# DEVELOPMENT OF A NEW TRIDENTATE PINCER PHOSPHINE *N*-HETEROCYCLIC CARBENE LIGAND

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# DEVELOPMENT OF COPPER II CATALYZED THREE COMPONENT TANDEM SYNTHESIS OF ISOINDOLINONE DERIVATIVES

*by*

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# Abstract

Two types of research were carried out in this thesis; the first section is about the development of a new phosphine-based tridentate pincer *N*-heterocyclic carbene ligand and examination of the catalytic activities of its transition metal compexes including conjugate addition, alkyne-aldehyde addition and Alkyne-Aldehyde-Amine (A-3) coupling reaction. The second section of the thesis is about the methodology development of an A-3 based tandem synthesis of isoindoline derivatives and gold (I) catalyzed cyclization for the synthesis of isoindolo[2,1-a]quinolines derivatives. The aim of these studies is to develop novel catalysts and synthetic methodologies that can approach conventional chemical syntheses in a “greener” manner, therefore substantially gain atom-economy, step-economy and leads to a more sustainable life.

# Résumé

Deux types de recherches ont été accompli dans cette thèse. La première section comporte sur le développement d'un nouveau ligand carbène hétérocyclique et l'analyse de ses complexes formés avec des métaux de transitions et leur efficacité lors des additions conjuguées, d'addition alcyne-alcène et des réactions de couplage entre un alcyne, une aldéhyde et une amine (A-3). La deuxième partie de cette thèse porte sur le développement d'une méthodologie de synthèse de dérivés d'isoindoline utilisant une réaction en tandem dérivés du couplage A-3 et la synthèse de dérivés d' isoindolo[2,1-1]quinolines par cyclisation catalysée par des sels d'or(I). Le but de ces études étant de développer des méthodologies de synthèse et des catalyseurs novateurs pouvant s'appliquer à des synthèses conventionnelles et de ce fait les rendre plus “vertes”, en augmentant leur économie d'atomes, économie d'étapes dans une perspective de développement durable.

## Acknowledgments

The successful completion of this thesis would not be made possible without the full support and assistance of a number of individuals whom I had the privilege of knowing.

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# LIST Of ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| ACN | acetonitrile |
| A-3 | Aldehyde-amine-alkyne |
| acac | acetylacetone |
| Ar | aryl |
| atm | atmosphere |
| $^{n}$Bu | *n*-butyl |
| $^{t}$Bu | *tert*-butyl |
| Bn | benzyl |
| BuLi | butyl lithium |
| Boc | *tert*-butoxy carbonyl |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| br | broad ($^{1}$H NMR) |
| $^{o}$C | degrees Celsius |
| cat | catalytic or catalyst |
| cm | centimeters |
| C-C | carbon-carbon |
| C-H | carbon-hydrogen |
| cod | 1,5-cyclooctadiene |
| coe | cyclooctene |
| Cy | cyclohexyl |
| Cp | cyclopentadienyl |
| Cp* | pentamethylcyclopentadienyl |
| δ | chemical shift |
| d | doublet ($^{1}$H NMR) |

| | |
|---|---|
| dm | doublet of multiplets |
| dt | doublet of triplets |
| ddt | doublet of doublet of triplets |
| DBU | 1, 8-diazabicyclo[5.4.0]undec-7-ene |
| DMF | *N*,*N*-dimethyl formamide |
| DMSO | dimethyl sulfoxide |
| DME | 1,2-dimethoxylethane |
| DCM | dichloromethane |
| DCE | 1, 2-dichloroethane |
| DDQ | 2, 3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DIAD | di-isobutyl-azodicarboxylate |
| DIPEA | *N*, *N*-diisopropylethylamine |
| DIBAL-H | di-isobutyl aluminum hydride |
| dppb | 1, 1'-Bis(diphenylphosphino)butane |
| dppp | 1, 1'-Bis(diphenylphosphino)pentane |
| dppf | 1, 1'-Bis(diphenylphosphino)ferrocene |
| *ee* | enantiomeric excess |
| EI | electron impact |
| Et | ethyl |
| Equiv. | equivalent(s) |
| FCC | flash column chromatography |
| HRMS | high resolution mass spectrometry |
| Hz | Hertz |
| h | hour(s) |
| IR | infra-red spectroscopy |
| *J* | coupling constant |
| LDA | lithium di-isopropyl amide |

| | |
|---|---|
| L | .liter or ligand |
| m | multiplet ($^1$H NMR) or medium (IR) |
| m.p. | melting point |
| M | unspecified metal, molecular ion or molarity |
| Me | methyl |
| MHz | mega hertz |
| min | minutes |
| MOM | methoxy methyl |
| μL | micro litres |
| mL | millilitre(s) |
| mmol | milli moles |
| mp | melting point |
| *m*-CPBA | meta-chloroperbenzoic acid |
| m/z | mass/charge ratio |
| MS | mass spectrometry |
| HR-MS | high-resolution mass spectrometry |
| NMR | nuclear magnetic resonance |
| Nu | nucleophile |
| NMP | *N*-methyl-2-pyrrolidinone |
| OTf | trifluoromethanesulfonate |
| Ph | phenyl |
| PMP | *para*-methoxyphenyl |
| ppm | parts per million |
| pyr | pyridine |
| $^i$Pr | isopropyl |
| q | quartet ($^1$H NMR) |
| R | unspecified carbon substituent |

| | |
|---|---|
| r.t | room temperature |
| rac | racemic |
| $R_f$ | retention factor |
| s | singlet |
| sat | saturated |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TBS | *tert*-butyldimethylsilyl |
| TMS | trimethyl silyl |
| TBAB | tetrabutyl ammonium bromide |
| TBAT | tetrabutyl ammonium triphenyldifluorosilicate |
| TBAF | tetrabutyl ammonium fluoride |
| t | triplet |
| tt | triplet of triplets |
| temp | temperature |
| TES | triethylsilyl |
| TFA | trifluoroacetic acid |
| T-HYDRO® | *tert*-butyl hydroperoxide, 70 wt% in water |
| TBHP | tert-butyl hydrogen peroxide |
| TIPS | tri-*iso*-propylsilyl |
| TLC | thin-layer chromatography |
| Ts | *para*-toluene sulfonyl |
| Tf | trifluoromethanesulfonyl |
| w | weak (IR) |
| W | Watt |

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# Chapter 1

# Introduction to Green Chemistry

## 1.1 Green Chemistry: Perspectives, Sustainability and Principles

The term “green chemistry”, also called “sustainable chemistry” as synonym, is a relatively new philosophy in chemical research and engineering that encourages environmentally friendly design of chemical products and processes. Up until later 20$^{th}$ century, people have been more focused on the fast growing economy and high life quality that’s been brought to us by modern industrial chemistry, and are less aware of the harsh damage we have done to our environment. The chemical industry is the major contributor to environmental pollution.

The concept of green chemistry was introduced in early 1990’s, it was meant to reverse the environmental crisis already done as much as possible, and the main component of it is that modern chemical process should minimize the use and generation of hazardous substances, and therefore to significantly reduce or even eliminate environmental pollution at its source.[1] Such goal can be accomplished by developing novel synthetic methodologies and following the 12 Principles of Green Chemistry[1]:

1. Prevention rather than remediation
2. Atom Economy
3. Less Hazardous Chemical Syntheses
4. Designing Safer Chemicals

5. Safer Solvents and Auxiliaries
6. Design for Energy Efficiency
7. Use of Renewable Feedstocks
8. Reduce Derivatives
9. Catalysis
10. Design for Degradation
11. Real-time analysis for Pollution Prevention
12. Inherently Safer Chemistry for Accident Prevention

The research conducted in this thesis mainly focused on a NHC-based catalyst development and exploration of a tandem/cascade transformation that builds fused heterocyclic architectures that can be applied in medicinal chemistry. Therefore, in the next two sections of this chapter, this thesis will provide a brief overview of water-tolerating catalysts and pollution prevention by shortening reaction steps.

## 1.2 Organic Reactions and Catalysis in Aqueous Media

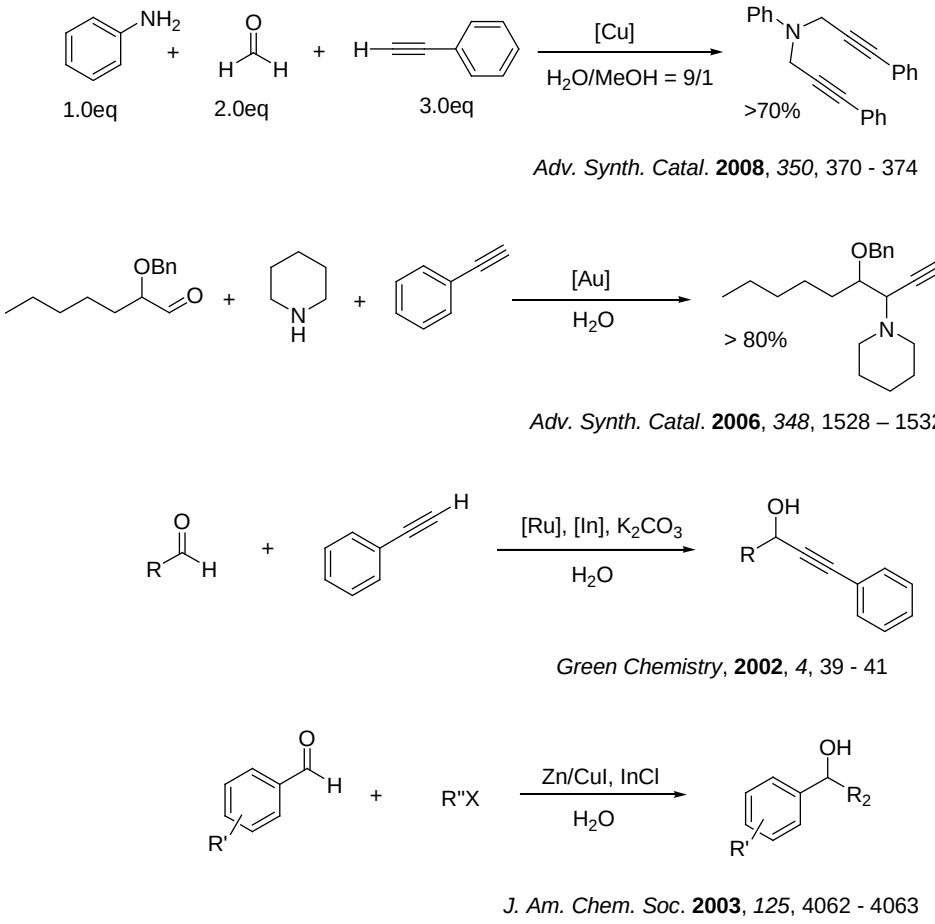
Water plays a very important role in life processes and evolution, from a biological standpoint, it has many distinct properties that set it apart from other solvents. During evolution, water acts as the solvent that allows small organic molecules to react with each other, and ultimately lead to replication. The unique physical property of water also allows living organisms to survive severe cold conditions.

However, despite being the cheapest, safest and environmentally benign solvent, water as a solvent for chemical transformations has been very limited in organic reactions, in most conventional organic methodologies water acts as a contaminant; this

is due to the fact that most reagents and catalysts are specifically designed to be operated in anhydrous media. Thus the application of water as a reaction medium for organic synthesis is one of the latest challenges in green chemistry.[2]

Over the past few years, the research of using water as reaction medium has made great progress[3]. Unfortunately, the simple switch from conventional organic solvents to water will not gain any benefits at the expense of synthetic efficiency. In addition, most organic reagents/ligands have very low or even zero solubility in water, and heterogeneous catalysis is less preferred in most cases. In order to solve this problem, chemists need to re-write the book of chemical science by developing new fundamental tools including methodologies and catalysts.[2]

There has been tremendous amount of experimental proof shown that certain reactions carried out in water can gain unusual enhancement in reaction rate and simplified purification procedures. For example, as shown in Scheme 1,[4] under transition metal catalysis, nucleophilic additions of terminal alkynes to carbonyl compounds, imines and enamines etc are well-known reactions that can perform well in water; they are crucial reactions in the sense that they produce propargyl alcohols and propargyl amines which are important chemical building blocks and precursors of biologically active molecules.




Scheme 1 Examples of organic reactions performed in water [4]

NHC-transition metal complexes possess high value in homogeneous catalysis in water. Their robustness in air due to strong metal-carbene bonding has provided them wide range of applications in synthesis. Looking through literature, numerous catalytic studies of NHC-Pd, NHC-Ag, NHC-Au etc have been reported.[5] This thesis will focus more on the development of water-tolerating NHC-metal complexes.[6]

## 1.3 Tandem Reactions

Tandem reaction, also called cascade or domino reaction, is defined as a consecutive series of intramolecular reactions that usually proceed via highly reactive intermediates; the product of each reaction acts as the substrate of subsequent reaction.[7] These reactions possess high synthetic value in the sense that they not only allow efficient construction of complex structures from simple acyclic precursor, but also display clean conversion and step-economy, which translates to reduced labor time, energy input and waste; therefore they have been the subjects of extensive investigations in recent years.[8] As such, cascade reactions can be considered to fall under the banner of green chemistry, as the savings involved when one carries out several transformations in one synthetic operation can be considerable.[9]

One important factor that worth to be mentioned is that one-pot sequential syntheses are not considered true tandem reactions. A one-pot sequential reaction is merely an alternative strategy to improve the efficiency of a reaction whereby a reactant is subjected to successive chemical transformations in the same reactor; this approach avoids unnecessary isolation of certain intermediates during a synthesis and thus would save time and resources used in purification procedures. However, in these processes the subsequent reactions must be able to tolerate the byproduct and side product generated in the previous reaction, and as a drawback, the reactions involved in the sequential steps usually cannot occur simultaneously due to the interference of conditions (i.e. temperature, solvent etc.) used in other steps.

This thesis will be focused on the development of a series of water-compatible transition metal catalysts and their applications toward the development of certain tandem reactions. The types of catalysts being studied are pincer transition metal-*N*-Heterocyclic carbene complexes and the tandem reaction being studied is aldehyde-alkyne-amine based one-pot synthesis of isoindolinone derivatives.

# Chapter 2

# Development of A New NHC Pincer [PCP] Ligands and Examination of Their Transition Metal Complexes in Catalysis

## 2.1 General Background of NHC Carbene Ligand

*N*-Heterocyclic carbenes (NHCs) are cyclic carbenes bearing at least one α-amino substituent.[10] In the early 20$^{th}$ century, scientists believed that all carbenes are too reactive to be isolated; this statement was soon proved to be an inaccurate assessment for NHCs. In 1957 Ronald Breslow proposed that stable carbenes can exist.[11]

In the 1970's Wanzlick, Ofele and co-workers first investigated the reactivity and stability of various NHCs,[12] Ever since then *N*-heterocyclic carbenes have remained an extensively researched area for the past few decades, Lappert *et al* conducted a series of primitive studies of NHC-organometallic complexes.[13] In the early stage of the research, carbenes were best known for their high reactivity and short life, despite this, they were still successfully applied as transition metal ligands. The milestone discovery would point to the successful synthesis and isolation of the stable *N*, *N*-diadamantyl NHC in 1991 by Arduengo *et al*,[14] ever since then there has been an increase interest in NHC as ligands in homogeneous catalysis, particularly in the field of coupling reactions between less reactive substrates.

There are many advantages of *N*-heterocyclic carbene's as ancillary ligands, to date they have been well established as efficient alternatives to phosphine ligands.[15] A

couple of key features can be summarized as follow: they are stronger *s*-donors than phosphine ligands, thus enabling enhanced rates of palladium catalyzed oxidative addition of aryl halides, the strong metal-carbenic bond of the NHC complex also facilitates ligand dissociation, and the presence of sterically hindered functional groups bound to the nitrogen atoms facilitate reductive elimination of the product from transition metal; last but not least, the carbon with unfilled orbitals is usually part of an heterocycle, such as an imidazole, triazole or thiazole ring system, thus the reactivity of NHC ligands can be fine tuned by the introduction of electronic directing substituents on the heterocyclic ring or the nitrogen atoms, which will provide them wide range of catalytic power.[16] Their high thermal stability and intense coordinative power also make them excellent multidentate ligands. The structures of some of the most commonly used classes of NHCs are shown in Figure 1.

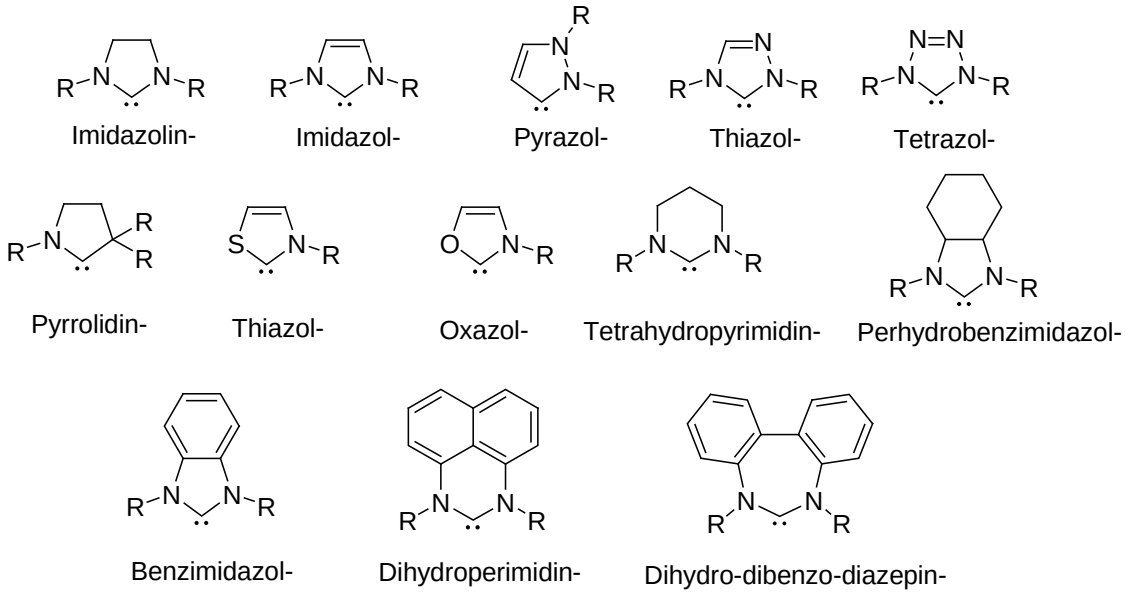



Figure 1 Common NHC sub-classes [10]

When properly combined with metal pre-catalyst, NHC imizazoline ligands with sterically bulky groups have been well applied in the palladium catalyzed cyclization of anilides,[17] arylation with ester enolates to form α-aryl esters,[18] amination of aryl halides,[19] Sonogashira coupling of alkyl bromides,[20] Ru-catalyzed Ring Closing Metathesis reactions etc.[21] Depending on the type of transition metal they are binding to, distinct chemistry can be granted, i.e. iridium and rhodium-NHC complexes are known for their successful catalytic power in transfer hydrogenation and hydroformylation,[22,23] palladium-NHC complexes have been discovered as good cross coupling catalysts (Suzuki & Heck-type reactions etc.).[24]

### 2.1.1 NHC-Metal Complexes

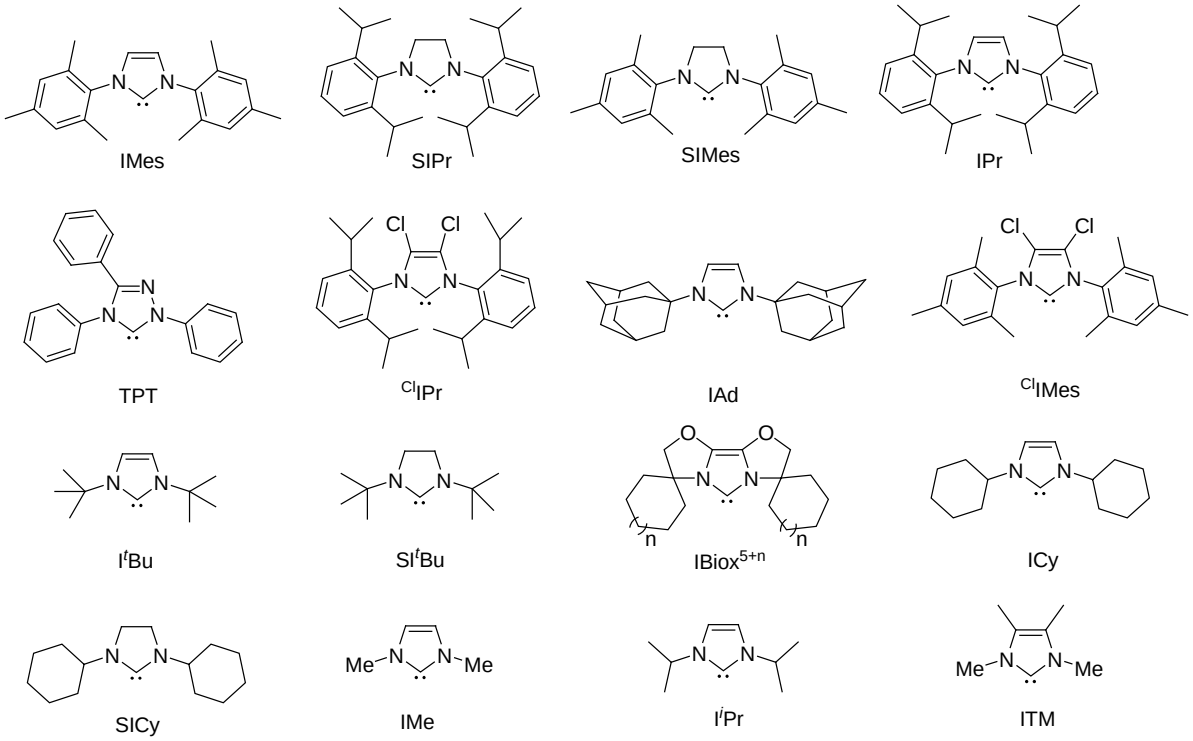



Figure 2 Acronyms of common NHCs [10]

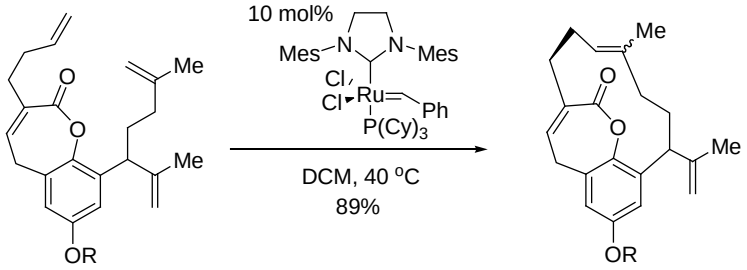
Because of the aforementioned advantages of *N*-heterocyclic carbenes, their applications as ligands are of much research interest and their transition metal complexes well known. The good catalytic power of these complexes is provided by the high electron-donating capabilities of NHC ligands. To date, countless publications on complexes of many transition metal (*d*-block from group 7 to group 11) derived from NHCs have been reported, alongside reports of their catalytic activities, mostly in coupling reactions which have already been mentioned in section **2.1**.

Due to time and content limitations in this section, it is beyond the scope of this thesis to fully review all aspects in catalysis that involve NHC-transition metals, therefore we will briefly discuss a limited number of representative examples in this section, including complexes with iron, ruthenium, cobalt, rhodium, palladium and silver, just for the purpose of demonstrating the significant power of NHC-transition metal complexes as catalysts in a wide range of organic transformations. Also, in the research conducted in this thesis on phosphine-based pincer NHC ligands, only palladium, silver and rhodium are selected as representatives for the synthesis and examination of NHC-metal complexes; research involving other transition metals will be conducted in the future work.

In 2000 Grubbs *et al* had reported the first application of NHC-Fe complex $[(I^{i}PrMe)_2FeX_2]$ in homogeneous catalysis.[25] The catalyst showed good performance in catalyzing atom transfer radical polymerization of styrene and methyl methylacrylate. This work in NHC-iron catalysts was expanded by Gibson *et al*, who synthesized a series

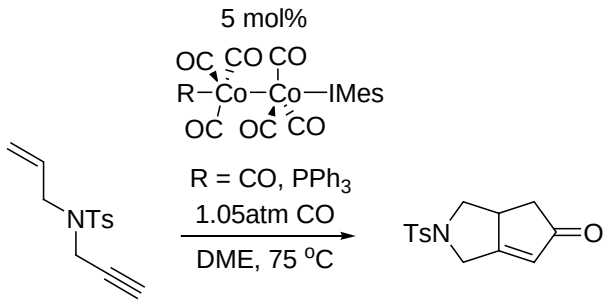
of iron (II) and (III) complexes bearing bis(NHC)-pyridine tridentate ligands, unfortunately their catalysts were found inactive in ethylene polymerization reactions. Later in 2006, Shen *et al* developed an NHC-phenoxide chelate compound and discovered that it is an active initiator for ring-opening polymerizations.[26]

Catalytic applications of NHC-ruthenium complexes have long been known in the field of hydrogenation process, such as transfer hydrogenation of ketones etc. They are also good catalysts for olefin isomerization and olefin metathesis, i.e. the application of famous Grubbs II catalyst in ring-closing metathesis.

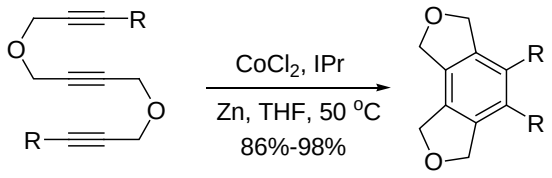



Scheme 2 Application of NHC-Ru catalyzed ring closing metathesis in the total synthesis of cyclophane floresolide

The NHC chemistry of cobalt is very similar to that of iron, major establishment have been achieved in organometallic synthesis rather than reaction catalysis. Many unusual NHC-cobalt species has been synthesized by Lappert *et al* since the 1970's,[27] their work has confirmed that NHCs are indeed effective and synthetically useful ligands for cobalt.[28]

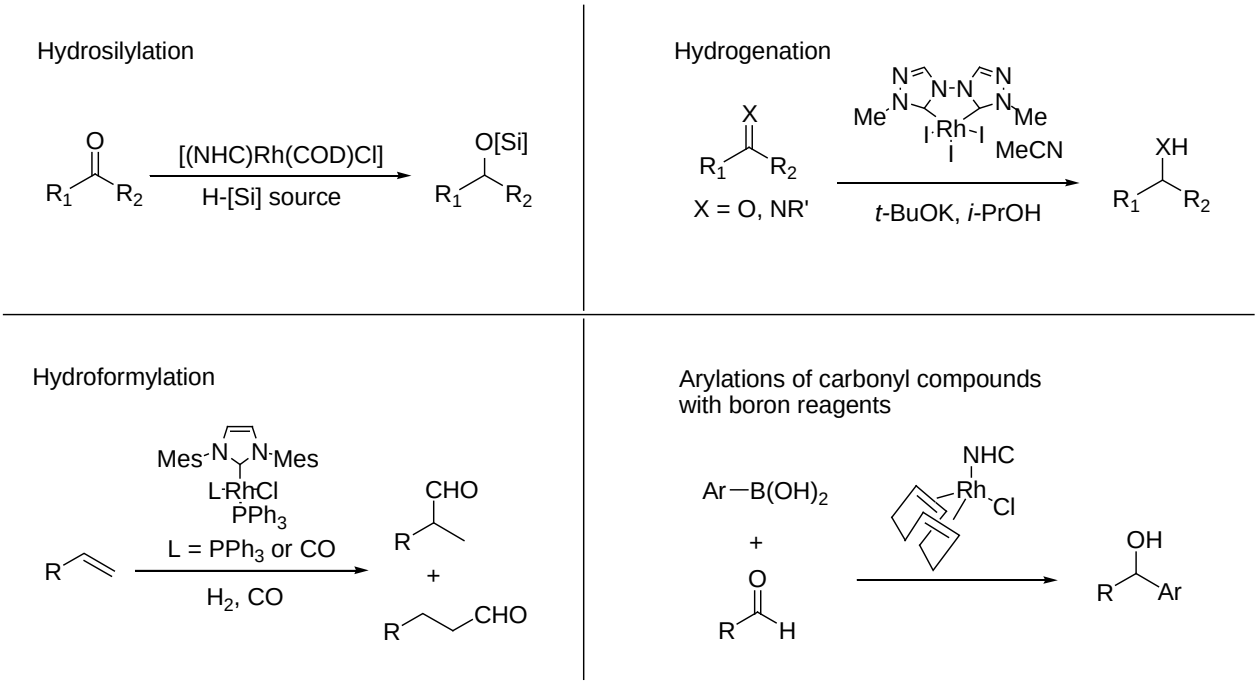



Scheme 3 NHC-Co catalyzed Pauson-Khand reaction




Scheme 4 NHC-Co catalyzed cyclotrimerization

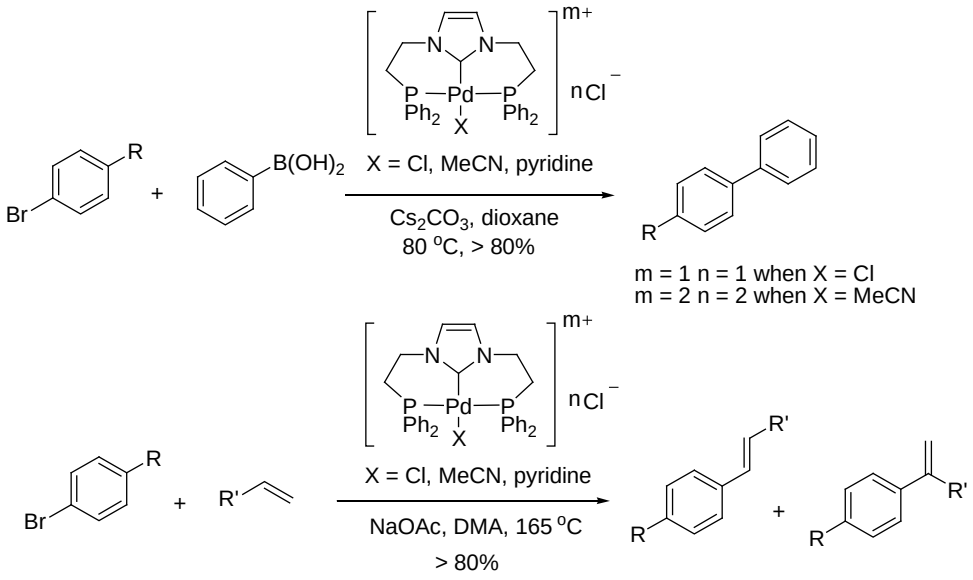
In 2003, Gibson and Loch reported the first NHC-cobalt catalyzed Pauson-Khand reaction as a proof of concept,[29] later Okamoto *et al* disclosed an efficient intramolecular cyctrimerization of triynes under the catalysis of IPr-$CoCl_2$-Zn power conjunction system.[30]




Scheme 5 Typical reactions catalyzed by NHC-Rh complexes [32,33,34,35,36]

Rhodium holds a very unique and important position in the late transition metals. Together with palladium and nickel, rhodium has very promising chemistry with NHC ligands, especially the polydentate ones. Other than applications in catalysis of organic reactions, NHC-Rh complexes also exhibit useful functions in biochemical applications.[31] The chemistry of most NHC-Rh catalysts synthesized has been well-explored so far, some of the typical catalytic applications of them can be summarized as follows (Scheme 5) 1) hydrosilylations of carbonyl compounds,[32] alkynes and alkenes;[33] 2) $H_2$-mediated hydrogenations and transfer hydrogenations;[34] 3) hydroformylations;[35] 4) arylations of carbonyl compounds with boron reagents.[36] Despite these successful establishments, nevertheless, we cannot claim that there is

nothing more to be investigated in this field, and we believed that modifications and improvements of existing NHC-Rh catalyzed reactions is still a rewarding and beneficial task.



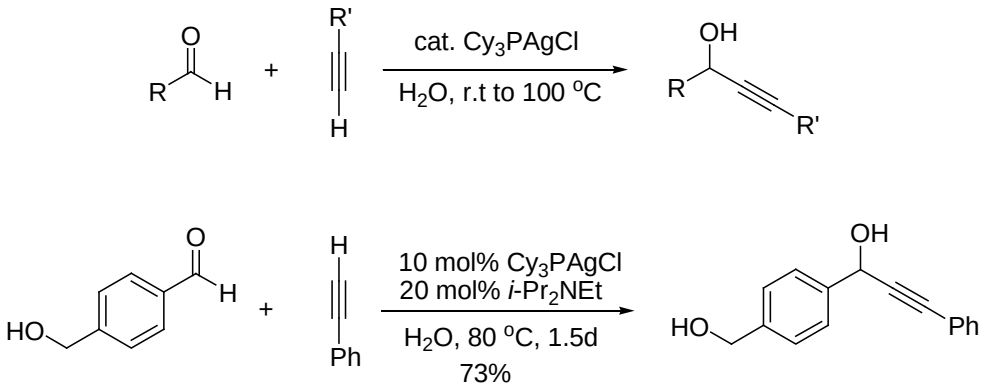

Scheme 6 NHC-Pd catalyzed Suzuki and Heck coupling reactions

Palladium is one of the most commonly applied transition metals in catalysis, and also undoubtedly the most studied transition metal with not only NHC ligands, but also other regular ligands (i.e. phosphines) as well. The success of NHC-Pd systems in C-C and C-N bond formations has certainly overshadowed all other systems to date.

As shown in Scheme 6, the catalytic capability of $[Pd(PC^{NHC}P)Cl]^{+}Cl^{-}$ was investigated by H. M. Lee *et al* in 2004, and they found it very effective in Suzuki coupling of phenylboronic acid with activated aryl bromides; but for unactivated substrates such as 4-bromoanisole the reaction required prolonged time. The complexes are very effective in Heck-couplings, an 1.25 X $10^{-6}$ mol% catalyst loading exhibits a

TON of 56,000,000 in the Heck-coupling reaction between the phenyl iodide and styrene. Such level of activity is significantly higher than those obtained by palladium complexes of phosphine-based pincer and bis-carbene CNC pincer ligands.[24]

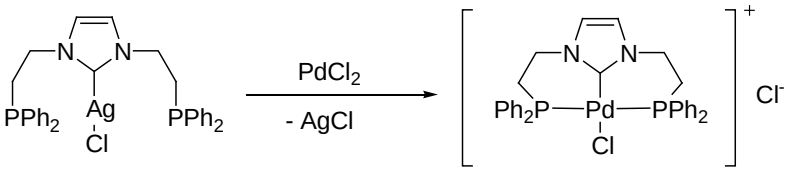
Apart from coupling reactions, NHC-Pd complexes are also known for their adequate catalytic power in a number of transformations such as polymerizations, C-H activations including direct arylations, hydroarylations of unsaturated compounds, cycloisomerizations, 1, 4-additions of alkyne to Michael systems, and oxidation of secondary alcohol to ketones etc.



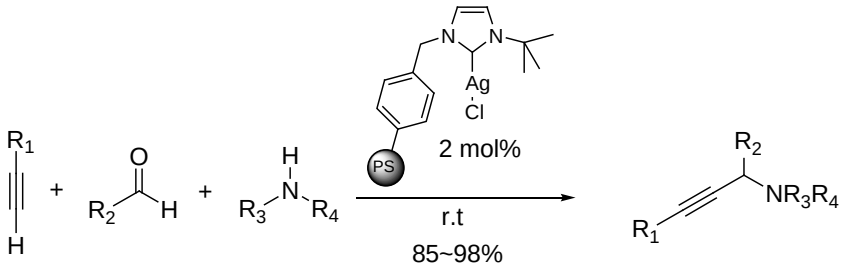

Scheme 7 Silver catalyzed alkyne addition to aldehyde without NHC as ligand

Last but not least, NHC-Ag complexes are equally important in the sense that they are often used as NHC transfer agents in the preparation of NHC systems involving different metals. Traditionally phosphines are applied more frequently as ligands for a number silver-catalyzed reactions (Scheme 7), it has been proven that switching from regular phosphines to NHCs can exhibit better catalytic process. NHC-Ag complexes are also known for being good catalysts for carbonyl-alkylation reactions [37] and

alkyne-amine-aldehyde (A-3) couplings (Scheme 8).[38] Compare to other transition metals, the application of silver in NHC-related catalysis is much less explored and underdeveloped. But due to their simple method of synthesis, we anticipate a bright future in their development.




Lee, H. M.; Zeng, J. Y.; Hu, C. H.; Lee, M .T.; *Inorg. Chem*. **2004**, *43*, 6822-6829.




Li, P.; Wang, L.; Zhang, Y.; Wang, M.; *Tetrahedron Lett*. **2008**, *49*, 6650-6654.

Scheme 8 Selected applications of NHC-Ag complexes

### 2.1.2 Pincer Carbene Ligands and Complexes

In 1976 Shaw *et al*. synthesized the first pincer-type complex. Since then, a large collection of this interesting family of compounds has been prepared, with a variety of transition metals and different donor atoms coordinated to the metallic center. The geometry of these pincer ligands can vary depending on the type of metal involved.

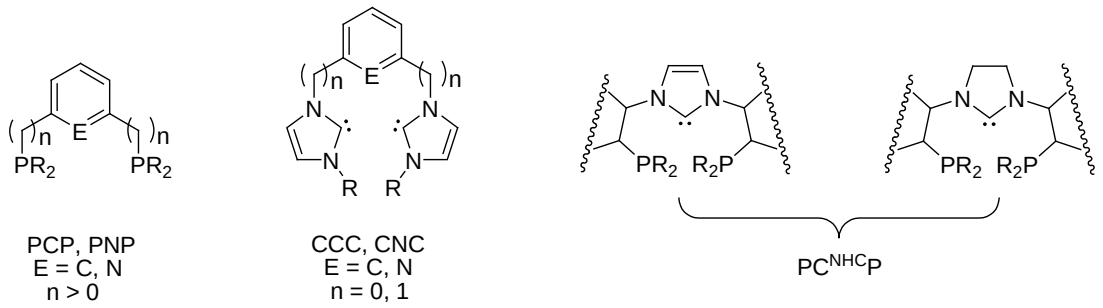



Figure 3 Type of pincer carbene ligands

In the previous section of this thesis we have briefly reviewed the representative applications of monodentate NHC transition metal complexes. Tridentate pincer NHC ligands not only have inherited most of the beneficial properties of monodentate NHC ligands such as the electron-donating capabilities from the carbene carbon, but also possess more special elements from coordinative groups on the side branches, which can be tuned in accordance to our needs. This thesis will not be providing a detailed review on pincer NHC ligands in this section due to limit of space,[39] nevertheless some of their important properties will be reviewed briefly in the following section.

## 2.2 Results and Discussion

### 2.2.1 Ligand Synthesis and Transition Metal Complexes

In general, rigid linear pincer ligands support meridional (octahedral geometries) or pseudo-meridional (trigonal bipyramidal, square pyramidal or square planar geometries) coordination. Investigations on pincer ligands bearing phosphine and amine donors were carried out by Shaw, van der Boom, Milstein, Albrecht and van Koten.[40] Linear rigid tridentate ligands are being studied by various research groups with

transition metals from across the periodic table.[41]


M = Cu, Ag; Ni, Pd etc.

X = Cl, Br or nitriles, pyridines etc.

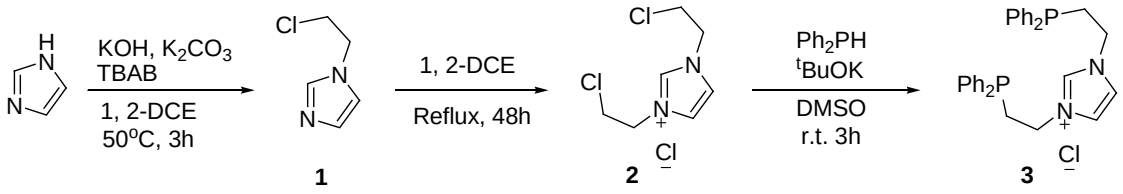
Figure 4 Desired NHC pincer carbene complexes

Transition metal complexes based on pincer structural framework possess special features in terms of a balance of stability and reactivity (catalytic power), which can be systematically tuned by ligand modifications and oxidation state of metal center.[42] In particular, transition metal complexes with phosphine-based ligands have shown excellent performance in bond activation (push-pull effect[43]), coordination and effective catalysis of Heck-type coupling reactions,[24, 42] due to their electron-rich feature on the metal centre that facilitates the oxidative insertion step.

Our research group has been dedicated to the development of catalysts for Heck-type and A-3 coupling reactions in aqueous medium, and thus this project on phosphine-based NHC pincer ligands began with the examination of literature reported PCP-M complexes in catalysis.

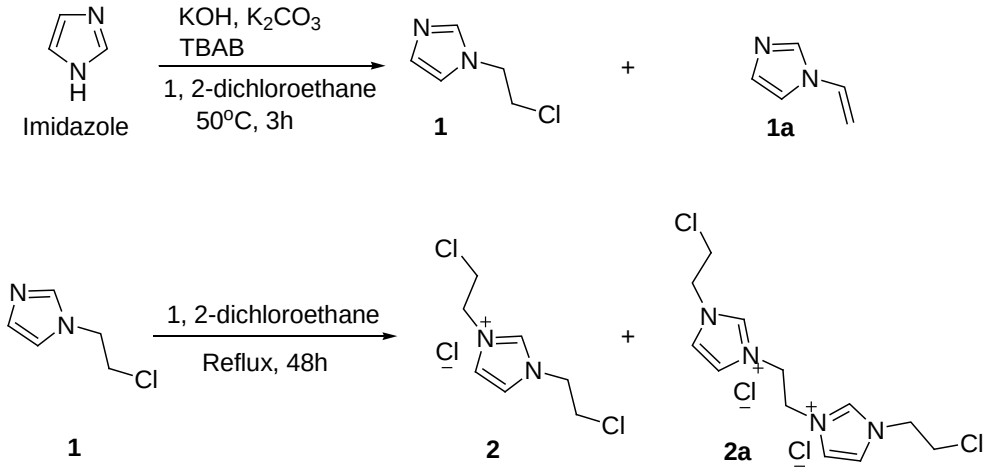
The whole idea behind these proposed structures is that the highly electron-donating nature of the NHC and the electron-pulling nature of the phoshpine groups would make the transition metal centre much more electron-rich, and thus can

easily perform the oxidative insertion and reductive elimination steps in a catalytic cycle.




Scheme 9 Literature procedures for the synthesis of
1,3-bis(2-diphenylphosphanylethyl)-3H-imidazol-1-ium chloride

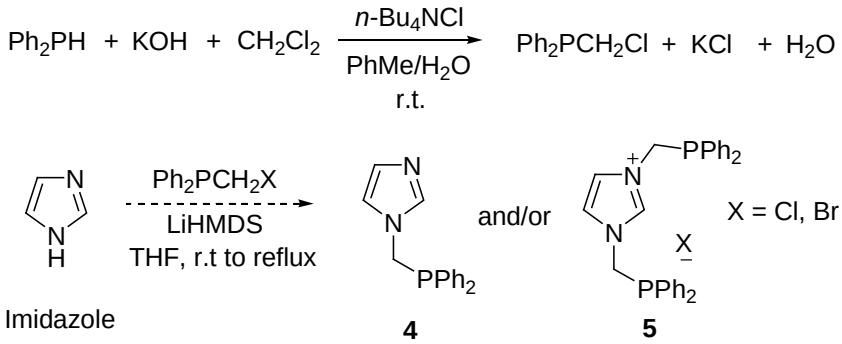
As shown in Scheme 9, in 2004 Hon Man Lee *et al* reported the first synthesis of a tridentate NHC-phosphine ligand that contains ethylene group as the spacer. Its palladium complexes were also synthesized. The author also carried out preliminary catalytic examinations and found that the dianionic $[Pd(PC^{NHC}P)(MeCN)](BF_4)_2$ possess moderate performance in Suzuki and Heck coupling.




Scheme 10 Side reactions from alkylation of imidazole using 1, 2-dichloroethane

Originally we want to take advantage of this publication by re-making the catalyst and directly subject it to A-3 reactions. However the synthetic procedure provided by Lee

was proven to be very problematic, and we were not able to reproduce the results provided in their publication. The first obstacle arose from alkylating the imidazolium nitrogen atoms: the first alkylation produces significant amount of E2 elimination products that requires purification by column chromatography, and the second alkylation in refluxing DCE causes dimerization as shown in Scheme 10. Due to the ionic-liquid nature of this dimerized product, separation using any conventional method is not feasible.

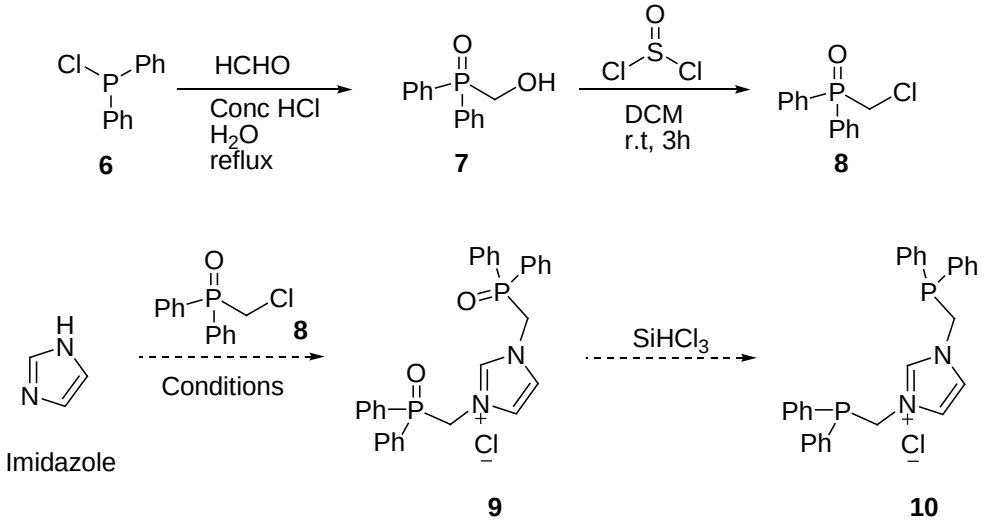



Scheme 11 Proposed synthetic route of 1,3-bis(2-diphenylphosphanylmethyl)-3H-imidazol-1-ium chloride

Upon few unsuccessful repetitions of the literature procedure, we changed our synthetic target and strategy to 1,3-bis(2-diphenylphosphanylmethyl)-3H-imidazol-1-ium chloride, the methylene spacer analogue of Lee's ligand. It is believed that the transition metal complex of such ligand would offer higher stability due to 5-membered ring strain.

Surprisingly, despite the simple structure it possesses, the ligand 1,3-bis (2-diphenylphosphinomethyl)-1H-imidazol-3-ium chloride has never been synthesized previously. Lee *et al* did some primitive calculations on the palladium complex of this

molecule and found that the entire complex has a planar geometry;[24] but no synthetic procedure was ever suggested in any literature to date. One would subjectively envision that such a ligand could be easily constructed using two consecutive $S_N2$ substitutions as shown in Scheme 11. However our experimental results have turned down such a route, no desired product can be obtained via $S_N2$ using $Ph_2PCH_2Cl$. This is because the second alkylation on the nitrogen atom requires elevated temperature which $Ph_2PCH_2Cl$ [(chloromethyl) diphenylphosphine] cannot survive. It has been proven that $Ph_2PCH_2Cl$ is very unstable even at ambient temperature, the self-coupling via $S_N2$ reaction is the most common way of decomposition.




Scheme 12 Alternative approach to the synthesis of 1,3-bis (2-diphenylphosphinomethyl)-1H-imidazol-3-ium chloride

(Chloromethyl)diphenylphosphine oxide **8** is a reported compound[44] and has very high chemical stability at both ambient and high temperature (*ca.* > 200 $^oC$), it is

non-nucleophilic and can be synthesized in large quantities in two steps starting from commercially available chlorodiphenylphosphine; this can be applied to our advantage in the di-alkylation step of imidazole. We proposed that upon obtaining the di-alkylated specie **9**, a simple silane reduction would yield the desired pincer ligand 1,3-bis (2-diphenylphosphinomethyl)-1H- imidazol-3-ium chloride.

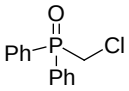
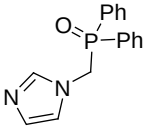
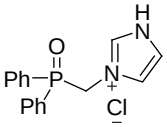
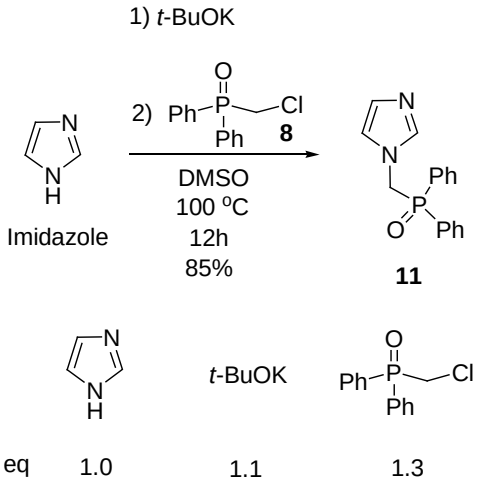
|  |  | Base | Solvent | Time/Temperature |  |  |
|---|---|---|---|---|---|---|
| 1.0 eq | 1.0 eq | No | PhMe | 48h/140$^{o}$C | No | No |
| 1.0 eq | 1.0 eq | No | THF | 48h/Reflux | No | No |
| 1.0 eq | 1.0 eq | No | PhMe/THF | Microwave 40min 140 $^{o}$C | No | No |
| Excess | 1.0 eq | No | PhMe/THF | Microwave 40min 140 $^{o}$C | No | No |
| 1.0 eq | 1.0 eq | No | No | Microwave 1min 120 $^{o}$C | No | No |
| 2.0 eq | 1.0 eq | No | No | Microwave 1min 120 $^{o}$C | No | No |
| 10 eq | 1.0 eq | No | No | Microwave 40min 140 $^{o}$C | 80% conversion | No |
| Excess | 1.0 eq | No | No | Microwave 40min 140 $^{o}$C | 90% conversion | No |
| 1.0 eq | 1.0 eq | $^{t}$BuOK | THF | 48h/60 $^{o}$C | 50% conversion | No |
| 2.0 eq | 1.0 eq | LiHMDS | THF | 48h/60 $^{o}$C | <50% | No |

Table 1 Optimization of 1$^{st}$ alkylation of imdazole using (chloromethyl)diphenylphosphine oxide



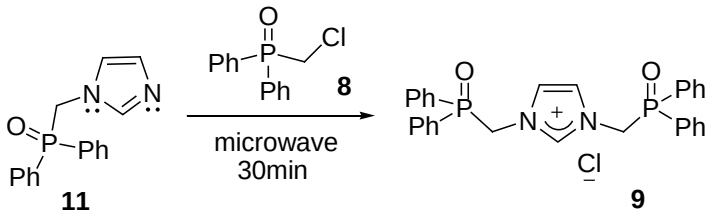

Scheme 13 Optimized conditions for the 1st alkylation of imidazole using (chloromethyl)diphenylphosphine oxide

After some preliminary screening of conditions (Table 1), we found that thermal conditions work better than microwave irradiation in terms of scaling up. Polar aprotic solvent is preferred due to the insolubility of (chloromethyl)diphenylphosphine oxide in most other solvent. The optimal conditions for the 1st alkylation were found to be using *t*BuOK as base and DMSO as the solvent at 100 °C for 12h, as shown in Scheme 13. Quantitative transformation can be accomplished when using the correct stoichiometry and no chromatography is needed.

More time and effort was invested into the reaction condition of the 2nd alkylation. We found that the solvent and stoichiometry plays the important role in the consequence of the reaction. Initially, a fair amount of time was spent in screening solvents, but all results turned out to be failures, we concluded that such alkylation must be performed in a solvent-free manner. Both starting materials are solids at ambient temperature, thus significantly higher temperature must be applied in order to melt them. Microwave

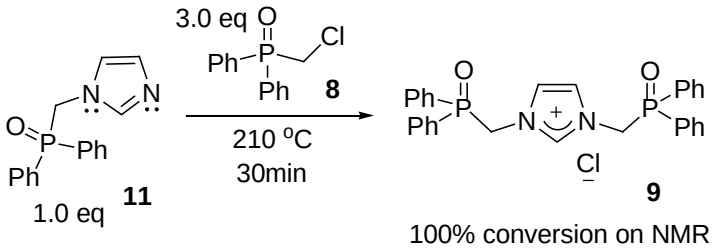
irradiation can also accomplish this transformation: as shown in Scheme 14, a 1 to 1 ratio between **11** and **8** will result in decomposition of starting materials. The desired product can only be formed when an excess amount of electrophile **8** was used.

Thermal conditions (Scheme 15) offer a higher yield than microwave irradiation, and a temperature over 200 $^{o}$C must be reached. The completion of reaction can be monitored by $^{1}$H NMR, in fact the chemical shift of $CH_2$ is characteristic for each compound. The product can be purified by conventional column chromatography or recrystalization in DCM, and very stable in its solid state in air.




| | | | |
|---|---|---|---|
| 1.0 eq | 1.0 eq | 140$^{o}$C | Decomposed |
| 1.0 eq | 3.0 eq | 140$^{o}$C | ~60% depends on trial scale |

Scheme 14 2$^{nd}$ alkylation in microwave using (chloromethyl)diphenylphosphine oxide




100% conversion on NMR
80% isolated yield (recrystalization+column)

Scheme 15 2$^{nd}$ alkylation under thermal condition using (chloromethyl)diphenylphosphine oxide

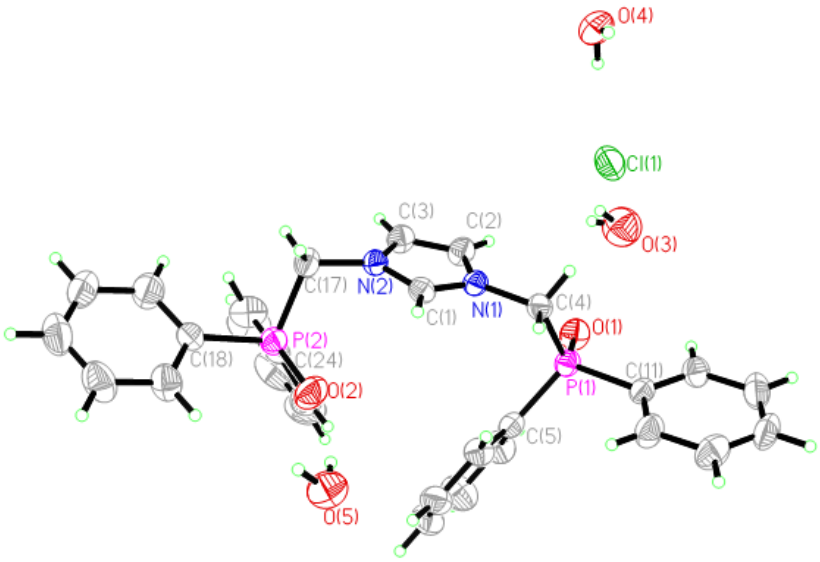
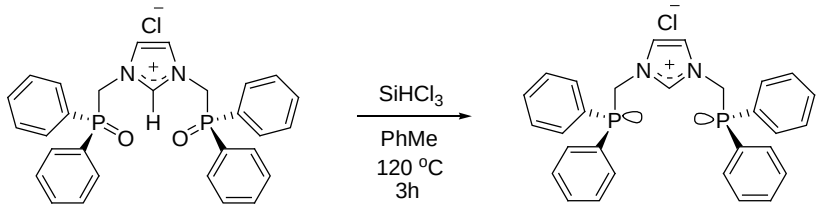
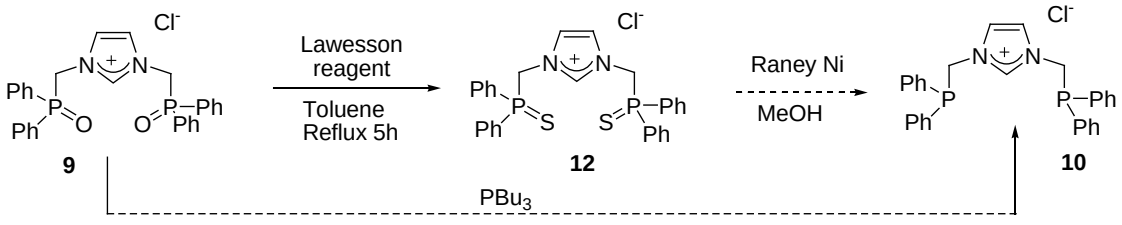



Figure 5 X-ray structure of 1,3-bis(2-diphenylphosphorylmethyl)-1H-imidazol-3-ium chloride

The structure of compound **9** was confirmed by $^{1}H$ NMR, $^{13}C$ NMR, $^{31}P$ NMR and X-ray crystallography (Figure 5). The crystal was obtained via a slow recrystalization process in DCM/MeOH at 4 $^{o}C$ in the fridge. Crystals of similar quality can also be obtained via slow evaporation of solvent in chromatography fractions.




**9** **10**

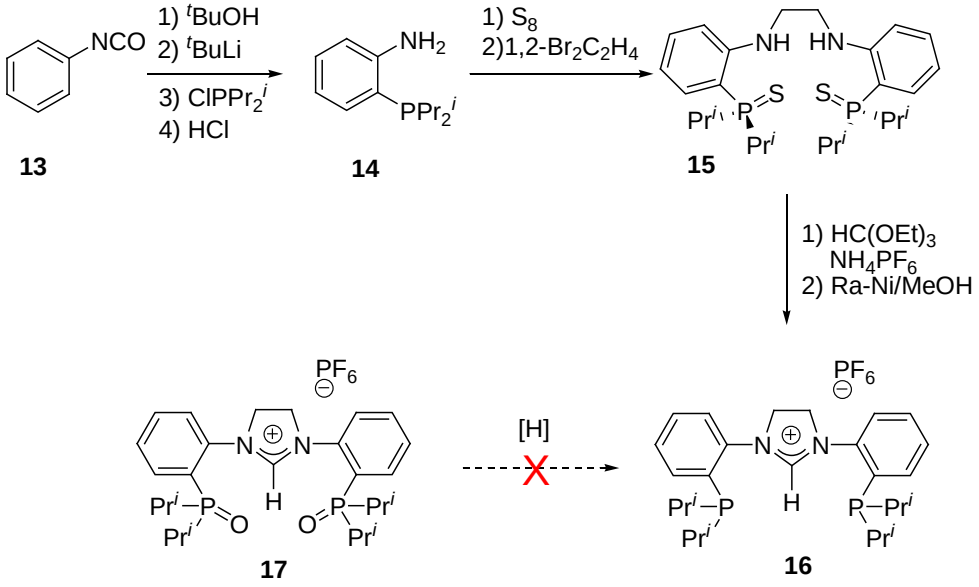



**9** **12** **10**

Scheme 16 Attempt reduction of 1,3-bis(2-diphenylphophorylmethyl)-1H-imidazol-3-ium chloride using Raney nickel

The reduction step from phosphine oxide to phosphine requires large excess (*ca*. > 10eq) of $SiHCl_3$ at 120 $^oC$ in chlorobenzene or toluene as solvent, one noteworthy fact is that stoichiometric amount of silane gave unpromising results. We attempted to circumvent this problem by thionating the phosphine oxide to its phosphine sulfide using Lawesson's reagent and then perform the reduction by Raney nickel in methanol (Scheme 16); quantitative yield was obtained in the thionation step but the reduction could not be accomplished using Raney nickel. An alternative attempt of "phosphine oxide exchange" in tri-*n*-butyl phosphine as solvent at elevated temperature also failed.

This phenomenon has clearly shown the high stability of such phosphine oxide and we suspected the presence of hydrogen bonding between the pro-carbene hydrogen atom and the oxygens. This postulation was confirmed by Fryzuk *et al*, who used to work on very similar structures such as compound **9** in Scheme 17.[45] According to his research postulate, "…under no conditions were we able to reduce bis(phosphineoxide) **17** to phosphine **16**. A preliminary X-ray crystal structure of **17** revealed short contacts between the C-H of the NHC and the two oxygens of phosphine oxide moieties that lie above and below the imidazolium ring, the presence of these **intramolcular H-bonds** likely enhances the stability of the oxide."[45] Therefore an alternative synthetic route was provided by them to reach phosphine **16** (Scheme 17).




*Organometallics*, **2009**, *28*, 2830-2836

Scheme 17 Fryzuk's synthesis of a tridentate *o*-phenylene-bridged diphosphine-NHC system[45]

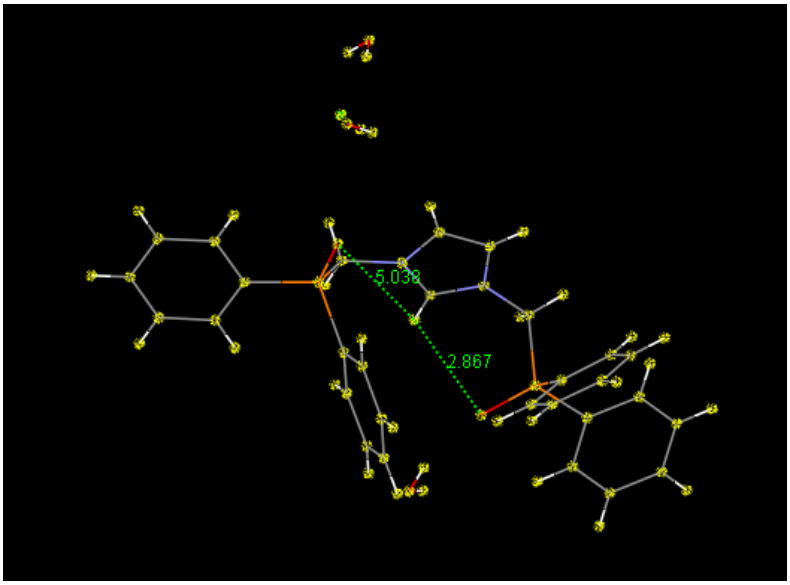
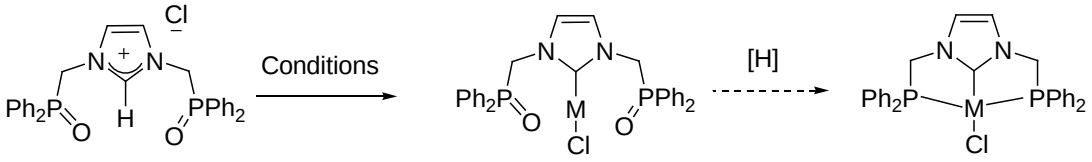



Figure 6 CCDC analysis of bond distance based on X-ray crystallography data

But our preliminary calculation of bond distance based on X-ray crystallography data suggested that no conclusion could be drawn to confirm the existence of hydrogen

bonding. On average, hydrogen bonds have a distance of 2.8 Å and some ultra-short hydrogen bonds have been reported with donor to acceptor distances of 2Å. As shown in Figure 6, the calculated distance between imidazolium hydrogen and phosphine oxide oxygens are 5.038 Å and 2.867 Å respectively, which fall outside the normal range of hydrogen bonding. FT-IR data showed very similar stretch patterns between compound **9** and **11**; and due to severe peak overlap from 1100~1200 $cm^{-1}$ range, the effect of hydrogen bonding on P=O stretch cannot be studied by IR.

Bisphosphine ligand **10** is very unstable and tends to be re-oxidized quickly under oxygen-containing atmosphere. It also slowly decomposes even under argon-protected environment. Originally we proposed a seemingly facile route to synthesize its transition metal complex, as shown in Scheme 18: the phosphine oxide **9** is first converted to its corresponding carbene-metal intermediate **18a, b**, and upon silane reduction, the tridentate pincer NHC-metal complex would form **19a, b** in situ.




**9** **18a, b** **19a, b**

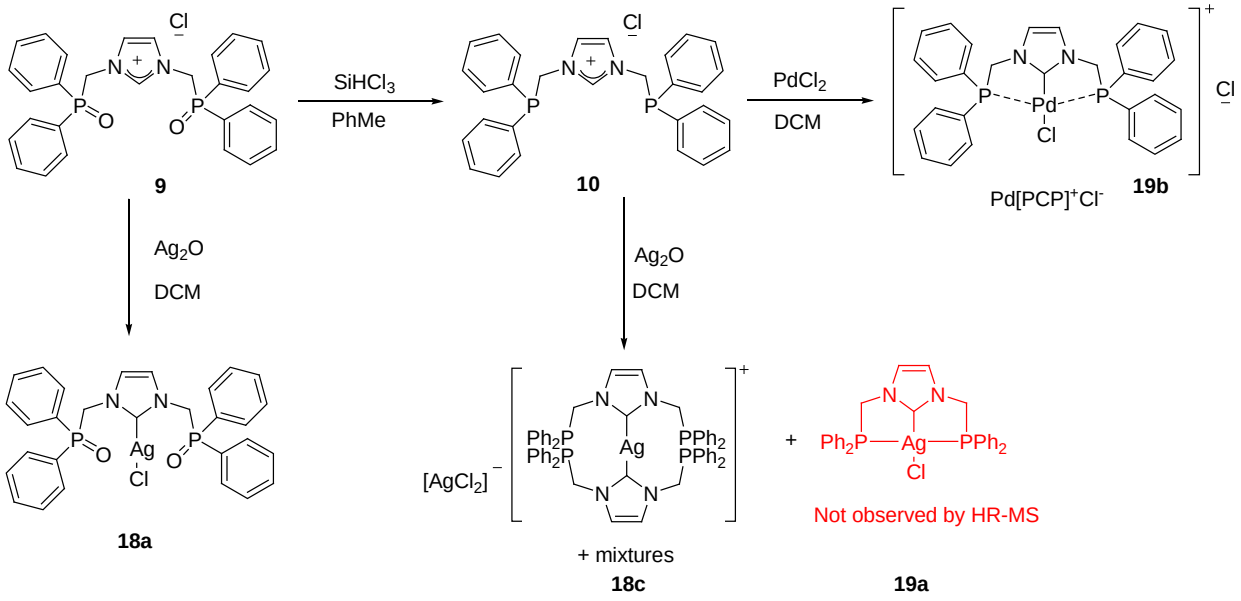
Conditions:

**18a**: $Ag_2O$, DCM, r.t, 16h
**18b**: $PdCl_2$, MeOH, r.t, 3h

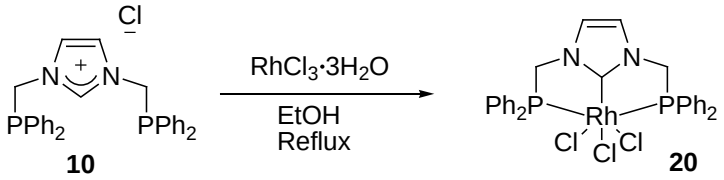
Scheme 18 Attempt reduction of 1,3-bis(2-diphenylphosphorylmethyl)-1H-imidazol-3-ium chloride via pre-formed transition metal complex

Unfortunately this idea could not be achieved as long as the reduction step employs $SiHCl_3$ in high boiling solvent. The structure of intermediate **18a, b** is too

delicate to survive such harsh conditions; hence it is more practical to reduce the phosphine oxide to its phosphine before reacting with any transition metal source.




Scheme 19 Silane reduction of 1,3-bis(2-diphenylphosphorylmethyl)-1H-imidazol-3-ium chloride and complexation with silver (I) and palladium (II)




Scheme 20 Synthesis of pincer NHC-Rh complex

NHC based pincer phosphine **10** is very unstable and quickly decompose in air, the level of purity from work-up after silane reduction does not allow clean conversion to the desired silver (I) complex. Upon several unsuccessful trials we determined that the best method for purification is to pass large quantity of un-purified phosphine **10** through pressurized column chromatography with short silica plug, during this process the pure

phosphine will pass through the column while the oxidized species (phosphine oxides) will stay on the column due to their high polarity.

Pincer NHC ligand **10** has unusual behaviour towards strong base; for instance, it quickly decomposes when reacting with *t*BuOK, NaOH and *n*BuLi, and therefore we could not deprotonate the pro-carbene hydrogen using any of the aforementioned bases. Weak bases such as NaOAc does not have the capability to efficiently perform this deprotonation. A yield of only 50% was obtained when trapping the carbene with $PdCl_2$. The best method for converting this imidazolium salt to its NHC carbene is to first convert it to its corresponding NHC-Ag complex, followed by transmetallation with other metal halides; or, utilizing the transition metals (i.e. Pd & Rh) that can promote C-H activation by directly adding into the pro-carbene C-H bond.

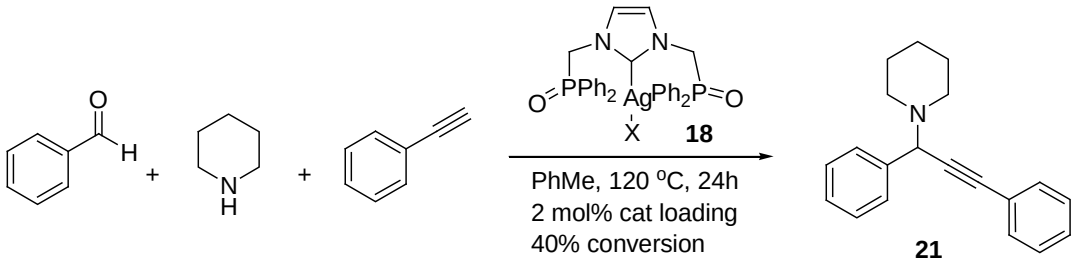
Starting from compound **9** and **10**, we have synthesized a number of transition metal complexes including silver, palladium and rhodium. As demonstrated in Scheme 19 and Scheme 20, following a procedure of the synthesis of a similar structure[24], when reacting phosphine **10** with 0.5 equiv. of $Ag_2O$, the formation of desired compound **19a** was not observed. Instead, we could only observed the formation of NHC homoleptic species $[Ag(NHC)_2]^+[AgX_2]^-$ compound **18c** and some unidentified impurities which do not correspond to anything related to the NHC substrate by $^1H$ NMR and MS. The formation of such homoleptic NHC compounds has also been previously reported as side products by a number of researchers.[46] We have also examined the quantity effect of $Ag_2O$ in this reaction, using a 1:1 ratio between phosphine **10** to $Ag_2O$ offered identical

results. Thus we could only synthesize the phosphine-oxide version of the NHC-Ag complex by reacting phosphine oxide **9** with 0.5 equiv. of $Ag_2O$; the separation of our desired product and the side product is achieved by recrystalization.

The palladium (II)-NHC complex **19b** was synthesized by directly reacting the phosphine-imidazolium salt with $PdCl_2$ or $Pd(OAc)_2$ in DCM at ambient temperature, without the requirement of a base; while the Rh (III)-NHC complex **20** was synthesized via a similar manner (Scheme 20) as the palladium case, but only at much elevated temperature. The [Pd] and [Rh] in this case can effectively insert into the C-H bond without assistance from any base.

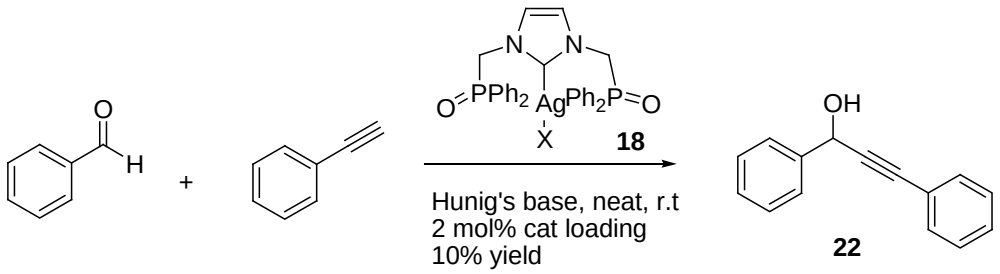
Upon obtaining the aforementioned NHC-transition metal complexes, we have made great efforts in attempting to grow their single crystals for the sake of full characterization, but no success has been achieved to date. The methanol-DCM/ether diffusion method only afforded clustered powder.

### 2.2.2 Examination of Catalysts in Various Reactions



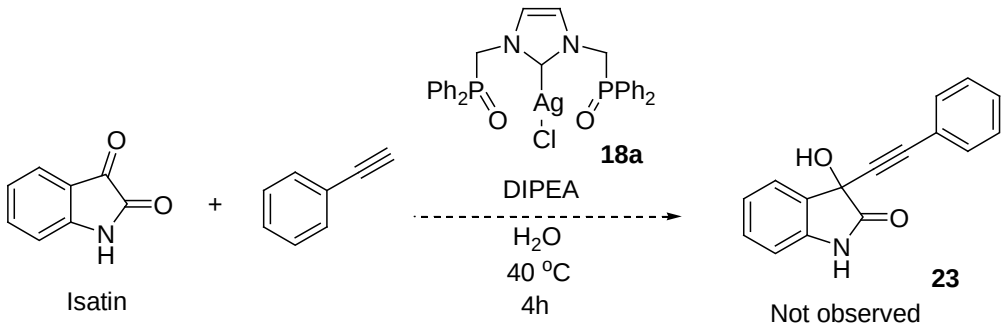

Note: 1 mol% $(CuOTf)_2PhMe$ or $Cu_2O$ can obtain >99% conversion

Scheme 21 NHC-Ag catalyzed A-3 coupling with 2nd amine




Scheme 22 NHC-Ag catalyzed alkyne-aldehyde addition

A series of organic reactions were subjected to the examination of the catalytic activity of the newly synthesized transition metal-NHC pincer carbene complexes. Counter intuitively, compound **18** showed a much reduced activity compare to AgCl or Cu (I) halide[47] in the A-3 coupling reaction between aryl aldehyde, 2nd amine and aryl alkyne; and also reduced activity in the alkyne-aldehyde addition compare to catalyst $Cy_3PAgCl$ (Scheme 21 & Scheme 22).[48] Performing the reaction in aqueous did not improve the effectiveness of the catalyst. The rationale for this phenomenon could be the weak coordination power of P=O and weak π-acidity of [Ag] in our "NHC-Ag-alkyne" intermediate that does not possess significant reactivity towards aldehydes.

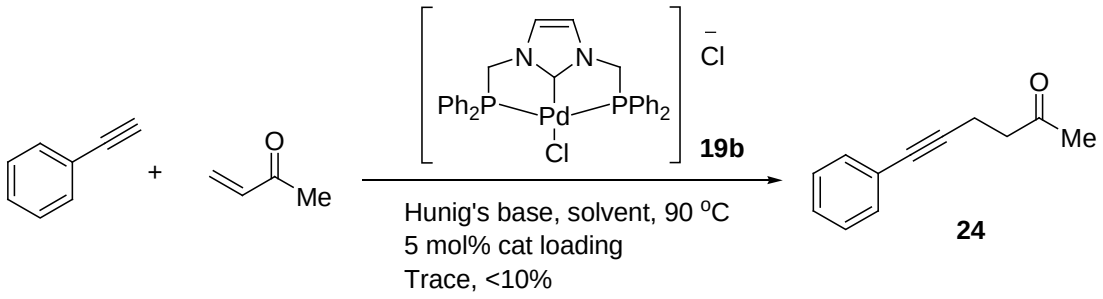



Scheme 23 NHC-Ag catalyzed alkynylation of isatin

3-Hydroxyindolin-2-one **23** is an important moiety with a wide range of biological activities for medicinal chemistry. One of the most direct and simplest ways to

construct this structure is alkynylation of isatin (Scheme 23) or isatin derivatives. Hao *et al* have recently reported a stoichiometric $ZnEt_2$ mediated alkynylation of isatin using phenylacetylene,[49] we attempted to perform the similar synthesis catalytically using NHC-Ag complex **18a** (Scheme 23), and postulated that the amide-carbonyl group would help directing/activating the aryl ketone and thus makes it more reactive towards the NHC-Ag catalyst. However our experimental result has turned down this proposal, the catalyst is not reactive at all in this transformation; no reaction was detected by $^1H$ NMR or GC-MS.

Conjugate additions of terminal alkynes to C=C bonds in water as media has not been well explored due to the reduced electrophilicity of C=C compare to carbonyl groups.[37] The first example of transformation was reported by Carreira *et al* in 2003, who utilized $Cu(OAc)_2$ as catalyst and sodium ascorbate as base to catalyze the addition of phenylacetylene to Meldrum's acid.[50] Later on, Li *et al* discovered that when using electron-rich ligand such as $Me_3P$, palladium alone could efficiently catalyze the 1, 4-addition of terminal alkynes to vinyl ketones in water.[51] Li has further expanded the scope of this chemistry by using highly electron-donating NHCs as ligands and discovered that the reactivity of palladium was increased, and allowed the facile direct addition of terminal alkynes to acrylates esters.[52]

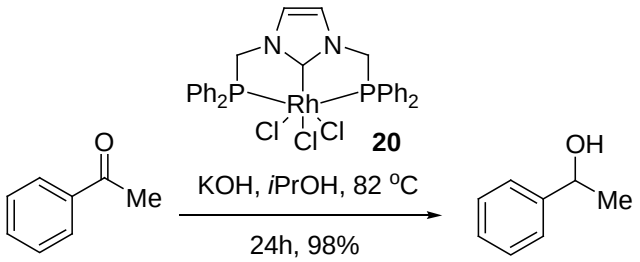



Scheme 24 NHC-Pd catalyzed conjugate addition

We believed that due to the electronic "push-pull" (see section **2.2.1**) effect of our NHC-Pd complex **19b**, the palladium (II) in such complex would perform better than metal catalysts that only possess electron-pushing NHC ligands. However the experimental result did not turn to be what we expected, less than 10% yield was obtained in various selected solvents. A possible explanation for this outcome could be the rigid fused 5-membered metallacycle system results in high stability of such complex in solvent, and therefore the difficult ligand-metal dissociation process prior to the oxidative insertion.

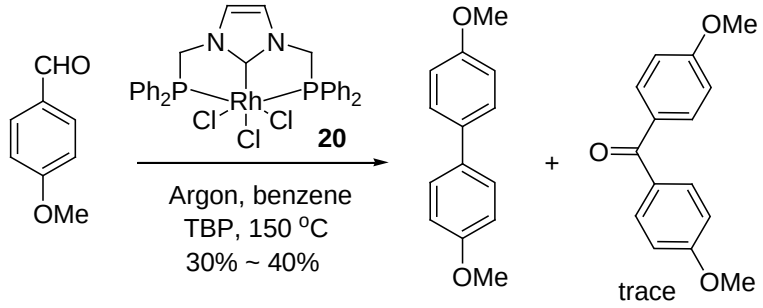
As demonstrated in Scheme 20, we have performed a facile synthesis to Rh (III) pincer NHC complexes via direct cyclometalation. The synthesized Rh (III) complex is air stable and non-sensitive towards moisture or light. Excellent result was obtained when using this catalyst in 2$^{nd}$ ketone reduction to its corresponding alcohol (Scheme 25), the desired alcohol can be achieved in 98% yield in 24h with high purity. A blank reaction was also carried out without the pincer NHC ligand and no reaction was detected. We have not expanded the scope of such transformation in other ketone substrates, this

work is currently under investigation.

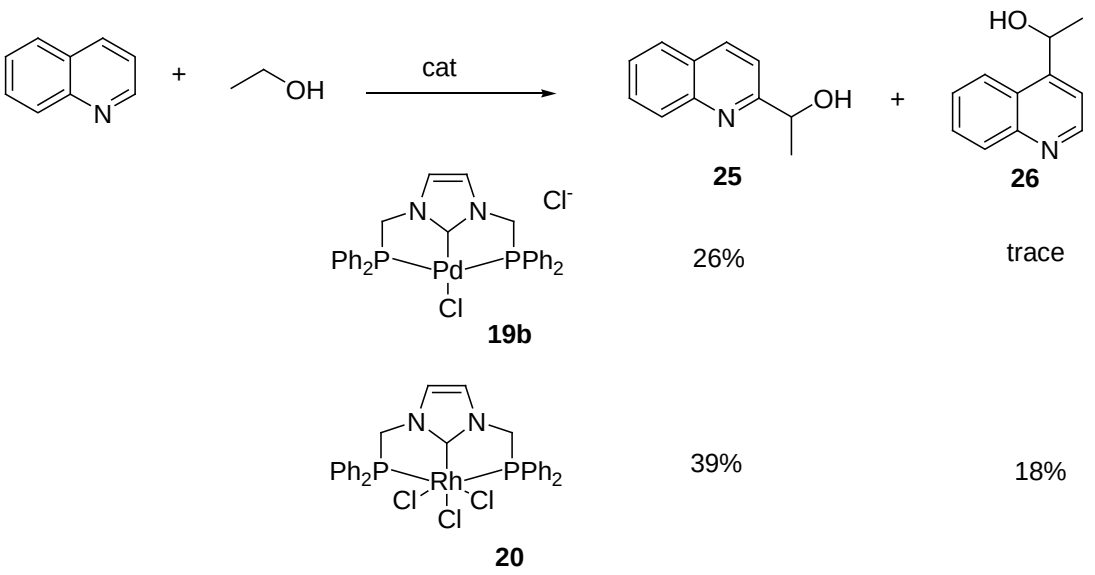



Note: under identical conditions, reaction does not occur only with $RhCl_3$

Scheme 25 NHC-Rh catalyzed transfer hydrogenation




Scheme 26 NHC-Rh catalyzed decarbonylative coupling




Scheme 27 NHC-Pd & NHC-Rh catalyzed direct coupling between quinoline and ethanol (C-H activation)

In collaboration with other colleagues in our research facility (Dr. Luo Yang & Camille Correia), we have attempted to explore a series of C-H activation related coupling reactions such as the NHC-Rh catalyzed decarbonylative coupling (Scheme 26) and direct coupling between alcohol and 2-position of quinolines (Scheme 27). Both compounds **19b** and **20** showed no significant activity in this transformation compared to $[(CO)_2RhCl]_2$ combined with conventional phosphine ligands such as $PPh_3$ or dppe; the C-H activation under such catalysts would preferentially occur at 2-position of quinoline than 4-position.

## 2.3 Summary and Future Work

In this chapter we have demonstrated the synthetic route of a novel NHC ligand 1,3-bis(2-diphenylphophorylmethyl)-1H-imidazol-3-ium chloride and its corresponding

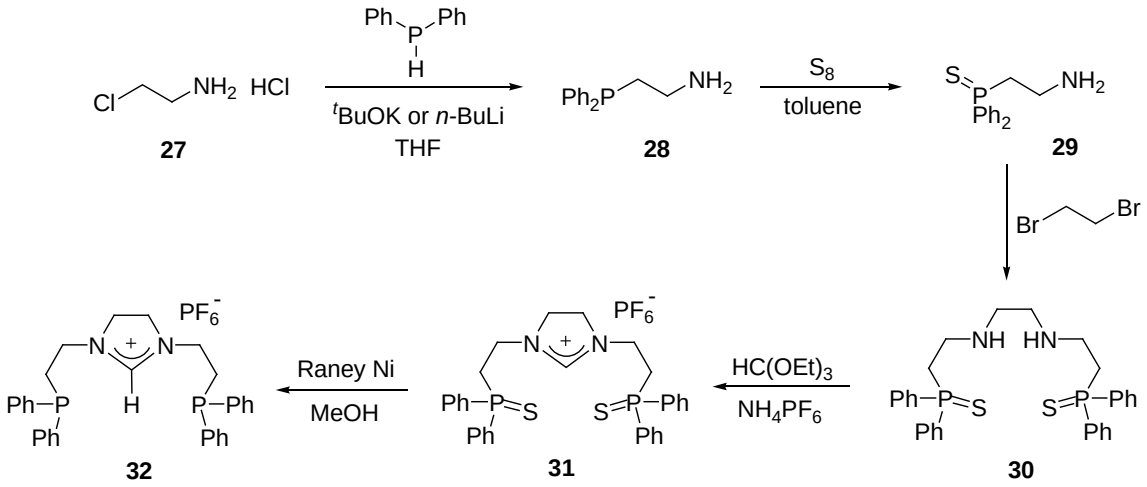
di-phosphine pincer ligand 1,3-bis(2-diphenylphosphinomethyl)-1H-imidazol-3-ium chloride, followed by the synthesis of their silver (I), palladium (II), and rhodium (III) complexes. A variety of catalytic organic reactions were examined including NHC-silver I catalyzed alkyne-aldehyde-amine coupling, NHC-palladium (II) catalyzed conjugate additions of terminal alkynes to C=C bonds, and NHC-rhodium (III) catalyzed transfer hydrogenation of secondary ketones to alcohols. Among these trials, the NHC-Rh (III) catalysts have shown excellent results regarding ketone reduction, while the other catalysts offered insignificant contribution to catalysis.

The most possible explanation for the failure of catalytic capability in the NHC-Pd (II) case is that 1) the rigid fused 5-membered metallacycle system results in high stability of such complex in solvent, and therefore the difficult ligand-metal dissociation process prior to the oxidative insertion; 2) the 3D conformation of compound **19b** (i.e. phosphine-metal-phosphine angle etc.) does not favour the coordination between itself and corresponding substrates in the aforementioned reactions.

For the future work, first of all it is imminent to expand the scope of substrates of the NHC-Rh (III) catalyzed hydrogenation of ketones; secondly, the reaction conditions of the aforementioned NHC-Pd catalysis shall be further explored; third, we will re-investigate the proper method for synthesizing $PC^{NHC}P$-Ag complex **19a** and compare its catalytic capability with $OC^{NHC}O$-Ag complex **18a** under similar conditions. Last but not least, since we have synthesized the imidazol- version of the ligand, it would also be a good idea to synthesize its corresponding imidazolin- counterpart, which possesses

more electron-donating carbene moiety compared to ligand **10**.

The proposed synthetic strategy has been outline in Scheme 28, in which the first two steps have been successfully completed to date. We can also take advantage of this route by utilizing a chiral aminophosphine **28a, b, c** (Figure 7), which upon full furnishing will provide a chiral version of ligand **32**. Conventionally, chiral NHC pincer ligands often have their chirality introduced at the imidazolium ring; however under our proposed strategy, one can easily install the desired chiral groups at the methylene spacer carbons, which could subsequently yield dramatically different chiral induction effects.




Scheme 28 Proposed synthesis of pincer imidazolin-phospine NHC ligands

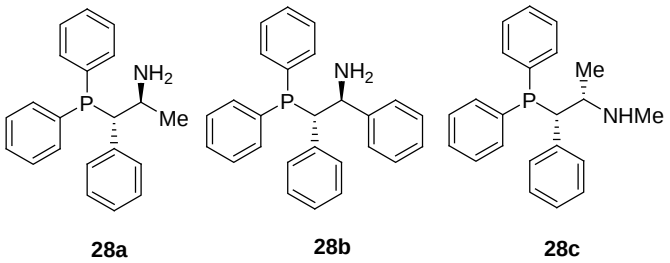


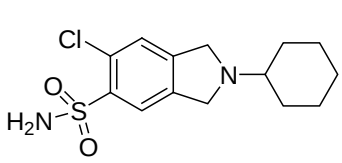

Figure 7 Possible chiral amino-phosphines to be examined for Scheme 28

# Chapter 3

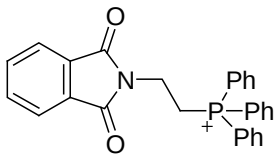
# DEVELOPMENT OF COPPER (II) CATALYZED THREE COMPONENT SYNTHESIS OF ISOINDOLINONE DERIVATIVES

## 3.1 Historical Background

Isoindoline derivatives are important pharmaceutical building blocks in medicinal chemistry. Their ability as a diuretic is 100 times more active than chlorothiazide;[53] isoindolylalkylphosphonium salts possess anti-tumour activities and have displayed substantial activity in the P-388 lymphocytic leukemia screen.[54] In some recent reports it has been proved that isoindolylalkylphosphonium salts possess herbicidal activity,[55] antagonism of the 5-$HT_{2c}$ receptor,[56] and various cancer treatment candidates including protein kinase inhibitors[57] etc. There also have been some recent research carried out for applying isoindoline derivatives in pigments.[58]



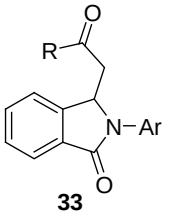
Isoindoline synthesized in 1963
with high diuretic activity



Isoindolinone synthesized in 1977
with substantial activity in the P-388
lymphocytic leukemia screen

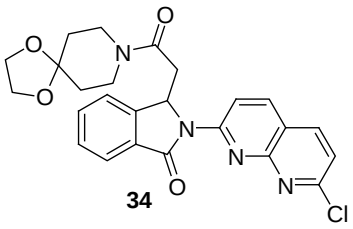
Figure 8 Early discoveries of isoindoline/isoindolinone derivatives

One of its most common derivatives is isoindolinone, which also have attracted much research interest due to its substantial biological activity. *N*-Substituted isoindolinones of general structure **33** possess anxiolytic activity and are commonly applied as sedatives, hypnotics, and muscle relaxants.[59] Some examples are shown below, anxiolytics pazinaclone, pagoclone (Aventis/Pfizer, phase III clinical trials), and the anticonvulsant zopiclone.[60]



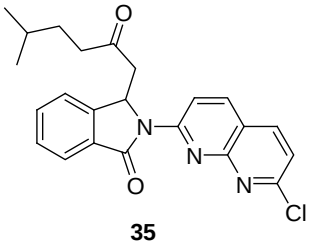
**33**

Isoindolinones



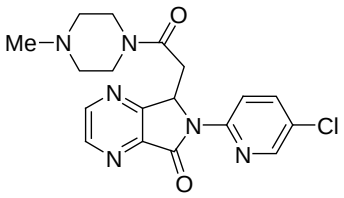
**34**

Pazinaclone



**35**

Pagoclone



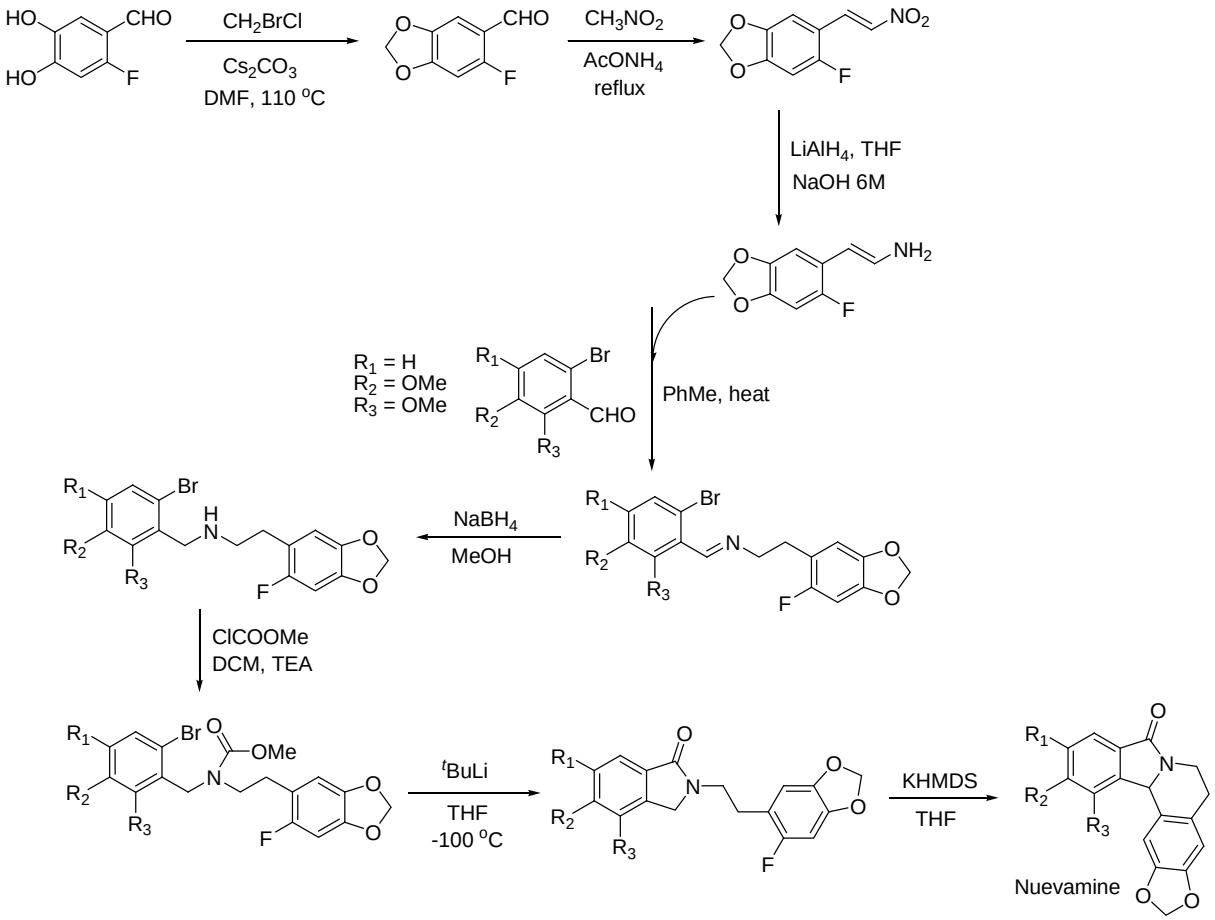
**36**

Zopiclone

Figure 9 Important *N*-substituted isoindolinone derivatives as pharmaceuticals [59]

Conventional synthetic methods adopted in approaching poly-substituted isoindolinone derivatives are usually unsatisfactory due to their harsh reaction conditions,

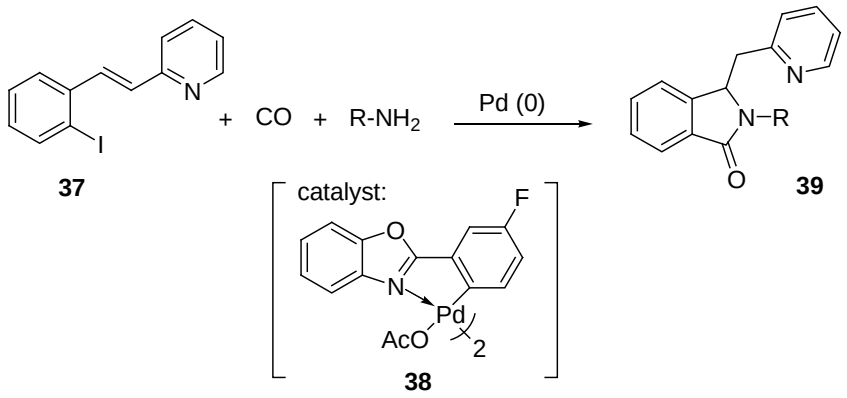
complex starting materials, and tedious steps that involve multi-staged purification procedures (i.e. benzylic oxidation from isoindoline to isoindolinone); atom economy was dramatically reduced in these cases. For example, the synthesis of nuevamine by A. Couture took 8 steps and offered an overall yield less than 10% (Scheme 29).[61]




Scheme 29 Couture's multi-step synthesis of Nuevamine[61]

In recent years, alongside the prosperity of cascade reactions, synthetic routes toward isoindolinones have been greatly altered due to the impact of cascade methodologies. More and more chemists tend to adopt one-step cascade reactions to construct the skeletons of these molecules. For example, palladium (0) catalyzed

three-component carbonylation-amination-Michael addition was used by Grigg *et al* in 2005 in their synthesis of various isoindolinones (Scheme 30).[59]




Scheme 30 Grigg's Pd (0) catalyzed three-component carbonylation-amination-Michael addition

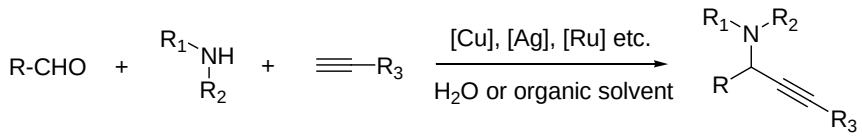
One of the drawbacks of this methodology is that the Michael acceptor **37** must be pre-synthesized and possess electron-withdrawing group, and the application of CO atmosphere is not environmentally friendly.

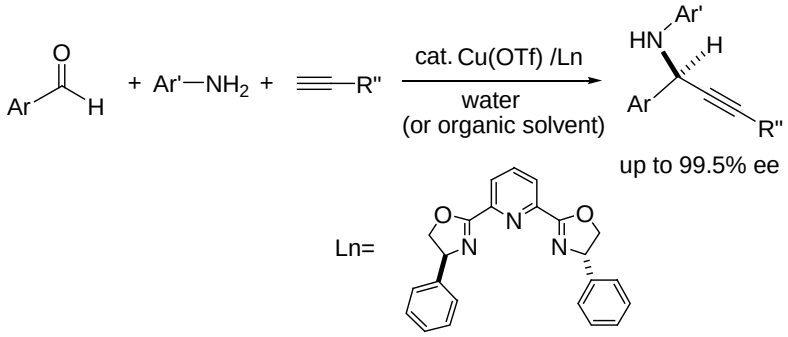
While working on the tandem methodology (Aldehyde-Alkyne-Amine coupling) for the synthesis of mono-propargyl amines, we envisioned that the secondary amine formed as the product can also be utilized as a nucleophile and perform consecutive reactions. Under proper conditions, this nucleophilic nitrogen can be treated as the building block for a lactam cycle, which upon furnishing of desired functional groups, could yield various isoindolinone derivatives (Scheme 33).

### 3.1.1 Three-Component Coupling of Aldehyde, Alkyne and Amine (A-3 Coupling)

Multi-component cascade reactions are powerful tools for constructing

complicated structures from simple precursors. In 2002, our group developed the first catalytic addition of acetylenes to various imine or acyliminium ions, this methodology was later extended to the Ag (I) catalyzed three component coupling of aldehyde, alkyne and amine;[62] subsequently, our group also modified the catalysts and reaction conditions such that this transformation can perform very well in water as the solvent.[63] Very low catalyst loading is required (less than 1%) and the propargyl amine formation is high yielding. This discovery has attracted much attention and also triggered intensive research in this area, because the final products are synthetically versatile building blocks for the preparation of many nitrogen-containing compounds that possess valuable biological activities.



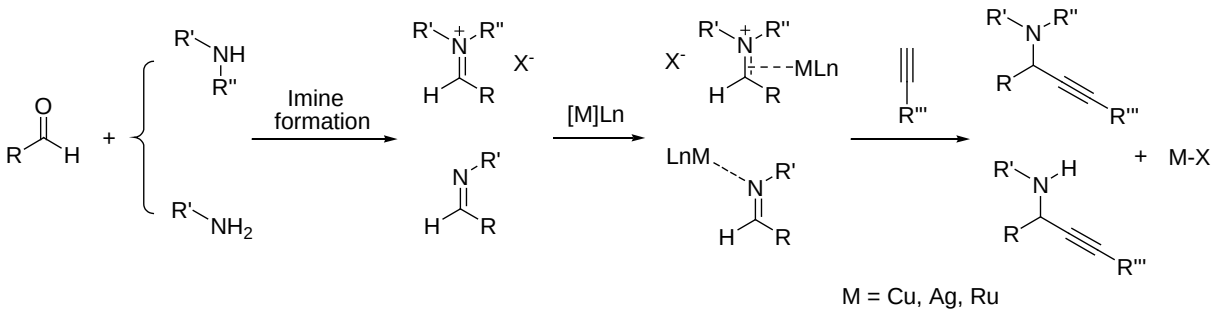




Scheme 31 Three-Component Coupling of Aldehyde, Alkyne and Amine (A-3 Coupling)

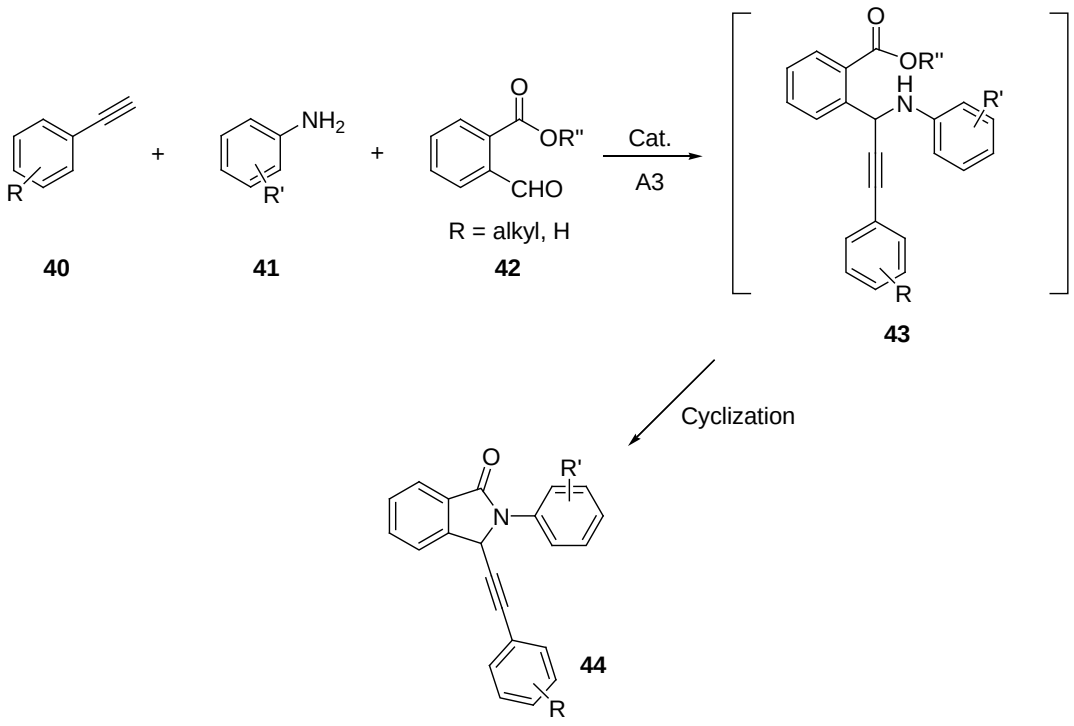
It has been proven that the A-3 coupling can be catalyzed by various types of transition metal catalysts, including Cu (I) salts, Cu (II) salts, Ag (I) salts, Au (I) and Au

(III) salts, Cu/Ru bimetallic systems etc., a plausible mechanism is provided in Scheme 32. Depending on the nature of the substrates, the reaction can proceed in organic solvent, water or neat. To minimize the loss of these precious catalysts, Li's group also examined the application of Ag (I) and Cu (I) catalysts in ionic liquids.[64]

Asymmetric A-3 coupling was initially examined by Li *et al* using a chiral Cu(I)-bis(oxazolinyl)pyridine (aka. pybox) complex in water (Scheme 31), in this case the product was obtained in very low conversions and the reason for such low catalytic activity of Cu (I) was postulated to be the strong C-Cu bond of copper acetylides. After certain amount of trials and errors, Li eventually found that the use of ligand pybox with Cu(OTf) can afford the corresponding propargylamine with both high enantioselectivity (up to 86%) and yields (up to 91%) in water.[65]




Scheme 32 Mechanism of A-3 Coupling with Secondary & Primary Amines under Transition Metal Catalysis




Scheme 33 Proposed Isoindoline Synthesis via A-3 Coupling Strategy

We proposed that (Scheme 33) from simple commercially available starting materials **40**, **41**, **42**, under transition metal catalysis, the A-3 coupling product **43** will quickly form in-situ; and upon intramolecular cyclization, the isoindolinone core will be constructed in one step.

### 3.1.2 From Isoindolinone to Isoindolo[2,1-a]quinolines

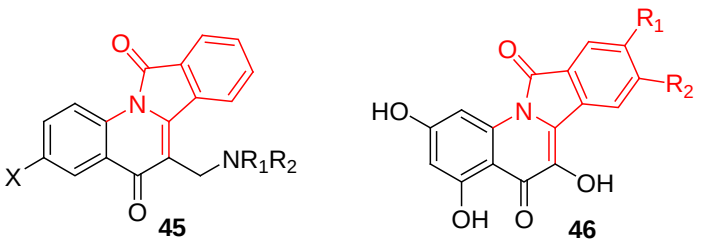
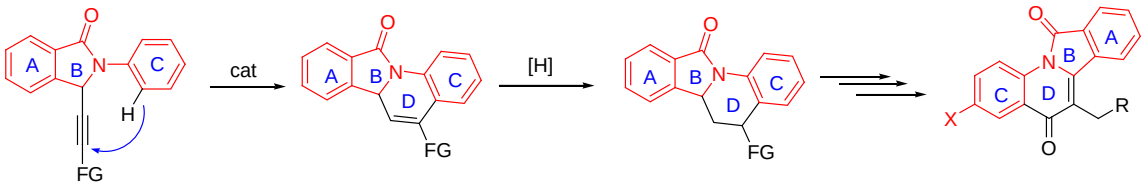



Figure 10 Bioactive isoindoloquinolines

Isoindolo[2,1-a]quinolines are a class of interesting compounds that possess a wide range of biological activities.[66] For example, 5,11-dioxo substituted isoindolo-[2,1-a]quinolines show protective effects against $N_2$-induced hypoxia.[67] Thus they are commonly used for prophylactic and therapeutic treatment of senile dementia, angina pectoris, myocardial infarction etc.; trihydroxyisoindolo-[2,1-a]quinolines have inhibitory activities against human topoisomerase (II) and bacterial DNA-gyrase.[68] These features made them attractive synthetic targets; unfortunately, few efficient syntheses for this system have been reported.

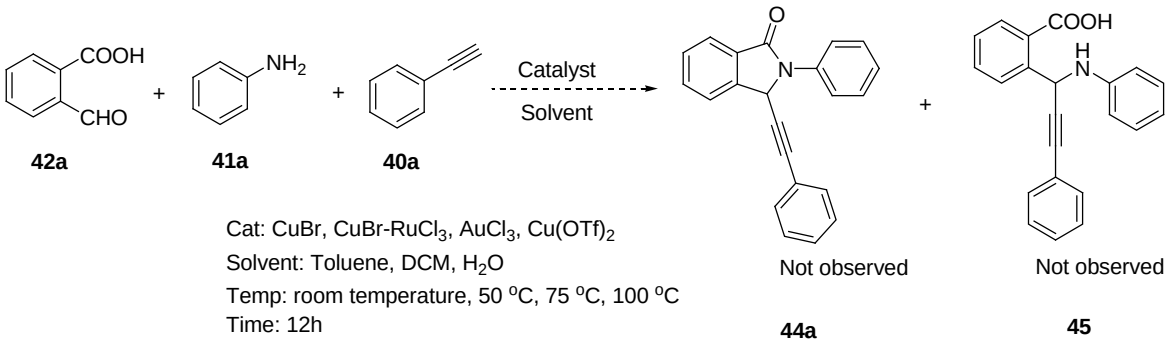



Scheme 34 Proposed one-step transformation from A-3 product to isoindolo[2,1-a]quinoline

It is very reasonable to envision that the products generated from the A-3 strategy described in **3.1.1** can be easily transformed to a series of isoindolo[2,1-a]quinoline derivatives by cyclization of the D ring and certain functional group manipulations (Scheme 34).

## 3.2 Results and Discussion

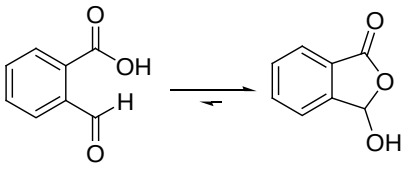
### 3.2.1 Methodology Study of A-3 based Synthesis of Isoindoline Derivatives




Scheme 35 Isoindolinone synthesis via A-3 coupling strategy using 2-carboxybenzaldehyde as the starting material

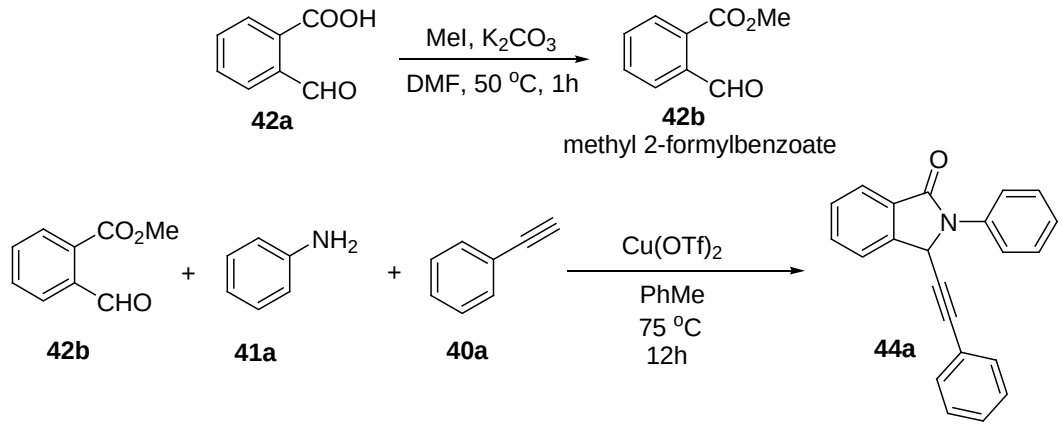
Our initial examination started by using 2-carboxybenzaldehyde, aniline and phenyl acetylene as the starting materials, all of which are inexpensive, readily available commercial products. A variety of transition metal catalysts were screened (Scheme 35) under logical conditions, some of which were expected to provide promising results. Surprisingly, not only there was no formation of the desired propargyl isoindolinone **44**, but also we did not observe the formation of A-3 intermediate **45**.

$^{1}$H NMR study showed that 2-carboxybenzaldehyde mainly exists in its fused bicyclic form (Scheme 36). We believed that such configuration obstructs the formation of imine and thus prevent A-3 coupling from occurring. Another factor responsible for the failure is that the substrate does not contain good leaving group to facilitate the cyclization of amido ring B.



Scheme 36 Equilibrium of 2-carboxybenzaldehyde

To implement a good leaving group into the substrate as well as converting it into its “open” form, we subsequently transformed the 2-carboxybenzaldehyde to its methyl ester (methyl 2-formylbenzoate) and re-subject it to the same sets of conditions examined previously; in this case all metal catalysts offered desired product in different yield, out of which the $Cu(OTf)_2$ has the highest product/impurities ratio. Thus we selected methyl 2-formylbenzoate and $Cu(OTf)_2$ in toluene as the starting point for further optimizations.



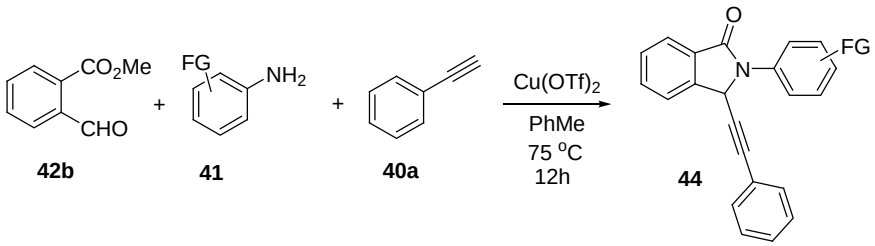
Scheme 37 Isoindoline Synthesis via A3 Coupling Strategy using methyl 2-formylbenzoate as substrate. Aldehyde : aniline : acetylene = 1.0 equiv. : 1.5 equiv. : 1.5 equiv.

As presented in Table 2, upon systematic screening, the optimized condition was determined to be 15 mol% of copper (II) triflate at 100 $^{o}$C for 12 hours in toluene. We did not perform screening of solvents because toluene in this case can already offer good result. One noteworthy fact is that the solvent is an essential component of the reaction in

this transformation, without which the condition provided would be too harsh for the substrates used, and in most cases the acetylene will be oxidized to the ketone.

Table 2 Optimization of reaction conditions

| Entry | Catalyst loading $Cu(OTf)_2$ (mol%) | Temperature ($^oC$) | Reaction time (h) | Isolated yield (%) |
|---|---|---|---|---|
| **1** | 5 | 50 | 12 | 63 |
| **2** | 5 | 75 | 12 | 66 |
| **3** | 5 | 100 | 12 | 29 |
| **4** | 5 | 75 | 6 | 50 |
| **5** | 5 | 75 | 24 | 51 |
| **6** | 10 | 75 | 12 | 80 |
| **7** | 15 | 75 | 12 | 93 |
| **8** | 20 | 75 | 12 | 95 |
| **9** | 15 | 100 | 12 | 95 |



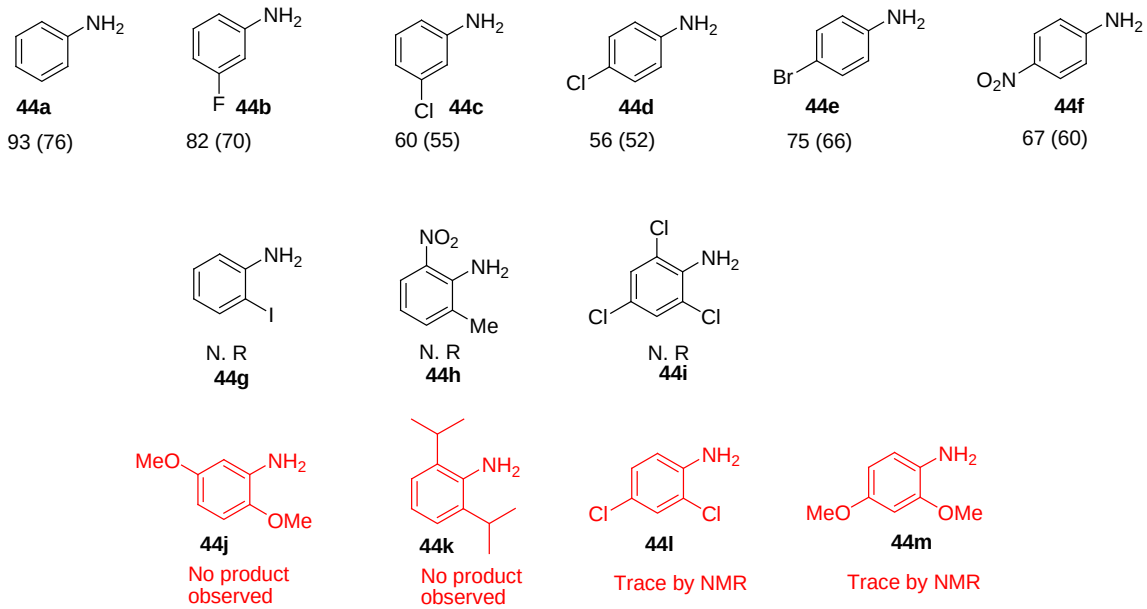




Table 3 Screening of anilines, NMR yield (isolated yield)

*Note: The compound numbering in Table 3 are designated for the cyclized isoindolinone

A fair amount of time was spent in screening various types of aniline derivatives. Experimental results (Table 3) indicated that any form of *ortho* substitution pattern on the aniline ring would impede the formation of desired product. Presence of electron withdrawing groups on the *meta* or *para* position can reduce yield compare to electron donating groups.

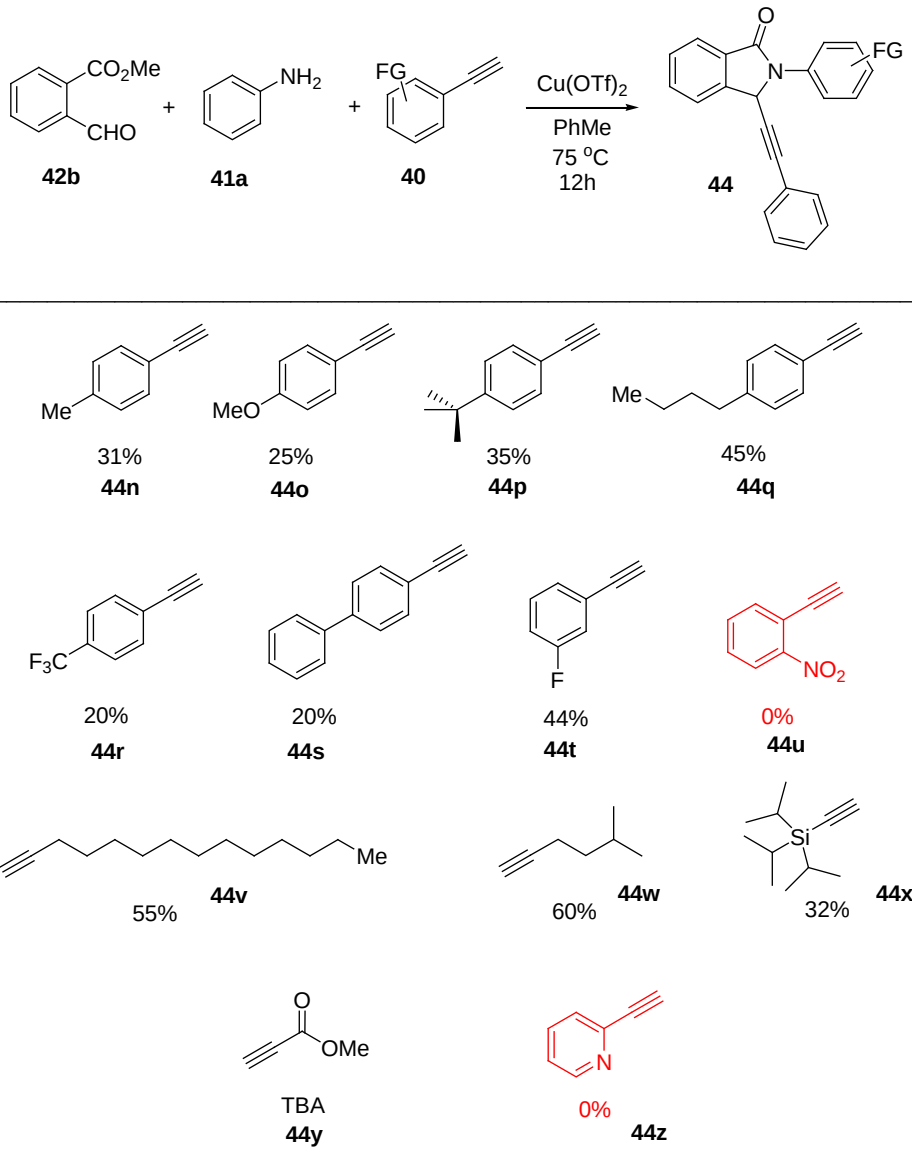



Table 4 Screening of alkynes

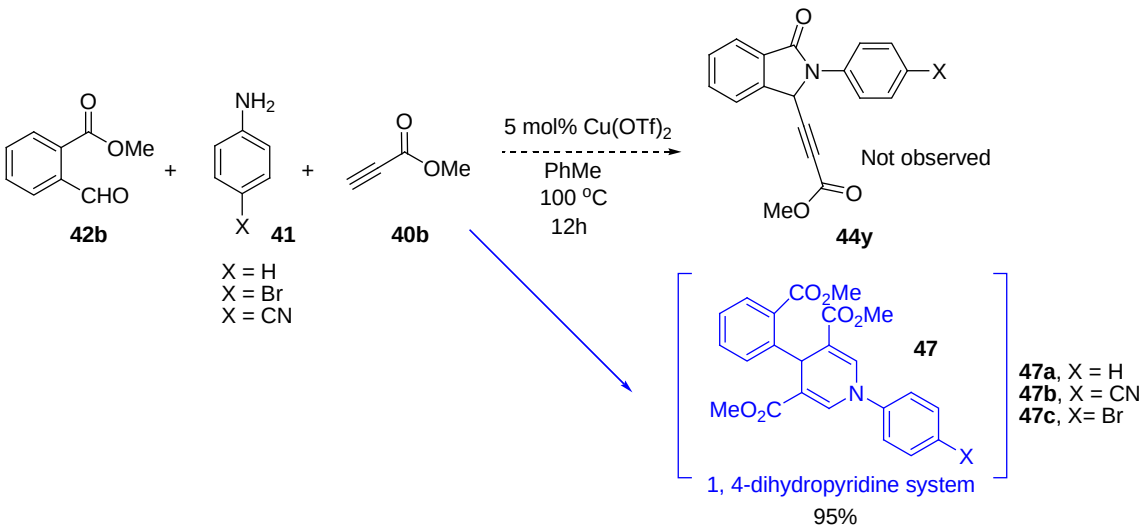
*Note: the compound numbering in Table 4 are designated for the cyclized isoindolinone

Screening of the acetylene substrates proved to be the greatest challenge within this methodology. The results of reactions tend to be irreproducible upon repetitions; thus each yield reported in Table 4 is averaged isolated yield among few trials. Similar to the results of anilines, *ortho* substitution patterns in aryl acetylenes do not favour formation of desired products; most importantly, electronic characters of the aryl cycles do not

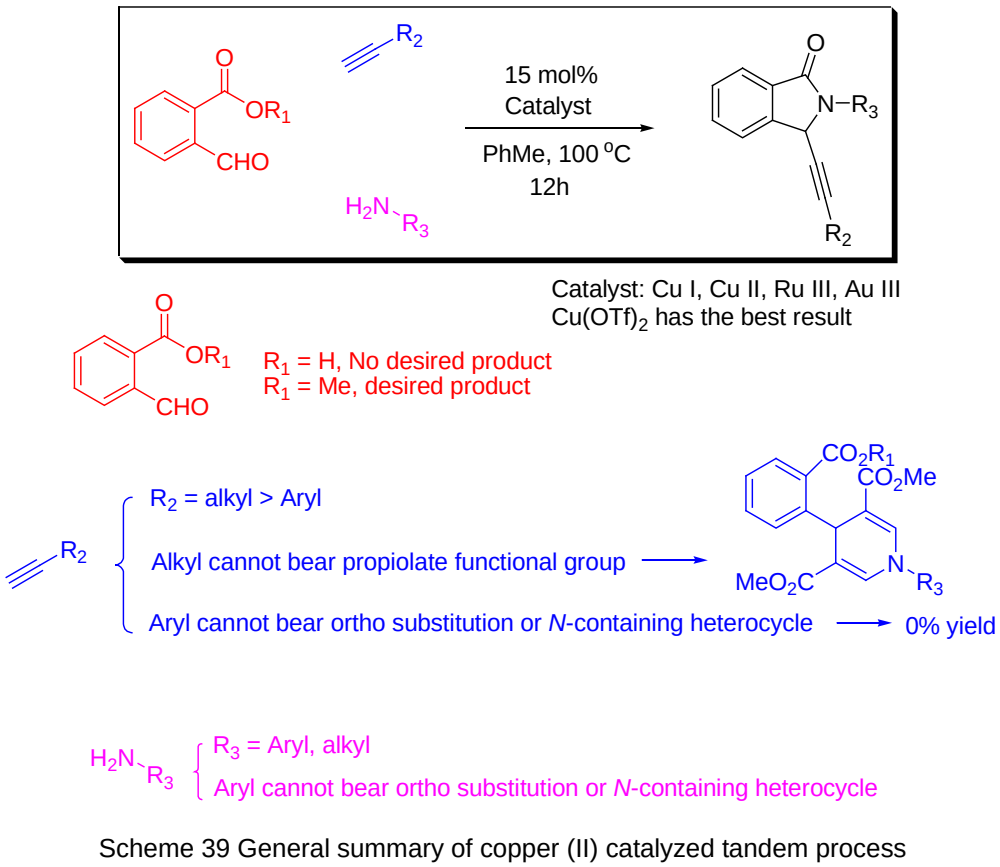
seem to play a crucial role on yield, despite that in the *para*-substituted cases electron donating groups seem to offer better yield than electron withdrawing groups. Alkyl acetylenes always provide higher yield than aryl acetylenes.

Two special situations have been observed. Firstly, when the aryl acetylene contains a nitrogen-heterocycle, the yield diminishes to nearly zero. Based on the colour of the catalyst and amount of starting materials recovered, we can clearly conclude that the catalyst is not turning over. We suspected this is caused by strong coordination and complexation between the heterocyclic nitrogen and copper (II) metal, which prevents the formation of Cu-acetylide. Elevated temperature or addition of catalytic amount of acid does not solve this problem. Secondly of all, when using propiolate as the alkyne, the desired isoindolinone core will not form, in this case the mechanistic pathway will alter and the reaction will yield exclusively the 1, 4-dihydropyridine system (>90% isolated), as shown in Scheme 38.

Initially, we were quite impressed by this outcome because known previous synthesis of 1, 4-dihydropyridines either requires expensive microwave apparatus such as Balalaie & Kowsari's synthesis in 2001,[69] or pre-formation of the imine and expensive rare earth metal catalyst (RE triflates, RE = Sc, Y, La, Ce, Pr, Nd, Sm, Yb) such as Fukuzawa's synthesis in 2007.[70] Unfortunately upon careful reviewing of synthetic literatures, we discovered that our methodology is not the greenest approach to date; During our studies, Antonello Mai in 2009 used Bronsted acid as catalyst and completed the same transformation in a one-pot tandem manner, no transition metal was applied.[71]




Scheme 38 Formation of 1, 4-dihydropyridine structural scaffold

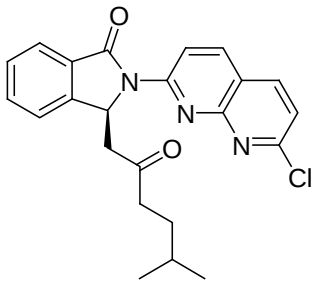



Scheme 39 General summary of copper (II) catalyzed tandem process

As a summary in Scheme 39, we have demonstrated that a tandem A-3 coupling followed by intramolecular cyclization can efficiently construct the desired isoindolinone core, starting from methyl 2-formylbenzoate, aniline derivative and alkynes as the precursors. Within this reaction scope, introduction of propiolates as the acetylene source will provide 1, 4-dihydropyridine as the only product, and no desired product can be obtained when using heterocyclic amines.

In the next two sections, we will demonstrate the application of this tandem methodology in synthesis of medicinal compounds and further transformation to isoindolo[2,1-a]quinolines.

### 3.2.2 Attempt Short Synthesis of Pagoclone

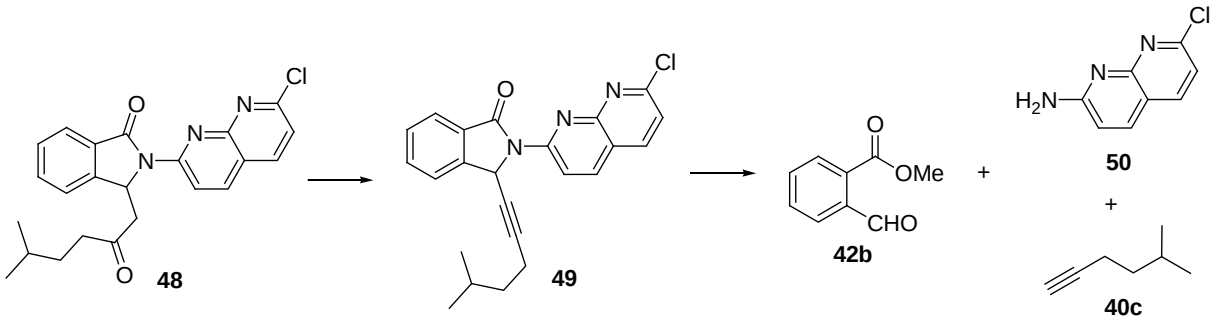



CI-1043 (pagoclone)

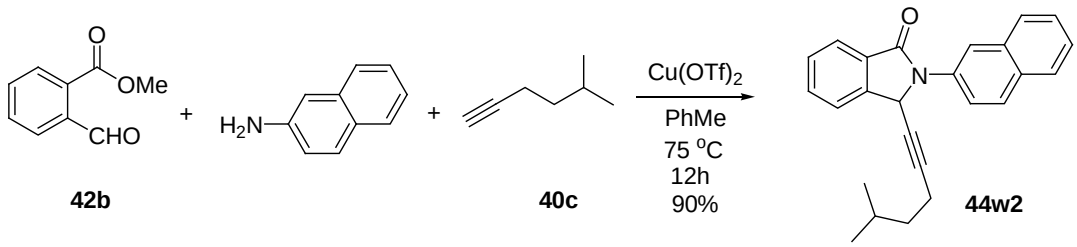
Figure 11 Structure of pagoclone

Pagoclone (Figure 11) is a license anxiolytic drug from the cyclopyrrolone family, it acts as a partial agonist at the benzodiazepine site of the $GABA_A$ receptor. This licensed compound was under development for the treatment of general anxiety disorder and panic disorder.[72] It is also one of a recently developed class of medicines known as the nonbenzodiazepines, which have similar effects to the benzodiazepine group. This

compound possesses an isoindoline bicyclic ring system which could be efficiently constructed via our aforementioned Cu (II) catalysis, as demonstrated in Scheme 40. The ketone moiety of pagoclone can be obtained in one step via oxymercuration.

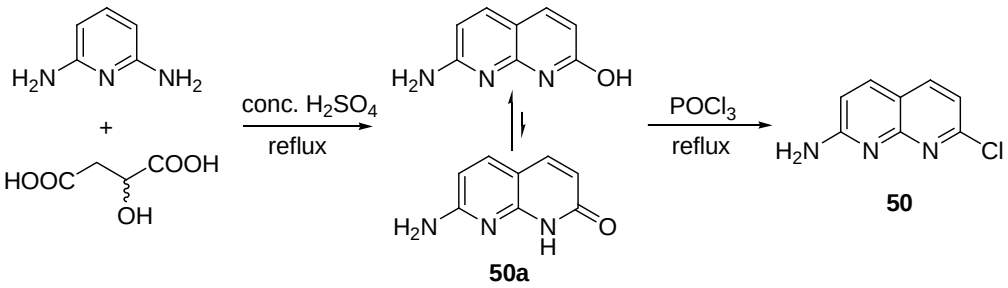



Scheme 40 Retrosynthetic analysis of pagoclone



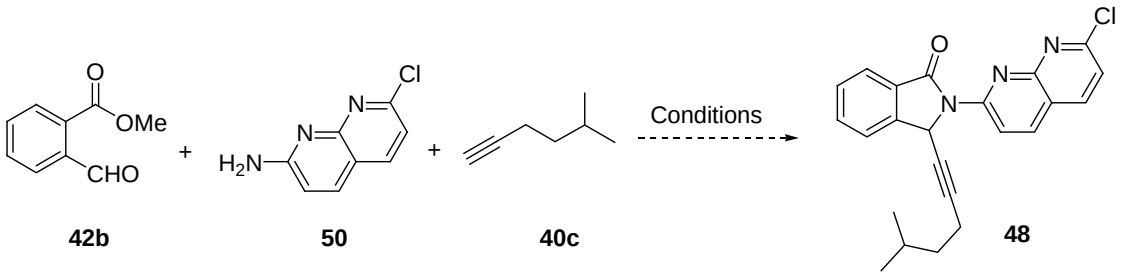

Scheme 41 Model study of pagoclone synthesis

Before proceeding to the actual synthesis of pagoclone, a model study (Scheme 41) was performed in order to examine the scope of reaction. 2-Naphthylamine was selected to mimic the structure of aminonaphthyridine systems; the reaction proceeded well and a yield of 90% was achieved.




Scheme 42 Synthesis of 2-amino-7-chloro-1,8-naphthyridine

The aryl amine in this study (2-amino-7-chloro-1,8-naphthyridine in Scheme 42) was synthesized in large quantity in two steps following published procedures.[72,73] The product **50** has very low solubility in most non-polar solvents, but has good solubility in DMSO and hot methanol.




Scheme 43 Proposed one-pot tandem synthesis of pagoclone

Table 5 Screening of conditions for the one-pot tandem synthesis of pagoclone

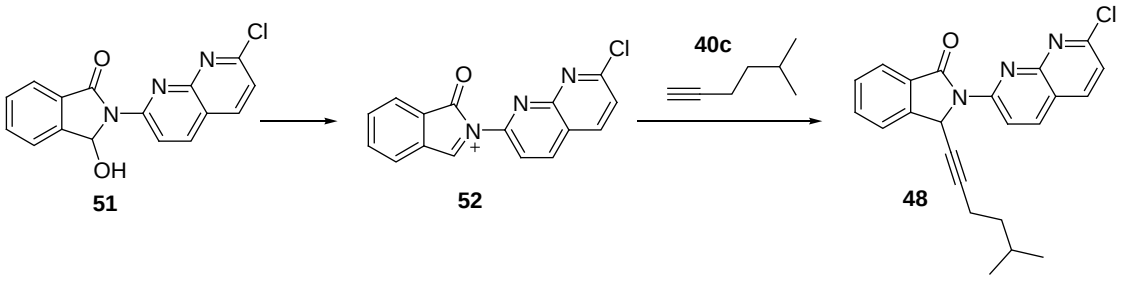
| Entry | Catalyst | Additive | Temp/$^{o}$C | Solvent | Time | Result |
|---|---|---|---|---|---|---|
| 1 | 15 mol% $Cu(OTf)_2$ | No | 100 | PhMe | 12h | N.R. |
| 2 | 15 mol% $Cu(OTf)_2$ | No | 100 | PhMe | 24h | N.R. |
| 3 | 15 mol% $Cu(OTf)_2$ | No | 120 | PhMe | 12h | N.R. |
| 4 | 20 mol% $Cu(OTf)_2$ | No | 120 | PhMe | 12h | N.R. |

| | | | | | | |
|---|---|---|---|---|---|---|
| 5 | 15 mol% $Cu(OTf)_2$ | Catalytic triflic acid | 100 | PhMe | 12h | N.R. |
| 6 | 15 mol% $Cu(OTf)_2$ | Catalytic HOAc | 100 | PhMe | 12h | N.R. |
| 7 | 15 mol% $Cu(OTf)_2$ | 1.0 equiv. HOAc | 100 | PhMe | 12h | N.R. |
| 8 | 15 mol% $Cu(OTf)_2$ | 1.0 equiv. HOAc | 100 | DMSO | 12h | N.R. |
| 9 | 15 mol% Cu(OTf) | Catalytic HOAc | 120 | DMSO/PhMe = 1/1 | 12h | N.R. |
| 10 | 15 mol% Cu(OTf) | Catalytic HOAc | 80 | THF | 12h | N.R. |
| 11 | 15 mol% $Cu(OTf)_2$ | 1.0 equiv. HOAc | 100 | MeCN | 12h | N.R. |
| 12 | 15 mol% $Cu(OTf)_2$ | No | 85 | DCM | 12h | N.R. |
| 13 | 15 mol% CuOTf | No | 100 | PhMe | 12h | N.R. |
| 14 | 15 mol% AgOTf | No | 100 | PhMe | 12h | N.R. |
| 15 | 15 mol% AgCl | No | 100 | PhMe | 12h | N.R. |
| 16 | 15 mol% $InCl_3$ | No | 100 | PhMe | 12h | N.R. |

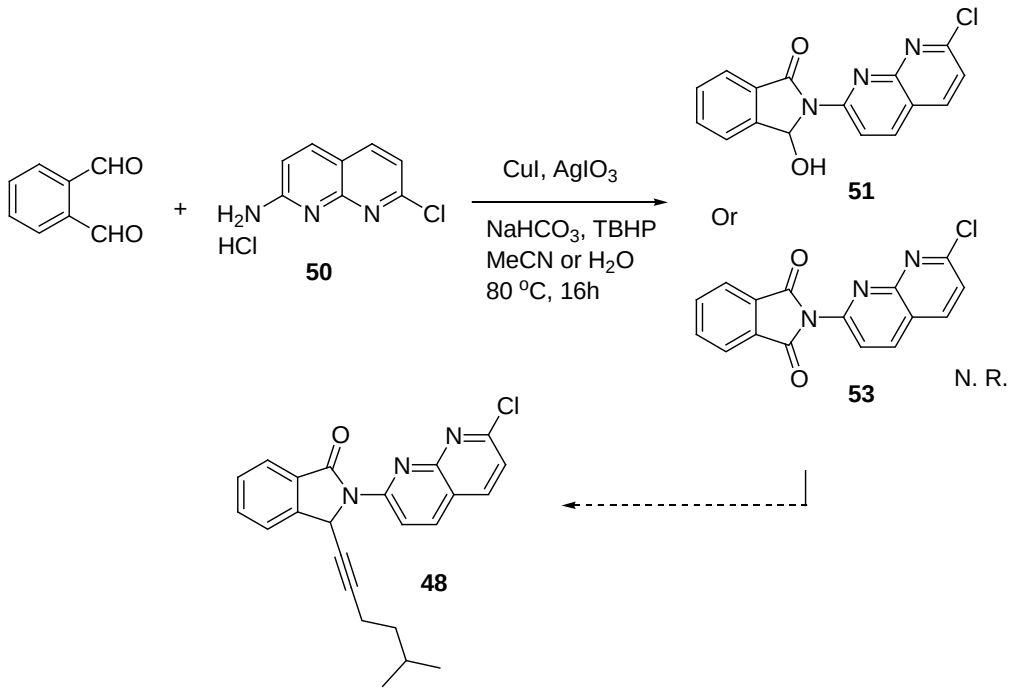
As demonstrated in Table 5, a variety of catalysts and conditions were examined, none of which has provided acceptable results. We suspected that the low insolubility of substrate **50** in apolar solvents may have a big impact in the reaction by preventing the formation of iminium ions, thus polar solvents such as THF and DMSO were used in order to solublize the aryl amine, unfortunately similar results were obtained. Based on previously published literature data[74], A-3 coupling in general does not favour polar solvents, which in many cases reduce the yield by producing excessive amount of side

products; in our specific case, the reaction could not proceed to any extent when being performed in polar solvent.

Upon several unsuccessful trials of the three-component tandem reaction, we changed our strategy to the two-component approach, by pre-forming the desired hydroxy-1-isoindolinone and react it with the acetylene, as shown in Scheme 44.

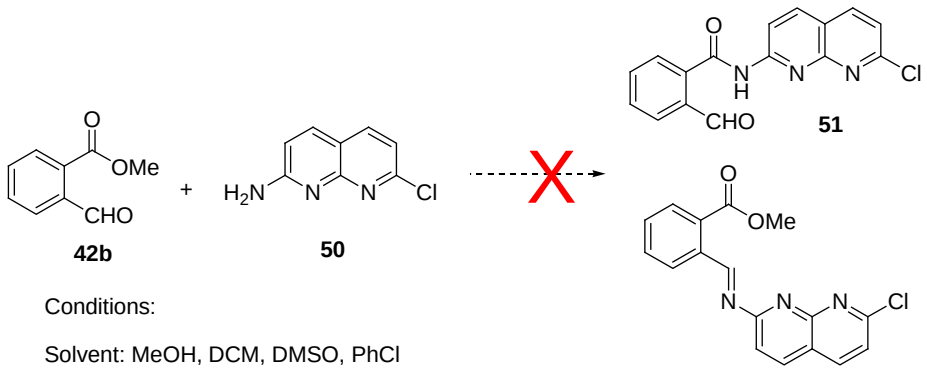



Scheme 44 Two-component tandem approach for the synthesis of pagoclone



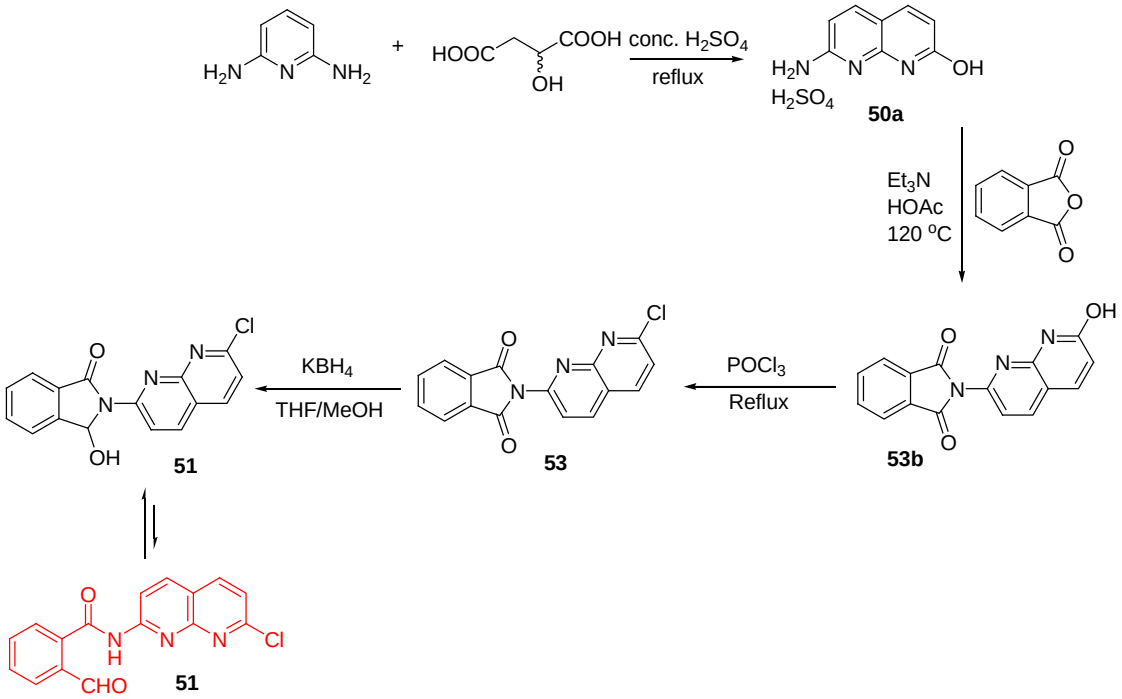

Scheme 45 Oxidative amidation approach for the synthesis of pagoclone

In 2006, C. J. Li and W. J. Yoo reported a copper-catalyzed oxidative amadation protocol for the formation of amides from aldehydes and amine HCl salts using TBHP as an oxidant (Scheme 45).[75] We tried to take advantage of this methodology by reacting *o*-phthaldialdehyde and 2-Amino-7-chloro-1,8-naphthyridine-HCl salt in the presence of $NaHCO_3$ as the base and TBHP as the oxidant, but we did not observe any reaction takes place. Under identical conditions, using the free base version of 2-amino-7-chloro -1,8-naphthyridine has offered same result.




Scheme 46 Attempt synthesis of +/- 2-(7-chloro-1, 8-naphthyridin-2-yl)-3-hydroxy-1-isoindolinone

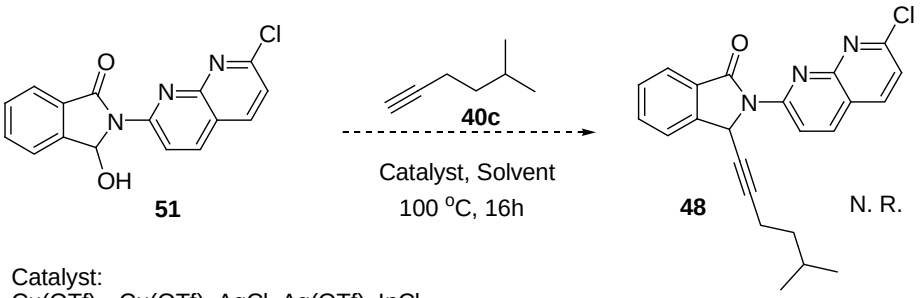
Direct amidation by reacting ester **42b** with naphthyridine **50** (Scheme 46) in the presence of drying agents also failed miserably. At this stage, we began questioning the nucleophilicity of naphthyridine **50** and sought for a new approach.




Scheme 47 Reported synthesis of +/- 2-(7-chloro-1,

8-naphthyridin-2-yl)-3-hydroxy-1-isoindolinone

The only well-established literature procedure for the synthesis of 2-(7-chloro-1, 8-naphthyridin-2-yl)-3-hydroxy-1-isoindolinone[72] is demonstrated in Scheme 47, despite that such route is tedious and has missed the point of green chemistry, but it worth the trial just for the reason of pure scientific examination. Compound **51** was synthesized in small quantities and subsequently subjected to transition metal catalyzed alkyne additon.



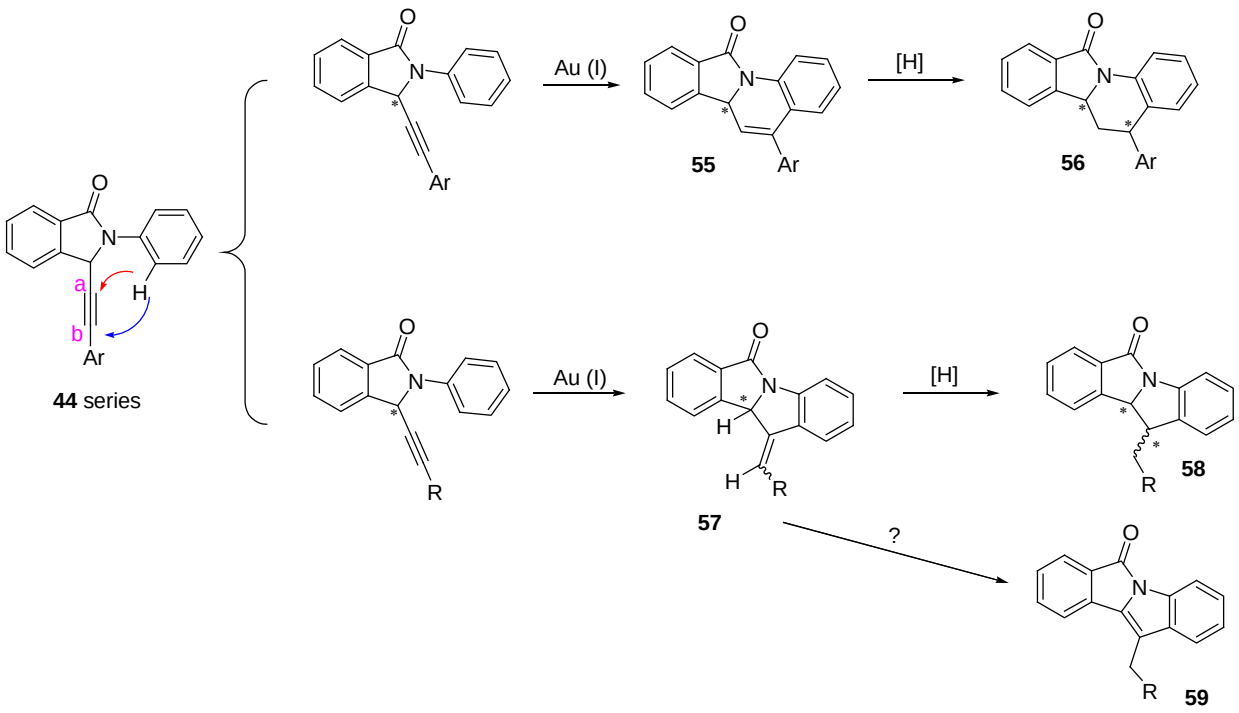

Catalyst:
$Cu(OTf)_2$, Cu(OTf), AgCl, Ag(OTf), $InCl_3$

Solvent:
PhMe, PhCl, DCM, DMSO, PhMe+MeCN

Scheme 48 Attempt two component tandem cyclization

Under similar methodology described in the three-component approach in Table 5, a variety of catalysts and solvents were examined for the two-component approach (Scheme 48), no desired product was detected via $^1$H NMR and GC-MS. We had to temporarily give up the effort in this synthetic practice and utilize the material in other transformations.

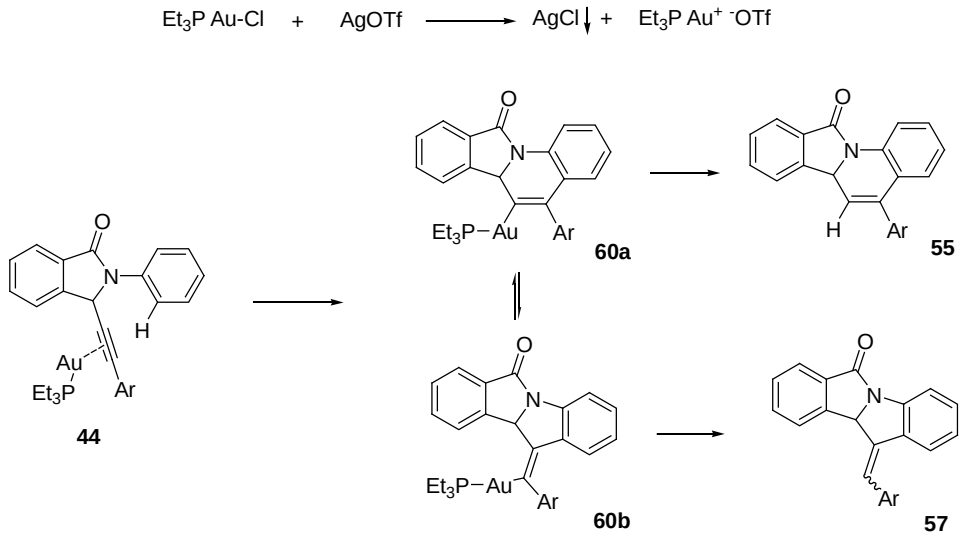
### 3.2.3 Gold Catalyzed Cyclization for the Synthesis of Isoindolo[2,1-a]quinolines



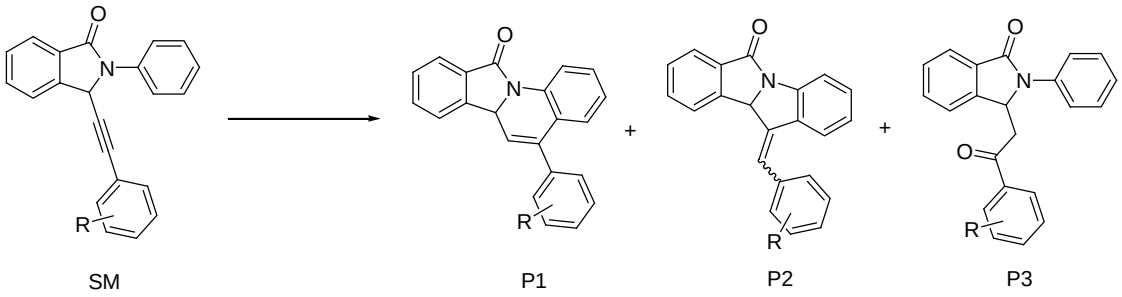

Scheme 49 Proposed outcome of gold catalyzed cyclization

Depending on the position of nucleophilic attack, two possible fused cyclic systems can be generated (Scheme 49). Based on the results obtained, we postulated that

the 5-membered and 6-membered gold intermediates are constantly co-existing in equilibrium as shown in Scheme 50; the specific conditions applied will determine the direction of equilibrium.




Scheme 50 Possible pathways of gold catalyzed cyclization




Scheme 51 Products generated from gold (I) catalyzed cyclization reaction

Table 6 Ratio of products formed from gold (I) catalyzed cyclization

| SM | Solvent | Catalyst | Temperature | Time | P1: P2: P3 |
|---|---|---|---|---|---|
| R = *para* | | 10 mol% | | | |

| | | | | | |
|---|---|---|---|---|---|
| *n*-butyl | PhMe | $Et_3PAuCl$, AgOTf | 80 $^oC$ | 48h | 61% : 13% : 26% |
| R = *para* *n*-butyl | PhMe | 10 mol% $Et_3PAuCl$, AgOTf | 25 $^oC$ | 3h | 10% : 80% : 10% |
| R = *para* *t*-butyl | DCM | 10 mol% $Et_3PAuCl$, AgOTf | 25 $^oC$ | 3h | 0 : 100% : 0 |

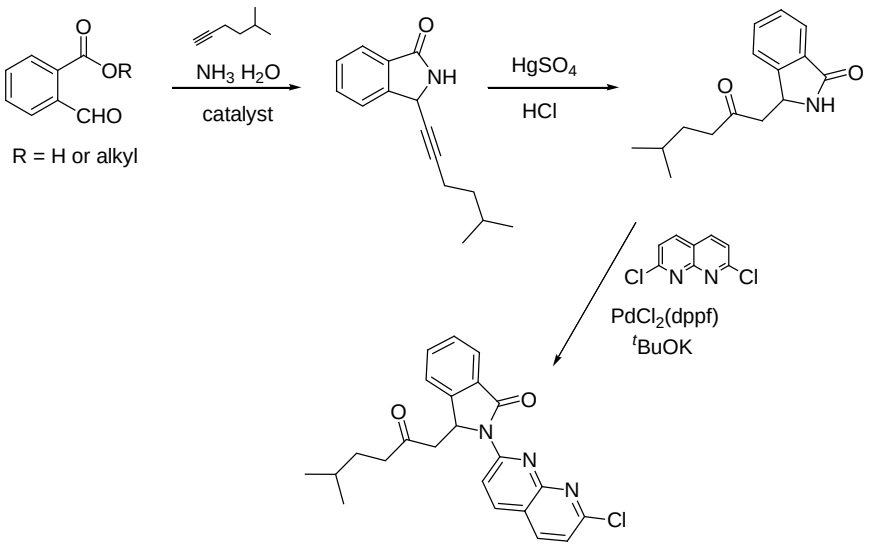
We have observed that under elevated temperature and extended period of reaction time, the thermal dynamic product (6-membered ring) is favoured; while under ambient temperature and shortened time, the kinetic product (5-membered ring) is favoured. Solvent also plays an important role in this transformation, for example dichloromethane has better regioselectivity than toluene. Due to time limitation we have not systematically examine the effect from aromatic substitution patterns in the substrate.

### 3.3 Summary and Future Work

In this chapter, we have demonstrated an efficient copper (II) catalyzed synthesis of various propargyl isoindolinone derivatives, and transformed them to isoindolo [2,1-a]quinolines under gold (I) catalysis. During this study, we also attempted to perform a one-pot, three-component tandem synthesis of medicinal compound pagoclone, however the proper conditions of transition metal catalyzed A-3 cyclization has not been found in this specific case, therefore the potential for efficient synthesis of pagoclone under such tandem methodology could not be properly evaluated at the moment.

For the future work, the scope of transition metal catalyzed A-3 coupling-cyclization should be further expanded to more fundamental substrates

including ammonium hydroxide as amine source and 2-carboxybenzaldhyde as the aldehyde source, the preferred solvent shall be water. One possible synthesis is outlined in Scheme 52, despite more steps was added, the benefits from using inexpensive, simple structured starting materials would counter balance the lost of step-efficiency. On the other hand, any loss in yield due to less refined tandem conditions at the primitive stage of the study is still more than made up for by the benefit of reduced purification steps.




Scheme 52 An example route to be explored for the synthesis of pagoclone

Last but not least, as an outlook for future development, chiral ligands should be introduced into the reaction in order to generate enantio- or diastereoselectivity. In the study of this thesis, we have only examined the catalytic power of various transition metals themselves, especially copper (II), how the ligand would affect their reactivity remains unknown, this should be explored in great details in the future work.

## Conclusions and Claims to Original Knowledge

Through the first research section of this thesis, we have successfully demonstrated the synthetic route of a novel phosphine oxide based NHC pincer ligand 1,3-bis(2-diphenylphophorylmethyl)-1H-imidazol-3-ium chloride and its corresponding di-phosphine counterpart 1,3-bis(2-diphenylphosphinomethyl)-1H-imidazol-3-ium chloride; we have also synthesized their silver (I), palladium (II), and rhodium (III) complexes. During the examination of their catalytic capability, we found that the NHC-Rh (III) have shown excellent results regarding ketone reduction to alcohols, while the NHC-Ag (I) catalyzed A-3 coupling and NHC-Pd (II) catalyzed conjugate additions showed low to mediocre yield. We postulated that the weak catalytic capability of NHC-Pd (II) case is caused by the rigid fused 5-membered metallacycle system, which results in high stability and therefore the difficult ligand-metal dissociation process prior to the oxidative insertion.

In the second section of this thesis, we have demonstrated an efficient copper (II) catalyzed synthesis of various propargyl isoindolinone derivatives, and their transformation to a series of isoindolo [2,1-a]quinolines under gold (I) catalysis. Based on this methodology, we were able to access a variety of complicated isoindolo-quinoline

structures from simple commercially available precursors.

Future work of the NHC pincer carbene project includes the further structural modification of the di-phosphine immidazolium ligand, such as introduction of stereogenic centres; and expansion of substrate scope of the NHC-Rh (III) catalyzed hydrogenation and NHC-Pd catalyzed conjugate addition. For the tandem synthesis of isoindolo-quinoline subject, it would be of great interest to further broaden the target scope to determine their usefulness in the synthesis of natural products.

# Chapter 4

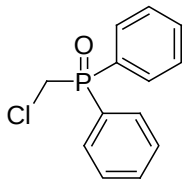
# Experimental Section

## General Experimental

All glassware used for moisture-sensitive reactions was flame-dried under vacuum and subsequently purged with nitrogen. Glassware was pre-dried in oven at 110$^{o}$C. All reagents were commercially available materials and were used without purification unless further specified. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Toluene and dichloromethane were distilled from calcium hydride. Standard column chromatography was performed on 20-60μm silica gel (obtained from Silicycle Inc.) or on SORBENT silica gel (30-60μm) using standard flash column chromatography techniques. Infrared analyses were recorded as a thin film on NaCl plates and solid compounds as KBr pellets. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on a Varian 400MHz and 100 MHz, or 300 MHz and 75 MHz NMR spectrometer, respectively. Chemical shifts for $^{1}$H NMR spectra were reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard (deuterated chloroform: δ 7.26 ppm, DMSO: 2.50 ppm). Chemical shifts for $^{13}$C NMR spectra were reported in parts per million (ppm) from tetramethylsilane with the

solvent resonance as the internal standard (deuterated chloroform: δ 77.0 ppm). MS data were obtained by using KRATOS MS25RFA Mass Spectrometer. HRMS-ESI measurements were performed at McGill University MS-laboratory.

**Experimental Procedures & Spectra Data**



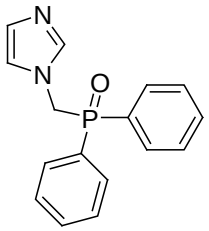

**8**

This compound was synthesized following a literature procedure [44] "Lawrence, N. J.; Liddle, J.; Jackson, D.; *J. Chem. Soc., Perkin Trans. 1,* **2002**, 2260-2267."

Step 1: Chlorodiphenylphosphine (6.1 g, 5 mL, 28 mmol) was added to 37% aq. Formaldehyde solution (50 mL, 617 mmol) and concentrated HCl (50 mL) and the mixture was heated at 100 $^{o}$C for 16h. Evaporation of the solvent at reduced pressure left an thick oil, which was neutralized with aq. $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layers were combined and dried over magnesium sulfate, filtered and concentrated in vacuo to afford the hydroxymethyldiphenylphosphine oxide (71% yield) as a white solid, mp 141-143 $^{o}$C. The product was purified by recrystalization in ethyl acetate. $^{1}$H NMR (300MHz; $CDCl_3$) 7.72-7.79 (4H, m), 7.43-7.58 (6H, m). 4.40 (2H, d, *J* = 0.9Hz); $^{13}$C{$^{1}$H}NMR (75MHz; $CDCl_3$) 132.12 (d, *J* = 2.2Hz), 131.33 (d, *J* = 10.5Hz), 130.49 (d, *J* = 96.7), 128.65 (d, *J* = 12Hz), 61.30 (d, *J* = 82Hz); *m/z* (FAB) 465 [$(2M + H)^{+}$, 7%], 233 [$(M + H)^{+}$, 100], 183 (7), 140 (23), 91 (7).

Step 2: Hydroxymethyldiphenylphosphine oxide (4.0 g, 17.24 mmol) was dissolved in DCM (25 mL). Thionyl chloride was added (2.5 mL, 34.26 mmol) and the solution was stirred for 3h at ambient temperature. The reaction was quenched with water (50 mL) and neutralized with aq. $NaHCO_3$ and extracted with DCM. The organic layers were combined and dried over magnesium sulfate, filtered and concentrated in vacuo to afford

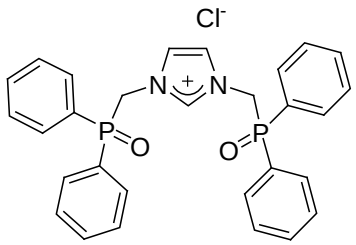
the compound **8** (66% yield) as a white solid, mp 133-135 $^{o}$C after recrystalization from ethyl acetate. $^{1}$H NMR (300MHz; $CDCl_3$) 7.78-7.85 (4H, m), 7.50-7.63 (6H, m), 4.05 (2H, d, *J* = 6.6Hz); $^{13}$C{$^{1}$H}NMR (75MHz; $CDCl_3$) 132.82 (d, *J* = 2.2Hz), 131.72 (d, *J* = 9.0Hz), 131.11 (d, *J* = 90Hz). 128.92 (d, *J* = 12Hz), 37.79 (d, *J* = 72Hz); *m/z* (FAB) 501 [(2M($^{35}$Cl) + H)$^{+}$, 4%], 251[(M($^{37}$Cl) + H)$^{+}$, 30], 251[(M($^{35}$Cl) + H)$^{+}$, 100], 215 (5), 183 (5), 91 (7).




**11**

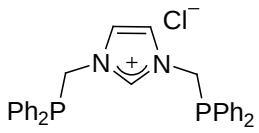
Under $N_2$ atmosphere, *t*BuOK (72 mg, 0.638 mmol, 1.07 eq) was dissolved in 3 mL of freshly distilled DMSO, to this solution was added imidazole (41 mg, 0.598 mmol, 1.00 eq) as solid. The resulting mixture was allowed to stir at ambient temperature for 30 min. To this reaction mixture was added chloromethyldiphenylphosphine oxide **8** (200 mg, 0.798 mmol, 1.33 eq) in 7 mL of freshly distilled DMSO dropwise. Upon completion of the addition, the reaction mixture was heated to 120 $^{o}$C for 10h, or until total consumption of SM (monitored by TLC). Upon completion of the reaction, the DMSO was removed under reduced pressure, DCM and water was added to the residue, the DCM phase was separated and washed with water, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by liquid column chromatography (Ethyl acetate 100% to 15% MeOH in DCM) afforded 144 mg pure **1** (85% yield). IR (KBr Disc)/cm$^{-1}$: $\nu_{max}$ 3479, 2950, 2364, 2344, 1508, 1438, 1229, 1185, 1157, 1026, 903, 820; $^{1}$H NMR (400MHz, DMSO-d$^{6}$, ppm): $\delta$ 7.83-7.79 (m, 4H), 7.61-7.51 (m, 6H), 7.43 (s, 1H), 6.94 (s, 1H), 6.76 (s, 1H), 5.27 (d, *J* = 6Hz , 2H); $^{13}$C{$^{1}$H}NMR (75MHz, DMSO-d$^{6}$, ppm): $\delta$ 138.5, 133.1 (d, *J* = 2.6Hz), 131.5 (d, *J* = 9.4Hz), 131.3 (d, *J* = 97.7Hz), 129.6 (d, *J* = 11.7Hz), 128.8, 120.9, 46.3 (d, *J* = 72.2Hz); $^{31}$P{$^{1}$H} NMR (80MHz, DMSO-d$^{6}$, ppm)

δ 25.9 (s); MS (EI) *m/z* (%) 283 ($M^+$), 201 (100), 199, 183, 152, 139, 91, 77, 68, 40; HRMS exact mass cacl'd for $C_{16}H_{16}ON_2P$ ([M+H]) *m/z* 283.1; found *m/z*: 283.0984.



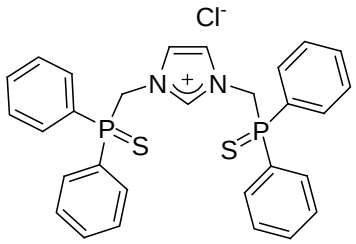

**9**

Compound **11** (40 mg, 0.1417 mmol, 1.0 eq) was homogeneously mixed with chloromethyl diphenylphosphine oxide **8** (106 mg, 0.4229 mmol, 3.0 eq) as solid, the solid mixture was heated to 200 $^oC$ and kept stirring for 40 min, monitored by $^1H$ NMR. Upon completion of the reaction the mixture was cooled down to ambient temperature, 5 mL of DCM was added to dissolve the solidified crude product; the resulting solution was allowed to air-dry in the fumehood, upon formation of crystal-like solid, minimum amount of DCM was added the suspension was filtered though a frit under vaccum. The filtered product was washed with 1mL of cold DCM and dried in vacuo. The filtrate still contains small amount of product and can be subjected to liquid column chromatography EtOAc 100% to 18% MeOH in DCM, gradient elution. The combined product was dried in vacuo. Afforded 62mg of **2** (83% yield). IR (KBr Disc)/$cm^{-1}$: $\nu_{max}$ 3388, 3128, 3082, 2981, 2923, 2883, 1672, 1648, 1439, 1207, 1117, 742, 620; $^1H$ NMR (400MHz, DMSO-$d^6$, ppm): δ 9.06 (s, 1H), 7.78-7.73 (m, 8H), 7.67-7.64 (m, 4H), 7.58-7.54 (m, 8H), 7.35 (d, *J* = 1.2 Hz, 1H), 5.63 (d, *J* = 6.4Hz, 4H); $^{13}C\{^1H\}$NMR (125MHz, DMSO-$d^6$, ppm): δ 137.20, 133.39, 131.31 (d, *J* = 10.3 Hz), 129.59 (d, *J* = 12Hz), 129.56 (d, *J* = 101Hz), 123.84, 48.29 (d, *J* = 67Hz); $^{31}P\{^1H\}$ NMR (80MHz, DMSO-$d^6$, ppm) δ 25.7 (s); HRMS exact mass cacl'd for $C_{29}H_{27}O_2N_2P_2$ ([M-H]) *m/z* 487.1621; found *m/z*: 497.1542.



**10**

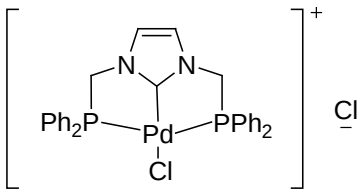
In a schlenk flask, under argon atmosphere, compound **2** (100 mg, 0.1876 mmol, 1.0 eq) was suspended into 5 mL of dried degassed toluene, $SiHCl_3$ (300 μL, 1.876 mmol, 10.0 eq) was added via a syringe and the flask was then sealed. The flask was heated at 120 $^oC$ for 10 h, upon completion of the reaction, the reaction mixture was cooled down to room temperature and subsequently quenched with degassed methanol. The entire reaction mixture was concentrated in vacuo and quickly subjected to liquid column chromatography 10% MeOH in DCM; the combined product was dried in vacuo, afforded 89mg of compound **3** (95% yield). $^1H$ NMR (400MHz, $CDCl_3$, ppm): δ 10.67 (s, 1H), 7.51-7.15 (m, 20H), 6.86 (d, 2H, *J* = 3.2Hz), 5.07 (d, 4H, *J* = 10.8Hz). $^{31}P\{^1H\}$ NMR (80MHz, $CDCl_3$, ppm) δ -11.82 (s); HRMS exact mass cacl'd for $C_{29}H_{27}N_2P_2$ ([M-H]) *m/z* 465.1628; found *m/z*: 465.1644.



**12**

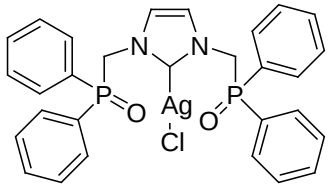
In a schlenk flask, under argon atmosphere, compound **9** (400 mg, 0.7506 mmol, 1.0 eq) was dissolved in 15 mL of anhydrous toluene at ambient temperature. To this solution was added Lawesson's regent (2, 4-bis(4-methoxyphenyl)-1, 3, 2, 4-dithiadiphosphetane -2, 4-disulfide, 607.2 mg, 1.5011 mmol, 2.0 eq) in three portions. The resulting reaction mixture was allowed to stir at ambient temperature for 3h, monitored by TLC. Upon

completion of the reaction, the volatile was removed under reduced pressure and the crude product was purified via liquid column chromatography (10% MeOH in DCM), afforded 381mg compound **12** (90% yield). $^{1}$H NMR (400MHz, DMSO-d$^{6}$, ppm): δ 8.98 (s, 1H), 7.91-7.86 (m, 8H), 7.68-7.65 (m, 4H), 7.61-7.58 (m, 8H), 7.10 (br s, 2H), 5.84 (d, 4H, *J* = 5.6 Hz). $^{31}$P{$^{1}$H} NMR (80MHz, DMSO-d$^{6}$, ppm) δ 41.36 (s); $^{13}$C{$^{1}$H}NMR (125MHz, DMSO-d$^{6}$, ppm) 137.3, 133.3, 131.8 (d, *J* = 10.6Hz), 129.7 (d, *J* = 12.5Hz), 129.1 (d, *J* = 81Hz), 123.4, 50.4 (d, *J* = 54Hz); HRMS exact mass cacl'd for $C_{29}H_{27}N_2P_2S_2^+$ ([M]) *m/z* 529.1085; found *m/z*: 529.1082.



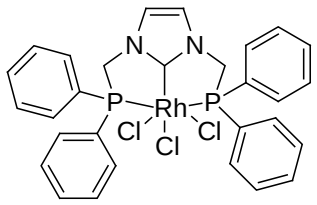

**19b**

In a schlenk flask, under argon atmosphere, compound **10** (100 mg, 0.1996 mmol, 1.0 eq) was dissolved in 2 mL of degassed anhydrous DCM, to this solution was added 35.4 mg $PdCl_2$, the reaction vessel was sealed and allowed to stir at ambient temperature for 16h. The reaction mixture was concentrated in vacuo and afforded 122 mg compound **19b** (95% yield). $^{1}$H NMR (400MHz, DMSO, ppm): δ 7.76-7.52 (m, 20H), 6.74 (s, 2H), 5.89 (s, *br*, 4H). $^{31}$P{$^{1}$H} NMR (80MHz, DMSO, ppm) δ 19.26 (s); $^{13}$C{$^{1}$H}NMR (125MHz, DMSO-d$^{6}$, ppm); 134.5, 132.4, 129.9, 129.2, 123.2, 114.9, 60.0; HRMS exact mass cacl'd for $C_{29}H_{26}N_2Cl_2P_2Pd$ ([M-H]) *m/z* 639.0057; found *m/z*: 639.0061.




**18a**

In the dark atmosphere, compound **9** (100 mg, 0.1876 mmol, 1.0 eq) was suspended in 2 mL anhydrous DCM and to this suspension was added $Ag_2O$ (22 mg, 0.0938 mmol, 0.5 eq) and the resulting mixture was allowed to stir at ambient temperature in the dark for 12h, monitored by TLC. Upon completion of the reaction, the reaction mixture was cooled to 0 $^oC$ and quickly filtered through celite and the volatiles was removed under reduced pressure. The product was triturated with DCM (2 X 0.5mL) and concentrated in vacuo. Afforded 117 mg product as brownish solid, 98% yield. $^1H$ NMR (500MHz, DMSO, ppm): δ 7.80-7.77 (m, 8H), 7.56-7.45 (m, 12H), 7.16 (s, 2H), 5.44 (s, 4H); $^{13}C\{^1H\}$NMR (75MHz, $CDCl_3$, ppm) 132.80 (d, *J* = 2.7Hz), 131.27 (d, *J* = 9.9Hz), 129.1 (d, *J* = 12.1Hz), 128.9 (d, *J* = 100.6Hz), 122.9, 51.4 (d, *J* = 69.8Hz); $^{31}P\{^1H\}$ NMR (80MHz, DMSO, ppm) δ 26.4 (s); HRMS exact mass cacl'd for $C_{29}H_{26}O_2N_2AgP_2$ ([M-H]) *m/z* 603.0513; found *m/z*: 603.0515.

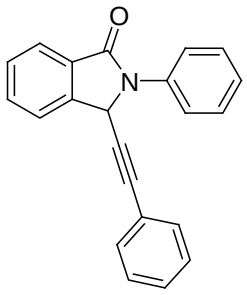



**20**

In a schlenk flask, under argon atmosphere, compound **10** (230 mg, 0.4591 mmol, 1.0 eq) was dissolved in 2 mL of degassed anhydrous ethanol, to this solution was added 96 mg $RhCl_3{\cdot}3H_2O$ (96 mg, 0.4588 mmol, 1.0 eq), the reaction was taken to reflux for 5 h. The reaction mixture was concentrated in vacuo and afforded 300 mg crude compound **20**. This crude product was further purified by mixed solvent recrystalization ($CHCl_3$/MeOH), afforded 290 mg compound **20** (94% yield). $^1H$ NMR (500MHz, DMSO, ppm): δ 7.98-7.97 (m, 7H), 7.73 (s, 2H), 7.73-7.39 (m, 13H), 5.39 (s, *br*, 4H). $^{13}C\{^1H\}$NMR (125MHz, $CDCl_3$, ppm) 133.59 (*t*, J = 6Hz), 131.05, 130.61, 129.59, 128.55 (*t*, 5Hz), 123.25, 55.37; $^{31}P\{^1H\}$ NMR (80MHz, DMSO, ppm) δ 38.8 (s);

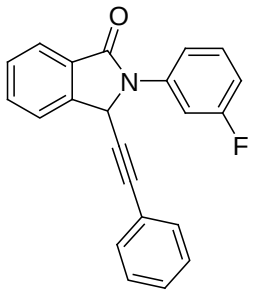
**General procedure of the synthesis of isoindolinones:**

Under argon atmosphere, acetylene (0.36 mmol), aniline (0.36 mmol), methyl 2-formylbenzoate (0.30 mmol), $Cu(OTf)_2$ (15 mol%) and anhydrous toluene was added into a tube and stirred at 100 $^oC$ for 12h. After the reaction, 15 mL of ethyl acetate was added into the tube and the entire reaction mixture was filtered through a short plug of silica. The filtrate was concentrated in vacuo and then subjected to liquid column chromatography (Hex : EtOAc = 7 : 1 to 5 : 1 gradient elution), the solvent of the combined fractions was removed under reduced pressure.



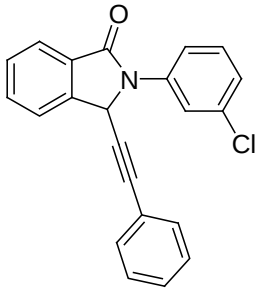

**44a**

$^1H$ NMR (400MHz, $CDCl_3$, ppm): δ 7.96 (d, 1H, *J* = 7.6Hz), 7.86 (dd, 2H, *J* = 7.8, 1.0 Hz), 7.72-7.68 (m, 2H), 7.58-7.45 (m, 3H), 7.32-7.26 (m, 6H), 6.04 (s, 1H). $^{13}C\{^1H\}$NMR (100MHz, $CDCl_3$, ppm) 166.7, 141.8, 137.7, 132.8, 131.8, 131.7, 129.3, 129.0, 128.9, 128.3, 125.3, 124.2, 123.0, 122.2, 121.7, 86.2, 83.5, 53.2; HRMS (ESI) exact mass cacl'd for $C_{22}H_{16}NO$ ([M+H]) *m/z* 310.1237; found *m/z*: 310.1230.



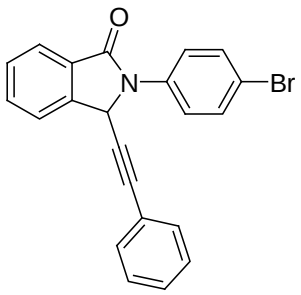

**44b**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 7.96 (d, 1H, *J* = 7.6Hz), 7.82-7.56 (m, 5H), 7.44-7.24 (m, 6H), 6.94 (td, 1H, *J* = 10.8, 2.6Hz), 6.00 (s, 1H); $^{13}$C{$^{1}$H}NMR (100MHz, $CDCl_3$, ppm) 165.6 (d, *J* = 211.8Hz), 161.3, 141.6, 139.3 (d, *J* = 13.9), 133.1, 131.8, 131.3, 130.1, 129.9, 129.4, 129.0, 128.3, 124.4, 123.1, 121.7, 116.6 (d, *J* = 4.3Hz), 111.8 (d, *J* = 27.9 Hz), 108.9 (d, *J* = 35.2 Hz), 86.5, 83.0, 53.1; HRMS (ESI) exact mass cacl'd for $C_{22}H_{13}NFO$ ([M-H]) *m/z* 326.0987; found *m/z*: 326.0988.



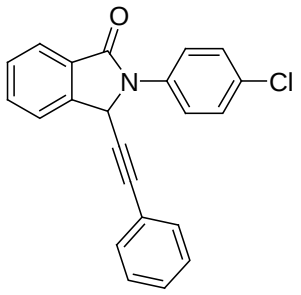

**44c**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 7.94 (d, 1H, *J* = 7.6Hz), 7.84 (d, 2H, *J* = 8.8Hz), 7.71-7.69 (m, 2H), 7.59-7.57 (m, 1H), 7.43 (d, 2H, *J* = 8.8Hz), 7.33-7.26 (m, 5H), 5.99 (s, 1H); $^{13}$C{$^{1}$H}NMR (100MHz, $CDCl_3$, ppm) 166.6, 141.6, 138.9, 134.6, 133.1, 131.8, 131.3, 129.9, 129.4, 129.0, 128.3, 125.1, 124.4, 123.1, 121.7, 121.5, 119.5, 86.6, 82.9, 53.0; HRMS (ESI) exact mass cacl'd for $C_{22}H_{15}ClNO$ ([M+H]) *m/z* 344.0837; found *m/z*: 344.0842.



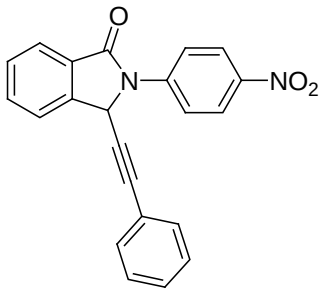

**44e**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 7.94 (d, 1H, *J* = 7.2Hz), 7.80 (d, 2H, *J* = 8.8Hz), 7.79-7.67 (m, 2H), 7.59-7.56 (m, 3H), 7.33-7.25 (m, 5H), 5.99 (s, 1H); $^{13}$C{$^{1}$H}NMR (100MHz, $CDCl_3$, ppm) 166.6, 141.6, 136.8, 133.0, 131.9, 131.8, 131.3, 129.4, 129.0, 128.3, 124.3, 123.2, 123.1, 121.5, 118.2, 86.5, 82.9, 52.9; HRMS (ESI) exact mass cacl'd for $C_{22}H_{15}BrNO$ ([M+H]) *m/z* 388.0332; found *m/z*: 388.0338.



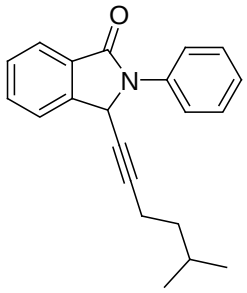

**44d**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 7.94 (d, 1H, *J* = 7.6Hz), 7.84 (d, 2H, *J* = 8.8Hz), 7.72-7.69 (m, 2H), 7.57-7.56 (m, 1H), 7.43 (dd, 2H, *J* = 7.0, 2.0Hz), 7.30-7.26 (m, 5H), 6.00 (s, 1H); $^{13}$C{$^{1}$H}NMR (100MHz, $CDCl_3$, ppm) 166.6, 141.6, 136.3, 132.9, 131.8, 131.3, 130.4, 129.4, 129.1, 128.8, 128.3, 124.3, 123.1, 122.9; HRMS exact mass cacl'd for $C_{22}H_{14}ONClNa$([M+H+Na]) *m/z* 366.0656; found *m/z*: 366.0664.



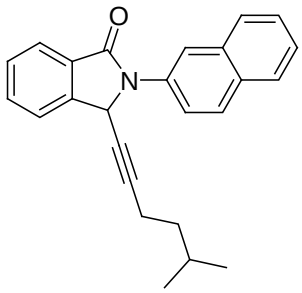
**44f**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 8.34 (dd, 2H, *J* = 7.2, 2.0 Hz), 8.19 (dd, 2H, *J* = 9.6, 2.0 Hz), 7.90-7.50 (m, 4H), 7.34-7.29 (m, 5H), 6.09 (s, 1H); $^{13}$C{$^{1}$H}NMR (100MHz, $CDCl_3$, ppm) 166.9, 143.6, 143.5, 141.5, 133.8, 131.8, 130.7, 129.7, 129.3, 128.4, 124.8, 124.6, 123.2, 121.1, 119.9, 87.1, 82.4, 52.7; HRMS (ESI) exact mass cacl'd for $C_{22}H_{13}N_2O_3$ ([M-H]) *m/z* 353.0932; found *m/z*: 353.0953.



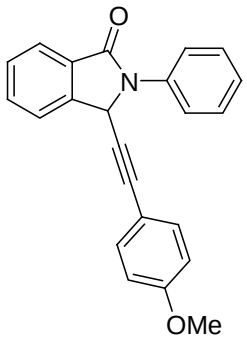
**44w**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 7.91 (d, 1H, *J* = 7.6Hz), 7.79 (d, 2H, *J* = 7.6Hz), 7.67-7.62 (m, 2H), 7.58-7.51 (m, 1H), 7.46-7.42 (m, 2H), 7.26-7.21 (m, 1H), 5.79 (s, 1H), 2.13-2.09 (m, 2H), 1.51-1.43 (m, 1H), 1.28-1.23 (m, 2H), 0.86-0.76 (m, 6H); $^{13}$C{$^{1}$H}NMR (75MHz, $CDCl_3$, ppm) 166.6, 142.4, 137.7, 132.6, 131.6, 128.9, 128.8, 125.1, 124.1, 122.9, 122.2, 87.3, 74.4, 52.9, 36.9, 26.9, 22.0, 21.9, 16.6; HRMS (ESI) exact mass cacl'd for $C_{21}H_{22}NO$ ([M+H]) *m/z* 304.1707; found *m/z*: 304.1698.



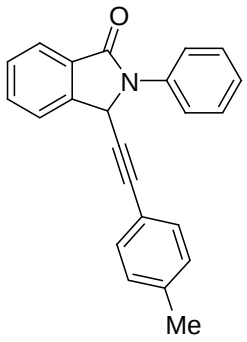
**44w2**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 8.18 (d, 1H, *J* = 2Hz), 8.02 (dd, 1H, *J* = 8.8Hz, 2.4Hz), 7.96-7.84 (m, 4H), 7.67 (dd, 1H, *J* = 2.8Hz, 1.2Hz), 7.58-7.44 (m, 3H), 5.94 (s, 1H), 2.10-2.06 (m, 2H), 1.38-1.33 (m, 1H), 1.25-1.18 (m, 2H), 0.68-0.64 (m, 6H); $^{13}$C{$^{1}$H}NMR (75MHz, $CDCl_3$, ppm) 166.6, 142.5, 135.3, 133.6, 132.6, 131.6, 131.1, 129.1, 128.6, 127.9, 127.5, 126.3, 125.5, 124.1, 122.9, 121.4, 119.8, 87.5, 74.5, 53.2, 36.9, 26.8, 21.8, 16.6; HRMS (ESI) exact mass cacl'd for $C_{25}H_{24}NO$ ([M+H]) *m/z* 354.1852; found *m/z*: 354.1851.



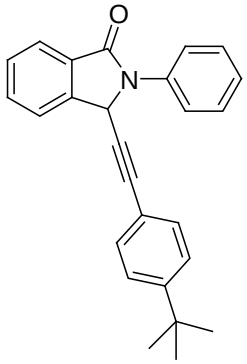
**44o**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 7.95 (d, 1H, *J* = 7.2Hz), 7.86 (d, 2H, *J* = 8Hz), 7.73-7.65 (m, 2H), 7.59-7.45 (m, 3H), 7.26-7.22 (m, 3H), 6.77 (d, 2H, *J* = 7.6Hz), 6.02 (s, 1H), 3.77 (s, 3H); $^{13}$C{$^{1}$H}NMR (75MHz, $CDCl_3$, ppm) 166.7, 159.9, 142.0, 137.7, 133.3, 132.7, 131.6, 129.2, 128.9, 125.3, 124.2, 123.0, 122.2, 113.9, 86.2, 82.0, 80.2, 55.3, 53.4; HRMS (ESI) exact mass cacl'd for $C_{23}H_{18}NO_2$ ([M+H]) *m/z* 340.1332; found *m/z*: 340.1333.



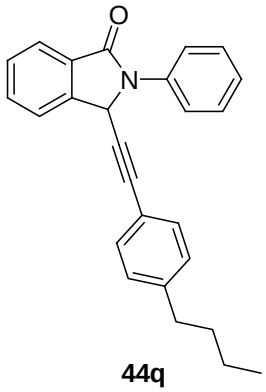

**44n**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 7.95 (d, 1H, *J* = 7.6Hz), 7.87 (d, 2H, *J* = 8Hz), 7.73-7.65 (m, 2H), 7.59-7.44 (m, 4H), 7.26-7.19 (m, 2H), 7.06 (d, 2H, *J* = 7.6Hz), 6.02 (s, 1H), 3.31 (s, 3H); $^{13}$C{$^{1}$H}NMR (75MHz, $CDCl_3$, ppm) 166.7, 141.9, 139.1, 137.7, 132.7, 131.7, 129.2, 129.1, 129.0, 128.9, 125.3, 124.2, 123.1, 122.2, 119.4, 118.7, 86.4, 82.8, 53.3; HRMS (ESI) exact mass cacl'd for $C_{23}H_{16}NO$ ([M-H]) *m/z* 322.1237; found *m/z*: 322.1231.



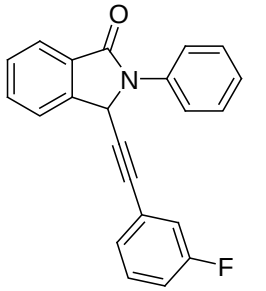

**44p**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 7.95 (d, 1H, *J* = 7.6Hz), 7.86 (d, 2H, *J* = 7.6Hz), 7.73-7.65 (m, 2H), 7.57(t, 1H, *J* = 7.6 Hz), 7.46 (t, 2H, *J* = 8.4Hz), 7.30-7.22 (m, 5H), 6.03 (s, 1H), 1.27 (s, 9H); $^{13}$C{$^{1}$H}NMR (75MHz, $CDCl_3$, ppm) 166.7, 152.2, 141.9, 137.7, 132.7, 131.7, 131.6, 129.2, 128.9, 125.3, 125.2, 124.2, 123.0, 122.2, 118.7, 86.3, 82.8, 53.4, 34.8, 31.1; HRMS (ESI) exact mass cacl'd for $C_{26}H_{23}NONa$ ([M+H+Na]) *m/z* 388.1672; found *m/z*: 388.1679.



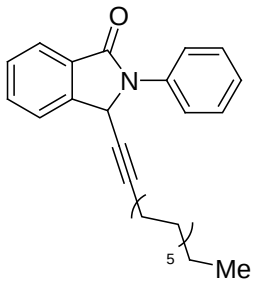
**44q**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 7.95 (d, 1H, *J* = 7.6Hz), 7.87 (d, 2H, *J* = 8Hz), 7.73-7.65 (m, 2H), 7.59-7.55 (m, 1H), 7.49-7.45 (m, 2H), 7.26-7.22 (m, 3H), 7.07 (d, 2H, *J* = 8Hz), 6.03 (s, 1H), 2.58-2.54 (m, 2H), 1.67-1.50 (m, 2H), 1.35-1.26 (m, 2H), 0.91-0.86 (m, 3H); $^{13}$C{$^{1}$H}NMR (75MHz, $CDCl_3$, ppm) 166.7, 144.1, 141.9, 137.7, 132.7, 131.7, 131.6, 129.2, 128.9, 128.4, 125.3, 124.2, 123.1, 122.2, 118.9, 86.4, 82.8, 53.3, 35.5, 33.3, 22.2, 13.9; HRMS (ESI) exact mass cacl'd for $C_{26}H_{23}NONa$ ([M+H]) *m/z* 388.1672; found *m/z*: 388.1678.



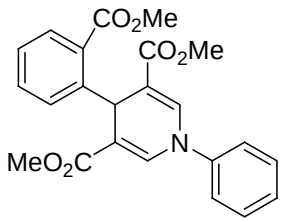
**44t**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 7.97-7.83 (m, 3H), 7.71-7.66 (m, 1H), 7.60-7.41 (m, 4H), 7.27-7.20 (m, 2H), 7.07 (d, 1H, *J* = 8Hz), 7.02-6.03 (m, 2H), 6.03 (s, 1H), 4.86 (s, 1H); $^{13}$C{$^{1}$H}NMR (75MHz, $CDCl_3$, ppm) 166.6, 141.5, 137.5, 132.8, 131.6, 129.9, 129.3, 129.2, 129.1, 129.0, 127.7, 127.6, 125.4, 124.3, 122.9, 122.1, 119.4, 118.6 (d, *J* = 22.5), 116.4, 116.3 (d, *J* = 21.9Hz), 84.5 (d, *J* = 29Hz), 53.1; HRMS (ESI) exact mass cacl'd for $C_{22}H_{13}NFO$ ([M-H]) *m/z* 326.0987; found *m/z*: 326.0995.



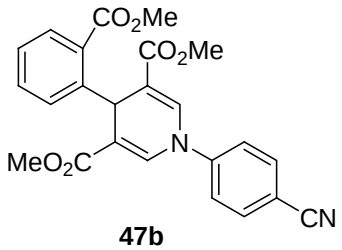

**44v**

$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 7.91 (d, 1H, *J* = 7.6Hz), 7.80 (d, 2H, *J* = 7.6Hz), 7.64 (d, 2H, *J* = 2.4Hz), 7.55-7.52 (m, 1H), 7.46-7.42 (m, 2H), 7.26-7.20 (m, 1H), 5.80 (s, 1H), 2.13-2.08 (m, 2H), 1.38-1.78 (m, 20H), 0.93-0.87 (m, 3H); $^{13}$C{$^{1}$H}NMR (75MHz, $CDCl_3$, ppm) 166.7, 142.4, 137.7, 134.4, 132.6, 131.5, 128.9, 128.8, 126.6, 125.1, 124.1, 123.7, 122.9, 122.1, 87.4, 74.5, 52.9, 31.9, 29.6, 29.4, 29.0, 28.6, 28.2, 22.7, 18.6, 14.1; HRMS (ESI) exact mass cacl'd for $C_{28}H_{36}ON$ ([M+H]) *m/z* 402.2791; found *m/z*: 402.2801.



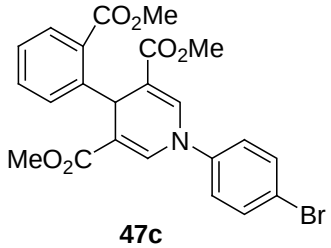

**47a**

$^{1}$H NMR (500MHz, $CDCl_3$, ppm): δ 7.75 (dd, 1H, *J* = 8Hz, 1.5Hz), 7.68 (s, 2H), 7.48-7.40 (m, 5H), 7.32-7.28 (m, 2H), 7.21 (m, 2H), 6.10 (s, 1H), 3.99 (s, 3H), 3.60 (s, 6H); $^{13}$C{$^{1}$H}NMR (75MHz, $CDCl_3$, ppm) 168.5, 167.0, 146.8, 143.0, 136.1, 131.9, 130.2, 130.1, 129.9, 129.7, 126.4, 126.3, 120.6, 111.4, 51.9, 51.4, 32.9; HRMS (ESI) exact mass cacl'd for $C_{23}H_{22}O_6N$ ([M+H]) *m/z* 408.1442; found *m/z*: 408.1439.




**47b**

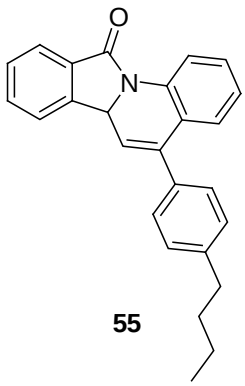
$^{1}$H NMR (400MHz, $CDCl_3$, ppm): δ 7.78-7.73 (m, 5H), 7.43-7.36 (m, 3H), 7.25-7.21 (m, 2H), 6.14 (s, 1H), 3.98 (s, 3H), 3.62 (s, 6H); $^{13}C\{^{1}H\}$NMR (75MHz, $CDCl_3$, ppm) 168.3, 166.5, 145.8, 145.7, 134.1, 134.0, 131.9, 130.3, 130.2, 129.9, 126.6, 119.8, 118.1, 113.5, 109.1, 52.02, 51.66, 32.97, 31.58, 22.65, 14.12; HRMS (ESI) exact mass cacl'd for $C_{24}H_{20}O_6N_2Na$ ([M+H+Na]) *m/z* 455.1214; found *m/z*: 455.1206.




**47c**

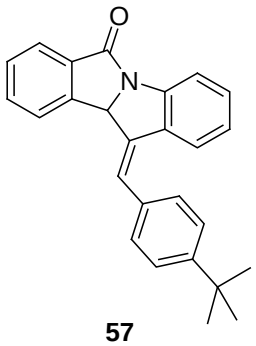
$^{1}$H NMR (500MHz, $CDCl_3$, ppm): δ 7.75 (d, 1H, *J* = 8Hz), 7.62 (s, 2H), 7.57 (dd, 2H, *J* = 6.8Hz, 2Hz), 7.42 (d, 2H, *J* = 4.4Hz), 7.21-7.18 (m, 3H), 6.10 (s, 1H), 3.98 (s, 3H), 3.60 (s, 6H); $^{13}C\{^{1}H\}$NMR (75MHz, $CDCl_3$, ppm) 168.4, 166.9, 146.5, 142.0, 135.5, 133.0, 131.9, 130.2, 130.1, 129.7, 129.4, 126.4, 122.0, 111.9, 51.9, 51.5, 32.8; HRMS (ESI) exact mass cacl'd for $C_{23}H_{20}O_6NBrNa$ ([M+H+Na]) *m/z* 508.0366; found *m/z*: 508.0371.

**General procedure of the synthesis of Isoindolo[2,1-a]quinolines**



**55**

Isoindolinone compound **44q** (51 mg, 0.1395 mmol, 1.0 eq) was dissolved in 2 mL of anhydrous toluene at ambient temperature, to this solution was added $Et_3P$-Au-Cl (5 mg, 0.0143 mmol, 0.1 eq) and Ag(OTf) (4 mg, 0.0156 mmol, 0.1 eq) and the resulting mixture was stirred at 80 $^oC$ for 48h, monitored by TLC. Upon total consumption of starting material, the volatiles were removed under reduced pressure. The crude product was purified by liquid column chromatography (Hex : EtOAc = 5 : 1), afforded 31 mg of compound **55** (61%). $^1H$ NMR (500MHz, $CDCl_3$, ppm): δ 9.06 (d, 1H, *J* = 8Hz), 7.94 (dt, 1H, *J* = 7.5Hz, 1Hz), 7.65 (d, 1H, *J* = 7.5Hz), 7.59 (td, 1H, *J* = 7.3, 1.5Hz), 7.53 (td, 1H, *J* = 7.5Hz, 1Hz), 7.33-7.28 (m, 1H), 7.24-7.05 (m, 6H), 6.05 (d, 1H, *J* = 4.5Hz), 4.97 (d, 1H, *J* = 4.5Hz), 2.57 (t, 2H, *J* = 8Hz), 1.60-1.52 (m, 2H), 1.39-1.31 (m, 2H), 0.93-0.89 (m, 3H); $^{13}C\{^1H\}$NMR (125MHz, $CDCl_3$, ppm) 165.4, 142.4, 141.8, 134.3, 133.8, 132.2, 132.1, 130.4, 130.2, 129.9, 128.9, 128.3, 127.7, 126.1, 124.9, 123.5, 119.6, 117.6, 107.8, 43.8, 35.2, 33.6, 22.4, 13.9; HRMS (ESI) exact mass cacl'd for $C_{26}H_{24}ON$ ([M+H]) *m/z* 366.1852; found *m/z*: 366.1864.



**57**

Isoindolinone compound **44p** (51 mg, 0.1395 mmol, 1.0 eq) was dissolved in 2 mL of anhydrous DCM at ambient temperature, to this solution was added $Et_3P$-Au-Cl (5 mg, 0.0143 mmol, 0.1 eq) and Ag(OTf) (4 mg, 0.0156 mmol, 0.1 eq) and the resulting mixture was stirred at ambient temperature for 3h, monitored by TLC. Upon total consumption of starting material, the volatiles were removed under reduced pressure. The crude product was purified by liquid column chromatography (Hex : EtOAc = 5 : 1), afforded 50 mg of compound **57** (99%). $^1$H NMR (400MHz, $CDCl_3$, ppm): δ 8.12 (d, 1H, 8.4Hz), 7.97-7.95 (m, 1H), 7.64-7.38 (m, 7H), 7.26 (d, 1H, *J* = 6.4Hz), 7.09 (t, 2H, *J* = 6.4Hz); $^{13}$C{$^1$H}NMR (125MHz, $CDCl_3$, ppm) 166.7, 151.1, 142.9, 139.5, 135.5, 135.2, 132.5, 132.1, 128.9, 128.6, 128.5, 127.9, 127.1, 125.3, 124.6, 124.5, 123.2, 121.9, 121.8, 58.5, 34.6, 31.3; HRMS (ESI) exact mass cacl'd for $C_{26}H_{24}ON$ ([M+H]) *m/z* 366.1852; found *m/z*: 366.1850.

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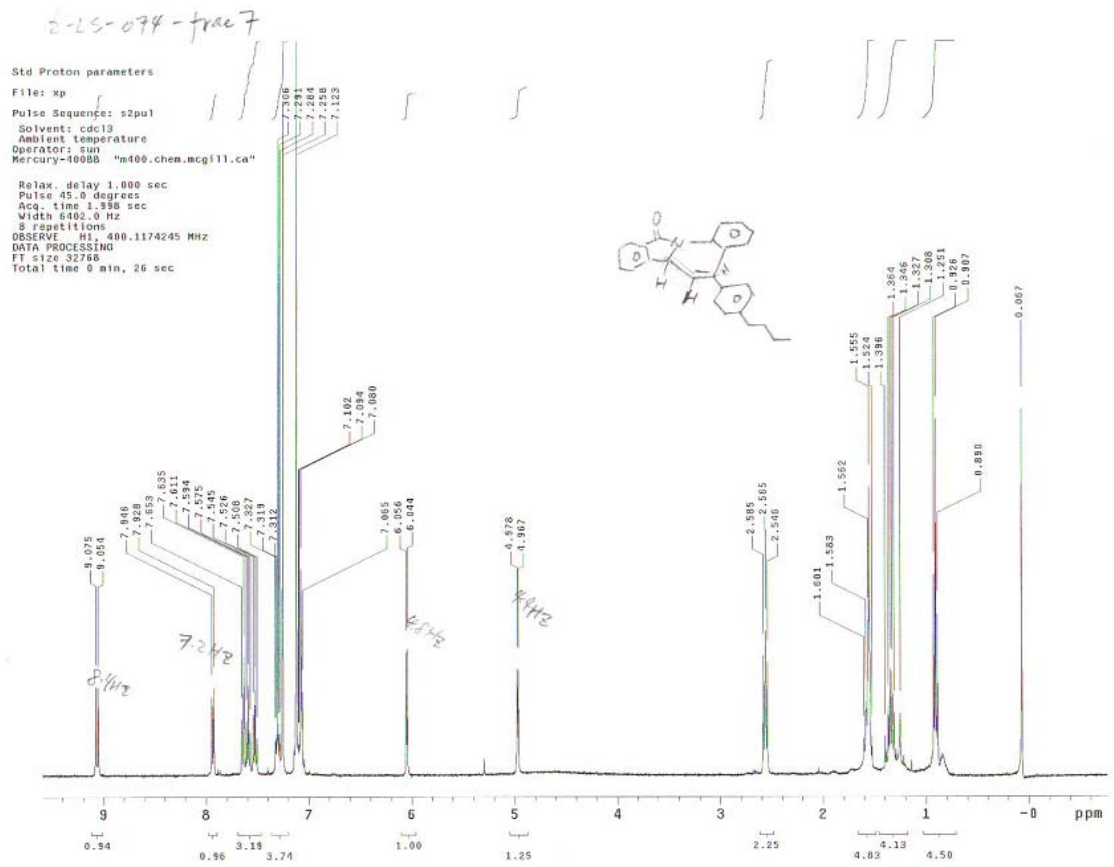
## Vita

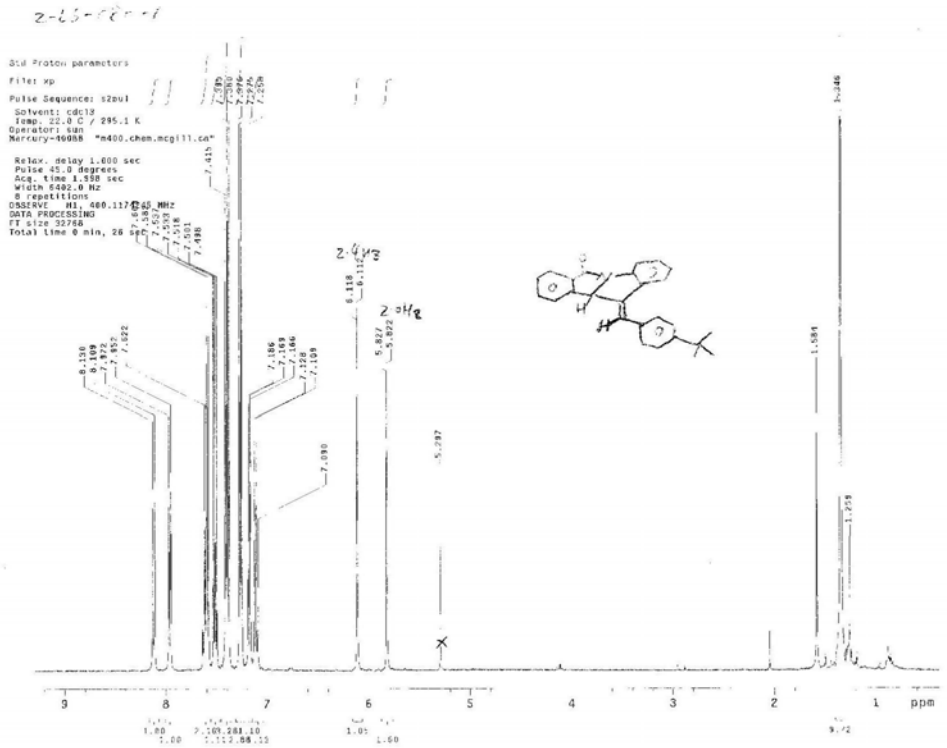
Leon Xuetong was born on October 12th, 1983 in Jinan, ShanDong, China. He moved to Canada in 2002 and completed his Bachelor of Science Degree in Chemistry at Brock University, Ontario in 2008 under the supervision of Prof. Thomas Hudlicky; he then started his graduate studies under the supervision of Professor Chao-Jun Li at McGill University, Quebec. He is currently completing his Master of Science Degree in Chemistry.

# Appendix

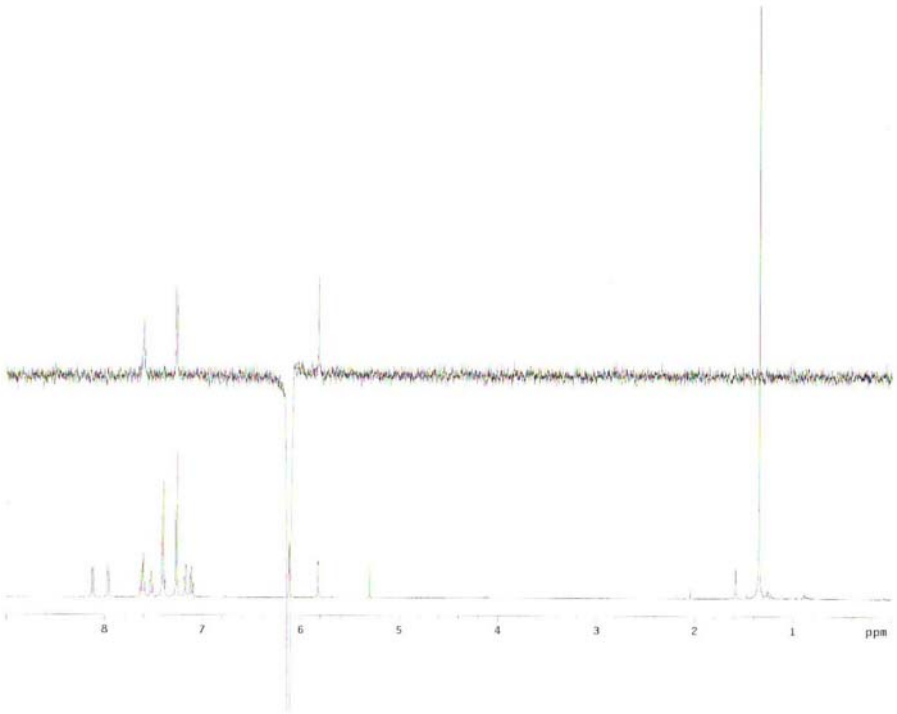
## (Selected 1H NMR Spectra)

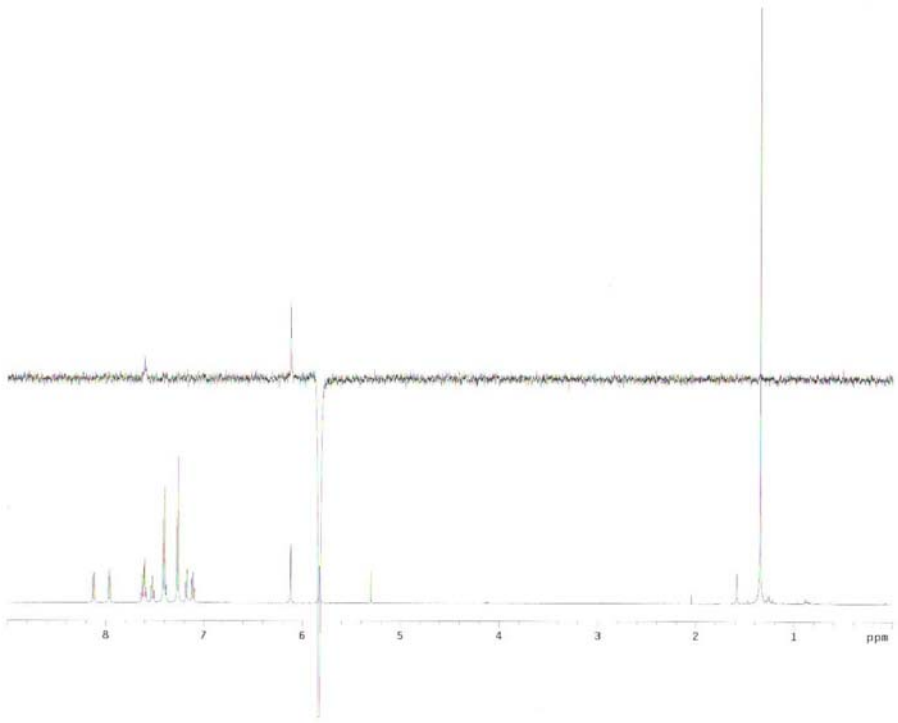
$^{1}$H NMR of compound **12a**, **13b**:




Std Proton parameters
File: xp
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 22.0 C / 295.1 K
Operator: sun
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 6402.0 Hz
8 repetitions
DATA PROCESSING
FT size 32768
2.4Hz
2.0Hz
9
8
7
6
5
4
3
2
1
ppm

1D-NOE test of **13b**:




8
7
6
5
4
3
2
1
ppm