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Development of New Catalytic Reactions for Efficient Syntheses of Two Versatile Building Blocks: Cyclic Imides and Biaryls

고리형 이미드와 바이아릴의 효율적인 합성을 위한 새로운 촉매 반응의 개발

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Abstract

Development of New Catalytic Reactions for Efficient Syntheses of Two Versatile Building Blocks: Cyclic Imides and Biaryls

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Chemical processes to afford complex molecules usually require laborious multi-step synthesis, accompanied by toxic waste generation. The development of efficient synthetic methods that can replace conventional procedures have gained increasing interest in organic chemistry. Catalytic reactions involving organometallic catalysts can provide an atom-economical and streamlined process. This thesis addresses the

development of novel catalytic reactions that enable the conversion from simple feedstock molecules to value-added chemicals.

Chapter 1 includes an introduction to amide synthesis via alcohol activation. Dehydrogenative amide synthesis using alcohols and amines as substrates offers an environmentally benign and efficient protocol, alternative to conventional amide synthesis. The principle of alcohol dehydrogenation can also be applied to the preparation of N-heterocycles. Chapter 2 describes synthesis of cyclic imides from alcohol and nitrile starting materials. The developed method provides an atom-economical and easily accessible method for forming cyclic imides from simple and versatile starting materials. Further mechanistic studies demonstrated that this reaction involves hydrogen transfer as a substrate-activating strategy to generate both reactive nucleophiles and electrophiles in the reaction mixture.

In Chapter 3, the direct C–H arylation of arenes is reviewed including the current state of the art as well as the background and basics of C–H activation chemistry. Direct arylation of arenes can provide an alternative approach to the syntheses of biaryls, which are conventionally produced by traditional cross-coupling reactions. Chapter 4 describes development of a Pd–diimine catalyst for direct C–H arylation of simple arenes without directing or activating groups. A diimine-assisted Pd catalyst exhibited the highest turnover number (TON) reported to date in the C–H arylation of benzene. It also showed superior efficiency with a small number of equivalents of arene substrates, whereas all previous examples required excess arenes. Mechanistic investigations including a kinetic study, identification of reaction intermediates, and stoichiometric reactions provided solid evidence of a cooperative bimetallic mechanism.

Keywords: amide, alcohol activation, cyclic imide, C–H activation, biaryl, cross-coupling, organometallic catalyst

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Chapter 1. Development and Application of Dehydrogenative Amide Bond Formation

1.1 Introduction

Amide bonds play a key role in biological systems as the chemical connections of proteins. They are also found in wide array of organic molecules, serving as a core building block in synthetic chemistry. However, most conventional synthetic methods for amide production suffer from low atom-economy and large amounts of waste. The pharmaceutical and green chemical community has indicated that the development of amide synthesis in an efficient manner, avoiding stoichiometric amount of coupling reagents, is a pressing challenge.[1]

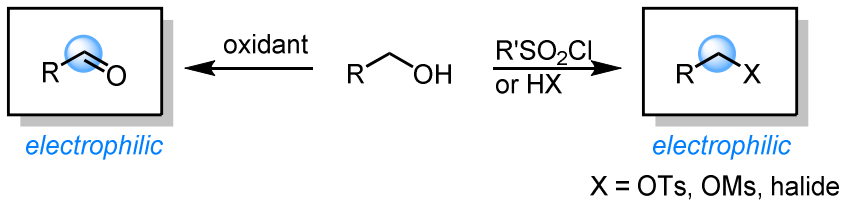
Recently, dehydrogenative transformations for amide synthesis from alcohols have been developed as alternative strategies. These methods involve transition metal catalysts, are highly atom economical, and environmentally benign, evolving hydrogen gas as the only by-product. For a decade, significant efforts have been dedicated to improving these catalytic systems and applying them to the syntheses of bioactive molecules. Including a brief introduction to the background of the field, this chapter mainly focuses on the progress and application of dehydrogenative amide formation over the last decade.

1.2 Amide synthesis via dehydrogenative alcohol activation

1.2.1 Dehydrogenative alcohol activation

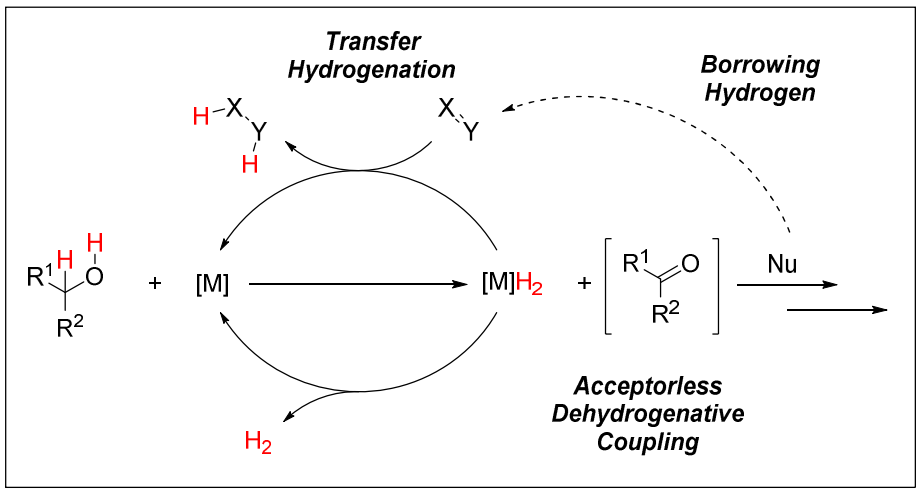
Recent decades have witnessed growing environmental concerns regarding industrial processes that generate a large amount of wastes. Green chemistry has attracted significant attention, and the development of atom-economical reactions minimizing pollution has become an important research topic. Replacing highly activated substrates with renewable resources is a promising strategy. In this context, alcohol is an ideal substrate for sustainable chemical processes. Alcohols are common starting materials in organic synthesis because they are stable and readily available from natural biomass or simple hydration of hydrocarbons.

The reactivity of alcohols can differ depending on reaction conditions. Under basic conditions, nucleophilic alkoxides can be afforded. On the other hand, utilizing alcohols as electrophiles is not a simple task because the hydroxide group is a poor leaving group. In traditional synthetic chemistry, alcohol is activated by changing the hydroxide group to sulfonate or halide to afford a better leaving group. Oxidation of the alcohol is another popular activation strategy. Using strong oxidants such as peroxides, iodates, or metal oxides, the alcohol can be transformed to an aldehyde, which reacts easily with a wide range of nucleophiles (Scheme 1.1). However, both activation strategies violate the principles of green chemistry. All reagents used in these processes directly generate a stoichiometric amount of waste, which are mostly toxic.



Scheme 1.1 Classical activation of alcohols

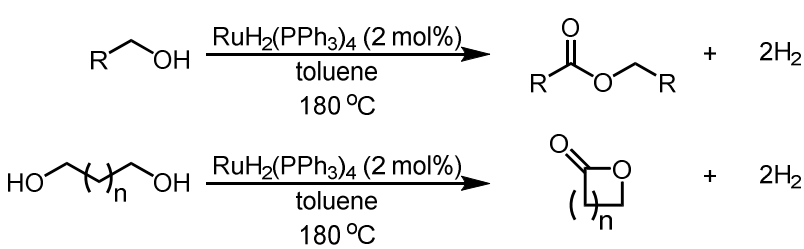
Transition metal catalyzed-alcohol dehydrogenation is an alternative approach to using alcohols as starting materials in an environmentally benign manner. It allows for more efficient chemical reactions devoid of additional activation steps (Scheme 1.2). In the presence of proper transition metal catalysts, alcohols can be transformed to their corresponding aldehydes or ketones, with concomitant removal of two hydrogen atoms. Subsequently, the carbonyl group of the intermediate species undergoes further transformation to form a new chemical bond with the nucleophile. The hydrogen removed from the alcohol can participate in the reaction to further hydrogenate other hydrogen acceptors. This process is called "*transfer hydrogenation*", and when the functionalized intermediate is hydrogenated, it is termed "*borrowing hydrogen*" or "*hydrogen autotransfer*".[2] Alternatively, molecular hydrogen gas can be liberated as an eco-friendly byproduct or alternative energy source, and this reaction type is termed "*acceptorless dehydrogenative coupling*".[3]



Scheme 1.2 Dehydrogenative alcohol activation

While the reaction can be varied depending on the terminal acceptor of hydrogen, the *dehydrogenative alcohol activation strategy* is a novel platform for an atom-economical substrate activation strategy, and has been widely studied in both the reaction development field and the renewable energy research field. The first example of alcohol dehydrogenation using a homogeneous transition metal catalyst was reported by Charman in 1996.[4] Under strongly acidic conditions with HCl, rhodium chloride catalyzed the dehydrogenation of isopropanol affording acetone and hydrogen gas. Although this early example required excess strong acid, the research has been followed by improved catalytic systems.

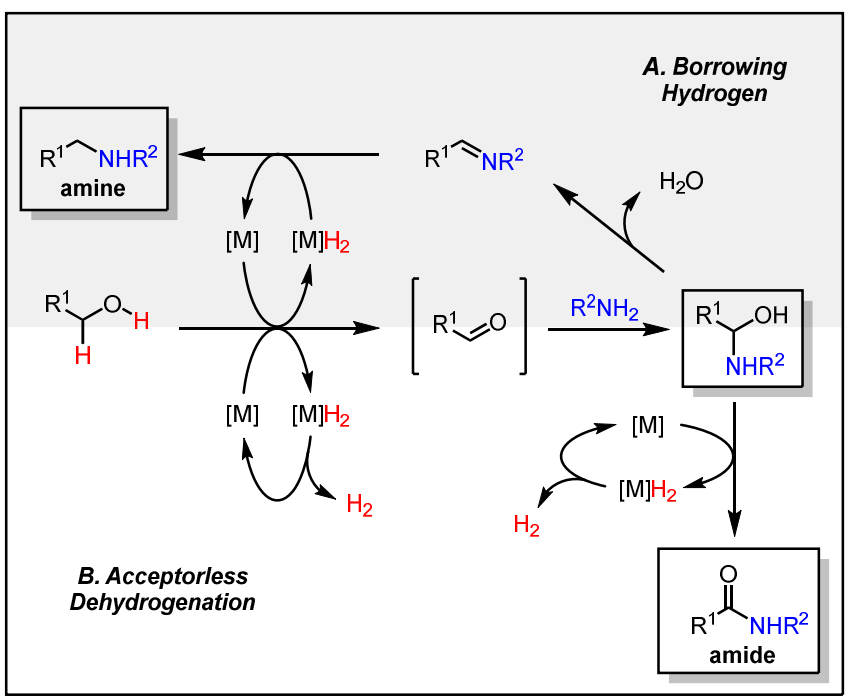
In 1981, Murahashi and co-workers reported the formation of esters from various alcohols using $RuH_2(PPh_3)_4$ as a catalyst under neutral conditions (Scheme 1.3). Aromatic or aliphatic primary alcohols afforded the corresponding esters at 180 °C. Diols were also subjected to the same catalytic conditions and converted to the corresponding lactones. This is the first example of the acceptorless alcohol dehydrogenative coupling reaction. Since then, the principle of the acceptorless alcohol dehydrogenation (AAD) has been widely applied to the reactions with various nucleophiles and new catalytic systems.



Scheme 1.3 Synthesis of esters and lactones from primary alcohols and diols respectively

1.2.2 Synthesis of amides from alcohols and amines

The introduction of an amine as a nucleophile to the alcohol dehydrogenation reaction leads to the formation of a C–N bond. Interestingly, the reaction between an amine and alcohol can follow two divergent pathways to afford different products (Scheme 1.4). After the dehydrogenation of the alcohol to afford the corresponding aldehyde, the amine attacks the aldehyde to produce a hemiaminal intermediate. Dehydration of the intermediate generates the corresponding imine, and subsequent hydrogenation affords an N-alkylation product, as depicted in borrowing hydrogen methodology. This reaction provides an amine as a final product with one equivalent water as a byproduct (Scheme 1.4 A). It is an overall redox neutral process because no net hydrogen evolution occurs.

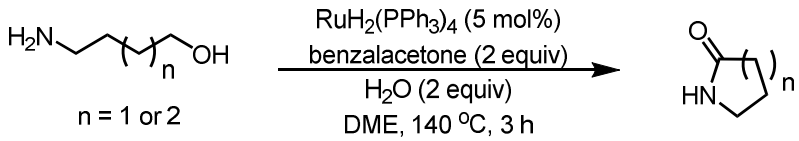


Scheme 1.4 Reactions of amines and alcohols via alcohol dehydrogenation

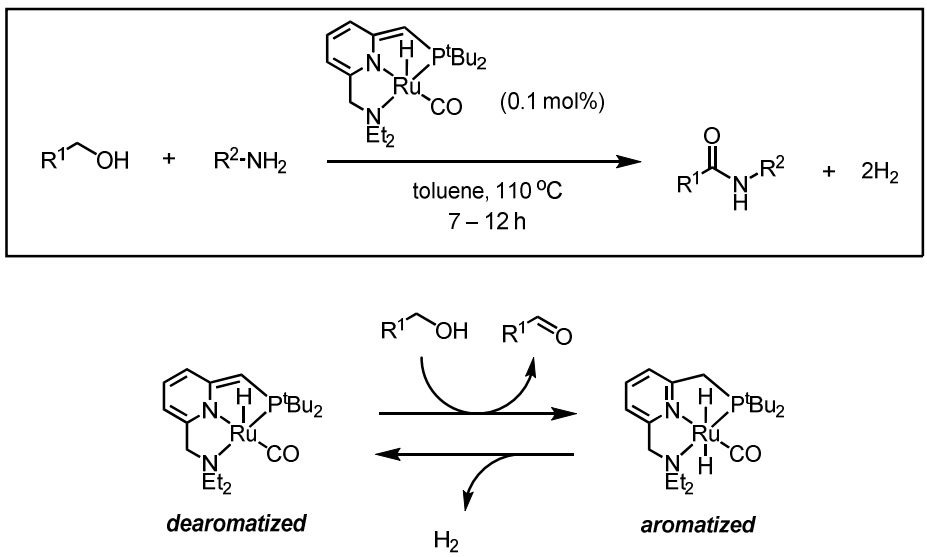
On the other hand, the hemiaminal intermediate can undergo dehydrogenation instead of dehydration. The final oxidation step affords the corresponding amide with concomitant evolution of two equivalents of hydrogen gas. This is an acceptorless dehydrogenative coupling (Scheme 1.4 B), and the liberation of hydrogen gas makes the process net oxidative.

The product identity is determined by the fate of the common hemiaminal intermediate, and the following step can be either dehydration/hydrogenation or dehydrogenation. Both processes have been extensively investigated with the development of various catalytic systems. Ruthenium, iridium, and rhodium-based catalysts, with activities for alcohol dehydrogenation, have been commonly applied to this system. However, it is a complicated question as to what factors of the catalytic system determine selectivity toward N-alkylation or amidation. Recent reports suggest that it is dependent on the solvent polarity, base, nature of the catalyst, and ligand type.[5] In this Chapter, emphasis will be placed on the amide synthesis. The significance of the alcohol dehydrogenative amide synthesis is that it is a promising alternative green method for avoiding the waste generated by conventional amide synthesis.

The first example of amide synthesis using alcohol dehydrogenative activation was reported by Murahashi and Naota in 1991 (Scheme 1.5).[6] Direct amide bond formation was achieved between the alcohol and amine group of 1,4- and 1,5-amino alcohols in an intramolecular manner. Using $RuH_2(PPh_3)_4$ as a catalyst, 5 or 6 membered lactams were synthesized in good yields. To avoid the formation of cyclic amines through dehydration and hydrogenation pathway, addition of water and hydrogen acceptor benzalacetone was essential.



Scheme 1.5 Synthesis of lactams from amino alcohols



Scheme 1.6 Amide synthesis catalyzed by PNN-Ru pincer complex

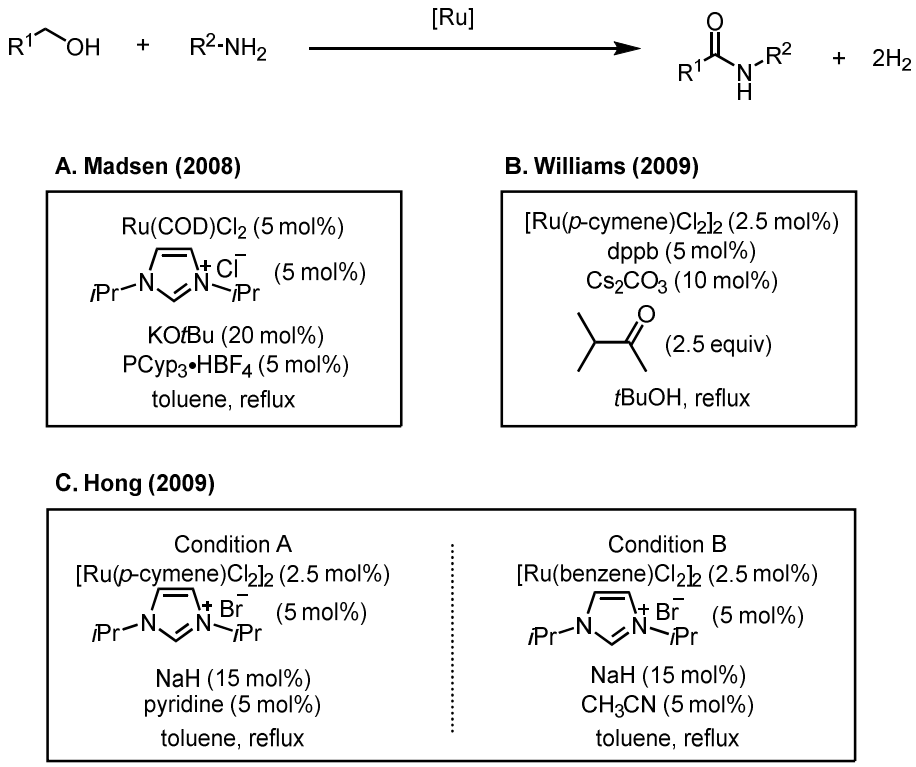
In 2007, the Milstein group reported a pioneering work of direct amidation between alcohols and amines in an intermolecular fashion (Scheme 1.6).[7] A PNN-Ru pincer type complex was used as a catalyst, and the reaction did not require either basic or acidic promoters, in the absence of the hydrogen acceptor. This exceptionally simple and clean process presents a highly atom-economical amide synthesis with hydrogen gas as the only byproduct. Transformation of the pincer ligand via aromatization and dearomatization plays a crucial role in the dehydrogenation and hydrogen evolution process. Addition of an alcohol to the dearomatized precatalyst initiates hydrogen abstraction, and the corresponding

aldehyde is afforded with the generation of a ruthenium dihydride species bearing an aromatized ligand. Subsequent elimination of molecular hydrogen regenerates the precatalyst, completing the catalytic cycle. The reaction proceeded efficiently with aliphatic primary amines and moderately with anilines. However, the catalytic system was unreactive towards secondary amines.

Since the groundbreaking research by the Milstein group, the synthesis of amides from alcohols and amines has been widely investigated. Although the Milstein catalyst enabled an excellent chemical process for amide formation, its synthesis and handling is strenuous. Therefore, developing alternative catalytic systems using commercially available ruthenium precursors and ligands has been an important research goal, although the Milstein catalyst is now commercialized. Several *in situ* catalytic systems were developed in 2008 and 2009 and are shown in Scheme 1.7.

Madsen and co-workers developed a new catalytic system using the combination of an N-heterocyclic carbene (NHC) and a phosphine as the ligand (Scheme 1.7 A).[8] The reaction afforded the corresponding amides efficiently from various alcohols and primary amines. The Williams group also reported the amide synthesis with a ruthenium-based catalyst (Scheme 1.7 B).[9] The catalytic system included a Ru(II) dimer, dppb ligand, and substoichiometric amount of base. To promote the reaction, addition of ketone compound such as 3-methyl-2-butanone was required as a hydrogen acceptor. Both catalytic systems developed by Madsen and Williams used a phosphine ligand, but it is not an ideal reagent in organic synthesis because of its toxicity and low thermal- and air-stability. In this context,

the phosphine-free catalytic system was developed by Hong and co-workers (Scheme 1.7 C).[10] Dimeric ruthenium precursors in combination with a NHC ligand, NaH base, and pyridine or acetonitrile efficiently promoted the amide formation from various alcohols and amines including less hindered secondary amines.

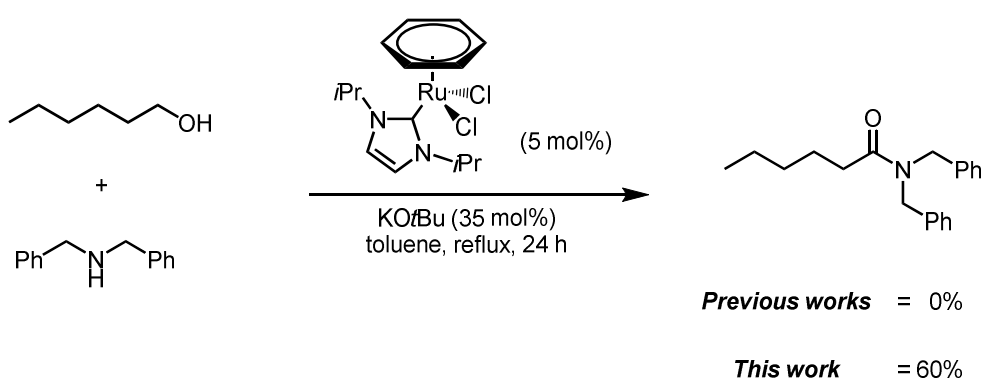


Scheme 1.7 Ruthenium based *in situ* catalytic systems

On the basis of the high reactivity of the catalytic systems with NHC ligands, further modification and improvement was continued by the groups of Hong[11] and Madsen[12] in 2010. They investigated both *in situ* generated and well-defined NHC–Ru catalysts. Although improvement of the catalytic systems was pursued in terms of efficiency and operational simplicity, there still were some limitations on reactivity.

One of the challenges in the alcohol dehydrogenative amide synthesis was the limited reactivity for the hindered secondary amines. In 2011, Hong and co-workers reported the direct amidation of alcohols with challenging secondary amines (Scheme 1.8).[13] The catalytic system with a well-defined NHC-based ruthenium complex afforded tertiary amides from secondary amines in high yields. In particular, dibenzylamine that resulted in no amide formation with the previously developed systems afforded the corresponding tertiary amide in 60% yield.

Recently, further modification of the catalytic system was conducted by the same group. Most of the NHC-based ruthenium catalytic systems for amide synthesis required strong base to promote the reaction. Hong and co-workers achieved the base-free conditions for amide formation by developing a well-defined NHC–Ru dihydride complex.[14] The reactions of various alcohols and amines proceeded well without any additional promoters.



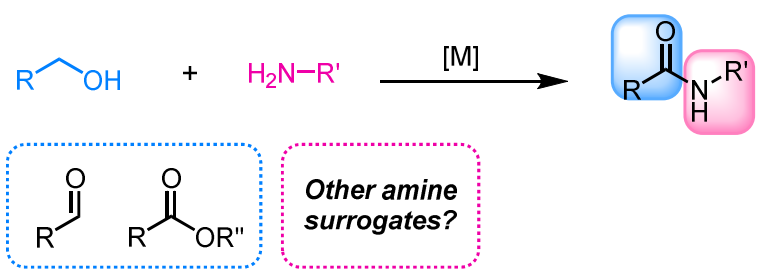
Scheme 1.8 Direct amidation of an alcohol with dibenzylamine

Since the first report on the amide synthesis from alcohols and amines by the Milstein group, the ruthenium-based catalytic systems have been most extensively investigated. However, other transition metal complexes also have good reactivity to the alcohol dehydrogenative amide formation. Grützmacher and co-workers developed a Rh-based catalytic system for amide synthesis with an *in situ* generated Rh(I)–diolefin amido complex as the catalyst and methylmethacrylate as a hydrogen acceptor.[15] Notably, the reaction can proceed under very mild conditions at room temperature. Besides, this catalytic system afforded the direct synthesis of primary amides from ammonia and alcohols as well as secondary amides from primary amines.

Recently, there have been some efforts to replace precious metal catalysts with base metal catalysts for dehydrogenative amide synthesis. In 2015, the Beller group developed the synthesis of lactams catalyzed by an iron pincer complex in an intramolecular manner.[16] The reaction employed amino alcohols as substrates, affording the corresponding lactams. On the other hand, the Mn-catalyzed amidation was also developed by Milstein and co-workers. The catalytic system with a PNN manganese pincer complex afforded the secondary amides in excellent yields from the primary alcohols and amines.

1.2.3 Synthesis of amides from alcohols and amine surrogates

Dehydrogenative amide synthesis has become firmly established as a promising research field for environmentally benign chemical processes. However, most of the research has focused on improving efficiency or operational convenience of the catalytic systems. Construction of amide linkages by dehydrogenative alcohol activation can be understood as a coupling of a carbonyl part and amino part derived from an alcohol and amine respectively (Scheme 1.9). Although there have been some reports regarding amide synthesis using aldehydes or esters instead of alcohols, studies on the replacement of amines with other nitrogen sources are scarce.[17] Recent progress on the substitution of amines with other N-containing reagents has enhanced the usability of dehydrogenative amide synthesis, overcoming disadvantages arising from the physical properties of amines.

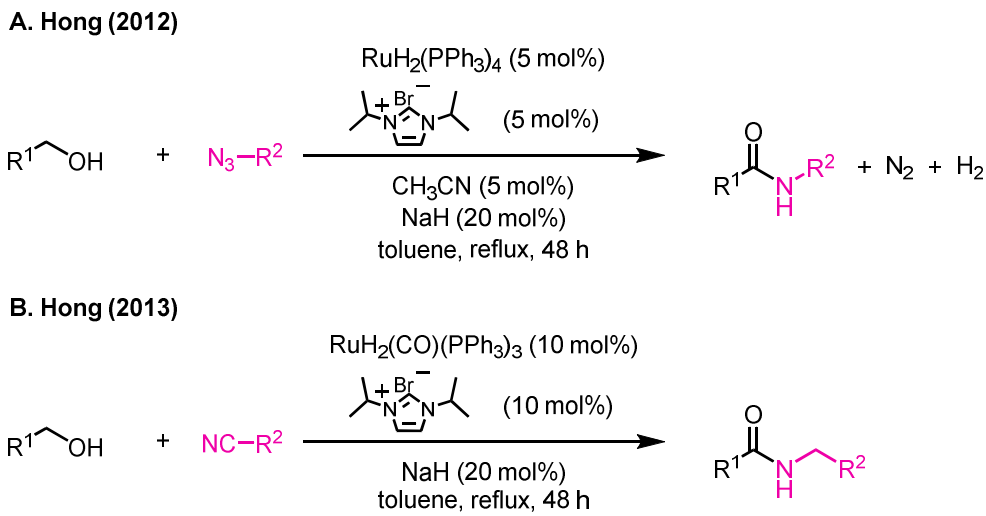


Scheme 1.9 Synthesis of an amide from alcohol and amine surrogates

In 2012, Hong and co-workers accomplished dehydrogenative amide synthesis from alcohols using organoazides as a nitrogen source (Scheme 1.10A).[18] The reaction employed the catalytic system consisting of $RuH_2(PPh_3)_4$ as a precatalyst, NHC ligand, and NaH. The *in situ* generated Ru–NHC active catalyst mediated the

hydrogen transfer from alcohols to azides to generate the corresponding aldehydes and amines along with concomitant evolution of nitrogen gas. Further C–N bond formation and dehydrogenation afforded the corresponding amides with N_2 and H_2 as a byproduct.

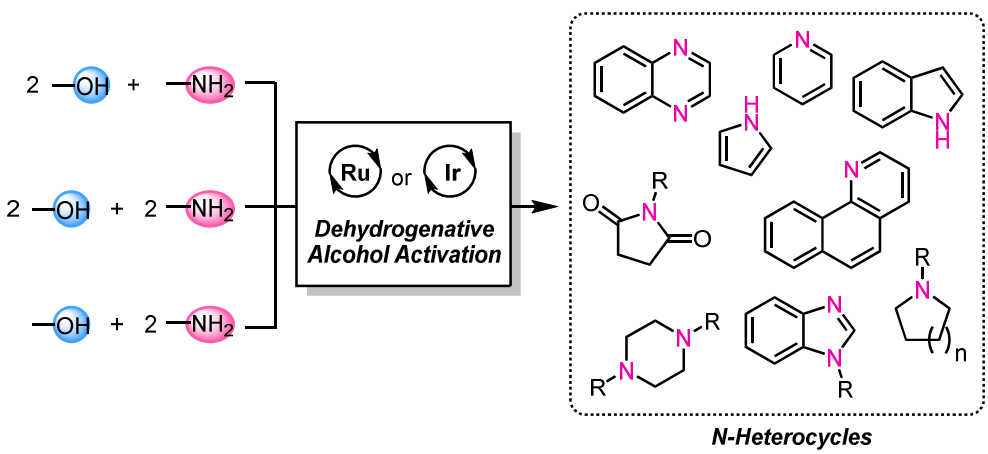
The replacement of amines with other N-sources has expanded to the utilization of nitriles. Hong and co-workers developed the first example of the direct amide synthesis from alcohols and nitriles as an N-source (Scheme 1.10B).[19] The *in situ* generated NHC–Ru dihydride catalyst achieved the redox-neutral amide synthesis involving hydrogen transfer from alcohols to nitriles. This reaction is a completely atom-economical process, which is not accompanied by any byproduct.



Scheme 1.10 Synthesis of amides using azides or nitriles as amine surrogates

1.3 Intermolecular cyclization of amines and alcohols via dehydrogenative alcohol activation

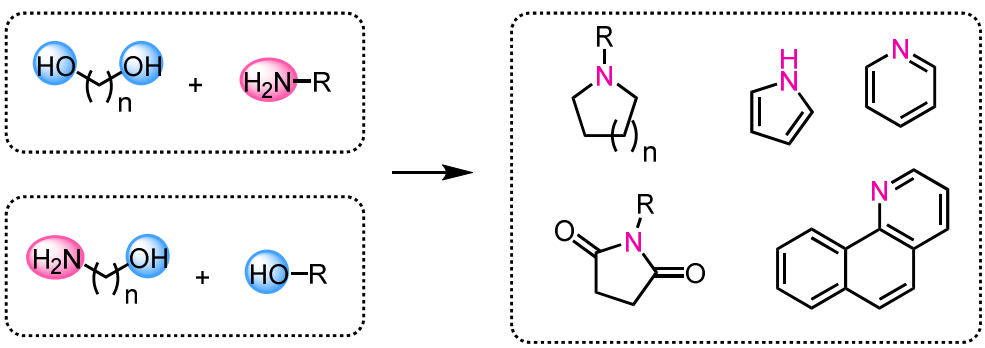
It has been demonstrated that the dehydrogenative alcohol activation strategy provides a powerful tool to develop environmentally benign and atom-economical synthetic methods for C–N bond formation. This reactivity has improved the accessibility to important structural motifs and led to new approaches for the construction of heterocyclic compounds.[20] While the reaction of one alcohol and one amine affords a single amide bond, intermolecular reactions of starting materials with multiple amine and alcohol groups can provide N-heterocycles. Although amino alcohols can afford lactams from intramolecular reactions as in previous reports[6], this section will focus primarily on intermolecular cyclization.



Scheme 1.11 Synthesis of heterocycles from starting materials with multiple amine and alcohol groups

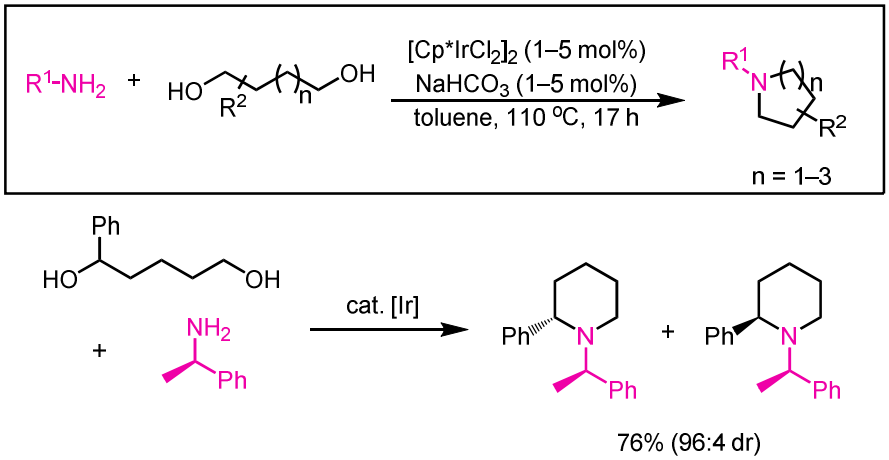
As shown in Scheme 1.11, the catalytic reactions reported to date utilize mainly Ru- or Ir-based catalytic systems to build the N-heterocycle.[20] The synthetic methods can be categorized according to the number of alcohol or amine groups that participate in the reaction to afford a single molecule of the desired product; (a) two alcohols and one amine; (b) two alcohols and two amines; and (c) one alcohol and two amines. A variety of substrates involving the corresponding functional groups have been used to synthesize either saturated or unsaturated N-heterocycles with various ring sizes.

■ **(a) two alcohols and one amine:**



Scheme 1.12 Synthesis of N-heterocycles from two alcohols and one amine

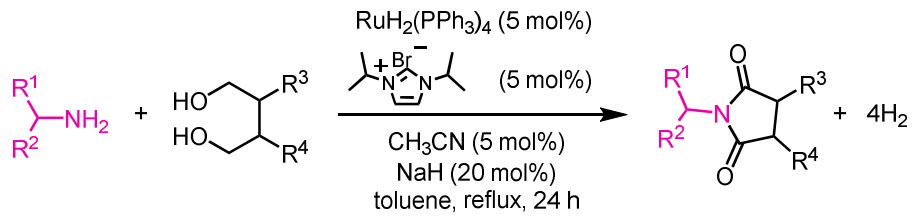
The most frequently used strategy is the reaction of two alcohols and one amine (Scheme 1.12). The substrates can include a combination of a diol and amine or an alcohol and amino alcohol. The earliest example is the synthesis of a pyrrolidine from 1,4-butanediol and benzylamine over a Rh-based catalyst, which was reported by Grigg and co-workers in 1981.[21]



Scheme 1.13 Ir-catalyzed synthesis of cyclic amines from diols and amines

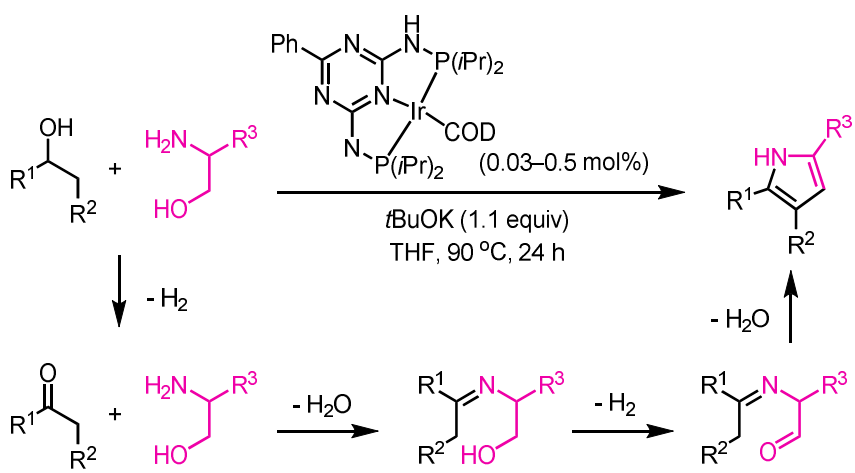
Since the first pyrrolidine synthesis, this reaction class has been expanded to provide general cyclic amines with larger ring sizes.[22] A representative example is the report by the Fujita and Yamaguchi group using an Ir-based catalyst (Scheme 1.13).[22a] The catalytic system afforded various five-, six-, and even seven-membered cyclic amines in good to excellent yield via the borrowing hydrogen methodology. Remarkably, the reaction between a chiral amine and racemic diol exhibited excellent diastereoselectivity.

From the same substrates, amines and diols, the formation of amide bonds can afford cyclic imides, as opposed to cyclic amines by N-alkylation. In 2010, Hong and co-workers reported the application of an *in situ* generated Ru-NHC-based catalytic system for the direct synthesis of cyclic imides (Scheme 1.14).[23] This was the first example of an atom economical and environmentally benign method for cyclic imide synthesis.



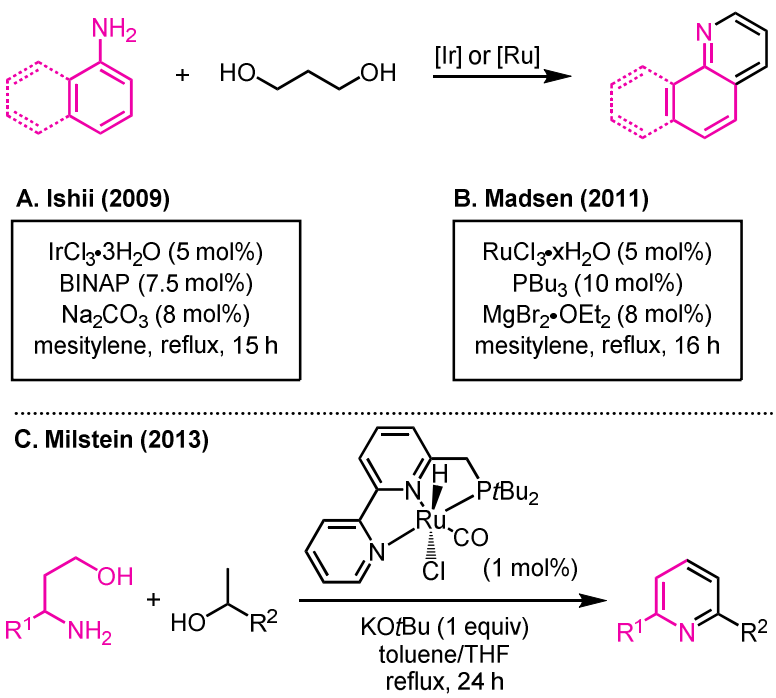
Scheme 1.14 Synthesis of cyclic imides from amines and diols

The similar strategy can provide the efficient accesses to aromatic N-heterocycles such as pyrroles[24], quinolines[25], and pyridines[26]. The Williams group presented the conversion of 1,4-alkynediols into pyrroles in 2007.[24a] The catalytic system employing the combination of $RuH_2(CO)(PPh_3)_3$ and Xantphos produced pyrroles in good yields, albeit formation of furans as a byproduct. Other approaches to pyrroles are also possible from different substrates. In 2013, the sustainable pyrrole synthesis from secondary alcohols and 1,2-amino alcohols was developed by Kempe and co-workers (Scheme 1.15).[24b] In the presence of a PNP pincer type Ir complex and a stoichiometric amount of base, consecutive dehydration and dehydrative condensation afforded di- or tri-substituted pyrroles in good yields.



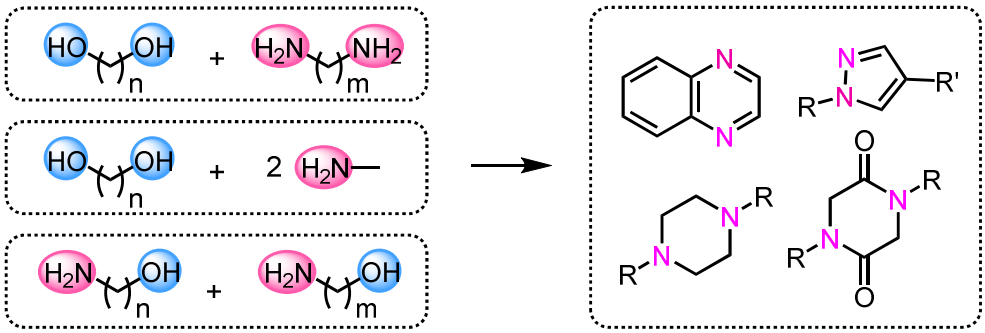
Scheme 1.15 Synthesis of pyrroles from secondary alcohols and 1,2-amino alcohols

Preparation of a quinoline and a pyridine can be conducted in the similar way. The reaction of aromatic amines and 1,3-diols efficiently provided quinoline derivatives through successive N-alkylation and intramolecular cyclization. The catalytic systems of either Ir complex by the Ishii group[25a] or Ru complex by the Madsen group[25b] mediated this process (Scheme 1.16 A and B). Analogous to the pyrrole synthesis by the Kempe group[24b], 1,3-amino alcohols in combination with secondary alcohols can offer pyridines. The Milstein group reported synthesis of pyridines using a pincer type Ru complex as a catalyst in 2013 (Scheme 1.16 C).[26] The catalytic system also can afford quinolines by using 2-aminobenzyl alcohols as substrates.



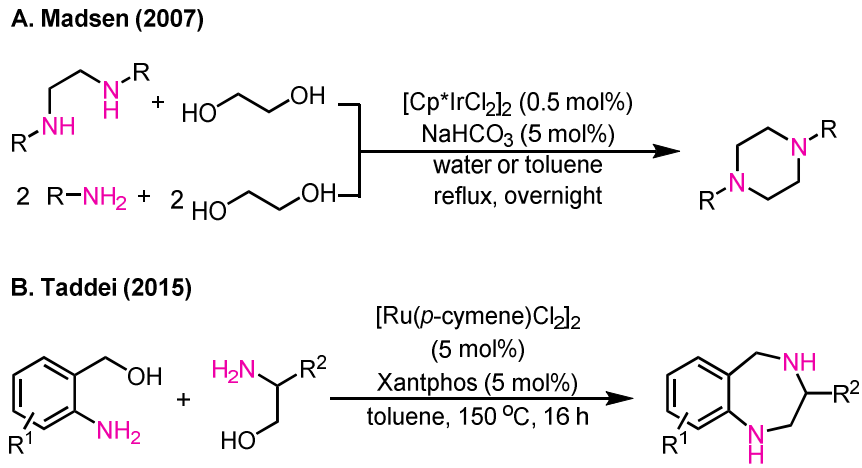
Scheme 1.16 Synthesis of quinolines and pyridines

■ **(b) two alcohols and two amines:**



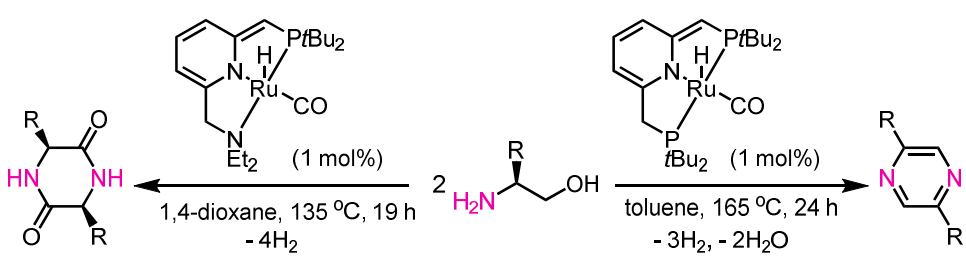
Scheme 1.17 Synthesis of N-heterocycles from two alcohols and two amines

Introduction of two amines to the dehydrogenative reaction of two alcohols can incorporate two nitrogen atoms into a heterocyclic molecule (Scheme 1.17).[27] In 2007, the Madsen group reported the synthesis of piperazines from 1,2-diamines and 1,2-diols via successive Ir-catalyzed N-alkylation (Scheme 1.18A).[28] The catalytic system was also applicable to the reaction of primary amines and two equivalents of diols. Fujita and co-workers presented another approach to piperazine synthesis, where the almost identical Ir-based catalytic system mediated dimerization of 1,2-amino alcohols to furnish piperazines.[29] Notably, the Taddei group demonstrated that the annulation of two different amino alcohols, 1,3- and 1,2-amino alcohols, could provide 7-membered ring products (Scheme 1.18B).[30] Starting from 2-amino benzyl alcohols and 1,2-amino alcohols, the domino process of N-alkylation by the Ru-based catalytic system afforded benzodiazepines.



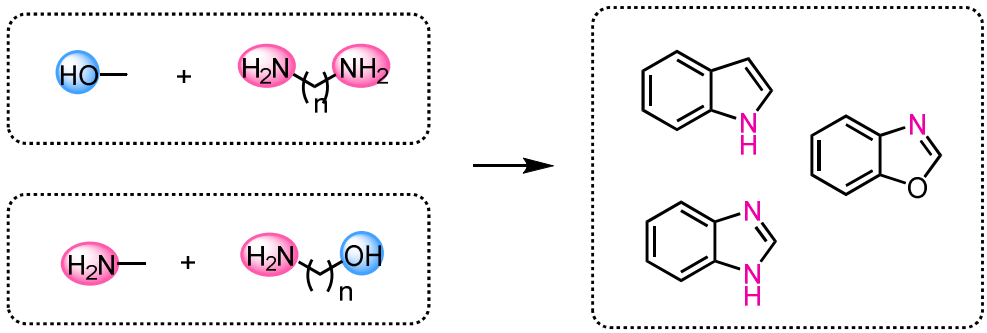
Scheme 1.18 Synthesis of piperazines and benzodiazepines

If the reaction conditions for dehydrogenative amide bond formation is applied to dimerization of 1,2-amino alcohols, the cyclic dipeptides can be generated instead of piperazines (Scheme 1.19, *left*).[31] The PNN Ru pincer complex developed by the Milstein group accomplished this process. Remarkably, change of the catalytic system to the PNP-Ru-based system led to the entirely different reaction pathway furnishing pyrazines as products from the same substrates (Scheme 1.19, *right*). Extrusion of water was facilitated by the high temperature and the catalyst with more rigid ligand structure.



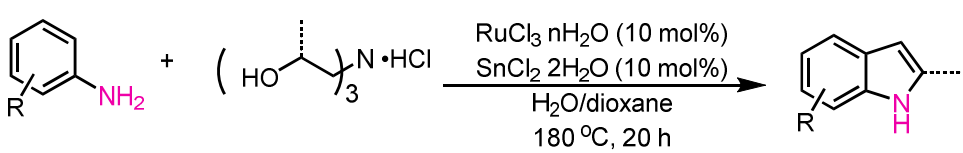
Scheme 1.19 Catalyst controlled synthesis of cyclic dipeptides and pyrazines

■ **(c) one alcohol and two amines:**



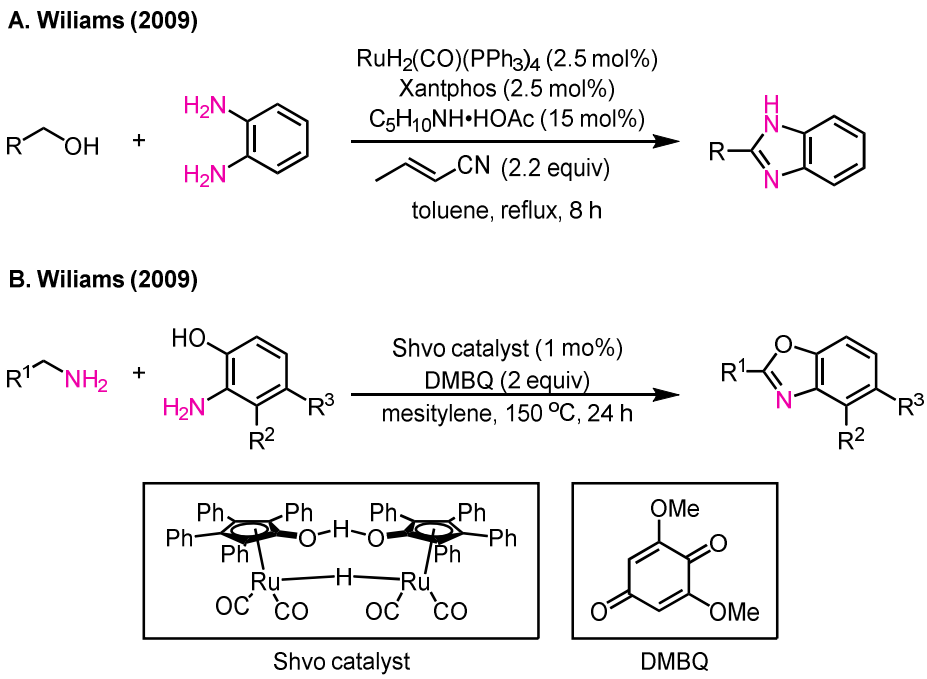
Scheme 1.20 Synthesis of N-heterocycles from one alcohol and two amines

The cyclization of one alcohol and two amines can result in construction of some other class of N-heterocycles (Scheme 1.20). Shim and co-workers reported an early example of Ru-catalyzed indole synthesis in which anilines and alkanolammonium chlorides were coupled via formation of C–N and C–C bonds (Scheme 1.21).[27a] The reaction of triisopropanolammnium chloride afforded 2-methylindole with exclusive regioselectivity. However, introduction of a substituent on C-3 position was unachievable by using α-substituted alkanolammonium chlorides.



Scheme 1.21 Synthesis of indoles from anilines and alkanolammonium chlorides

In 2009, the Williams group reported the conversion of alcohols and ortho-phenylenediamines into benzimidazoles (Scheme 1.22A).[32] The reaction was conducted by using a ruthenium dihydride complex in combination with Xantphos ligand and crotonitrile as a hydrogen acceptor. Addition of piperidinium acetate promoted the efficiency of the reaction significantly, which was attributed to the temporary formation of iminium ion from the intermediate aldehyde. Following that, the same group also reported the synthesis of benzoxazoles in the similar manner (Scheme 1.22B).[33] The catalytic system employing Shvo catalyst and DMBQ as a hydrogen acceptor was active for the direct condensation of amines and 2-aminophenols to furnish benzoxazoles.



Scheme 1.22 Synthesis of benzimidazoles and benzoxazoles

1.4 Conclusion

This Chapter provides a review on the development of amide synthesis via the alcohol dehydrogenation strategy, including current cutting edge research as well as its origins and background. Compared to conventional amide synthesis, dehydrogenative amide synthesis offers a highly atom-economical and environmentally benign protocol, accompanied by hydrogen gas production as a green byproduct. The mainstream research in this field has been focused on the development and modification of catalytic systems to mainly improve the efficiency and availability of Ru-based systems. Recent progress has also been made in the development of base-metal catalysts. Another important research topic is the expansion of the scope of the nitrogen coupling partner beyond amines. Recent notable achievements include the utilization of azides and nitriles as amine surrogates for amide synthesis. On the other hand, the established strategy of amide synthesis has also been widely applied for the construction of N-heterocycles. Intermolecular cyclization via dehydrogenative C–N bond formation of alcohols has been extensively investigated.

Despite remarkable progress in this field, several problems remain unaddressed. Current catalytic systems usually require high temperatures, above 100 °C, and high catalyst loading. Unsaturated bonds in substrates are frequently not tolerated, resulting in reductions. Asymmetric catalysis or the utilization of amine surrogates in heterocycle synthesis is another less explored area. Further research in this field is required to overcome current limitations and will increase the value of dehydrogenative amide synthesis.

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Chapter 2. Synthesis of Cyclic Imides from Nitriles and Diols Using Hydrogen Transfer as a Substrate-Activating Strategy *

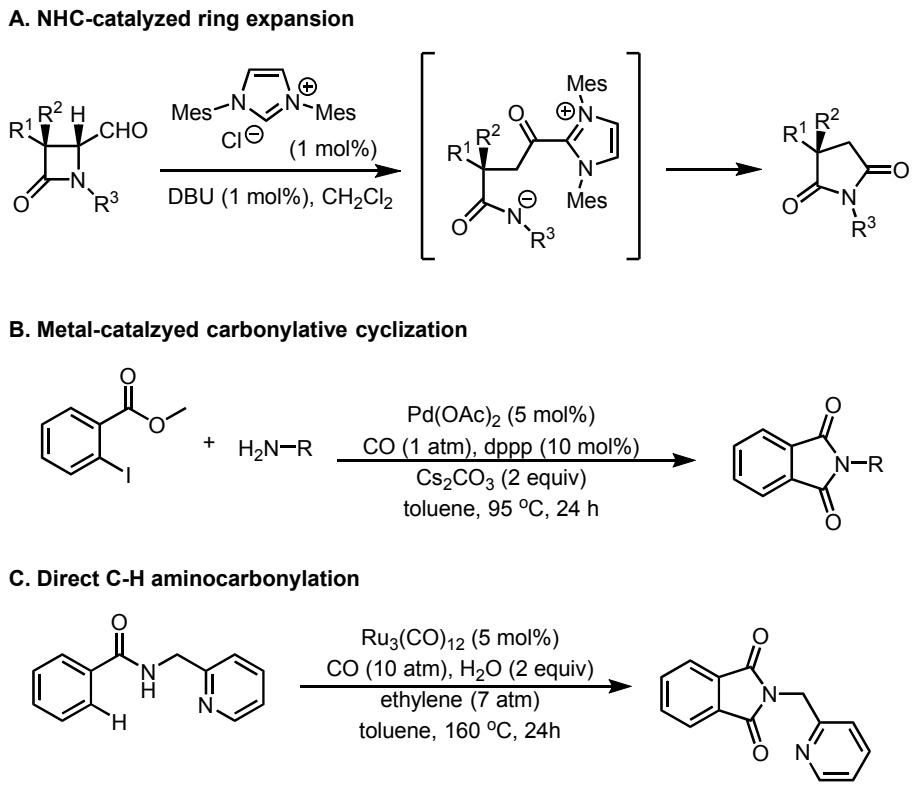
2.1 Introduction

Cyclic imide is a key functional group in synthetic, biological, medicinal, and polymer chemistry.[1] In particular, the cyclic imide group is found in several drugs such as thalidomide, [2] phensuximide,[3] buspirone,[4] and lurasidone,[5] and several derivatives have been recently evaluated as attractive new drug candidates with high bioactivities.[6] Despite their utility, the conventional methods for the preparation of cyclic imides have many limitations such as harsh thermal reaction conditions and harmful waste generation from the activating reagents used.[1,7]

Recently, some newer methods involving transition metal catalysis or skeleton rearrangement have been developed to overcome poor atom-economy and low efficiency. One approach is the ring expansion of 4-formyl-β-lactams to afford succinimide derivatives, which involves the Breslow intermediate during the catalysis by N-heterocyclic carbene (NHC) (Scheme 2.1 A).[8] This reaction also provided the enantioselective synthesis via kinetic resolution.[9] Another approach to synthesize cyclic imide is the Pd-catalyzed carbonylative cyclization (Scheme 2.1 B).[10] The reaction of *o*-halobenzoate with a variety of amines afforded phthalimides

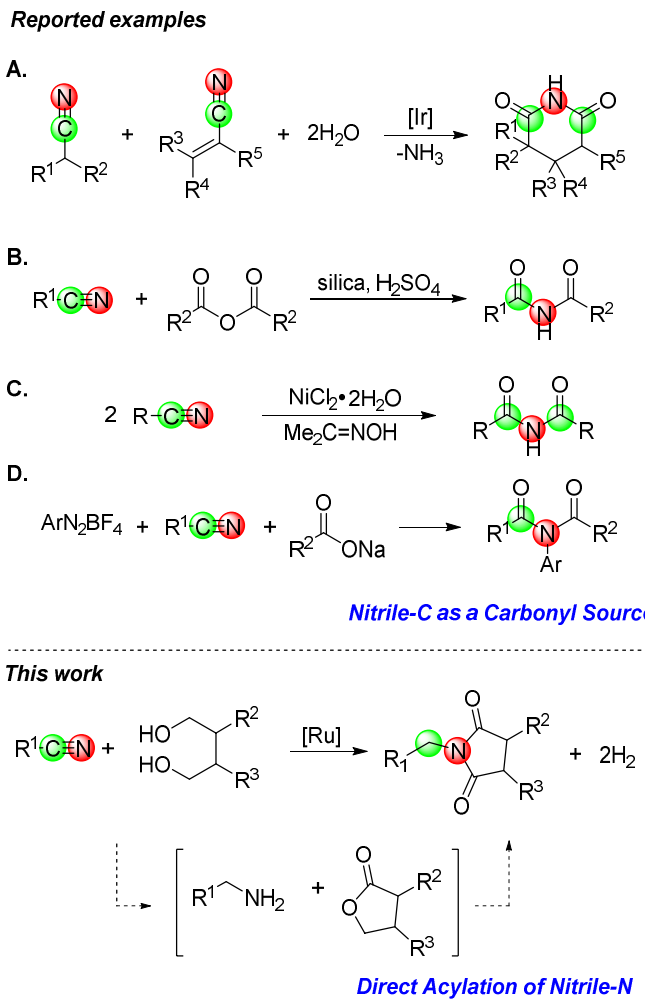
* The majority of this work has been published: Jaewoon Kim and Soon Hyeok Hong*, *Org.Lett*. **2014**, *16*, 4404-4407.

in good yield under a CO atmosphere. In a similar way, the carbonylative cyclization via C–H activation was reported (Scheme 2.1 C).[11] The amide with the pyridine directing group was subjected to Ru-catalyzed direct C–H aminocarbonylation conditions, which afforded phthalimides. Although these reactions have provided new approaches to cyclic imide synthesis, limited access to starting materials has restricted the utility of these methods.[8-12] To address the challenge, our group previously reported an efficient synthetic strategy for cyclic imides from diols and amines.[13]



Scheme 2.1 Recently developed reactions for cyclic imide synthesis

Nitrile is a useful and versatile functional group to incorporate a nitrogen atom into a chemical skeleton. Several studies have focused on the synthesis of imides from nitriles. Murahashi and co-workers developed a three-component reaction involving nitriles, vinylnitriles, and water to afford the corresponding glutarimides, using the carbons of the nitriles as the carbonyl source by the hydration of the nitrile groups (Scheme 2.2 A).[12a] In other examples, the imide moiety is generated by the addition of a nitrile to an electrophilic carbonyl carbon followed by the hydration of the nitrile (Scheme 2.2 B–D).[14]



Scheme 2.2 Synthesis of imides from nitriles

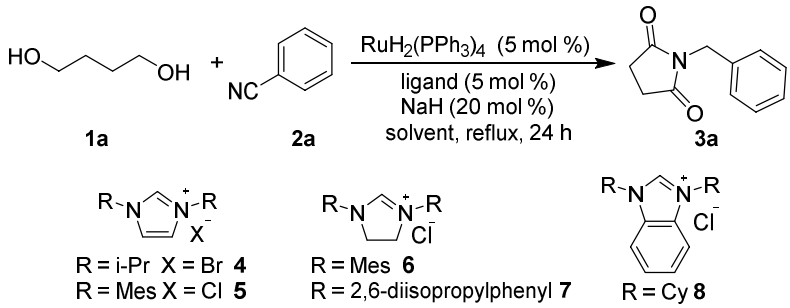
Inspired by our recently developed catalytic amide synthesis from nitriles and alcohols,[15] we developed a novel atom-economical and catalytic synthetic method for cyclic imides from versatile nitriles and alcohols (Scheme 2.2). This is a distinct method for imide synthesis directly from nitriles, compared to the other methods using nitrile carbon as the carbonyl source (Scheme 2.2 A–D). Initially, we hypothesized that first a direct amide bond formation would occur between one of the alcohol groups of diol and nitrile in the same manner as described in the previous study.[15] However, we observed that the nitrile was fully reduced to an amine using the hydrogen atoms of the diol along with the generation of a lactone (Scheme 2.2). Notably, this reaction adopts redox-neutral hydrogen transfer as the substrate-activating strategy to generate both the reactive nucleophile and electrophile in the reaction mixture.

2.2 Results and discussion

2.2.1 Optimization for imide synthesis from alcohol and nitrile

The reaction of 1,4-butanediol (**1a**) with benzonitrile (**2a**) was selected as the model system to optimize the reaction conditions (Table 2.1). $RuH_2(PPh_3)_4$ was selected as the precatalyst for the reaction after screening various ruthenium complexes and their analogs known as the catalysts for dehydrogenative amide synthesis (See Table 2.3 for details). When the reaction was performed in a closed system, the yield of the product decreased (entry 2). Because the reaction generates hydrogen gas, liberating hydrogen in an open system facilitated the reaction. The reaction proceeded better with lower concentrations (entries 3–5 and 10–11). Among the N-heterocyclic carbene (NHC) precursors investigated, **4** resulted in the highest yield (entries 6–9). Among the various solvents investigated, benzene produced the highest yield (77%) under reflux conditions (entries 10–15).

Table 2.1 Optimization of reaction conditions[a]



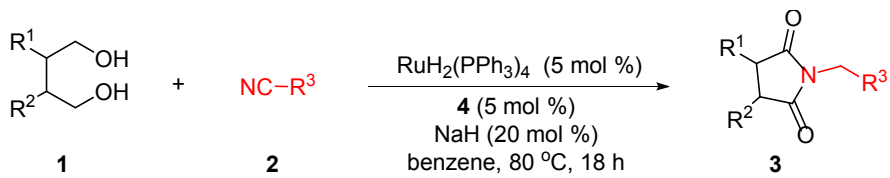
entry	ligand	solvent	concn (M)	yield (%)[b]
1	**4**	toluene	0.8	61
2[c]	**4**	toluene	0.8	48
3	**4**	toluene	0.4	66
4	**4**	toluene	1.3	63
5	**4**	toluene	1.7	59
6	**5**	toluene	0.8	22
7	**6**	toluene	0.8	24
8	**7**	toluene	0.8	39
9	**8**	toluene	0.8	47
10[d]	**4**	benzene	0.8	71
11[d]	**4**	benzene	0.4	77
12	**4**	anisole	0.8	61
13[e]	**4**	anisole	0.8	44
14	**4**	xylene	0.8	53
15	**4**	DMF	0.8	0

[a]Reaction conditions: **1a** (0.55 mmol, 1.1 equiv), **2a** (0.50 mmol, 1.0 equiv), $RuH_2(PPh_3)_4$ (5 mol %), ligand (5 mol %), NaH (20 mol %), solvent (0.6 mL for 0.8 M), 110 °C in an open system under argon atmosphere for 24 h unless otherwise noted. [b]Determined by GC. [c]In a closed system. [d]80 °C. [e]140 °C.

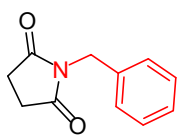
2.2.2 Substrate scope

With the optimized conditions in hand, the reactions of various nitriles with diols were investigated, affording the corresponding cyclic imides (Table 2.2). Various aliphatic nitriles afforded the corresponding succinimides in good yields, including secondary cyanides which were moderately hindered (**3b**–**3f** and **3j**). The reactions of benzonitrile derivatives also proceeded well, affording **3g**–**3i** in good yields. Noticeably, electron-poor benzonitriles exhibited relatively lower activity (**3h** and **3i**). When an aliphatic nitrile bearing an olefin group, 5-hexenenitrile, was applied, the corresponding amide **3j** was obtained in a moderate yield with the reduction of the olefin group. We also investigated the reactions with various diols (**3k**–**3s**). Sterically favored *cis*-1,2-cyclohexanedimethanol afforded bicyclic succinimide derivatives in very good yields (**3k**–**3n**). Phthalimide derivatives were synthesized from 1,2-benzenedimethanol in good yields (**3o**–**3q**). Moreover, the reaction with 2-phenylbutanediol afforded the corresponding cyclic imide in a fair yield (**3r**). In the case of 1,5-pantanediol, six-membered glutarimide (**3s**) was obtained in 43% yield with unidentified messy byproducts. Heterocyclic nitriles such as pyridinecarbonitriles and thiophenecarbonitriles did not work well under our reaction conditions presumably due to their coordination to catalytically active Ru species.

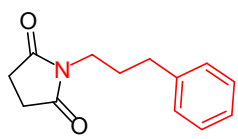
Table 2.2 Cyclic imides from diols and nitriles[a, b]



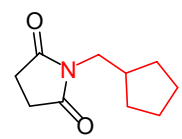
1 **2** **3**



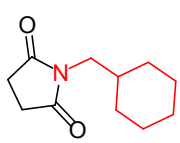
3a, 72%



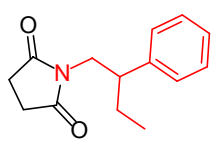
3b, 86%



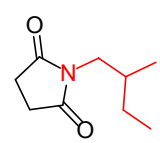
3c, 77%



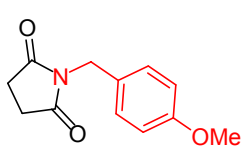
3d, 80%



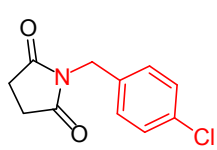
3e, 82%



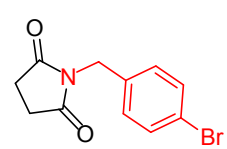
3f, 72%



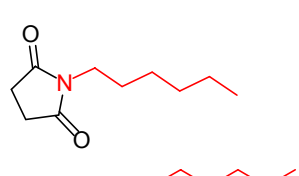
3g, 74%



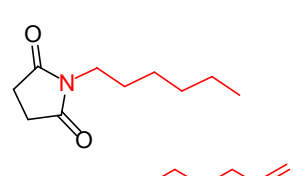
3h, 67%



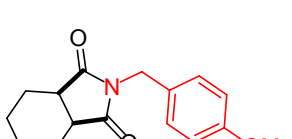
3i, 59%



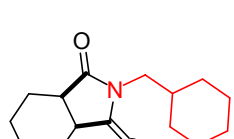
3j, 77% from



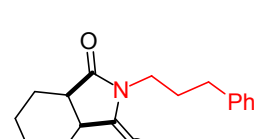
3j, 64% from



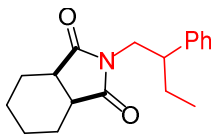
3k, 70%



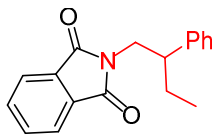
3l, 84%



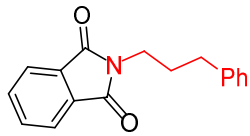
3m, 86%



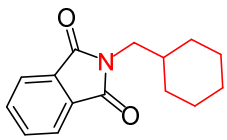
3n, 81%



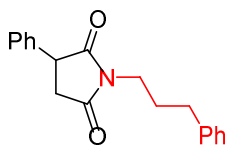
3o, 60%



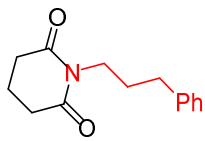
3p, 73%



3q, 70%



3r, 51%



3s, 43%

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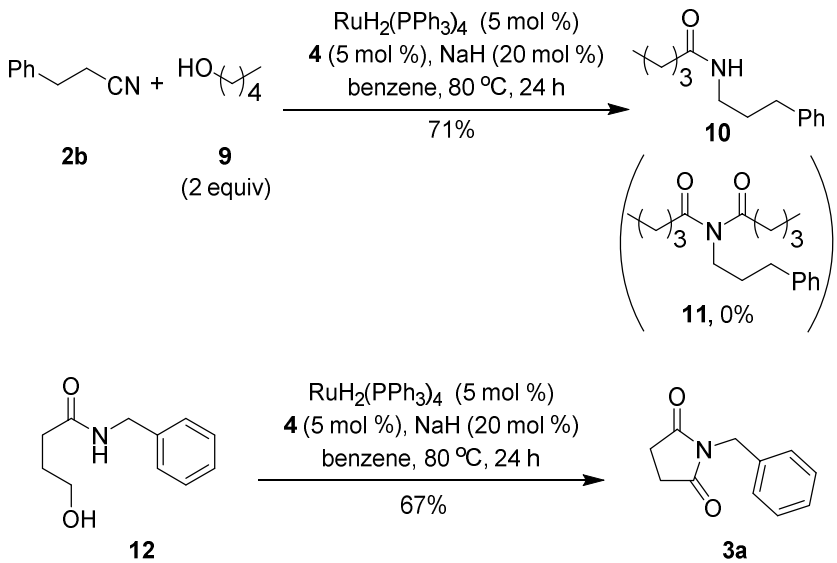
[a]Reaction conditions: diol (0.55 mmol, 1.1 equiv), nitrile (0.50 mmol, 1.0 equiv), $RuH_2(PPh_3)_4$ (5 mol %), **4** (5 mol %), NaH (20 mol %), benzene (1.2 mL, 0.4 M), 80 °C in an open system under argon atmosphere for 18 h. [b]Isolated yield

2.2.3 Mechanistic studies

Inspired by the results, the synthesis of a linear imide was attempted with 2 equiv of alcohol (**9**) and nitrile (**2b**) (Scheme 2.3). However, we could obtain only amide (**10**) without any formation of the target linear imide (**11**). When the reaction was performed with hydroxyamide (**12**), which is a possible intermediate for the cyclic imide formation, the reaction proceeded well in 67% yield (Scheme 2.3). This suggests that the formation of the second C–N bond to afford cyclic imide requires a kinetic favor of intramolecular ring formation after the formation of the first intermolecular amide bond.



Scheme 2.3 Attempts to synthesize imides

To investigate a possible reaction mechanism, a kinetic study was conducted by monitoring the progress of the reaction of **1a** with **2a** (Figure 2.1). Interestingly, γ-butyrolactone (**13**) and benzylamine (**14**) were observed as the major intermediates. We found that **13** and **14** were quickly generated along with the rapid consumption of **1a** and **2a**, while the formation of **12** was slow. The concentrations of **12**, **13**, and **14** slowly decreased while that of cyclic imide (**3a**) gradually increased. This reaction profile is different than our previously reported amidation of nitrile.[15] In the presence of a mono-alcohol and nitrile, an imine was detected without any amine indicating an inner-sphere-type mechanism.[15] In contrast, the diol and nitrile substrates generated an equivalent amount of lactone (**13**) and amine (**14**) constantly. This strongly suggests the involvement of lactone and amine as the intermediates in the reaction.

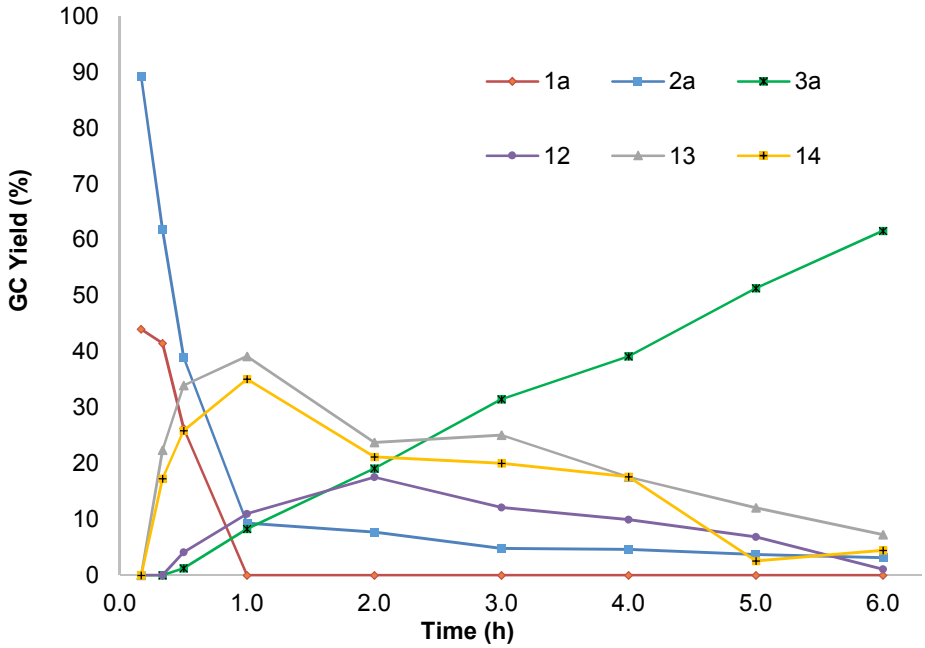
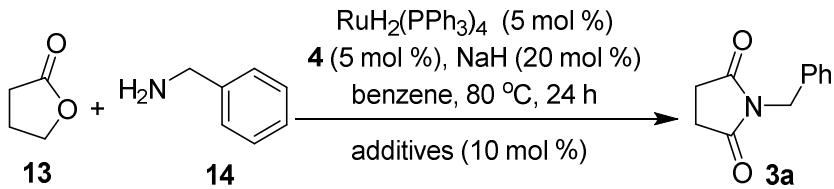


Figure 2.1 Reaction profiles showing the relative amounts of substrates and products. **1a** (0.55 mmol, 1.1 equiv), **2a** (0.50 mmol, 1.0 equiv), $RuH_2(PPh_3)_4$ (5 mol %), **4** (5 mol %), NaH (20 mol %), benzene (0.6 mL), 80 °C in an open system under argon atmosphere. The progress of the reaction was monitored by GC analysis using dodecane as the internal standard.

Additional experiments were performed to verify that **13** and **14** were involved in the major reaction pathway (Scheme 2.4). In the presence of a catalytic amount of both diol (**1a**) and nitrile (**2a**), the reaction of **13** with **14** proceeded smoothly to afford **3a** in 76% yield. This result also supports that hydrogen transfer from the diol to the nitrile affording a lactone and an amine is a key step in the mechanism of cyclic imide formation. Notably, the reaction failed in the absence of **1a** or **2a** (Scheme 2.4, entries 1–3). This result indicates that both the nitrile and diol are necessary for the catalysis. We assume that the nitrile not only works as a substrate

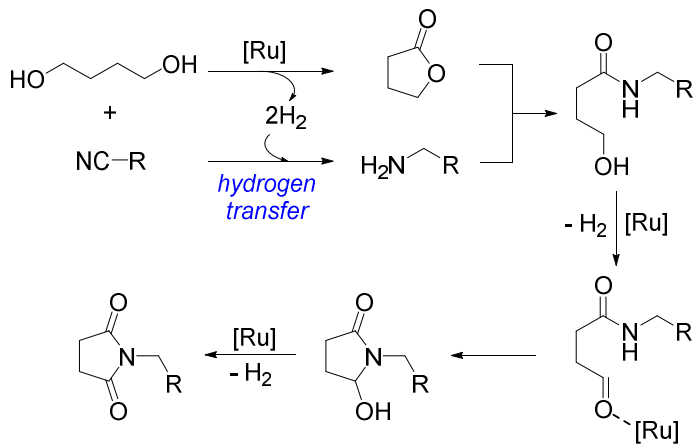
but also works as a ligand, and the diol works as a hydrogen source for the generation of an active Ru-hydride catalytic intermediate.



entry	additive		GC yield (%)
	1,4-butanediol (**1a**)	benzonitrile (**2a**)	
1	x	x	trace
2	o	x	11
3	x	o	5
4	o	o	76

Scheme 2.4 Cyclic imide from lactone and amine

On the basis of the experimental observation, we propose the following reaction mechanism (Scheme 2.5). First, the hydrogen transfer from the diol to the nitrile affords the corresponding lactone and amine. Then, the reaction of the lactone with the amine affords the corresponding hydroxyamide. The remaining alcohol group is then dehydrogenated by the Ru catalyst to generate hydrogen gas and aldehyde, which further reacts with the nitrogen atom of the amide group to afford a hemiaminal intermediate. Finally, the dehydrogenation of the hemiaminal provides the cyclic imide product. Although the hydroxyamide can be formed directly from the nitrile and alcohol without the involvement of the lactone and amine, this would be less likely because we observed the rapid generation of the lactone and amine as the major intermediates at the initial stage of the reaction (Figure 2.1).



Scheme 2.5 Proposed mechanism

2.3 Conclusion

In conclusion, we developed an atom-economical and versatile protocol for the synthesis of cyclic imides from nitriles and diols, readily available starting materials. The reaction involves a Ru-catalyzed transfer-hydrogenation reaction to simultaneously activate the two substrates, diol and nitrile, into the corresponding lactone and amine in a redox-neutral manner. This operationally simple protocol provides an efficient route to diverse cyclic imides.

2.4 Experimental section

2.4.1 General information

Unless otherwise noted, all reactions were carried out using standard Schlenk techniques or in an argon-filled glove box. All anhydrous solvents were purchased from commercial suppliers and degassed with dry argon before usage. NMR spectra were recorded in $CDCl_3$, and residue solvent signals were used as references. GC analyses were carried out using dodecane as an internal standard. $RuH_2(PPH_3)_4$,[16] $RuH_2(CO)(PPh_3)_3$,[17] and other metal reagents were prepared by literature procedures or purchased from commercial suppliers. Compound **4** was prepared according to the reported procedure.[18] Compounds **5**, **6**, **7**, and **8** were purchased from commercial suppliers and used as received without further purifications.

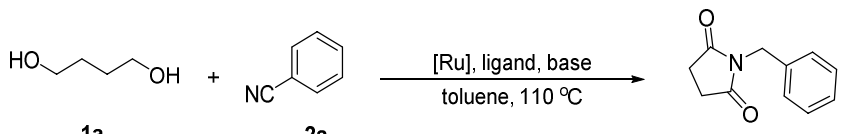
2.4.2 General procedure for the synthesis of cyclic imides

$RuH_2(PPH_3)_4$ (28.8 mg, 0.025 mmol), **4** (5.8 mg, 0.025mmol), NaH (2.4 mg, 0.10 mmol), and benzene (1.2 mL) were added to oven dried 4 mL vial equipped with septum screw cap inside a glove box. If solid nitrile (0.50 mmol) or diol (0.55 mmol) substrates were used, they were also added to the reaction mixture inside the glove box. Liquid nitrile or diol substrates were added into the vial using micro-syringe under Ar flow after the vial was taken out of the glove box. The septum of vial cap was pierced with 22-gauge needle connected to a manifold under inert atmosphere to make an open system. The mixture was heated to reflux for 18~24 h before being

cooled to room temperature. All the volatiles were removed under vacuum. Purification of the crude products was performed with silica gel column chromatography using hexane and ethyl acetate solvent mixture as an eluent to afford the corresponding cyclic imide.

2.4.3 Optimization table

Table 2.3 Evaluation of catalysts for cyclic imide synthesis[a]



1a **2a** **3a**

Entry	Ru complex	Ligand	Base	Time(h)	Yield (%)[b]
1	$RuHCl(CO)(PPh_3)_3$	**4**	NaH	48	17
2	$RuCl_2(PPh_3)_3$	**4**	NaH	48	12
3	$RuH_2(CO)(PPh_3)_3$	**4**	NaH	48	58
4	Milstein cat.	-	-	24	0
5	$[Ru(benzene)Cl_2]_2$	**4**, CH_3CN	NaH	24	0
6	$[Ru(p\text{-}cymene)Cl_2]_2$	**4**, pyridine	NaH	24	0
7	$RuH_2(PPh_3)_4$	**4**	NaH	24	61

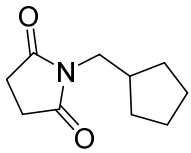
[a]Reaction conditions: **1a** (0.55 mmol, 1.1 equiv), **2a** (0.50 mmol, 1.0 equiv), [Ru] (5 mol%), ligand (5 mol%), NaH (20 mol%), toluene (0.6 mL), 110 °C in an open system under argon atmosphere. [b]Determined by GC.

2.4.4 GC analysis for reaction intermediate detection

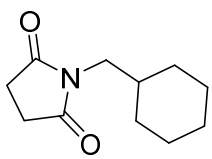
$RuH_2(PPH_3)_4$ (14.4 mg, 0.0125 mmol), **4** (2.9 mg, 0.0125 mmol), NaH (1.2 mg, 0.05 mmol), and benzene (0.6 mL) were added to oven dried 4 mL vial equipped with septum screw cap inside the glove box. **1a** (24.5 μL, 0.275 mmol), **2a** (26.0 μL, 0.25 mmol) were added into the vial using micro-syringe under Ar flow after the vial was taken out of the glove box. The septum of vial cap was pierced with 22-gauge needle connected to a manifold under inert atmosphere to make an open system. The each single mixture was heated to reflux for 10 min, 20 min, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, and 6 h, respectively, before being cooled to room temperature. The sample was diluted with dichloromethane, filtered with celite, analyzed with GC. The respective response factor was obtained by the GC analysis of a series of samples of known concentration, plotting the ratio of the areas, Asample/Astandard of each versus the ratio of the concentrations, [Sample]/[Standard]. Average data of independent 4 runs were plotted for the reaction profile in Figure 2.1.

2.4.5 Characterization of cyclic imides

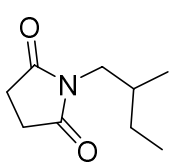
The reaction was performed in 0.50 mmol scale. All reported compounds, **3a**[1d] (white solid, 68.3 mg, 0.361 mmol, 72%), **3b**[19] (white solid, 92.8 mg, 0.427 mmol, 86%), **3e**[20] (brown oil, 95.1 mg, 0.411 mmol, 82%), **3g**[21] (white solid, 80.5 mg, 0.367 mmol, 74%), **3j**[22] (colorless oil, 70.5 mg, 0.385 mmol, 77%), **3k**[19] (colorless oil, 95.1 mg, 0.348 mml, 70%), **3p**[23] (colorless oil, 96.4 mg, 0.363 mmol, 73%) were identified by spectral comparison with literature data.



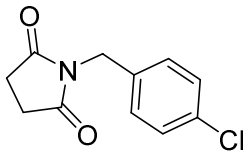
1-(Cyclopentylmethyl)-2,5-pyrrolidinedione (3c): yellow oil (69.8 mg, 0.385 mmol, 77%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 3.45 (d, *J* = 7.8 Hz, 2 H), 2.70 (s, 4 H), 2.26 (spt, *J* = 1.0 Hz, 1 H), 1.71 - 1.62 (m, 4 H), 1.57 - 1.46 (m, 2 H), 1.26 - 1.17 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.4, 43.4, 38.2, 30.2, 28.0, 24.7; HRMS–FAB (*m/z*) $[M+H]^+$ calcd for $C_{10}H_{16}NO_2$, 182.1181; found: 182.1178.



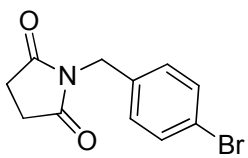
1-(Cyclohexylmethyl)-2,5-pyrrolidinedione (3d): white crystalline solide (78.4 mg, 0.402 mmol, 80%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 3.35 (d, *J* = 7.3 Hz, 2 H), 2.71 (s, 4 H), 1.74 - 1.66 (m, 3 H), 1.66 - 1.57 (m, 3 H), 1.22 - 1.12 (m, 3 H), 1.01 - 0.90 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.5, 44.9, 36.1, 30.7, 28.1, 26.1, 25.6; HRMS–FAB (*m/z*) $[M+H]^+$ calcd for $C_{11}H_{18}NO_2$, 196.1338; found: 196.1334.



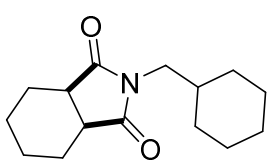
1-(2-Methylbutyl)-2,5-pyrrolidinedione (3f): dark brown oil (61.1 mg, 0.361 mmol, 72%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 3.40 (dd, *J* = 6.6, 13.0 Hz, 1 H), 3.32 (dd, *J* = 8.1, 13.0 Hz, 1 H), 2.70 (s, 4 H), 1.87 - 1.76 (m, 1 H), 1.40 - 1.29 (m, 1 H), 1.18 - 1.07 (m, 1 H), 0.90 (t, *J* = 7.3 Hz, 3 H), 0.83 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75MHz, $CDCl_3$) δ = 177.4, 44.7, 33.2, 28.0, 26.9, 16.7, 11.0; HRMS–FAB (*m/z*) $[M+H]^+$ calcd for $C_9H_{16}NO_2$, 170.1181; found: 170.1177.



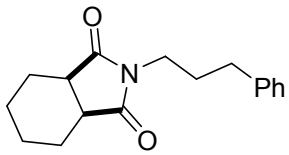
1-(4-Chlorobenzyl)-2,5-pyrrolidinedione (3h): white crystalline solid (74.8 mg, 0.334 mmol, 67%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.35 - 7.32 (m, *J* = 8.8 Hz, 1 H), 7.29 - 7.26 (m, *J* = 8.3 Hz, 1 H), 4.62 (s, 2 H), 2.71 (s, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.7, 134.2, 134.0, 130.5, 128.8, 41.7, 28.2; HRMS–FAB (*m/z*) $[M+H]^+$ calcd for $C_{11}H_{11}ClNO_2$, 224.0478; found: 224.0480.



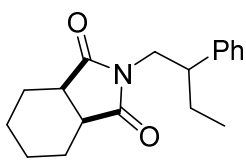
1-(4-Bromobenzyl)-2,5-pyrrolidinedione (3i): white crystalline solid (78.5 mg, 0.293 mmol, 59%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 8.3 Hz, 2 H), 7.28 (d, *J* = 8.3 Hz, 2 H), 4.60 (s, 2 H), 2.71 (s, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 176.70, 134.67, 131.78, 130.76, 122.13, 41.77, 28.19; HRMS–FAB (*m/z*) $[M+H]^+$ calcd for $C_{11}H_{11}BrNO_2$, 267.9973; found: 267.9975.



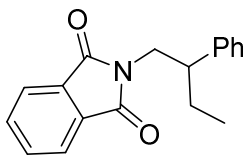
2-(Cyclohexylmethyl)-*cis*-hexahydro-1H-isoindole-1,3(2H)-dione (3l): white crystalline solid (104.4 mg, 0.419 mmol, 84%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 3.32 (d, *J* = 7.3 Hz, 2 H), 2.87 - 2.80 (m, 2 H), 1.92 - 1.82 (m, 2 H), 1.79 - 1.73 (m, 2 H), 1.73 - 1.66 (m, 3 H), 1.66 - 1.56 (m, 3 H), 1.51 - 1.37 (m, 4 H), 1.27 - 1.09 (m, 3 H), 1.01 - 0.89 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 180.10, 44.54, 39.66, 36.26, 30.76, 26.21, 25.61, 23.90, 21.72; HRMS–FAB (*m/z*) $[M+H]^+$ calcd for $C_{15}H_{24}NO_2$, 250.1807; found: 250.1801.



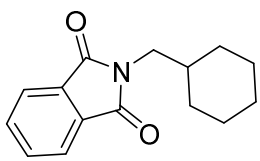
2-(3-Phenylpropyl)-*cis*-hexahydro-1H-isoindole-1,3(2H)-dione (3m): colorless oil (116.6 mg, 0.430 mmol, 86%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.30 - 7.26 (m, 2 H), 7.20 - 7.15 (m, 3 H), 3.54 (t, *J* = 7.3 Hz, 2 H), 2.81 - 2.73 (m, 2 H), 2.63 (t, *J* = 7.3 Hz, 2 H), 1.95 - 1.88 (m, 2 H), 1.88 - 1.79 (m, 2 H), 1.76 - 1.67 (m, 2 H), 1.50 - 1.34 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 179.66, 140.95, 128.29, 128.18, 125.89, 39.55, 38.20, 33.11, 28.98, 23.61, 21.47; HRMS–FAB (*m/z*) $[M+H]^+$ calcd for $C_{17}H_{22}NO_2$, 272.1651; found: 272.1655.



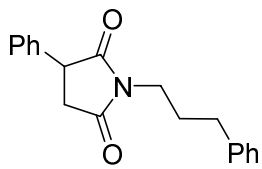
2-(2-Phenylbutyl)-*cis*-hexahydro-1H-isoindole-1,3(2H)-dione (3n): colorless oil (114.9 mg, 0.403 mmol, 81%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.26 - 7.21 (m, 2 H), 7.19 - 7.12 (m, 3 H), 3.81 (dd, *J* = 10.3, 13.2 Hz, 1 H), 3.55 (dd, *J* = 6.4, 13.2 Hz, 1 H), 3.18 - 3.08 (m, 1 H), 2.67 - 2.55 (m, 2 H), 1.73 - 1.55 (m, 4 H), 1.55 - 1.46 (m, 1 H), 1.38 - 1.29 (m, 1 H), 1.26 - 1.08 (m, 4 H), 0.79 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer: δ = 179.6, 141.2, 128.3, 128.3, 126.8, 45.0, 43.5, 39.5, 27.1, 23.4, 21.6, 11.8; Minor rotamer: δ = 179.8, 141.2, 128.3, 128.3, 126.8, 45.0, 43.5, 39.2, 27.1, 23.7, 11.8; HRMS–FAB (*m/z*) $[M+H]^+$ calcd for $C_{18}H_{24}NO_2$, 286.1807; found: 286.1799.



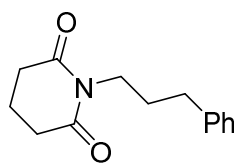
2-(2-Phenylbutyl)isoindoline-1,3-dione (3o): colorless oil (83.7 mg, 0.300 mmol, 60%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.81 - 7.75 (m, 2 H), 7.69 - 7.64 (m, 2 H), 7.26 - 7.14 (m, 5 H), 3.92 - 3.79 (m, 2 H), 3.14 - 3.04 (m, 1 H), 1.80 - 1.60 (m, 2 H), 0.79 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.3, 141.4, 133.8, 131.9, 128.3, 128.0, 126.7, 123.1, 46.1, 43.8, 26.2, 11.8; HRMS–FAB (*m/z*) $[M+H]^+$ calcd for $C_{18}H_{18}NO_2$, 280.1338; found: 280.1337.



2-(Cyclohexylmethyl)isoindoline-1,3-dione (3q): white crystalline solid (85.0 mg, 0.349 mmol, 70%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.86 - 7.81 (m, 2 H), 7.72 - 7.68 (m, 2 H), 3.52 (d, *J* = 7.3 Hz, 2 H), 1.84 - 1.75 (m, 1 H), 1.75 - 1.59 (m, 5 H), 1.26 - 1.11 (m, 3 H), 1.07 - 0.94 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.7, 133.8, 132.1, 123.1, 44.1, 37.0, 30.7, 26.2, 25.6; HRMS–FAB (*m/z*) $[M+H]^+$ calcd for $C_{15}H_{18}NO_2$, 244.1338; found: 244.1333.



3-Phenyl-1-(3-phenylpropyl)-2,5-pyrrolidinedione (3r): colorless oil (74.2 mg, 0.253 mmol, 51 %); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.42 - 7.33 (m, 3 H), 7.33 - 7.27 (m, 2 H), 7.25 - 7.14 (m, 5 H), 3.93 - 3.85 (m, 1 H), 3.66 - 3.60 (m, 2 H), 3.10 (m, 1 H), 2.76 (m, 1 H), 2.66 (m, 2 H), 2.05 - 1.93 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.7, 176.1, 140.9, 137.2, 129.2, 128.4, 128.3, 127.9, 127.3, 126.0, 45.8, 38.9, 37.1, 33.2, 28.8; HRMS–FAB (*m/z*) $[M+H]^+$ calcd for $C_{19}H_{20}NO_2$, 294.1494; found: 294.1487.



1-(3-Phenylpropyl)-2,6-piperidinedione (3s): black oil (49.6 mg, 0.214 mmol, 43%); ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.28 - 7.24 (m, 2 H), 7.20 - 7.14 (m, 3 H), 3.83 (t, *J* = 7.8 Hz, 2 H), 2.64 (t, *J* = 7.8 Hz, 2 H), 2.57 (t, *J* = 6.6 Hz, 4 H), 1.92 - 1.80 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.42, 141.42, 128.25, 128.17, 125.79, 39.44, 33.20, 32.77, 28.97, 17.00; HRMS–FAB (*m/z*) $[M+H]^+$ calcd for $C_{14}H_{18}NO_2$, 232.1338; found: 232.1339.

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Chapter 3. Transition Metal-Catalyzed C–H Arylation of Unactivated Simple Arenes

3.1 Introduction

C–H functionalization is an ideal synthetic strategy in the context of green chemistry, providing significant atom-economic and environmental advantages.[1] Activation of C–H bonds using a proper transition metal catalyst enables the direct introduction of a functional group into the C–H bond without prefunctionalization of the starting materials. In particular, direct arylation of arenes has attracted considerable attention as a novel alternative approach for the syntheses of biaryls, a key building block of natural products and pharmaceuticals.[2] Although their conventional production heavily relies on cross-coupling reactions, the use of aryl halides and organometallic reagents causes severe problems including the requirement for preparation steps of activated coupling partners and significant generation of waste. Direct C–H arylation offers a step- and atom-economical alternative methodology for biaryl synthesis.

For more than a decade, remarkable progress has been made in the field of C–H arylation. This Chapter provides an introduction to several classes of C–H arylation and specific examples, including mechanistic considerations, with emphasis on unactivated, undirected simple arene substrates.

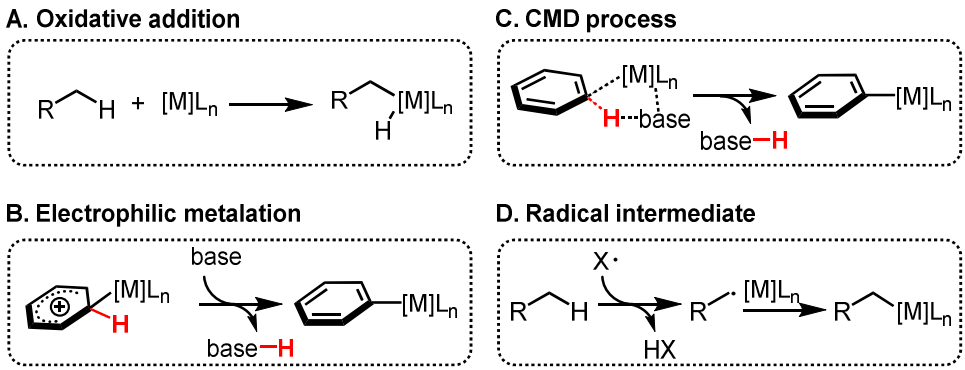
3.2 Types of C–H cleavage and activation strategy

The direct conversion of carbon–hydrogen bonds to carbon–carbon or carbon–heteroatom bonds is the ultimate goal of C–H functionalization chemistry. To achieve functionalization, transition metals have been widely used, and their reactivity towards hydrocarbons has been deeply investigated in the past decades. C–H bonds in organic molecules are replaced by C–M bonds with transition metals, and this process is termed "*C–H activation*".[3] The following installation of functional groups accomplishes "*C–H functionalization*" and determines a category of the reactions as arylation, alkylation, or halogenation. Prior to discussing this field of research, types and properties of the *C–H activation step* must be understood.

The types of C–H activation can be classified based on the mechanism of the elementary C–H cleavage step.[4] Traditionally, the most common mode of C–H bond cleavage is oxidative addition to transition metal to form a metal-hydride complex (Scheme 3.1 A).[5] Experimental studies regarding stoichiometric reactions support that this type of process is common for electron-rich late transition-metals. The reaction proceeds mainly with an aliphatic C–H bond via agostic interaction. However, the oxidative addition generally does not occur with an aryl C–H bond, with only limited exceptions.[4b, 6]

Another traditionally accepted mechanism is electrophilic metalation, which is also called the S_EAr type mechanism (Scheme 3.1 B).[2, 4c] This process involves mainly electron-rich arenes as substrates, especially heteroarenes. As in the electrophilic aromatic substitution reaction, the electron-deficient late transition metal attacks an electron-rich aromatic substrate, affording a Wheland-type

intermediate. Subsequent deprotonation by a base completes the C–H activation, where a stoichiometric amount of base is required.



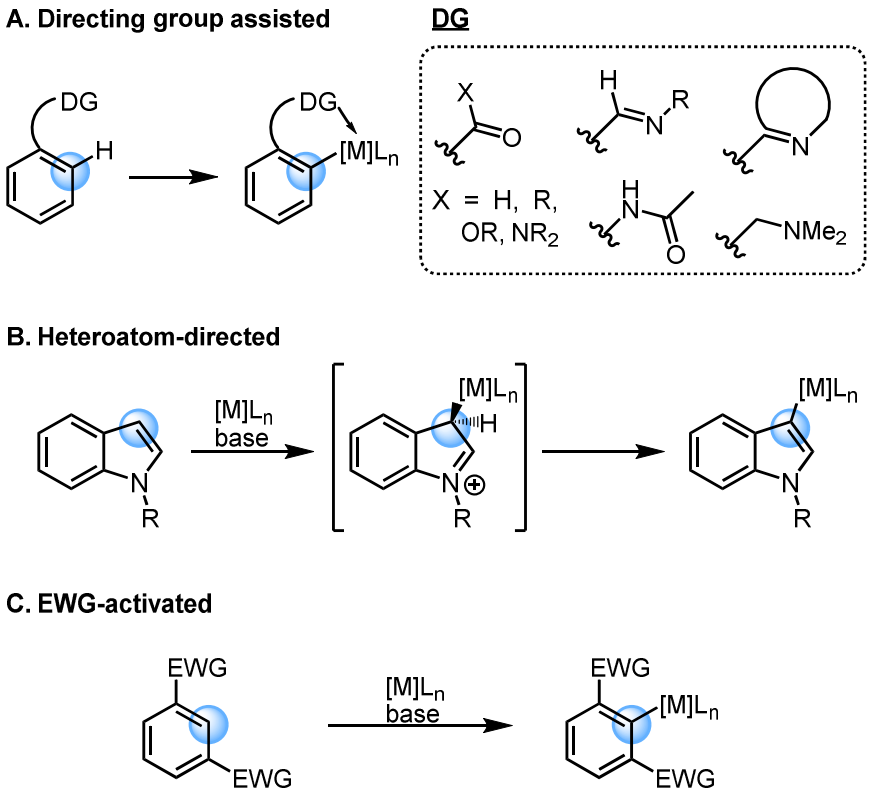
Scheme 3.1 Types of C–H bond cleavage steps

A relatively recently suggested activation mode is the concerted metalation-deprotonation (CMD) process (Scheme 3.1 C).[7] In this transformation, a co-catalytic amount of carboxylate base plays a key role in the mechanism. First, the C–H bond of the substrate interacts with the metal, increasing the acidity of the C–H bond. Then, the C–H bond undergoes an intramolecular-type deprotonation facilitated by the coordinated carboxylate on the metal, with concomitant formation of a carbon–metal bond. This process is also called internal electrophilic substitution (IES)[8] or ambiphilic metal ligand activation (AMLA)[9].

The formation of metal–carbon bond also can occur by stepwise pathways. In some reactions, such as photo-reactions, generation of an alkyl radical via hydrogen atom transfer (HAT) and recombination of the radical with a metal complex occurs step-wise (Scheme 3.1 D).[4a] Although this process is widely studied in the field of photo catalysis, it will not be discussed further as it is beyond the scope of this Chapter.

The C−H bond activation can occur following various mechanisms depending on the C−H bond type and reaction conditions. However, it is not a facile process, and two fundamental challenges must be addressed to achieve direct C–H functionalization. First, C–H bonds are thermodynamically strong and kinetically inert, which result in their low reactivity. The other major challenge is controlling selectivity among the many C–H bonds in organic molecules. These problems can be overcome by using several strategies where one C–H bond is selectively activated to react over the other C–H bonds present in the molecule.

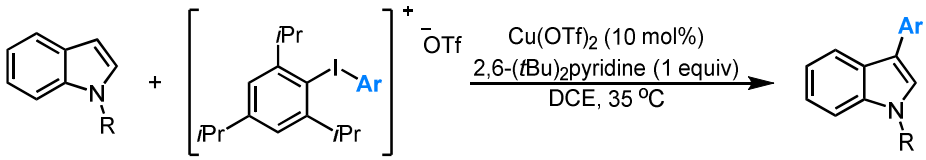
Arylation reactions of C(sp^2)–H bonds in arenes have been performed mainly following three different types of strategies. The most widely applied strategy is the use of substrates containing "*directing groups*" (DGs, Scheme 3.2 A).[3] The DGs are Lewis base functional groups that can coordinate to transition metals, such as carbonyl derivatives, N-heterocycles, or amino groups. A DG binds to the metal center bringing the catalyst into close proximity to a specific C–H bond. This results in particularly increased reactivity in a specific C–H bond and consequently high selectivity over other C–H bonds. Because metallacycle intermediates are produced, this process is also called chelation-assisted C–H activation or cyclometalation. Although a variety of C–H arylations have been realized using this DG-assisted strategy, the requirement for DGs limits the scope of accessible products. Furthermore, the installation and removal of DGs require additional synthetic labor.



Scheme 3.2 Activation strategies of arene C–H bonds

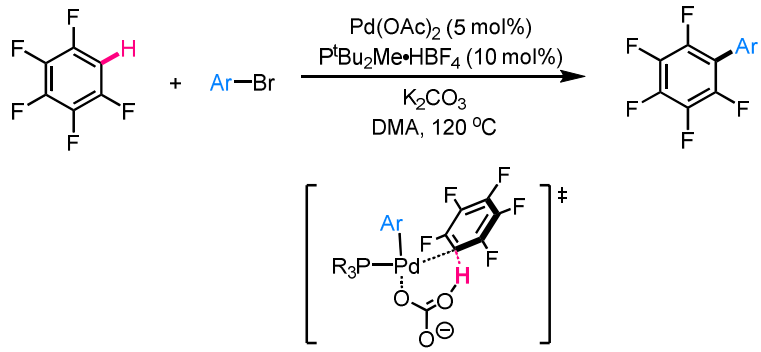
Heteoarenes are another class of substrates that have been extensively used to the direct C−H arylation (Scheme 3.2 B).[10] The presence of even only one heteroatom in an aromatic compound makes the electronic properties of all C–H bonds differentiated. This electronic bias dominates the overall reactivity and enables selective C–H activation. Electron-rich heteroarenes usually react with electrophilic transition metals following the S_EAr mechanism as depicted in Scheme 3.1. For example, direct arylation of indoles on C-3 position was reported by Gaunt and co-workers in 2008 (Scheme 3.3).[11] A copper complex was employed as a catalyst, and the mechanism involving electrophilic addition of cationic copper into C-3 position

of an indole was proposed. The S_EAr mechanism has been the most supported pathway of the C–H arylation of a wide range of heteroarenes. However, recent researches have demonstrated that results of computational studies support the CMD process as a plausible mechanism for C–H activation of electron-rich arenes, rather than S_EAr.[4c, 12]



Scheme 3.3 Direct C–H arylation of indoles using a copper catalyst

As with heteroarenes, introduction of electron withdrawing groups (EWGs) also can induce electronic perturbation in arene substrates, complementary to electron-rich arenes (Scheme 3.2 C).[13] Usually two or more EWGs are installed to activate the *ortho*-C–H bond by increasing its acidity. It is widely accepted that this class of substrates undergoes C–H activation following the CMD process and there is a parallel trend between the reactivity and acidity.[12] In 2006, Fagnou and co-workers reported the first intermolecular direct C–H arylation of electron-deficient benzenes (Scheme 3.4).[14] Direct coupling between polyfluorinated benzenes and aryl bromides was achieved using a Pd-based catalytic system in combination with a phosphine ligand and carbonate base. On the basis of high reactivity of electron-deficient arenes, which are inaccessible by S_EAr mechanism, the CMD process was proposed where the carbonate base promotes C–H activation via a six-membered transition state.



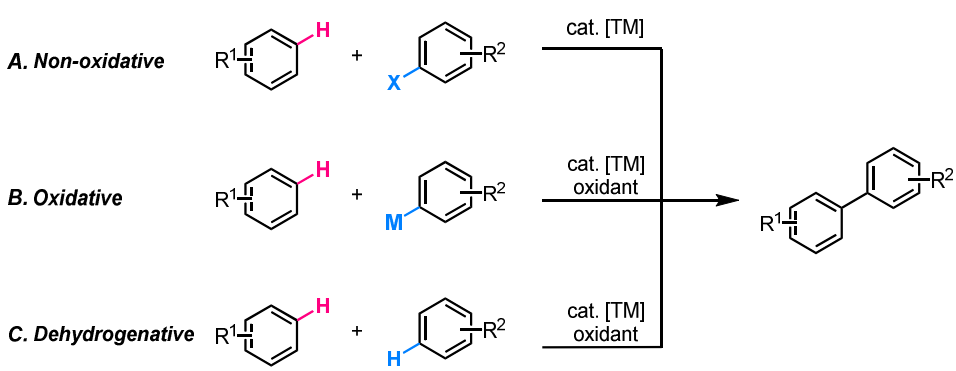
Scheme 3.4 Direct C–H arylation of polyfluorinated benzene using a Pd catalyst

For decades, tremendous progress has been made in the direct C–H arylation by three activation strategies: DG-assisted, heteroatom-directed, and EWG-activated strategies. However, reactions designed based on these principles are applicable only to a limited range of substrates, requiring the further manipulation of arenes. Therefore, expansion of the scope of direct C–H arylation to "*simple arenes*" such as benzene or toluene, which do not contain DGs or activating functional groups, is an important research goal.[4b, 15] Furthermore, recent studies have indicated that C–H activation via the CMD mechanism is a facile process for not only electron-deficient arenes but also the other arenes,[16] which has already prompted investigation into C–H arylation of simple arenes as described in the following section.

3.3 C–H arylation of simple arenes

Simple arenes are readily available and abundant chemical feedstocks, being produced from petrochemicals in quantities on the order of tens of millions of tons per year.[17] Direct synthesis of benzenoid motifs from simple arenes in an efficient manner is desirable for industrial applications. In particular, the biaryl moiety has been extensively applied as a core structural motif in drug development, agrochemicals, and material science. The direct C–H arylation of simple arenes to afford biaryls can provide a sustainable and streamlined alternative to conventional cross-coupling processes.

The C–H arylation reactions can be classified based on the coupling partners used.[4b, 15] Firstly, simple arenes can be coupled with aryl halides without an oxidant (Scheme 3.5 A). In the presence of a stoichiometric oxidant, organometallic reagents can act as the coupling partner (B). Another approach is double C–H activation to form biaryls with a net loss of two hydrogen atoms under oxidative conditions (C). This classification is important because the coupling partner has a significant influence on the reaction conditions, functional group tolerance, and overall reaction mechanisms.

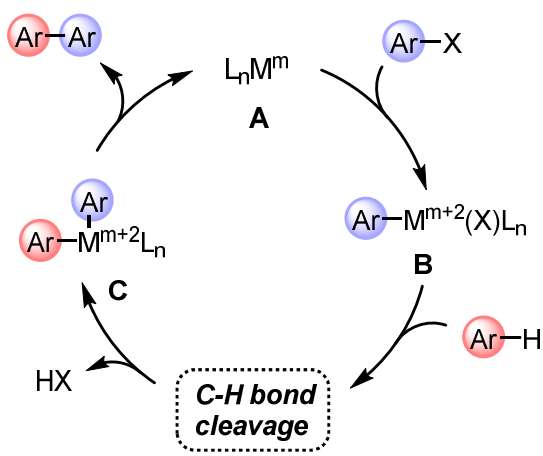


Scheme 3.5 Biaryl synthesis via direct C–H arylation of simple arenes

3.3.1 Non-oxidative direct C–H arylation

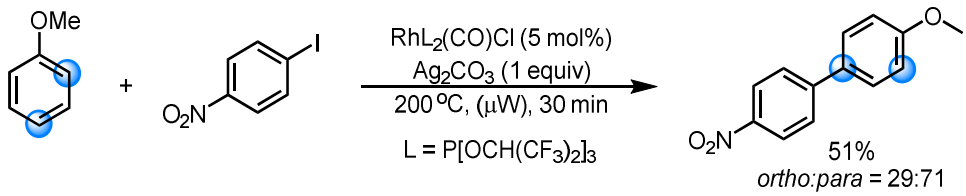
Aryl halides are the most frequently used arylating reagent in direct C–H arylation reactions. Their reasonably good stability and broad availability have enabled the development of versatile C–H arylations. Because the coupling of aryl halides and simple arenes is a redox-neutral process, it can be performed under oxidant-free conditions, which can tolerate oxidant-sensitive functional groups.

The general mechanism of arylation reactions with aryl halides is simply depicted in Scheme 3.6. First, oxidative addition of the aryl halide to active catalyst generates the metal aryl complex B. Subsequent C–H activation of the simple arene affords the diaryl metal complex C. Finally, reductive elimination from C furnishes the biaryl product with concomitant regeneration of the active catalyst A. Most arylation reactions with aryl halides can be understood based on this general mechanism.



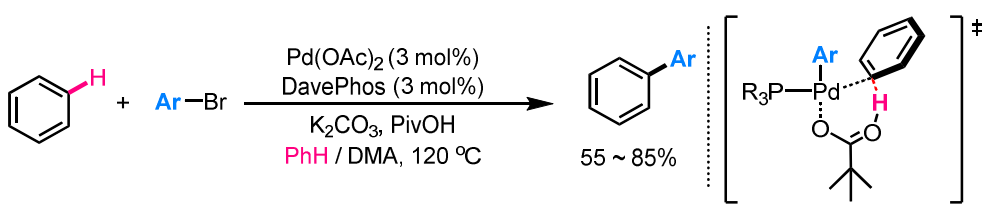
Scheme 3.6 General mechanism of C–H arylation with aryl halides

In 2006, Itami and co-workers reported the direct C–H arylation of anisole with aryl iodides and a Rh-based catalyst (Scheme 3.7).[18] Although the focus of this work was the arylation of electron-rich heteroarenes, the catalytic system using Rh(I) complex and π-accepting phosphite ligands also could accomplish arylation on the anisole. The *para*-favored selectivity was attributed to the electrophilic metalation mechanism.



Scheme 3.7 Rh-catalyzed direct C–H arylation of anisole

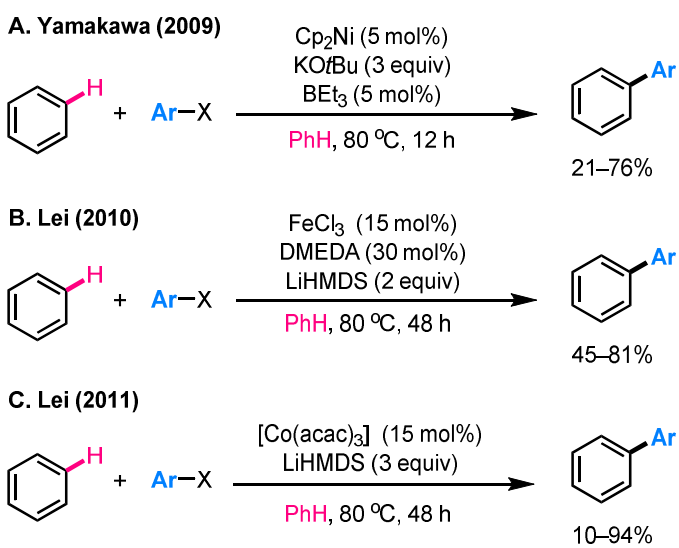
In the same year, the Fagnou group developed the first direct C–H arylation of benzene (Scheme 3.8).[19] The reaction proceeded with aryl bromides and mixture of benzene and DMA as the solvent, with the catalytic system consisting of $Pd(OAc)_2$, DavePhos ligand, carbonate base, and pivalic acid. The success of this groundbreaking work was based on the co-catalytic pivalate that acts as a proton shuttle from benzene in the CMD process. Benzene is so unactivated that it had been an inaccessible substrate for C–H activation until this report.



Scheme 3.8 Pd-catalyzed direct C–H arylation of benzene with the aid of pivalate

After the report by the Fagnou group, C–H arylation of benzene with first row transition metals was attempted. In 2009, Yamakawa and co-workers accomplished direct C–H arylation of benzene using a Ni-based catalyst (Scheme 3.9 A).[20] Arylation reactions with aryl bromides and iodides afforded biaryl products in moderate to good yields in benzene solvent, and aryl chlorides were also applicable albeit low yields.

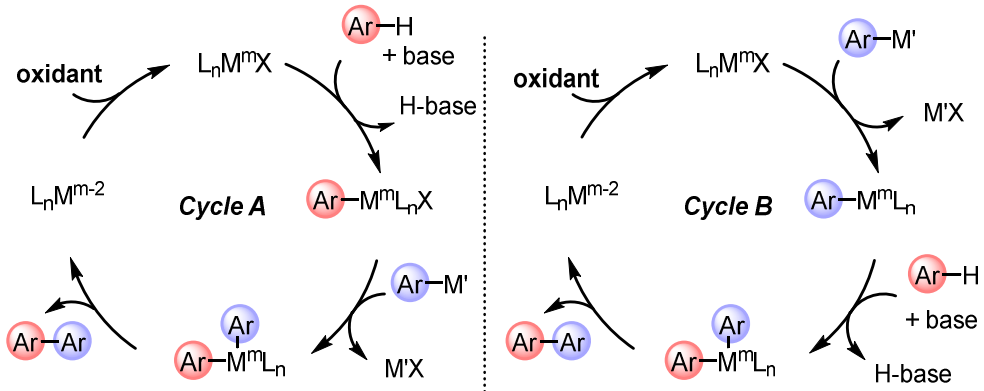
The same transformation was also possible with an iron catalyst. Lei and co-workers used $FeCl_3$ as a precatalyst in combination with DMEDA as a ligand and LiHMDS base (Scheme 3.9 B).[21] Aryl bromides and iodides were successfully applied to the reactions, and even aryl chlorides with electron-donating groups afforded the products in reasonable yields. However, electron-deficient ArCls did not produced the desired products. In 2011, the same group reported the cobalt-catalyzed C–H arylation of benzene (Scheme 3.9 C). The Co catalyst exhibited high efficiency even with aryl chlorides as well as aryl bromides and iodides.[22]



Scheme 3.9 Direct C–H arylation of benzene by first row transition metals

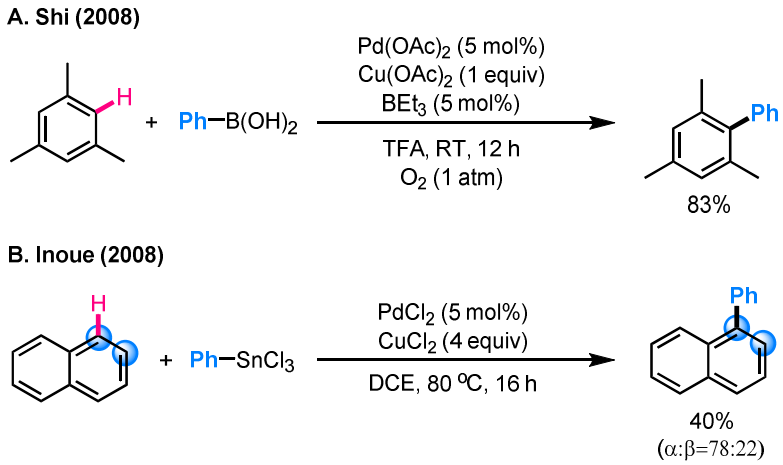
3.3.2 Oxidative direct C–H arylation

Direct C–H arylation with organometallic reagents has been relatively less explored. Coupling of nucleophiles requires a stoichiometric amount of oxidant, resulting in a different catalytic cycle from that of non-oxidative coupling. Although two catalytic cycles are possible depending on the sequence of C–H activation and transmetalation, both cycle A and B afford the diaryl metal complex after two elementary steps (Scheme 3.10). After reductive elimination of a biaryl product, the oxidation process regenerates the active catalyst, completing the catalytic cycle.



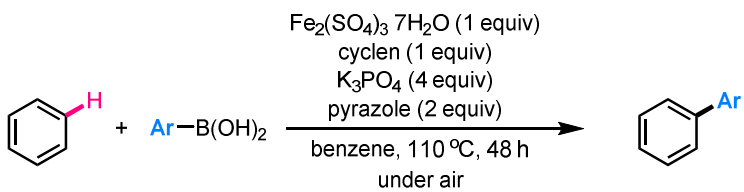
Scheme 3.10 General mechanisms of C–H arylation with organometallic reagents

In 2008, the Shi group developed Pd-catalyzed oxidative coupling of boronic acids with arenes (Scheme 3.11 A).[23] The reaction proceeded in room temperature, employing dioxygen as the terminal oxidant with $Cu(OAc)_2$ as a co-oxidant. Aryltin reagents were also applied to the direct arylation of simple arenes by the Inoue group, albeit with the narrow substrate scope (Scheme 3.11 B).[24] The reaction could afford the direct arylation of naphthalene with α-favored selectivity.



Scheme 3.11 Pd-catalyzed direct C–H arylation with arylbronic acids and aryltins

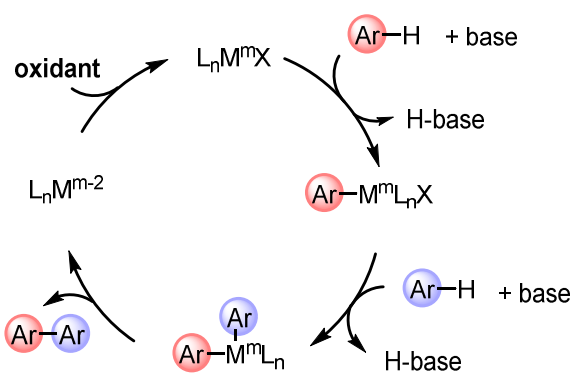
More general C–H arylation of simple arenes with arylboronic acids was accomplished using an iron catalyst (Scheme 3.12). Yu and co-workers developed the reaction conditions with a stoichiometric amount of iron salt in combination with a pyrazole additive and cyclen, the aza analogue of the crown ether, as a ligand.[25] The direct aylation of various arylboronic acids showed good reactivity with benzene as well as other simple arenes. To investigate the reaction mechanism, a radical scavenger TEMPO was added to the reaction of phenylboronic acid and benzene. The reaction proceeded well without any interruption, indicating no involvement of radical species.



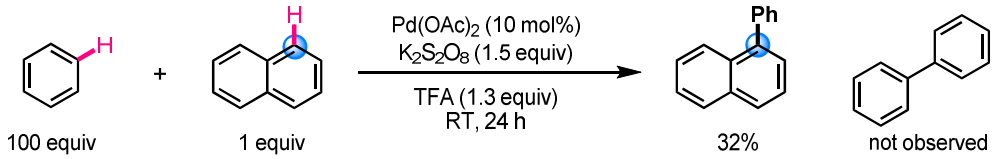
Scheme 3.12 Fe-catalyzed direct C–H arylation with arylboronic acids

3.3.3 Cross-dehydrogenative direct C–H arylation

Although direct C–H arylation has advantages over traditional cross-coupling such as improved step- and atom-economy by reducing pre-functionalization, limitations remain as long as aryl halides or aryl metals are used as coupling partners. Therefore, direct coupling of two arenes by dual C–H activation is the most green process, as no waste is generated from the starting materials.[4b] The activation of two C–H bonds in two simple arenes is a challenging task because of the selectivity problem, which may cause homocoupling. As depicted in Scheme 3.13, after the C–H activation of one arene in the first step, the second C–H activation should exclusively involve the second arene. After reductive elimination, oxidation of the metal regenerates the active catalyst. Besides the issues of low reactivity and regioselectivity, homocoupling suppression must be addressed to achieve dehydrogenative C–H arylation. While many studies regarding the homocoupling of arenes were reported from the 1960s to 80s,[15] the cross-coupling of arenes is mainly discussed in this Chapter.



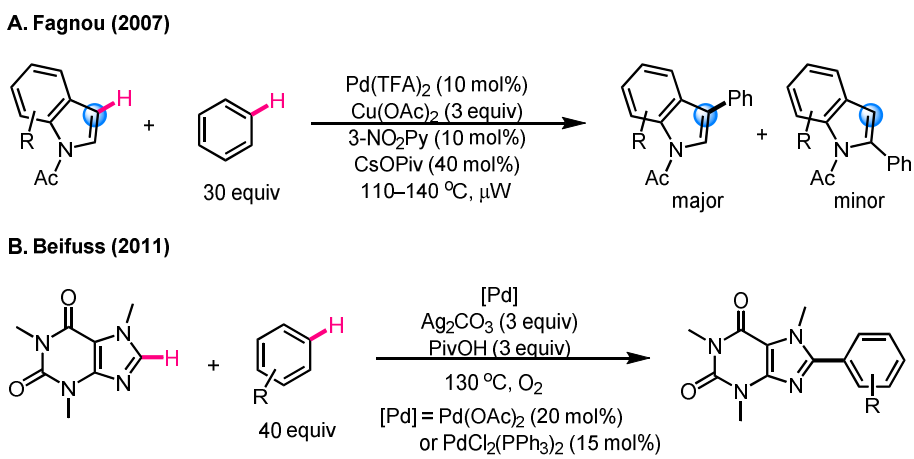
Scheme 3.13 General mechanism of dehydrogenative direct C–H arylation



Scheme 3.14 Pd-catalyzed oxidative coupling of benzene and naphthalene

In 2006, Lu and co-workers reported the pioneering work of cross-coupling of two unactivated simple arenes.[26] Palladium acetate was employed as a catalyst with persulfate oxidant at room temperature. To enhance the selectivity for cross-coupling, the ratio of two arenes and the amount of TFA were carefully controlled. For example, the reaction of benzene and naphthalene afforded the cross-coupling product exclusively albeit low yield (Scheme 3.14).

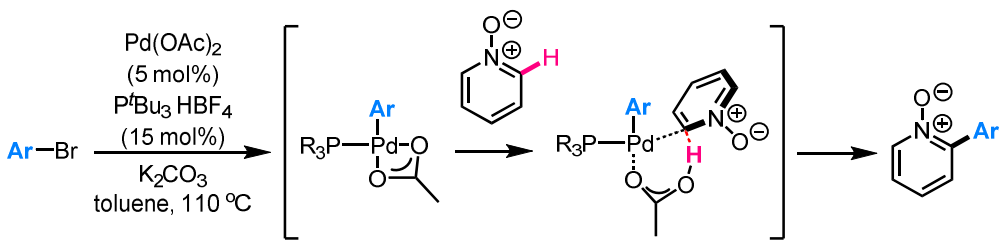
To achieve selective cross-coupling, electronically different arenes were applied to arylation reaction (Scheme 3.15). Fagnou and co-workers accomplished the coupling of indole and benzene using a Pd catalyst and Cu oxidant.[27] C3-favored selectivity was observed without homocoupling. The Beifuss group also reported similar strategy using xanthines with excellent selectivity.[28]



Scheme 3.15 Pd-catalyzed cross-coupling of electronically different arenes

3.4 Introduction to the cooperative bimetallic mechanism

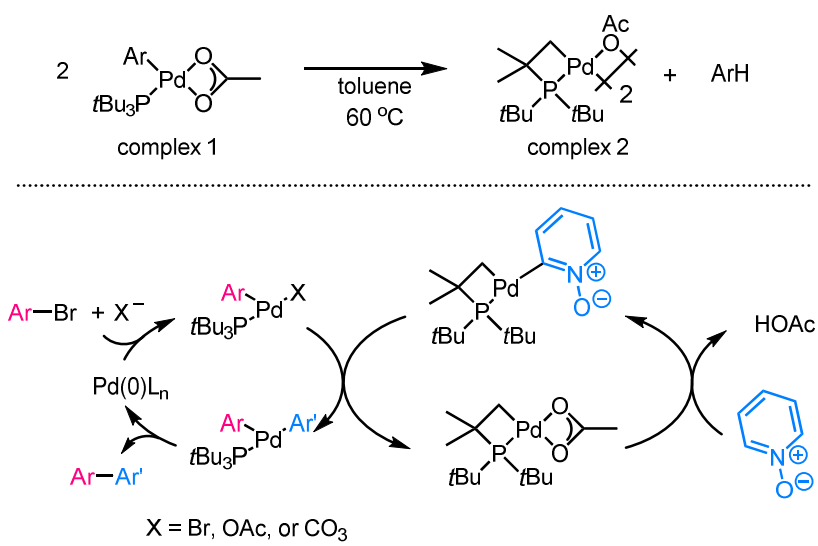
Since the advent of direct C–H arylation, numerous remarkable developments have been achieved in the synthesis of biaryls in terms of efficiency and environmentally friendliness. The scope of arenes has become increasingly general, and significant improvements in selectivity and reactivity have been achieved. These accomplishments were possible due to the mechanistic understanding of the C–H activation and coupling process. Although slight differences depending on the coupling partners and reaction conditions exist, most reaction mechanisms have been interpreted based on the general mechanism involving one active catalyst. However, a novel mechanism involving two different catalytic metal species has been recently suggested, called the *cooperative bimetallic mechanism*.



Scheme 3.16 Direct C–H arylation of pyridine N-oxide

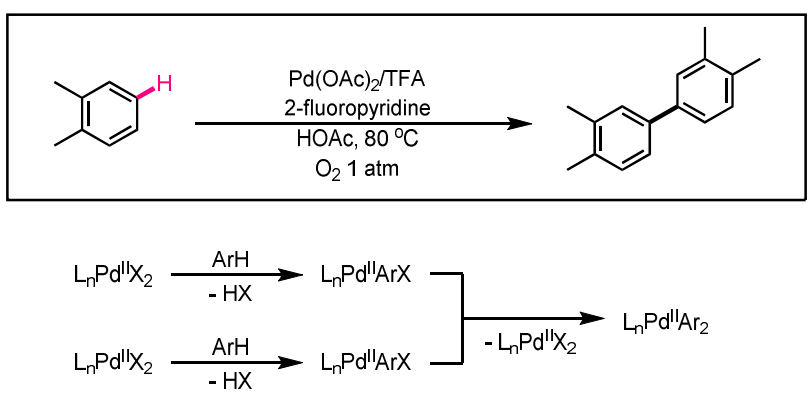
In 2012, Hartwig and co-workers reported an intensive mechanistic study on the direct arylation of pyridine N-oxide (PyO).[29] The original development of the reaction was reported by the Fagnou group in 2005,[30] who proposed a mechanism similar to the general one involving the CMD process (Scheme 3.6) supported by

various experimental observations in 2010 (Scheme 3.16).[31] However, the Hartwig group showed that the coupling of PyO and aryl halide does not follow the mechanism suggested by the Fagnou group, but instead, cooperative bimetallic catalysis is working in the reaction. During the investigation of the oxidative addition intermediate, complex 1, the generation of cyclometalated complex 2 was observed (Scheme 3.17). Experimental data regarding complex 2 supported that a monomer cyclometalated complex derived from complex 2 is responsible for the C–H activation of PyO. Based on experimental evidence, the authors proposed a cooperative bimetallic mechanism where a single Pd species undergoes oxidative addition with ArBr and the other cyclometalated Pd species performs C–H cleavage of PyO. Subsequent transmetalation and reductive elimination afford a biaryl product and complete the catalytic cycle (Scheme 3.17). This was the first experimental demonstration of cooperative bimetallic catalysis for the C–H arylation of arenes.



Scheme 3.17 Cooperative bimetallic mechanism of arylation of pyridine N-oxide

The reaction that follows the cooperative bimetallic mechanism was also discovered during investigations into cross-dehydrogenative coupling. In 2014, Stahl and co-workers reported a mechanistic study on the Pd-catalyzed aerobic oxidative coupling of *o*-xylene.[32] Previously, this cross-dehydrogenative coupling was considered to follow the "monometallic" mechanism involving sequential C–H activation at a single Pd center, as shown in Scheme 3.13. However, the Stahl group proposed the "bimetallic" mechanism where parallel C–H activation occurs at two separate Pd centers followed by transmetalation between the two Pd species (Scheme 3.18). This mechanism was supported by evidence from related kinetic data. When the C–H cleavage step is rate-determining under normal catalytic conditions, both monometallic and bimetallic mechanisms exhibit a first-order dependence in Pd concentration ([Pd]). However, if [Pd] is far lower than under the catalytic conditions in the bimetallic mechanism, the transmetalation step becomes rate-determining, and a second-order dependence in [Pd] is observed. The kinetic study on [Pd] clearly confirmed the bimetallic mechanism.



Scheme 3.18 Pd-catalyzed aerobic oxidative coupling of *o*-xylene

3.5 Conclusion

This Chapter summarizes the long history of direct C–H arylation research. It has been one of the most popular topics in organic chemistry in recent decades, presenting an elegant alternative for the synthesis of biaryls in a cost-effective and environmentally friendly manner. The chemistry of C–H arylation can be understood in terms of several criteria such as type of C–H cleavage, arene activation strategy, and arylation coupling partner. Among the numerous C–H arylation reactions that have been developed, the reactions of simple arenes without installation of directing groups or activating functional groups are considered the most significant. In these cases, although the low reactivity of the C–H bond and difficulty of controlling selectivity make the related transformations challenging, they can provide general C–H arylation methods of broad synthetic value.

However, the direct C–H arylation reactions of simple arenes that have been developed to date highlight the limited reactivity of the catalytic system with low TON. Considering the substantial value of this process, great opportunities remain for development of catalytic systems with high reactivity and selectivity. Furthermore, mechanistic studies examining the fundamental principles of C–H arylation will provide new opportunities for improving the greenness of the chemical process.

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Chapter 4. Ligand-Promoted Direct C–H Arylation of Simple Arenes: Evidence for a Cooperative Bimetallic Mechanism*

4.1 Introduction

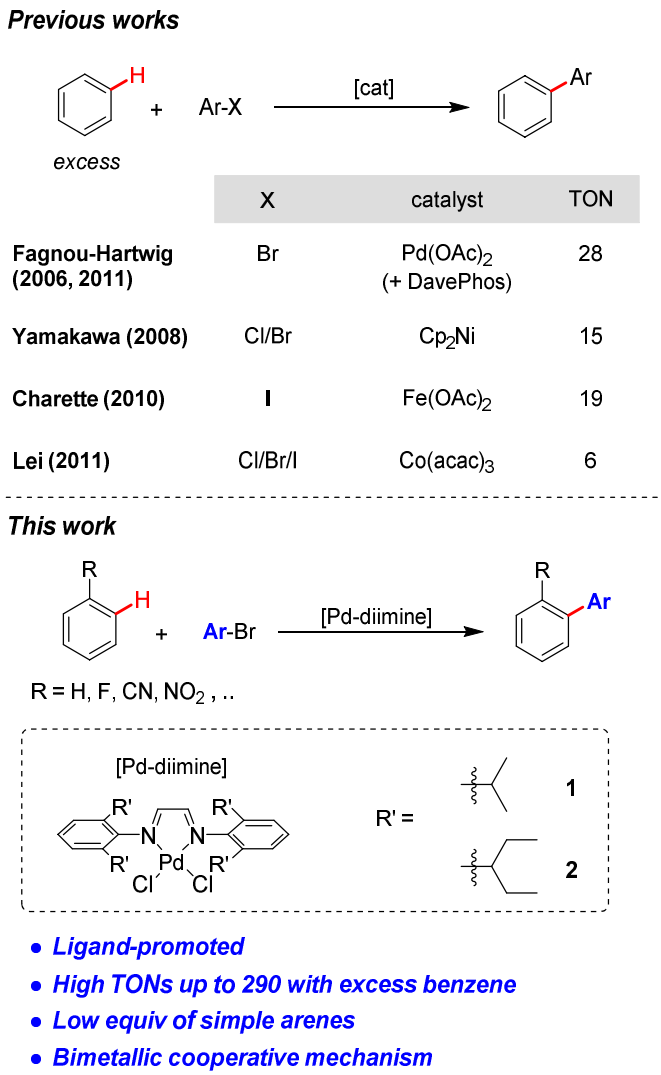
As discussed in Chapter 3, direct C–H arylation reaction is a powerful methodology for constructing biaryl linkages in an efficient manner, avoiding prefunctionalization of the substrates.[1] Over the past decade, tremendous efforts have been dedicated to the development of this reaction using transition metal catalysis. The most prominent advances have been achieved through the chelation-assisted strategy.[2] However, this approach often requires additional synthetic operations to remove or transform the directing group. While electronic biases have also been successfully utilized to activate certain C–H bonds in aromatic substrates,[3] only suitably functionalized or activated substrates could be utilized, limiting the applicability of the reaction.

In this context, the activation and functionalization of simple arenes devoid of any directing group or electronic activation is greatly important for broadening the synthetic value of the direct C–H arylation reactions.[1j, 1m, 4] Despite its importance, this topic remains relatively underexplored. In particular, benzene, a perfectly unactivated arene, is one of the most challenging substrates for C–H arylation. In this respect, pioneering works were performed by Fagnou and Hartwig. Fagnou and

* The majority of this work has been published: Jaewoon Kim and Soon Hyeok Hong*, *ACS Catal.* **2017**, *7*, 3336-3343.

co-workers reported the first direct C–H arylation of benzene catalyzed by a palladium complex in 2006, where the DavePhos ligand and pivalic acid were used as key components of the catalytic system, facilitating a "concerted metallation deprotonation (CMD)" process.[5] However, in 2011, Hartwig and co-workers performed some mechanistic studies of the same reaction and reported that the reaction did not require a phosphine ligand and a "ligandless" complex was found to be more reactive.[6]

Since the first report by Fagnou, other catalytic systems for the C–H arylation of benzene have been developed on the basis of Pd, Ni, Fe, and Co metal complexes (Scheme 4.1).[5-7] However, all these systems require an excess or solvent amount of benzene because of its low reactivity and suffer from low turnover numbers (TONs) within the range of 5–28. Indeed, for this reaction to be practically useful, it is necessary to develop a catalytic system that can function at low catalyst loadings with high TONs and allow the performance of the reaction with a small number of equivalents of arene substrates.[1j, 8] Even though the Hartwig group revealed that the original Pd-catalyzed direct arylation of benzene with aryl bromide did not require any external ligand, we postulated that a certain "ligand-assisted" catalytic system could address the current limitations such as low reaction efficiency.



Scheme 4.1 Direct C–H arylation of simple arenes. TONs are calculated on the basis of the highest yield among the substrate scopes reported.

Diimines are some of the most widely used bidentate ligands.[9–11] They possess a high degree of structural diversity because of their facile synthesis using economical and readily available precursors, compared to other bidentate ligands such as bisphosphine ligands. They have been most widely used in Ni- or Pd-

catalyzed ethylene polymerization since their introduction by Brookhart and co-workers and trademarked as the Versipol catalyst system by DuPont.[9] Significant effort has also been devoted to studying the C–H activation using Pd– or Pt–diimine complexes. Tilset, Bercaw, and others thoroughly investigated the mechanism of the C–H activation step in the reaction between a Pd– or Pt–diimine complex and hydrocarbons, including benzene and methane, mainly in a stoichiometric manner.[10] Diimine ligands were also utilized for various other reactions such as Suzuki–Miyaura coupling.[11] Recently, the Sanford group reported a catalytic direct C–H arylation of naphthalene using Pd–diimine complexes.[4e] They systematically investigated the influence of the electronic properties of the diimine ligands to achieve high activity and selectivity.

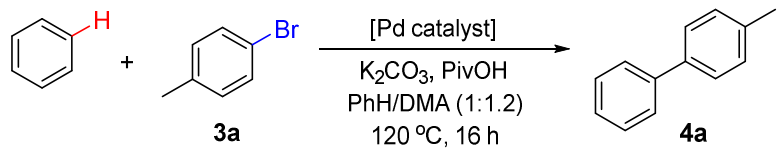
Herein, we wish to describe how a diimine-assisted Pd catalyst can efficiently facilitate the direct C–H arylation of simple arenes, including benzene with high TONs of $\leq$290 (Scheme 4.1). To the best of our knowledge, this is the highest TON described to date among the reported transition metal-catalyzed direct C–H arylations of benzene. The developed catalyst also shows an improved functional group tolerance compared to that obtained with the previously developed Fagnou–Hartwig conditions. The efficiency of the catalytic system was further proven by the reactions of simple arenes with small number of equivalents. A little as 2–3 equiv of simple arenes, including benzene, can afford biaryl products in good yields. Furthermore, experimental evidence, including kinetic data, supports the existence of a bimetallic cooperative mechanism for this reaction.

4.2 Results and discussion

4.2.1 Reaction optimization

Initial investigations were performed with 4-bromotoluene **3a** in a benzene/DMA solution (1:1.2, 0.1 M). In the presence and absence of the DavePhos ligand, palladium acetate afforded the desired biaryl product **4a** in good yields, faithfully reproducing the reported results (Table 4.1, entries 1 and 2).[5-6] A decreased catalyst loading (1 mol %) resulted in a significantly reduced reactivity (entry 3). The change of the Pd source to palladium chloride led to an increased reactivity (entry 4). To demonstrate our hypothesis, we employed Pd–diimine complex **1** bearing 2,6-diisopropylphenyl groups as a catalyst, which displayed an excellent reactivity (entry 5). To our delight, the use of bulkier diimine complex **2** further improved the reaction efficiency affording a quantitative yield (entry 6) (See Table 4.4 for more detailed screening results of diimines). The enhanced reactivity was further demonstrated by its TOF (26 h^{-1}) being higher than those of $PdCl_2$ (16 h^{-1}), $Pd(OAc)_2$ (6 h^{-1}), and $Pd(OAc)_2$/DavePhos (5 h^{-1}). A lower loading of complex **2** (0.5 mol %) still furnished biaryl product **4a** in good yield (entry 7). Notably, when we performed the reaction on a larger scale (0.6 g of **3a**, 4 mmol**)** in the presence of a lower loading of **2** (0.1 mol %), the TON reached 290, which is the highest TON reported so far for the C–H arylation of benzene (entry 8). Other nitrogen-based bidentate ligands, such as 1,10-phenanthroline (phen) and tetramethylethylenediamine (tmeda), did not show any reactivity (entries 9 and 10). Control experiment indicated that pivalic acid was essential for the reaction (entry 11).

Table 4.1 Optimization of reaction conditions[a]



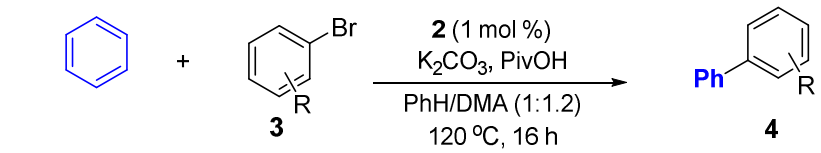
entry	catalyst	loading (mol %)	additive (equiv)	yield (%)	TON [TOF(h^{-1})][c]
1	$Pd(OAc)_2$/ DavePhos	3	PivOH (0.3)	75	25(5)
2	$Pd(OAc)_2$	3	PivOH (0.3)	81	27
3	$Pd(OAc)_2$	1	PivOH (0.3)	27	27(6)
4	$PdCl_2$	1	PivOH (0.3)	60	60(16)
5	**1**	1	PivOH (0.3)	83	83
6	**2**	1	PivOH (0.3)	>99	99(26)
7	**2**	0.5	PivOH (0.3)	77	154
8[b]	**2**	0.1	PivOH (0.3)	29	290
9	$PdCl_2$/phen	1	PivOH (0.3)	0	0
10	$PdCl_2$/tmeda	1	PivOH (0.3)	0	0
11	**2**	1	-	0	0

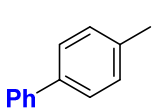
[a]Reaction conditions: **3a** (0.2 mmol), K_2CO_3 (2.5 equiv), pivalic acid (0.3 equiv), and catalyst in a benzene/DMA mixture (1:1.2, 0.1 M) at 120 °C for 16 h; GC yields using dodecane as an internal standard. [b]On a 4 mmol scale. [c]TOF at 1 h. DMA = dimethylacetamide; PivOH = pivalic acid.

4.2.2 Substrate scope

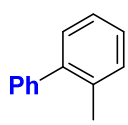
With the optimized conditions in hand, we investigated the scope of aryl bromides as coupling partners (Table 4.2). Generally, a variety of electron-rich aryl bromides, including heteroatom-containing derivatives, provided the corresponding biaryl products **4** in excellent to quantitative yields (**4a**–**l**). In particular, aryl bromides with ether group **3h** and **3i** and with amine group **3j**–**l**, which can coordinate to the metal center and thus hamper the reaction, were chosen to compare the functional group tolerance of different catalytic systems (Scheme 4.2). When the reactions were conducted under the reported conditions, ether- or amine- substituted biaryls **4h**–**l** were produced in yields lower than those obtained using Pd–diimine catalyst **2,** indicating a better functional group tolerance of the developed catalytic system. Electron-deficient aryl bromides with a trifluoromethyl substituent at the *meta* position also provided the desired products in good to excellent yields (**4m** and **4n**). However, the presence of an electron-withdrawing substituent at the *para* position resulted in a noticeably lowered reactivity (**4o** and **4p**), implying a significant dependence on the electronic effect of the substrates.

Table 4.2 Substrate scope[a]

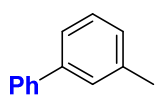




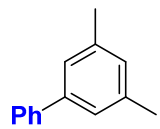
4a, >99%



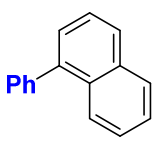
4b, 91%



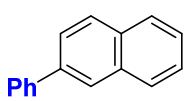
4c, >99%



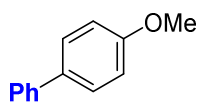
4d, >99%



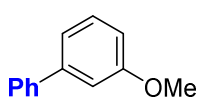
4e, >99%



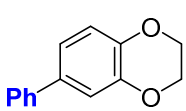
4f, >99%



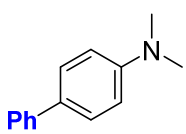
4g, >99%



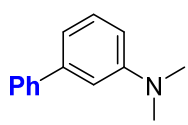
4h, >99%



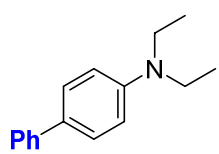
4i, >99%



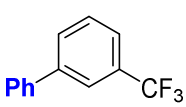
4j, 77%(92%[b])



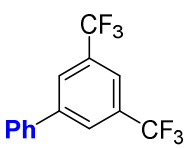
4k, 88%



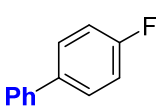
4l, 82%(>99%[b])



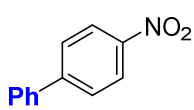
4m, 90%[b]



4n, 71%

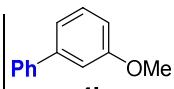
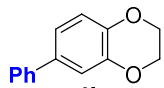
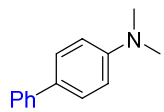
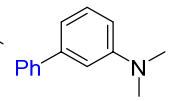
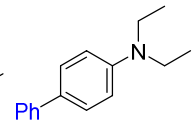


4o, 20%



4p, 13%

[a]In 0.2 mmol of aryl bromide; isolated yields. [b]At a 3 mol % loading of **2**.

catalyst	 **4h**	 **4i**	 **4j**	 **4k**	 **4l**
$Pd(OAc)_2$[b]	63%	44%	47%	54%	36%
$PdCl_2$[b]	42%	56%	46%	46%	55%
2	>99%	>99%	77%	88%	82%

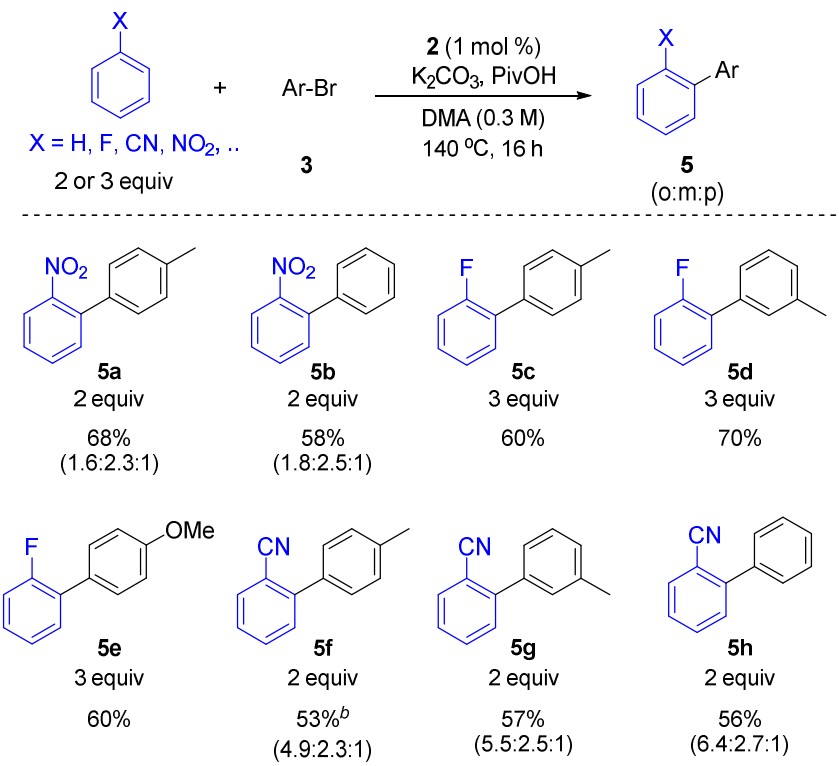
Scheme 4.2 Comparison of functional group tolerance. Reactions using the corresponding catalyst (1 mol %) under standard conditions; isolated yields. [a]NMR yields.

4.2.3 Enhanced reactivity with a small number of equivalents of simple arenes

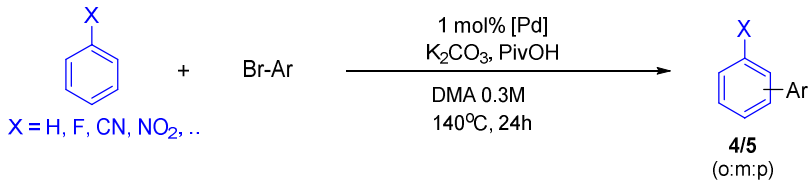
To explore the reactivity of the catalyst further, we turned our attention to the reaction of other simple arenes. The previous works by Fagnou[5] or Hartwig[6] focused on only benzene, and the arylation of other simple arenes was not attempted. Until now, the direct C–H arylation of simple arenes has suffered from the requirement for an excess amount of arenes because of their low reactivity, significantly limiting the practical applicability of this reaction.[8] We conducted the arylation reactions using 2 or 3 equiv of arenes (Table 4.3). Two equivalents of nitrobenzene[12] furnished a mixture of regioisomers in modest yields (**5a** and **5b**). Interestingly, fluorobenzene displayed an excellent *ortho* selectivity and good yields affording only trace amounts of *meta* and *para* products (**5c**–**e**). Such particular selectivity of fluorobenzene has been reported previously.[5] When benzonitrile[13] was subjected to the reaction, good *ortho*-favored selectivity was observed with modest yields (**5f**–**h**). Notably, this reaction can provide convenient access to **5f**, which is a precursor of angiotensin II

antagonists, by a one-step reaction starting from benzonitrile.[14] To investigate the effect of the ligand on the reactivity to simple arenes, some of the reactions were also conducted with Fagnou's conditions[5] (using $Pd(OAc)_2$ and DavePhos) or "ligandless"[6] conditions (using $PdCl_2$). They afforded yields (4–55%) lower than those using Pd–diimine complex **2** (Scheme 4.3).

Table 4.3 C–H arylation with small numbers of equivalents of simple arenes[a]



[a]Reaction conditions: aryl bromide (0.2 mmol), simple arene (2 or 3 equiv), K_2CO_3 (2.5 equiv), pivalic acid (0.3 equiv), and **2** (1 mol %) in DMA (0.3 M) at 140 °C for 16 h; isolated yields and selectivities were determined by GC. [b]With a 3 mol % loading of **2**.



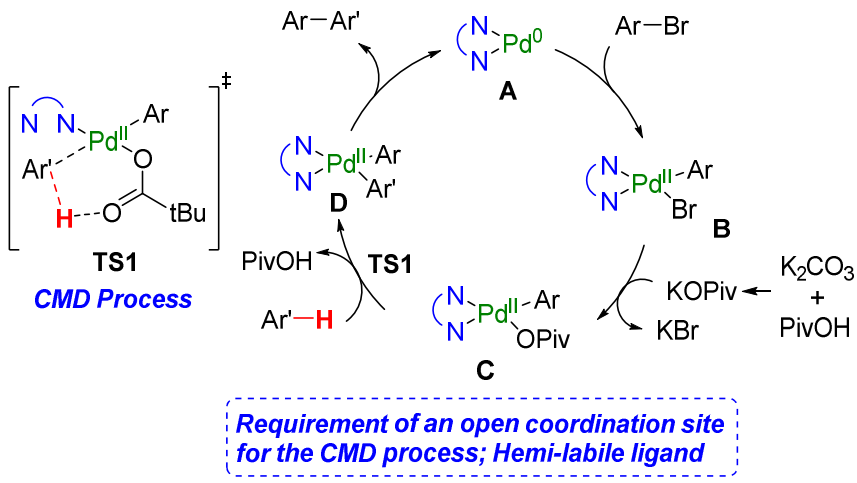
	Pd(OAc)$_2$ [a]	Pd(OAc)$_2$/ DavePhos [a]	PdCl$_2$ [a]	**2** [b]
4a 3 equiv	2%	5%	5%	20%
5a 2 equiv	20% (1.7:2.3:1)	29% (2.2:2.4:1)	55% (1.7:2.3:1)	68% (1.6:2.3:1)
5b 2 equiv	27% (1.3:1.9:1)	13% (2.0:2.7:1)	39% (1.7:2.5:1)	58% (1.8:2.5:1)
5d 3 equiv	45%	39%	54%	70%
5e 3 equiv	28%	48%	48%	60%
5f 2 equiv	4% (3.3:2.4:1)	14% (6.5:2.7:1)	30% (4.7:2.4:1)	57% (4.9:2.3:1)
5h 2 equiv	11% (5.4:2.6:1)	15% (7.5:2.7:1)	27% (5.8:2.6:1)	56% (6.4:2.7:1)

Scheme 4.3 Comparison of the reactivity to simple arenes. [a] GC yields. [b]isolated yields. Selectivities were determined by GC.

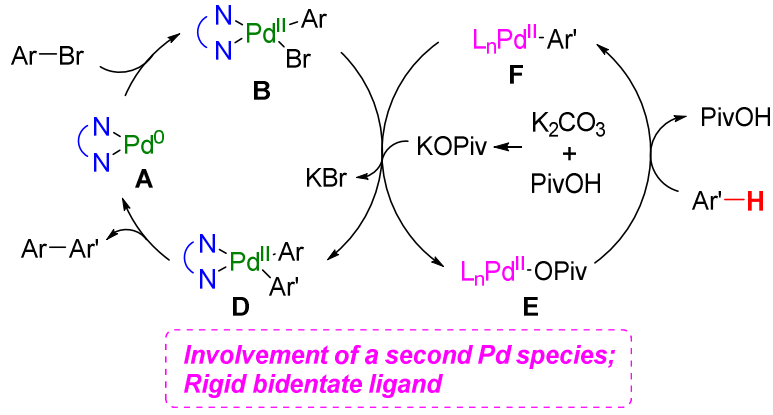
4.2.4 Mechanistic considerations

For the Pd-catalyzed C–H arylation reaction, a typical Pd(0/II) cycle can be considered as a plausible mechanism (Scheme 4.4a). As shown in a control experiment (Table 4.1, entry 11), the essential role of pivalic acid implies that this reaction is likely to occur through a pivalate-promoted CMD process, as proposed by many literature reports.[15] After oxidative addition of aryl bromide to Pd(0) complex **A**, the resulting Pd(II) complex **B** undergoes ligand exchange with pivalate, affording complex **C**. The next C–H cleavage step with the aid of pivalate generates Pd(II)ArAr' complex **D**, which undergoes reductive elimination furnishing the biaryl product and complex **A**. For an arene substrate to undergo a CMD process, there should be an open coordination site that can be approached by the C–H bond of the arene. At the same time, the pivalate should be coordinated to the Pd center to direct the C–H cleavage. This means that the bidentate diimine ligand should shift to a monodentate form to provide transition state **TS1**, which is feasible only when the ligand is not rigid but flexible and hemilabile. In other words, such hemilability of the diimine ligand is an essential feature of mechanism A to involve the κ^1-diimine complex.

a) Possible mechanism A: Classical monometallic mechanism



b) Possible mechanism B: Cooperative bimetallic mechanism

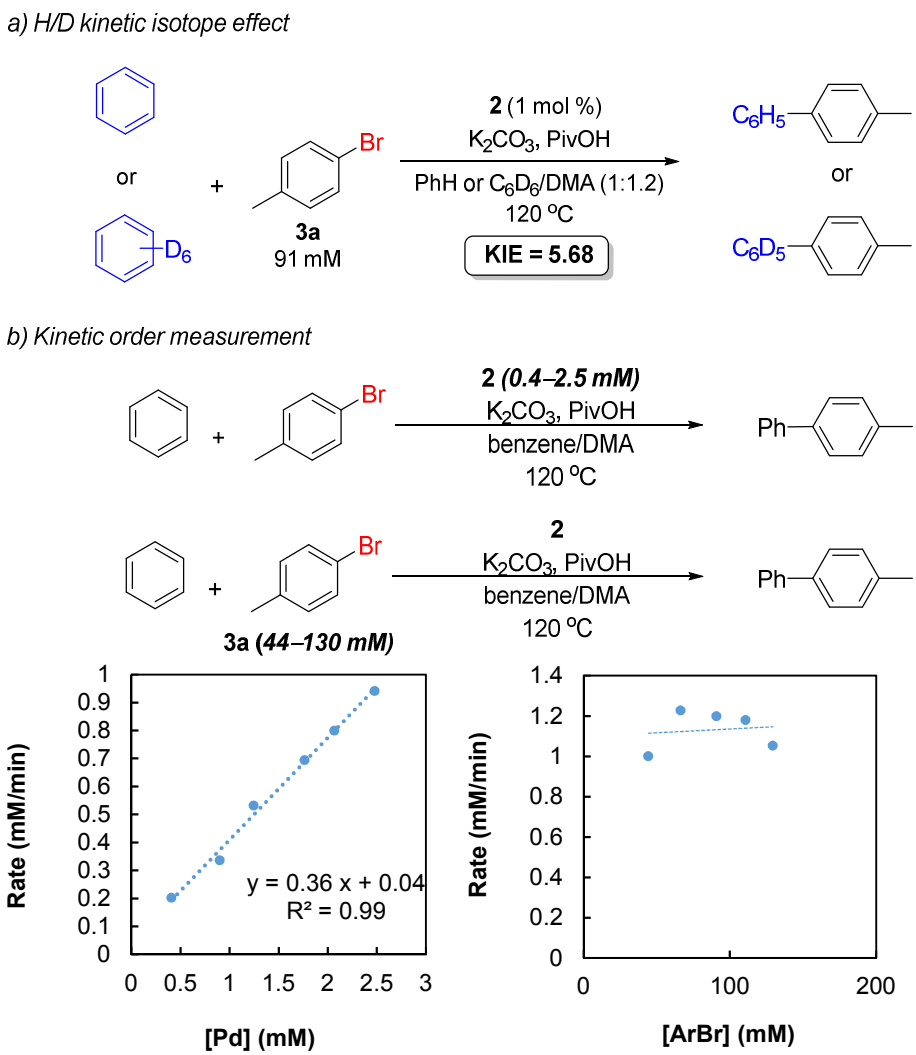


Scheme 4.4 Mechanistic hypotheses

Another possible mechanistic pathway consists of a cooperative bimetallic mechanism (Scheme 4.4b). Over the past few years, mechanisms involving two palladium species have been well established for the C–H arylation of pyridine N-oxide and oxidative biaryl coupling by Hartwig[16] and Stahl,[17] respectively. Recently, a cooperative mechanism for a C–H functionalization mediated by two different metal species has been also reported.[18] However, in the case of the direct C–H arylation of benzene with aryl bromides, no detailed experimental proofs have been presented to distinguish between these two mechanisms since the initial proposition of monometallic mechanism by Fagnou,[5] although Gorelsky theoretically suggested that a bimetallic mechanism could be favored.[19] In our reaction, one Pd–aryl species **B** can be generated from the oxidative addition of aryl bromide to **A**, while another species **F** can be generated from the C–H activation by **E**. Both **B** and **F** can undergo transmetalation to afford Pd(II)ArAr' complex **D**. In this mechanism, the transmetalation can operate even if the diimine ligand chelates the Pd center. To distinguish the exact mechanism from these possible scenarios, detailed studies, including kinetic measurements and other investigations that aimed to identify the catalytic intermediates, were performed.

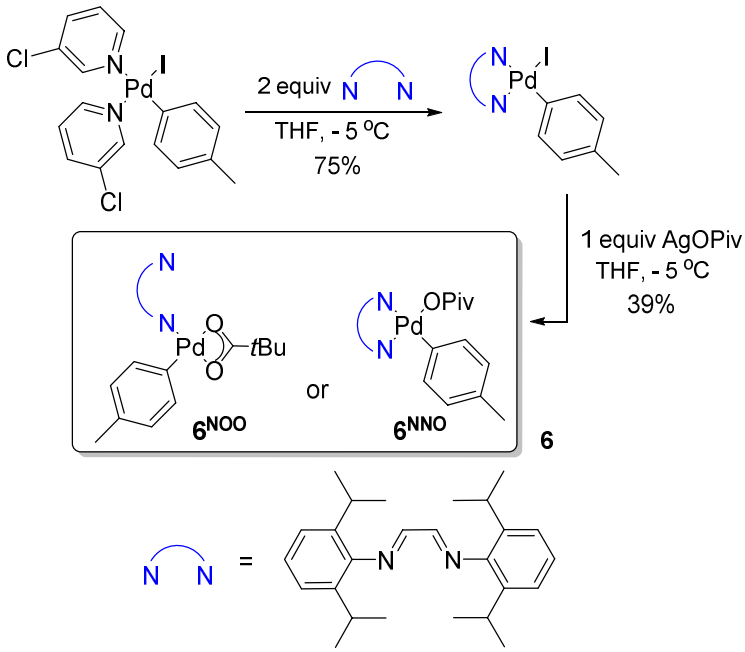
We started our investigation by conducting kinetic experiments. The deuterium intermolecular kinetic isotope effect (KIE) was measured using benzene and benzene-d_6 as substrates. Independent reactions using different isotopologues of benzene afforded a large primary KIE (k_H/k_D = 5.68) (Scheme 4.5a). This is in agreement with related reports, implying the significant involvement of C–H bond cleavage in the turnover-limiting step.[5] We further investigated the dependence of

the reaction rates on Pd and ArBr concentrations (Scheme 4.5b). The initial rates of the reactions with varying concentrations of Pd or ArBr were measured by GC. A first-order dependence in Pd concentration and a zero-order dependence in ArBr concentration were observed. These results further support the hypothesis that the turnover-limiting step might be the C–H cleavage step involving a palladium species and an arene substrate.



Scheme 4.5 Kinetic study

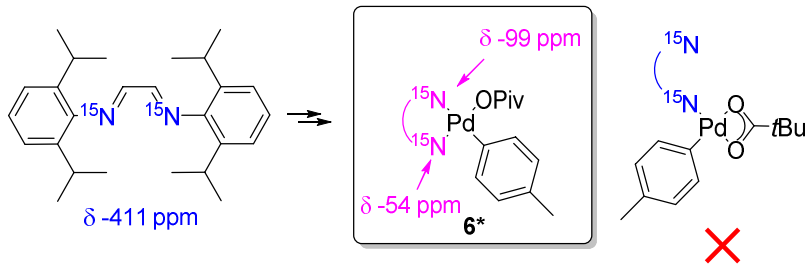
Then, we synthesized PdAr(diimine)(OPiv) complex **6**, which can be hypothetically regarded as a potential catalytic intermediate (Scheme 4.6). It is analogous to complexes **B** and **C** in Scheme 4.4, which are obtained after oxidative addition and ligand exchange. 2,6-Diisopropylphenyl-substituted diimine was selected as the model ligand, because attempts to synthesize the complex with bulky 3-pentyl-substituted diimine, analogous to **2**, were unsuccessful. Only fast decomposition leading to the homodimerization of the aryl group was observed because of a rapid reductive elimination accelerated by the bulky ligand. The structure of complex **6** can be expected to correspond to either $\mathbf{6}^{\mathbf{NOO}}$ or $\mathbf{6}^{\mathbf{NNO}}$, which cannot be easily distinguished by ^{1}H and ^{13}C NMR. According to literature reports describing the synthesis of the PdAr(OPiv) complex, when phosphines are used as ancillary ligands, only one phosphine coordinates to Pd with a bidentate pivalate ligand.[6] If one imine group of the diimine ligand would be easily dissociated from Pd and undergo free rotation, complex **6** could exist as $\mathbf{6}^{\mathbf{NOO}}$ with κ^2-pivalate and κ^1-diimine. However, if the diimine lacks flexibility to rotate because of its bulky substituents and the Pd–N bond is stronger than the Pd–O bond, it would rigidly bind to Pd as a bidentate ligand as in $\mathbf{6}^{\mathbf{NNO}}$.



Scheme 4.6 Synthesis of a possible catalytic intermediate

To determine the exact structure of complex **6**, we synthesized ^{15}N-labeled complex **6*** and conducted ^{1}H–^{15}N HMBC NMR spectroscopic experiments (Figure 4.1a). The nitrogen atoms of the free ^{15}N-labeled diimine were assigned at –411 ppm in the ^{15}N NMR spectrum. However, the spectrum of **6*** presented two different chemical shifts at –54 and –99 ppm, which fall in a range distinctly different from that of free diimine, indicating that both nitrogen atoms in the diimine are coordinated to Pd in solution. In addition, the structure of $\mathbf{6}^{\mathbf{NNO}}$ in the solid state was further unambiguously confirmed by single-crystal X-ray analysis (Figure 4.1b). Therefore, we concluded that the diimine ligand of complex **6** binds to Pd in a bidentate form both in solution and in the solid state. This implies that the preservation of a chelate ring in its bidentate form is favored for complex **6** with a low hemilability at least in the ground state.

a) ^{15}N labeling study - ^{1}H-^{15}N HMBC NMR in CD_2Cl_2



b) Single crystal structure

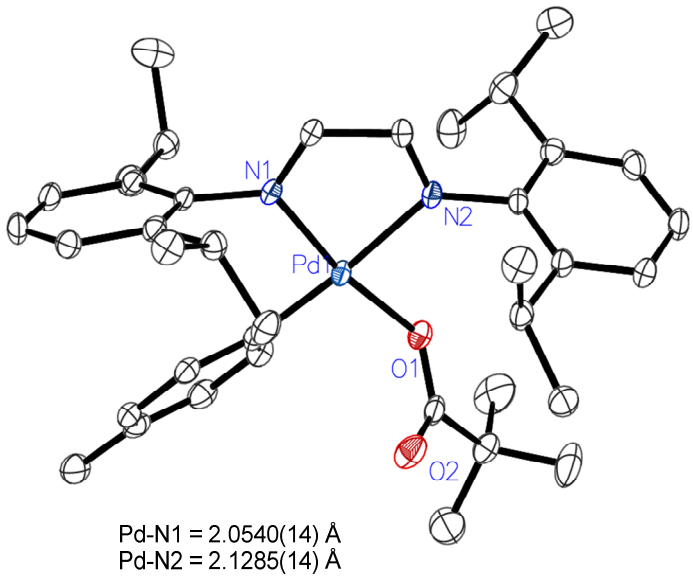
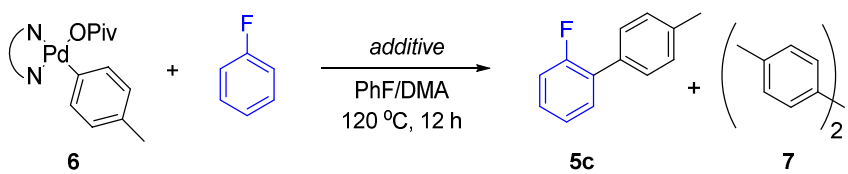


Figure 4.1 Determination of the structure of intermediate complex **6**. (a) ^{1}H–^{15}N HMBC NMR in CD_2Cl_2; (b) ORTEP drawing of intermediate complex **6**. Hydrogen atoms have been omitted for the sake of clarity.

Complex **6** was subjected to a stoichiometric reaction with fluorobenzene in DMA (Scheme 4.7). The reaction in the absence of any additive provided only a small amount of desired product **5c**, while a large amount of homocoupled product **7** was detected instead. To improve the reaction conditions in analogy to the catalytic reaction, the concentration of **6** was decreased and KOPiv and a bromide anion were added. The reactions afforded higher yields of **5c**. Notably, when Pd–diimine complex **1** was added, **5c** was obtained in 70% yield with the concomitantly suppressed generation of **7**. An additional palladium source in the stoichiometric reaction mixture significantly enhanced the reactivity. If the reaction follows a monometallic mechanism like mechanism A (Scheme 4.4a), the addition of a palladium complex would not improve the reaction. However, complex **6** requires another palladium complex to achieve high reactivity according to mechanism B (Scheme 4.4b).

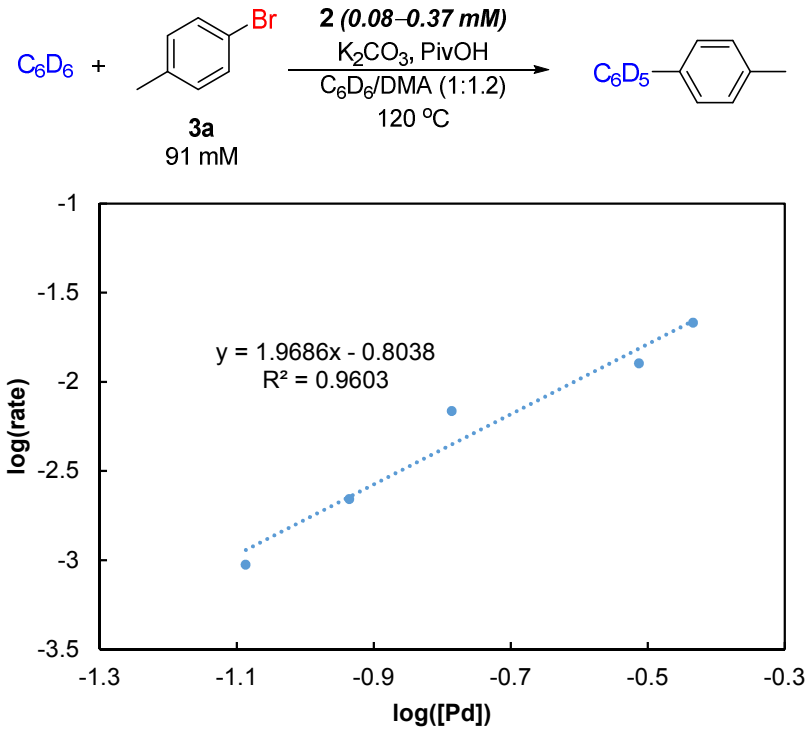


6 **5c** **7**

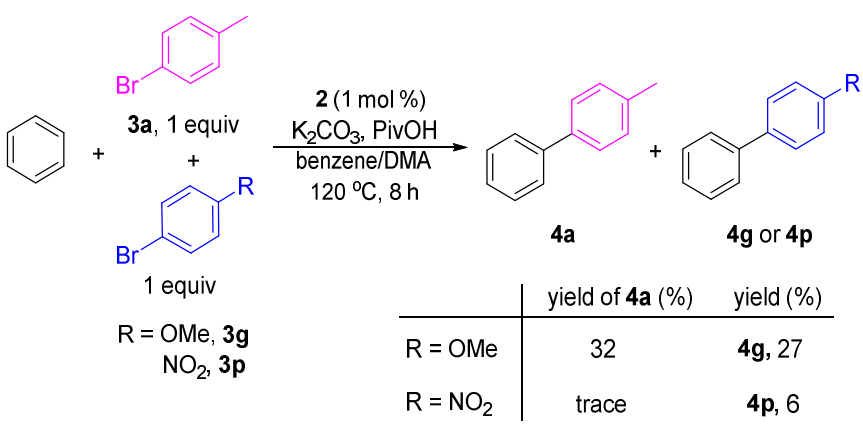
conc. (mM)	additive	yield of **5c** (%)	yield of **7** (%)
1.4	none	7	50
1.4	20 equiv KOPiv, 20 equiv NBu_4Br	35	20
0.7	20 equiv KOPiv, 20 equiv NBu_4Br	36	15
0.7	20 equiv KOPiv, 20 equiv NBu_4Br, 3 equiv **1**	70	12

Scheme 4.7 Stoichiometric reaction of complex **6**. Yields were determined by GC using dodecane as an internal standard.

To verify this hypothesis further, we conducted another kinetic experiment. As reported by the Stahl group, a C–H arylation reaction following a bimetallic pathway displays a first-order dependence at high Pd concentration, but a second-order dependence at low Pd concentration where the transmetalation becomes rate-limiting.[17] A second-order dependence is more pronounced in deuterated arenes because the slower rate of C–D bond cleavage lowers the Pd–Ar concentration and thus further retards the transmetalation. For our catalytic system, a first-order dependence in Pd concentration was already observed using benzene (Scheme 4.5). We performed the arylation reaction of C_6D_6 with very low Pd concentrations and measured the initial rates (Scheme 4.8). Remarkably, the plot clearly revealed a second-order dependence at low Pd concentrations. This evidence strongly supports the assumption that our reaction follows a cooperative bimetallic mechanism (Scheme 4.4b).

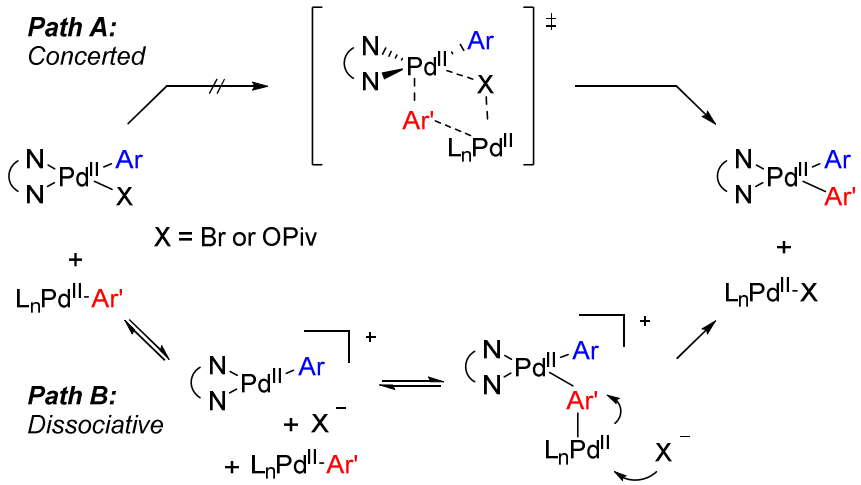


Scheme 4.8 Kinetic order in Pd at low concentrations



Scheme 4.9 Competition experiments with different aryl bromides

To gain more information about the mechanism, competition experiments were performed using electronically different sets of aryl bromides (Scheme 4.9). A first reaction was conducted with electron-rich aryl bromides **3a** and **3g** at the same time, while another reaction involved **3a** and electron-deficient **3p** as competing substrates. When the former reaction was stopped after 8 h, moderate and similar yields of **4a** and **4g** were detected with a combined 59% GC yield. In contrast, in the presence of **3p**, only a trace amount of **4a** was produced from electron-rich **3a**. If the oxidative addition in the developed reaction were reversible before the rate-determining step, the coupling with the electron-rich aryl bromide would occur in reasonable yields, although the electron-poor substrate is more reactive to the oxidative addition.[20] Instead, the observed results suggest that the oxidative addition is irreversible and occurs before the rate-limiting step. For this reason, albeit in a low yield, **4p** is the dominant product over **4a**. On the other hand, after the predominant and fast oxidative addition of the electron-poor aryl bromide, the next steps become sluggish. The same trend of low reactivity with electron-poor aryl bromides was observed via examination of the substrate scope (Table 4.2, **4o** and **4p**). We hypothesized that the reason why these substrates exhibited poor yields despite a fast oxidative addition could be attributed to the transmetalation step.



Scheme 4.10 Possible mechanistic pathways for the transmetalation step

While the transmetalation between two metal complexes is commonly involved in many cooperative dual-catalysis reactions, its detailed mechanism depends on the reaction conditions and thus has not been fully understood.[21] The Hashmi group recently reported a detailed theoretical study of a transmetalation step in a Au/Pd-mediated cross coupling reaction involving monodentate or bidentate ligands.[22] On the basis of this study, we can consider two possible pathways for the transmetalation with a bidentate Pd–diimine complex (Scheme 4.10). Path A is a concerted mechanism going through a four-membered transition state. Considering the properties of the diimine ligand, which presents a steric bulk in the axial sites of the square plane, this pathway might be avoided because of an inaccessibly high energy barrier.[23]

Alternatively, we propose path B as a possible mechanism involving a multistep process. In path B, the anionic ligand undergoes dissociation, generating a cationic palladium complex with a vacant coordination site. The aryl group of a second Pd species binds to the open site of the cationic complex, and sequentially, the anion aids the transfer of the aryl group, completing the transmetalation step. The sluggish reaction of electron-deficient aryl bromides observed in the substrate scope in Table 4.2 and the results of the competition reaction in Scheme 4.9 could be attributed to the involvement of a cationic palladium intermediate. The presence of an electron-deficient aryl group could make the dissociation of the anion ligand unfavorable, interrupting the further progress of the reaction. Furthermore, we observed a significant influence of the solvent on the outcome of the reaction (Table 4.5). Only DMA was effective for this reaction, implying the stabilization of an ionic intermediate complex by a polar solvent.[24]

4.3 Conclusion

In summary, we developed a highly efficient catalytic system based on a Pd–diimine complex for the direct C–H arylation of simple arenes. This system not only delivers the highest TON reported so far for the arylation of benzene but also presents a better functional group tolerance, and the reactions can be performed efficiently at numbers of equivalents of arene substrates smaller than those previously reported. Notably, mechanistic investigations, including a kinetic study and stoichiometric reactions with potential intermediate complexes, clearly supported a cooperative bimetallic mechanism. The significant effect of the electronic properties of aryl bromides to the reaction could be attributed to a transmetalation step.

4.4 Experimental section

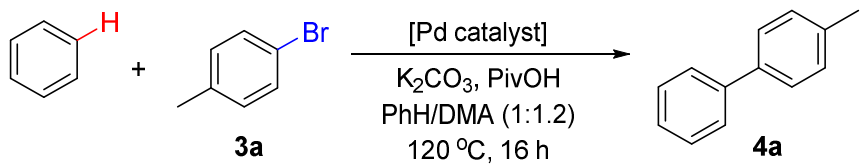
4.4.1 General information

Unless otherwise stated, all reactions were carried out using standard Schlenk techniques or in an argon-filled glove box. All anhydrous solvents were purchased from Aldrich and used without further purification. All 1D NMR spectroscopy experiments were conducted with a Varian 400 and 500 MHz or a Bruker 300 MHz. NMR spectra were processed with either ACD NMR Processor or MestReNova. Chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^1H, 77 ppm for ^{13}C; CH_2Cl_2 in CD_2Cl_2: 5.32 ppm for ^1H, 54 ppm for ^{13}C). Coupling constants are reported in Hertz. GC analyses were carried out with a 7980A GC system from Agilent Technologies, equipped with an HP-5 column and FID detector using dodecane as internal standard. Elemental analysis and ^1H-^{15}N HMBC NMR spectroscopy were conducted at the National Center for Inter-University Research Facilities of Seoul National University (NCIRF) using a Thermo Scientific Flash 2000 elemental analyzer and a Bruker Avance-600, respectively. ^1H-^{15}N HMBC NMR spectroscopic experiments were also conducted at the National Instrumentation Center for Environmental Management (NICEM) of Seoul National University. Single crystal X-ray crystallography was conducted at the Center for Research Facilities in the Research Institute of Pharmaceutical Sciences of Seoul National University, using an Agilent SuperNova X-ray diffractometer. 2,6-Di(3-pentyl)aniline for the synthesis of the bulky diimine was prepared following a literature procedure.[25] All diimine ligands and complexes were synthesized by adaptation of published procedures.[4e, 10b, 26] All starting materials and reagents were

purchased from Acros, Aldrich, Alfa Aesar, TCI, and Strem Chemical Inc., and used without further purification unless otherwise stated.

4.4.2 Optimization table

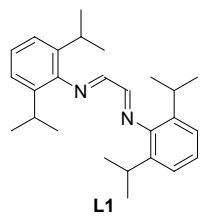
Table 4.4 Evaluation of ligands for the direct C-H arylation of benzene[a]



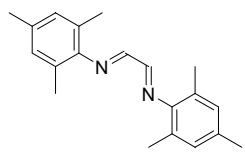
entry	Pd source	ligand	loading (mol %)	yield (%)
1	$Pd(OAc)_2$	DavePhos	3	75
2	$Pd(OAc)_2$	-	3	81
3	$Pd(OAc)_2$	-	1	27
4	$PdCl_2$	-	1	60
5	$PdCl_2$	**L1**	3	95
6	$PdCl_2$	**L2**	3	47
7	$PdCl_2$	**L3**	3	34
8	$PdCl_2$	**L4**	3	52
9	$PdCl_2$	**L5**	3	23
10	$PdCl_2$	**L6**	3	15
11	$PdCl_2$	**L7**	3	3
12	$PdCl_2$	**L8**	3	19
13	$PdCl_2$	**L9**	3	86

14	**1**	-	1	83
15	**2**	-	1	>99
16	**2**	-	0.5	77
17	$PdCl_2$	1,10-phenanthroline	1	0
18	$PdCl_2$	tmeda	1	0

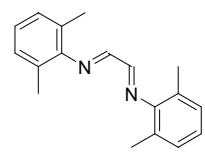
[a]Reaction conditions: **3a**(0.2 mmol), K_2CO_3 (2.5 equiv), pivalic acid (0.3 equiv), and catalyst in a benzene/DMA mixture (1:1.2, 0.1 M) at 120 °C for 16 h; GC yields using dodecane as an internal standard.



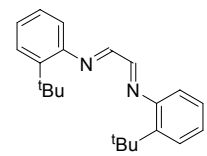
L1



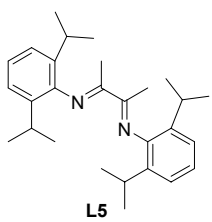
L2



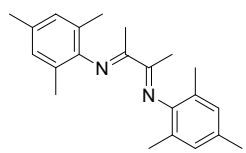
L3



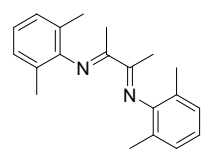
L4



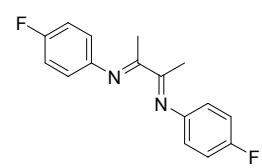
L5



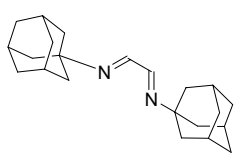
L6



L7

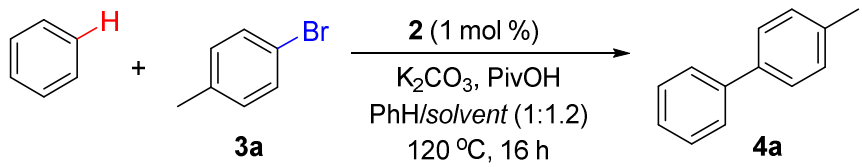


L8



L9

Table 4.5 Solvent screening[a]



entry	solvent	yield (%)
1	DMA	99
2	benzene	0
3	1,2-dichloroethane	0
4	acetonitrile	1
5	1,4-dioxane	2
6	THF	11
7	1,2-dimethoxyethane	0
8	cyclohexane	0

[a]Reaction conditions: **3a**(0.2 mmol), K_2CO_3 (2.5 equiv), pivalic acid (0.3 equiv), and **2** (1 mol %) in a benzene/solvent mixture (1:1.2, 0.1 M) at 120 °C for 16 h; GC yields using dodecane as an internal standard.

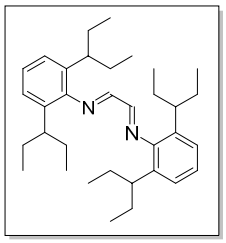
4.4.3 Synthesis of diimines and complexes

General procedure for the synthesis of diimines from glyoxal; ***L1–L4, L9***

The diimine ligands were prepared according to a literature procedure.[26] To a stirred solution of aniline (2.0 equiv) in methanol was added glyoxal (40% in H_2O, 1.2 equiv) followed by a catalytic amount of formic acid (0.3 equiv) at room temperature. The desired diimine started to precipitate from the reaction media and the stirring was continued overnight until completion of the reaction. The pure diimine was successfully obtained by either recrystallization of the crude residue from methanol or ethanol or by filtration through a pad of silica.

General procedure for the synthesis of diimines from glyoxal; ***L5–L8***

The diimine ligands were prepared according to a literature procedure.[10b] To a stirred solution of aniline (2.0 equiv) in methanol was added 2,3-butanedione (1.0 equiv) followed by a catalytic amount of formic acid (0.3 equiv) at room temperature. The desired diimine started to precipitate from the reaction media and the stirring was continued overnight until completion of the reaction. The pure diimine was successfully obtained by either recrystallization of the crude residue from methanol or ethanol or by filtration through a pad of silica.

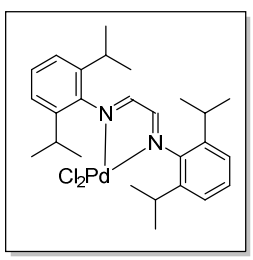


N,N'-Bis(2,6-di(3-pentyl)phenyl)ethane-1,2-diimine

2,6-Di(3-pentyl)aniline was prepared following a reported literature procedure.[26] To a stirred solution of 2,6-di(3-pentyl)aniline (934 mg, 4 mmol, 2.0 equiv) in regular methanol (10 mL) was added glyoxal (40% in H2O, 273 μL, 2.4 mmol, 1.2 equiv) followed by formic acid (23 μL, 0.6 mmol, 0.3 equiv) at room temperature. The desired diimine started to precipitate from the reaction media and the stirring was continued until completion of the reaction (12 h). The solid was isolated by filtration and the filtrate was concentrated under vacuum. The resulting brownish solid was recrystallized from methanol. Both solids were combined and dried under high vacuum to afford the pure desired diimine as a bright and shiny yellow crystalline powder (772 mg, 80%). The NMR spectral data match that reported in the literature.[26] ^{1}H NMR (499 MHz, $CDCl_3$) δ = 8.03 (s, 2 H), 7.14 (t, J = 7.3 Hz, 2 H), 7.07 (d, J = 7.3 Hz, 4 H), 2.55 - 2.44 (m, 4 H), 1.69 - 1.62 (m, 8 H), 1.59 - 1.51 (m, 8 H), 0.80 (t, J = 7.3 Hz, 24 H)

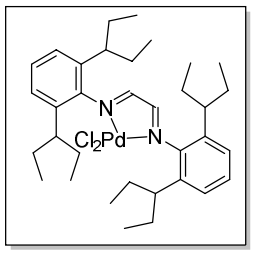
*General procedure for the synthesis of Pd-diimine complexes **1** and **2***

Pd-diimine complexes were prepared according to a modified literature procedure.[4e] $PdCl_2$ (1 equiv) was dissolved in acetonitrile (0.1 M), and the resulting suspension was heated to reflux until a clear, orange solution formed (indicative of $Pd(MeCN)_2Cl_2$). The appropriate diimine ligand (1 equiv) was then added, and the reaction mixture was heated to reflux overnight. The reaction was cooled to room temperature, and the orange precipitate was collected on a fritted filter, washed with acetonitrile and ether, and dried under vacuum.



Complex 1

The general procedure was followed using PdCl2 (88.7 mg, 0.5 mmol), diimine ligand L1 (118.3 mg, 0.5 mmol), and MeCN (5 mL). Complex **1** was obtained as a bright orange solid (216.0 mg, 78% yield). The NMR spectral data matched those reported in the literature.[27] ^{1}H NMR (499MHz, $(CD_3)_2CO$) δ = 8.64 (s, 2 H), 7.34 (d, *J* = 7.8 Hz, 2 H), 7.28 - 7.24 (m, 4 H), 3.46 - 3.40 (m, 4 H), 1.43 (d, *J* = 6.8 Hz, 12 H), 1.22 (d, *J* = 6.8 Hz, 12 H)



Complex 2

The general procedure was followed using PdCl2 (88.7 mg, 0.5 mmol), diimine ligand (244.4 mg, 0.5 mmol), and MeCN (5 mL). Complex **2** was obtained as a bright orange solid (273.1 mg, 82% yield). NMR characterization of this complex was not possible due to its low solubility. The purity of all samples of complex **2** used for catalysis was confirmed by elemental analysis. Anal. Calcd. for $C_{34}H_{52}Cl_2N_2Pd$: C, 61.31; H, 7.87; N, 4.21; Found: C, 61.32; H, 7.84; N, 4.23.

4.4.4 General arylation procedure

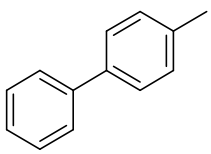
General procedure A: with excess amount of benzene

K_2CO_3 was dried at 120 °C in an oven overnight. Inside a glove box, a 10 mL Schlenk tube containing a magnetic stirring bar was charged with K_2CO_3 (2.5 equiv, 69.1 mg, 0.5 mmol) and complex **2** (1 mol %, 1.3 mg, 0.002 mmol). Pivalic acid (0.3 equiv, 0.06 mmol) was then added to the Schlenk tube as a solution in DMA (0.05 M, 1.2 mL), followed by benzene (1.0 mL) and the aryl halide (1.0 equiv, 0.2 mmol). The Schlenk tube was sealed and heated to 120 °C for 16 h. Upon completion of the reaction, the mixture was cooled to room temperature. When possible, the solvents were removed by distillation and the resulting residue was purified by silica gel flash chromatography typically using hexane as eluent. If the product was too volatile to remove DMA by distillation, it was directly loaded onto a silica gel packed flash chromatography column and eluted with hexane.

General procedure B: with simple arenes at low equivalents

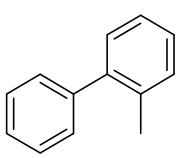
K_2CO_3 was dried at 120 °C in an oven overnight. Inside a glove box, a 3 mL Schlenk tube containing a magnetic stirring bar was charged with K_2CO_3 (2.5 equiv, 69.1 mg, 0.5 mmol) and complex **2** (1 mol %, 1.3 mg, 0.002 mmol). Pivalic acid (0.3 equiv, 0.06 mmol) was then added to the Schlenk tube as a solution in DMA (0.1 M, 0.6 mL), followed by the simple arene (2 or 3 equiv, 0.4 or 0.6 mmol) and the aryl halide (1.0 equiv, 0.2 mmol). The Schlenk tube was sealed and heated to 140 °C for 16 h. Upon completion of the reaction, the mixture was cooled to room temperature. When possible, the solvents were removed by distillation and the resulting residue was

purified by silica gel flash chromatography typically using hexane as eluent. If the product was too volatile to remove DMA by distillation, it was directly loaded on a silica gel packed flash chromatography column and eluted with hexane. Selectivity was measured by GC and compared with authentic samples.



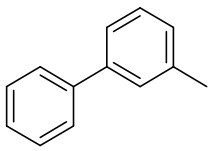
4-methylbiphenyl (4a)

A modification of general procedure A was employed for the reaction of 4-bromotoluene (**3a**, 0.2 mmol). The title compound was obtained as a white solid (33.6 mg, >99% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.61 (d, J = 7.3 Hz, 2 H), 7.57 - 7.49 (m, 2 H), 7.46 (t, J = 7.8 Hz, 2 H), 7.39 - 7.33 (m, 1 H), 7.33 - 7.24 (m, 2 H), 2.45 (s, 3 H). Its identity was confirmed by comparison with reported data.[28]



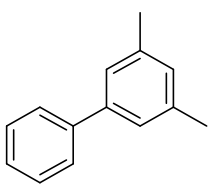
2-methylbiphenyl (4b)

A modification of general procedure A was employed for the reaction of 2-bromotoluene (**3b**, 0.2 mmol). The title compound was obtained as a colorless liquid (30.6 mg, 91% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.45 - 7.39 (m, 2 H), 7.38 - 7.31 (m, 3 H), 7.30 - 7.22 (m, 4 H), 2.28 (s, 3 H). Its identity was confirmed by comparison with reported data.[28]



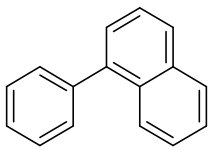
3-methylbiphenyl (4c)

A modification of general procedure A was employed for the reaction of 3-bromotoluene (**3c**, 0.2 mmol). The title compound was obtained as a colorless liquid (33.6 mg, >99% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.60 (d, J = 7.8 Hz, 2 H), 7.48 - 7.38 (m, 4 H), 7.35 (t, J = 7.8 Hz, 2 H), 7.18 (d, J = 7.3 Hz, 1 H), 2.44 (s, 3 H). Its identity was confirmed by comparison with reported data.[28]



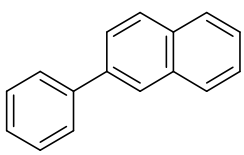
3,5-dimethylbiphenyl (4d)

A modification of general procedure A was employed for the reaction of 5-bromo-m-xylene (**3d**, 0.2 mmol). The title compound was obtained as a yellow oil (36.5 mg, >99% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.59 (d, J = 8.3 Hz, 2 H), 7.43 (t, J = 7.8 Hz, 2 H), 7.34 (t, J = 7.8 Hz, 1 H), 7.24 - 7.20 (m, 2 H), 7.01 (s, 1 H), 2.40 (s, 6 H). Its identity was confirmed by comparison with reported data.[29]



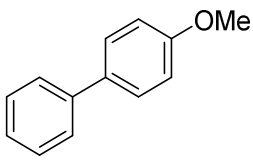
1-phenylnaphthalene (4e)

A modification of general procedure A was employed for the reaction of 1-bromonaphthalene (**3e**, 0.2 mmol). The title compound was obtained as a colorless oil (40.9 mg, >99% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.92 (d, J = 8.8 Hz, 2 H), 7.88 (d, J = 8.3 Hz, 1 H), 7.56 - 7.53 (m, 1 H), 7.53 - 7.48 (m, 5 H), 7.47 - 7.42 (m, 3 H). Its identity was confirmed by comparison with reported data.[28]



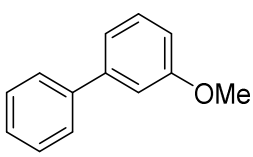
2-phenylnaphthalene (4f)

A modification of general procedure A was employed for the reaction of 2-bromonaphthalene (**3f**, 0.2 mmol). The title compound was obtained as a white solid (40.9 mg, >99% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 8.05 (s, 1 H), 7.95 - 7.86 (m, 3 H), 7.79 - 7.71 (m, 3 H), 7.53 - 7.47 (m, 4 H), 7.41 - 7.36 (m, 1 H). Its identity was confirmed by comparison with reported data.[30]



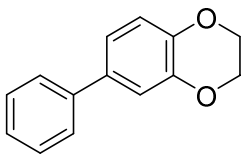
4-methoxybiphenyl (4g)

A modification of general procedure A was employed for the reaction of 4-bromoanisole (**3g**, 0.2 mmol). The title compound was obtained as a white solid (36.8 mg, >99% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.58 - 7.51 (m, 4 H), 7.42 (t, J = 7.8 Hz, 2 H), 7.34 - 7.28 (m, 1 H), 6.98 (d, J = 8.8 Hz, 2 H), 3.86 (s, 3 H). Its identity was confirmed by comparison with reported data.[31]



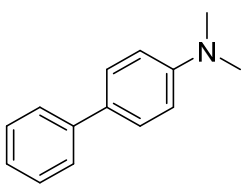
3-methoxybiphenyl (4h)

A modification of general procedure A was employed for the reaction of 3-bromoanisole (**3h**, 0.2 mmol). The title compound was obtained as a white solid (36.8 mg, >99% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.61 - 7.58 (m, 2 H), 7.44 (t, J = 7.6 Hz, 2 H), 7.39 - 7.34 (m, J = 3.9 Hz, 2 H), 7.21 - 7.17 (m, 1 H), 7.15 - 7.12 (m, 1 H), 6.91 (dd, J = 2.2, 8.6 Hz, 1 H), 3.88 (s, 3 H). Its identity was confirmed by comparison with reported data.[31]



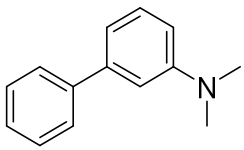
6-phenyl-2,3-dihydrobenzo[b][1,4]dioxine (4i)

A modification of general procedure A was employed for the reaction of 6-bromo-1,4-benzodioxane (**3i**, 0.2 mmol). The title compound was obtained as a white solid (42.5 mg, >99% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.56 - 7.52 (m, 2 H), 7.41 (t, J = 7.6 Hz, 2 H), 7.33 - 7.29 (m, 1 H), 7.13 (d, J = 2.4 Hz, 1 H), 7.09 (t, J = 2.4 Hz, 1 H), 6.94 (d, J = 8.3 Hz, 1 H), 4.30 (s, 4 H). Its identity was confirmed by comparison with reported data.[31]



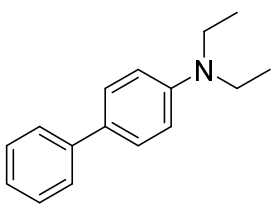
N,N-dimethylbiphenyl-4-amine (4j)

A modification of general procedure A was employed for the reaction of 4-bromo-N,N-dimethylaniline (**3j**, 0.2 mmol). The title compound was obtained as a yellow oil (30.4 mg, 77% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.57 (dd, J = 1.5, 8.3 Hz, 2 H), 7.55 - 7.51 (m, 2 H), 7.41 (t, J = 7.8 Hz, 2 H), 7.27 (t, J = 7.1 Hz, 1 H), 6.84 (d, J = 8.3 Hz, 2 H), 3.01 (s, 6 H). Its identity was confirmed by comparison with reported data.[32]



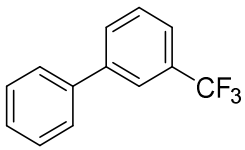
N,N-dimethylbiphenyl-3-amine (4k)

A modification of general procedure A was employed for the reaction of 3-bromo-N,N-dimethylaniline (**3k**, 0.2 mmol). The title compound was obtained as a colorless oil (34.7 mg, 88% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.61 (dd, J = 1.5, 8.3 Hz, 2 H), 7.44 (t, J = 7.6 Hz, 2 H), 7.34 (dd, J = 7.3, 16.6 Hz, 2 H), 7.00 - 6.94 (m, 2 H), 6.78 (d, J = 6.8 Hz, 1 H), 3.02 (s, 6 H). Its identity was confirmed by comparison with reported data.[30]



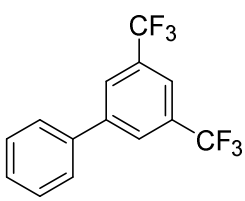
N,N-diethylbiphenyl-4-amine (4l)

A modification of general procedure A was employed for the reaction of 4-bromo-N,N-diethylaniline (**3l**, 0.2 mmol). The title compound was obtained as a white solid (37.0 mg, 82% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.56 (d, J = 7.3 Hz, 2 H), 7.49 (d, J = 8.3 Hz, 2 H), 7.39 (t, J = 7.6 Hz, 2 H), 7.28 - 7.22 (m, 1 H), 6.82 - 6.69 (m, 2 H), 3.41 (q, J = 6.8 Hz, 4 H), 1.21 (t, J = 7.1 Hz, 6 H). Its identity was confirmed by comparison with reported data.[33]



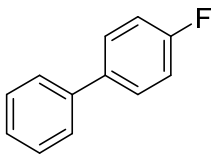
3-(trifluoromethyl)biphenyl (4m)

A modification of general procedure A was employed for the reaction of 3-bromobenzotrifluoride (**3m**, 0.2 mmol). The title compound was obtained as a yellow oil (40.0 mg, 90% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.84 (s, 1 H), 7.77 (d, J = 7.3 Hz, 1 H), 7.63 - 7.59 (m, 3 H), 7.56 (t, J = 7.3 Hz, 1 H), 7.48 (t, J = 7.3 Hz, 2 H), 7.43 - 7.38 (m, J = 7.3 Hz, 1 H). Its identity was confirmed by comparison with reported data.[29]



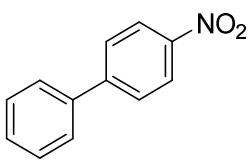
3,5-bis(trifluoromethyl)-biphenyl (4n)

A modification of general procedure A was employed for the reaction of 1,3-Bis(trifluoromethyl)-5-bromobenzene (**3n**, 0.2 mmol). The title compound was obtained as a yellow oil (41.2 mg, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.02 (s, 2 H), 7.86 (s, 1 H), 7.62 (m, 2 H), 7.56 - 7.42 (m, 3 H). Its identity was confirmed by comparison with reported data.[29]



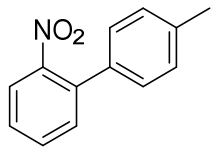
4-fluorobiphenyl (4o)

A modification of general procedure A was employed for the reaction of 1-bromo-4-fluorobenzene (**3o**, 0.2 mmol). The title compound was obtained as a white solid (6.9 mg, 20% yield). ^{1}H NMR (499MHz, $CDCl_3$) δ = 7.57 - 7.52 (m, 4 H), 7.44 (t, J = 7.6 Hz, 2 H), 7.36 (t, J = 7.3 Hz, 1 H), 7.13 (t, J = 8.8 Hz, 2 H). Its identity was confirmed by comparison with reported data.[28]



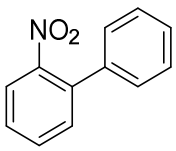
4-nitrobiphenyl (4p)

A modification of general procedure A was employed for the reaction of 1-bromo-4-nitrobenzene (**3p**, 0.2 mmol). The title compound was obtained as a yellow oil (5.2 mg, 13% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 8.30 (d, J = 8.8 Hz, 2 H), 7.74 (d, J = 8.8 Hz, 2 H), 7.63 (d, J = 7.8 Hz, 2 H), 7.50 (t, J = 7.3 Hz, 2 H), 7.46 (t, J = 7.3 Hz, 1 H). Its identity was confirmed by comparison with reported data.[28]



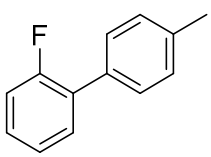
4'-methyl-2-nitrobiphenyl (5a)

A modification of general procedure B was employed for the reaction of nitrobenzene (0.4 mmol) and 4-bromotoluene (**3a**, 0.2 mmol). The isomeric mixture of compound was obtained as a yellow oil (29.0 mg, 68% yield). Its identity was confirmed by comparison with NMR and GC spectra of authentic samples. ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.82 (d, J = 8.3 Hz, 1 H), 7.59 (t, J = 7.3 Hz, 1 H), 7.49 - 7.40 (m, 2 H), 7.25 - 7.20 (m, 4 H), 2.40 (s, 3 H). The meta isomer; ^{1}H NMR (499 MHz, $CDCl_3$) δ = 8.44 (t, J = 2.0 Hz, 1 H), 8.17 (dd, J = 2.2, 8.1 Hz, 1 H), 7.90 (d, J = 6.8 Hz, 1 H), 7.59 (t, J = 7.8 Hz, 1 H), 7.53 (d, J = 8.3 Hz, 2 H), 7.31 (d, J = 7.8 Hz, 2 H), 2.42 (s, 3 H). The para isomer; ^{1}H NMR (499 MHz, $CDCl_3$) δ = 8.29 (d, J = 8.8 Hz, 2 H), 7.72 (d, J = 8.8 Hz, 2 H), 7.53 (d, J = 8.3 Hz, 2 H), 7.31 (d, J = 8.3 Hz, 2 H), 2.43 (s, 3 H). Their identity was confirmed by comparison with reported data.[34]



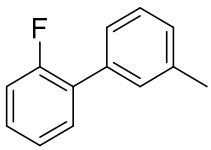
2-nitrobiphenyl (5b)

A modification of general procedure B was employed for the reaction of nitrobenzene (0.4 mmol) and bromobenzene (0.2 mmol). The isomeric mixture of compound was obtained as a yellow oil (23.1 mg, 58% yield). Its identity was confirmed by comparison with NMR and GC spectra of authentic samples. ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.86 (d, J = 8.3 Hz, 1 H), 7.61 (t, J = 7.8 Hz, 1 H), 7.51 - 7.47 (m, 1 H), 7.47 - 7.40 (m, 4 H), 7.33 (dd, J = 1.7, 7.6 Hz, 2 H). The meta isomer; ^{1}H NMR (499 MHz, $CDCl_3$) δ = 8.46 (s, 1 H), 8.21 (dd, J = 1.2, 8.1 Hz, 1 H), 7.92 (d, J = 8.3 Hz, 1 H), 7.66 - 7.59 (m, 3 H), 7.50 (t, J = 6.8 Hz, 2 H), 7.44 (t, J = 7.8 Hz, 1 H). The para isomer; ^{1}H NMR (499 MHz, $CDCl_3$) δ = 8.30 (d, J = 8.8 Hz, 2 H), 7.74 (d, J = 8.8 Hz, 2 H), 7.63 (d, J = 7.8 Hz, 2 H), 7.50 (t, J = 7.3 Hz, 2 H), 7.46 (t, J = 7.3 Hz, 1 H). Their identity was confirmed by comparison with reported data.[28]



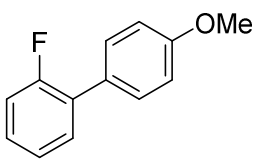
2-fluoro-4'-methylbiphenyl (5c)

A modification of general procedure B was employed for the reaction of fluorobenzene (0.6 mmol) and 4-bromotoluene (**3a**, 0.2 mmol). The title compound was obtained as a colorless oil (22.2 mg, 60% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.52 - 7.41 (m, 3 H), 7.32 - 7.25 (m, 3 H), 7.24 - 7.09 (m, 2 H), 2.42 (s, 3 H). Its identity was confirmed by comparison with reported data.[34]



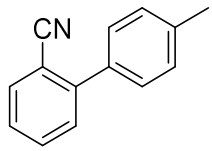
2-fluoro-3'-methylbiphenyl (5d)

A modification of general procedure B was employed for the reaction of fluorobenzene (0.6 mmol) and 3-bromotoluene (**3c**, 0.2 mmol). The title compound was obtained as a yellow oil (26.1 mg, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.47 - 7.39 (m, 1 H), 7.39 - 7.27 (m, 4 H), 7.23 - 7.10 (m, 3 H), 2.42 (s, 3 H). Its identity was confirmed by comparison with reported data.[35]



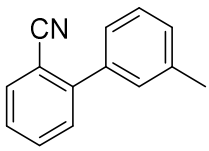
2-fluoro-4'-methylbiphenyl (5e)

A modification of general procedure B was employed for the reaction of fluorobenzene (0.6 mmol) and 4-bromoanisole (**3g**, 0.2 mmol). The title compound was obtained as a colorless oil (24.3 mg, 60% yield). ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.52 - 7.49 (m, 2 H), 7.42 (dt, J = 1.5, 7.8 Hz, 1 H), 7.30 - 7.26 (m, 1 H), 7.22 - 7.09 (m, 2 H), 7.01 - 6.98 (m, 2 H), 3.86 (s, 3 H). Its identity was confirmed by comparison with reported data.[36]



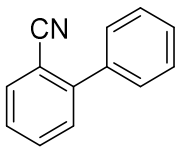
2-cyano-4'-methylbiphenyl (5f)

A modification of general procedure B was employed for the reaction of benzonitrile (0.4 mmol) and 4-bromotoluene (**3a**, 0.2 mmol). The isomeric mixture of compound was obtained as a colorless oil (24.3 mg, 60% yield). Its identity was confirmed by comparison with NMR and GC spectra of authentic samples. ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.75 (dd, J = 1.2, 7.6 Hz, 1 H), 7.63 (dt, J = 1.0, 7.3 Hz, 1 H), 7.51 (dd, J = 1.5, 7.8 Hz, 1 H), 7.46 (d, J = 8.3 Hz, 2 H), 7.42 (dt, J = 1.0, 6.8 Hz, 1 H), 7.30 (d, J = 7.8 Hz, 2 H), 2.42 (s, 3 H). The meta isomer; ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.85 (t, J = 1.5 Hz, 1 H), 7.79 (td, J = 1.0, 7.8 Hz, 1 H), 7.60 (td, J = 1.5, 8.3 Hz, 1 H), 7.53 (t, J = 7.8 Hz, 1 H), 7.46 (d, J = 8.3 Hz, 2 H), 7.29 (d, J = 7.8 Hz, 2 H), 2.41 (s, 3 H). The para isomer; ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.71 (d, J = 8.3 Hz, 2 H), 7.67 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.3 Hz, 2 H), 7.29 (d, J = 7.8 Hz, 2 H), 2.42 (s, 3 H). Their identity was confirmed by comparison with reported data.[37]



2-cyano-3'-methylbiphenyl (5g)

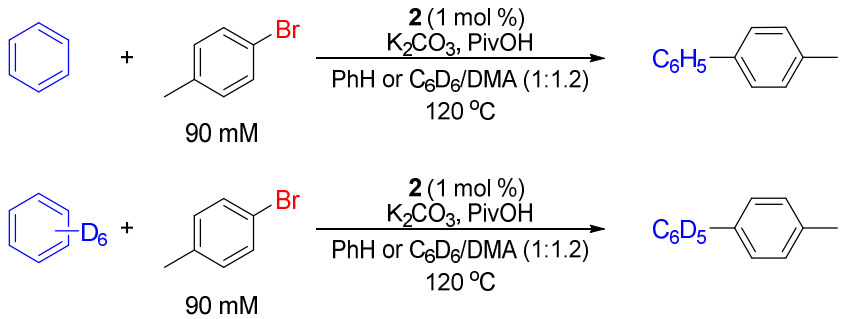
A modification of general procedure B was employed for the reaction of benzonitrile (0.4 mmol) and 3-bromotoluene (**3c**, 0.2 mmol). The isomeric mixture of compound was obtained as a colorless oil (22.1 mg, 57% yield). Its identity was confirmed by comparison with NMR and GC spectra of authentic samples. ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.76 (d, J = 7.8 Hz, 1 H), 7.63 (t, J = 7.6 Hz, 1 H), 7.51 (d, J = 7.8 Hz, 1 H), 7.46 - 7.38 (m, 2 H), 7.37 - 7.34 (m, 2 H), 7.27 (d, J = 5.4 Hz, 1 H), 2.44 (s, 3 H). The meta isomer; ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.86 (s, 1 H), 7.80 (d, J = 7.8 Hz, 1 H), 7.62 (d, J = 7.8 Hz, 1 H), 7.53 (t, J = 7.8 Hz, 1 H), 7.37 (d, J = 6.4 Hz, 3 H), 7.27 - 7.20 (m, 1 H), 2.44 (s, 3 H). The para isomer; ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.72 (d, J = 8.3 Hz, 2 H), 7.68 (d, J = 8.3 Hz, 2 H), 7.42 - 7.36 (m, 3 H), 7.27 - 7.23 (m, 1 H), 2.44 (s, 3 H). Their identity was confirmed by comparison with reported data.[38]



2-cyanobiphenyl (5h)

A modification of general procedure B was employed for the reaction of benzonitrile (0.4 mmol) and bromobenzene (0.2 mmol). The isomeric mixture of compound was obtained as a colorless oil (20.1 mg, 56% yield). Its identity was confirmed by comparison with NMR and GC spectra of authentic samples. ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.77 (d, J = 7.8 Hz, 1 H), 7.65 (t, J = 7.3 Hz, 1 H), 7.57 (d, J = 7.3 Hz, 2 H), 7.54 - 7.48 (m, 3 H), 7.45 (t, J = 8.3 Hz, 2 H). The meta isomer; ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.87 (s, 1 H), 7.82 (d, J = 7.8 Hz, 1 H), 7.63 (d, J = 7.3 Hz, 1 H), 7.59 - 7.52 (m, 3 H), 7.49 (t, J = 7.6 Hz, 2 H), 7.42 (t, J = 7.3 Hz, 1 H). The para isomer; ^{1}H NMR (499 MHz, $CDCl_3$) δ = 7.73 (d, J = 8.8 Hz, 2 H), 7.69 (d, J = 8.3 Hz, 2 H), 7.59 (d, J = 7.8 Hz, 2 H), 7.49 (t, J = 7.6 Hz, 2 H), 7.44 (t, J = 7.3 Hz, 1 H). Their identity was confirmed by comparison with reported data.[39]

4.4.5 Procedure for the KIE experiments



The KIE was determined by comparing the initial reaction rates of the reactions with benzene and benzene-*d*6. Both reactions were conducted using the above general procedure A with the following modifications. After adding all the reagents, 4-bromotoluene (**3a**, 0.2 mmol), and dodecane (0.2 mmol, 45 μL) as internal standard were added to a 10 mL Schlenk tube, and each tube was heated to 120 °C in an oil bath. At each required time period, each tube was immediately placed into an ice bath, and then a small aliquot was withdrawn. Each aliquot was filtered through Celite and then analyzed by GC.

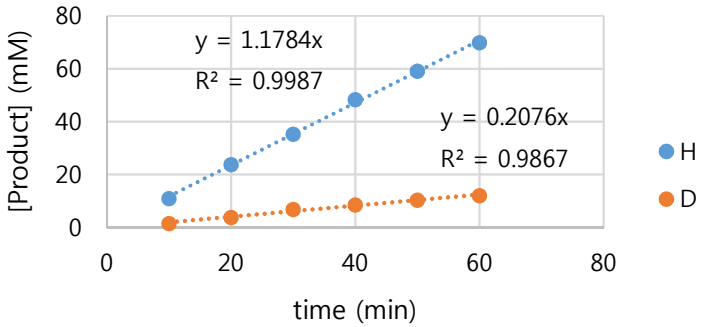
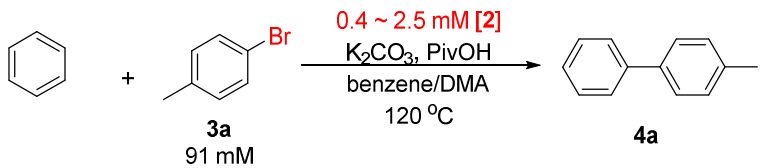


Figure 4.2 Initial rates of the C-H arylation of benzene and benzene-d6

$$KIE = k_H/k_D = 1.1784/0.2076 = 5.68$$

4.4.6 Kinetic data

Order in [Pd]



The order in [Pd] was determined by obtaining the initial rate of the C–H arylation at differing concentrations of Pd-diimine complex **2**. Each reaction was conducted using the general procedure A with the following modifications. After adding all the reagents, different amounts of **2** and dodecane (0.2 mmol, 45 μL) as an internal standard were added to a 10 mL Schlenk tube, and each tube was heated at 120 °C in an oil bath. At each required time period, each tube was immediately placed into an ice bath, and then a small aliquot was withdrawn. Each aliquot was filtered through Celite and then analyzed by GC.

Table 4.6 Amounts of **2** and results used to determine the order in **2**

entry	amount of **2**			rate (mM/min)
	mg	mmol	mM	
1	0.5	0.000903	0.410306	0.2015819
2	1.1	0.001986	0.902674	0.3357273
3	1.52	0.002744	1.247331	0.5316474
4	2.15	0.003881	1.764317	0.6939314
5	2.52	0.004549	2.067943	0.7991302
6	3.02	0.005452	2.47825	0.9402261

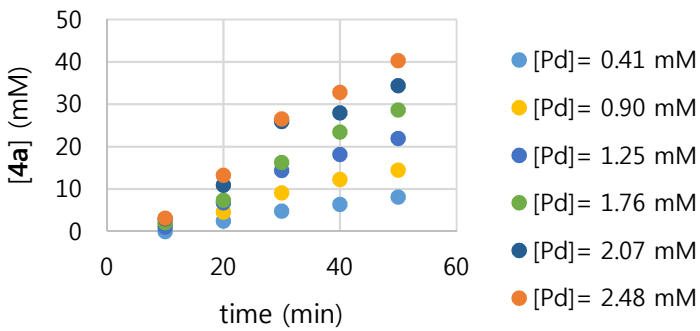


Figure 4.3 Initial rates of the C-H arylation with different concentrations of **2**

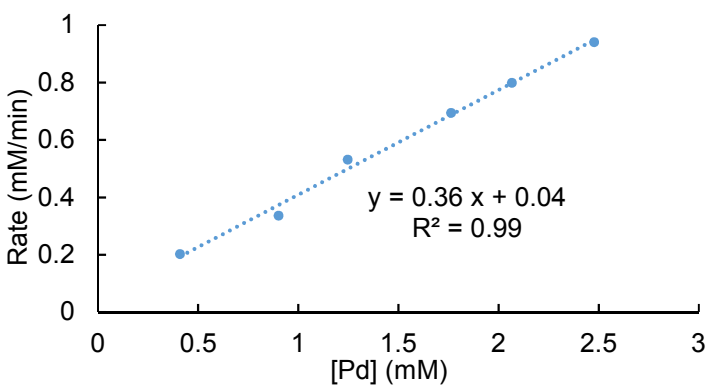
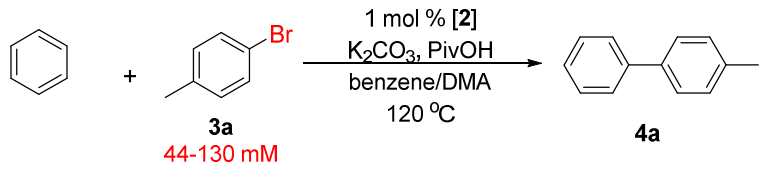


Figure 4.4 Plot of initial rates with varying [**2**]

Order in [ArBr]



The order in [ArBr] was determined by obtaining the initial rate of the C–H arylation at differing concentrations of 4-bromotoluene **3a**. It was conducted following the above procedure.

Table 4.7 Amounts of **3a** and results used to determine the order in [ArBr]

entry	amount of **2**			rate (mM/min)
	mg	mmol	mM	
1	16.7	0.09753	44.3459	0.9995
2	25.0	0.14629	66.51885	1.2264
3	34.2	0.19993	90.90909	1.1986
4	41.7	0.24382	110.8647	1.1787
5	48.7	0.28445	129.3422	1.0524

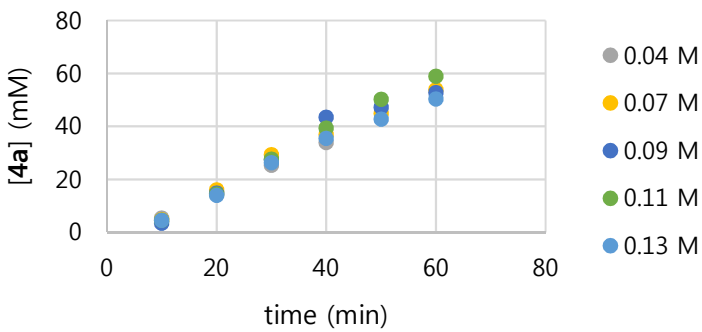


Figure 4.5 Initial rates of C-H arylation with different concentrations of **3a**

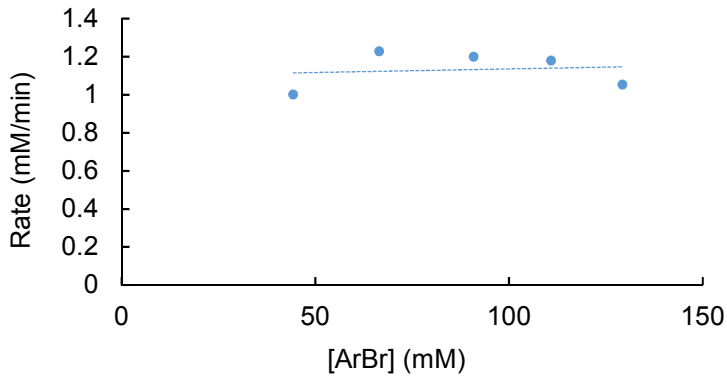
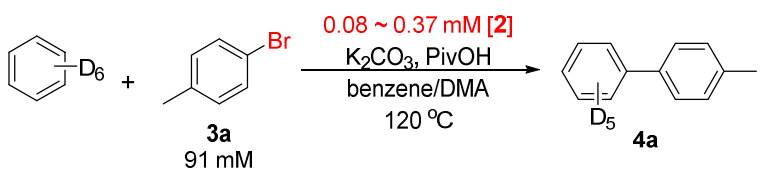


Figure 4.6 Initial rates of C-H arylation with different concentrations of **4a**

Order in [Pd] at low concentrations



The order in [Pd] was determined by obtaining the initial rate of the C–H arylation at low concentrations of Pd-diimine complex **2** in benzene-*d*6. It was conducted following the above procedure using benzene-*d*6 instead of benzene.

Table 4.8 Amounts of **2** and results used to determine the order in **2**

entry	amount of **2**			rate (mM/min)
	mg	mmol	mM	
1	0.12	0.00018	0.081885	0.0009434
2	0.17	0.000255	0.116004	0.0022031
3	0.24	0.00036	0.163771	0.0068654
4	0.45	0.000676	0.30707	0.0127002
5	0.54	0.000811	0.368484	0.0214776

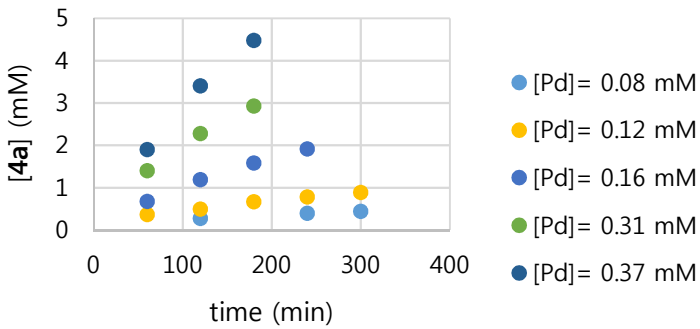


Figure 4.7 Initial rates of C-H arylation with different concentrations of **2**

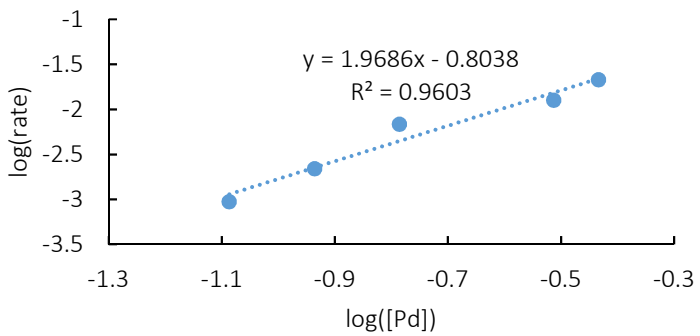
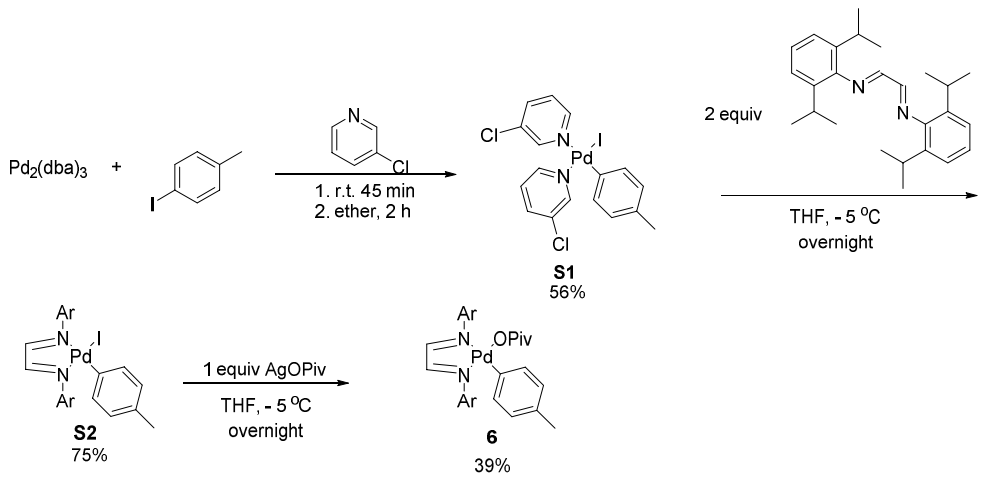


Figure 4.8 Plot of initial rates with varying [**2**]

4.4.7 Synthesis of Complex 6



Scheme 4.11 Synthesis of complex **6**

*Synthesis of [(3-chloropyridine)$_2$Pd(4-PhMe)(I)] (**S1**)*

The synthesis was conducted by modifying a procedure used for an analogous complex.[40] $Pd_2(dba)_3$ (1.37 g, 1.5 mmol, 1.0 equiv) was added to a solution of iodotoluene (1.31 g, 6.0 mmol, 4.0 equiv) in 3-chloropyridine (6.2 mL, 65.0 mmol, 43.0 equiv). The suspension was stirred at room temperature for 45 min, diethyl ether (25 mL) was then added, and the mixture was allowed to stir for a further 2 h. It was then filtered and the solid residue was washed with diethyl ether (3 x 10 mL) and dried in vacuum. This provided the title compound as a green/grey solid (0.92 g, 56%). Due to the instability of this compound, it was immediately submitted to the next step (see below) without further characterization.

*Synthesis of [(diimine)Pd(4-PhMe)(I)] (**S2**)*

[(3-Chloropyridine)$_2$Pd(4-PhMe)(I)] (**S1**, 920 mg, 1.67 mmol, 1.0 equiv) and 1,4-bis(2,6-diisopropylphenyl)diazabutadiene (1.26 g, 3.34 mmol, 2.0 equiv) were placed into a 250 mL Schlenk flask. The reaction mixture was cooled in an ice bath and THF (50 mL) was then added. The mixture was stirred at -5 °C overnight in an Eyela low temperature bath. The solution was filtered through Celite, and all the volatiles were removed under vacuum. The resulting solid residue was dissolved in THF (5 mL) upon cooling in an ice bath, followed by the addition of pentane (30 mL), and recrystallized. Further filtration and drying afforded the title compound as a dark red solid (877 mg, 75%). ^{1}H NMR (499 MHz, CD_2Cl_2) δ = 8.20 (s, 1 H), 8.21 (d, *J* = 12.2 Hz, 2 H), 7.35 - 7.21 (m, 3 H), 7.11 (d, *J* = 7.8 Hz, 1 H), 6.99 (d, *J* = 7.3 Hz, 2 H), 6.72 - 6.64 (m, *J* = 7.8 Hz, 2 H), 6.45 - 6.36 (m, *J* = 7.8 Hz, 2 H), 3.23 (dt, *J* = 3.4, 6.8 Hz, 4 H), 2.03 (s, 3 H), 1.46 (d, *J* = 6.4 Hz, 6 H), 1.27 (d, *J* = 6.8 Hz, 6 H), 1.19 (d, *J* = 6.8 Hz, 6 H), 1.11 (d, *J* = 6.8 Hz, 6 H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ = 165.23, 163.16, 161.26, 139.74, 139.34, 138.68, 137.15, 136.66, 135.67, 131.20, 129.38, 128.79, 127.55, 126.64, 124.92, 123.23, 123.06, 122.94, 29.34, 29.00, 28.37, 27.94, 25.27, 24.47, 24.21, 23.08, 22.55, 22.22, 21.92.

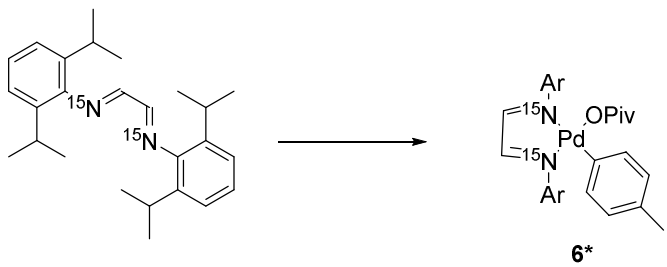
*Synthesis of [(Diimine)Pd(4-PhMe)(OPiv)] (**6**)*

[(Diimine)Pd(4-PhMe)(I)] (**S2**, 372 mg, 0.53 mmol, 1.0 equiv) and AgOPiv (114 mg, 0.53 mmol, 1.0 equiv) were placed in a 100 mL Schlenk flask. The reaction mixture was cooled in an ice batch and THF (25 mL) was the added. The mixture was stirred at -5 °C overnight in an Eyela low temperature bath. The solution was filtered through Celite followed by concentration to a 5 mL volume. The addition of pentane (30 mL) and recrystallization, followed by filtration and drying afforded the title compound as a pink solid (139 mg, 39%). This compound was unambiguously characterized by X-ray crystallography. ^{1}H NMR (300MHz ,CD_2Cl_2) δ = 8.18 (s, 1 H), 8.10 (s, 1 H), 7.31 - 7.21 (m, 4 H), 7.14 - 7.04 (m, 2 H), 6.50 (d, *J* = 8.1 Hz, 2 H), 6.40 (dd, *J* = 0.6, 8.3 Hz, 2 H), 3.60 - 3.44 (m, 2 H), 3.29 - 3.15 (m, 2 H), 2.06 (s, 3 H), 1.47 - 1.17 (m, 12 H), 1.16 - 1.03 (m, 12 H), 0.60 (s, 9 H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 168.56, 164.43, 160.16, 140.68, 140.36, 134.04, 132.70, 128.67, 128.17, 126.58, 123.92, 123.81, 29.20, 28.88, 28.46, 25.49, 22.31.

4.4.8 Stoichiometric reactions with complex 6

Complex **6** (2.0 mg, 0.0030 mmol, 1.0 equiv) and the corresponding additive (see Scheme 4.7) were weighed in a 4 mL vial (additive: KOPiv (8.4 mg, 0.060 mmol, 20 equiv); NBu_4Br (19.3 mg, 0.060 mmol, 20 equiv); complex **1** (5.0 mg, 0.0090 mmol, 3.0 equiv)). The mixture was then transferred to a 10 mL Schelenk tube as a solution in 2.4 mL of DMA and 2.0 mL of fluorobenzene. The reaction mixture was then heated at 120 °C with stirring. After 12 h, the mixture was cooled to room temperature and analyzed by GC using dodecane as internal standard.

4.4.9 ^{15}N labeling study



6*

A ^{15}N labeled 2,6-diisopropylaniline was prepared according to a literature procedure,[41] followed by the synthesis of a ^{15}N labeled diimine. Complex **6*** was synthesized following the same procedure utilized for complex **6** from ^{15}N labeled diimine. ^{15}N-^{1}H HMBC experiments were conducted with the ^{15}N labeled diimine and complex **6*** in CD_2Cl_2. Urea in DMSO (-302.6 ppm) was used as external standard for the ^{15}N NMR.

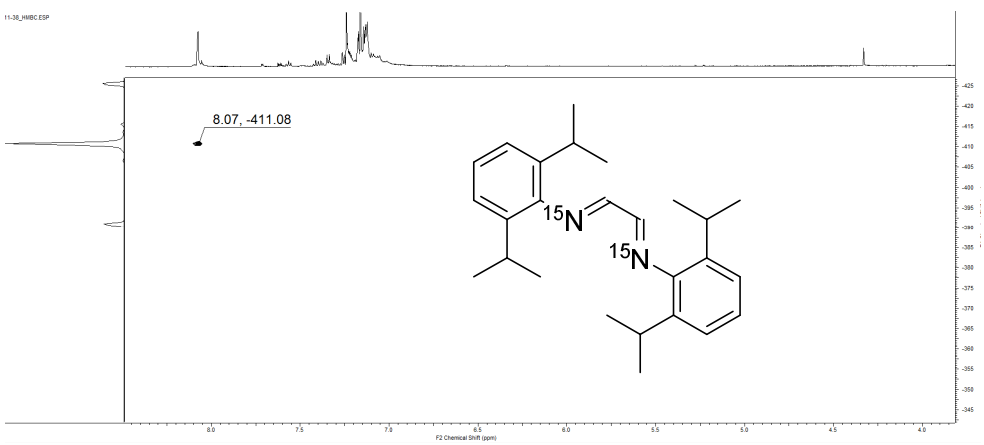


Figure 4.9 ^{15}N-^{1}H HMBC spectrum of ^{15}N labeled diimine

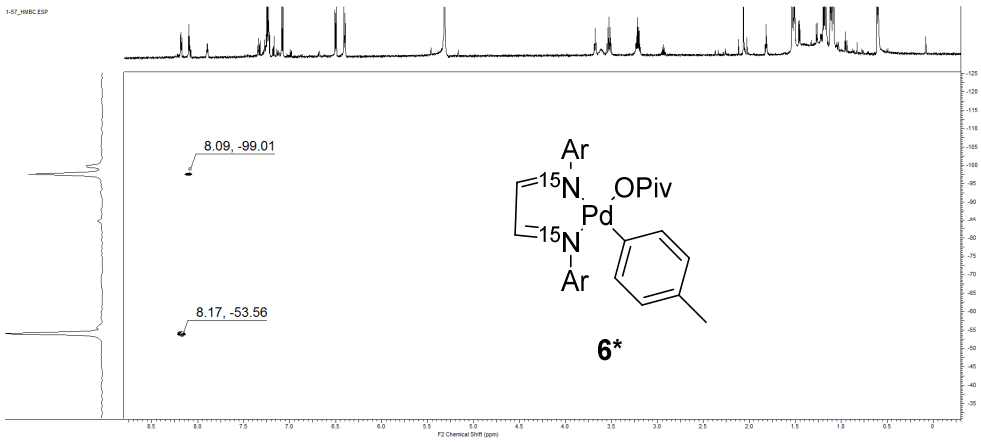


Figure 4.10 ^{15}N-^{1}H HMBC spectrum of ^{15}N labeled complex **6***

4.4.10 Competition experiments

*Set A: 4-bromotoluene (**3a**) vs. 4-bromoanisole (**3g**)*

The reaction was conducted by modifying the general procedure A. Inside a glove box, a 10 mL Schlenk tube containing a magnetic stirring bar was charged with K_2CO_3 (2.5 equiv, 69.1 mg, 0.5 mmol) and complex **2** (1 mol %, 1.3 mg, 0.002 mmol). Pivalic acid (0.3 equiv, 0.06 mmol) was then added to the Schlenk tube as a solution in DMA (0.05 M, 1.2 mL), followed by benzene (1.0 mL), **3a** (34.2 mg, 0.2 mmol, 1.0 equiv), and **3g** (25 μL, 0.2 mmol, 1.0 equiv). The Schlenk tube was sealed and heated to 120 °C for 8 h. Upon completion of the reaction, the mixture was cooled to room temperature. It was then filtered through Celite and analyzed by GC using dodecane as internal standard.

*Set B: 4-bromotoluene (**3a**) vs. 1-bromo-4-nitrobenzene (**3p**)*

The reaction was conducted according to the above procedure using **3a** (34.2 mg, 0.2 mmol, 1.0 equiv) and **3g** (40.4 mg, 0.2 mmol, 1.0 equiv) as competing substrates.

4.5 References

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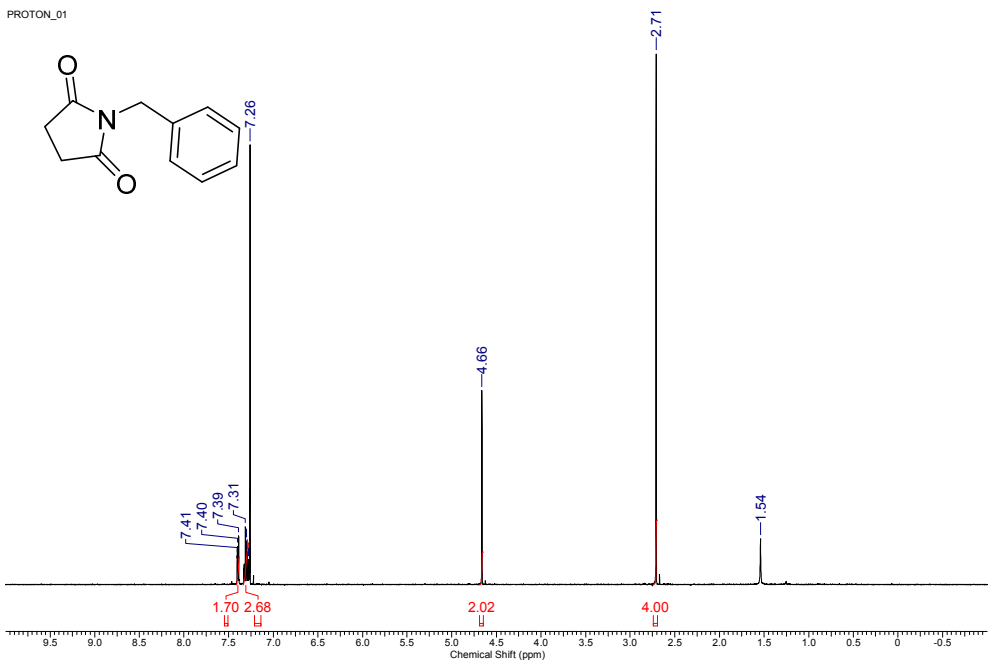
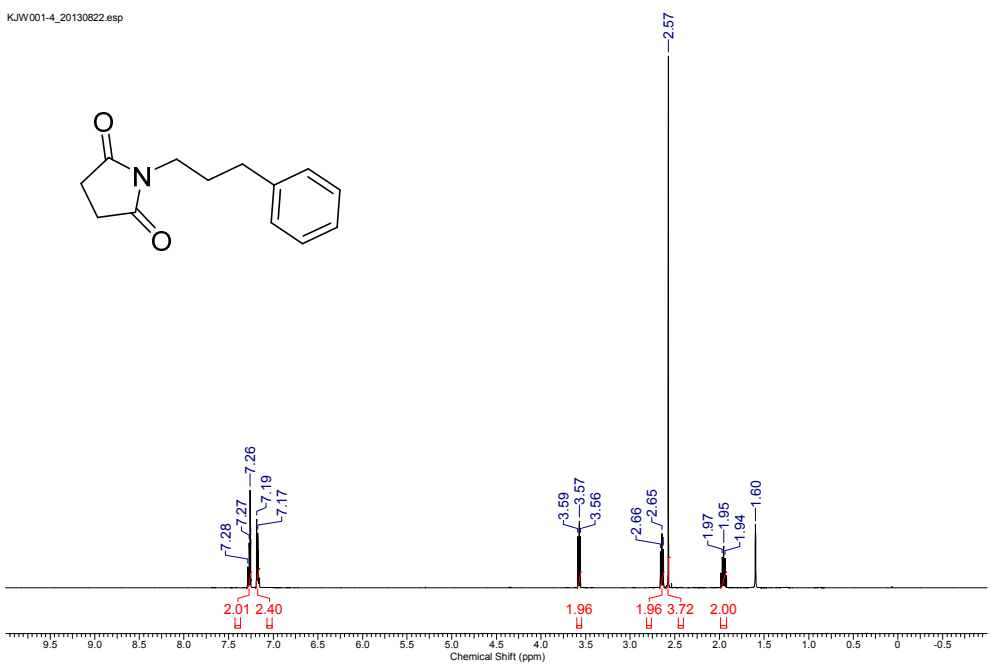
Appendix

Chapter 2 - NMR Spectra

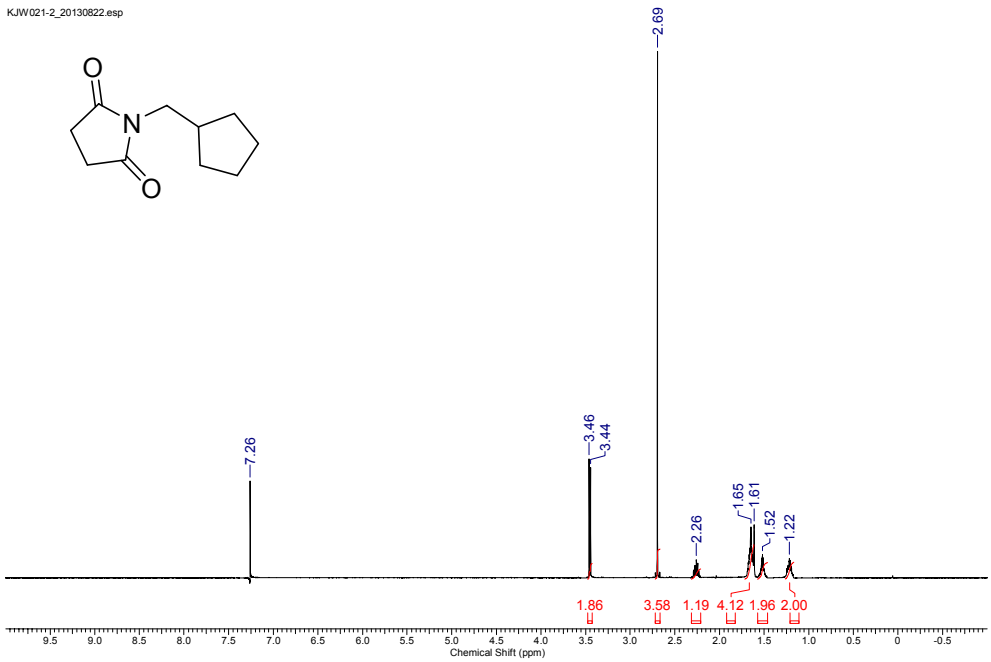
^{1}H NMR (**3a**) ($CDCl_3$)



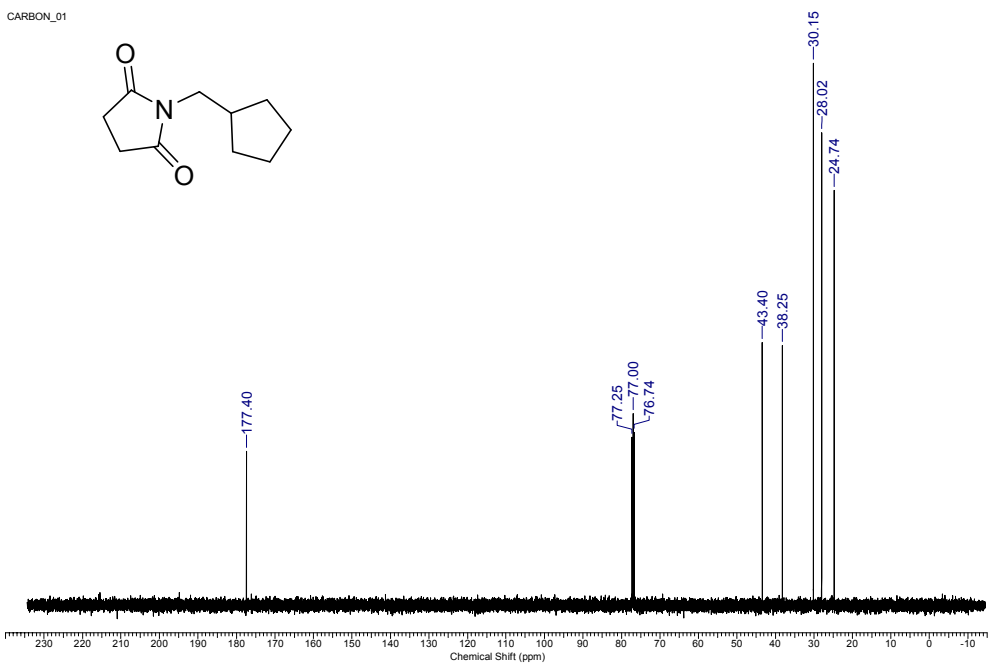
^{1}H NMR (**3b**) ($CDCl_3$)



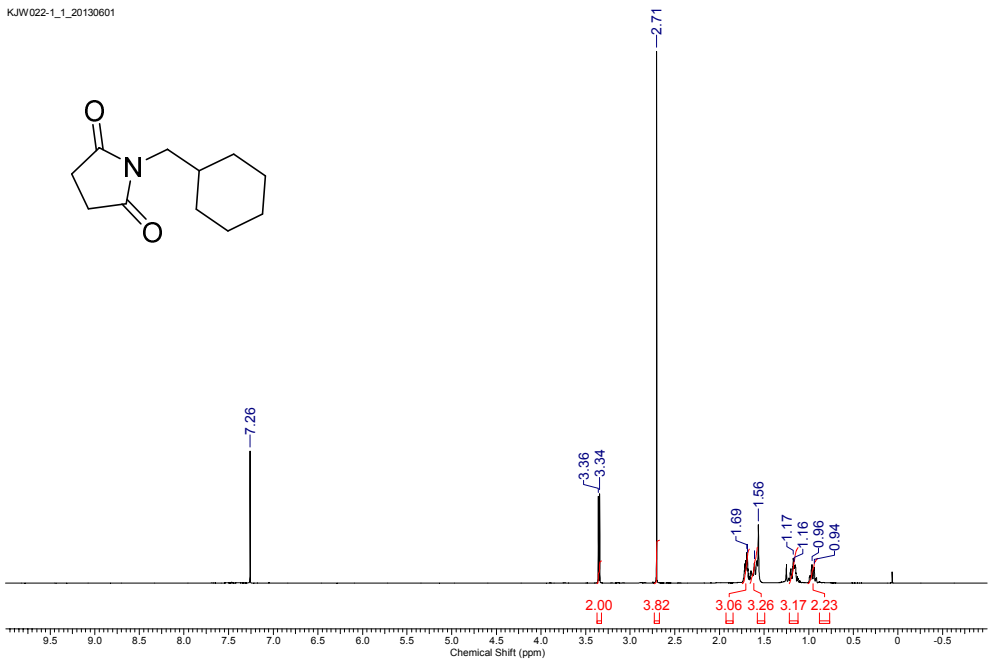
^{1}H NMR (**3c**) ($CDCl_3$)



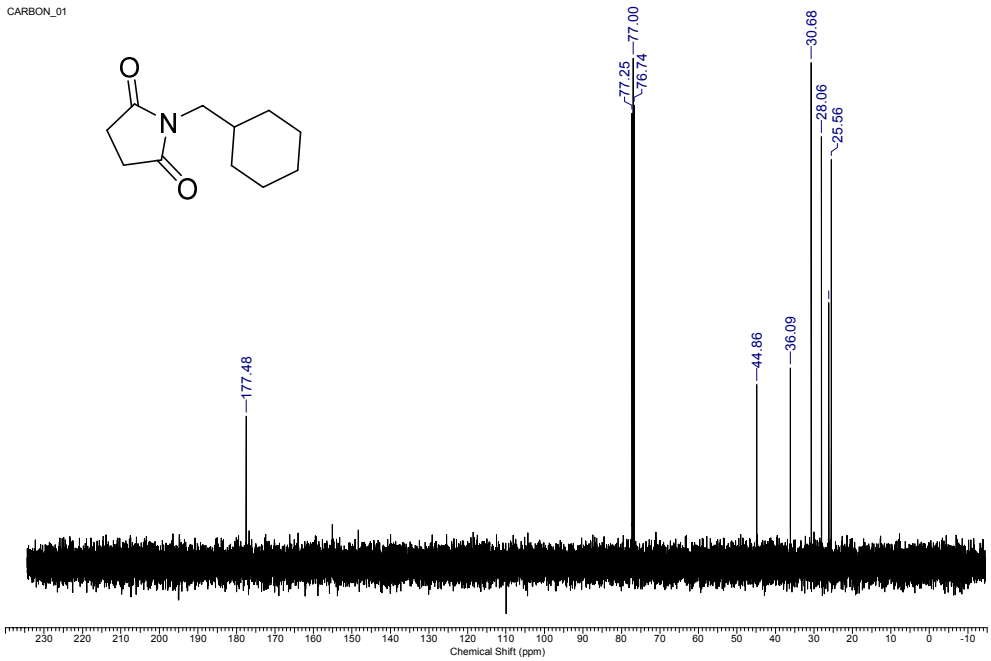
^{13}C NMR (**3c**) ($CDCl_3$)



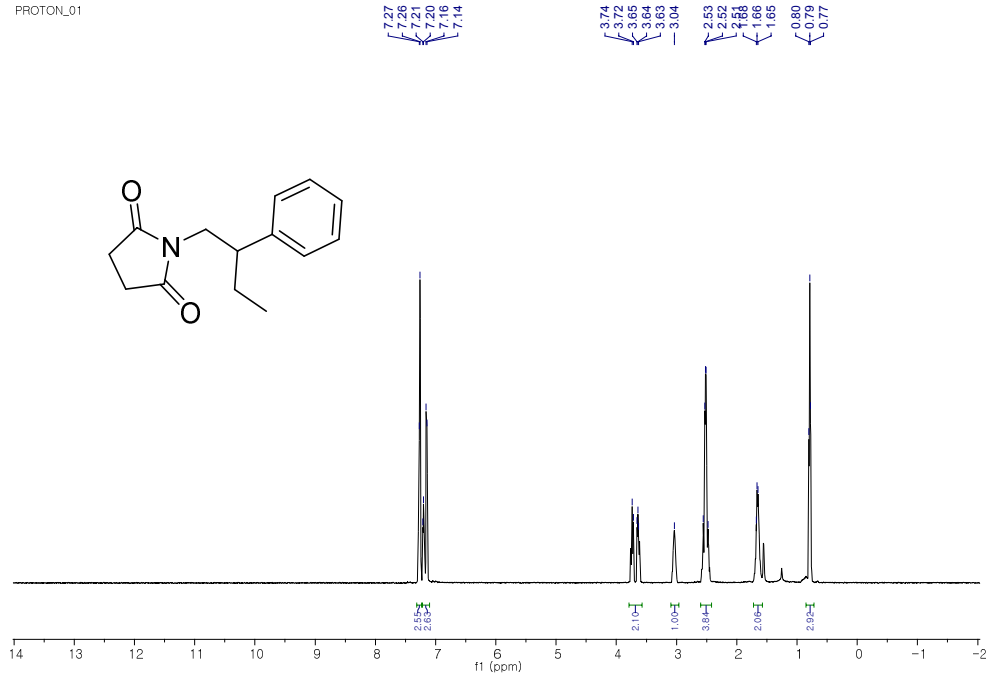
^{1}H NMR (**3d**) ($CDCl_3$)



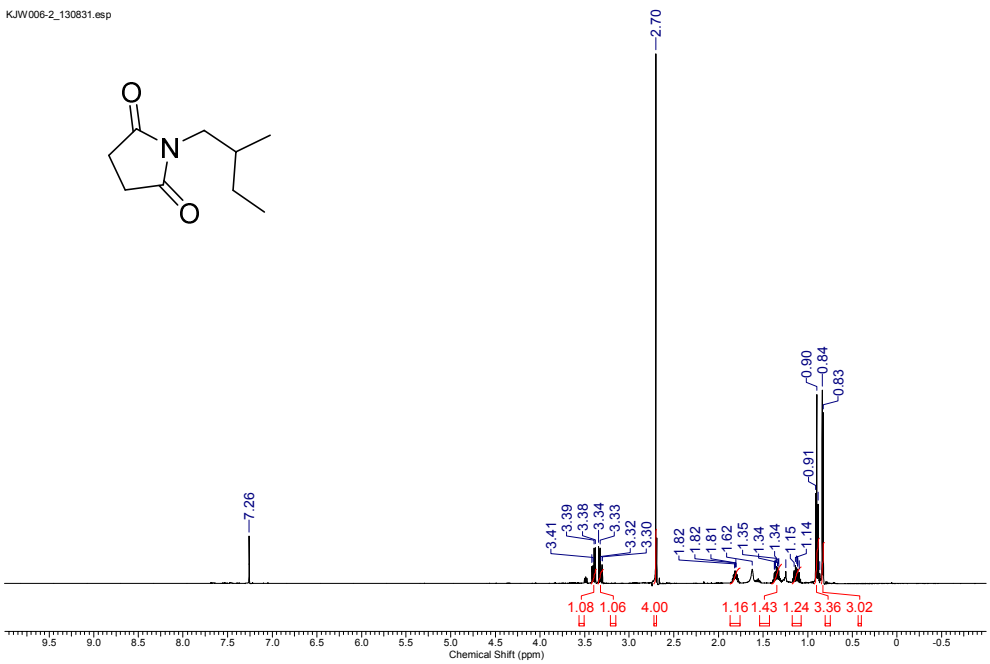
^{13}C NMR (**3d**) ($CDCl_3$)



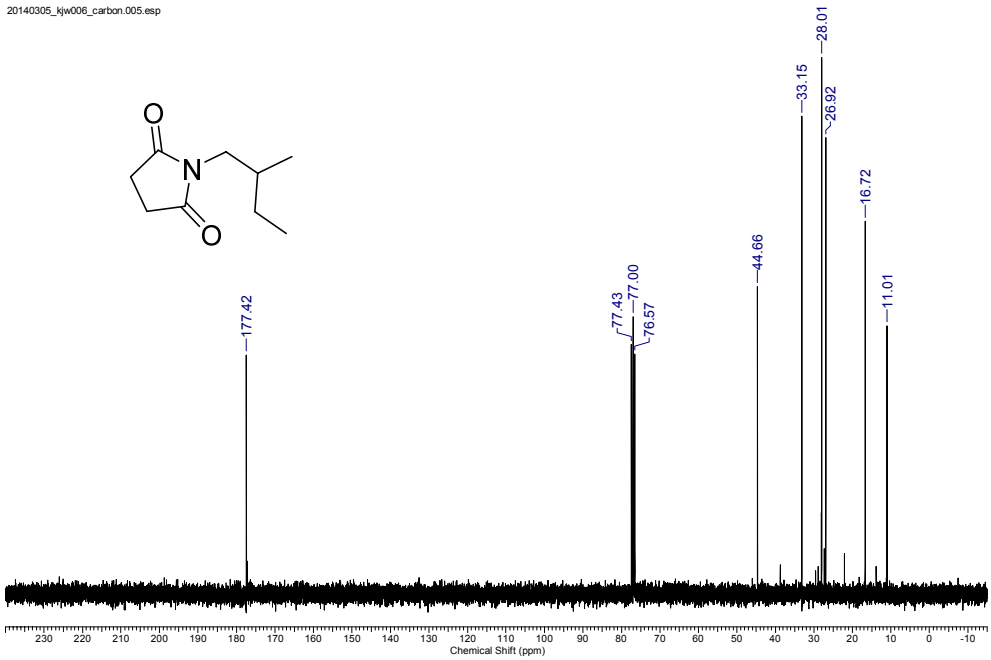
^{1}H NMR (**3e**) ($CDCl_3$)



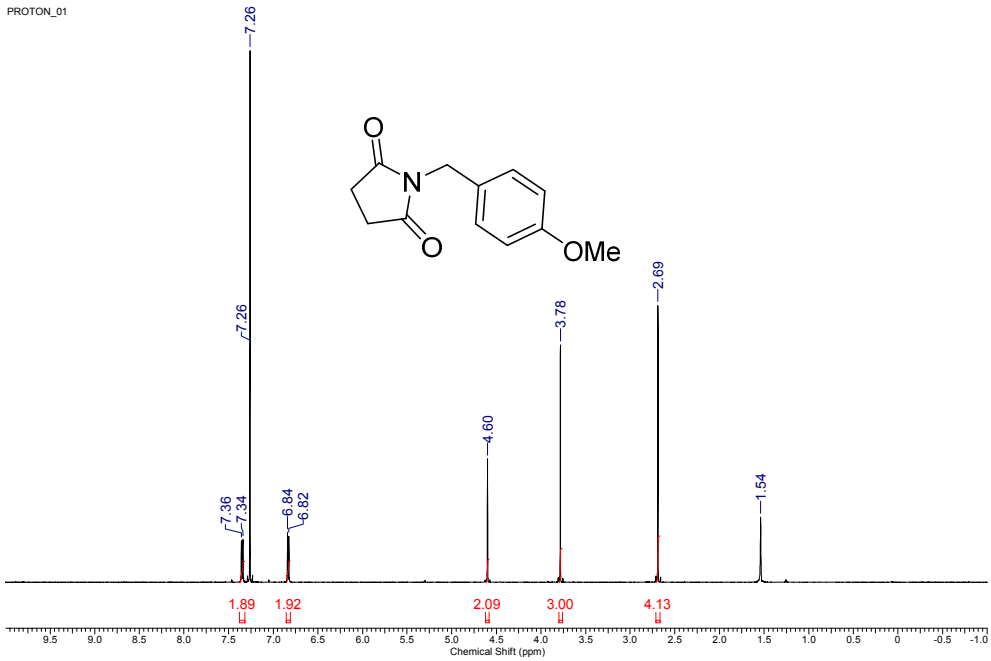
^{1}H NMR (**3f**) ($CDCl_3$)



^{13}C NMR (**3f**) ($CDCl_3$)

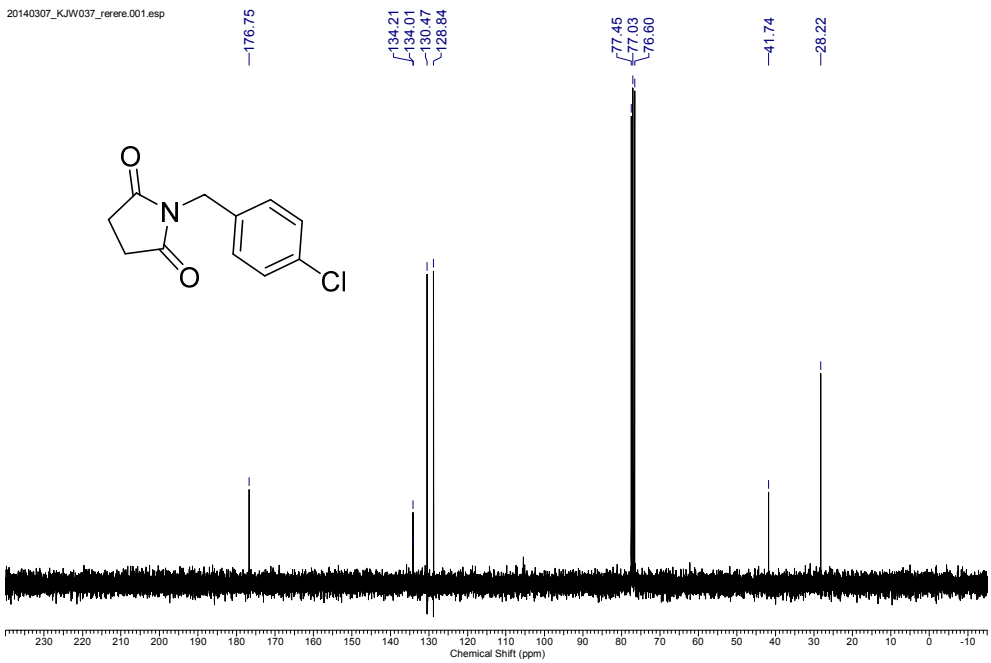


^{1}H NMR (**3g**) ($CDCl_3$)

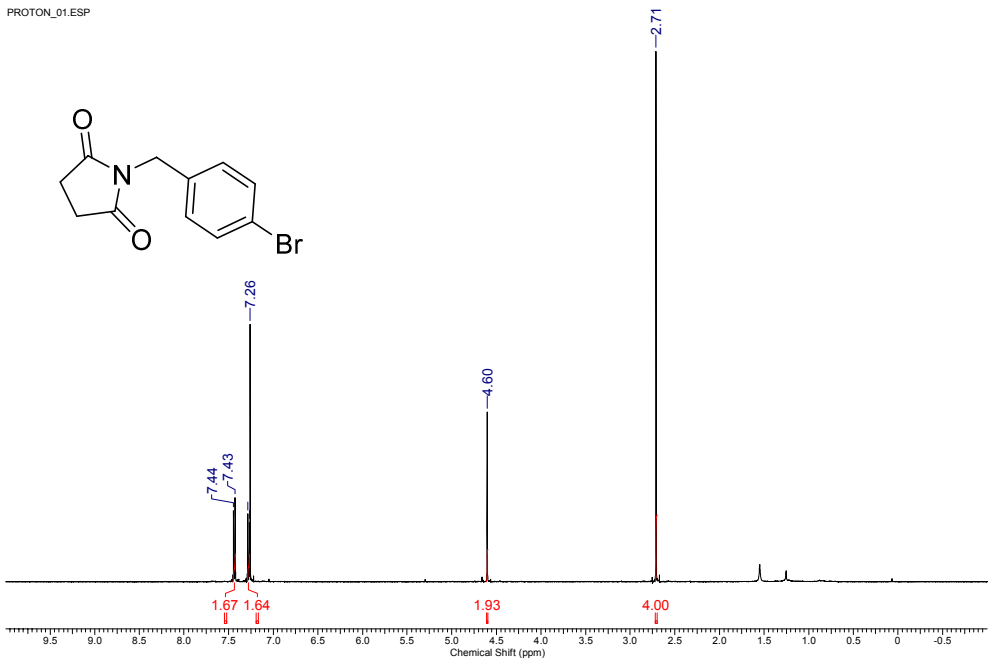


^{1}H NMR (**3h**) ($CDCl_3$)

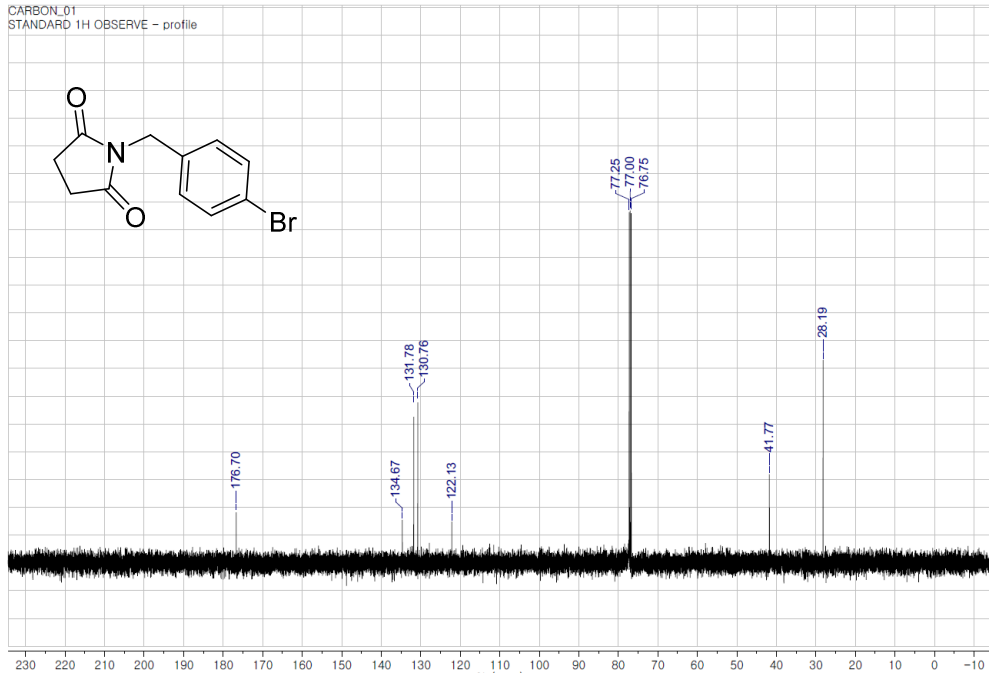
^{13}C NMR (**3h**) ($CDCl_3$)



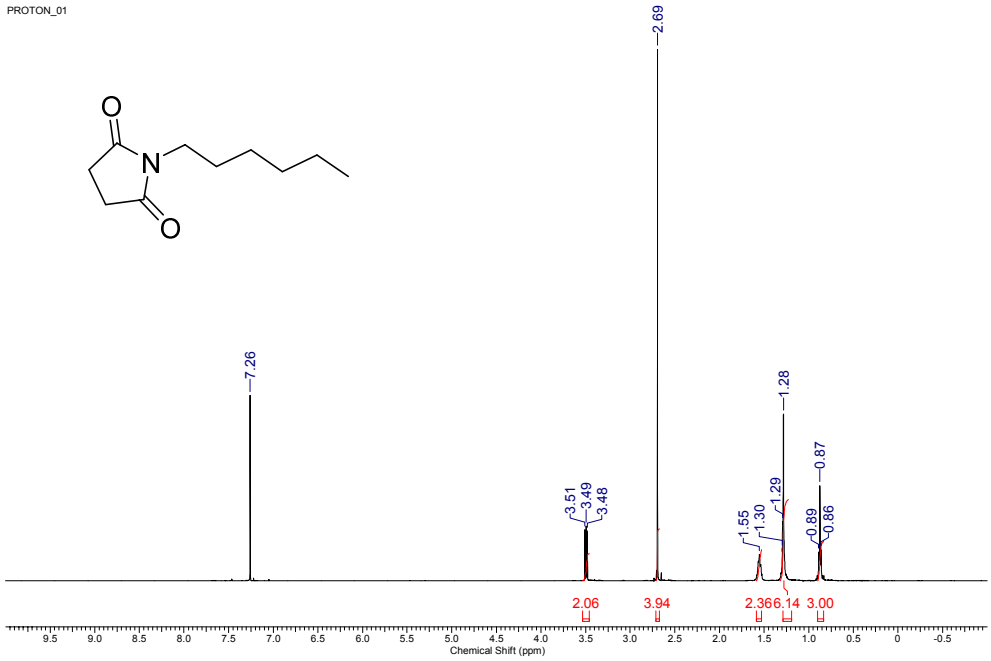
^{1}H NMR (**3i**) ($CDCl_3$)



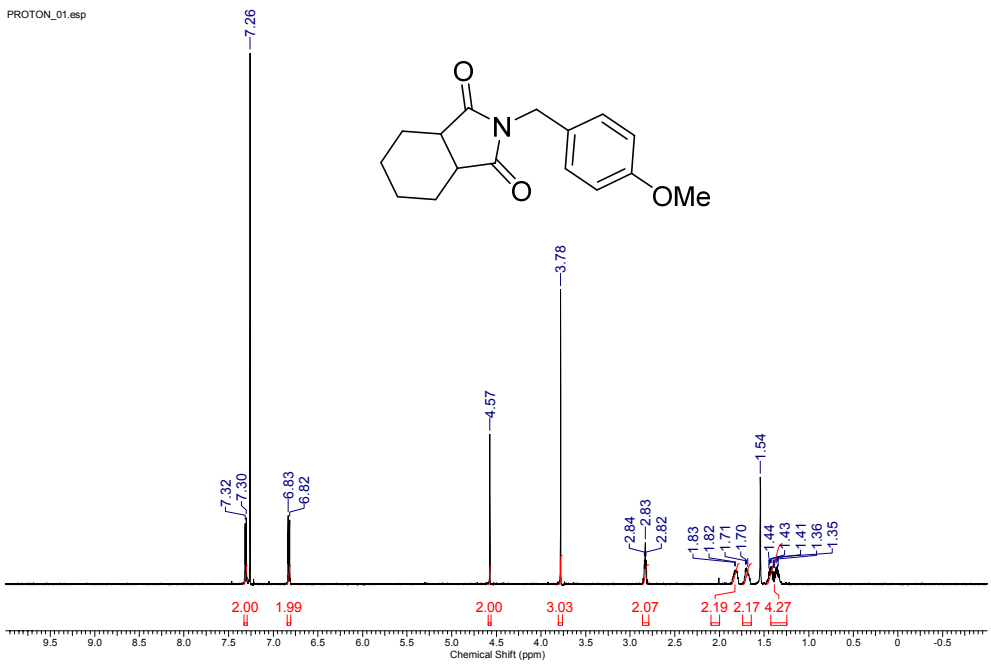
^{13}C NMR (**3i**) ($CDCl_3$)



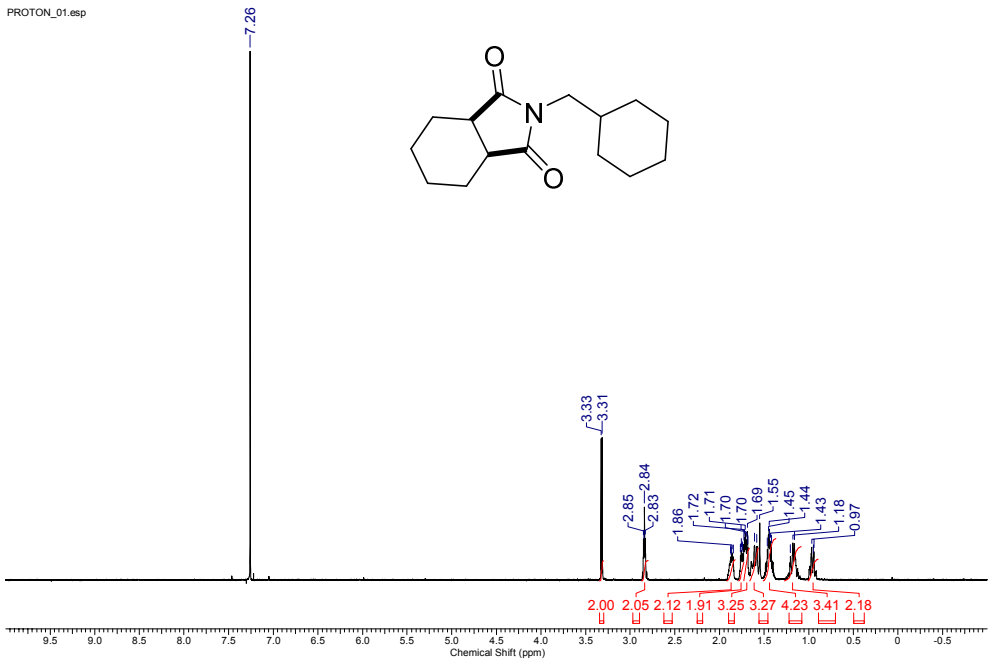
^{1}H NMR (**3j**) ($CDCl_3$)



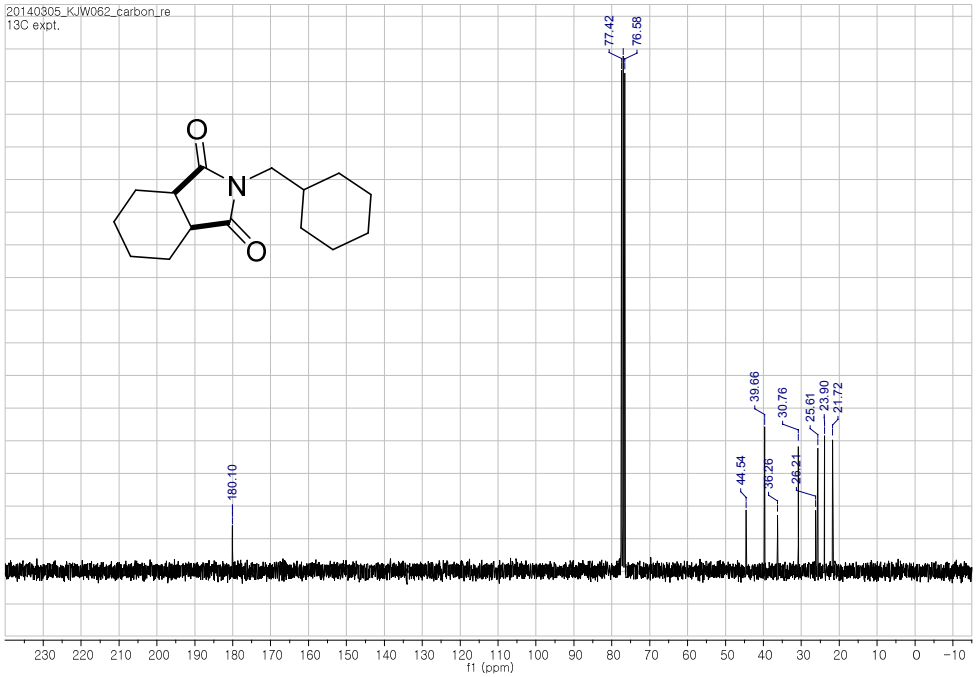
^{1}H NMR (**3k**) ($CDCl_3$)



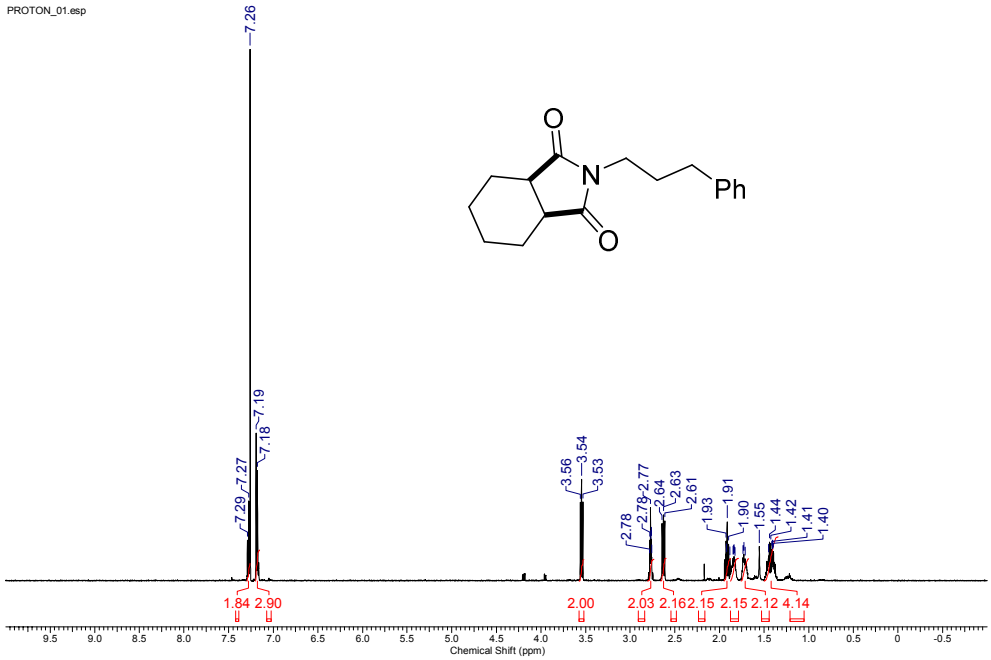
^{1}H NMR (**3l**) ($CDCl_3$)



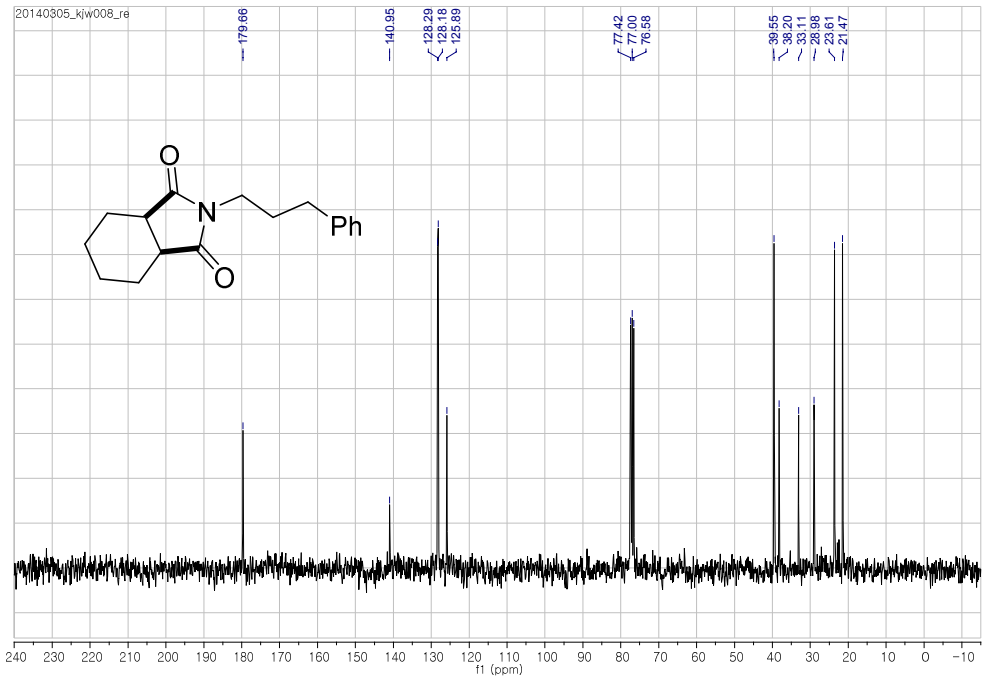
^{13}C NMR (**3l**) ($CDCl_3$)



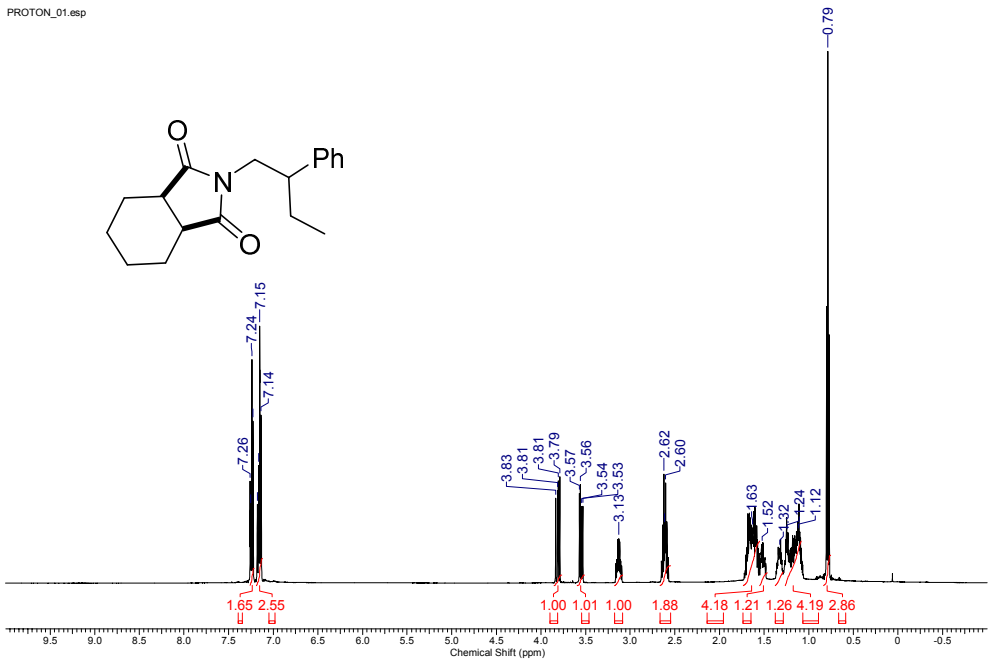
^{1}H NMR (**3m**) ($CDCl_3$)



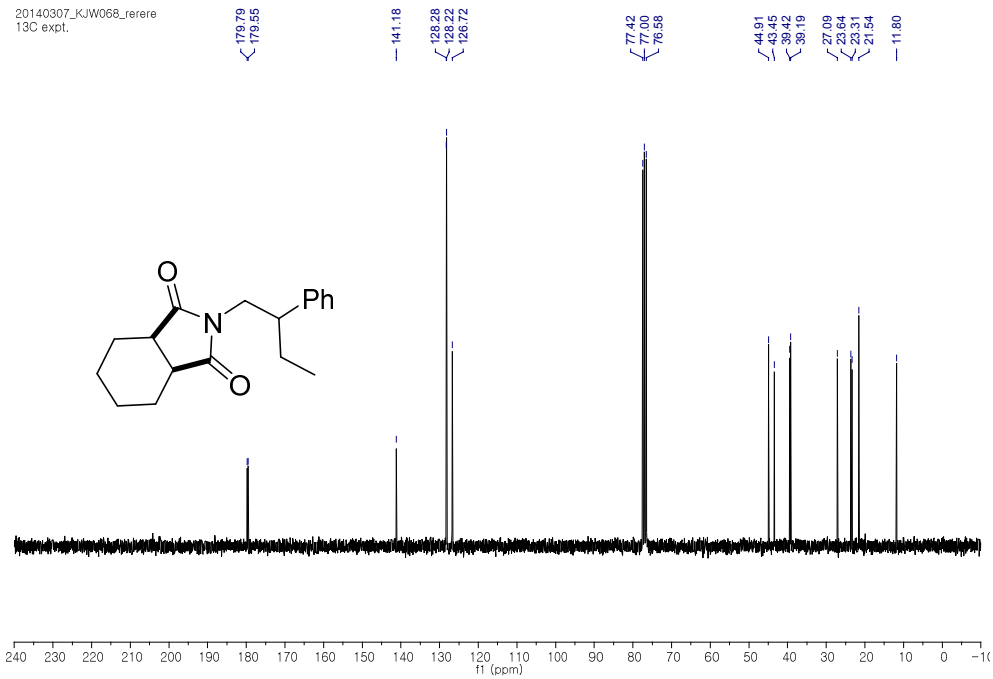
^{13}C NMR (**3m**) ($CDCl_3$)



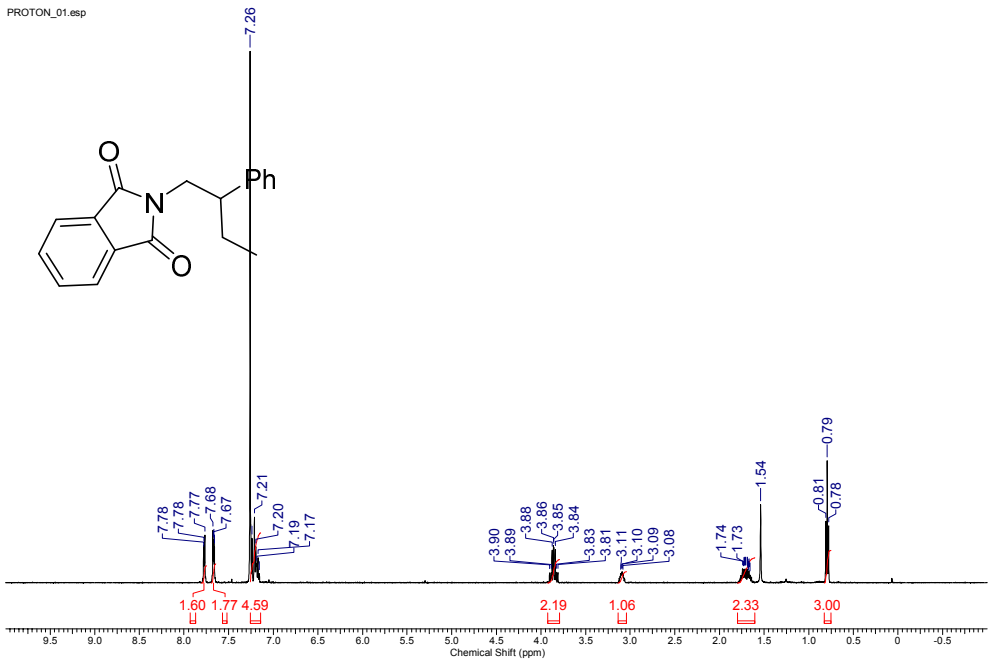
^{1}H NMR (**3n**) ($CDCl_3$)



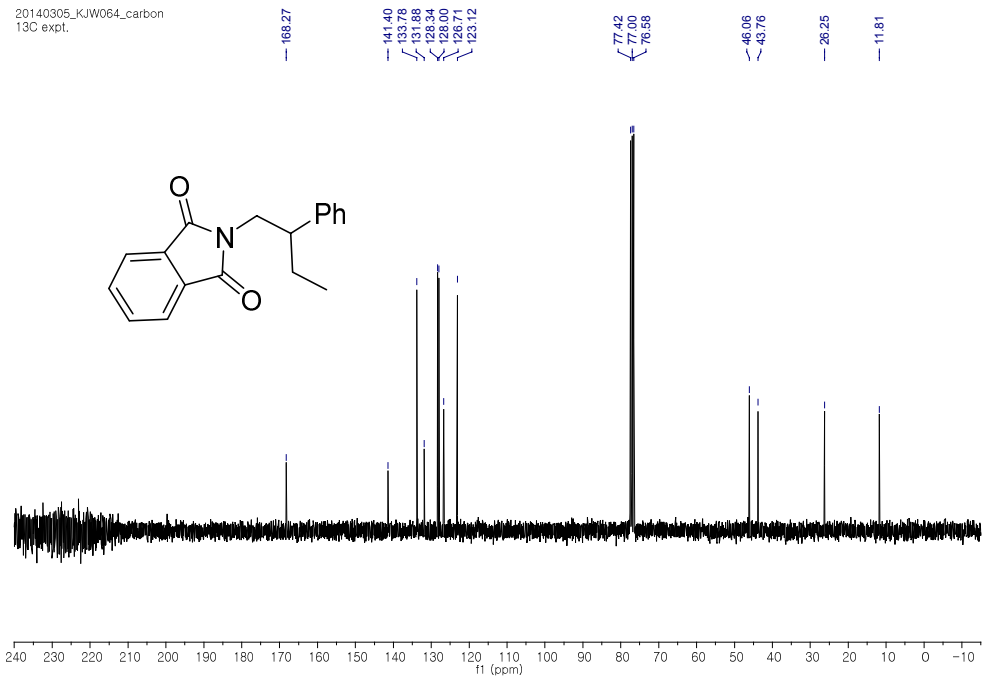
^{13}C NMR (**3n**) ($CDCl_3$)



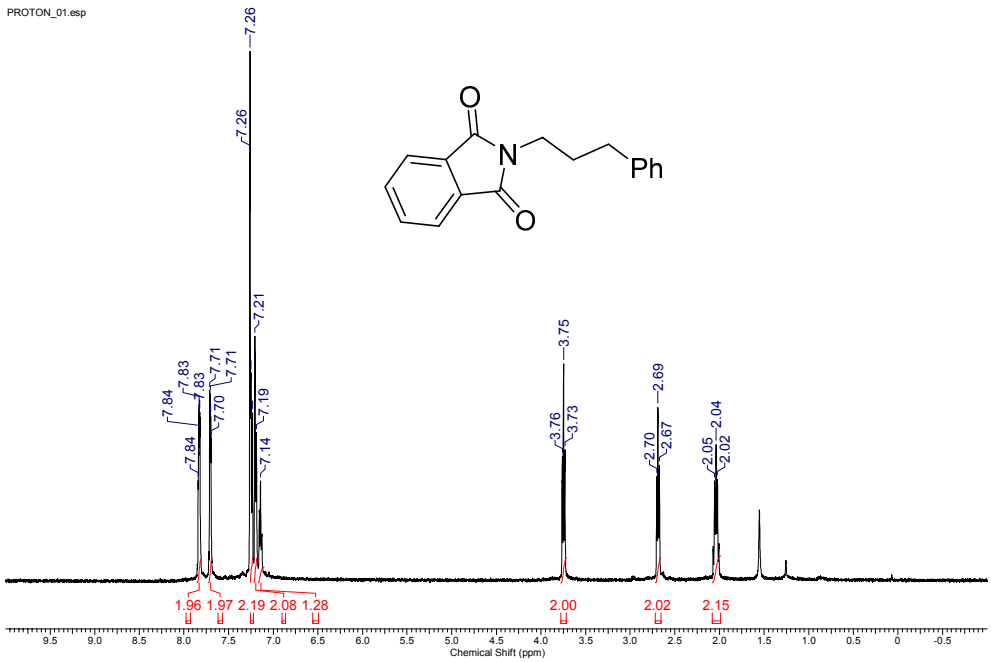
^{1}H NMR (**3o**) ($CDCl_3$)



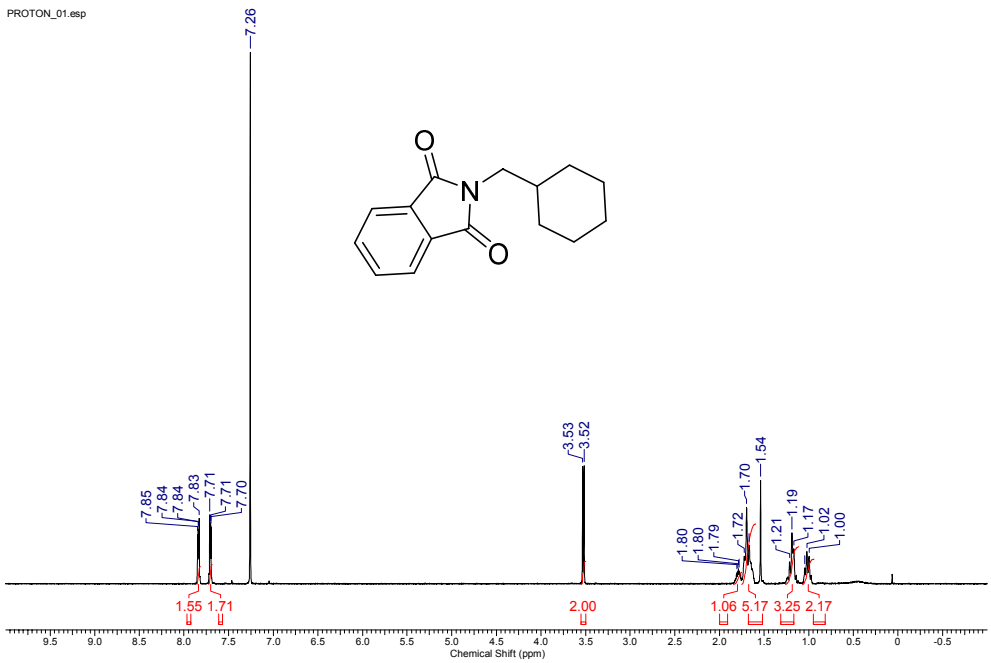
^{13}C NMR (**3o**) ($CDCl_3$)



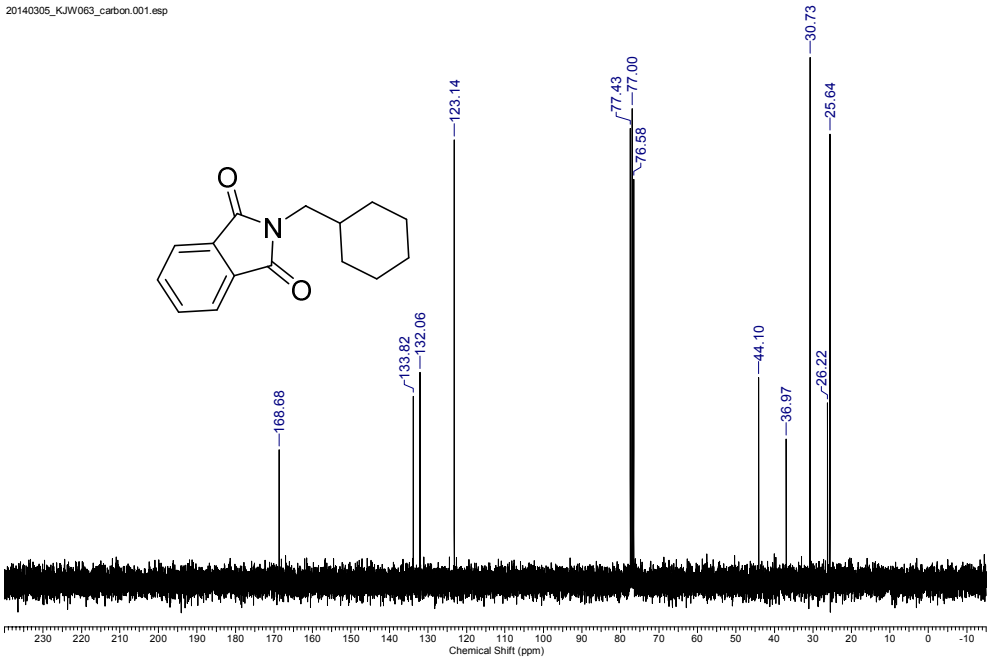
^{1}H NMR (**3p**) ($CDCl_3$)



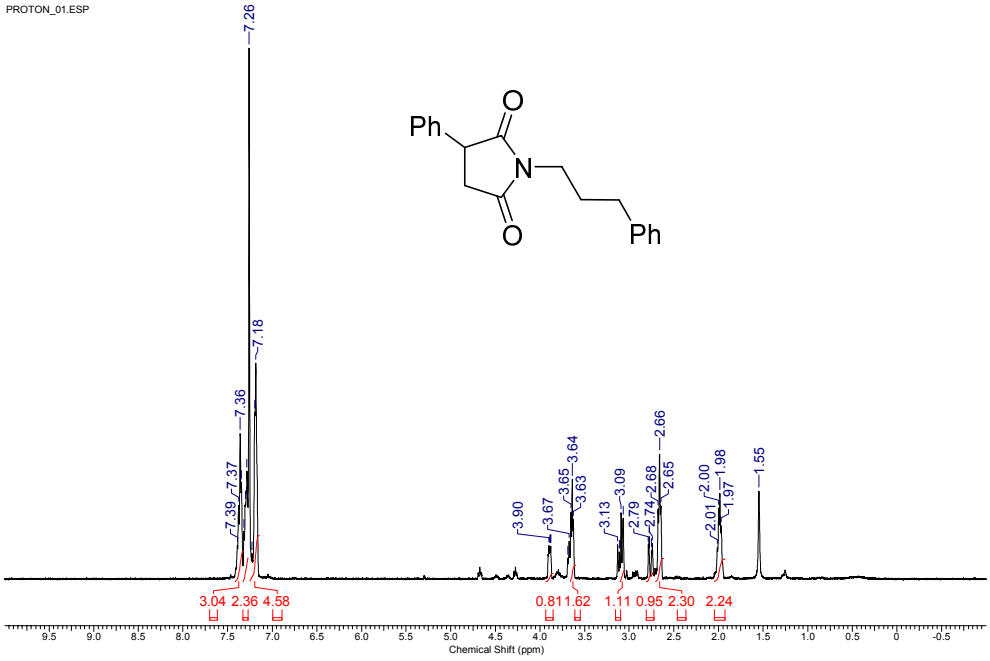
^{1}H NMR (**3q**) ($CDCl_3$)



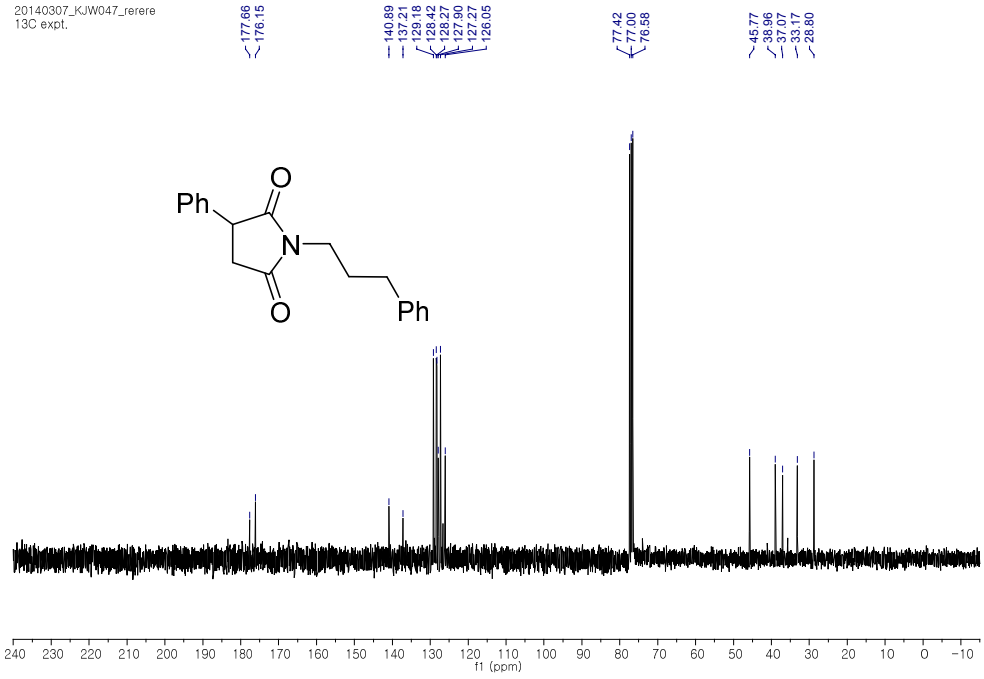
^{13}C NMR (**3q**) ($CDCl_3$)



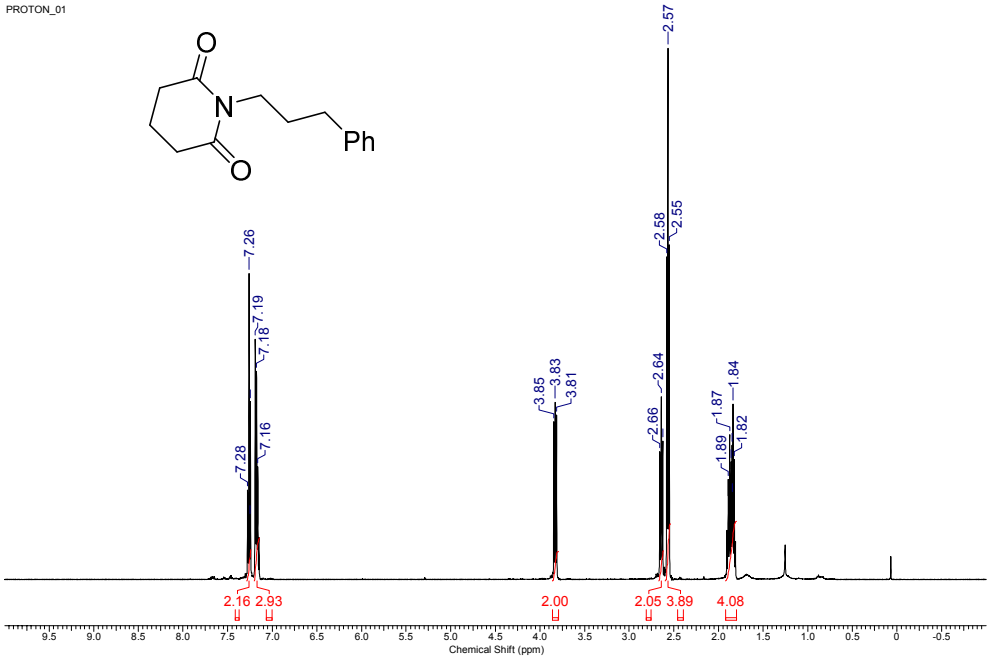
^{1}H NMR (**3r**) ($CDCl_3$)



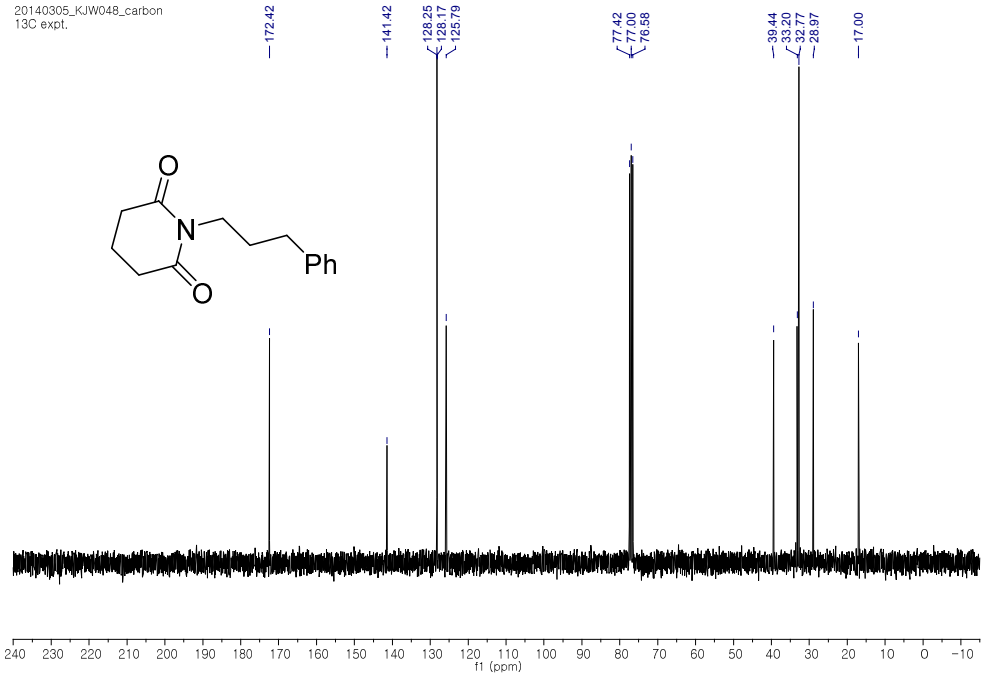
^{13}C NMR (**3r**) ($CDCl_3$)



^{1}H NMR (**3s**) ($CDCl_3$)

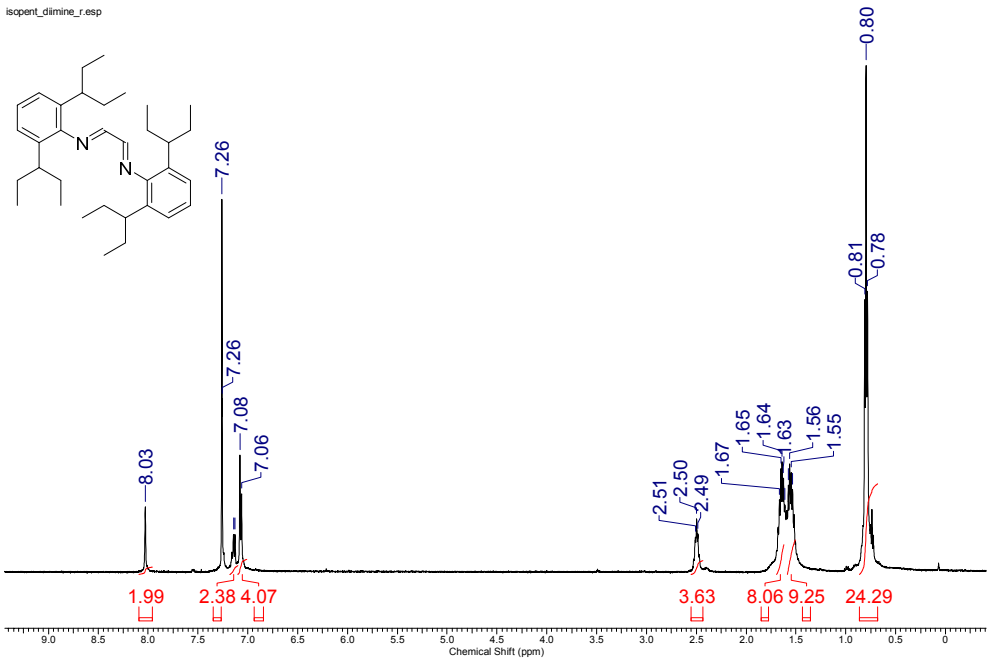


^{13}C NMR (**3s**) ($CDCl_3$)

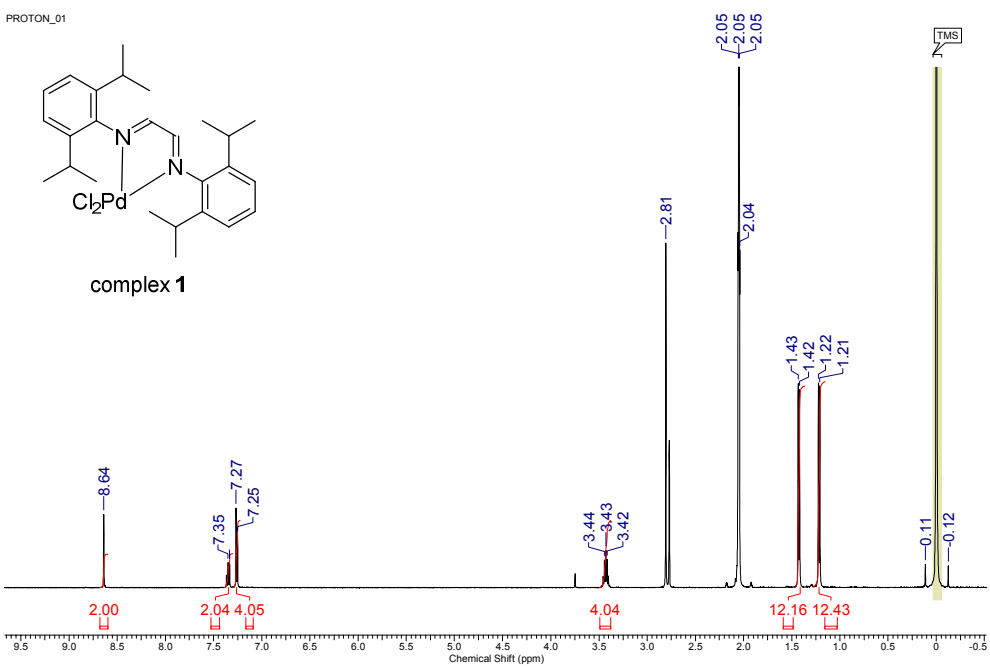


Chapter 4 - NMR Spectra

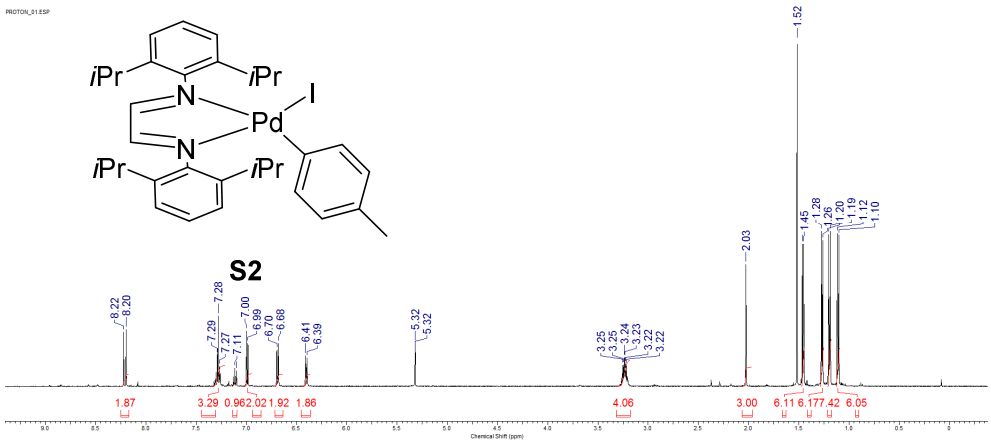
^{1}H NMR (**N,N'-bis(2,6-di(3-pentyl)phenyl)ethane-1,2-diimine**) ($CDCl_3$)



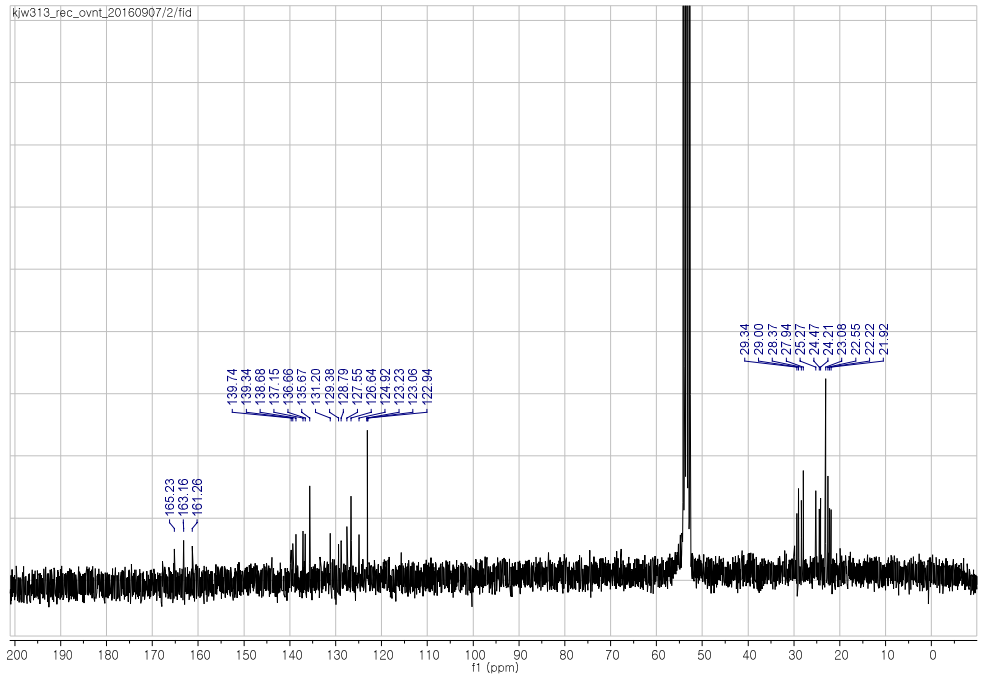
^{1}H NMR (complex **1**) ($(CD_3)_2CO$)



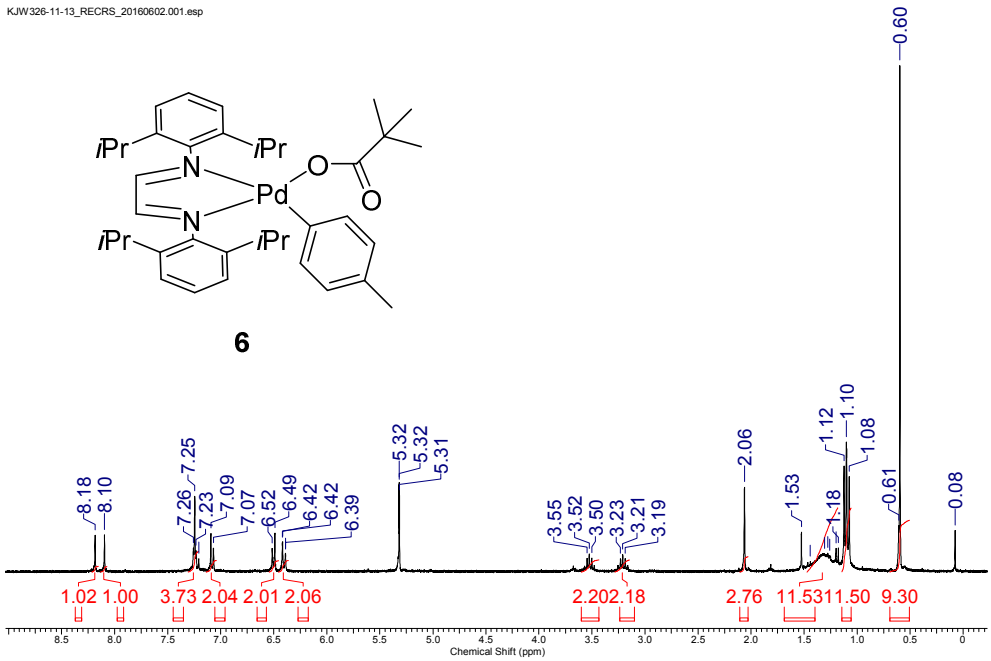
^{1}H NMR (**S2**) (CD_2Cl_2)



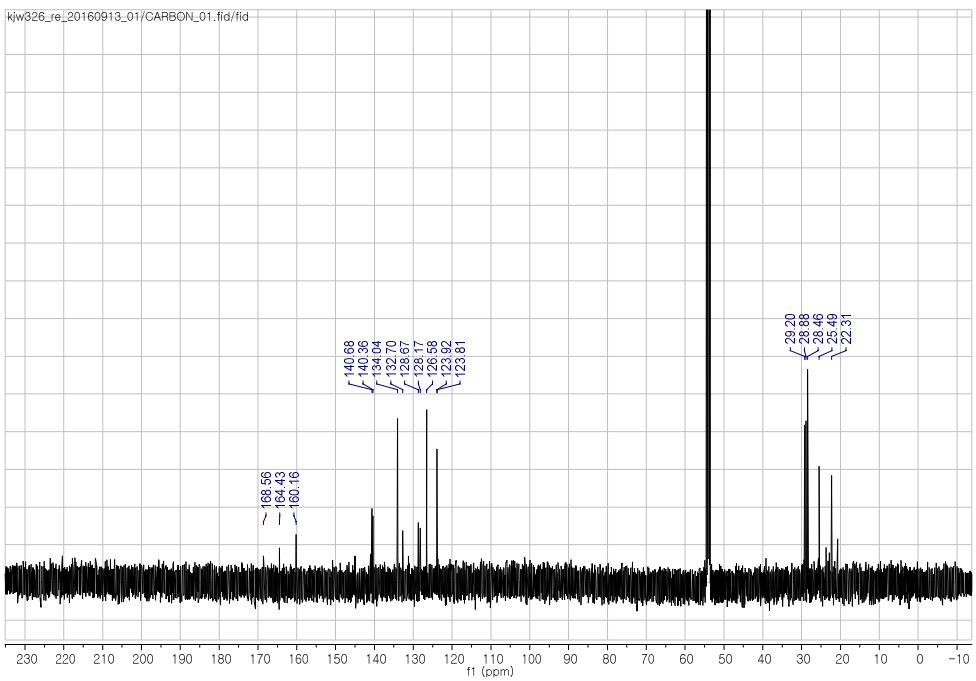
^{13}C NMR (**S2**) (CD_2Cl_2)



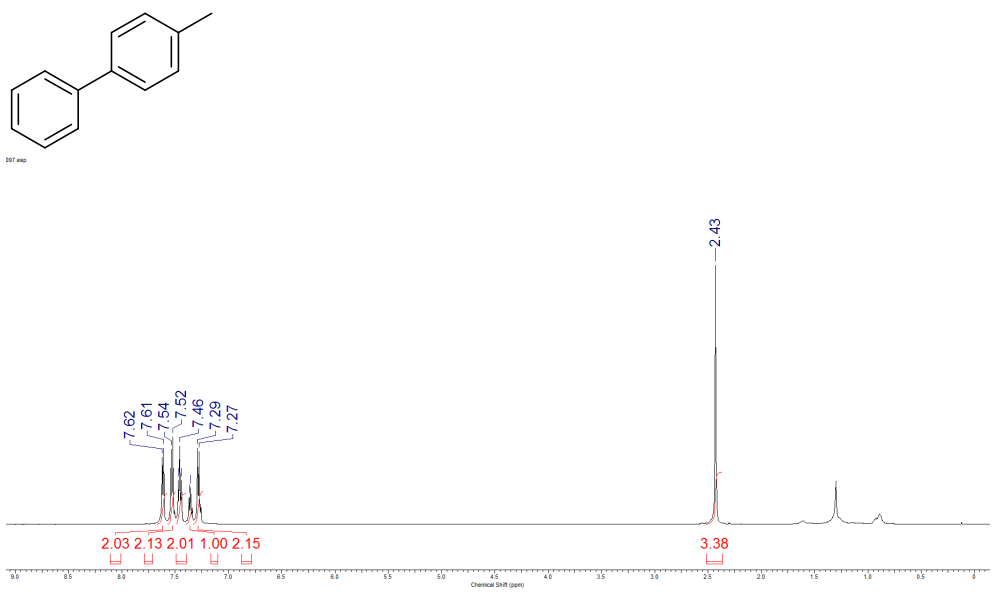
^{1}H NMR (complex **6**) (CD_2Cl_2)



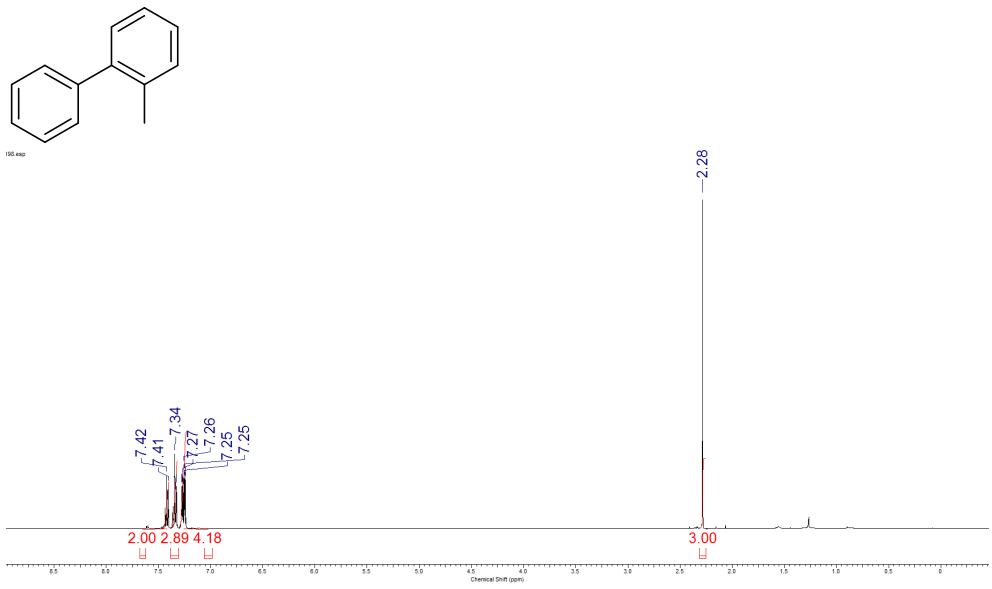
^{13}C NMR (complex **6**) (CD_2Cl_2)



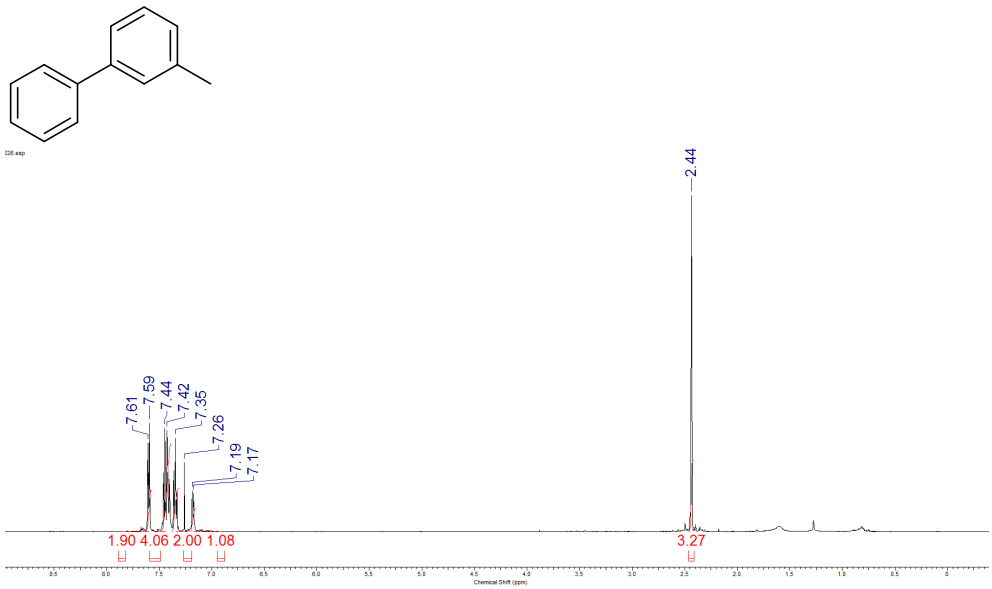
^{1}H NMR (**4a**) ($CDCl_3$)



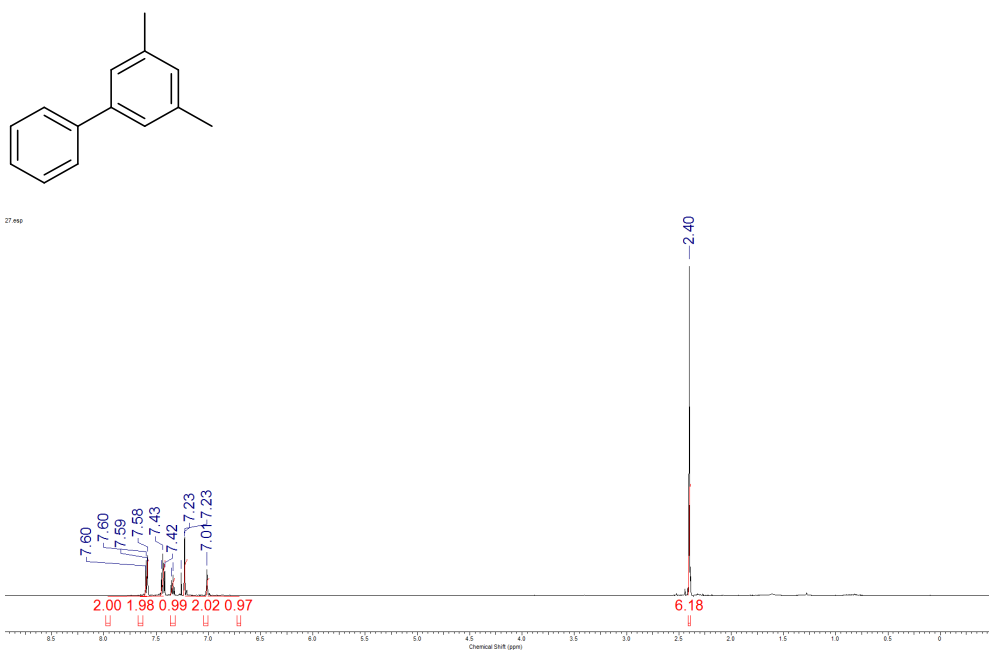
^{1}H NMR (**4b**) ($CDCl_3$)



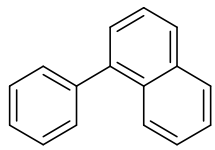
^{1}H NMR (**4c**) ($CDCl_3$)

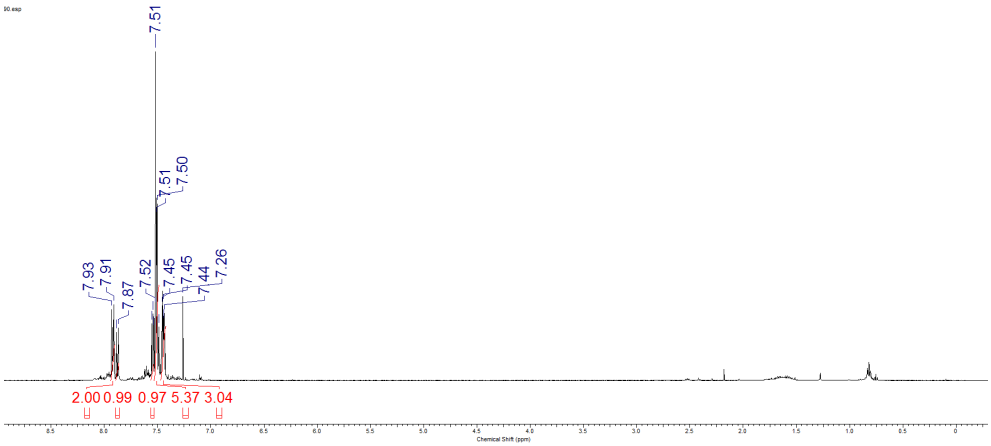


^{1}H NMR (**4d**) ($CDCl_3$)

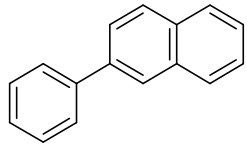


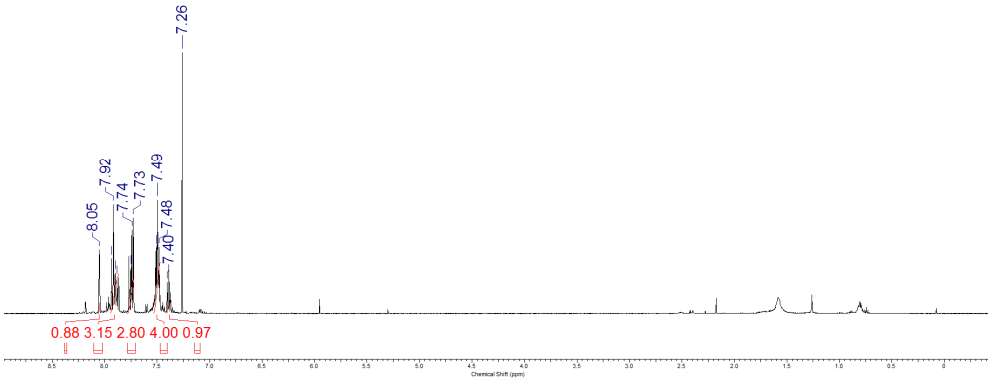
^{1}H NMR (**4e**) ($CDCl_3$)



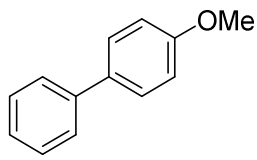


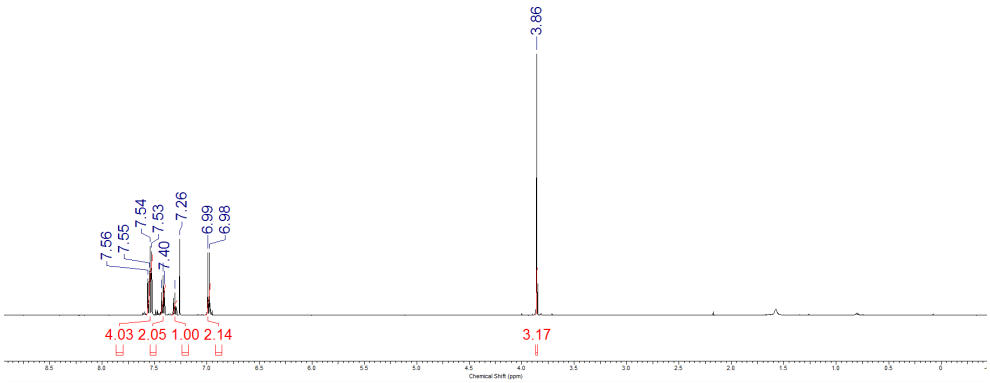
^{1}H NMR (**4f**) ($CDCl_3$)



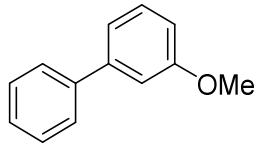


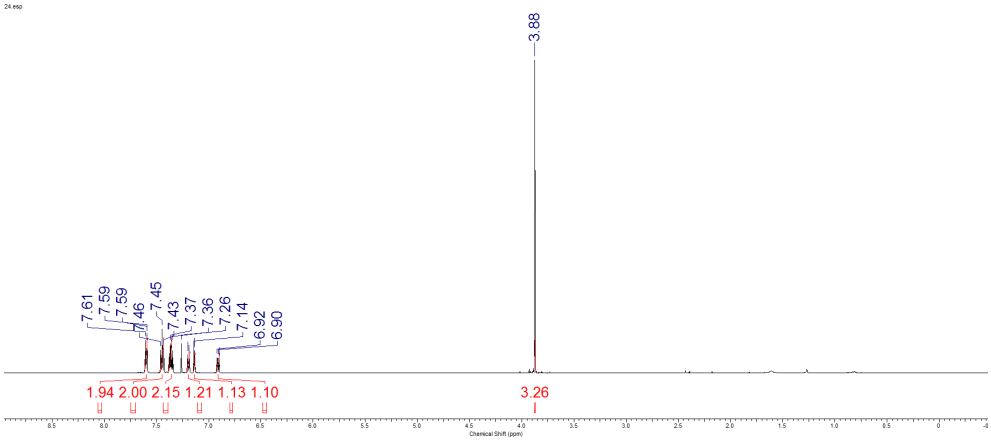
^{1}H NMR (**4g**) ($CDCl_3$)



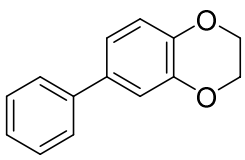


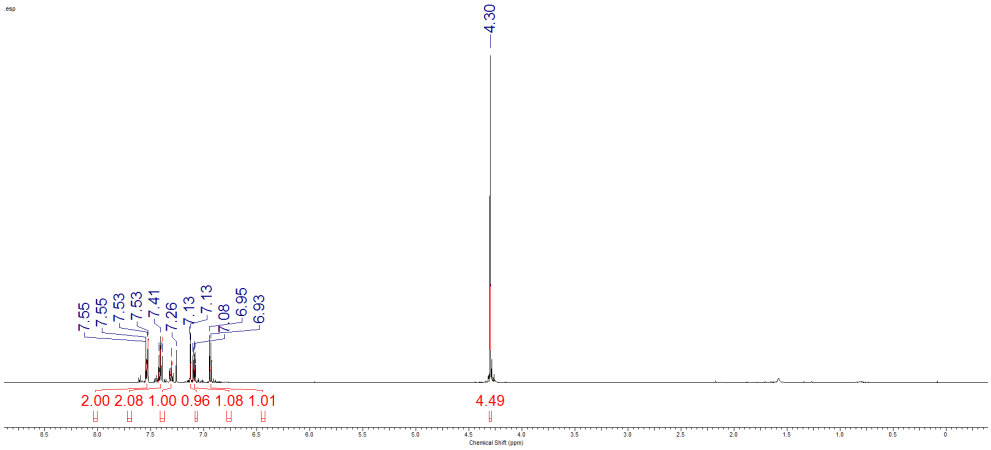
^{1}H NMR (**4h**) ($CDCl_3$)



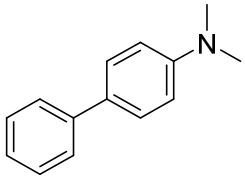


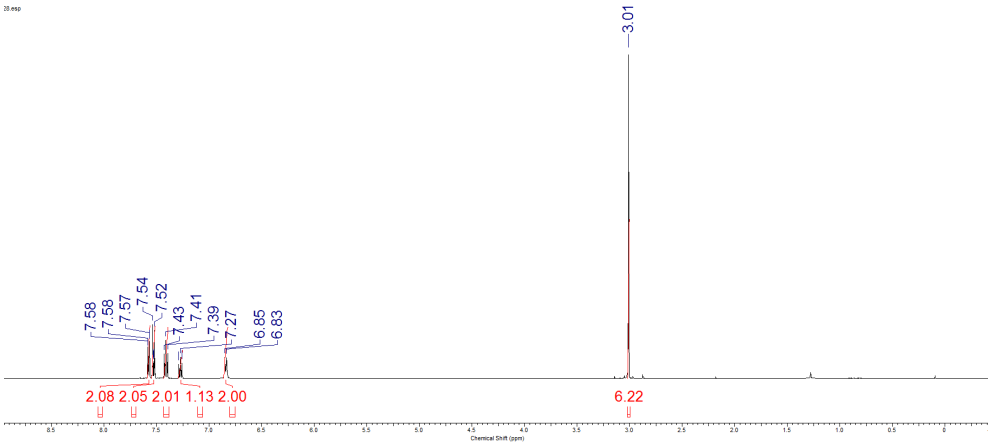
^{1}H NMR (**4i**) ($CDCl_3$)



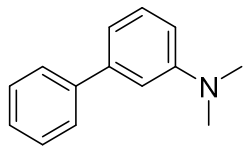


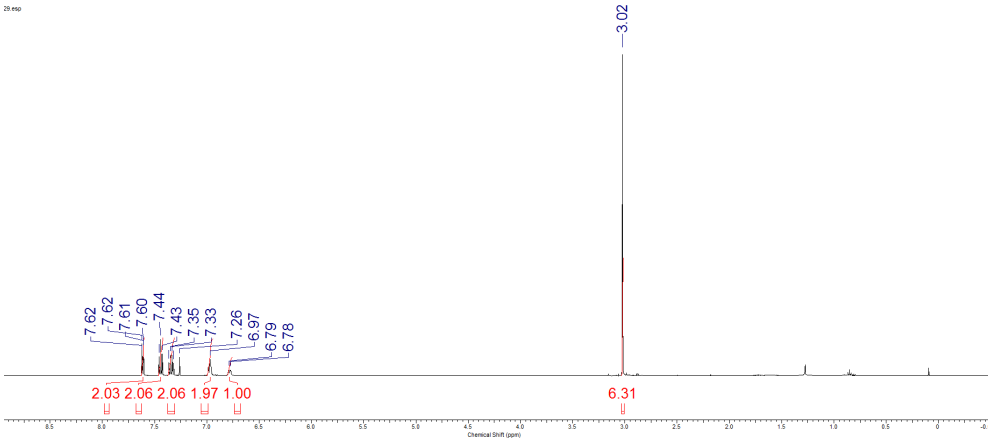
^{1}H NMR (**4j**) ($CDCl_3$)



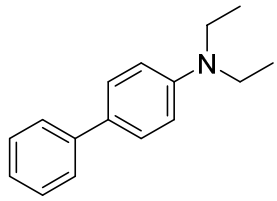


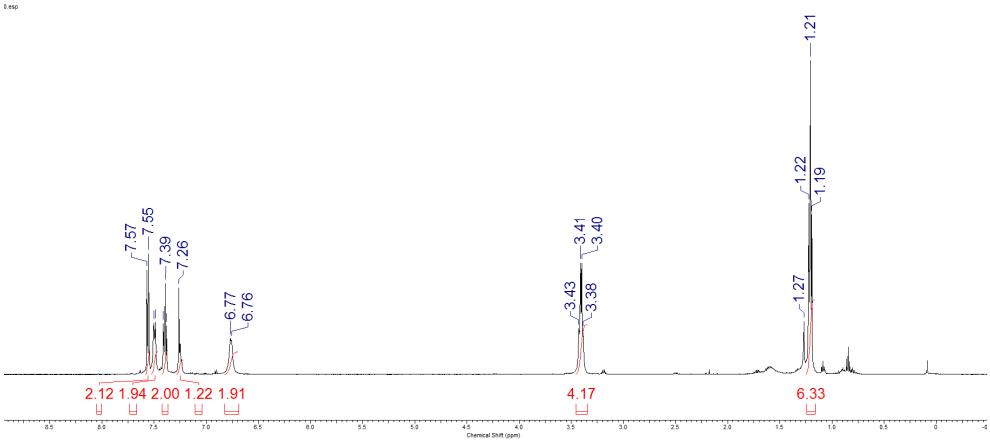
^{1}H NMR (**4k**) ($CDCl_3$)



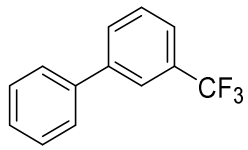


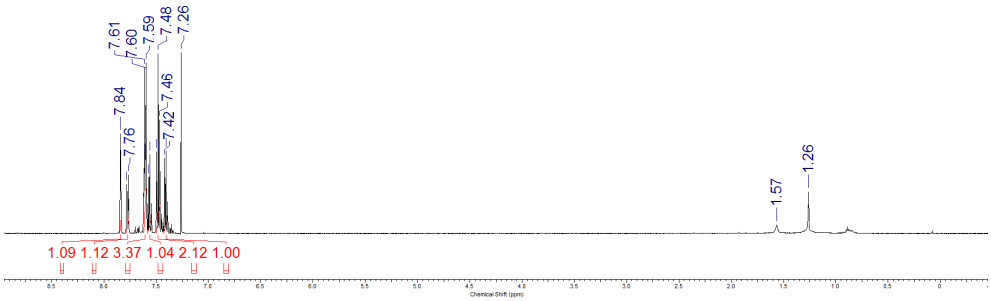
^{1}H NMR (**4l**) ($CDCl_3$)



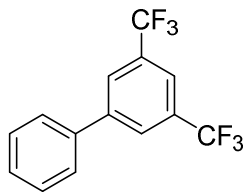


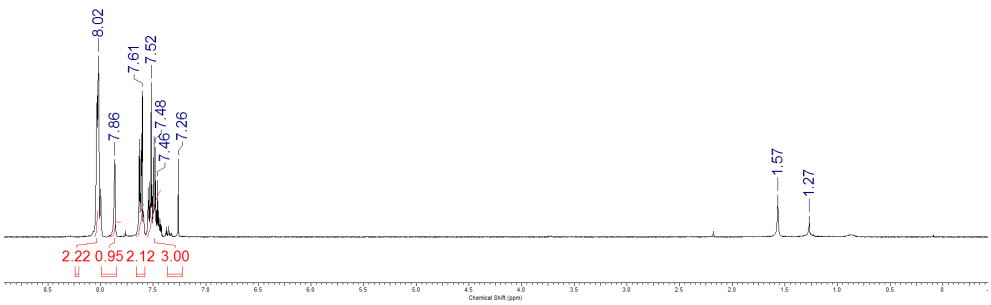
^{1}H NMR (**4m**) ($CDCl_3$)



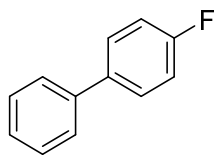


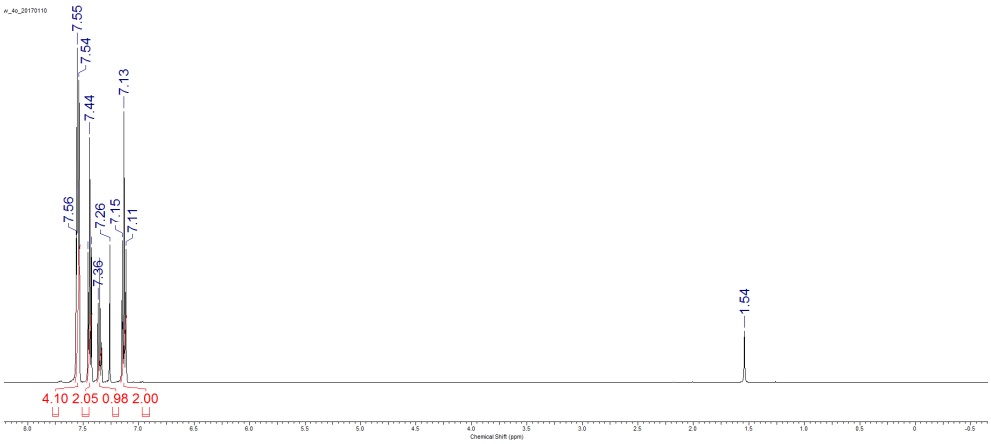
^{1}H NMR (**4n**) ($CDCl_3$)



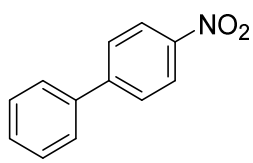


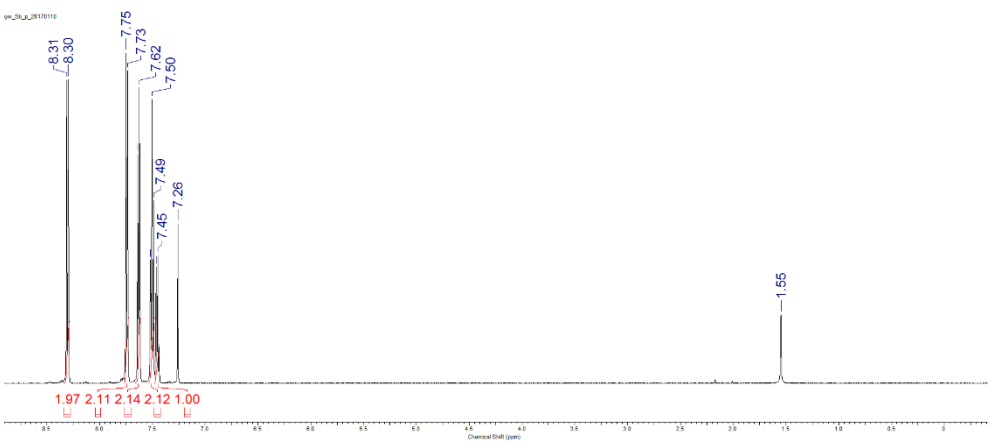
^{1}H NMR (**4o**) ($CDCl_3$)



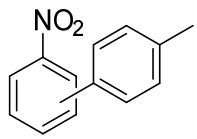


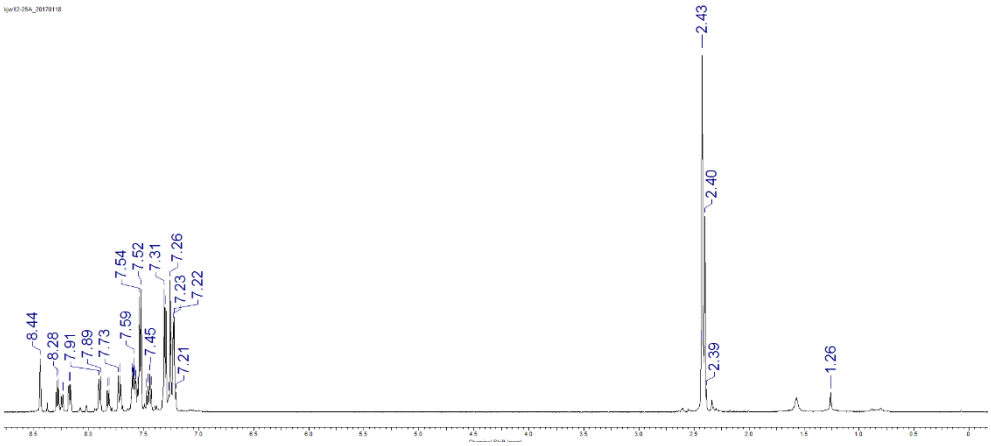
^{1}H NMR (**4p**) ($CDCl_3$)



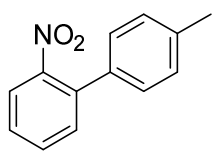


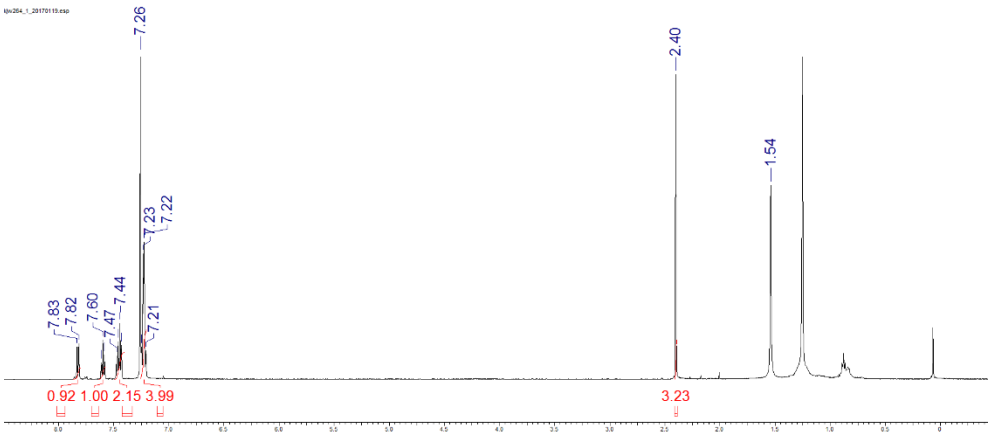
^{1}H NMR (**5a**) ($CDCl_3$)



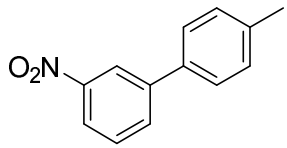


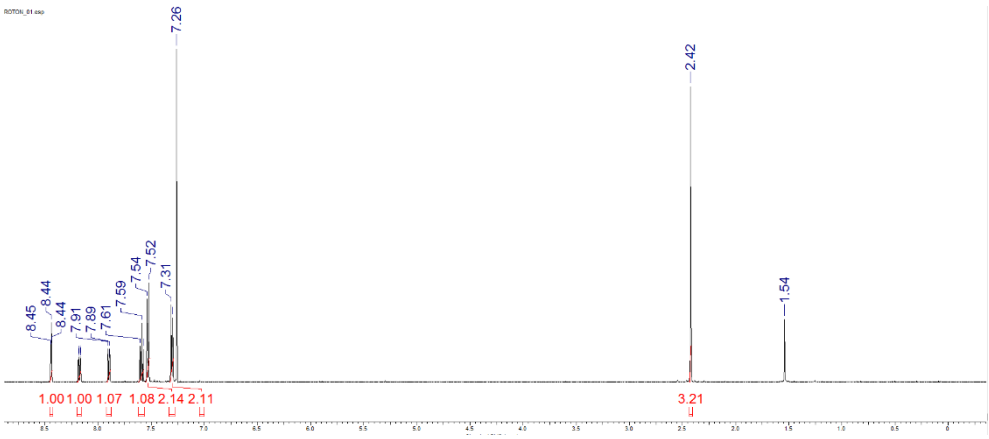
^{1}H NMR (**5a-*o***) ($CDCl_3$)



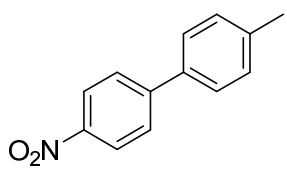


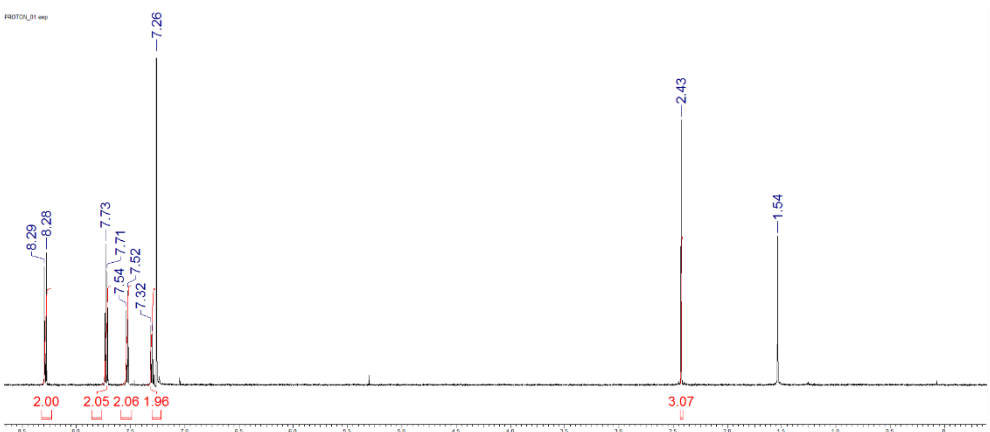
^{1}H NMR (**5a-*m***) ($CDCl_3$)



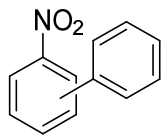


^{1}H NMR (**5a-*p***) ($CDCl_3$)

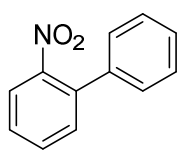


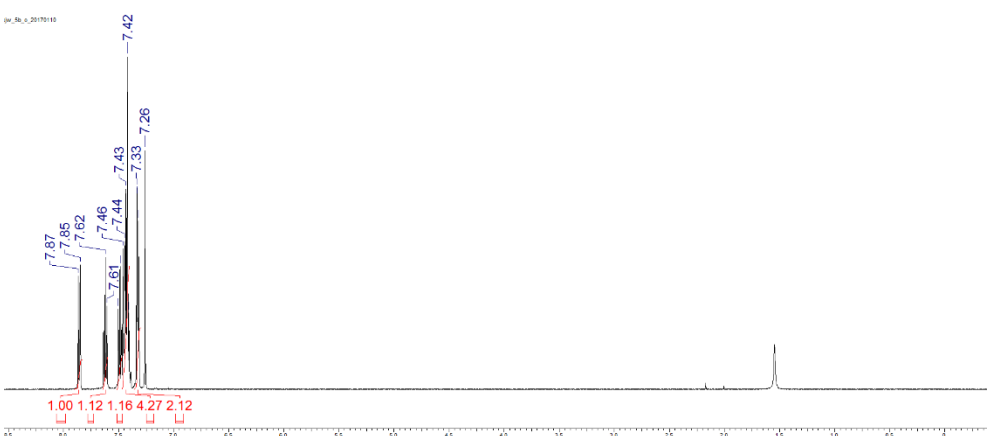


^{1}H NMR (**5b**) ($CDCl_3$)

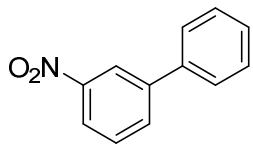


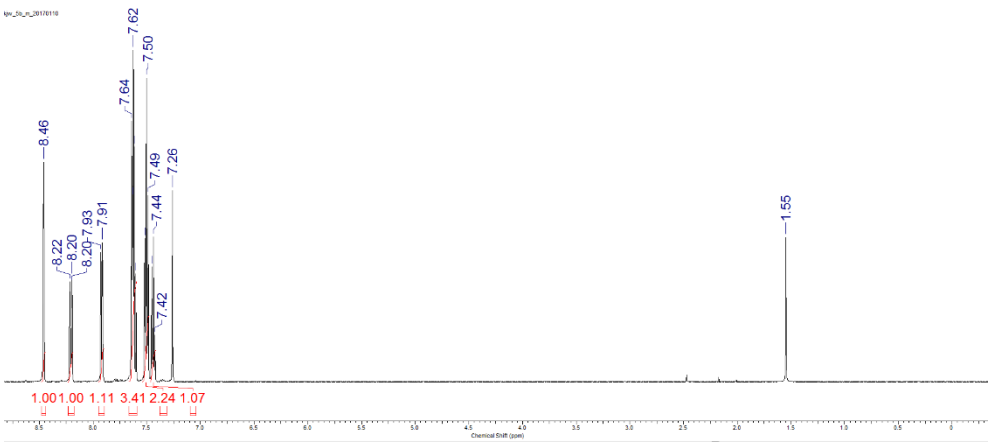
^{1}H NMR (**5b-*o***) ($CDCl_3$)



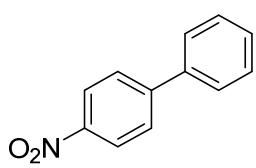


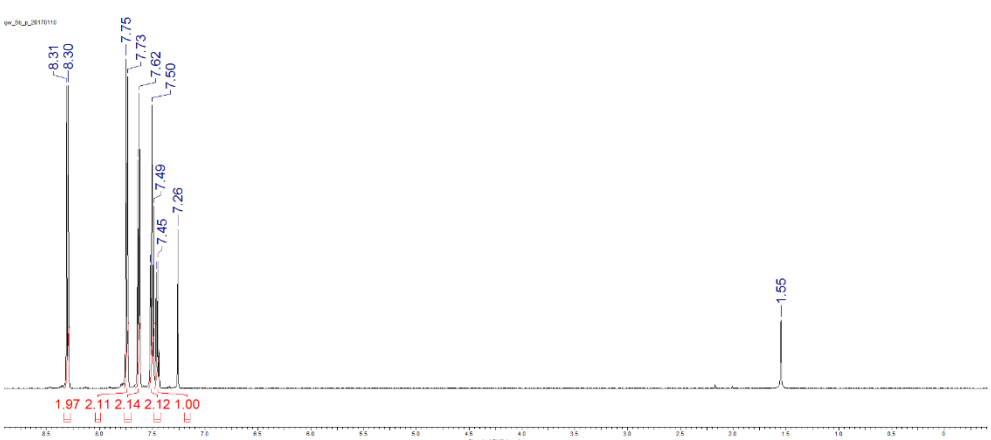
^{1}H NMR (**5b-*m***) ($CDCl_3$)



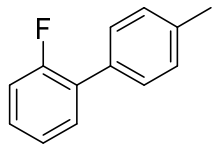


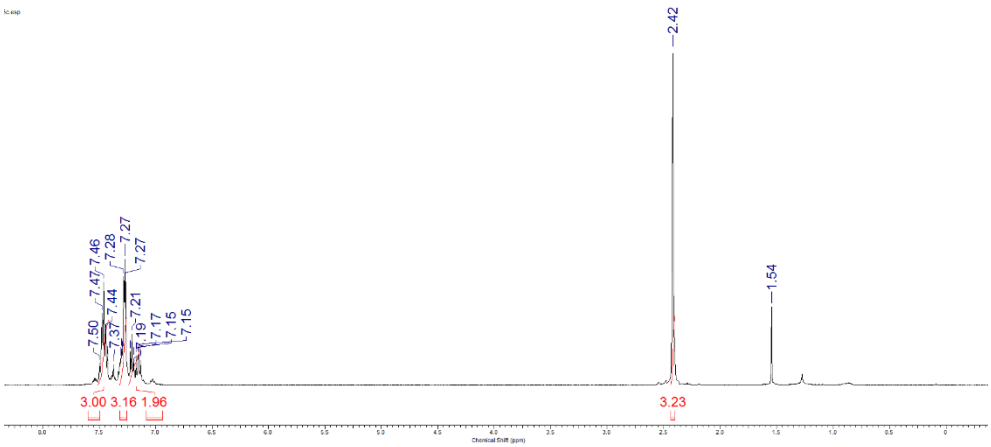
^{1}H NMR (**5b-*p***) ($CDCl_3$)



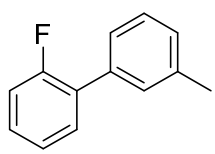


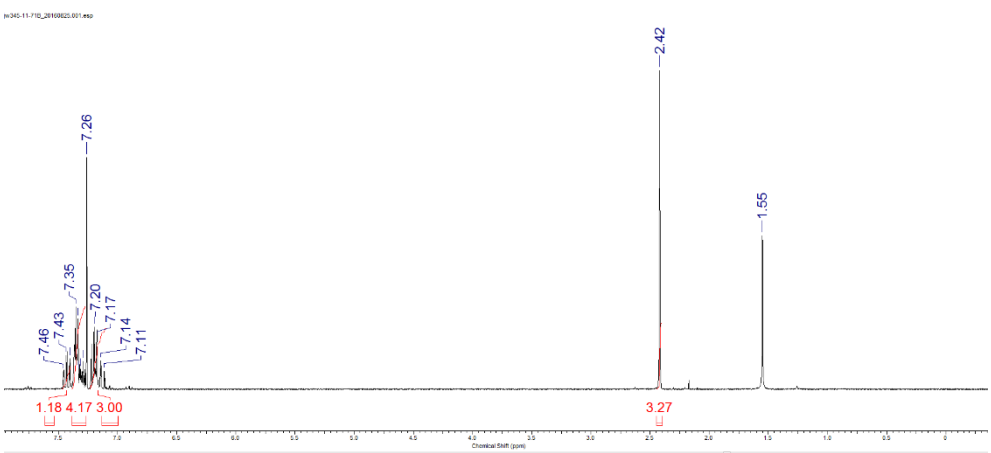
^{1}H NMR (**5c**) ($CDCl_3$)



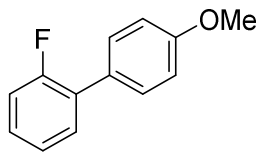


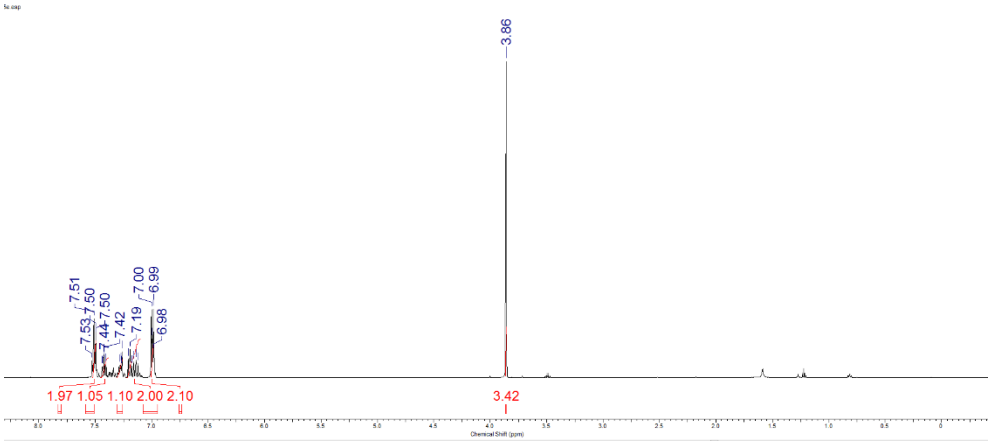
^{1}H NMR (**5d**) ($CDCl_3$)



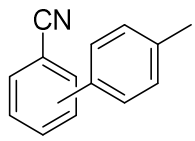


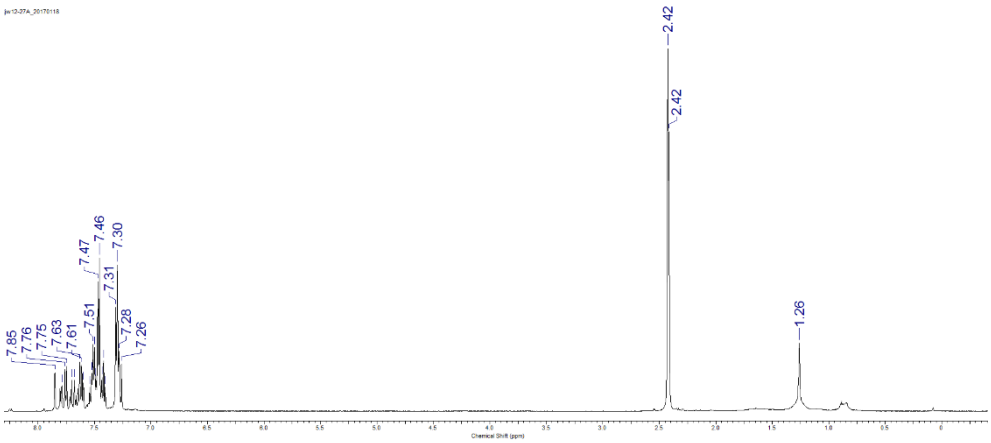
^{1}H NMR (**5e**) ($CDCl_3$)



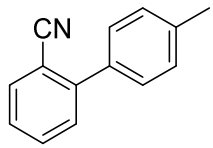


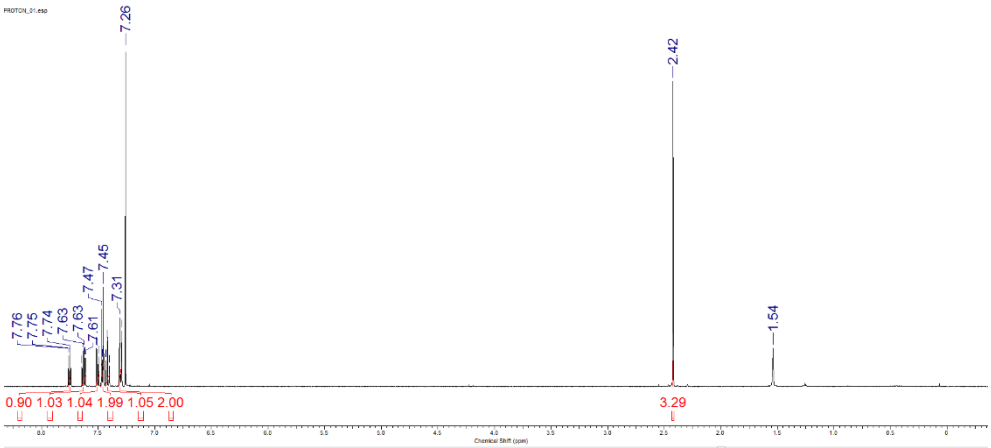
^{1}H NMR (**5f**) ($CDCl_3$)



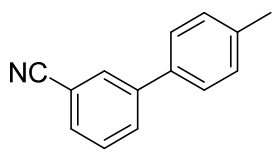


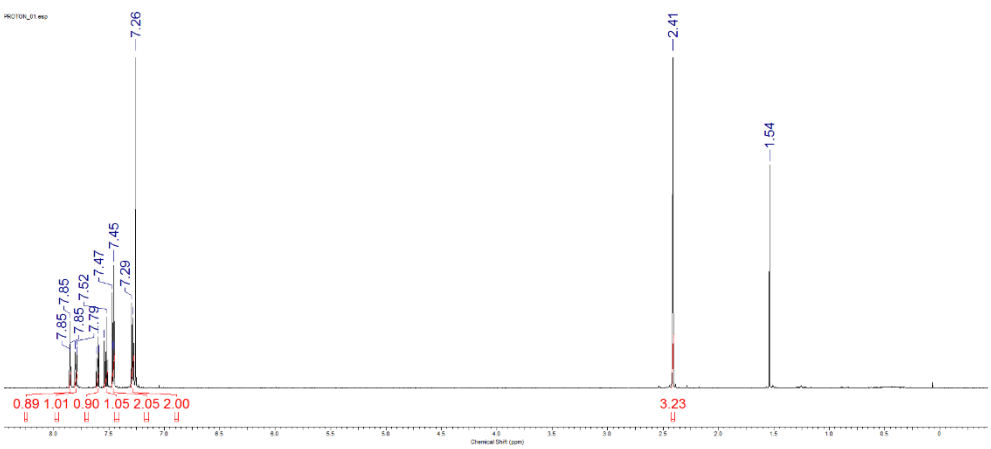
^{1}H NMR (**5f-*o***) ($CDCl_3$)



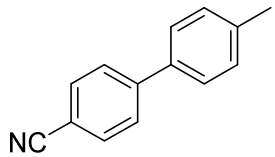


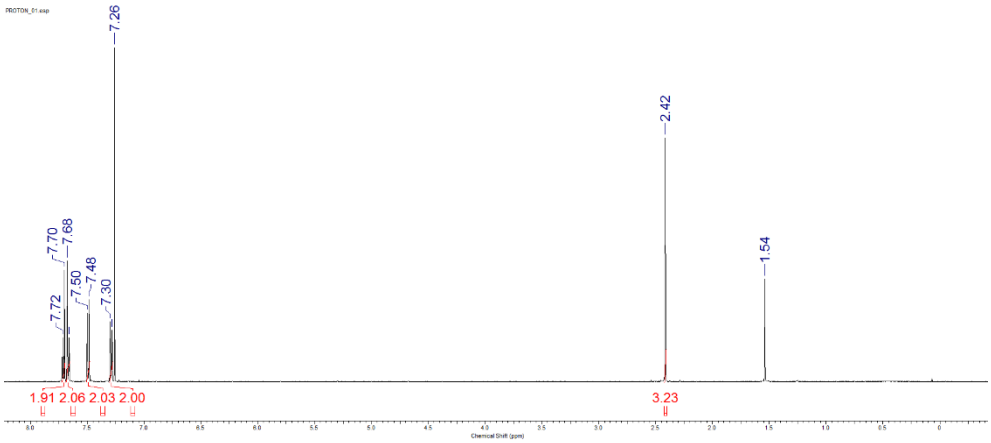
^{1}H NMR (**5f-*m***) ($CDCl_3$)



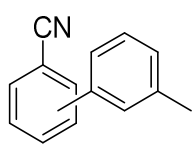


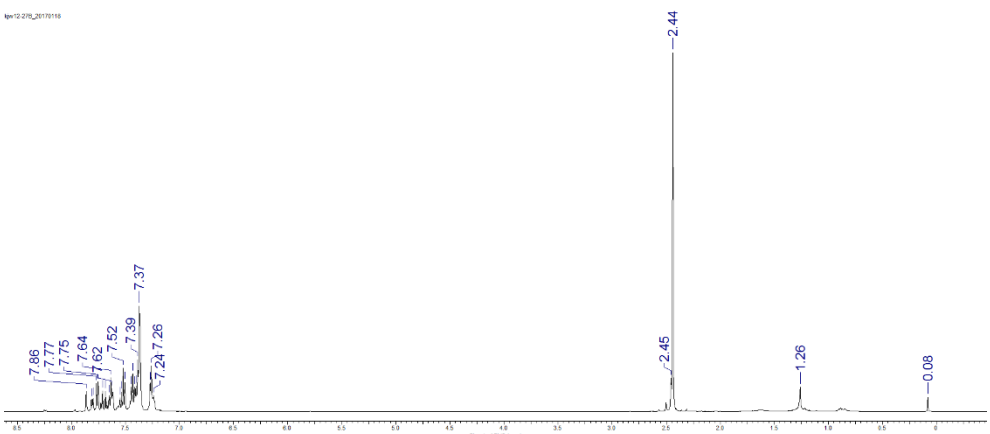
^{1}H NMR **(5f-*p*)** ($CDCl_3$)



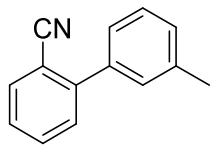


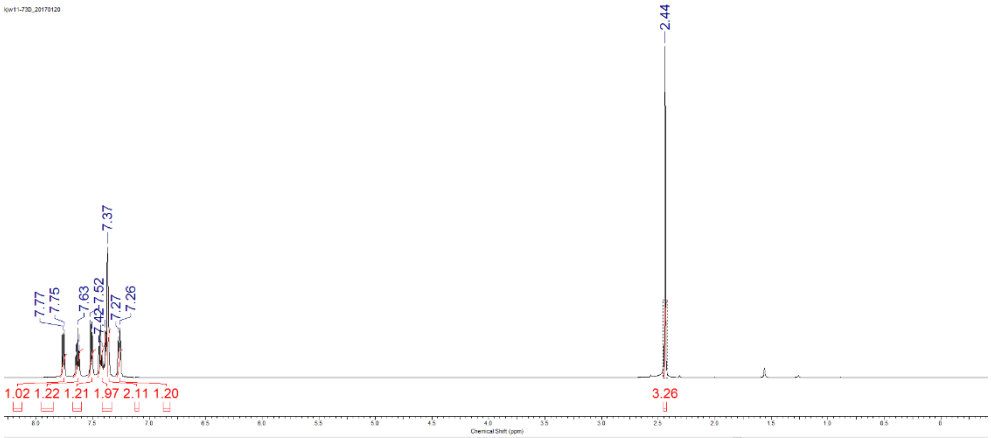
^{1}H NMR (**5g**) ($CDCl_3$)



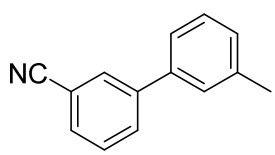


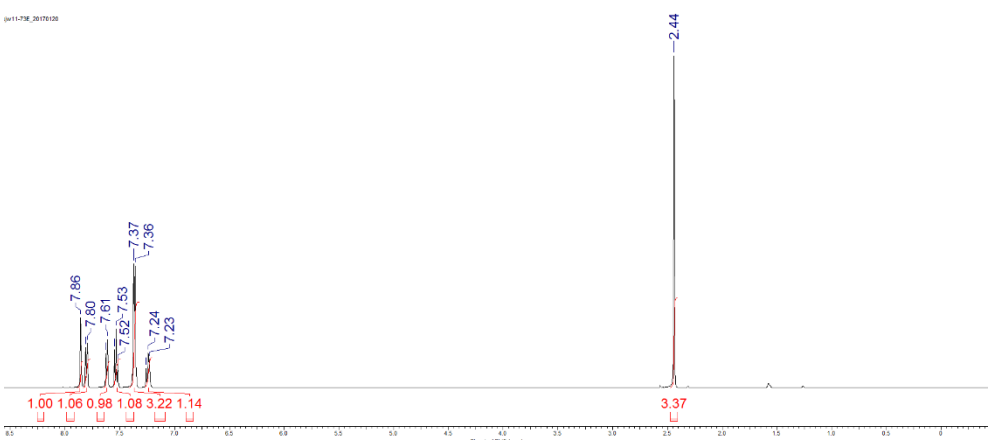
^{1}H NMR (**5g-*o***) ($CDCl_3$)



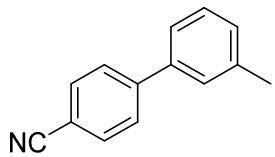


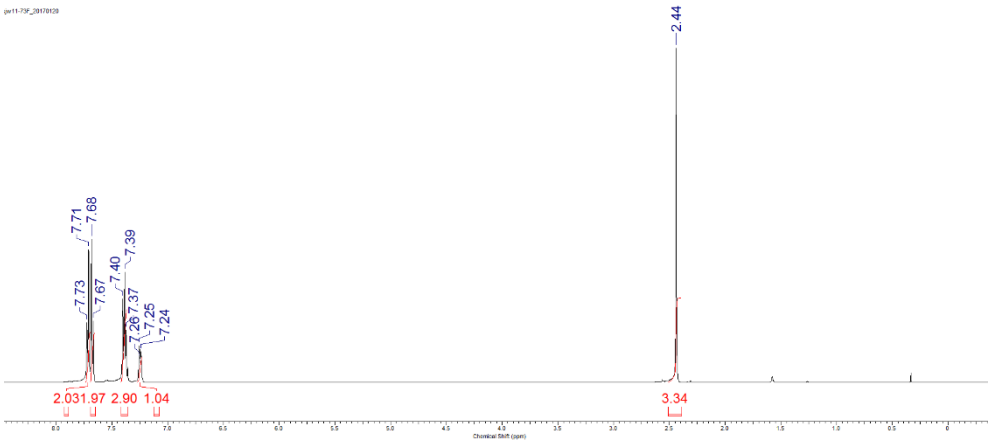
^{1}H NMR (**5g-*m***) ($CDCl_3$)



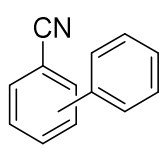


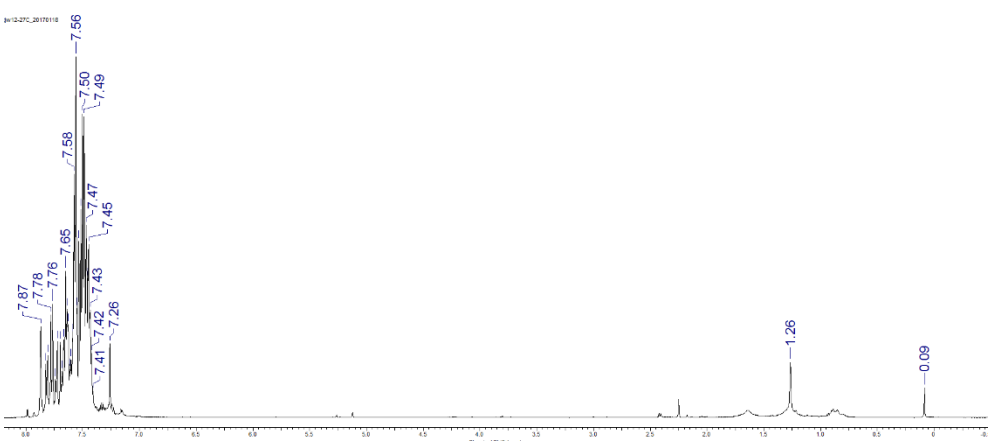
^{1}H NMR (**5g-*p***) ($CDCl_3$)



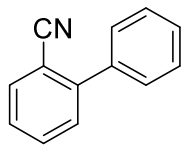


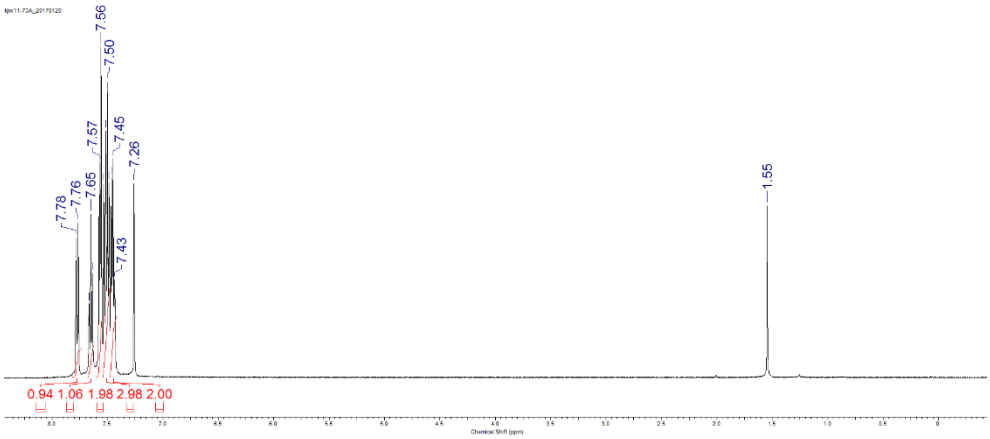
^{1}H NMR (**5h**) ($CDCl_3$)



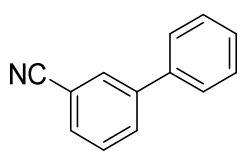


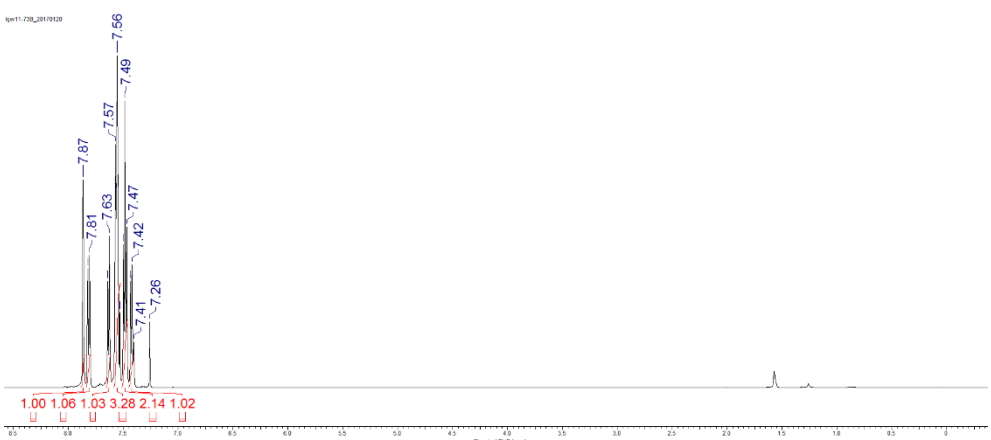
^{1}H NMR (**5h-*o***) ($CDCl_3$)



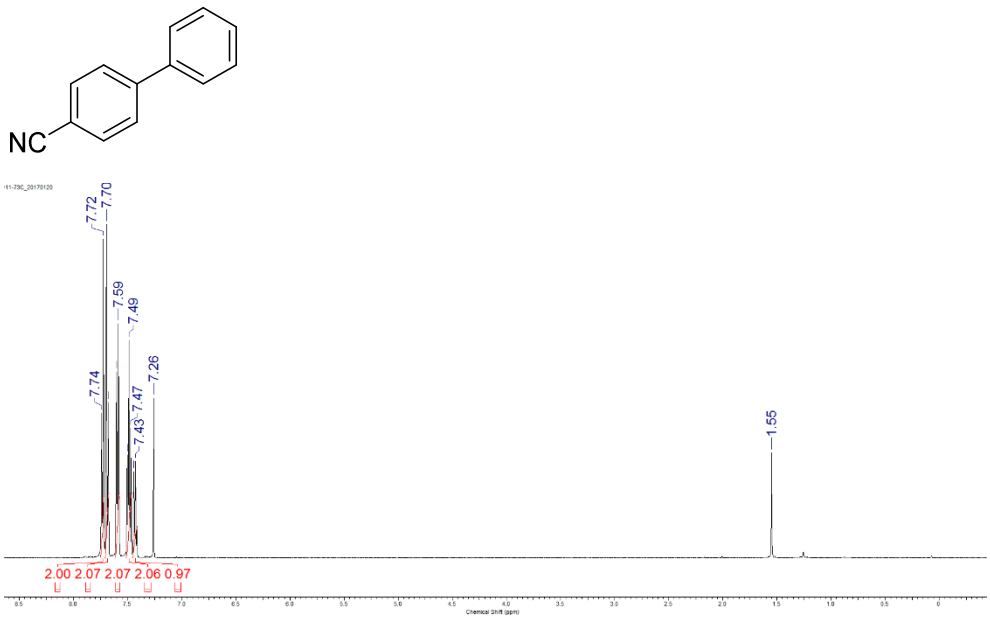


^{1}H NMR (**5h-*m***) ($CDCl_3$)





^{1}H NMR (**5h-*p***) ($CDCl_3$)



Crystallographic data of complex 6

The crystal structure was deposit at the Cambridge Crystallographic Data Center.

CCDC: 1516120

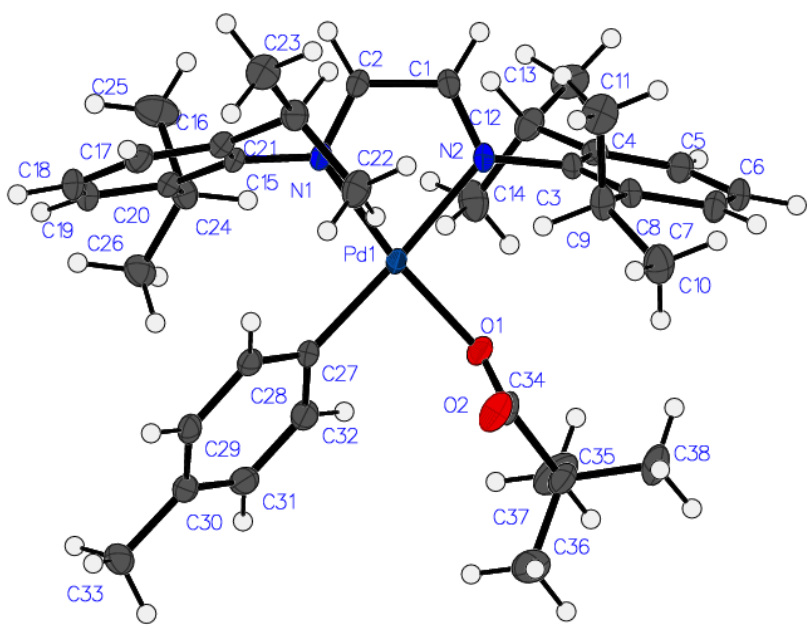


Table S1. Crystal data and structure refinement for complex 6.

Identification code	complex 6
Empirical formula	$C_{38}H_{52}N_2O_2Pd$
Formula weight	675.21
Temperature/K	100.0(3)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	12.47076(8)
b/Å	21.63215(13)
c/Å	13.10657(8)
α/°	90
β/°	99.4700(6)
γ/°	90
Volume/Å^3	3487.56(4)
Z	4
ρ_{calc}g/cm^3	1.286
μ/mm^{-1}	4.542
F(000)	1424.0
Crystal size/mm^3	0.262 × 0.079 × 0.073
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.186 to 153.22
Index ranges	$-15 \leq h \leq 15$, $-27 \leq k \leq 27$, $-11 \leq l \leq 16$
Reflections collected	70688
Independent reflections	7324 [R_{int} = 0.0397, R_{sigma} = 0.0165]
Data/restraints/parameters	7324/0/400
Goodness-of-fit on F^2	1.030
Final R indexes [I>=2σ (I)]	R_1 = 0.0247, wR_2 = 0.0608

Final R indexes [all data] $R_1 = 0.0259$, $wR_2 = 0.0616$

Largest diff. peak/hole / e $Å^{-3}$ 0.71/-0.71

Table S2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for complex 6. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Pd1	3358.4(2)	1662.6(2)	3939.1(2)	15.33(4)
O1	2430(1)	1042.3(6)	3052.6(9)	21.2(2)
N1	4170.2(11)	2247.7(6)	5037.2(11)	15.9(3)
O2	2279.1(12)	1606.2(6)	1607.3(11)	30.2(3)
N2	2123.0(11)	1906.0(6)	4809.5(11)	16.3(3)
C7	-733.0(15)	1686.7(9)	3575.4(15)	23.4(4)
C27	4589.3(13)	1411.2(8)	3228.5(13)	18.1(3)
C3	1026.9(13)	1678.9(7)	4623.3(13)	17.1(3)
C29	6165.1(14)	1617.0(8)	2406.2(13)	19.9(3)
C22	3715.2(16)	3356.5(9)	3379.0(16)	28.5(4)
C12	1544.2(15)	904.7(8)	6095.7(14)	23.6(4)
C17	6431.5(15)	3268.6(8)	4617.4(14)	22.3(4)
C31	5574.2(15)	577.2(9)	2542.7(14)	23.6(4)
C20	6127.1(13)	2074.4(8)	5344.2(13)	18.0(3)
C35	1550.9(15)	571.9(9)	1496.0(15)	25.2(4)
C21	4406.1(14)	3520.4(8)	4427.6(14)	21.5(3)
C2	3609.6(13)	2442.2(7)	5713.9(13)	16.8(3)
C1	2468.9(13)	2241.4(8)	5601.7(13)	17.7(3)
C9	653.8(14)	2492.2(9)	3215.0(14)	23.5(4)
C8	311.1(13)	1937.8(8)	3798.5(13)	19.5(3)

C23	4727.9(17)	4201.5(9)	4448.1(16)	28.4(4)
C15	5253.9(13)	2480.1(8)	5054.0(12)	16.0(3)
C34	2134.2(13)	1133.8(8)	2082.7(14)	21.4(3)
C32	4725.8(14)	780.5(8)	3030.8(14)	22.4(4)
C19	7162.7(14)	2286.2(9)	5254.8(14)	22.6(4)
C16	5375.8(14)	3085.3(8)	4705.1(13)	18.7(3)
C4	740.9(14)	1185.8(8)	5218.3(13)	18.7(3)
C33	7238.0(15)	764.7(10)	1717.4(15)	27.8(4)
C26	6633.9(15)	929.5(9)	5402.6(15)	26.0(4)
C6	-1032.5(14)	1197.0(9)	4141.2(15)	24.8(4)
C30	6308.8(14)	990.7(9)	2227.9(13)	22.4(4)
C28	5320.1(14)	1821.9(8)	2903.5(13)	18.9(3)
C24	5961.0(14)	1441.8(8)	5798.1(14)	21.7(3)
C14	2353.5(16)	484.6(9)	5663.7(17)	30.4(4)
C5	-311.8(14)	950.4(8)	4953.1(14)	22.4(4)
C18	7310.0(14)	2872.0(9)	4880.5(14)	24.5(4)
C11	564.3(18)	3085.3(9)	3839.0(17)	33.3(4)
C13	994.3(17)	557.5(9)	6883.3(15)	29.5(4)
C10	12.6(16)	2559.3(10)	2122.0(15)	31.4(4)
C25	6218(2)	1475.7(10)	6976.4(16)	35.3(5)
C38	353.1(17)	747.2(12)	1195(2)	42.0(5)
C37	1652(2)	-11.2(10)	2162.5(19)	43.1(6)
C36	2055(2)	457.8(12)	527.0(18)	40.6(5)

Table S3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for complex 6. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Pd1	10.99(6)	16.66(7)	17.52(7)	-1.97(4)	-0.02(4)	-1.78(4)
O1	18.7(6)	22.9(6)	21.1(6)	-3.2(5)	0.4(5)	-6.4(5)
N1	12.4(6)	16.0(6)	17.9(7)	0.3(5)	-1.7(5)	-0.3(5)
O2	31.0(7)	25.4(7)	30.2(7)	5.4(5)	-6.6(6)	-7.4(5)
N2	10.9(6)	16.7(7)	20.6(7)	1.6(5)	0.2(5)	-0.1(5)
C7	14.4(8)	31.5(10)	23.0(9)	-0.6(7)	-1.1(7)	-0.6(7)
C27	12.1(7)	23.9(9)	17.4(8)	-2.7(6)	-0.4(6)	0.4(6)
C3	10.9(7)	19.1(8)	21.3(8)	-3.4(6)	3.0(6)	-1.6(6)
C29	15.0(8)	26.9(9)	16.5(8)	2.4(6)	-1.0(6)	0.1(6)
C22	23.1(9)	29.3(10)	30.1(10)	3.4(8)	-4.6(8)	1.8(7)
C12	24.0(9)	18.1(8)	26.7(9)	0.6(7)	-2.0(7)	-3.0(7)
C17	21.5(9)	24.1(9)	21.1(9)	-2.9(7)	3.4(7)	-6.4(7)
C31	23.2(9)	23.6(9)	22.2(9)	-4.7(7)	-1.4(7)	4.2(7)
C20	14.0(8)	23.0(8)	16.0(8)	-3.5(6)	-0.4(6)	0.2(6)
C35	22.3(9)	26.4(9)	25.4(9)	-4.6(7)	-0.6(7)	-6.5(7)
C21	19.7(8)	21.2(8)	23.1(9)	1.9(7)	2.2(7)	0.7(7)
C2	14.0(8)	16.4(7)	18.7(8)	-0.2(6)	-1.5(6)	-0.6(6)
C1	12.9(7)	17.3(8)	22.7(8)	0.2(6)	2.8(6)	0.6(6)
C9	15.1(8)	28.5(9)	25.9(9)	6.5(7)	0.9(7)	0.7(7)
C8	13.0(8)	23.6(8)	21.6(8)	-0.7(7)	1.8(6)	0.5(6)
C23	30.7(10)	21.6(9)	31.9(10)	1.7(7)	2.0(8)	0.8(7)
C15	11.5(7)	19.8(8)	15.8(7)	-3.7(6)	-0.4(6)	-2.3(6)
C34	12.5(7)	26.0(9)	24.0(9)	1.8(7)	-1.9(6)	-4.4(6)
C32	20.1(8)	22.2(9)	23.9(9)	-1.7(7)	0.3(7)	-0.4(7)
C19	13.2(8)	30.3(9)	23.3(9)	-4.2(7)	0.0(6)	1.4(7)
C16	16.7(8)	19.9(8)	18.4(8)	-2.9(6)	0.2(6)	-1.8(6)

C4	17.1(8)	18.0(8)	20.7(8)	-3.3(6)	2.1(6)	-0.5(6)
C33	22.6(9)	35.9(10)	24.3(9)	-1.2(8)	2.0(7)	9.4(8)
C26	25.0(9)	25.8(9)	27.1(9)	1.3(7)	4.1(7)	6.7(7)
C6	13.5(8)	31.1(10)	29.4(9)	-5.3(8)	2.8(7)	-6.6(7)
C30	18.1(8)	30.4(9)	16.9(8)	-1.9(7)	-2.4(6)	6.0(7)
C28	16.7(8)	21.2(8)	17.2(8)	-1.1(6)	-1.9(6)	1.6(6)
C24	17.5(8)	22.5(9)	24.8(9)	2.1(7)	2.4(7)	3.9(7)
C14	22.7(9)	25.3(9)	42.6(12)	7.7(8)	3.2(8)	3.1(7)
C5	19.6(8)	22.6(8)	25.6(9)	-2.1(7)	5.4(7)	-6.3(7)
C18	13.7(8)	32.9(10)	27.3(9)	-5.3(8)	4.2(7)	-6.4(7)
C11	35.4(11)	25.4(10)	37.6(11)	6.0(8)	1.4(9)	-0.6(8)
C13	38.2(11)	21.8(9)	27.3(10)	2.2(7)	2.3(8)	-2.0(8)
C10	24.5(9)	40.7(11)	27.9(10)	10.0(8)	1.3(8)	1.7(8)
C25	48.8(13)	33.6(11)	25(1)	4.3(8)	11.2(9)	10.2(10)
C38	21.3(10)	47.7(13)	53.9(14)	-15.9(11)	-2.8(9)	-8.7(9)
C37	56.0(15)	26.7(11)	42.8(13)	-2.5(9)	-2.9(11)	-17.2(10)
C36	40.3(12)	44.7(13)	38.0(12)	-14.8(10)	9.7(10)	-10.5(10)

Table S4. Bond Lengths for complex 6.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
Pd1	O1	2.0121(12)	C17	C18	1.390(3)
Pd1	N1	2.0540(14)	C31	C32	1.395(3)
Pd1	N2	2.1285(14)	C31	C30	1.391(3)
Pd1	C27	1.9975(17)	C20	C15	1.402(2)
O1	C34	1.279(2)	C20	C19	1.393(2)
N1	C2	1.287(2)	C20	C24	1.520(2)
N1	C15	1.439(2)	C35	C34	1.554(2)

O2	C34	1.226(2)	C35	C38	1.529(3)
N2	C3	1.435(2)	C35	C37	1.528(3)
N2	C1	1.282(2)	C35	C36	1.527(3)
C7	C8	1.397(2)	C21	C23	1.526(2)
C7	C6	1.379(3)	C21	C16	1.528(2)
C27	C32	1.404(2)	C2	C1	1.471(2)
C27	C28	1.389(2)	C9	C8	1.521(2)
C3	C8	1.401(2)	C9	C11	1.535(3)
C3	C4	1.402(2)	C9	C10	1.528(3)
C29	C30	1.391(3)	C15	C16	1.403(2)
C29	C28	1.399(2)	C19	C18	1.382(3)
C22	C21	1.539(3)	C4	C5	1.398(2)
C12	C4	1.522(2)	C33	C30	1.512(2)
C12	C14	1.534(3)	C26	C24	1.531(2)
C12	C13	1.527(3)	C6	C5	1.382(3)
C17	C16	1.398(2)	C24	C25	1.526(3)

Table S5. Bond Angles for complex 6.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	Pd1	N1	170.41(5)	C23	C21	C22	110.20(15)
O1	Pd1	N2	94.36(5)	C23	C21	C16	113.26(15)
N1	Pd1	N2	77.81(5)	C16	C21	C22	112.05(15)
C27	Pd1	O1	87.85(6)	N1	C2	C1	117.42(15)
C27	Pd1	N1	99.58(6)	N2	C1	C2	116.04(15)
C27	Pd1	N2	175.40(6)	C8	C9	C11	109.88(15)
C34	O1	Pd1	121.00(11)	C8	C9	C10	113.54(16)
C2	N1	Pd1	115.05(11)	C10	C9	C11	110.31(16)

C2	N1	C15	119.38(14)	C7	C8	C3	117.38(16)
C15	N1	Pd1	125.42(11)	C7	C8	C9	122.06(16)
C3	N2	Pd1	125.27(11)	C3	C8	C9	120.49(15)
C1	N2	Pd1	113.42(11)	C20	C15	N1	118.12(15)
C1	N2	C3	121.04(14)	C20	C15	C16	123.48(15)
C6	C7	C8	120.78(17)	C16	C15	N1	118.22(14)
C32	C27	Pd1	118.45(13)	O1	C34	C35	113.94(15)
C28	C27	Pd1	124.20(13)	O2	C34	O1	126.27(17)
C28	C27	C32	117.35(16)	O2	C34	C35	119.79(16)
C8	C3	N2	117.55(15)	C31	C32	C27	121.00(17)
C8	C3	C4	123.06(15)	C18	C19	C20	120.69(17)
C4	C3	N2	119.23(15)	C17	C16	C21	121.66(16)
C30	C29	C28	120.95(17)	C17	C16	C15	116.45(16)
C4	C12	C14	110.43(15)	C15	C16	C21	121.89(15)
C4	C12	C13	113.21(15)	C3	C4	C12	121.89(15)
C13	C12	C14	110.72(16)	C5	C4	C3	116.97(16)
C18	C17	C16	121.29(17)	C5	C4	C12	121.12(16)
C30	C31	C32	121.32(17)	C7	C6	C5	120.73(16)
C15	C20	C24	121.34(15)	C29	C30	C33	121.25(17)
C19	C20	C15	117.45(16)	C31	C30	C29	117.85(16)
C19	C20	C24	121.12(15)	C31	C30	C33	120.90(17)
C38	C35	C34	106.96(16)	C27	C28	C29	121.51(16)
C37	C35	C34	112.02(16)	C20	C24	C26	113.67(15)
C37	C35	C38	109.72(19)	C20	C24	C25	109.47(16)
C36	C35	C34	108.36(16)	C25	C24	C26	109.99(15)
C36	C35	C38	110.14(18)	C6	C5	C4	121.08(17)
C36	C35	C37	109.60(19)	C19	C18	C17	120.59(16)

Table S6. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for complex 6.

Atom	*x*	*y*	*z*	U(eq)
H7	-1243	1855	3028	28
H29	6648	1910	2187	24
H22A	3049	3605	3276	43
H22B	3525	2917	3370	43
H22C	4131	3443	2823	43
H12	1969	1252	6469	28
H17	6551	3672	4373	27
H31	5652	148	2423	28
H21	3932	3463	4966	26
H2	3920	2705	6264	20
H1	2016	2354	6087	21
H9	1436	2436	3153	28
H23A	5180	4279	3917	43
H23B	5138	4305	5130	43
H23C	4072	4458	4311	43
H32	4233	488	3233	27
H19	7774	2025	5453	27
H33A	7558	1115	1400	42
H33B	6966	460	1183	42
H33C	7792	572	2238	42
H26A	6499	928	4645	39
H26B	6426	529	5659	39
H26C	7408	1004	5651	39
H6	-1742	1027	3971	30
H28	5244	2252	3022	23
H24	5176	1331	5601	26
H14A	1962	139	5288	46
H14B	2887	324	6235	46
H14C	2728	722	5192	46

H5	-536	615	5337	27
H18	8018	3005	4802	29
H11A	-199	3160	3894	50
H11B	845	3435	3488	50
H11C	990	3039	4533	50
H13A	414	814	7080	44
H13B	1532	465	7498	44
H13C	685	170	6577	44
H10A	69	2176	1735	47
H10B	310	2903	1770	47
H10C	-753	2642	2160	47
H25A	6989	1573	7191	53
H25B	6055	1077	7271	53
H25C	5774	1799	7224	53
H38A	46	836	1821	63
H38B	-44	403	820	63
H38C	290	1115	752	63
H37A	2422	-117	2364	65
H37B	1272	-353	1767	65
H37C	1328	63	2784	65
H36A	1991	833	102	61
H36B	1673	117	129	61
H36C	2824	350	728	61

국문초록

고리형 이미드와 바이아릴의 효율적인 합성을 위한 새로운 촉매 반응의 개발

복잡한 분자를 생산하기 위한 화학 공정은 일반적으로 다단계 반응을 필요로 하고, 유독한 폐기물의 발생을 수반한다. 기존 화학반응을 대체할 수 있는 효율적인 합성법의 개발은 유기화학 분야에서 더욱 중요해졌다. 유기금속촉매를 이용하여 개발된 촉매 반응은 원자경제적이고 간소화된 공정을 제공할 수 있다. 본 학위 논문은 단순한 원료 분자에서 고부가가치 화합물로의 전환을 가능하게 하는 새로운 촉매 반응의 개발에 관한 연구를 다룬다.

제 1 장에서는 알코올 활성화를 통한 아미드 합성을 소개하였다. 알코올과 아민을 반응물로 사용한 탈수소적 아미드 합성은 기존의 아미드 합성법에 대한 대안으로 환경 친화적이고 효율적인 방안을 제공한다. 알코올 탈수소화의 원리는 N-헤테로고리의 제조에도 적용될 수 있다. 제 2 장은 알코올과 나이트릴을 출발물질로 사용한 고리형 이미드의 합성법의 개발을 다룬다. 개발된 반응을 이용하여 간단하고 다양한 출발물질로부터 고리형 이미드를 형성하는 원자경제적이고 손쉬운 합성법을 확보할 수 있다. 추가적인 메커니즘 연구를 통해 본

반응이 수소전달을 기질 활성화 전략으로 사용하여 활성이 높은 친핵체와 친전자체를 생성한다는 것을 증명하였다.

제 3 장에서는 C–H 활성화 분야의 기초와 배경에 대한 소개와 함께 아렌의 C–H 아릴화 반응의 최신 연구 결과를 정리하였다. 아렌에 대한 직접적인 아릴화 반응은 일반적으로 전통적인 교차 짝지음 반응을 통해 생성되는 바이아릴의 합성에 대한 대안적인 접근법을 제공 할 수 있다. 제 4 장에서는 지향기나 활성화 작용기가 없는 단순한 아렌의 C–H 아릴화 반응을 수행하는 Pd–다이이민 촉매의 개발에 대해 설명한다. 개발된 Pd–다이이민 촉매는 현재까지 보고된 가장 높은 TON을 나타내었다. 또한 기존에 보고된 촉매 시스템들은 과량의 아렌을 필요로 하는 반면, 본 촉매는 수 당량의 아렌으로도 우수한 효율을 보였다. 반응 메커니즘을 탐구하기 위한 화학 반응 속도론 실험 및 반응 중간체 확인, 당량 반응 실험 등을 통하여 협동적 이금속 메커니즘에 대한 유력한 증거를 제시하였다.

주요어: 아미드, 알코올 활성화, 고리형 이미드, C–H 활성화, 바이아릴, 교차 짝지음 반응, 유기금속촉매

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