2-Hydroxypyridine-Ligated Pd-complexes as pre-catalysts in Hydrogen Borrowing Chemistry

α -Alkylation of Ketones Using Alcohols

Master of Science Thesis

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Popular scientific summary

In certain parts of chemistry, it is important to be able to design organic molecules so that they have exactly same structure that you are looking for. C-C bond formation is very important reaction in synthesis of products such as pharmaceuticals, natural products, agrochemical and in the plastics industry. There are variety of organic reactions that can be used to couple and build molecules differently.

Recently, there has been great interest in using alcohols as starting materials for C-C bond formation processes. As they are less toxic, cheap, environmentally friendly. Alcohols are readily available alkylating agents however they are unreactive as alkylating agents because hydroxy group cannot be easily replaced by nucleophilic reagents. The common ways to convert alcohols to carbonyl compounds is by using wide range of oxidizing agents in stoichiometric and over stoichiometric amount by using metal oxides or metal salts for oxidation. These procedures produce heavy metal waste that is not compatible with environmental regulations. Therefore, the search for environmentally friendly, selective, and efficient methods is a great challenge for chemists. Metal catalyzed dehydrogenation or oxidative dehydrogenation have been found an interesting alternative. Catalysis has become one of the cornerstones in organic synthesis, as it increases the rate of a chemical reaction, theoretically without being consumed itself. This occurs by lowering the activation energy compared to uncatalyzed reaction.

Transition metal catalyzed cross coupling reaction between alcohols and ketones is attractive strategy for alpha alkylation of ketone. 2-Hydroxy pyridine ligands have been found to catalyze hydrogenation and dehydrogenation reactions. Therefore, the aim of the project is to prepare 2-hydroxy pyridine and quinoline ligands then coupled with palladium chloride to study hydrogenation and dehydrogenation reactions between alcohols and ketones. An advantage of this reaction is it follows borrowing hydrogen approach for α-alkylation of benzyl alcohol with acetophenone and produces water as only byproduct which is in accordance with green chemistry. The reaction is proceeding via hydrogen transfer strategy and alcohols are source of hydrogen.

The reactions were performed without additional additives under mild reaction conditions using KOtBu, 1-Pd catalyst in toluene at 120^{o}C for 48 hours under nitrogen in carousal. The reaction proceeds via dehydrogenation reaction, aldol condensation and hydrogenation processes using hydrogen borrowing approach.

Acknowledgements

I would first like to thank my supervisor Magnus Johnson for accepting me as a Master student in his research group where I learned a lot, struggled and had a fantastic time during my stay.

I would like to thank S. Manojveer for being helpful and guiding the project, for making me learn a lot regarding chemistry, research and experimental techniques and the project itself was interesting.

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Table of Contents

Abstract

An efficient method for selective alpha-alkylation of ketones with alcohols was developed using 2-hydroxypyridine-based ligands coordinated by palladium as pre-catalysts. The reactions were performed without additional additives under mild reaction conditions. The method is environmentally friendly to build C-C bond as water is the only byproduct. This tandem reaction proceeds via dehydrogenation reaction, aldol condensation and hydrogenation processes using hydrogen borrowing from the alcohols. The pre-catalyst was characterized by NMR, IR and XRD. Time profile study investigated by NMR and GC.

Abbreviations

$CDCl_3$ Deuterated Chloroform

MeOH Methanol

EtOH Ethanol

DCM Dichloromethane

MeCN Acetonitrile

EtOAc Ethyl Acetate

C Carbon

DMF Dimethylformamide

$AlCl_3$ Aluminum Chloride

KOH Potassium Hydroxide

n-BuLi n-Butyl lithium

$NaBH_4$ Sodium Borohydride

$PdCl_2$ Palladium Chloride

THF Tetrahydrofuran

TFA Trifluoro-acetic Acid

NMR Nuclear magnetic resonance

DMSO Dimethyl sulfoxide

ESI Electrospray ionization

XRD X-Ray Diffractometer

MHz Megahertz

TLC Thin layer chromatography

K_2CO_3 Potassium carbonate

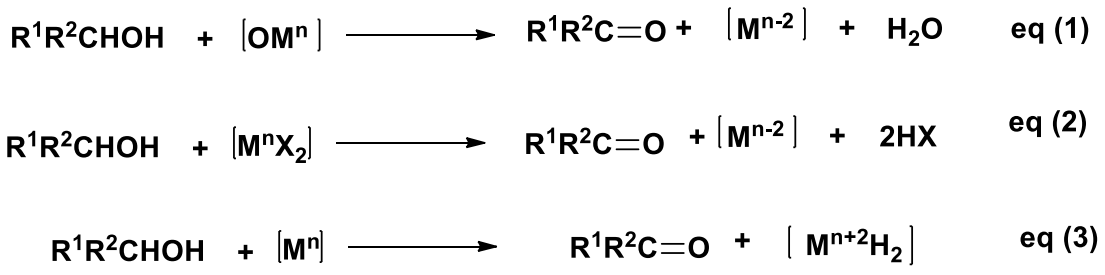
Equiv. Equivalent

1.Introduction

1.1 C-C Bond Formation

C-C bond formation through exploiting the reactivity of the carbonyl functionality is a very important reaction in synthesis of products such as pharmaceuticals, natural products, agrochemical and in the plastics industry. Aldol reaction, Grignard reaction, Diels-Alder reaction, Heck reaction, Michael reaction and Wittig reaction are some common ways to form C-C bond. Carbonyl compounds, such as aldehydes and ketones play a very important role in this context as they can participate in different reactions due to their carbonyl functional group, and the acidity of the α-hydrogen, to form C-C bonds.

Recently, there has been great interest in using alcohols as starting materials for C-C bond formation processes. This is because they are less toxic, abundant, cheap, easy to handle and store. Additionally, they are often more environmentally friendly and renewable alternatives to petroleum based compounds. Alcohols are readily available alkylating agents however they are unreactive as alkylating agents because hydroxy group cannot be easily replaced by nucleophilic reagents. Therefore, alcohols have to be used in the form of halides, tosylates, triflates, sulfonates etc. The common ways to convert alcohols to carbonyl compounds is by using wide range of oxidizing agents in stoichiometric and over stoichiometric amount by using metal oxides (eq. 1) or metal salts (eq. 2) for oxidation. These procedures produce heavy metal waste that is not compatible with environmental regulations. Therefore, the search for environmentally friendly, selective, and efficient methods is a great challenge for chemists. Metal catalyzed dehydrogenation or oxidative dehydrogenation have been found an interesting alternative (eq. 3).



Traditional cross coupling reaction for alkylation require unfriendly organic or organometallic coupling partner, and in some cases dangerous chemical materials. Alcohols are readily available alkylating agents. Although several alkylating compounds have been explored, still there is need to develop readily available alkylating agents and catalytic system for carbon alkylation, secondary alcohols and related compounds.

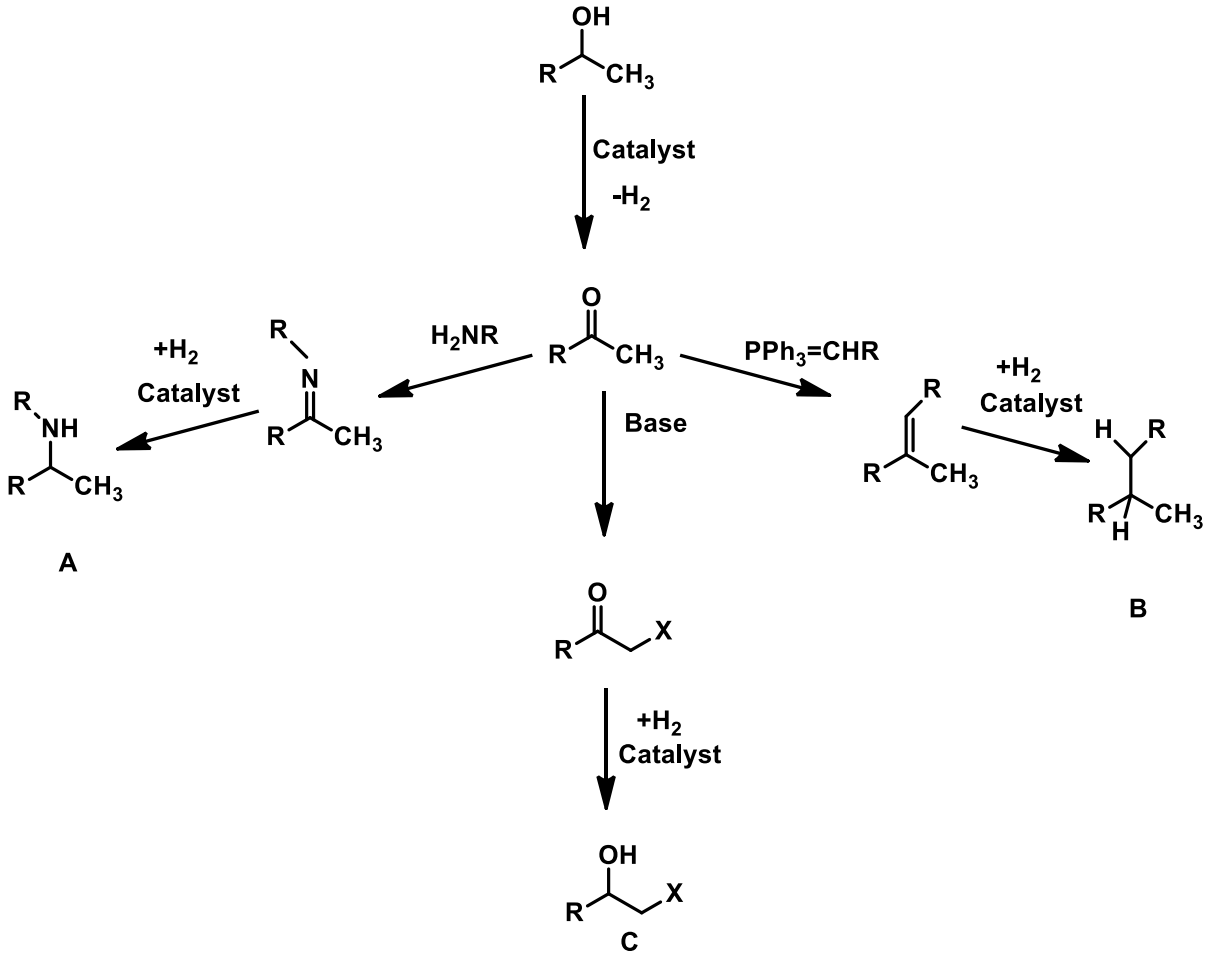
Recently, transition metal catalyzed cross coupling reaction between alcohols and ketones is attractive strategy for alpha alkylation of ketone as it produces water as only byproduct which is in accordance with green chemistry. The reaction is proceeding via hydrogen transfer strategy and alcohols are source of hydrogen, which has been paid much attention recent years. [1]

1.2 Catalysis

Catalysis has become one of the cornerstones in organic synthesis, as it increases the rate of a chemical reaction, theoretically without being consumed itself. This occurs by lowering the activation energy compared to uncatalyzed reaction. Homogeneous catalysis has the advantage of often being selective towards one reaction, while functioning at mild reaction conditions. Transition metal catalysts are often used to transform unreactive C-H bonds (C-H activation) into C-X (X usually N, O, C or halogen), and is an attractive area of research as it can be applied to reduce energy input on an industrial scale. Through catalysis, it is further possible to reduce the amount of waste and side products.

1.3 Hydrogen Borrowing in activation of alcohols

As reagents, alcohols are highly versatile and can react in many ways. Classically, the reactivity can be increased by addition of base or acid. In hydrogen borrowing, the activation method is through temporary conversion of alcohol to carbonyl by dehydrogenation, as the carbonyl compounds are more reactive than the corresponding alcohols. The oxidation process as an activation method can be performed catalytically if the final carbonyl compound is reduced in the end, thus the name hydrogen borrowing. Some examples of such activation reaction are given in Scheme 1. The additional reactivity is due to formation of alkene, imine and enolization. [2]



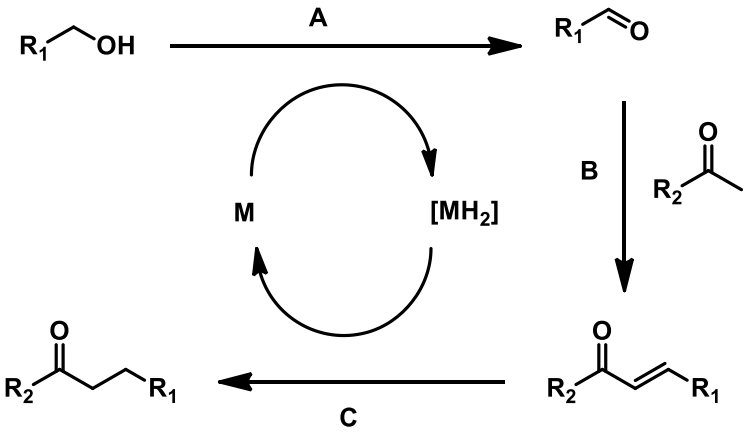
Scheme 1. Alcohol activation by borrowing hydrogen method.

(A) Imine formation and reduction to amine. (B) Alkene formation and reduction to alkane.

(C) Enolization, Electrophilic trap and reduction.

Classical methods for the interconversion of alcohols to carbonyl compounds using oxidants is typically not environmentally friendly. However, in hydrogen borrowing approach there is no waste product other than water. The hydrogen is transferred from the substrate and returned to the final product, thus the name hydrogen borrowing.

The dehydrogenation of alcohols using transition metal catalysis is a very clean and straightforward way to alkylate various substrates. The metal catalyst after removing hydrogen from alcohol keep temporarily with it and return it to unsaturated product at last stage of reaction. In this way, new C-C bond is formed through a process called borrowing hydrogen or hydrogen auto transfer catalysis with loss of water that is only by product, Scheme 2. [3]

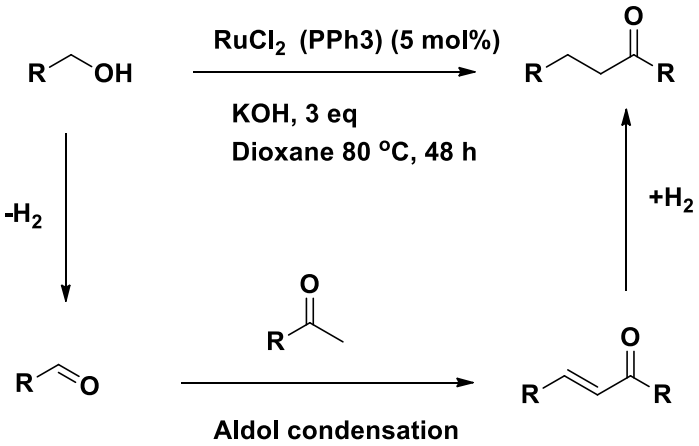


Scheme 2. The borrowing hydrogen concept (A) Dehydrogenation (B) Condensation

(C) Hydrogenation.

The condensation of dehydrogenated alcohols with ketones catalyzed by transition metal complexes has been shown very important method for synthesizing alkylated ketones. Traditionally, metal oxides or metal salts are used for such reactions, but are generally less efficient. Following on from pioneering work done by Grigg and coworkers, the hydrogen borrowing approach has been investigated by different groups. A variety of transition metal catalysts, including $RuCl_2(DMSO)_4$, $Ir(cod)Cl_2/PPh_3$, Pd/C and $RuHCl(CO)(PPh_3)_3$, have been investigated for alpha alkylation of carbonyl compounds using alcohols. The reactions are generally conducted in the presence of base. Recent achievement in the transition metal catalyzed alpha-alkylation of nitriles, acetonitriles, esters and acetoamides have been studied using alcohol as alkylated partner via hydrogen borrowing approach [21]. The environmentally friendly Guerbet reaction converts aliphatic alcohols to *β*-alkylated alcohols with water as the only byproduct. However, the Cannizzaro reaction can be a competing reaction [4].

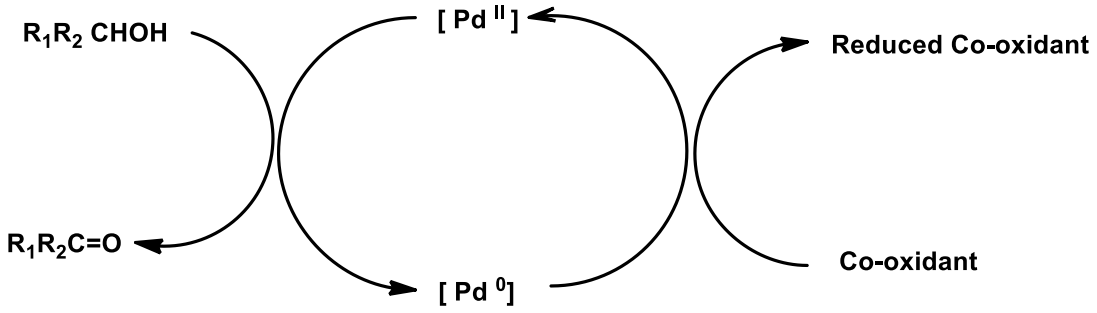
Cho, Shim and coworkers have used $RuCl_2$-$(PPh_3)_3$ for alkylation of acetophenone with benzyl alcohol, Scheme 3 [5].



Scheme 3. Alkylation reaction by using Ruthenium catalyst.

1.4 Palladium in Catalysis

The transformation of the hydroxy group to a carbonyl group is a frequently used reaction in organic chemistry. Palladium have been widely used as catalyst for oxidation of primary and secondary alcohols. Such oxidations require stoichiometric and over stoichiometric amounts of metal salts and oxides and generate metal containing waste. An alternative is oxidative dehydrogenation using metal catalysts. In general, during catalysis Pd(II) is reduced to Pd(0), and therefore it requires stoichiometric amount of co-oxidant. Oxygen, hydrogen peroxide, halogen based co-oxidants and metal salts have commonly been used as oxidants, Scheme 4.



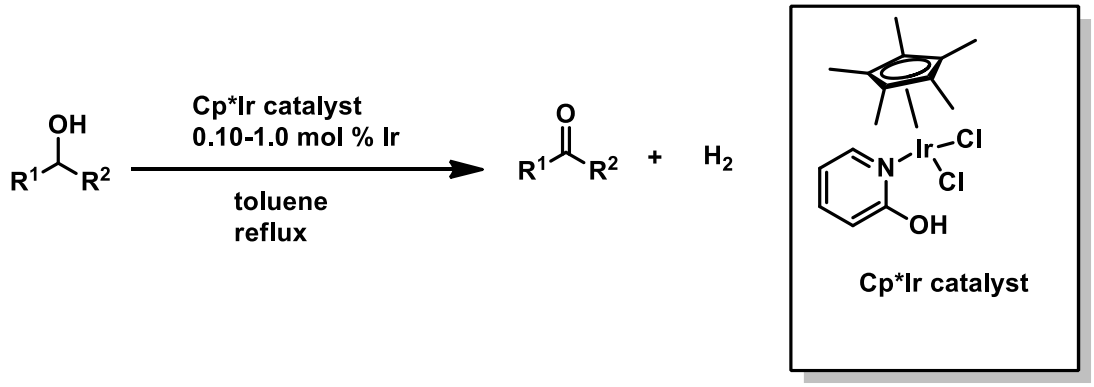
Scheme 4. Palladium catalyzes oxidation of alcohols.

Since the discovery of stoichiometric oxidation of alcohols by Pd(II), different methods have been developed using only catalytic amount of palladium to give high yield of carbonyl compounds. [6]

Palladium catalysts have been used for alkylation reaction for alcohols and ketones, with Pd/C and palladium nanoparticles being able to catalyze the reaction. An interesting catalyst developed by Park and co-workers for alkylation reaction using Pd/AlO(OH) composed of palladium nanoparticles entrapped in aluminum hydroxide. With this system range of ketones were alkylated with various alcohols. When this reaction was performed in the presence of Pd/AlO(OH) (0.2 mol%) and K_3PO_4 in toluene at 80 ^oC under Ar, corresponding alkylated product was 92%. When reaction was conducted under an atmosphere oxygen (1atm) instead of Ar, the oxygen acted as hydrogen acceptor, and chalcone was selectively obtained in 95%. [7,8]

1.5 Project aim and scope

In catalysis, the ligand plays a very important role with respect to the activity of the catalyst. This in turns affect the selectivity and products of the reaction. The ligand environment around the metal plays a significant role for the activity of the catalyst. Oxidant free dehydrogenative system for oxidation of alcohols using different metal catalysts is great area of research. Catalytic system bearing 2-hydroxypyridine ligand have been investigated by different research groups on the concept of ligand promoted dehydrogenation. Yamaguchi and co-workers investigated ligand promoted dehydrogenation of alcohols by Cp*Ir complexes (Scheme 5 and 6).

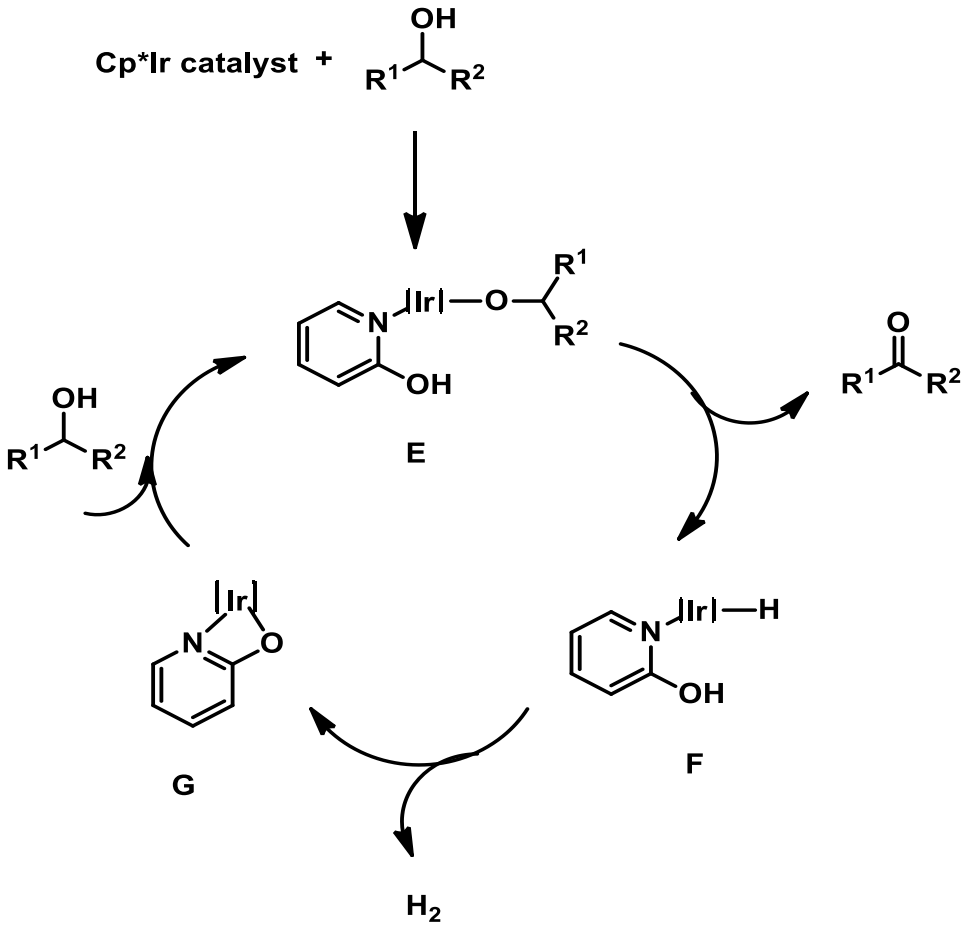


Scheme 5. Dehydrogenation of alcohols by Cp*Ir catalyst bearing 2-hydroxypyridine.

They synthesized new Cp*Ir complexes bearing hydroxy pyridine ligands and developed an efficient system for oxidation of alcohols under mild reaction conditions with high turnover number. They also investigated that chelated iridium complex acts as highly active catalyst supporting the catalytic cycle. [9]

The first step is formation of an alkoxy iridium intermediate E by reaction of alcohol with Cp*Ir catalyst. β-hydrogen elimination of **E** gives ketone product and iridium hydride species **F**. The formation of dihydrogen accompanied by formation of 2-hydroxypyridinate chelated intermediate **G**. (Scheme 6)

Considering that 2-hydroxy pyridine system work for dehydrogenation of alcohols we started to design and develop new bidentate ligands containing 2-hydroxy pyridine for dehydrogenation of alcohols. In this way, we can tune and optimize the catalytic activity. We found that 2-hydroxypyridine ligands facilitates both hydrogenation and dehydrogenation reactions, through their cooperative abilities.



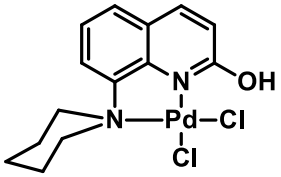
Scheme 6. Proposed mechanism for dehydrogenation of alcohols by Cp*Ir catalyst bearing 2-hydroxypyridine. [9]

Therefore, the aim was to synthesize new bidentate ligands containing 2-hydroxypyridine and 2-hydroxyquinoline, to study the hydrogenation and dehydrogenation reactions. We decided to optimize the reaction conditions to get good yield using different bases, catalysts, solvents and temperature. Further, we used optimized conditions to explore different substrates using hydrogen borrowing concept for hydrogenation and dehydrogenation reactions. We also studied acceptorless dehydrogenative coupling of benzyl alcohols using palladium catalyst.

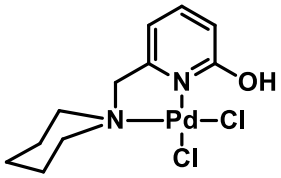
2. Preparation of catalysts

2.1 General remarks about synthesis of catalysts

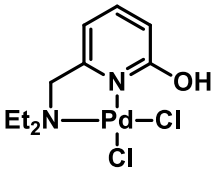
The synthesis of palladium catalysts 1,2 and 3 involved many steps using literature procedures Scheme 7.



Catalyst 1



Catalyst 2



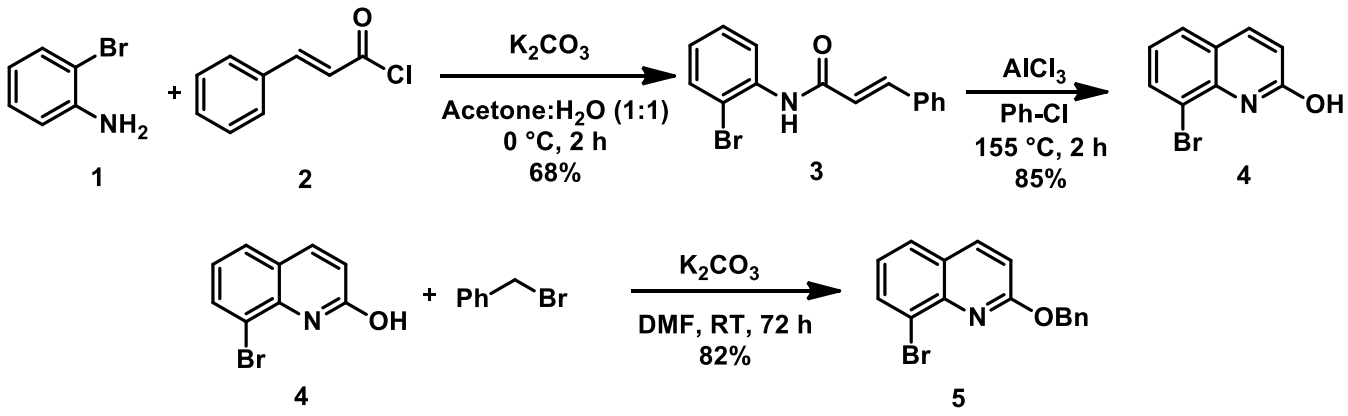
Catalyst 3

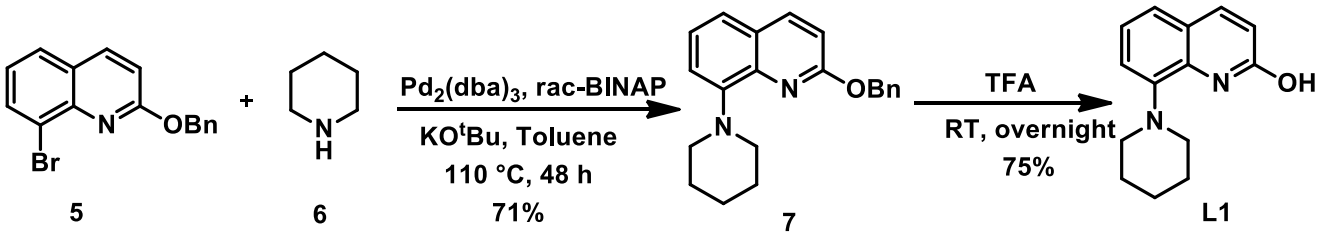
Scheme 7. Catalyst 1, 2 and 3 bearing 2-hydroxy pyridine ligands.

2.2 Synthesis of catalyst 1

2.2.1 Synthesis of 2-hydroxyquinoline Ligand (L.1) and 1-(Pd) catalyst

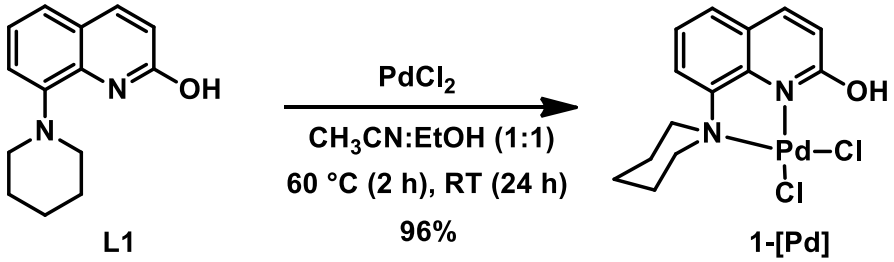
The synthetic route for preparation of ligand 1 is shown in scheme 8. The first step is preparation of amide from bromoaniline **1** and cinnamoyl chloride **2** which takes place by nucleophilic attack on carbonyl group, followed by amide cyclization. The protection of hydroxy group was done by using benzyl bromide in the presence of potassium carbonate. The Pd catalyzed C-N coupling reaction between compound **5** with piperidine gave product **7** after 48 h reflux at 110^{o} C.





Scheme 8. Synthetic route for preparation of ligand 1.

The deprotection of compound 7 with TFA yielded ligand L-1 (8- (piperidine 1-yl) quinoline-2-ol). The complexation of ligand-1 with $PdCl_2$ was performed in EtOH:CH_3CN (1:1) at 60 ^{o} C and then 24h only stirring at room temperature, Scheme 9.

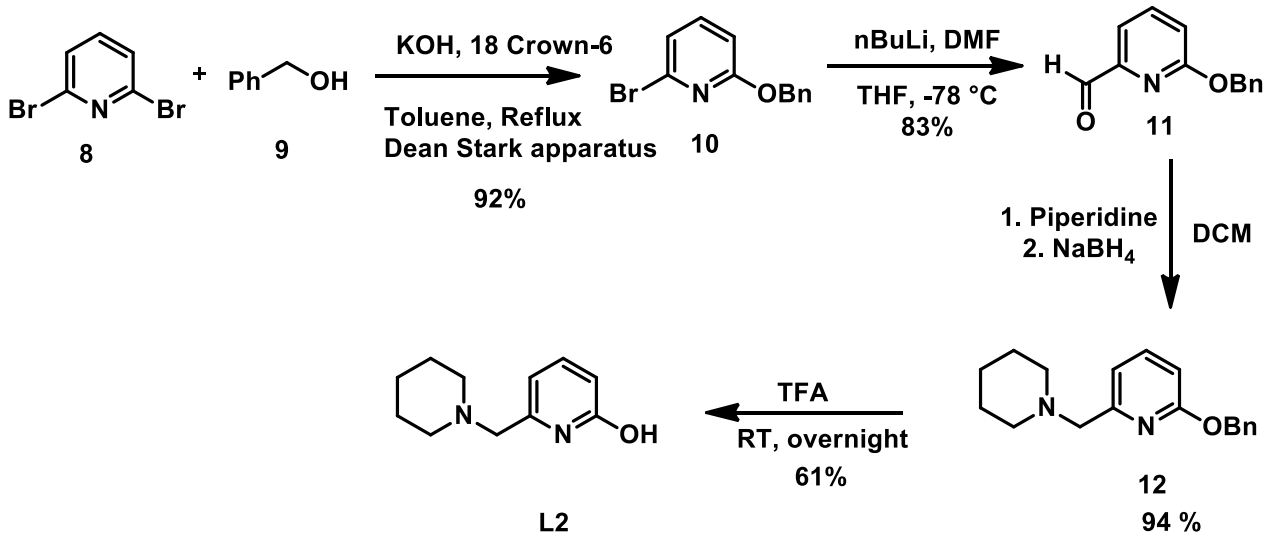


Scheme 9. Synthesis of catalyst 1.

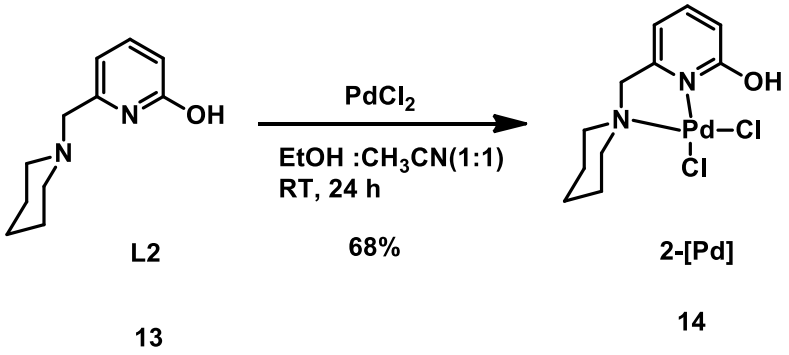
2.3 Synthesis of Catalyst 2

2.3.1 Synthesis of 2-hydroxypyridine Ligand (L.2) and 2-(Pd) catalyst

The preparation of L-2 involved different steps. The first step is reaction between 2,6-dibromopyridine with benzyl alcohol using Dean-Stark apparatus to remove water to get compound 10. The compound 11 was synthesized in the presence of n-BuLi at -78^{o}C. Reductive amination of 11 with piperidine and debenzylation of 12 gave the final ligand L. 2 (6-(piperidine-1-yl methyl pyridine-2-ol), Scheme 10. The final complex is prepared by reaction of 13 with palladium chloride in ethanol and acetonitrile, scheme 11.



Scheme 10. Synthetic route for preparation of ligand 2.

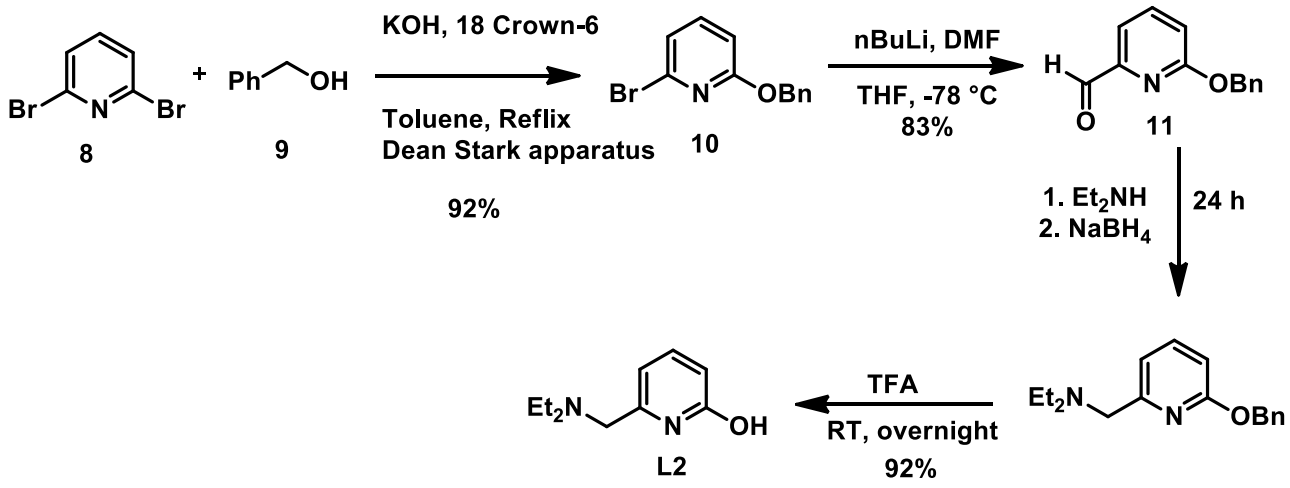


Scheme 11. Synthesis of catalyst 2.

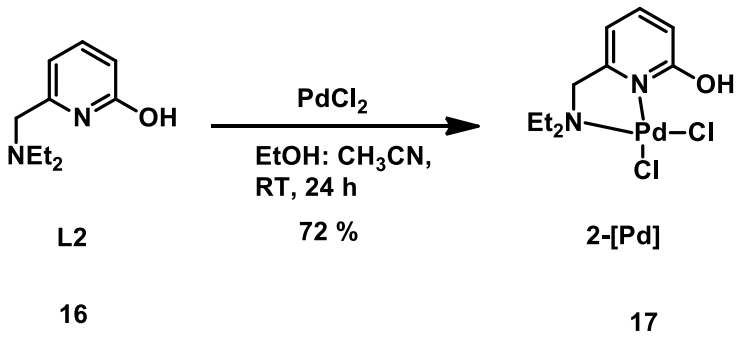
2.4 Synthetic route for preparation of catalyst 3

Synthesis of 2-hydroxypyridine Ligand (L.3) and 3-(Pd) catalyst

The synthetic route for ligand-3 is like that of ligand-2. The first step is the reaction between 2,6-dibromopyridine with benzyl alcohol using Dean-Stark apparatus to remove water and to get compound **10**. The compound **11** was synthesized in the presence of n-BuLi at -78 ^{o}C. Reductive amination of **11** with diethyl amine and debenzylation of **15** gave final ligand L.3 (6-((diethylamino) methyl) pyridine-2-ol) scheme 12. The final complex is prepared by reaction of 16 with palladium chloride in ethanol and acetonitrile, scheme 13.



Scheme 12. Synthetic route for preparation of ligand 3.



Scheme 13. Synthesis of catalyst 3

3. Experimental Section

The laboratory experimental work was done by using standard laboratory equipment's, Schenk line and high vacuum line for drying. ^{13}C and ^{1}H-NMR measurements were made on a Bruker 400 MHz NMR spectrometer with deuterated solvents, primarily deuterated chloroform. GC-MS measurements were carried out by Agilient 6890 GC coupled to an Agilent 5973 mass detector with ESI. XRD has been used for conformation of complexes formation. Detection and separation of compounds during ligand preparation was performed by using glass TLC plates with silica gel 60 F254-coating. Column chromatography was used for separation of compounds. Solvents in synthesis were used from solvent dispenser containing minimal amount of water, typically 3-15 ppm.

3.1 Preparation of catalyst-1

The preparation catalyst-1 involved 6 steps. In this section, all experimental steps are described in detail.

1- 1 equivalent (2000 mg) of 2-Bromoaniline and 1.02 equivalent (1972 mg) of Cinnamyl Chloride were dissolved in acetone and water (1:1) and cooled in ice bath. K_2CO_3 was 1.5 equivalent (2.4 g) added under cooled conditions. Reaction mixture was stirred at same temperature for 2 hours. The reaction mixture was poured in water and precipitates were filtered and washed with petroleum ether. White precipitates were dried in vacuum. Yield: 1.75 g (68%). [10, 11]

2- 1 equivalent (1.75 g) of N (2-Bromo Phenyl) Cinnamide and 5.1 equivalent (3.87g) of $AlCl_3$ was refluxed at 155^oC for 2h. The starting material was consumed after 2h checked with TLC then reaction mixture was poured in ice cold water. The precipitate was collected and dried under vacuum. Yield: 0.99 g (77%). [12]

3- 1.2 equivalent (0.72 g) of K_2CO_3 was added to solution of 8-Bromoquinoline 1 equivalent (0.99 g) in DMF at room temperature and stirred for 15 minutes. 1.01 equivalent (0.76 g) of benzyl bromide was added to reaction mixture and allowed to stir at room temperature for 72 h. The compound was extracted with ethyl acetate and dried with $MgSO_4$.Column purification with petroleum ether gave 1.15 g (84 %). [13]

4- 1 equivalent (0.5 g) of 2-(Benzyloxy)-8-bromoquinoline, 0.1 eq (0.098 g) of rac-BINAP, 0.1 eq (0.035 g) of Palladium acetate, 1.2 eq (0.162 g) of piperidine and 1.5 eq (0.0267 g) of KOtBu in toluene at room temperature. Air from reaction mixture was removed and refilled with nitrogen. Reaction mixture was stirred at 110^oC for overnight. Work up with ethyl acetate and Column purification with petroleum ether. Yield: 0.35 g (70 %) as orange precipitates. [14]

5- 1 equivalent (0.15 g) of 2-Benzyloxy-8-Pipridine-1-yl Quinoline and 3 ml of TFA was added and stirred for overnight. After neutralizing with $NaHCO_3$ work up was done with DCM and column purification with petroleum ether. Yield :0.08 g (80 %) as white precipitates.

6- Palladium chloride 1 equivalent (0.058 g) and 1.2 equivalent (0.08 g) in ethanol and acetonitrile heated at 50 ^oC under nitrogen and then stirred at room temperature overnight. Add petroleum ether and stirred for some time. Decant the solvent and dry precipitates under vacuum. Yield: orange precipitates 0.15 g (96%).

The complex has been successfully isolated, the structure has been determined by IR, ^1H and ^{13}C NMR spectroscopy and XRD.

IR (cm^{-1}): 3356, 2927, 2806, 1648, 1602, 1567, 1462, 1395, 1335, 1271, 1257, 1035, 1005, 975, 863, 849, 832, 747, 715, 667, 620.

^1H NMR ($CDCl_3$, 400 MHz) δ, 9.70(s, 1 H), 7.94 (d, J = 9.6Hz, 1 H), 7.45(d, J = 8.0 Hz, 2 H), 7.19 (t, J = 7.6 Hz, 1 H), 6.55 (d, J = 9.6Hz, 1 H), 2.80(br s, 4 H) 1.76 (br m, J = 5.3 Hz, 6 H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 162.75 (s), 141.21 (s), 140.59 (s), 133.60 (s), 123.88 (s), 122.82 (s), 122.52 (s), 122.00 (s), 120.43 (s), 54.29 (s), 26.59 (s), 24.11 (s).

3.1.1 Crystal structure of ligand 1

Space group: P-1
C1-N1: 1.379Å
C1-O1: 1.232Å

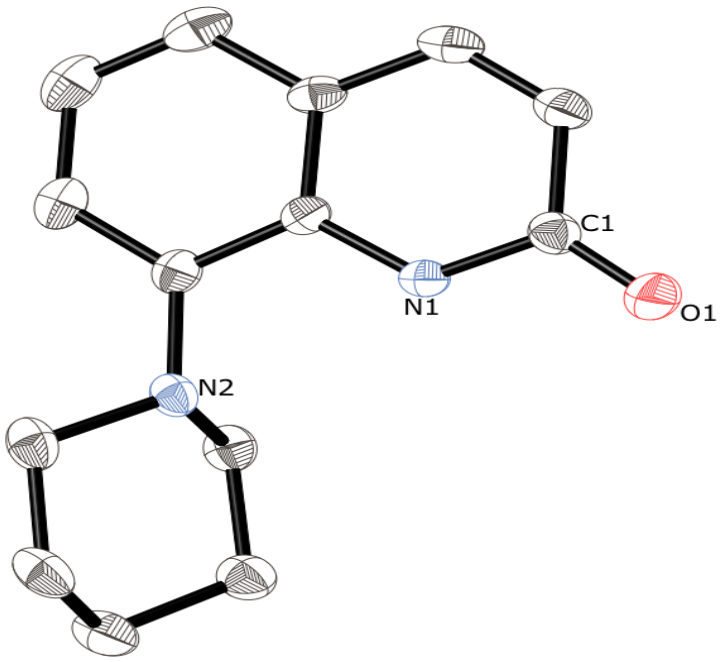


Figure 1. Crystal structure of ligand 1 (Hydrogen atoms are omitted for clarity)

3.2 Preparation of catalyst-2

The preparation of ligand-1 2 involved 5 steps. In this section, all experimental steps are described in detail.

1- A mixture of 1 equivalent (5.03 g) 2,6-dibromopyridine of, 1.15 equivalent (2.64 g) of benzyl alcohol, 2.2 eq (2.62 g) of KOH and 0.04 eq (0.224 g) of 18-crown-6 in toluene (60 ml) was heated under reflux in Dean Stark apparatus to remove water for 2 hours. The reaction mixture was cooled and quenched with addition of ice and work up with toluene. The combined organic layer was dried, filtered and evaporated to dryness to give 2-Bromo-6-Benzyloxy Pyridine as organic liquid. Yield :5.12 g (92 %). [15]

2- 1.2 eq (1.49 g) of N-BuLi was added to 1 eq (5.12 g) 2-Bromo-6-Benzyloxy Pyridine in THF at -78 ^{o}C (dry ice and acetone). Reaction mixture was stirred for 45 minutes and 1.2 eq (1.79 ml) of DMF was added at same temperature. After 1 hour sodium bicarbonate solution was added and compound was extracted using diethyl ether. Yield:4.22 g (83 %). [16]

3- 1 eq (0.6 g) of 6(Phenyl methoxy)-2-Pyridine carboxaldehyde in DCM, 1.2 eq (0.33 ml) of Piperidine was added and stirred for 16 h. 1.2 eq (0.12 g) of $NaBH_4$ was added and reaction

mixture was stirred for 20 minutes and quenched with acetic acid at 0^{O}C. After work up with ethyl acetate and column purification gave product 0.74 g, (94%). [17]

4- The debenzylation was done by adding TFA to reaction mixture and stirred overnight. Neutralization with saturated $NaHCO_3$ and extraction with chloroform. After column purification with DCM: MeOH (20:1) gave ligand 2.
5- Complexation was done by addition of 1 eq (0.0468g) of palladium chloride to ligand-2 in EtOH:CH_3CN (1:1). Reaction mixture was stirred overnight and heated at 60 ^{o}C for 2 hours. Decant solvent and apply vacuum to make dryness of precipitates. Product was collected as orange precipitates. yield 0.12 g (68 %).

The complex has been successfully isolated, the structure has been determined by ^{1}H and ^{13}C NMR spectroscopy and XRD.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), δ 7.35 – 7.28 (m, J= 7.48 Hz, 1H), 6.46 (d, J= 9.2 Hz, 1H), 6.03 (d, J = 7.5Hz, 1H), 3.36 (s, 2H), 2.43 (br, m, 4H), 1.63-1.48 (m, J= 9.8 Hz, 4H), 1.30-1.26 (m, J= 7.12 Hz, 2H).

^{13}C: ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.05 (s), 153.49 (s), 138.99 (s), 137.81 (s), 128.50 (s), 128.21 (s), 127.82 (s), 116.01 (s), 109.00 (s), 67.52 (s), 64.92 (s), 54.74 (s), 26.12 (s), 24.35 (s).

3.2.1 Crystal Structure of Catalyst 2

The crystals were grown in Petroleum ether and DMSO by slow evaporation figure 2.

Space group: P21/n
C1-N1: 1.336Å
C1-O1: 1.326Å
Pd1-N1: 2.065Å
Pd1-N2: 2.086Å
Pd1-Cl1: 2.306Å
Pd1-Cl2: 2.298Å

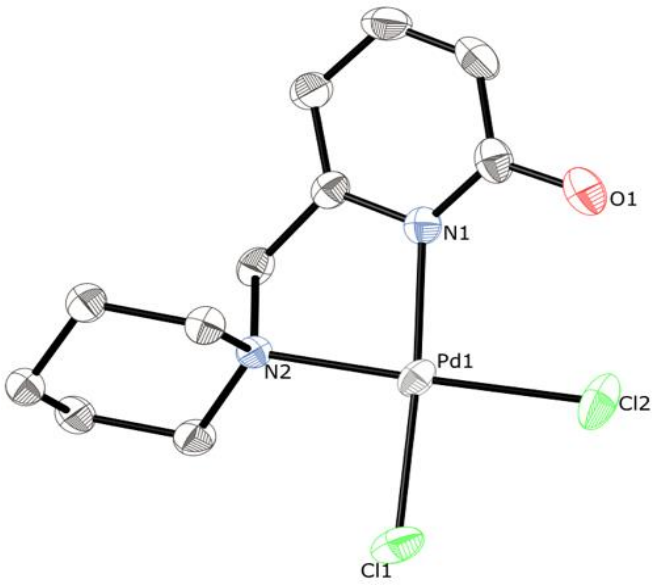


Figure 2. Crystal structure of complex-2 (Hydrogen atoms are omitted for clarity

3.3 Preparation of Catalyst 3

The preparation catalyst 3 involved five steps. In this section, all experimental steps are described in detail.

1- The synthetic route for ligand 3 is almost same as for ligand 2. The first step is reaction between 2,6-dibromopyridine with benzyl alcohol using Dean-Stark apparatus to get compound 10. The compound 11 was synthesized in the presence of n-BuLi at -78 ^{o}C.

2- Reductive amination of 11 with 1.2 eq (0.24 g) of diethyl amine, 1 eq (0.6 g) of 6(Phenyl methoxy)-2-Pyridine carboxaldehyde in DCM stirred for 16 hours. 1.2 eq (0.12 g) of NaBH4 was added and stirred for 20 minutes, quenched with acetic acid at 0^{o}C. After work up with ethyl acetate and column purification gave product (80%). [18]

3- The debenzylation was done by adding TFA to reaction mixture and stirred overnight. After neutralizing with saturated $NaHCO_3$ and extraction with chloroform. After column purification with DCM: MeOH (20:1) gave ligand-3 (92%). [19]

4- Complexation was done by addition of 1 equiv. of palladium chloride to ligand-3 in EtOH:CH_3CN (1:1). Reaction mixture was stirred overnight and heated at 60 ^{o}C for 2 hours.

5- Decant solvent and apply vacuum to make dryness of precipitates. Product was collected as orange precipitates. yield 0.12 g (72 %).

The complex has been successfully isolated, the structure has been determined by ^{1}H and ^{13}C NMR spectroscopy.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s,1H), 7.28 (m, 6.72 Hz, 1H), 6.35 (d, 8.32 Hz, 1H), 6.00 (d, 6.72 Hz, 1H), 3.40 (s, 2H), 2.51-2.46 (m, 7.15 Hz, 4H), 0.98 (m, 7.16 Hz, 6H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 163.05 (s), 146 (s), 141(s), 118 (s), 103 (s), 53 (s), 47(s), 11 (s)

IR (cm-1): 2971, 1648, 1610, 1449, 1198, 1176, 1126, 798, 718, 557

3.4 General Procedure for Alkylation Reaction

All catalytic reactions were performed in carousel, with vigorous stirring, closed carefully and under nitrogen for 48 hours. Care was taken to replicate the procedure as any deviation may result in erroneous results as amount of substance and reactants were so small.

1) 1 equivalent (0.05 g) of acetophenone, 2 equivalent (0.08 g) benzyl alcohol, 1 equiv. Of base, 0.02 equiv. of catalyst in toluene (3 ml) in carousel at 120 ^{o}C kept under nitrogen for 48 hours. After 48 hours add 1 equiv. (0.074 g) ferrocene as internal standard and stirred for some time. Add water to separate organic layer.

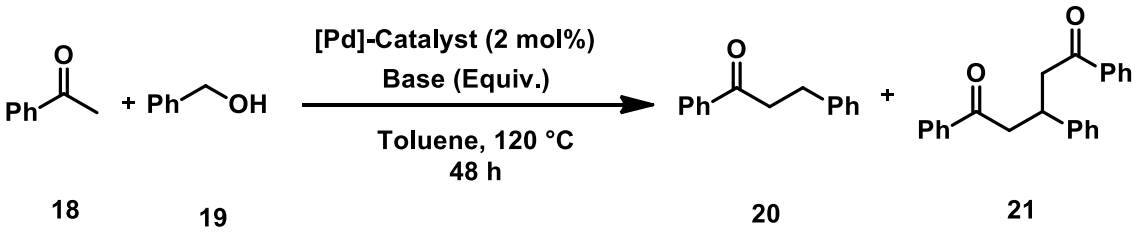
2) After work up take 1 ml of organic layer evaporate it and keep under vacuum for some time to make it completely dry. Prepare NMR sample to calculate yield or sometimes sample injected to GC for analysis to confirm product and side products.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J=7.18 Hz, 2H), δ 7.99 (m, J=7.28 Hz, 1H), δ 7,61 (m, J= 7.44 Hz, 2H), δ 7.47(m, 7.28 Hz, 2H), δ 7.33 (d, 8.48 Hz, 2H), δ 7.27 (m, J= 7.12 Hz ,1H), δ 3.35 (t, 7.24 Hz, 2H), δ 3.12 (t, 7.94 Hz, 2H)

4- Results and Discussions

Attempted Catalytic Reactions with complexes

Using [Pd] complex-1 we initially studied the alkylation reaction of acetophenone **18** in the presence of benzyl alcohol **19** as coupling partner in the presence of tert-butoxide base in toluene at 110°C. We were surprise to see the formation of alkylated product **20** and side product **21** in



First, we decided to optimize the alkylation of acetophenone reaction and results are shown in Table 1. The reactions were carried with sub-stoichiometric amounts of different bases and we obtained product **20** in low yield (Table 1, entries 1-4). Then we increased the amount of base to stoichiometric and found that the formation of product **20** selectively in the presence of potassium *tert*-butoxide after 48 h (Table 1, entry 6).

4.1.1: Table 1. Optimization Study with Different Bases

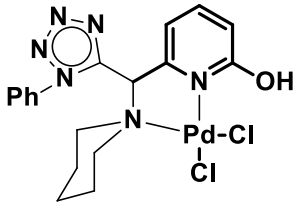
S. No	*Catalyst*	*Base (Equiv.)*	*Product-20 %*	*Product-21 %*
1	No catalyst	NaOtBu (1.0)	11	12
2	1-[Pd]	NaOtBu (0.25)	18	No
3	1-[Pd]	Cs_2CO3 (0.25)	20	No
4	1-[Pd]	KOtBu (0.25)	13	No
5	1-[Pd]	KOtBu (0.5)	39	No
6	1-[Pd]	KOtBu (1.0)	94	No Product
7	1-[Pd]	KOH (1.0)	47	No
8 [a]	1-[Pd]	KOtBu (1.0)	23	No

8 [a]. The reaction was performed in dioxane.

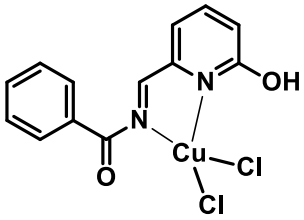
The reaction also works without any catalyst only in the presence of base but yield is very low and reaction is not selective. The reactions with other palladium catalysts such as palladium chloride, 2-[Pd], 3-[Pd] and SSA-35 resulted in mixture of products **20** and 21 (Table 2). From

these results, we may conclude that OH group in the 1-[Pd]-complex could promote both dehydrogenation and hydrogenation for selective formation of product **20** in very good yield.

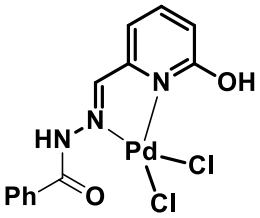
4.1.2: Table 2. Optimization Study with Different Catalysts



SSA-35



SSA-42



SSA-39

S. No	*Catalyst*	*Base (Equiv.)*	*Product-20 (%)*	*Product-21 (%)*
1	**No-Catalyst**	**KOtBu (1.0)**	**25**	**26**
2	**$PdCl_2$**	**KOtBu (1.0)**	**62**	**34**
3	**2-[Pd]**	**KOtBu (1.0)**	**87**	**trace**
4	**3-[Pd]**	**KOtBu (1.0)**	**31**	**16**
5	**SSA-35**	**KOtBu (1.0)**	**14**	**18**
6	**Pd/C**	**KOtBu (1.0)**	**10**	**11**
7	**SSA-42**	**KOtBu (1.0)**	**27**	**17**
8	**SSA-39**	**KOtBu (1.0)**	**31**	**12**

The reaction with silver triflate showed that it does not play any role during reaction Table 3.

4.1.3: Table 3. Reaction Study with 1-[Pd] and silver triflate

S. No	*Catalyst*	*Base (Equiv.)*	**Silver triflate**	*Product-20 (%)*	*Product-21 (%)*
1	**No Catalyst**	**KOtBu (1.0)**	**0.022 (eq.)**	**11**	**15**
2	**1-[Pd]**	**KOtBu (1.0)**	**0.022 (eq.)**	**21**	**23**

To study the reaction mechanism, we tried some reactions with some reagents. With 1,7 octadiene in the presence of 1-[Pd] we got 46 % product **20** as expected because it acts as hydrogen acceptor during reaction. The reaction with two drops of mercury in the presence of 1-[Pd] catalyst we got only 13 % (table 4). We can conclude that reaction follows heterogeneous pathway.

4.1.4: Table 4. Reaction Study with and 1,7-Octadiene and Hg

S. No	*Catalyst*	*Base (Equiv.)*	Reagents	*Product-20 (%)*	*Product-21 (%)*
1	1-[Pd]	KOtBu (1.0)	1,7-Octadiene (2 eq)	46	No Product
2	1-[Pd]	KOtBu (1.0)	2 drops of Hg	13	15

5-Time profile study for α-alkylation of benzyl alcohol with acetophenone

We studied α-alkylation of benzyl alcohol with acetophenone to give 1,3 diphenylprop-1-one with time. Yield was calculated using ferrocene as internal standard by ^{1}H-NMR. Results are shown in figure 3. We found that reaction is very fast in the beginning and gives 30% yield after 5 minutes. After that it turns slow and give 60% yield in 24 hours. We found 94 % product after 48 hours.

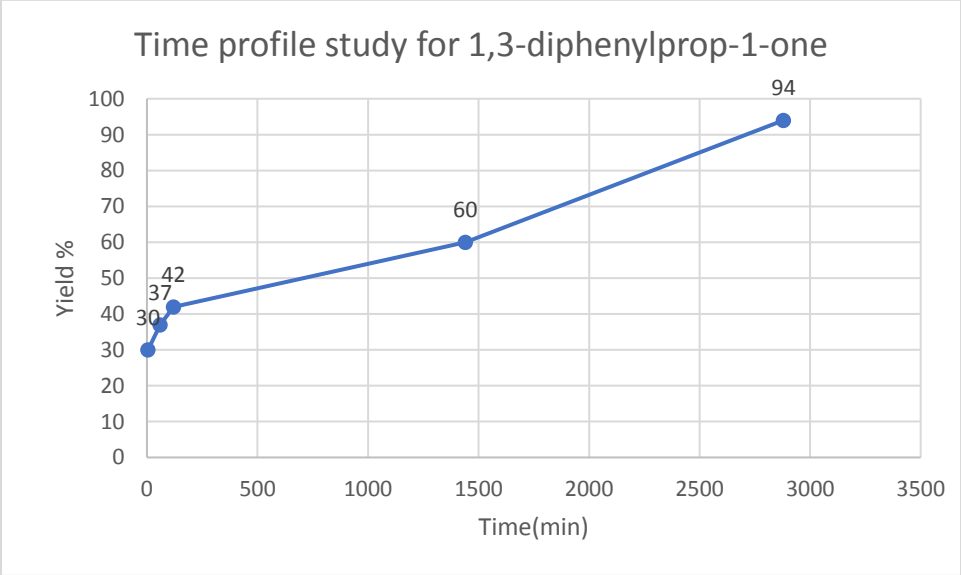


Figure 3. Time profile study for 1,3 diphenylprop-1-one

We studied time profile of α-alkylation product 1,3 diphenyl prop-1-one by GC using decane as internal standard. The retention times of decane, benzyl alcohol, 1,3 diphenyl prop-1-one are 3.31, 3.78 and 12.02 respectively. Samples were collected after 15 minutes of intervals for 75 minutes and then after 24 hours. The results are shown in figure 4.

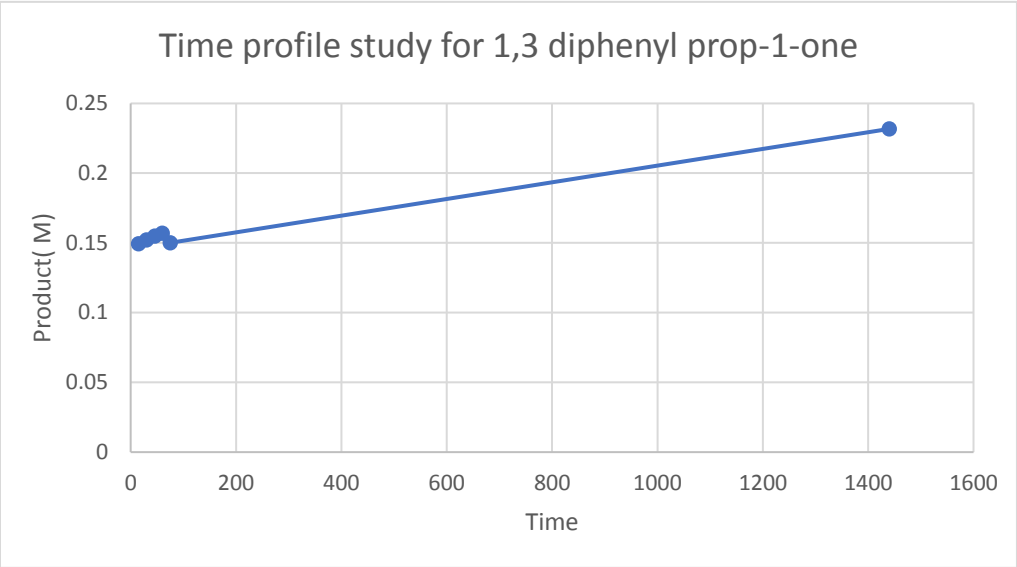


Figure 4. Time profile study for 1,3 diphenylprop-1-one by GC

We also studied time profile of benzyl alcohol by GC using decane as internal standard. The results are depicted in figure 5. Benzyl alcohol is decreasing with time.

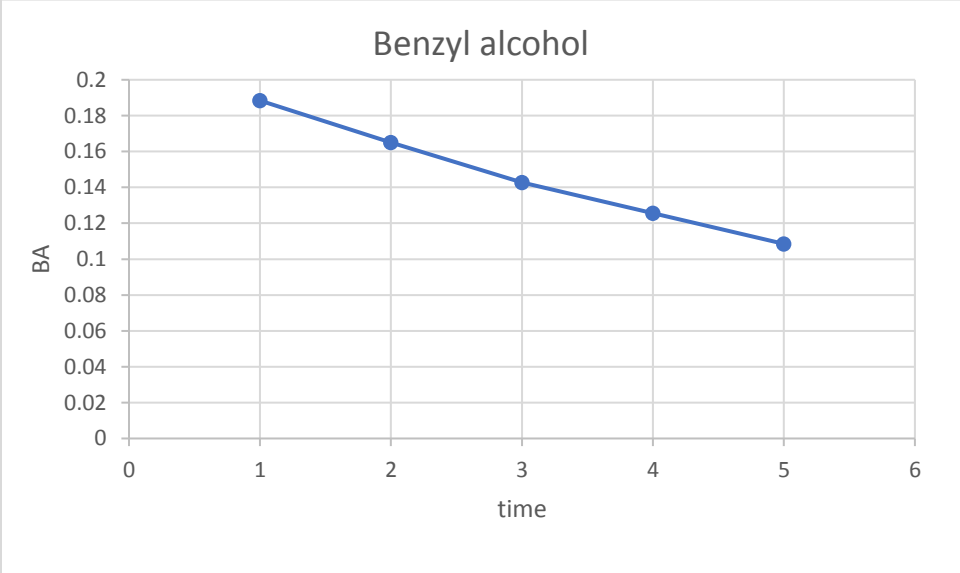


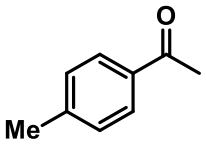
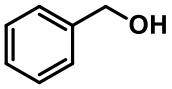
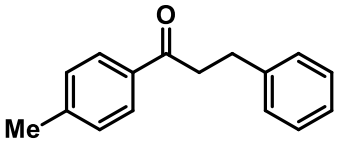
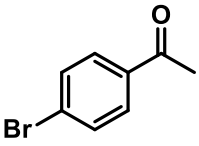
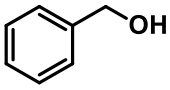
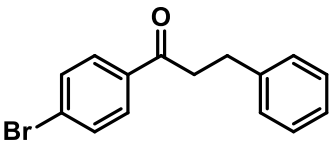
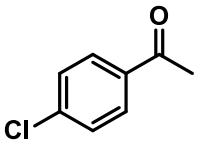
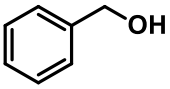
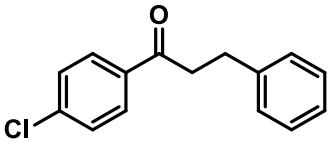
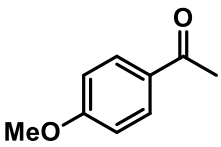
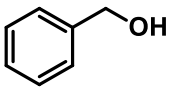
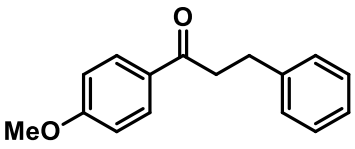
Figure 5. Time profile study for benzyl alcohol by GC

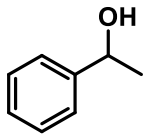
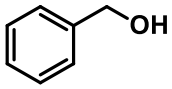
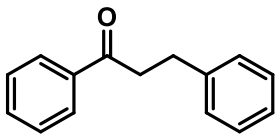
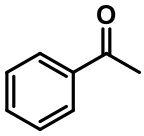
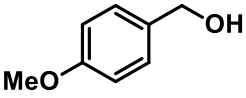
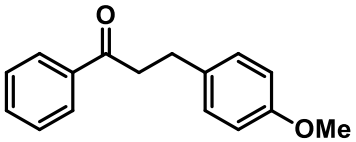
6. Substrate Scope

After finding out that the 1-[Pd] is the most active catalyst for alpha alkylation of ketones with alcohols, we have explored the substrate scope of reactions catalyzed by 1-[Pd]. In these catalytic experiments, one equivalent of ketone, two equivalents of alcohols, 2 mole% of palladium

catalyst and one equivalent of base in toluene was heated for 48 hours. The reactions are carried out in carousal under nitrogen. Reaction product analyzed by ^{1}H-NMR. The results are shown in table 5.

Table 5. α alkylation using different substrates.

Entry	Acetophenone	Primary alcohol	Product (yield)
1			 61 %
2			 58 % Dehalogenated product
3			 61 % Dehalogenated product
4			 0 %

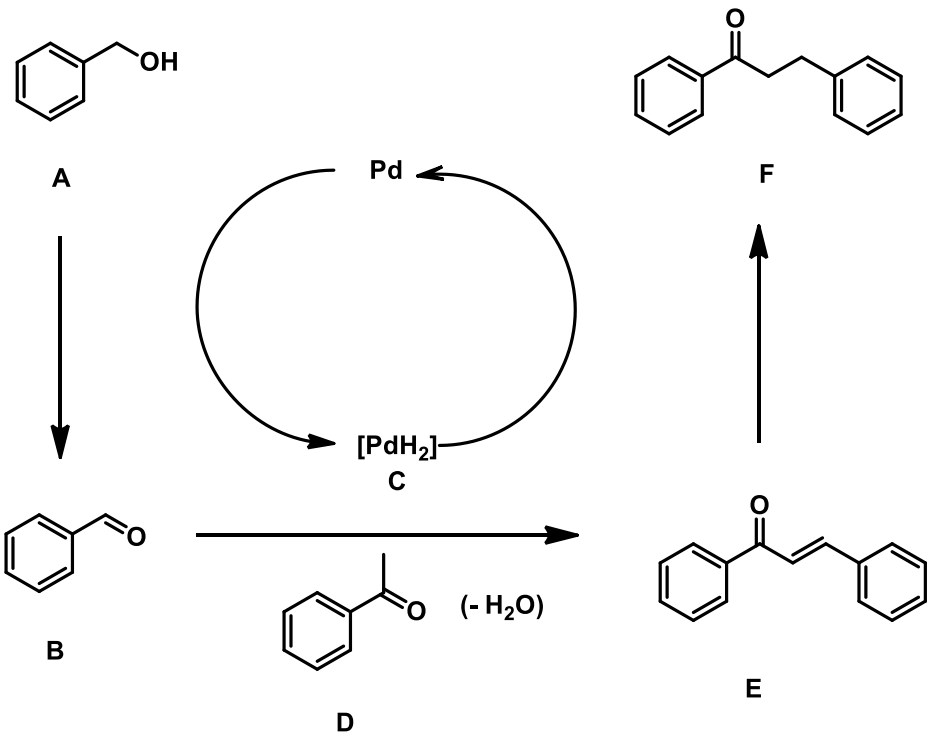
Entry	Acetophenone	Primary alcohol	Product (yield)
5			 32 %
6			 21%

As shown in table. 5 palladium catalyst 1 effectively catalyzed alpha alkylation between primary alcohols and ketones, giving desired product in 61 % (entry 1). With halogenated acetophenone we got our desired product and dehalogenated product (entry 2, 3). We also tried to study alpha alkylation between primary and secondary alcohols we got 32 % yield and 22% of product **21** (entry 5). Reaction with aliphatic alcohol and furan-2-ylmethanol gave no product (entry 6, 7).

7- Proposed reaction mechanism

Hydrogen borrowing for alpha alkylation of carbonyl compound using alcohols occurs via the process shown in scheme 14. Hydrogen auto transfer from alcohol **A** to metal would lead to the formation of aldehyde **B** and metal hydride intermediate **C**. Subsequent base mediated aldol condensation of an enol form from carbonyl compound with **D** would give α, β unsaturated ketone **E**, which would underdo hydrogenation reaction in the presence of metal hydride **C** to give α alkylated carbonyl compound **F**.

(Borrowing hydrogen approach). [20, 21]



Scheme 14. Alkylation of acetophenone with benzyl alcohol via hydrogen borrowing approach.

8- [Pd] Catalyzed acceptorless dehydrogenation coupling of benzyl alcohol

Table 6. describes the optimization study of acceptorless dehydrogenative coupling of benzyl alcohol **19** to give benzyl benzoate **22** under the palladium catalysis. The reactions were tried with different palladium complexes and bases in various solvents. We found that Cs_2CO_3 gave the expected product. Later we studied the coupling with different amounts of bases and different temperatures. Trace amount of product was observed at 120 ^{O}C (entry 11). At 70 ^{O}C the reaction was clean we observed only the product and starting material (entry 6). In most of the screened reaction conditions, we found that the coupling was more sluggish and afforded the benzyl benzoate in low yield. Then, we used 1,4-benzoquinoline as an external oxidant to improve the yield of **22.** But it did not help for this coupling reaction (entry 12). We found less starting material it seems that toluene or benzoic acid forms during reaction that are lost during work up and evaporation. Further investigation study needed to be done in order to increase the yield of acceptorless dehydrogenative coupling product.

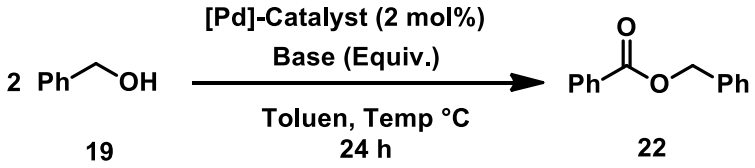


Table 6. Optimization study

Serial No	Catalyst	Base (equiv.)	Temperature	Product (%)	SM (%)
1	1-[Pd]	KOtBu (1.0)	90	-	24
2	1-[Pd]	Cs_2CO_3 (1.0)	90	12	25
3	1-[Pd]	Cs_2CO_3 (0.5)	90	13	42
4	$PdCl_2$	Cs_2CO_3 (0.5)	90	8	trace
5	2-[Pd]	Cs_2CO_3 (0.5)	90	13	15
6	1-[Pd]	Cs_2CO_3 (0.5)	70	13	31
7	1-[Pd]	Cs_2CO_3 (0.05)	70	11	59
8	1-[Pd]	Cs_2CO_3 (0.5)	60	13	16
9_a	1-[Pd]	Cs_2CO_3 (0.5)	70	11	36
9	3-[Pd]	Cs_2CO_3 (0.5)	70	12	32
10	1-[Pd]	NaOMe (0.5)	70	13	40
11	1-[Pd]	Cs_2CO_3 (0.5)	120	-	23
12_b	1-[Pd]	Cs_2CO_3 (0.5)	70	13	41

[a] The reaction was carried out in acetonitrile. [b] 1,4-Benzoquinone (1.0 equiv.) was used as an oxidant.

9- Conclusions and future perspectives

We have accomplished the design and the synthesis of new Pd complexes bearing hydroxy pyridine ligands and developed a new efficient catalytic system for α alkylation of alcohols through borrowing hydrogen pathway. All catalysts and product were confirmed by ^{1}H NMR, ^{13}C NMR, IR and XRD. We optimized reaction conditions using different bases, catalysts, catalytic loading and solvents. We found that KOtBu, palladium catalyst **1** and toluene are good for reaction. With these reaction conditions, we studied α alkylation of acetophenone with benzyl alcohol and got 94% yield (quantitively) selectively. Further, we also explore substrate scope using different substrates and we found reaction works well for many aromatic substrates. We also tried to study acceptorless dehydrogenation of alcohols but further studies are needed.

Reaction with mercury indicates that it is a heterogeneous reaction. We believe that it follows hydrogen borrowing pathway via dehydrogenation, aldol condensation and hydrogenation steps. Time profile study shows that reaction is fast in beginning then it takes time to complete in 48 hours. Mechanistic study and kinetics is needed for detailed study of reaction pathway.

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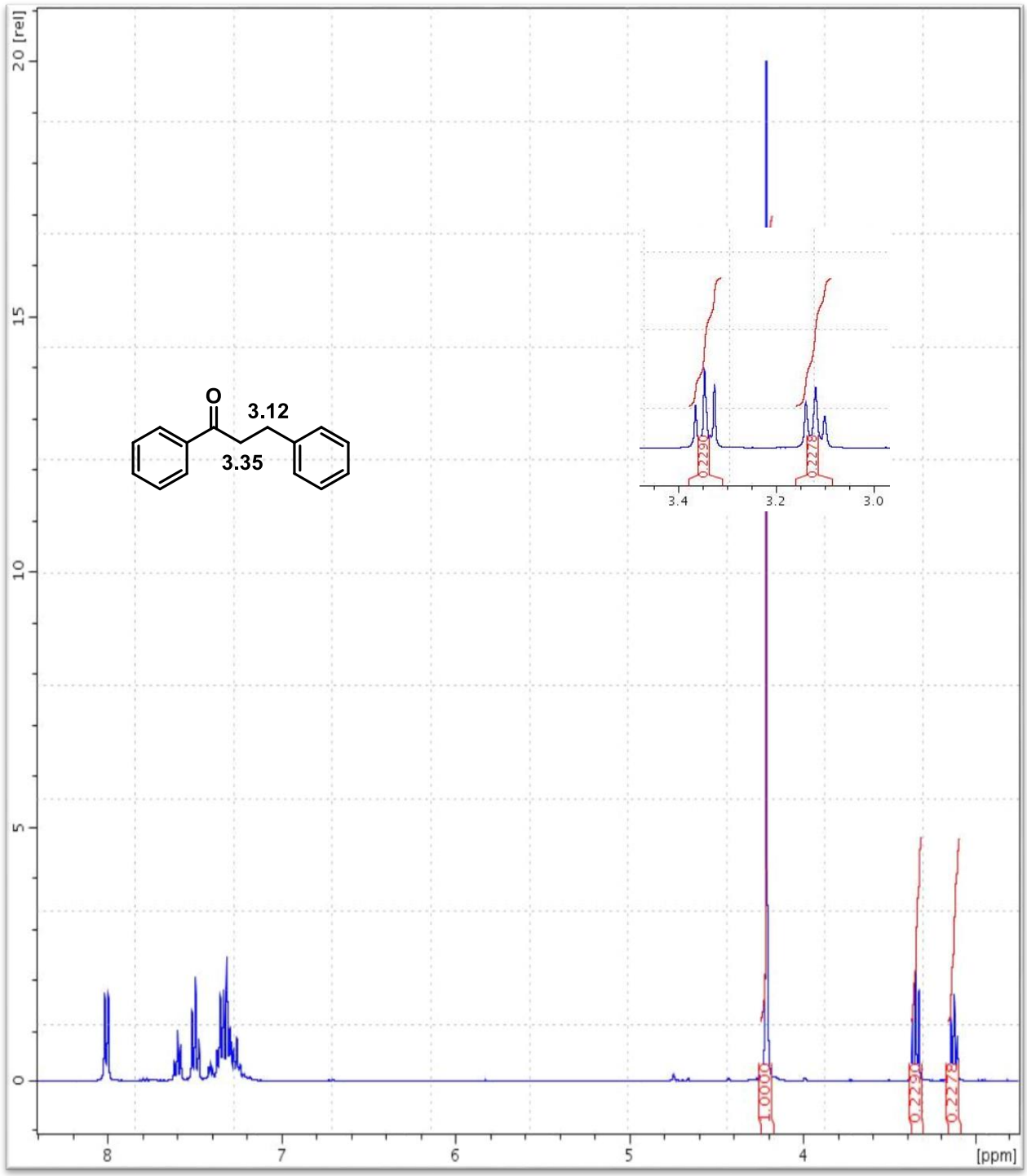
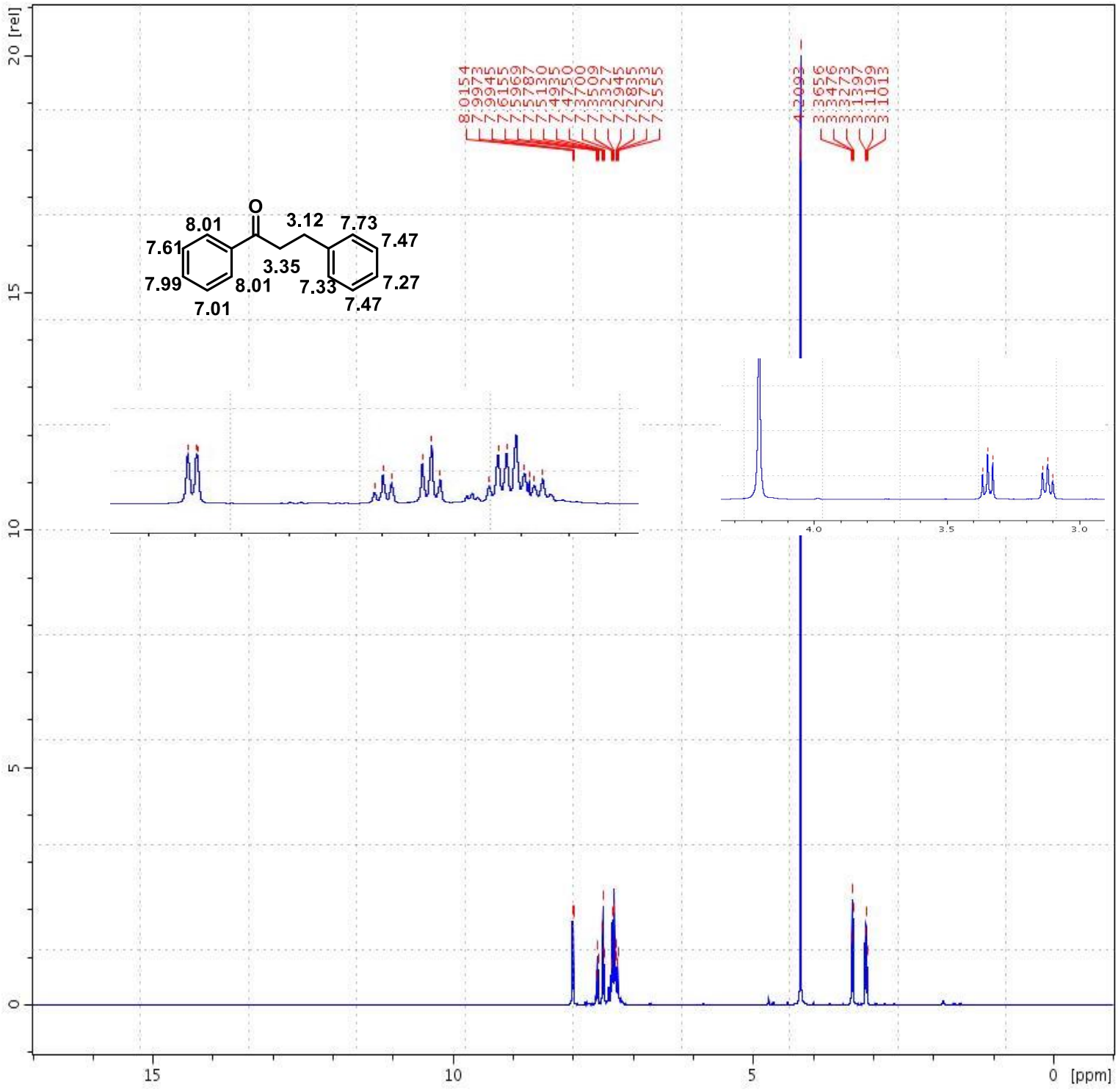
Supporting Information's

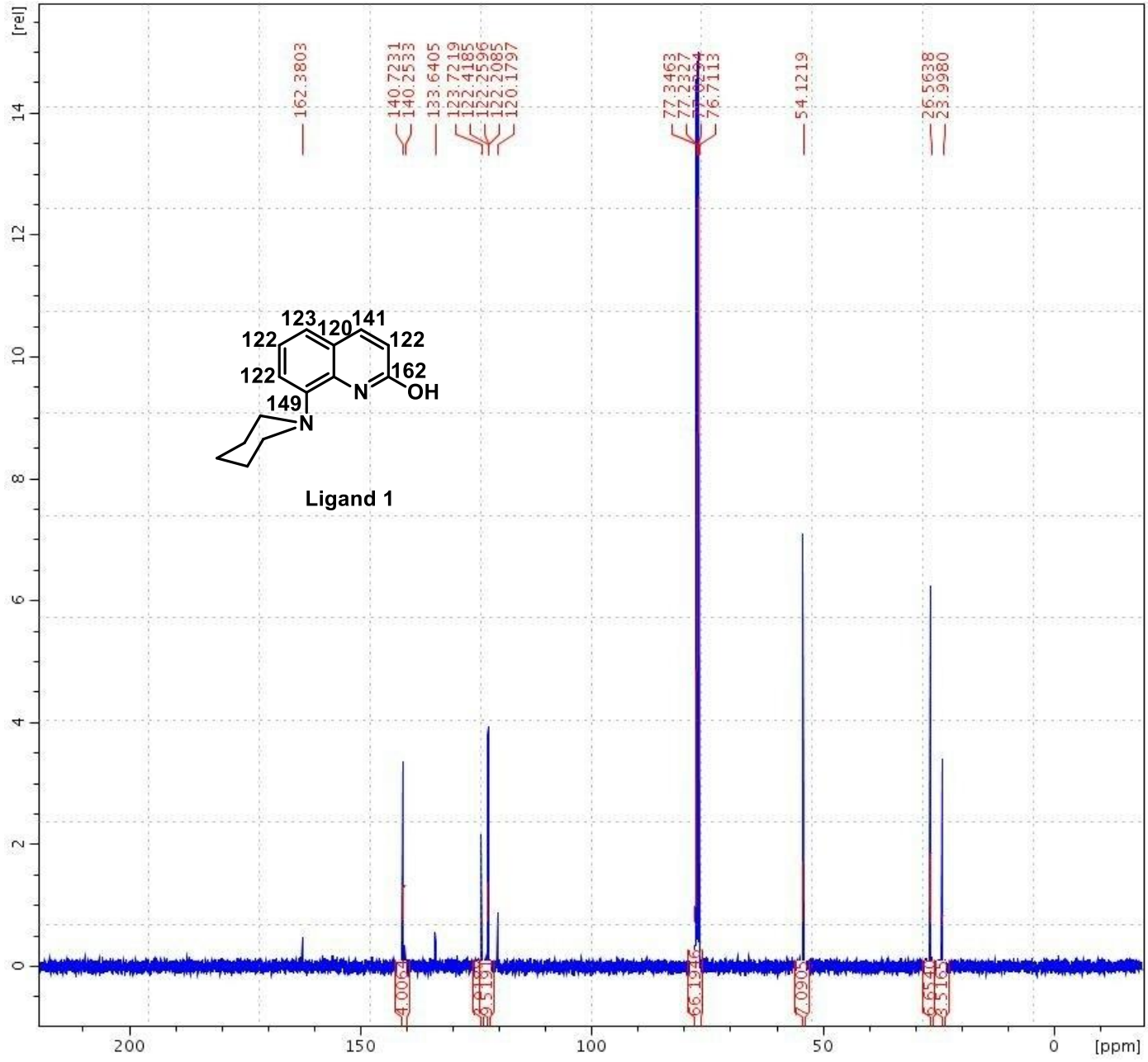
^{1}H NMR of product 20



^{1}H NMR of product 20



^{13}C NMR of Ligand 1



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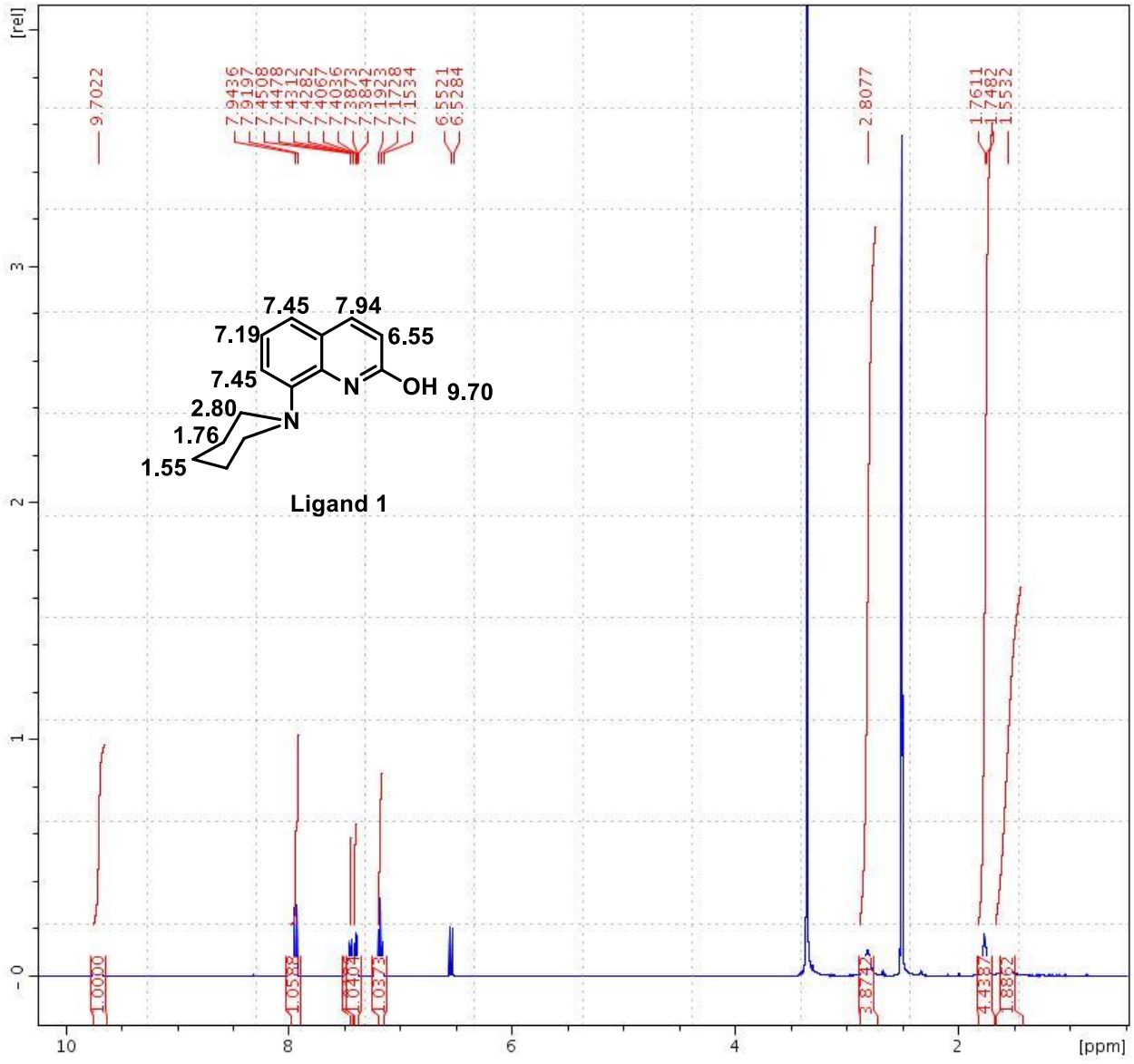

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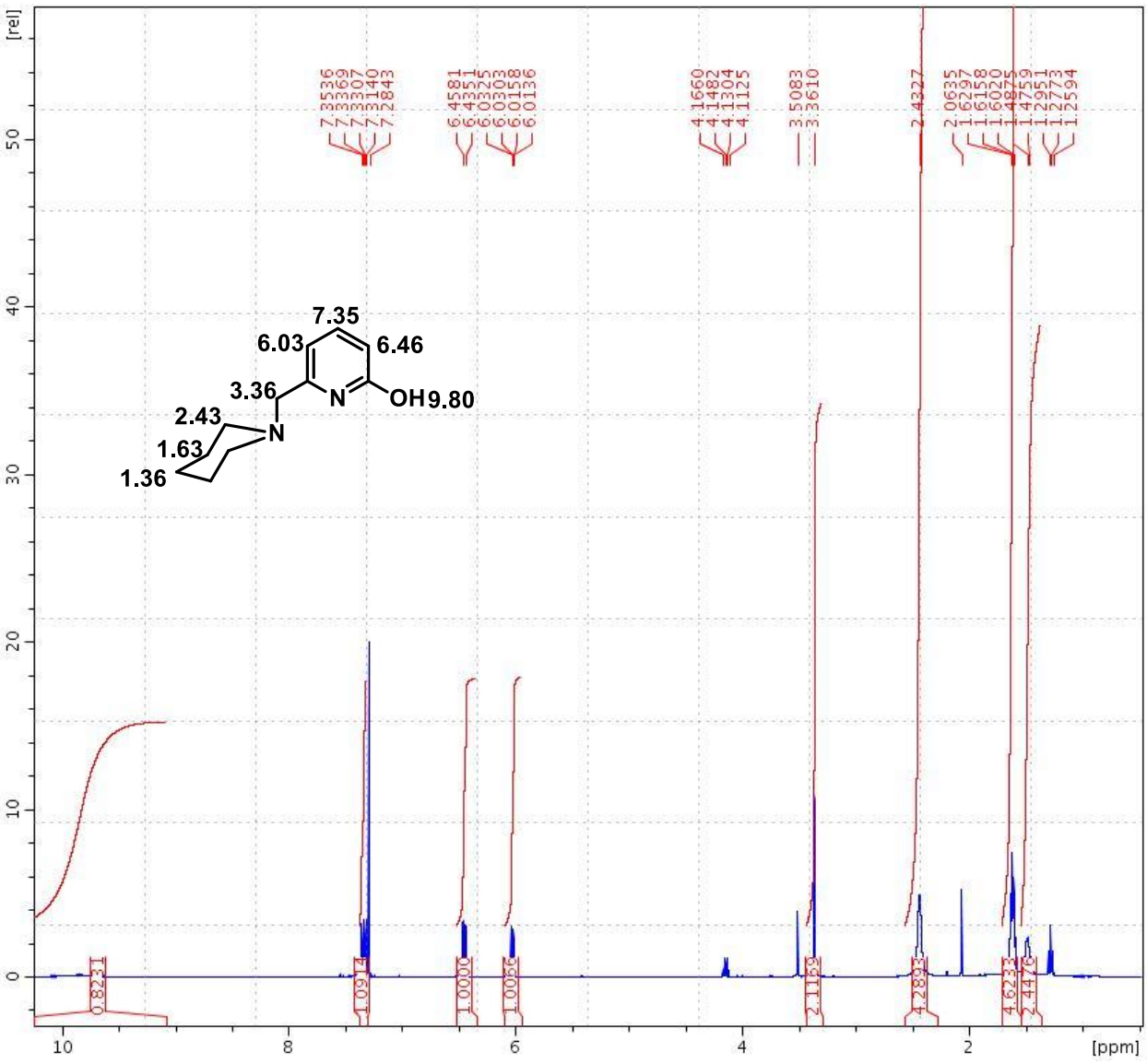

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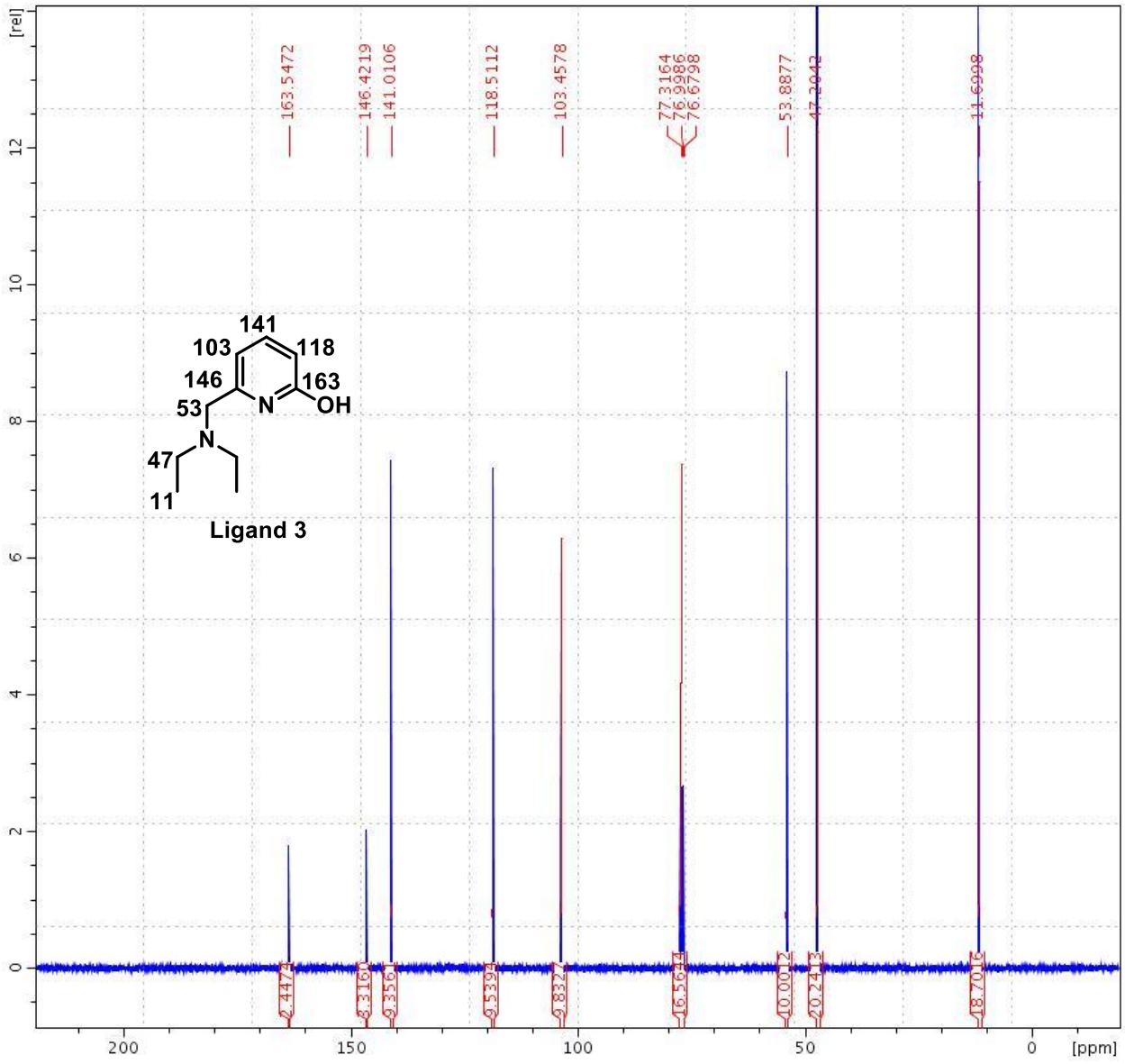

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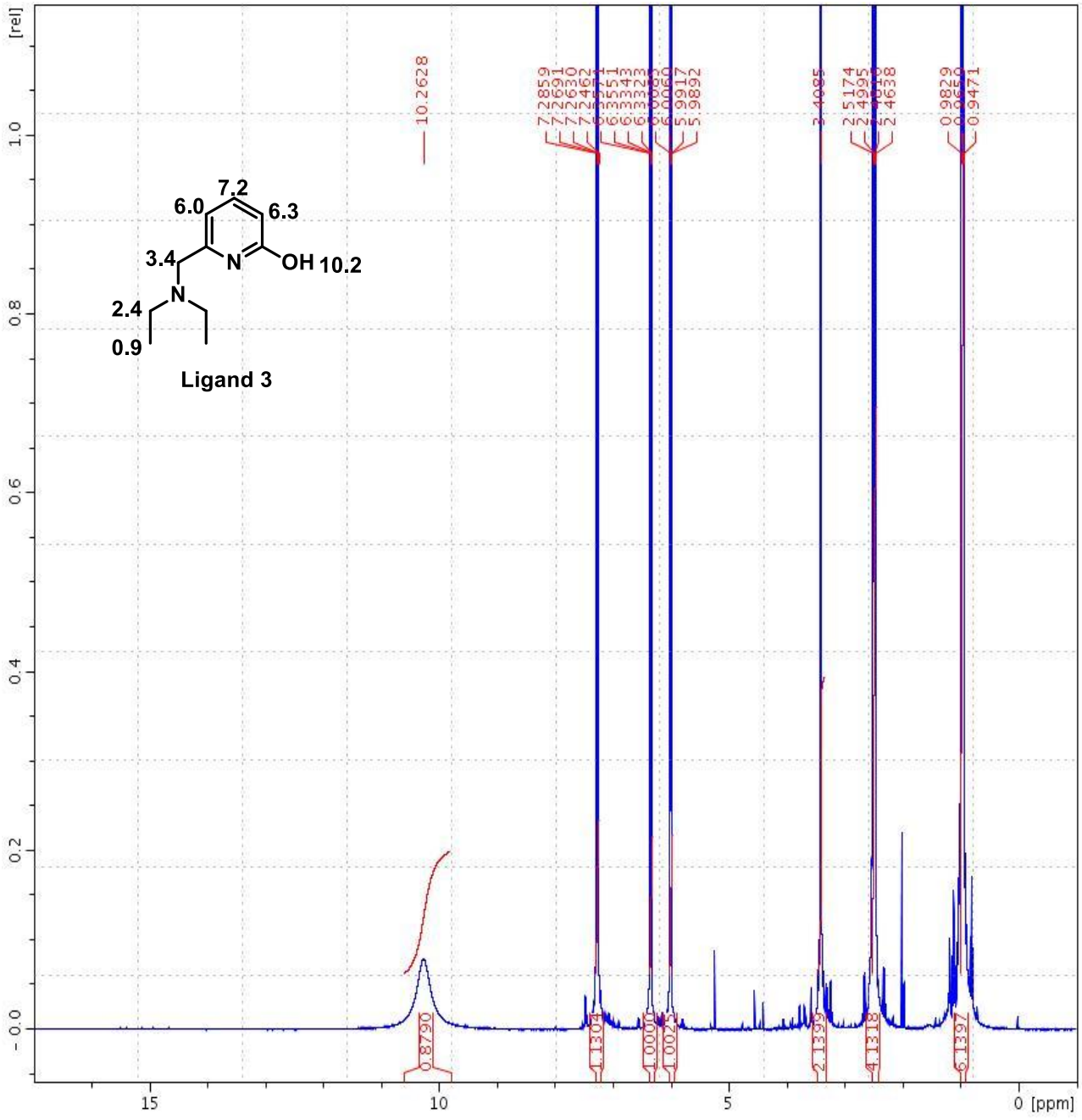
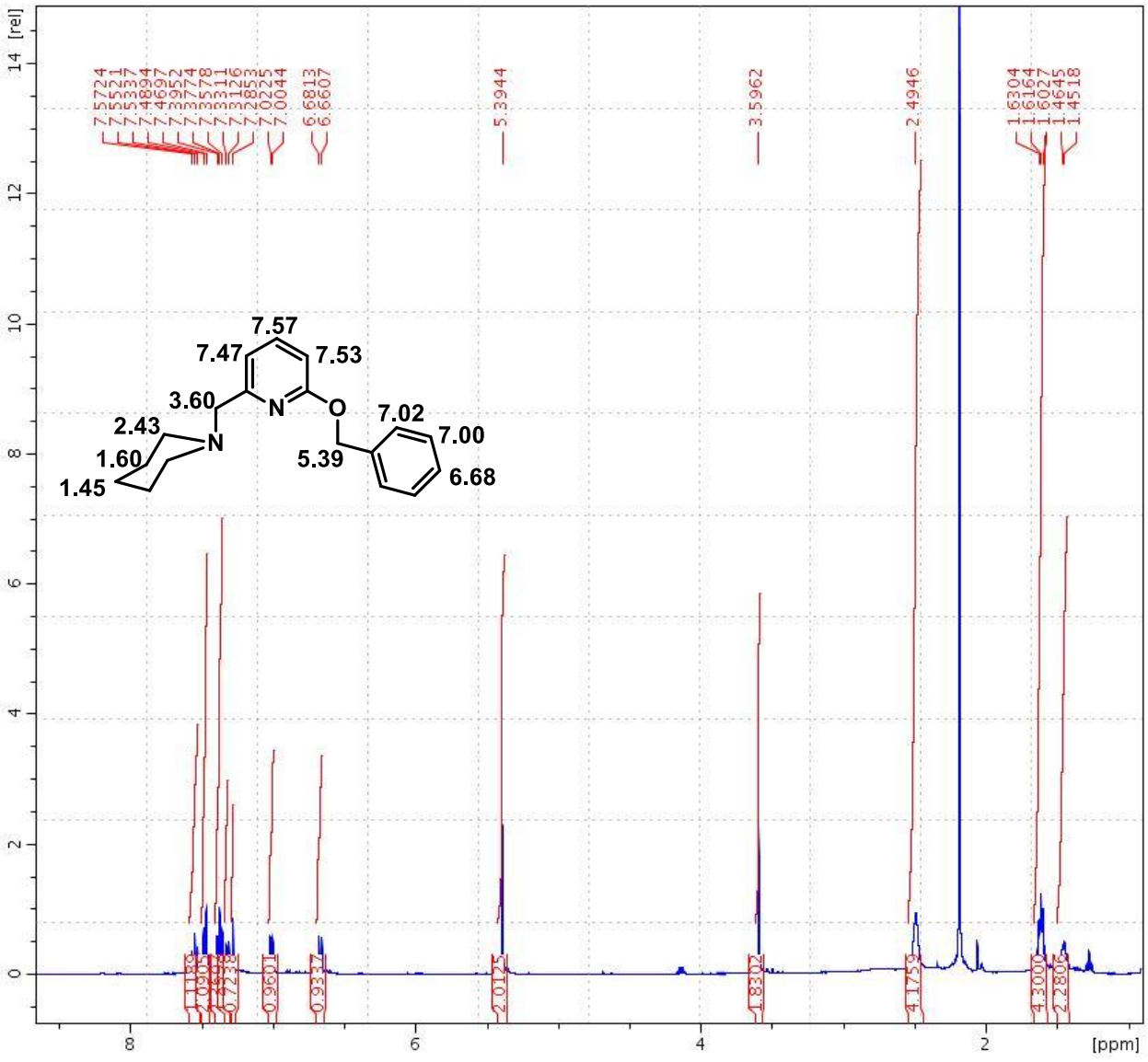
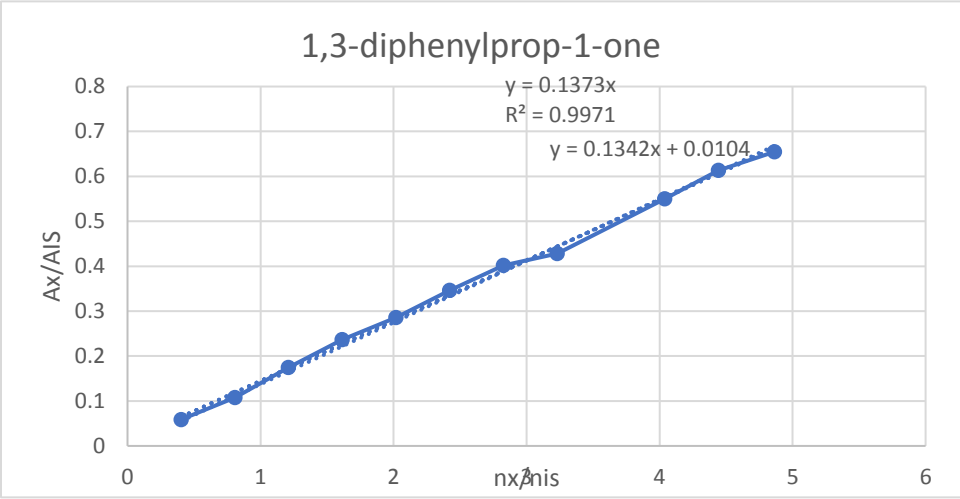


^{1}H NMR of Intermediate 12



Calibration curve for 1,3 diphenyl prop-1-one



Calibration curve for benzyl alcohol