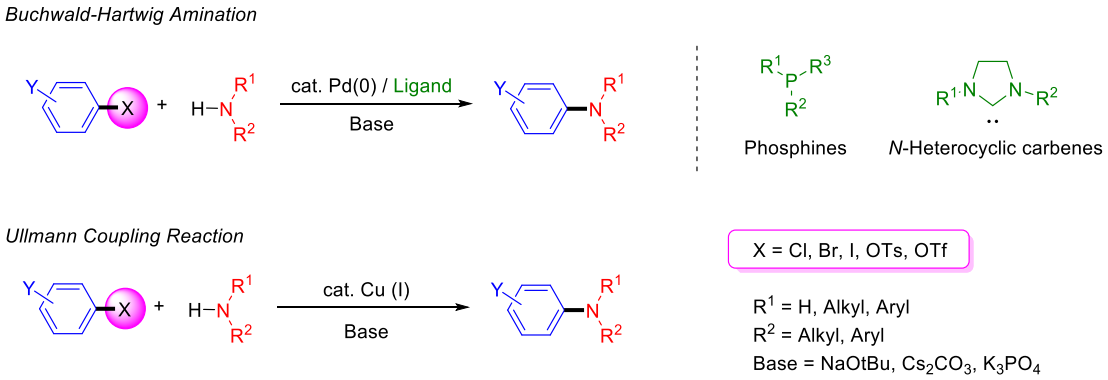
Scheme 2.1. Traditional method for arylamine synthesis



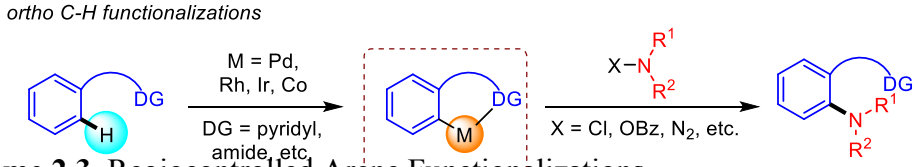
Electrophilic Aromatic Nitration *Nitro-reduction*

Alternative synthetic approaches involving transition metal catalyzed cross-coupling reactions of amines and aryl halides were therefore developed. Both the Buchwald-Hartwig amination reaction and Ullman coupling reaction are widely employed in industrial synthesis for a broad variety of amines with excellent yield under mild conditions (Scheme 2.2). Yet, these reactions required the prefunctionalization of arenes to aryl halides and the regioselectivity of the reactions therefore depends on the position of the halogen.

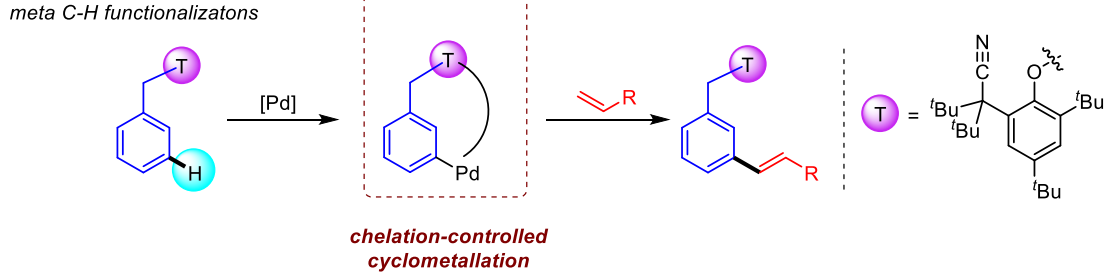
Scheme 2.2. Transition metal catalyzed cross-coupling reactions



Chelation-assistance strategy was established to directly functionalize a C-H bond for further transformation and was highly successful in achieving ortho-selectivity. With the appropriate design of the directing group, Prof. JQ Yu and co-workers also succeeded in meta-selective arene vinylations[55] (Scheme 2.3). The high degree of region-control was achieved by pre-coordination of the donor groups to the transition metal for the desired C-H bond cyclometallation in close proximity.

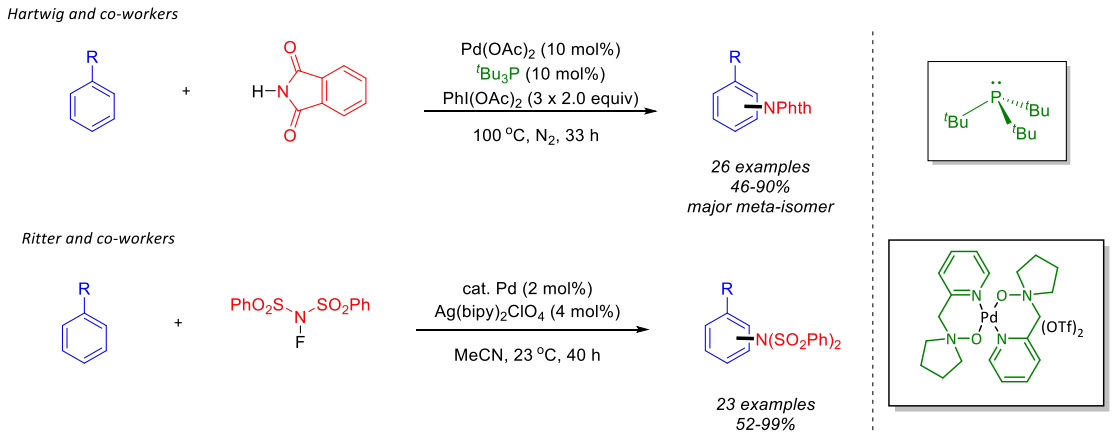


Scheme 2.3. Regiocontrolled Arene Functionalizations



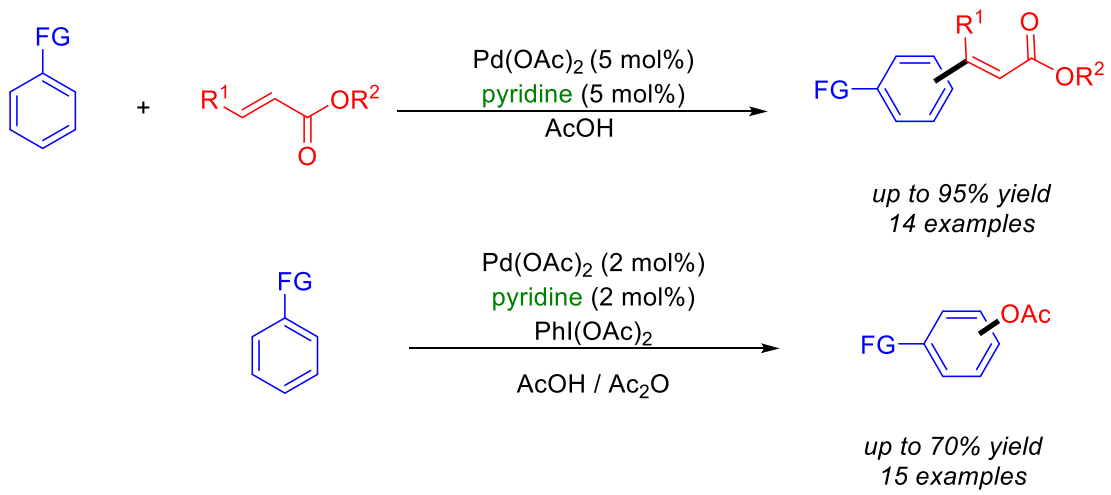
The chelation-assistance approach requires pre-installation of the donor groups on the substrates that limits the diversity of the scope. Notably, Hartwig and co-workers have established the Pd-catalyzed non-directed amidation of unactivated arenes by employing tri-t-butyl phosphine ligand.[56] The arenes were amidated at the less hindered sites (Scheme 2.4). While Ritter and co-workers[57] also developed the analogous imdiation of unactivated arenes with the chelated pyridyl amine N-oxide ligand and *para*-imidation was observed for those electron-rich arenes. (Scheme 2.4) Apparently, regio-selective C-H bond functionalization can be accessible through the rational design of the catalyst.

Scheme 2.4. Non-directed Arenes Functionalizations



Recently, Sanford and co-workers reported the Pd-catalyzed vinylation and acetoxylation of simple arenes with pyridine as the ligand (Scheme 2.5).[58] It was believed that the reactions should have passed through the Pd(IV) intermediate for transformation. These results indicated the N-donor type ligands can effectively stabilize the higher oxidation state of Palladium.[59]

Scheme 2.5. Non-directed Arenes Functionalizations



In this chapter, we described the Pd-catalyzed cross coupling reaction of non-directed arenes with phthalimide for the synthesis of regiocontrolled-arylamides.

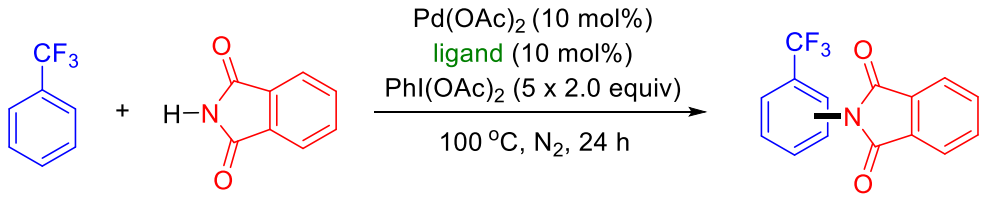
2.2. Results and Discussion

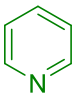
2.2.1. Preliminary results

With the ongoing interest to develop the C-H bond cross-coupling amination reaction,[60] We initiated our study by first examining the catalytic activity of Pd $(OAc)_2$ for the arene amidation. Treating the α,α,α-trifluorotoluene (80 equiv; 1 ml) with Pd $(OAc)_2$ (10 mol%), phthalimide (1 equiv) and $PhI(OAc)_2$ (5 x 2 equiv / 10 h) at 100 ^oC for 24 h afforded the desired *N*-arylphthalimides in about 10% combined yield (Table 2.1).

Notably, spontaneous palladium black formation was observed within 30 mins *in the absence of* $PhI(OAc)_2$; no amidation products or biaryls were detected by GC-MS analysis of the reaction mixture. As expected, no amidation products were found in the absence of the Pd catalyst. Interestingly, only 17% amidation product was obtained in the presence of the pyridine ligand (10 mol%) as depicted in Table 2.1. With the preliminary results, pyridine might not be a suitable ligand to stabilize the Pd(IV) intermediate effectively for the amination reaction.

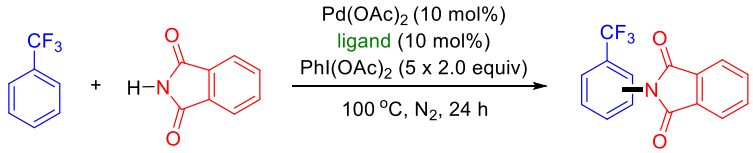
Table 2.1. Preliminary study

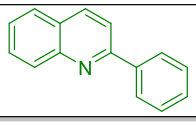
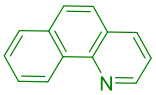
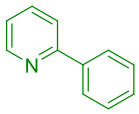
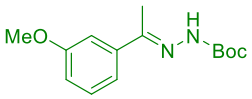
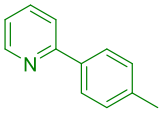
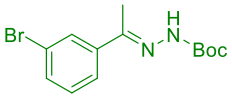
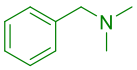
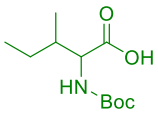


entry	ligand	yield
1	without ligand	10%
2		17%

Inspired from the chelation assistance strategy, we turned our focus to the bidentate N-type ligand, which help stabilize the Pd(IV) intermediate. Several bidentate ligands were investigated for the Pd-catalyzed amidation of α,α,α-trifluorotoluene. As depicted in Table 2.2, the best result was obtained when 2-phenylquinoline was employed as ligand (entry 1) with 60% yield. Other ligands gave less satisfactory results (entries 2-8).

Table 2.2. Ligand screening



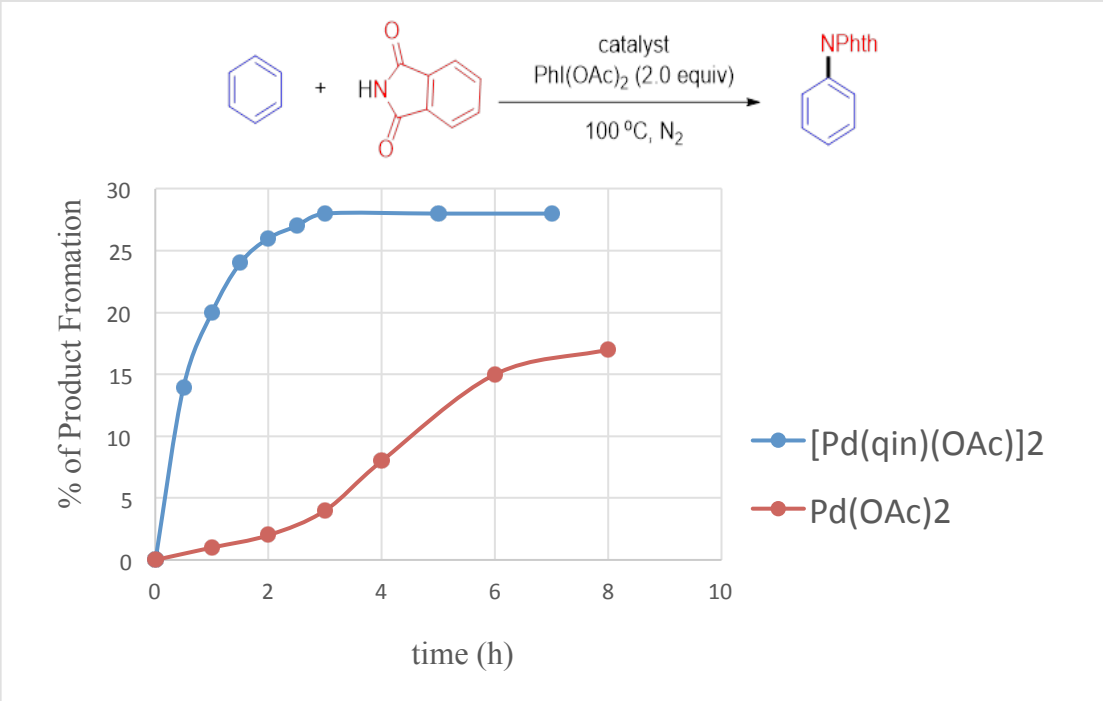
entry	ligand	yield	entry	ligand	yield
1		60%	5[a]		14%
2[a]		40%	6		44%
3		20%	7		33%
4		33%	8		23%

[a]Preformed Pd catalyst used in the form of $[Pd(ligand)(OAc)]_2$

To verify the acceleration effect of 2-phenylquinoline, a time course analysis of the catalytic amidation of benzene was performed. Samples were drawn at a regular interval from the reaction mixture containing benzene (1 ml), $[Pd(qin)(OAc)]_2$ (5 mol%), phthalimde (0.1 mmol) and $PhI(OAc)_2$ (2 equiv) at 100 ^oC and the aliquots were analyzed by GC-MS with dodecane as internal standard. As depicted in Figure 2.2, the reaction showed a significant product formation during the first half hour with the presence of the 2-phenylquinoline.

Notably, in the absence of the 2-phenylquinoline, a latent period of about 4 h prior to product formation was observed. It may imply certain derivatization of the $Pd(OAc)_2$ to some active forms for effecting product formation.[14] Based on the results revealed here, we concluded that 2-phenylquinoline would effectively promote the Pd-catalyzed direct arene amidation.

Figure 2.2. Reaction profile study



2.2.2. Synthesis of cyclopalladium complexes & characterization

A mixture of 2-phenylquinoline (100 mg, 0.49 mmol), $Pd(OAc)_2$ (99 mg, 0.44 mmol) and glacial acetic acid (5 mL) was refluxed under nitrogen for 1 h and then allowed to reach room temperature overnight. The precipitate formed was filtered and washed with water and then dissolved in dichloromethane and dried over Na_2SO_4. Filtration, concentration and drying under vacuum gave the cyclopalladium complex $[Pd(qin)(OAc)]_2$ as brown solid as depicted in Scheme 2.6 and was fully characterized by X-ray crystallography as shown in Figure. 2.3.

Such cyclopalladium complex $[Pd(qin)(OAc)]_2$ was then treated with α,α,α-trifluorotoluene (80 equiv; 1 ml), phthalimide (1 equiv) and $PhI(OAc)_2$ (5 x 2 equiv / 10 h) at 100 ^oC for 24 h and afforded the desired *N*-arylphthalimides in about 63% yield, implying that $[Pd(qin)(OAc)]_2$ might probably the active form of the catalyst for such amidation reaction.

Scheme 2.6. Synthesis of cyclopalladium complex

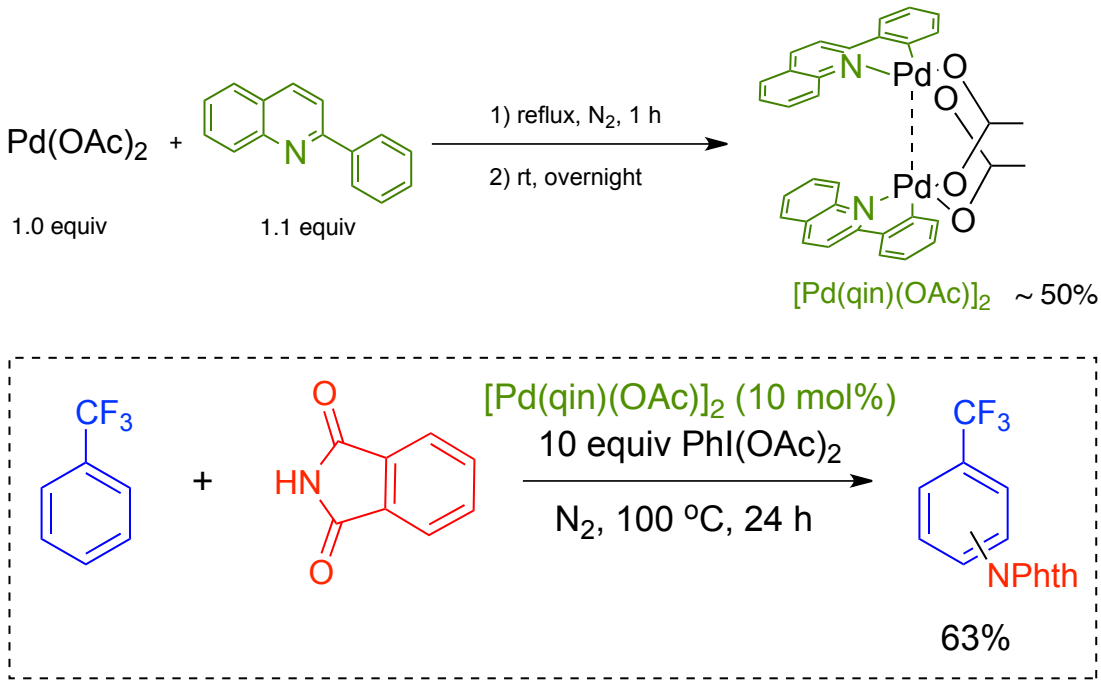
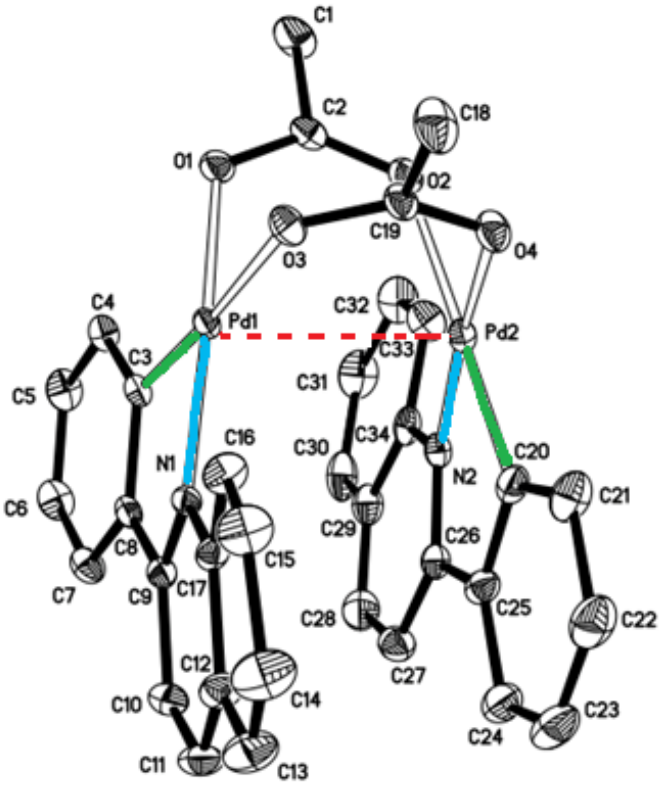


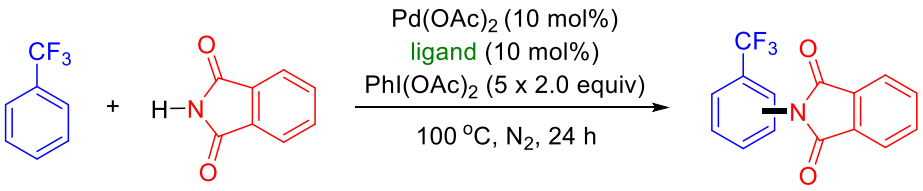
Figure 2.3. Structure of $[Pd(qin)(OAc)]_2$ characterized by X-ray crystallography

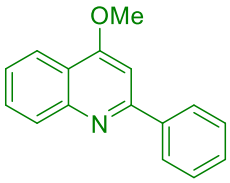
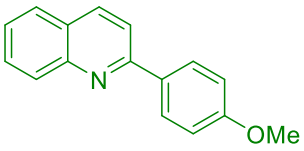
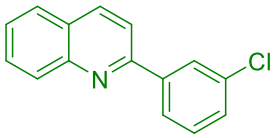
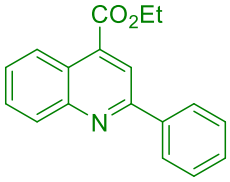


2.2.3. Optimization of reaction conditions

With this encouraging result, we first began the optimization study by examining the effect of electronic properties of 2-phenylquinoline on the amidation reaction (Table 2.3).

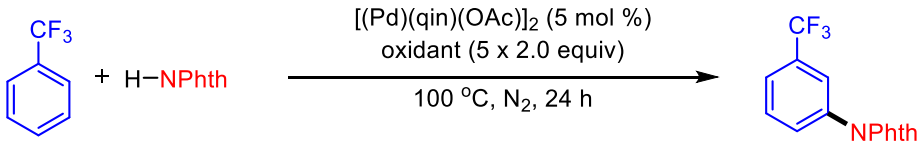
Table 2.3. Effect of electronic properties of 2-phenylquinoline on the amidation



entry	ligand	yield (%)
1		60
2		64
3		58
4		43

As depicted in Table 2.3, several derivatives of the 2-phenylquinoline ligand were examined. Interestingly, no significant change was observed with both electron-donating and weakly deactivating substituents on the ligand (Table 2.3 entry 1 - 3) except entry 4, with the 2-phenylquinoline ligand containing a moderately electron-withdrawing ester group. Probably a reduction on electron density less stabilize the Pd(IV) intermediate and lead to an obvious drop in product yield.

Table 2.4. Screening of oxidants



entry	oxidant	yield (%)[a]
1	$PhI(OAc)_2$	60
2	$PhI(TFA)_2$	2
3	TBHP	< 2
4	$Na_2S_2O_8$	< 2
5	oxone	< 2
6	$Cu(OAc)_2$	not detected
7	O_2	not detected
8	1-fluoro-2,4,6-trimethylpyridin-1-ium tetrafluoroborate	< 2
9	benzoyl peroxide	< 2
10	NFSI	< 2
11	none	not detected

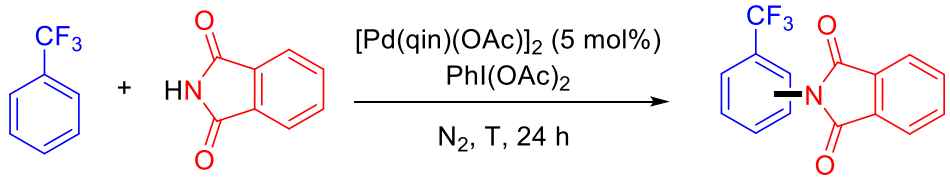
[a]Isolated yield.

During our optimization study, several features pertinent to this amidation reaction werer revealed:[6] (1) $PhI(OAc)_2$ was found to be the only effective oxidant for the amidation reaction. Other oxidants tested in this work, including TBHP, Na_2S_2O8, oxone, 1-fluoro-2,4,6-trimethylpyridin-1-ium tetrafluoroborate, gave far inferior results (Table 2.4 entry 2 -11). (2) An excess of oxidant (6 equiv) is required to sustain the Pd catalyst in its solution form (Table 2.5 entry 6). (3) Spontaneous palladium black formation occurred when less oxidant (e.g. 2 equiv) (Table 2.5 entry

4 -12) was used. (4) Competitive arene acetoxylation versus amidation was especially noteworthy. For instance, the amidation of α,α,α-trifluorotoluene under the Pd-catalyzed conditions afforded *N*-arylphthalimde and arylacetate (acetoxylation) in a molar ratio of 1:4 with similar regioselectivities (i.e. *meta*-regioisomer being the major product). (5) *No acetoxylation products were found in the absence of phthalimide*.

Findings (4) and (5) strongly implicates that the competing C-H amidation and acetoxylation reactions are probably mechanistically-related.

Table 2.5. Effect of temperature and amount of oxidant



1 ml 0.1 mmol *o:m:p* = 1:15:2 [c]

entry	time intervals of addition of $PhI(OAc)_2$	total amount of $PhI(OAc)_2$ used (equiv)	T (°C)	yield (%)[a]
1	2.0 equiv / 2 h	10.0	80	10[b]
2	2.0 equiv / 2 h	10.0	100	60
3	2.0 equiv / 2 h	10.0	120	35[b]
4	2.0 equiv / 2 h	2.0	100	28
5	2.0 equiv / 2 h	4.0	100	40
6	2.0 equiv / 2 h	6.0	100	60
7	2.0 equiv / 2 h	8.0	100	61

[a]Isolated yield. [b]GC yield with dodecane as the internal standard.
[c]Regioselectivity was determined by GC-MS.

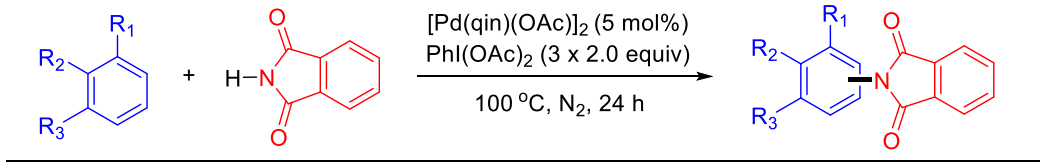
2.2.4. Scope and limitations

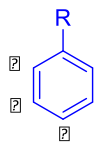
Table 2.6 depicts the results of substrate scope study. In all cases of monosubstituted arenes, the amidation preferentially occurred at the less hindered sites (i.e. the *meta*- and *para*- positions). For arenes with electron-withdrawing groups like CF_3, *meta*- amidation is especially favored.[6] Amidation at the *para*-positions become more dominant for electron rich arens like anisole. This observed regioselectivity is comparable to the analogous amidation reaction reported by Hart-wig's group.[6] Similar findings were also reported in related acetoxylation and arylation of unactivated arenes.

The amidation of di- and tri-substituted arenes afford the products in good yields with the amide group being located *meta* to the substitutents. Notably, arenes containing carbon-halogen bonds were effectively transformed to the corresponding amides without any proto-dehalogenation or carbon-halogen bond amidation. Apparently, in all cases, the reactions were selective for the less hindered *meta*- and *para*- positions. With naphthalene as substrate, amidation at the C1 position is more dominant.

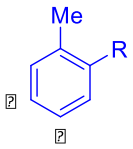
The regioselectivity of the arene amidation was studied in the absence of the Pd catalyst (see Supporting Information for details). In most cases, the uncatalyzed conditions[16] produced the *N*-arylphthalimides in much lower yields. Importantly, regioisomers in which the phthalimide group *ortho* to the substituents were obtained in most cases. With naphthalene as substrate, the C2-amidation became the major product (a:b = 1:11). Based on this finding, we concluded that the $[Pd(qin)(OAc)]_2$ catalyst has a major influence in determining the regioselectivity of the arene amidation reaction.

Table 2.6. Substrate scope

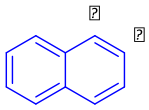




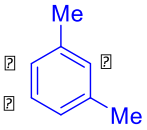
(**1**) R = H; 66%
(**2**) R = Me; 68% *(1:11:12)*
(**3**) R = OMe; 50% *(1:1:5)*
(**4**) R = ^{i}Pr; 67% *(1:7:6)*
(**5**) R = CF_3; 60% *(1:15:2)*
(**6**) R = I; 61% *(1:22:29)*



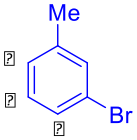
(**7**) R = Br; 79% *(3:5)*
(**8**) R = I; 79% *(1:10)*



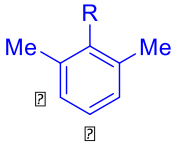
(**9**)
40% *(5:1)*



(**10**)
R = Me; 44% *(1:3:6)*



(**11**)
R = Br; 61% *(5:11:1)*



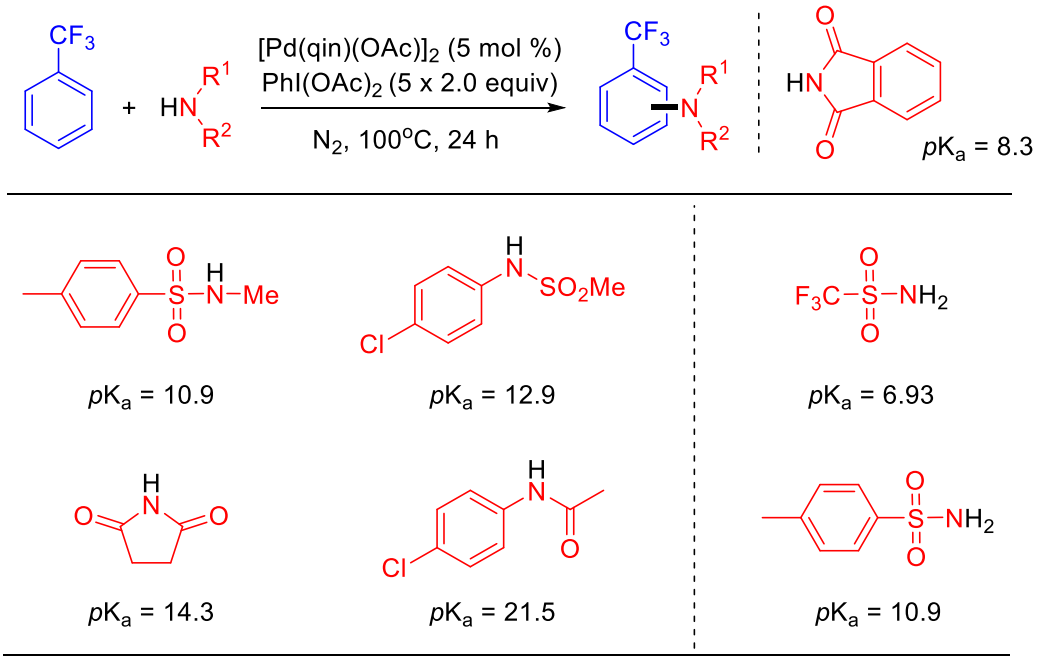
(**12**) R = OMe; 74% *(1:11)*
(**13**) R = Cl; 78% *(1:24)*
(**14**) R = Br; 80% *(1:19)*

[a]Reaction conditions: arene (1 mL), phthalimide (0.1 mmol), $[Pd(qin)(OAc)]_2$ (5 mol%), $PhI(OAc)_2$ (3 x 2.0 equiv), 100 °C, 24 h under N_2; isolated yield and regioisomers ratio □□□□□ shown in parathesis. [b]Regioselectivity was determined by ^{1}H NMR with dibromomethane as an internal standard.

Extending the scope of the nitrogen nucleophiles was proved to be challenging.

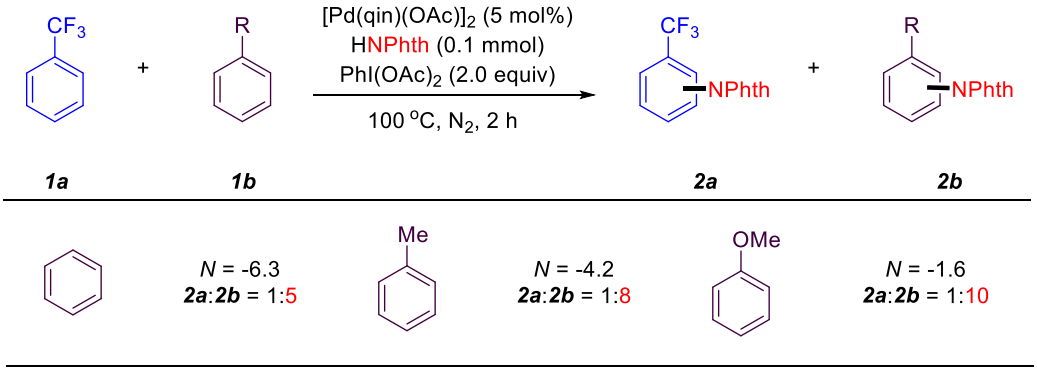
With α,α,α-trifluorotoluene as substrate, nucleophiles other than phthalimide such as succinimide, *p*-toluenesulfonamide and trifluoromethylsulfonamide failed to effect significant arene amidation. For all unsuccessful cases, formation of acetoxylation products was not observed.

Table 2.7. Scope of nitrogen nucleophiles



2.2.5. Chemoselectivity and kinetic isotope effect

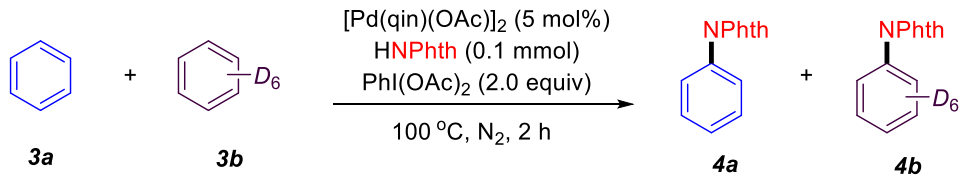
Table 2.8. Chemoselectivity of the amidation reaction



N is nucleophilicity; ratio ***2a***:***2b*** was determined by GC-MS using dodecane as an internal standard

In this work, the chemoselectivity of the [Pd(qin)(OAc)]$_2$-catalyzed amidation was studied by subjecting a 1:1 mixture of α,α,α-trifluorotoluene and some electron-rich arenes (including benzene, toluene and anisole) to the standard reaction conditions with phthalimide (0.1 mmol) and PhI(OAc)$_2$ (0.2 mmol). In all cases, the amidation occurred more selectively to the more electron-rich arenes with a product ratio of 10:1 (anisole) to 8:1 (toluene) to 4:1 (benzene). The observed chemoselectivity correlate well with the nucleophilicity of the arenes (Table 4).[17] This finding suggests that the chemoselectivity-determining step may proceed via the classical electrophilic aromatic substitution pathway.

Table 2.9. Kinetic isotope effect



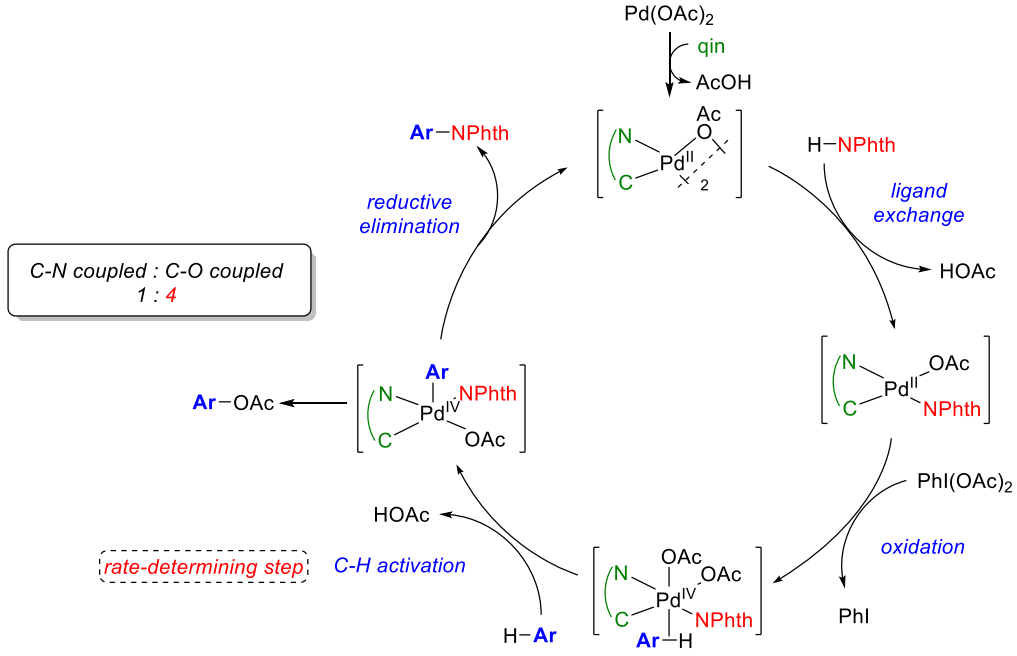
3a + ***3b*** → ***4a*** + ***4b***

trial	***4a*** : ***4b***
1	3.6 : 1
2	3.7 : 1
3	3.4 : 1
average	3.6 : 1

The primary H/D kinetic isotope effect (KIE) was also determined by competitive experiments. A 1:1 mixture of benzene and benzene-d_6 was treated with phthalimide (0.1 mmol) and $PhI(OAc)_2$ (0.2 mmol) in the presence of $[Pd(qin)(OAc)]_2$ (5 mol%) at 100 °C for 2 h. The average KIE value (k_H/k_D = 3.6) is comparable to the reported values (3.1-3.8) of some Pd-catalyzed arene functionalization reactions.[6,9,15] The sizable KIE value suggests that C-H bond cleavage is probably the turnover-determining step of the reaction.

2.2.6. Plausible mechanism

Scheme 2.1 depicts a postulated mechanism consistent with our observation. The catalytic amidation involves (i) generation of the phthalimide-palladium(II) complex by ligand exchange reaction, (ii) oxidation by $PhI(OAc)_2$ to afford the Pd(IV) complex, (iii) arene C-H palladation[18] to form arylpalladium(IV) phthalimide complex, and (iv) C-N bond forming reductive elimination to release the *N*-arylphthalimide product. Consistent with this mechanism, competitive C-O bond reductive elimination was observed. Both the acetoxylation and amidation exhibit identical regioselectivity, and this indicates that the regioselectivity step (probably the C-H palladation) occurs prior to the reductive elimination steps.



2.3. Concluding summary

In conclusion, we developed the 2-phenylquinoline ligand-enabled Pd-catalyzed regioselective nondirected amidation of unactivated arenes. The amidation is directed to the less hindered positions of the arenes. Preliminary mechanistic study suggested a Pd(II)/Pd(IV) reaction manifold involving arene C-H activation by Pd(IV), and this is followed by C-N bond forming reductive elimination. This work demonstrates that it is plausible to manipulate the reactivity and selectivity of organopalladium(IV) species by ligand modification. We are currently applying a similar strategy to develop other catalyst-controlled cross coupling reactions of arenes.

2.4. Experimental Section

2.4.1. Chemicals

Palladium and Ligands:

$Pd(OAc)_2$ and ligands such as 1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-ium chloride, 1,3-dimesityl-1*H*-imidazol-3-ium chloride, 1,3-di-*tert*-butyl-1*H*-imidazol-3-ium chloride, 1,3-diisopropyl-1*H*-imidazol-3-ium chloride, 2-phenylquinoline, 2-phenylpyridine, 2-(*p*-tolyl)pyridine, *N,N*-dimethylbenzamine, benzo[*h*]quinoline and Boc-L-isoleucine were purchased from commercial sources (Strem, Aldrich and Acros as available), stored in a dry box and used as received. All quinoline-typed derivatives and hydrazine carboxylate derivatives are synthesized according to literature reports.[1-2]

Oxidants:

Iodobenzene diacetate, sodium persulfate, Oxone, copper(II) acetate, TBHP, 1-fluoro-2,4,6-trimethylpyridin-1-ium tetrafluoroborate and benzoyl peroxide were purchased from commercial sources (Aldrich and Acros as available) and used as received.

Arenes:

α,α,α-Trifluoromethylbenzene, toluene, isopropylbenzene, iodobenzene, anisole, ethylbenzoate, biphenyl, phenylacetate, benzene, naphthalene, 2-bromotoluene, 2-iodotoluene, *m*-xylene, 3-bromotoluene and 2,6-dimethylanisole were purchased from commercial sources (TCI and Aldrich as available) and used as received.

Nitrogen nucleophiles:

Phthalimide, succinimide, p-toluenesulfonamide and trifluoromethylsulfonamide were purchased from commercial source (Aldrich) and used as received.

Other reagents:

Dodecane (TCI) was purchased commercially and used without purification.

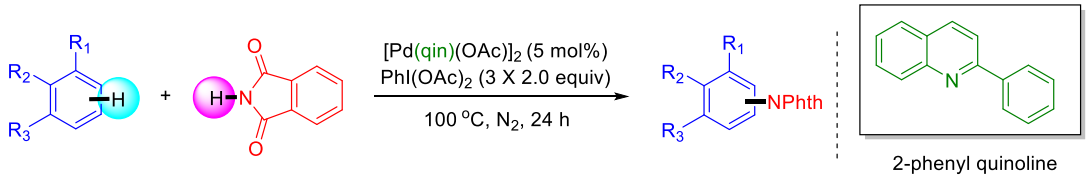
2.4.2. Methods

Thin layer chromatography was performed on silica gel plates. Flash column chromatography was performed on a silica gel (Merck, 230-400 mesh) column. ^{1}H and ^{13}C NMR spectra were recorded on a Brüker DPX-400 MHz spectrometer. The chemical shift (δ) values given in ppm and are referenced to residual solvent peaks; carbon multiplicities were determined by DEPT-135 experiments. Coupling constants (J) were reported in hertz (Hz).

Gas Chromatography/Mass Spectrometry: GC-MS analyses were performed on Agilent Technologies 6890N equipped with an HP-5MS (Crosslinked 5% PH ME Siloxane) column Model 19091S-433 from Agilent (30 m x 0.25 mm x 0.25 μm) with a Mass Selective Detector and helium as the carrier gas. The analysis method used in all cases was 1 μL injection sample, injector temperature of 300 ^{o}C, and 10:1 split ratio. The initial pressure was 10 psi, but varied as the column flow was held constant at 1.3 mL/min for the duration of the run. The interface temperature was held at 300 ^{o}C, and the electron impact (EI, 30 eV) ion source was at 300 ^{o}C. The initial oven temperature was held at 45 ^{o}C for 2.25 min with the detector off, followed by a temperature ramp to 300 ^{o}C at 15 ^{o}C/min with the detector turned on at 3.75 min. The final temperature was held at 300 ^{o}C for 3 min. The total run time was 22.5 min. Data are reported in the form of m/z (intensity relative to the base peak = 100, ion).

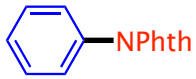
2.4.3. General Experimental Procedure and Physical Characterization

Procedure for the Pd(II)-Catalyzed Intermolecular Oxidative Amidation of Arenes



Phthalimide (0.1 mmol, 14.7 mg), $[(Pd)(qin)(OAc)]_2$ (0.005 mmol, 7.4 mg), $PhI(OAc)_2$ (0.6 mmol, 64.4 mg) and arenes (1 mL) were added to a 10 mL-Schlenk tube, and the reaction tube was evacuated and back-filled with N_2 for three times. The reaction was allowed to react at 100 ^oC oil bath. At 2, 4 and 6 h, the reaction was cooled to room temperature, and evacuated and back-filled with N_2 for three times. Three portions of additional 2.0 equiv of $PhI(OAc)_2$ were added to the crude mixture. After 24 h, the reaction mixture was treated with silica gel. 100 mL of n-hexane was used to remove all arenes and then 100 mL of ethyl acetate was used to extract the products from the silica gel. The solvent was removed by vacuum and the crude mixture was diluted with dichloromethane (2 mL) and dodecane (5 μL) was added as an internal standard for GC-MS analysis. 1 mL of sample was withdrawn and analyzed by GC-MS for determination of regioselectivity ratio of the amidation products. The amidation products were purified by flash chromatography with n-hexane/EA (8:2) as eluent. The products were collected as a mixture of regioisomeric products, and isolated yields were registered.

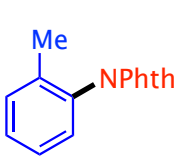
Amidation of Benzene (1)



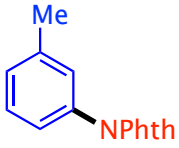
Isolated yield: 60 %; off-white solid

TLC: R_f 0.33 (n-hexane:EtOAc = 8:2)

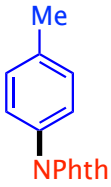
Amidation of Toluene (2)



2a



2b



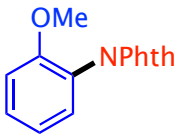
2c

Isolated yield: 68 %; off-white solid

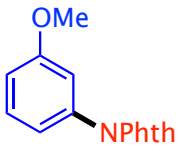
Regioselectivity ratio (**2a:2b:2c**): *1:11:12*

TLC: R_f 0.43 (n-hexane:EtOAc = 8:2)

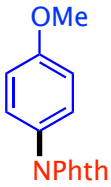
Amidation of Anisole (3)



3a



3b



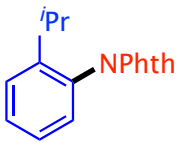
3c

Isolated yield: 50 %; off-white solid

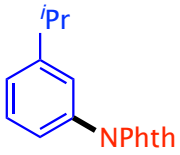
Regioselectivity ratio (**3a**:**3b**:**3c**): *1:1:5*

TLC: R_f 0.27 (n-hexane:EtOAc = 8:2)

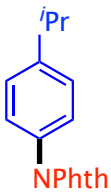
Amidation of Isopropylbenzene (4)



4a



4b



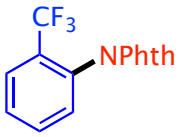
4c

Isolated yield: 67 %; off-white solid

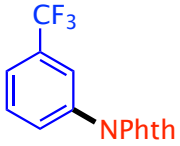
Regioselectivity ratio (**4a**:**4b**:**4c**): *1:7:6*

TLC: R_f 0.47 (n-hexane:EtOAc = 8:2)

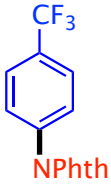
Amidation of α,α,α-Trifluorotoluene (5)



5a



5b



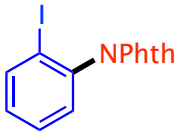
5c

Isolated yield: 60 %; off-white solid

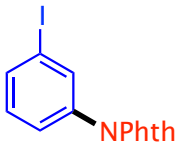
Regioselectivity ratio (**5a**:**5b**:**5c**): *1:15:2*

TLC: R_f 0.43 (n-hexane:EtOAc = 8:2)

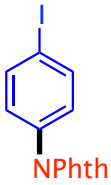
Amidation of Iodobenzene (6)



6a



6b



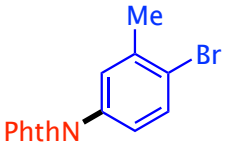
6c

Isolated yield: 61 %; off-white solid

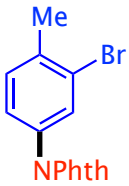
Regioselectivity ratio (**6a**:**6b**:**6c**): *1:22:29*

TLC: R_f 0.4 (n-hexane:EtOAc = 8:2)

Amidation of 2-Bromotoluene (7)



7a



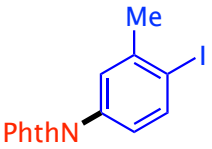
7b

Isolated yield: 79 %; off-white solid

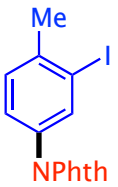
Regioselectivity ratio (**7a**:**7b**): *3:5*

TLC: R_f 0.47 (n-hexane:EtOAc = 8:2)

Amidation of 2-Iodotoluene (8)



8a



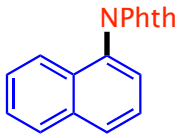
8b

Isolated yield: 79 %; off-white solid

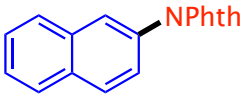
Regioselectivity ratio (**8a**:**8b**): *1:10*

TLC: R_f 0.47 (n-hexane:EtOAc = 8:2)

Amidation of Naphthalene (9)



9a



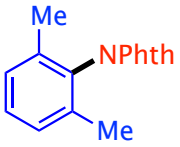
9b

Isolated yield: 40 %; off-white solid

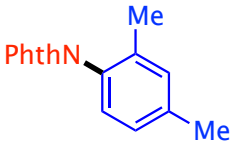
Regioselectivity ratio (**9a**:**9b**): *5:1*

TLC: R_f 0.4 (n-hexane:EtOAc = 8:2)

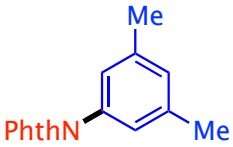
Amidation of *m*-Xylene (10)



10a



10b

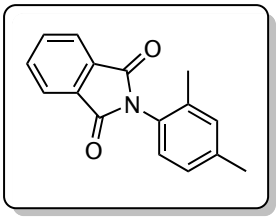


10c

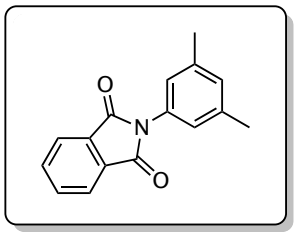
Isolated yield: 44 %; yellow liquid

Regioselectivity ratio (**10a**:**10b**:**10c**): *1:3:6*

TLC: R_f 0.47 (n-hexane:EtOAc = 8:2)

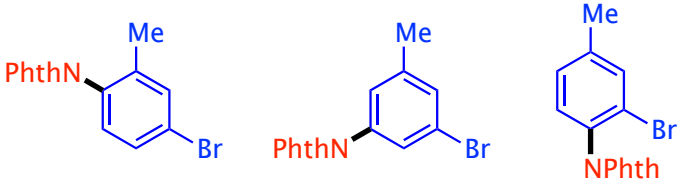


^{1}H NMR (400 MHz, d_6-acetone): δ 7.93 (m, 4 H), 7.21 (m, 2 H), 7.15 (d, *J* = 8 Hz, 1 H), 2.37 (s, 3 H), 2.15 (s, 3 H). 13C NMR (100 MHz, d_6-acetone): δ 167.1, 165.8, 134.7, 132.1, 131.8, 131.7, 130.9, 129.3, 127.8, 124.0, 61.4, 14.4.



^{1}H NMR (400 MHz, d_6-acetone): δ 7.91 (m, 4 H), 7.08 (d, *J* = 5.6 Hz, 3 H), 2.35 (s, 6 H). ^{13}C NMR (100 MHz, d_6-acetone): δ 167.1, 138.5, 134.6, 132.4, 132.2, 129.5, 125.0, 123.3, 20.5.

Amidation of 3-Bromotoluene (11)



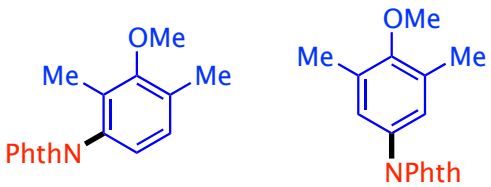
11a 11b 11c

Isolated yield: 61 %; white solid

Regioselectivity ratio (**11a**:**11b**:**11c**): *5:11:1*

TLC: R_f 0.47 (n-hexane:EtOAc = 8:2)

Amidation of 2,6-Dimethylanisole (12)



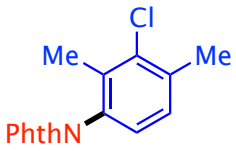
12a 12b

Isolated yield: 74 %; off-white solid

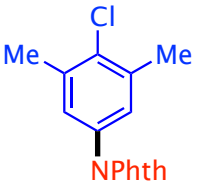
Regioselectivity ratio (**12a**:**12b**): *1:11*

TLC: R_f 0.3 (n-hexane:EtOAc = 8:2)

Amidation of 2-Chloro-1,3-dimethylbenzene (13)



13a



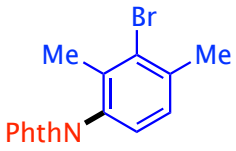
13b

Isolated yield: 78 %; yellow solid

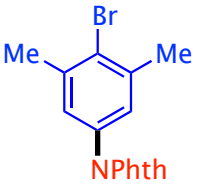
Regioselelivity ratio (**13a**:**13b**): *1:24*

TLC: R_f 0.3 (n-hexane:EtOAc = 8:2)

Amidation of 2-Bromo-1,3-dimethylbenzene (14)



14a



14b

Isolated yield: 80 %; orange solid

Regioselectivity ratio (**14a**:**14b**): *1:19*

TLC: R_f 0.47 (n-hexane:EtOAc = 8:2)

Chapter 3

Ligand Enabled Pd-Catalyzed Site Selective Nondirected Iodination of Unactivated Arenes with Inorganic Iodide

Chapter 3

Ligand Enabled Pd-Catalyzed Site Selective Nondirected Iodination of Unactivated Arenes with Inorganic Iodide

3.1 Introduction

Aryl iodides are essential and versatile starting materials for cross-coupling reactions that are employed for synthesizing various pharmaceuticals,[61-68] natural products[69-73] and functional compounds.[74-80] Conventionally, aryl iodides can be prepared by Sandmeyer-type reactions of diazonium salts,[81-84] direct lithiation/halogenation[85] and Friedel-Crafts-type electrophilic halogenation.[86] Despite these apparent successes, these traditional routes suffer from several limitations such as low functional group tolerance, poor regio-control, limited substrate scope (only activated arenes), stoichiometric metal salts byproducts and over halogenation.

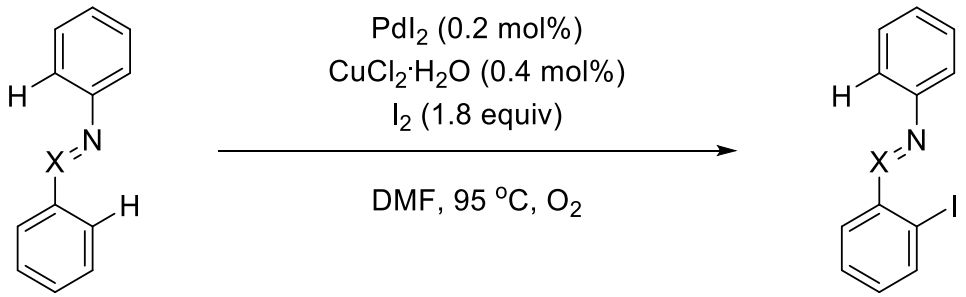
Currently, transition metal assisted C-H functionalization has posed a great impact on the aspect of synthetic chemistry, in particular the formation of carbon-halogen bonds from unactivated C-H bonds are now easily achieved. Formation of aryl iodides via transition metal assisted C-H activation was found to be an alternative pathway to

traditional synthetic routes.

The number of reported catalytic strategies employing high valent Pd(IV) species has recently increase in spite of the dominance of low valent Pd (0 or +2 oxidation state) species owing to the better knowledge stems from clear structure characterizations and thorough reactivity understanding.[87, 88] Reactions involving carbon-halogen bond forming through reductive elimination occurring at Pd(IV) intermediates have posed a massive impact on such field. Pd(IV) intermediates allow such carbon-halogen reductive elimination leading to the facile formation of C-I bond compared to Pd(II) intermediates that such reductive elimination is both kinetically and thermodynamically unfavorable.

Raida and co-workers established catalytic *ortho*-iodination of azobenzene by employing PdI_2 and $CuCl_2$ as catalyst and co-catalyst respectively in 1996 as shown in scheme 3.1.[89] The Pd/Cu ratio and also the concentration of chloride ion were found to significantly influence the overall reaction efficiency and the reaction efficiency would be increased with lower values of both.

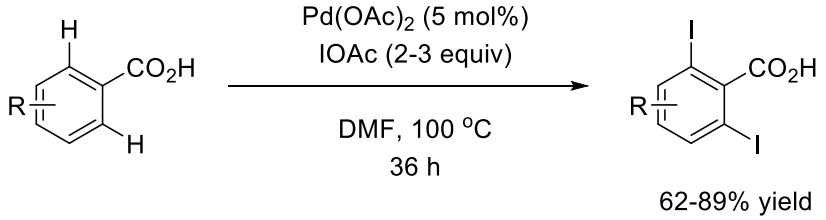
Scheme 3.1. Pd-catalyzed *ortho*-iodination of azobenzene



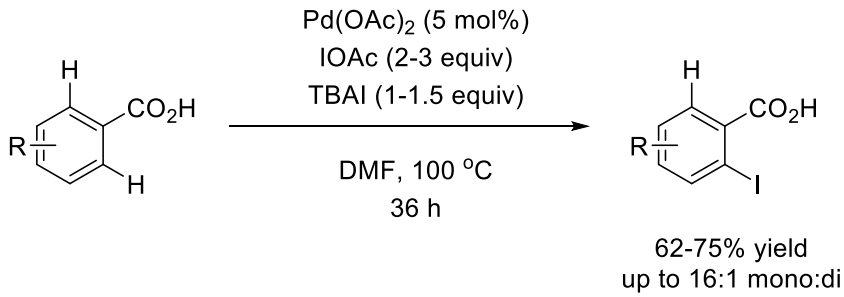
Yu's group developed both mono- and di-selective *ortho*-C-H bromination/iodination of aryl carboxylic acids[90] by employing $Pd(OAc)_2$ and iodonium acetate as the catalyst and oxidizing halogen source[91] respectively in 2008 (Scheme 3.2) The addition of tetrabutylammonium acetate significantly improved the mono-/di-selectivity, apart from promoting the C-H insertion only in the absence of any other base (Scheme 3.2 (b)).

Scheme 3.2. Pd-catalyzed oxidative mono-/di-iodination of aryl carboxylic acids

(a) Diiodination



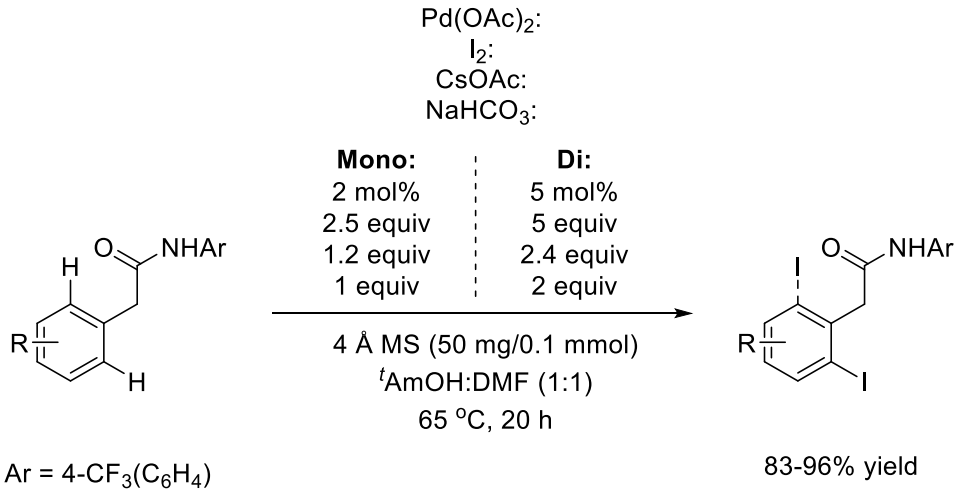
(b) Monoiodination with tetrabutylammonium acetate



The same group has also established the *ortho*-arene C-H iodination of phenylacetic acid, benzoic acid and heterocylic carboxamide derivatives by employing I_2 as both the only halogenating reagent and the oxidant in 2012 (Scheme 3.3). Coordinating solvent mixture was adopted in these conditions for assisting the solubility of PdI_2 catalyst as well as the anionic exchange while the addition of CsOAc helped enhance the overall turnover number.

Scheme 3.3. Pd-catalyzed *ortho*-arene C-H iodination

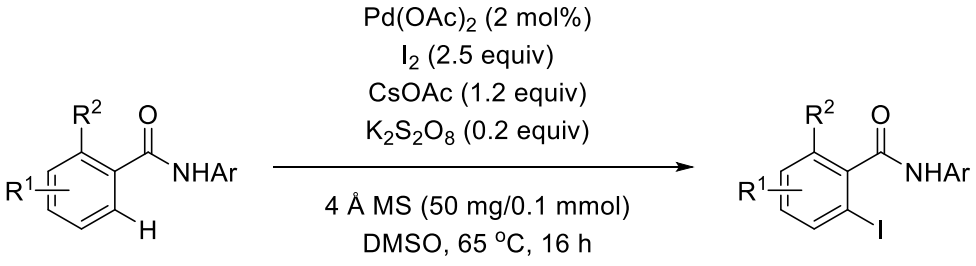
(a)ortho-mono- and di-iodination of phenylacetic acid derivatives



Ar = 4-$CF_3(C_6H_4)$

83-96% yield

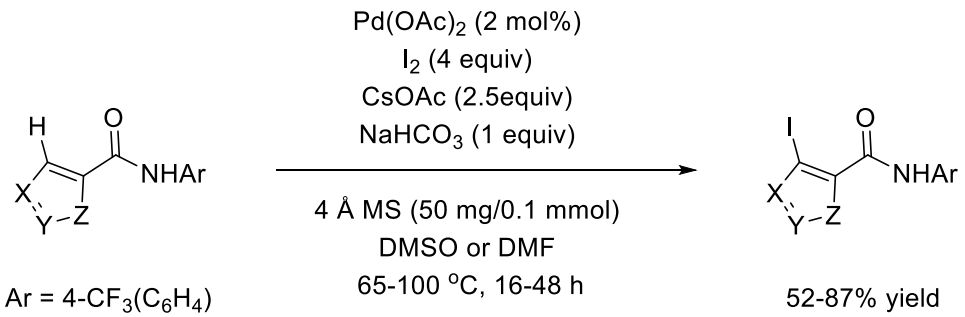
(b)ortho-mono- and di-iodination of benzoic acis carboxamides



Ar = 4-$CF_3(C_6H_4)$

41-96% yield

(c)ortho-mono- and di-iodination of heterocyclic carboxamides



Ar = 4-$CF_3(C_6H_4)$

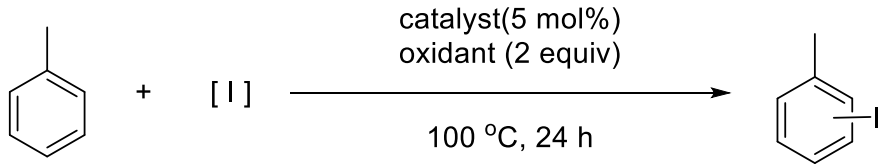
52-87% yield

3.2. Results and Discussion

3.2.1. Preliminary results

To begin, we first reacted potassium iodide (KI, 0.2 mmol) with diacetoxy iodobenzene ($PhI(OAc)_2$, 2 equiv) in the presence of $[Pd(qin)(OAc)]_2$ (5 mol%) as the catalyst in toluene (1 ml) at 100 ^oC for 24 hours. Desired product, iodotoluene, was obtained in 10% GC yield and was characterized by GC-MS as shown in scheme 3.4, entry 1.

Scheme 3.4. Preliminary result



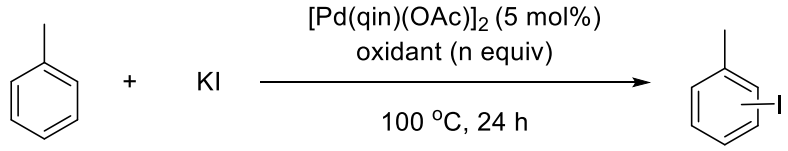
entry	catalyst	oxidant	[I]	yield (%)[a]
1	$[Pd(qin)(OAc)]_2$	$PhI(OAc)_2$	KI	10
2	$[Pd(qin)(OAc)]_2$	-	-	not detected
3	-	$PhI(OAc)_2$	-	not detected
4	-	-	KI	not detected

[a]GC yield with Dodecane as the internal standard

3.2.2. Optimization of Reaction Conditions

With the preliminary data, we started to establish the best catalytic system by several sets screening and optimization.

Table 3.1. Oxidant screening[a]



entry	oxidant	equiv	yield (%)
1	$PhI(TFA)_2$	2.0	10
2	$PhI(OAc)_2$	2.0	10
3	NFSI	2.0	5
4	$Na_2S_2O_8$	2.0	not detected
5	$K_2S_2O_8$	2.0	not detected
6	$PhI(TFA)_2$	2 X 2.0	10
7	$PhI(TFA)_2$	3 X 2.0	10
8	$PhI(OAc)_2$	2 X 2.0	10
9	$PhI(OAc)_2$	3 X 2.0	10
10	NFSI	2 X 2.0	5
11	NFSI	3 X 2.0	5

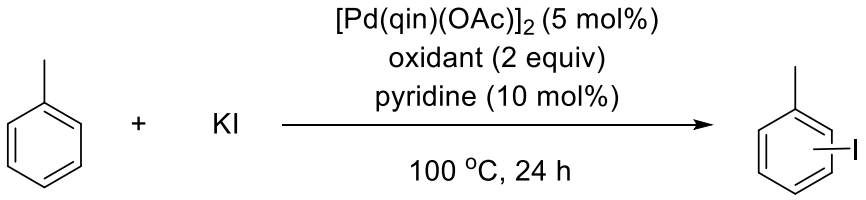
[a] GC yield with dodecane as internal standard

Again, as observed in the amidation reaction presented in chapter 2 earlier, the inorganic oxidants were ineffective for such Pd-catalyzed iodination (Table 3.1, entry 4-5), probably due to the low solubility of these inorganic oxidants in neat non-polar arene solvent. Interestingly, regarding the organic oxidants, both NFSI and $PhI(TFA)_2$ could promote the iodination reaction with desired iodotoluene obtained in 5% and 10% respectively (Table 3.1, entry 1 and 3) apart from $PhI(OAc)_2$, which would generate acetoxylated toluene as side product.

Excessive amount of these organic oxidants were also investigated (Table 3.1, entry 6-11) for this iodination reaction. Notably, unlike the amidation reaction, an excess of oxidant was not necessary to effect the iodination reaction.

It is noteworthy that when 10 mol% pyridine was added to the reaction, a significant increase in product generation was observed, giving 40% yield of the desired product by employing $PhI(TFA)_2$ as the oxidant (Table 3.2, entry 1) while no much effect was observed with NFSI as the oxidant. Probably the additional pyridine helped stabilize the Pd(IV) intermediate as well as helped break down the rigid dimeric $[Pd(qin)(OAc)]_2$ catalyst which therefore increased the overall reaction rate.

Table 3.2. Effect of pyridine as the additive

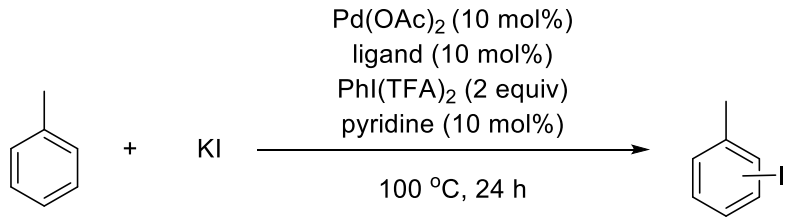


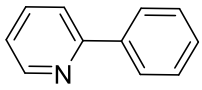
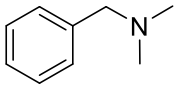
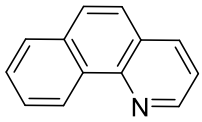
entry	oxidant	yield[a] (%)
1	$PhI(TFA)_2$	40
2	$PhI(OAc)_2$	20
3	NFSI	5

[a] GC yield with dodecane as internal standard

Several ligands were also investigated for the iodination reaction. However, 2-phenylquinoline was the sole ligand to promote the Pd-catalyzed iodination reaction effectively upon our investigation as depicted in table 3.3.

Table 3.3. Ligand screening

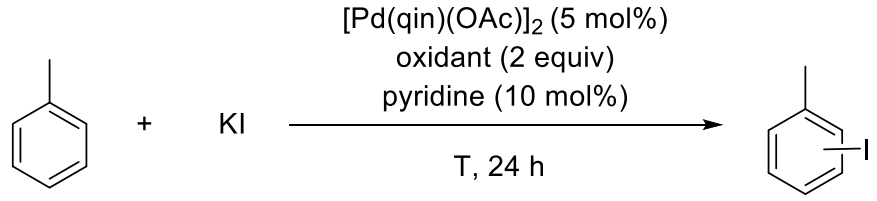


entry	ligand	yield[a] (%)
1	PPh_3	not detected
2		not detected
3		not detected
4		not detected

[a] GC yield with dodecane as internal standard

The effect of temperature was also examined for the best catalytic reaction conditions. Again, based on the screening before, the three organic oxidants were selected for the reaction temperature screening. Reacting the KI (0.2 mmol) with toluene (1 ml) with $PhI(TFA)_2$ (2.0 equiv) as the oxidant at 100 ^oC gave the best result while no much obvious differences when using $PhI(OAc)_2$ and NFSI as the oxidant at different reaction temperature as shown in table 3.4.

Table 3.4. Effect of reaction temperature

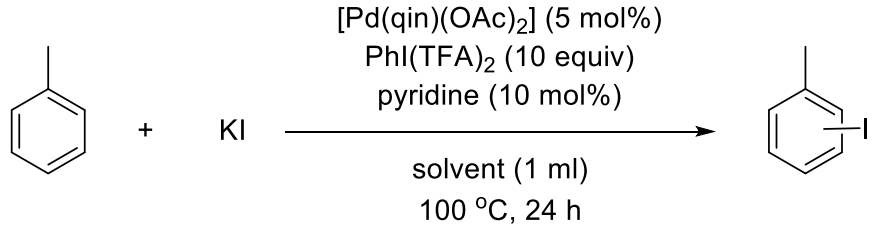


entry	oxidant	temp (^{o}C)	yield (%)
1	$PhI(TFA)_2$	rt	not detected
2	$PhI(TFA)_2$	40	10
3	$PhI(TFA)_2$	60	30
4	$PhI(TFA)_2$	80	35
5	$PhI(TFA)_2$	120	40
6	$PhI(OAc)_2$	rt	not detected
7	$PhI(OAc)_2$	40	10
8	$PhI(OAc)_2$	60	15
9	$PhI(OAc)_2$	80	15
10	NFSI	rt	not detected
11	NFSI	40	not detected
12	NFSI	60	not detected
13	NFSI	80	not detected
14	NFSI	120	not detected

[a] GC yield with dodecane as internal standard

Several common solvent were examined for the iodination reaction as depicted in table 3.5 that aimed to make arene become the limiting reagent by treating toluene (0.5 mmol) with KI (0.5 mmol) in the presence of $PhI(TFA)_2$ (2.0 equiv), pyridine (10 mol%) and $[Pd(qin)(OAc)]_2$ catalyst in 1 ml solvent at 100 ^oC while the results were all unsatisfactory.

Table 3.5. Solvent screening

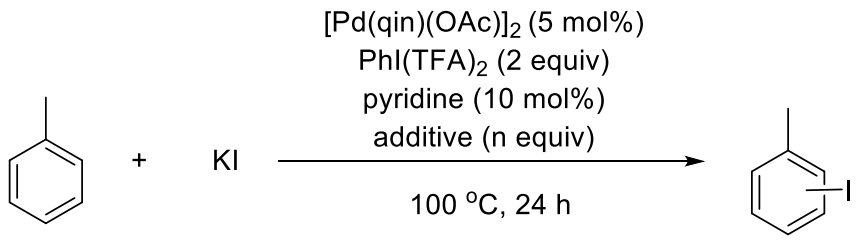


entry	solvent	yield[a] (%)
1	MeCN	not detected
2	DCM	not detected
3	*n*-Hexane	not detected
4	DCE	not detected
5	Dioxane	not detected
6	acetone	not detected
7	HFIP	not detected

[a] GC yield with dodecane as internal standard

In addition, several additives that providing donor atoms were added as depicted in table 3.6 that aimed to help break down the aggregation of the Pd-catalysts by treating toluene (1 ml) with KI (0.2 mmol) in the presence of $PhI(TFA)_2$ (2.0 equiv), pyridine (10 mol%), $[Pd(qin)(OAc)]_2$ catalyst and the donor additives at 100 ^oC while the results were all unsatisfactory.

Table 3.6. Effect of additives

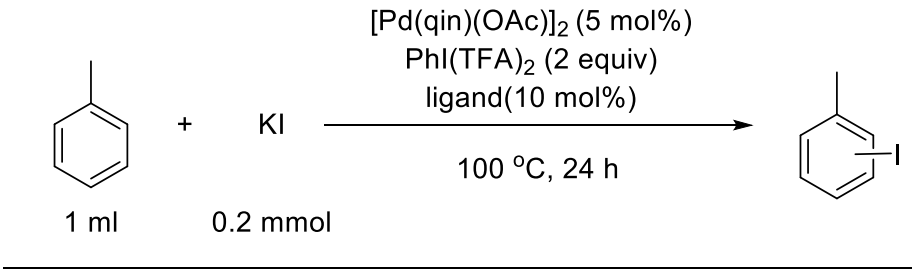


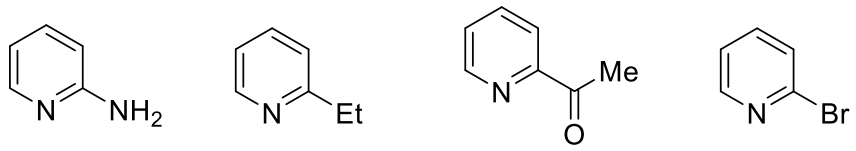
entry	additive	equiv	yield[a] (%)
1	TFE	20 mol%	not detected
2	TFE	50 mol%	not detected
3	TFE	1.0	not detected
4	TFA	20 mol%	not detected
5	TFA	50 mol%	not detected
6	TFA	1.0	not detected
7	DMF	20 mol%	not detected
8	DMF	50 mol%	not detected
9	DMF	1.0	not detected
10	DMA	20 mol%	not detected
11	DMA	50 mol%	not detected
12	DMA	1.0	not detected

[a] GC yield with dodecane as internal standard

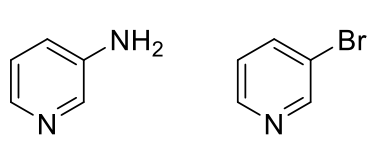
The addition of pyridine effectively promoted the iodination reaction as mentioned earlier. Therefore, a series of pyridine derivatives were examined for the best catalytic reaction conditions (table 3.7). Surprisingly, by changing the electron densities or increasing the steric bulkiness of the pyridine ligands, there was no much effect on the product yield.

Table 3.7. Screening of pyridine derivatives





28% 27% 28% 30%



27% 28% 27% 29%

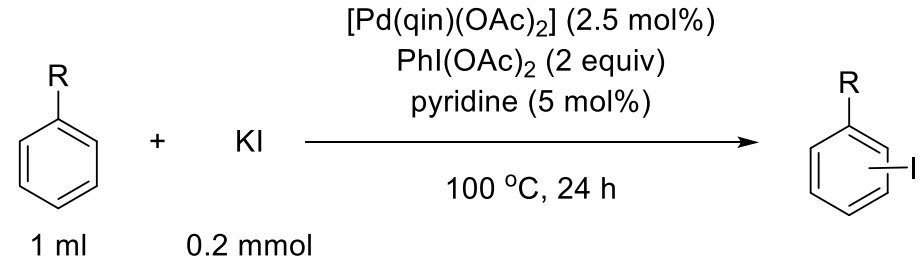
31% 24%

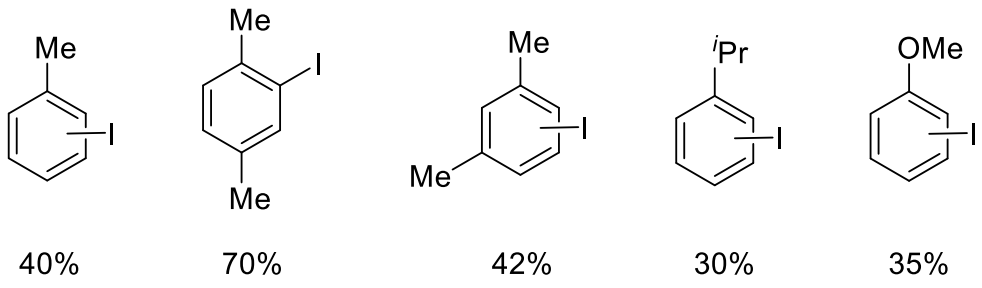
[a] GC yield with dodecane as internal standard

3.2.3. Substrate scope and limitations

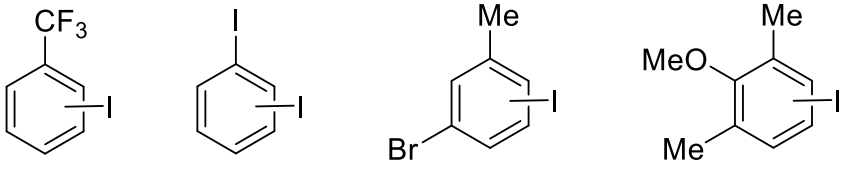
Table 3.8 depicts the results of substrate scope study. The iodination of mono-, di- and tri-substituted arenes afford the products in moderate yields, unlike the amidaiton reaction mentioned in chapter 2, which a higher product yields could be observed in both di- and tri-substituted arenes compared to mono-substituted arenes. It is noteworthy that only *para*-xylene gave the most outstanding yielding, the same reactivity of the four identical C-H bonds might helped enhance the reaction rate and therefore boosted up the yielding.

Table 3.8. Substrate scope





40% 70% 42% 30% 35%



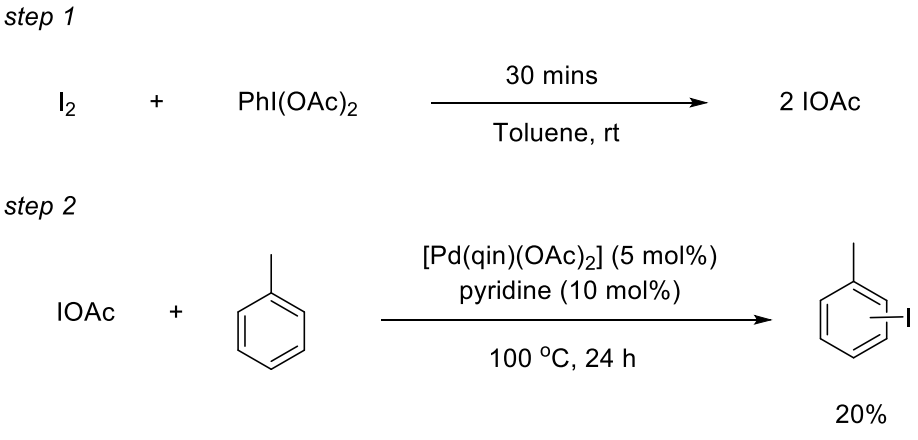
40% 37% 27% 31%

3.2.4. Mechanistic study

Understanding that IOAc is one of the popular oxidants for effective iodination reaction and realizing that IOAc might be generated through reacting NaI with $PhI(OAc)_2$, we therefore tried to investigate the possibility of involving IOAc in our iodination reaction.

IOAc was prepared *in situ* by treating iodine with $PhI(OAc)_2$ in toluene for 30 minutes at room temperature. $[Pd(qin)(OAc)]_2$ catalyst (5 mol%) and pyridine (10 mol%) were added to the solution and the solution mixture was immediately heated to 100 ^oC for 24 hours as shown in scheme 3.5. Notably, the reaction was reproducible with 20% desired iodinated product being generated, indicating that the active IOAc oxidant might involve in the reaction generated from KI and $PhI(OAc)_2$.

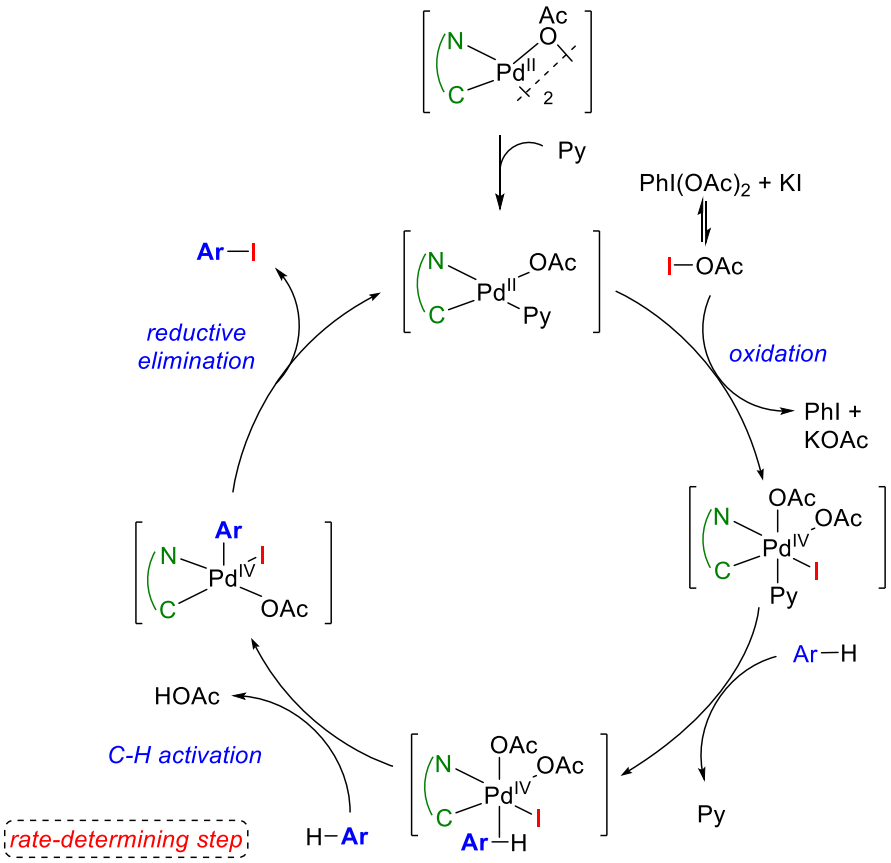
Scheme 3.5. Preparation of IOAc



3.2.5. Plausible Mechanism

Scheme 3.6 depicts a postulated mechanism consistent with our observation. The catalytic iodination cycle involves (i) generation of the active oxidant, IOAc, through the reation between $PhI(OAc)_2$ and Potassium Iodide, (ii) oxidation by IOAc to afford the Pd(IV) complex, (iii) arene C-H palladation to form iodopalladium(IV) complex, and (iv) C-I bond forming reductive elimination to release the iodoarene product. Consistent with this mechanism, competitive C-O bond reductive elimination was observed.

Scheme 3.6. Proposed mechanistic cycle for the iodination reaction



3.3. Concluding summary

In conclusion, we developed the 2-phenylquinoline ligand-enabled Pd-catalyzed nondirected iodination of unactivated arenes with moderate yields. Preliminary mechanistic study suggested a Pd(II)/Pd(IV) reaction manifold involving arene C-H activation by Pd(IV), and this is followed by C-I bond forming reductive elimination. This work demonstrates that it is plausible to manipulate the reactivity and selectivity of organopalladium(IV) species by ligand modification.

3.4. Experimental Section

3.4.1. Chemicals

Palladium and Ligands:

$Pd(OAc)_2$ and ligands such as 1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-ium chloride, 1,3-dimesityl-1*H*-imidazol-3-ium chloride, 1,3-di-*tert*-butyl-1*H*-imidazol-3-ium chloride, 1,3-diisopropyl-1*H*-imidazol-3-ium chloride, 2-phenylquinoline, 2-phenylpyridine, 2-(*p*-tolyl)pyridine, *N,N*-dimethylbenzamine, benzo[*h*]quinoline and Boc-L-isoleucine were purchased from commercial sources (Strem, Aldrich and Acros as available), stored in a dry box and used as received. All quinoline-typed derivatives and hydrazine carboxylate derivatives are synthesized according to literature reports.[1-2]

Oxidants:

Iodobenzene diacetate, sodium persulfate, Oxone, copper(II) acetate, TBHP, 1-fluoro-2,4,6-trimethylpyridin-1-ium tetrafluoroborate and benzoyl peroxide were purchased from commercial sources (Aldrich and Acros as available) and used as received.

Arenes:

α,α,α-Trifluoromethylbenzene, toluene, isopropylbenzene, iodobenzene, anisole, *m*-xylene, 3-bromotoluene and 2,6-dimethylanisole were purchased from commercial sources (TCI and Aldrich as available) and used as received.

Iodine Source:

Potassium Iodide was purchased from commercial source (Aldrich) and used as received.

Other reagents:

Dodecane (TCI) was purchased commercially and used without purification.

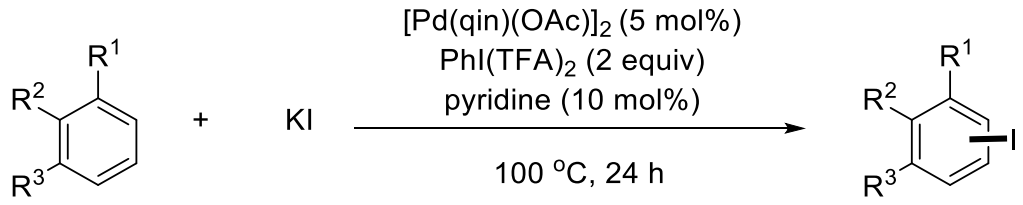
3.4.2. Methods

Thin layer chromatography was performed on silica gel plates. Flash column chromatography was performed on a silica gel (Merck, 230-400 mesh) column. ^{1}H and ^{13}C NMR spectra were recorded on a Brüker DPX-400 MHz spectrometer. The chemical shift (δ) values given in ppm and are referenced to residual solvent peaks; carbon multiplicities were determined by DEPT-135 experiments. Coupling constants (J) were reported in hertz (Hz).

Gas Chromatography/Mass Spectrometry: GC-MS analyses were performed on Agilent Technologies 6890N equipped with an HP-5MS (Crosslinked 5% PH ME Siloxane) column Model 19091S-433 from Agilent (30 m x 0.25 mm x 0.25 μm) with a Mass Selective Detector and helium as the carrier gas. The analysis method used in all cases was 1 μL injection sample, injector temperature of 300 ^{o}C, and 10:1 split ratio. The initial pressure was 10 psi, but varied as the column flow was held constant at 1.3 mL/min for the duration of the run. The interface temperature was held at 300 ^{o}C, and the electron impact (EI, 30 eV) ion source was at 300 ^{o}C. The initial oven temperature was held at 45 ^{o}C for 2.25 min with the detector off, followed by a temperature ramp to 300 ^{o}C at 15 ^{o}C/min with the detector turned on at 3.75 min. The final temperature was held at 300 ^{o}C for 3 min. The total run time was 22.5 min. Data are reported in the form of m/z (intensity relative to the base peak = 100, ion).

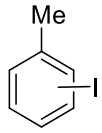
3.4.3. General Experimental Procedure and Physical Characterization

Procedure for the Pd(II)-Catalyzed Intermolecular Oxidative Iodination of Arenes



Potassium iodide (0.2 mmol, 33.2 mg), $[(Pd)(qin)(OAc)]_2$ (0.005 mmol, 7.4 mg), $PhI(TFA)_2$ (0.4 mmol, 172.2 mg) and arenes (1 mL) were added to a 10 mL-Schlenk tube. The reaction was allowed to react at 100 ^{o}C oil bath. After 24 h, the reaction mixture was treated with silica gel. 100 mL of n-hexane was used to remove all arenes and then 100 mL of ethyl acetate was used to extract the products from the silica gel. The solvent was removed by vacuum and the crude mixture was diluted with dichloromethane (2 mL) and dodecane (5 μL) was added as an internal standard for GC-MS analysis. 1 mL of sample was withdrawn and analyzed by GC-MS for determination of the product yield.

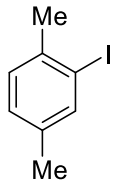
Iodination of Toluene



GC-MS yield: 40 %;

Retention Time: 9.082 min

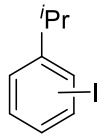
Iodination of *p*-Xylene



GC-MS yield: 70 %;

Retention Time: 9.110 min

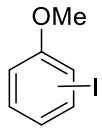
Iodination of ^{i}*Pr*-Benzene



GC-MS yield: 30%

Retention Time: 9.581 min

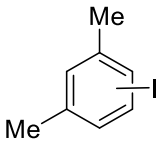
Iodination of *Anisole*



GC-MS yield: 35%

Retention Time: 9.624 min

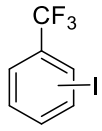
Iodination of *m*-Xylene



GC-MS yield: 42%

Retention Time: 9.183 min

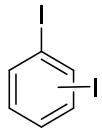
Iodination of α,α,α-Trifluorotoluene



GC-MS yield: 40%

Retention Time: 9.710 min

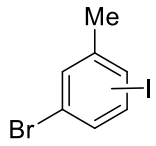
Amidation of Iodobenzene



GC-MS yield: 37%

Retention Time: 10.974 min

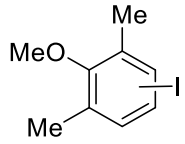
Amidation of 3-Bromotoluene



GC-MS yield: 27%

Retention Time: 10.974 min

Amidation of 2,6-Dimethylanisole



GC-MS yield: 31%

Retention Time: 10.966 min

Chapter 4

Conclusions

Chapter 4

Conclusion

In chapter 2, we established the $[Pd(qin)(OAc)]_2$ complex catalyzed amidation of simple non-directing arenes and the amidated arenes were obtained in 40– 80% yields with up to 14 examples. In general, tri-substituted simple arenes amidation products were obtained in excellent yields, while corresponding amidation products of both mono- and di-substituted simple arenes were obtained in44-80% yields. For the coupling amidating reagent, amides apart from phthalimide were all ineffective in our reactions. In addition, $PhI(OAc)_2$ was the sole oxidant to effect the amidation reaction and competitive C-O bond reductive elimination was observed and exhibiting same regioselectivity with amidation.

Several bidentate ligands were investigated in the screening process and affording the corresponding amidating product of trifluorotoluene in 14-60% yields. 2-phenylquinoline was found to be the most effective ligand, yielding 60% amidation product of trifluorotoluene. Time trace analysis was performed and indicated the catalytic effect of 2-phenylquinoline ligand on the amidation reaction.

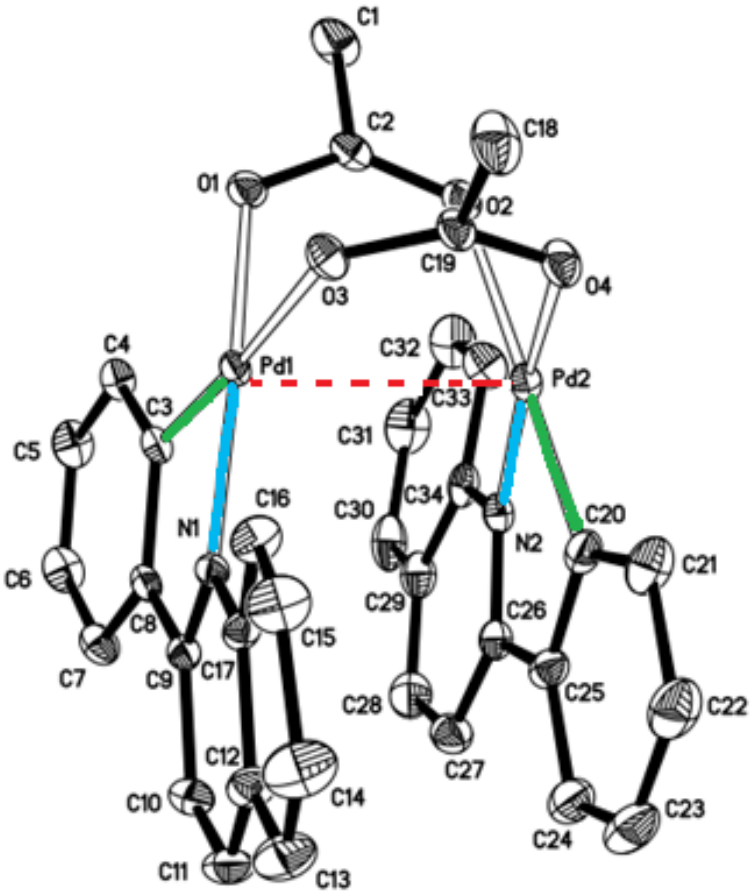
Chemoselectivity experiments were performed and suggested that the Chemoselectivity-determining step may proceed through the classical electrophilic aromatic substitution pathway.

In chapter 3, we established the $[Pd(qin)(OAc)]_2$ complex catalyzed iodination of simple non-directing arenes using simple inorganic iodide as the halogenating reagent. $PhI(TFA)_2$ was the effective oxidant to promote the iodination reaction and competitive C-O bond reductive elimination was avoided that was observed in chapter 2.

Appendices

A-I X-ray Crystallographic Data

Figure A. Molecular structure of $[Pd(OAc)(qin)]_2$



Crystal data and structure refinement for $[Pd(qin)(OAc)]_2$

Table 1. Crystal data and structure refinement for $[Pd(qin)(OAc)]_2$.

Identification code	lck2	
Empirical formula	C29 H26 N2 O4 Pd2	
Formula weight	679.32	
Temperature	273(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.4726(2) Å	α= 90°.
	b = 16.3484(4) Å	β= 90°.
	c = 20.7462(5) Å	γ = 90°.
Volume	2873.63(12) $Å^3$	
Z	4	
Density (calculated)	1.570 Mg/m^3	
Absorption coefficient	10.382 mm^{-1}	
F(000)	1352	
Crystal size	0.28 x 0.10 x 0.08 mm^3	
Theta range for data collection	3.44 to 72.24°.	
Index ranges	-10<=h<=10, -20<=k<=20, -25<=l<=25	
Reflections collected	33490	
Independent reflections	5645 [R(int) = 0.0367]	
Completeness to theta = 72.24°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7536 and 0.4775	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5645 / 0 / 388	
Goodness-of-fit on F^2	1.004	
Final R indices [I>2sigma(I)]	R1 = 0.0298, wR2 = 0.0787	
R indices (all data)	R1 = 0.0303, wR2 = 0.0792	
Absolute structure parameter	0.00	
Extinction coefficient	0.00056(3)	
Largest diff. peak and hole	0.831 and -0.809 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for lck2. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pd(1)	1439(1)	965(1)	3878(1)	29(1)
Pd(2)	3582(1)	24(1)	3071(1)	34(1)
O(1)	622(3)	-141(1)	4189(1)	42(1)
O(2)	2310(3)	-904(1)	3616(1)	46(1)
O(3)	145(3)	714(1)	3002(1)	43(1)
O(4)	1786(3)	-56(2)	2414(1)	47(1)
N(1)	2472(3)	2091(1)	3697(1)	30(1)
N(2)	5493(3)	250(2)	3662(1)	36(1)
C(1)	727(7)	-1547(2)	4398(2)	66(1)
C(2)	1269(5)	-808(2)	4024(1)	41(1)
C(3)	2507(3)	1123(2)	4704(1)	33(1)
C(4)	2362(4)	644(2)	5252(2)	41(1)
C(5)	3216(5)	814(2)	5797(2)	52(1)
C(6)	4238(5)	1460(2)	5812(2)	54(1)
C(7)	4446(4)	1956(2)	5272(2)	47(1)
C(8)	3552(4)	1786(2)	4719(1)	34(1)
C(9)	3561(4)	2292(2)	4130(1)	34(1)
C(10)	4624(4)	2944(2)	4035(2)	47(1)
C(11)	4518(5)	3399(2)	3483(2)	53(1)
C(12)	3335(4)	3236(2)	3039(2)	46(1)
C(13)	3110(5)	3716(2)	2478(2)	64(1)
C(14)	1861(6)	3577(3)	2075(2)	73(1)
C(15)	800(5)	2955(3)	2220(2)	60(1)
C(16)	1014(4)	2445(2)	2739(2)	45(1)
C(17)	2282(4)	2573(2)	3155(2)	36(1)
C(18)	-659(5)	311(3)	1963(2)	64(1)
C(19)	517(4)	321(2)	2514(1)	38(1)
C(20)	4625(4)	879(2)	2560(2)	42(1)
C(21)	4216(5)	1133(2)	1951(2)	57(1)
C(22)	4977(6)	1791(3)	1671(2)	73(1)
C(23)	6133(5)	2223(3)	2010(2)	68(1)
C(24)	6545(5)	1964(2)	2610(2)	57(1)

C(25)	5817(4)	1294(2)	2890(2)	41(1)
C(26)	6230(4)	954(2)	3520(2)	40(1)
C(27)	7317(4)	1317(2)	3947(2)	50(1)
C(28)	7630(5)	949(3)	4519(2)	59(1)
C(29)	6960(4)	191(2)	4668(2)	52(1)
C(30)	7346(6)	-251(3)	5235(2)	67(1)
C(31)	6734(6)	-1008(3)	5339(2)	76(1)
C(32)	5726(6)	-1357(3)	4887(2)	71(1)
C(33)	5328(5)	-954(2)	4333(2)	56(1)
C(34)	5900(4)	-160(2)	4223(2)	42(1)

Table 3. Bond lengths [Å] and angles [°] for lck2.

Pd(1)-C(3)	1.954(3)
Pd(1)-O(1)	2.041(2)
Pd(1)-N(1)	2.073(2)
Pd(1)-O(3)	2.162(2)
Pd(1)-Pd(2)	2.9100(3)
Pd(2)-C(20)	1.965(3)
Pd(2)-O(4)	2.046(2)
Pd(2)-N(2)	2.064(3)
Pd(2)-O(2)	2.176(2)
O(1)-C(2)	1.267(4)
O(2)-C(2)	1.232(4)
O(3)-C(19)	1.240(4)
O(4)-C(19)	1.256(4)
N(1)-C(9)	1.329(4)
N(1)-C(17)	1.382(4)
N(2)-C(26)	1.343(4)
N(2)-C(34)	1.388(4)
C(1)-C(2)	1.508(5)
C(1)-H(1A)	0.9600
C(1)-H(1B)	0.9600
C(1)-H(1C)	0.9600
C(3)-C(4)	1.386(4)
C(3)-C(8)	1.400(4)
C(4)-C(5)	1.372(5)
C(4)-H(4A)	0.74(3)
C(5)-C(6)	1.366(6)
C(5)-H(5A)	0.9300
C(6)-C(7)	1.393(5)
C(6)-H(6A)	0.87(5)
C(7)-C(8)	1.403(4)
C(7)-H(7A)	0.9300
C(8)-C(9)	1.475(4)
C(9)-C(10)	1.409(4)
C(10)-C(11)	1.369(5)
C(10)-H(10A)	0.9300
C(11)-C(12)	1.388(5)

C(11)-H(11A)	0.9300
C(12)-C(13)	1.417(5)
C(12)-C(17)	1.425(4)
C(13)-C(14)	1.368(6)
C(13)-H(13A)	0.9300
C(14)-C(15)	1.390(6)
C(14)-H(14A)	0.9300
C(15)-C(16)	1.373(5)
C(15)-H(15A)	0.9300
C(16)-C(17)	1.395(5)
C(16)-H(16A)	0.9300
C(18)-C(19)	1.516(5)
C(18)-H(18A)	0.9600
C(18)-H(18B)	0.9600
C(18)-H(18C)	0.9600
C(20)-C(21)	1.374(5)
C(20)-C(25)	1.397(5)
C(21)-C(22)	1.382(6)
C(21)-H(21A)	0.9300
C(22)-C(23)	1.398(7)
C(22)-H(22A)	0.9300
C(23)-C(24)	1.359(6)
C(23)-H(23A)	0.9300
C(24)-C(25)	1.384(5)
C(24)-H(24A)	0.9300
C(25)-C(26)	1.463(5)
C(26)-C(27)	1.409(5)
C(27)-C(28)	1.355(6)
C(27)-H(27A)	0.9300
C(28)-C(29)	1.398(6)
C(28)-H(28A)	0.9300
C(29)-C(34)	1.410(5)
C(29)-C(30)	1.418(6)
C(30)-C(31)	1.361(7)
C(30)-H(30A)	0.9300
C(31)-C(32)	1.390(7)
C(31)-H(31A)	0.9300
C(32)-C(33)	1.368(6)

C(32)-H(32A)	0.9300
C(33)-C(34)	1.403(5)
C(33)-H(33A)	0.9300

C(3)-Pd(1)-O(1)	89.82(10)
C(3)-Pd(1)-N(1)	81.15(11)
O(1)-Pd(1)-N(1)	170.91(9)
C(3)-Pd(1)-O(3)	175.36(11)
O(1)-Pd(1)-O(3)	85.74(9)
N(1)-Pd(1)-O(3)	103.31(9)
C(3)-Pd(1)-Pd(2)	106.59(8)
O(1)-Pd(1)-Pd(2)	85.69(6)
N(1)-Pd(1)-Pd(2)	95.87(6)
O(3)-Pd(1)-Pd(2)	74.46(6)
C(20)-Pd(2)-O(4)	91.17(12)
C(20)-Pd(2)-N(2)	80.80(12)
O(4)-Pd(2)-N(2)	171.86(10)
C(20)-Pd(2)-O(2)	177.04(12)
O(4)-Pd(2)-O(2)	86.18(10)
N(2)-Pd(2)-O(2)	101.81(10)
C(20)-Pd(2)-Pd(1)	102.42(9)
O(4)-Pd(2)-Pd(1)	87.31(7)
N(2)-Pd(2)-Pd(1)	93.04(7)
O(2)-Pd(2)-Pd(1)	76.14(6)
C(2)-O(1)-Pd(1)	122.0(2)
C(2)-O(2)-Pd(2)	128.52(19)
C(19)-O(3)-Pd(1)	131.0(2)
C(19)-O(4)-Pd(2)	119.68(19)
C(9)-N(1)-C(17)	119.4(2)
C(9)-N(1)-Pd(1)	112.95(17)
C(17)-N(1)-Pd(1)	127.16(19)
C(26)-N(2)-C(34)	118.8(3)
C(26)-N(2)-Pd(2)	112.9(2)
C(34)-N(2)-Pd(2)	127.4(2)
C(2)-C(1)-H(1A)	109.5
C(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
C(2)-C(1)-H(1C)	109.5

H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(2)-C(2)-O(1)	127.2(3)
O(2)-C(2)-C(1)	118.0(3)
O(1)-C(2)-C(1)	114.7(3)
C(4)-C(3)-C(8)	118.4(3)
C(4)-C(3)-Pd(1)	127.1(2)
C(8)-C(3)-Pd(1)	114.5(2)
C(5)-C(4)-C(3)	121.0(3)
C(5)-C(4)-H(4A)	120(2)
C(3)-C(4)-H(4A)	119(2)
C(6)-C(5)-C(4)	120.6(3)
C(6)-C(5)-H(5A)	119.7
C(4)-C(5)-H(5A)	119.7
C(5)-C(6)-C(7)	120.8(3)
C(5)-C(6)-H(6A)	125(3)
C(7)-C(6)-H(6A)	114(3)
C(6)-C(7)-C(8)	118.4(3)
C(6)-C(7)-H(7A)	120.8
C(8)-C(7)-H(7A)	120.8
C(3)-C(8)-C(7)	120.8(3)
C(3)-C(8)-C(9)	114.8(3)
C(7)-C(8)-C(9)	124.3(3)
N(1)-C(9)-C(10)	122.4(3)
N(1)-C(9)-C(8)	114.7(3)
C(10)-C(9)-C(8)	122.9(3)
C(11)-C(10)-C(9)	119.1(3)
C(11)-C(10)-H(10A)	120.4
C(9)-C(10)-H(10A)	120.4
C(10)-C(11)-C(12)	119.9(3)
C(10)-C(11)-H(11A)	120.1
C(12)-C(11)-H(11A)	120.1
C(11)-C(12)-C(13)	122.4(3)
C(11)-C(12)-C(17)	119.1(3)
C(13)-C(12)-C(17)	118.5(3)
C(14)-C(13)-C(12)	120.9(4)
C(14)-C(13)-H(13A)	119.6
C(12)-C(13)-H(13A)	119.6

C(13)-C(14)-C(15)	119.4(4)
C(13)-C(14)-H(14A)	120.3
C(15)-C(14)-H(14A)	120.3
C(16)-C(15)-C(14)	121.9(4)
C(16)-C(15)-H(15A)	119.1
C(14)-C(15)-H(15A)	119.1
C(15)-C(16)-C(17)	119.7(3)
C(15)-C(16)-H(16A)	120.1
C(17)-C(16)-H(16A)	120.1
N(1)-C(17)-C(16)	120.6(3)
N(1)-C(17)-C(12)	119.9(3)
C(16)-C(17)-C(12)	119.5(3)
C(19)-C(18)-H(18A)	109.5
C(19)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(19)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
O(3)-C(19)-O(4)	127.3(3)
O(3)-C(19)-C(18)	117.0(3)
O(4)-C(19)-C(18)	115.7(3)
C(21)-C(20)-C(25)	119.0(3)
C(21)-C(20)-Pd(2)	126.8(3)
C(25)-C(20)-Pd(2)	114.0(2)
C(20)-C(21)-C(22)	120.3(4)
C(20)-C(21)-H(21A)	119.8
C(22)-C(21)-H(21A)	119.8
C(21)-C(22)-C(23)	120.5(4)
C(21)-C(22)-H(22A)	119.7
C(23)-C(22)-H(22A)	119.7
C(24)-C(23)-C(22)	118.9(4)
C(24)-C(23)-H(23A)	120.6
C(22)-C(23)-H(23A)	120.6
C(23)-C(24)-C(25)	121.1(4)
C(23)-C(24)-H(24A)	119.4
C(25)-C(24)-H(24A)	119.4
C(24)-C(25)-C(20)	120.1(3)
C(24)-C(25)-C(26)	124.7(3)

C(20)-C(25)-C(26)	115.2(3)
N(2)-C(26)-C(27)	121.8(3)
N(2)-C(26)-C(25)	114.2(3)
C(27)-C(26)-C(25)	124.0(3)
C(28)-C(27)-C(26)	119.5(3)
C(28)-C(27)-H(27A)	120.2
C(26)-C(27)-H(27A)	120.2
C(27)-C(28)-C(29)	120.5(4)
C(27)-C(28)-H(28A)	119.8
C(29)-C(28)-H(28A)	119.8
C(28)-C(29)-C(34)	118.4(3)
C(28)-C(29)-C(30)	122.8(4)
C(34)-C(29)-C(30)	118.8(4)
C(31)-C(30)-C(29)	120.5(4)
C(31)-C(30)-H(30A)	119.7
C(29)-C(30)-H(30A)	119.7
C(30)-C(31)-C(32)	120.0(4)
C(30)-C(31)-H(31A)	120.0
C(32)-C(31)-H(31A)	120.0
C(33)-C(32)-C(31)	121.4(4)
C(33)-C(32)-H(32A)	119.3
C(31)-C(32)-H(32A)	119.3
C(32)-C(33)-C(34)	119.8(4)
C(32)-C(33)-H(33A)	120.1
C(34)-C(33)-H(33A)	120.1
N(2)-C(34)-C(33)	119.8(3)
N(2)-C(34)-C(29)	120.7(3)
C(33)-C(34)-C(29)	119.4(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for lck2. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1)	37(1)	24(1)	25(1)	-3(1)	1(1)	0(1)
Pd(2)	41(1)	32(1)	30(1)	-3(1)	3(1)	4(1)
O(1)	55(1)	34(1)	37(1)	-1(1)	8(1)	-9(1)
O(2)	60(1)	29(1)	51(1)	-2(1)	7(1)	-2(1)
O(3)	53(1)	44(1)	32(1)	-8(1)	-6(1)	0(1)
O(4)	52(1)	54(1)	36(1)	-11(1)	-5(1)	2(1)
N(1)	34(1)	25(1)	31(1)	0(1)	4(1)	0(1)
N(2)	39(1)	35(1)	34(1)	-3(1)	2(1)	10(1)
C(1)	108(3)	37(2)	52(2)	10(2)	16(2)	-13(2)
C(2)	58(2)	31(1)	33(1)	3(1)	-7(1)	-5(1)
C(3)	38(1)	29(1)	30(1)	-5(1)	-1(1)	7(1)
C(4)	49(2)	36(1)	37(2)	1(1)	0(1)	3(1)
C(5)	67(2)	56(2)	34(2)	4(1)	-4(2)	13(2)
C(6)	65(2)	58(2)	38(2)	-7(2)	-21(2)	11(2)
C(7)	49(2)	45(2)	48(2)	-6(2)	-11(2)	1(2)
C(8)	38(1)	31(1)	33(1)	-9(1)	-3(1)	6(1)
C(9)	37(1)	29(1)	35(1)	-4(1)	3(1)	2(1)
C(10)	49(2)	40(2)	54(2)	-6(1)	-3(2)	-8(1)
C(11)	53(2)	41(2)	66(2)	8(2)	5(2)	-15(2)
C(12)	47(2)	38(1)	54(2)	13(1)	7(2)	-1(1)
C(13)	65(3)	55(2)	72(2)	31(2)	4(2)	-9(2)
C(14)	77(3)	74(2)	67(2)	43(2)	-7(2)	-3(2)
C(15)	61(2)	67(2)	51(2)	23(2)	-12(2)	3(2)
C(16)	47(2)	47(2)	40(2)	13(1)	-3(1)	-1(1)
C(17)	40(2)	30(1)	38(2)	5(1)	8(1)	3(1)
C(18)	64(2)	85(3)	44(2)	-20(2)	-14(2)	11(2)
C(19)	46(2)	40(1)	28(1)	-4(1)	-1(1)	-4(1)
C(20)	47(2)	40(2)	40(2)	3(1)	12(1)	6(1)
C(21)	65(2)	67(2)	38(2)	14(2)	7(2)	5(2)
C(22)	83(3)	85(3)	51(2)	25(2)	12(2)	12(2)
C(23)	68(3)	60(2)	75(2)	27(2)	21(2)	4(2)
C(24)	50(2)	50(2)	70(2)	8(2)	14(2)	-3(2)
C(25)	36(1)	37(1)	50(2)	5(1)	10(1)	7(1)

C(26)	36(1)	38(1)	47(2)	-5(1)	8(1)	8(1)
C(27)	39(2)	49(2)	63(2)	-6(2)	-1(2)	-3(1)
C(28)	46(2)	74(2)	58(2)	-14(2)	-6(2)	3(2)
C(29)	48(2)	63(2)	43(2)	-7(2)	-2(1)	17(2)
C(30)	73(3)	92(3)	38(2)	-7(2)	-6(2)	20(2)
C(31)	94(3)	90(3)	43(2)	17(2)	-7(2)	27(3)
C(32)	93(3)	60(2)	61(2)	22(2)	-2(2)	20(2)
C(33)	72(2)	43(2)	52(2)	5(2)	-10(2)	13(2)
C(34)	44(2)	47(2)	35(2)	-1(1)	5(1)	17(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for lck2.

	x	y	z	U(eq)
H(1A)	1266	-2025	4241	99
H(1B)	-390	-1616	4343	99
H(1C)	961	-1472	4846	99
H(5A)	3097	487	6161	63
H(7A)	5159	2388	5278	57
H(10A)	5387	3063	4343	57
H(11A)	5238	3817	3406	64
H(13A)	3822	4132	2382	77
H(14A)	1723	3895	1708	87
H(15A)	-80	2882	1958	72
H(16A)	316	2015	2812	54
H(18A)	-1581	616	2084	97
H(18B)	-951	-243	1869	97
H(18C)	-189	555	1589	97
H(21A)	3424	862	1727	68
H(22A)	4717	1948	1253	88
H(23A)	6612	2680	1829	82
H(24A)	7329	2240	2835	68
H(27A)	7815	1804	3838	60
H(28A)	8296	1203	4813	71
H(30A)	8023	-20	5537	81
H(31A)	6989	-1293	5713	91
H(32A)	5313	-1875	4964	85
H(33A)	4682	-1205	4029	67
H(6A)	4830(60)	1590(30)	6140(20)	68(13)
H(4A)	1820(40)	289(19)	5247(15)	24(8)

Table 6. Torsion angles [°] for lck2.

C(3)-Pd(1)-Pd(2)-C(20)	-96.73(13)
O(1)-Pd(1)-Pd(2)-C(20)	174.75(12)
N(1)-Pd(1)-Pd(2)-C(20)	-14.24(12)
O(3)-Pd(1)-Pd(2)-C(20)	87.98(12)
C(3)-Pd(1)-Pd(2)-O(4)	172.66(11)
O(1)-Pd(1)-Pd(2)-O(4)	84.14(10)
N(1)-Pd(1)-Pd(2)-O(4)	-104.85(9)
O(3)-Pd(1)-Pd(2)-O(4)	-2.63(9)
C(3)-Pd(1)-Pd(2)-N(2)	-15.48(11)
O(1)-Pd(1)-Pd(2)-N(2)	-104.00(10)
N(1)-Pd(1)-Pd(2)-N(2)	67.00(10)
O(3)-Pd(1)-Pd(2)-N(2)	169.23(9)
C(3)-Pd(1)-Pd(2)-O(2)	85.94(11)
O(1)-Pd(1)-Pd(2)-O(2)	-2.59(9)
N(1)-Pd(1)-Pd(2)-O(2)	168.42(9)
O(3)-Pd(1)-Pd(2)-O(2)	-89.36(9)
C(3)-Pd(1)-O(1)-C(2)	-100.4(3)
N(1)-Pd(1)-O(1)-C(2)	-94.0(6)
O(3)-Pd(1)-O(1)-C(2)	81.0(2)
Pd(2)-Pd(1)-O(1)-C(2)	6.3(2)
C(20)-Pd(2)-O(2)-C(2)	-61(2)
O(4)-Pd(2)-O(2)-C(2)	-88.1(3)
N(2)-Pd(2)-O(2)-C(2)	90.3(3)
Pd(1)-Pd(2)-O(2)-C(2)	0.1(3)
C(3)-Pd(1)-O(3)-C(19)	-101.9(13)
O(1)-Pd(1)-O(3)-C(19)	-84.9(3)
N(1)-Pd(1)-O(3)-C(19)	94.2(3)
Pd(2)-Pd(1)-O(3)-C(19)	1.8(3)
C(20)-Pd(2)-O(4)-C(19)	-97.6(3)
N(2)-Pd(2)-O(4)-C(19)	-87.9(7)
O(2)-Pd(2)-O(4)-C(19)	81.1(2)
Pd(1)-Pd(2)-O(4)-C(19)	4.8(2)
C(3)-Pd(1)-N(1)-C(9)	13.0(2)
O(1)-Pd(1)-N(1)-C(9)	6.5(7)
O(3)-Pd(1)-N(1)-C(9)	-168.3(2)
Pd(2)-Pd(1)-N(1)-C(9)	-92.90(19)

C(3)-Pd(1)-N(1)-C(17)	-175.5(3)
O(1)-Pd(1)-N(1)-C(17)	178.1(5)
O(3)-Pd(1)-N(1)-C(17)	3.2(2)
Pd(2)-Pd(1)-N(1)-C(17)	78.6(2)
C(20)-Pd(2)-N(2)-C(26)	15.7(2)
O(4)-Pd(2)-N(2)-C(26)	5.9(8)
O(2)-Pd(2)-N(2)-C(26)	-162.9(2)
Pd(1)-Pd(2)-N(2)-C(26)	-86.4(2)
C(20)-Pd(2)-N(2)-C(34)	-175.5(3)
O(4)-Pd(2)-N(2)-C(34)	174.7(6)
O(2)-Pd(2)-N(2)-C(34)	5.9(3)
Pd(1)-Pd(2)-N(2)-C(34)	82.4(2)
Pd(2)-O(2)-C(2)-O(1)	5.0(5)
Pd(2)-O(2)-C(2)-C(1)	-171.9(3)
Pd(1)-O(1)-C(2)-O(2)	-8.6(5)
Pd(1)-O(1)-C(2)-C(1)	168.4(3)
O(1)-Pd(1)-C(3)-C(4)	-8.8(3)
N(1)-Pd(1)-C(3)-C(4)	172.2(3)
O(3)-Pd(1)-C(3)-C(4)	8.2(15)
Pd(2)-Pd(1)-C(3)-C(4)	-94.2(3)
O(1)-Pd(1)-C(3)-C(8)	169.5(2)
N(1)-Pd(1)-C(3)-C(8)	-9.5(2)
O(3)-Pd(1)-C(3)-C(8)	-173.5(12)
Pd(2)-Pd(1)-C(3)-C(8)	84.1(2)
C(8)-C(3)-C(4)-C(5)	0.2(5)
Pd(1)-C(3)-C(4)-C(5)	178.4(3)
C(3)-C(4)-C(5)-C(6)	-0.4(5)
C(4)-C(5)-C(6)-C(7)	-0.5(6)
C(5)-C(6)-C(7)-C(8)	1.5(6)
C(4)-C(3)-C(8)-C(7)	0.8(5)
Pd(1)-C(3)-C(8)-C(7)	-177.6(2)
C(4)-C(3)-C(8)-C(9)	-176.5(3)
Pd(1)-C(3)-C(8)-C(9)	5.1(3)
C(6)-C(7)-C(8)-C(3)	-1.6(5)
C(6)-C(7)-C(8)-C(9)	175.4(3)
C(17)-N(1)-C(9)-C(10)	-5.1(4)
Pd(1)-N(1)-C(9)-C(10)	167.1(2)
C(17)-N(1)-C(9)-C(8)	174.1(2)

Pd(1)-N(1)-C(9)-C(8)	-13.7(3)
C(3)-C(8)-C(9)-N(1)	6.1(4)
C(7)-C(8)-C(9)-N(1)	-171.1(3)
C(3)-C(8)-C(9)-C(10)	-174.7(3)
C(7)-C(8)-C(9)-C(10)	8.2(5)
N(1)-C(9)-C(10)-C(11)	1.2(5)
C(8)-C(9)-C(10)-C(11)	-177.9(3)
C(9)-C(10)-C(11)-C(12)	2.6(5)
C(10)-C(11)-C(12)-C(13)	176.3(4)
C(10)-C(11)-C(12)-C(17)	-2.4(5)
C(11)-C(12)-C(13)-C(14)	-175.0(4)
C(17)-C(12)-C(13)-C(14)	3.6(6)
C(12)-C(13)-C(14)-C(15)	0.0(7)
C(13)-C(14)-C(15)-C(16)	-3.6(7)
C(14)-C(15)-C(16)-C(17)	3.4(6)
C(9)-N(1)-C(17)-C(16)	-171.2(3)
Pd(1)-N(1)-C(17)-C(16)	17.8(4)
C(9)-N(1)-C(17)-C(12)	5.2(4)
Pd(1)-N(1)-C(17)-C(12)	-165.9(2)
C(15)-C(16)-C(17)-N(1)	176.8(3)
C(15)-C(16)-C(17)-C(12)	0.4(5)
C(11)-C(12)-C(17)-N(1)	-1.5(5)
C(13)-C(12)-C(17)-N(1)	179.8(3)
C(11)-C(12)-C(17)-C(16)	174.9(3)
C(13)-C(12)-C(17)-C(16)	-3.8(5)
Pd(1)-O(3)-C(19)-O(4)	1.6(5)
Pd(1)-O(3)-C(19)-C(18)	-176.3(3)
Pd(2)-O(4)-C(19)-O(3)	-5.3(5)
Pd(2)-O(4)-C(19)-C(18)	172.6(3)
O(4)-Pd(2)-C(20)-C(21)	-8.6(3)
N(2)-Pd(2)-C(20)-C(21)	172.8(3)
O(2)-Pd(2)-C(20)-C(21)	-35(2)
Pd(1)-Pd(2)-C(20)-C(21)	-96.1(3)
O(4)-Pd(2)-C(20)-C(25)	166.1(2)
N(2)-Pd(2)-C(20)-C(25)	-12.5(2)
O(2)-Pd(2)-C(20)-C(25)	139(2)
Pd(1)-Pd(2)-C(20)-C(25)	78.6(2)
C(25)-C(20)-C(21)-C(22)	0.1(6)

Pd(2)-C(20)-C(21)-C(22)	174.5(3)
C(20)-C(21)-C(22)-C(23)	-2.2(7)
C(21)-C(22)-C(23)-C(24)	2.8(7)
C(22)-C(23)-C(24)-C(25)	-1.4(6)
C(23)-C(24)-C(25)-C(20)	-0.7(6)
C(23)-C(24)-C(25)-C(26)	177.4(4)
C(21)-C(20)-C(25)-C(24)	1.4(5)
Pd(2)-C(20)-C(25)-C(24)	-173.7(3)
C(21)-C(20)-C(25)-C(26)	-176.9(3)
Pd(2)-C(20)-C(25)-C(26)	8.0(4)
C(34)-N(2)-C(26)-C(27)	-4.7(4)
Pd(2)-N(2)-C(26)-C(27)	165.1(2)
C(34)-N(2)-C(26)-C(25)	174.7(3)
Pd(2)-N(2)-C(26)-C(25)	-15.5(3)
C(24)-C(25)-C(26)-N(2)	-172.7(3)
C(20)-C(25)-C(26)-N(2)	5.4(4)
C(24)-C(25)-C(26)-C(27)	6.6(5)
C(20)-C(25)-C(26)-C(27)	-175.2(3)
N(2)-C(26)-C(27)-C(28)	-0.2(5)
C(25)-C(26)-C(27)-C(28)	-179.5(3)
C(26)-C(27)-C(28)-C(29)	4.0(6)
C(27)-C(28)-C(29)-C(34)	-2.9(6)
C(27)-C(28)-C(29)-C(30)	174.8(4)
C(28)-C(29)-C(30)-C(31)	-176.0(4)
C(34)-C(29)-C(30)-C(31)	1.6(6)
C(29)-C(30)-C(31)-C(32)	0.2(7)
C(30)-C(31)-C(32)-C(33)	0.1(8)
C(31)-C(32)-C(33)-C(34)	-2.3(7)
C(26)-N(2)-C(34)-C(33)	-170.2(3)
Pd(2)-N(2)-C(34)-C(33)	21.6(4)
C(26)-N(2)-C(34)-C(29)	5.8(4)
Pd(2)-N(2)-C(34)-C(29)	-162.4(2)
C(32)-C(33)-C(34)-N(2)	-179.8(4)
C(32)-C(33)-C(34)-C(29)	4.1(6)
C(28)-C(29)-C(34)-N(2)	-2.1(5)
C(30)-C(29)-C(34)-N(2)	-179.8(3)
C(28)-C(29)-C(34)-C(33)	174.0(3)
C(30)-C(29)-C(34)-C(33)	-3.8(5)

Symmetry transformations used to generate equivalent atoms:

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