SELECTIVE REDUCTION OF CARBONYL COMPOUNDS WITH RHODACYCLES

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of MPhil in Philosophy

by

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ABSTRACT

Reduction of carbonyl compounds is a fundamental transformation in organic synthesis to produce valuable products in both academia and industry. Transfer hydrogenation (TH) using non-H_2 hydrogen source is a convenient and safe alternative to direct hydrogenation with hazardous hydrogen gas. Compared with other TH of carbonyl compounds, transfer hydrogenation with methanol as hydrogen source is less developed, especially in obtaining high chemo-selectivity. Furthermore, TH and methylation of unsaturated compounds may be achieved in one reaction; the development of this area is even rarer.

Chapter 1 provides a brief introduction of catalytic transfer hydrogenation and the use of formic acid, isopropanol, and methanol as hydrogen sources. It also describes previous achievements on the TH of carbonyl compounds. Moreover, the application of iridium and rhodium catalysts in TH has also been introduced.

Chapter 2 presents a highly efficient cyclometaled rhodium complex for the TH of various ketones with methanol as hydrogen source. The rhodacycle showed excellent chemo-selectivity of the reduction of C=C in the TH of α,β-unsaturated ketones. The hydroxy functionality on the imine ligand is shown to be crucial for this remarkable activity.

Chapter 3 describes a simple and efficient method for TH and methylation of α,β-unsaturated ketones in a one pot reaction. Despite the scope of substrate being limited, it still provides the possibility of chain growth with mild reaction conditions.

ABBREVIATIONS

α	Alpha
β	Beta
Ac	Acetyl
Acac	Acetylacetonate
Ar	Aryl
Bu	Butyl
atm	Atmosphere
Bn	Benzyl
^{13}C	Carbon 13
Cat.	Catalyst
CD_3OD	Deuterated methanol
conv.	Conversion
Cp*	Pentamethylcyclopentadiene
Cy	Cyclohexyl
DCM	Dichloromethane
DME	Dimethyl ether
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets

ddq	Doublet of doublet of quartets
ddt	Doublet of doublet of triplets
dm	Doublet of multiplet
dq	Doublet of quartets
dt	Doublet of triplets
equiv.	Equivalent(s)
Et	Ethyl
Et_3N	Triethylamine
Et_2O	diether ether
EtOAc	ethyl acetate
Et al.	And others
FT	Formic acid/triethylamine azeotrope
g	Gram(s)
h	Hour(s)
^1H	Proton
H_2	Molecular hydrogen
HRMS	High resolution mass spectroscopy
Hz	Hertz
IR	Infrared
m	Multiplet
Me	Methyl
mg	Milligram(s)

min	Minute(s)
mL	Milliliter
mmol	Millimole(s)
MS	Mass spectrometry
OAc	Acetate
Ph	Phenyl
PhMe	Toluene
PPh_3	Triphenylphosphine
ppm	Parts per million
q	Quartet
Rh	Rhodium
r. t.	Room temperature
s	Singlet
sept	Septet
t	Triplet
td	Triplet of doublets
TFE	2,2,2-Trifluoroethanol
TH	Transfer hydrogenation
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TOF	Turnover frequency
tt	Triplet of triplets

CONTENTS

Chapter 1: Introduction and objectives

1.1 Hydrogenation

The essence of catalytic chemistry is to synthesis the required compounds with the simplest, most economical, and most convenient pathways. In the early history of organic chemistry, the synthesis of the desired compounds always required complex synthetic routes and leads to lots of by-products, which also involved a lot of purification steps. In recent years, with continuous exploratory studies, various catalysts have been created and used to simplify the route of organic synthesis. Among this, the catalysts with transition metal complexes have become one of the most important and efficient solutions in organic chemistry. Transition metal catalysts have been widely applied as useful tools in modern synthetic organic chemistry due to their different reactivity in the realization of various molecular transformations,[1] such as hydrogenation of aldehydes,[2-3] ketones[4] and other unsaturated compounds.[5-7]

The hydrogenation reaction is one of the most important reactions in organic chemistry, and it is widely used in industrial applications, such as synthesis of pharmaceuticals, agrochemicals, fine chemicals, flavours and fragrances.[8-10] This reaction generally has the characteristics of high selectivity and being easy to carry out. It is usually used to reduce or hydrogenate unsaturated compounds with the presence of catalysts such

as those based on Rh, Pt, Ru.[8] Rylander used to define it as “one of the most powerful weapons in the arsenal of the synthetic organic chemist.”[11]

In around 1823, the first hydrogenation reaction was applied to the commercial production, which is the Pt-catalysed reaction of hydrogen with oxygen.[12] Soon thereafter, Normann obtained a patent for liquid phase hydrogenation.[13] This was the beginning of the hydrogenation of edible oils and fatty acids and has now been developed into a global industry. Normann firstly used Ni catalysts to "harden" liquid oleic acid into more valuable solid stearic acid, and then applied these catalysts in the hydrogenation of fats and oils.

In the early twentieth century, hydrogenation was used for the industrial production of methanol, ammonia, and liquid hydrocarbons. Among them, Haber and Bosch discovered that the hydrogenation of nitrogen could be used to produce fertilizers in large quantities.[14] Then in 1913, Mittasch and Schneider obtained the Fischer – Tropsch (FT) process patent, which converts carbon monoxide and hydrogen into hydrocarbons in the presence of a heterogeneous catalyst. Since then, hydrogenation has been widely used in the synthesis of various compounds.[15]

Usually, hydrogenation catalysts include homogeneous catalysts and heterogeneous catalysts. The homogeneous catalysts are usually based on

platinum group metals.[16,17] In more recent years, due to the requirement of green chemistry and environmental chemistry, some earth-abundant metals, such as iron, copper, and nickel,[18] have also been widely applied in different catalytic systems. Moreover, heterogeneous catalysts have also received extensive attention due to their being commercially economic, and they have attracted more attention in the industrial field. Compared with homogeneous catalysis, heterogeneous catalysis has the advantages of easy processing of product separation and the potential for recycling of catalyst, such as Pd/C based catalyst.[18]

1.2 Transfer hydrogenation

Compared with direct hydrogenation, the hydrogen source for the hydrogenation reaction from non-hydrogen is called transfer hydrogenation (TH) reaction. Braude and Linstead pointed out that hydrogen transfer reactions can be grouped into three different types:[19]

1. Hydrogen transfer occurs within one molecule.

2. Transferring between identical donor and acceptor units; this class is called hydrogen disproportionation.

3. The reactions that occurs between different acceptor and donors is called transfer dehydrogenation.

With the difference from direct hydrogenation reactions, TH is a reaction in which H is transferred to an acceptor molecule from another molecular species (other than molecular hydrogen) acting as a donor. TH is also a robust and convenient method to produce saturated compounds using hydrogen sources other than hazardous and pressurized H_2, and no special equipment is required. And also, the reaction could be achieved under milder condition. The hydrogen sources for TH are usually inexpensive and readily available, such as isopropanol and formic acid.[19,20] Hence, TH has been widely used during the last few decades and has gained great attention in organic synthesis.[17,18]

1.2.1 Hydrogen donors in TH

The selection of hydrogen donor is an important part of the reaction. If the hydrogen molecule is able to coordinate to the catalytic centre and get activated, it could be the most beneficial choice.

The process of the abstraction of hydrogen from a hydrogen donor with a catalyst under mild conditions may be easily achieved,[21] and also the donor should not strongly bind to the catalytic centre before the donation being achieved.

The selection of the hydrogen donor is mainly due to the following

parameters:

(a) the type of reaction (transition metal catalysed, MPV reaction, etc.).

(b) the chemical nature of the targeted functional group that is to be converted.

(c) the solubility in the reaction medium (ability to act as a solvent of the corresponding reaction).

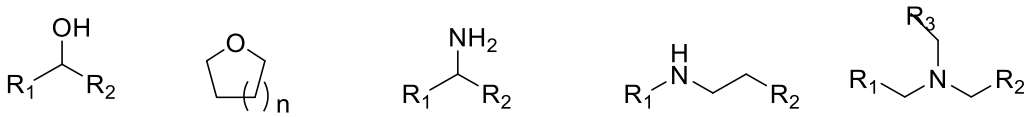
(d) the influence on the equilibrium of the reaction.

(e) no formation of toxic side products.

(f) allows mild reaction conditions.

(g) the rate of the exchange between the metal-coordinated and the bulk form of the donor molecule.[21]

Various compounds such as hydrocarbons, alcohols, formic acid, and its derivatives could be applied as hydrogen donor in catalytic TH reactions (Scheme **1**). Among them, alcohols are the major group of hydrogen donors for TH reactions, which include primary and secondary alcohols. Secondary alcohols are better donor molecules than the primary counterparts (ethanol) due to the sigma inductive electronic effect.



R_1, R_2, R_3=H, alkyl n=1,2

Scheme **1**. Selected hydrogen donor molecules.

On the other hand, when primary alcohols are used as hydrogen donor, the generated aldehydes could cause catalyst poisons. The activity of the metal centre could be hindered by CO molecules (from decomposed primary alcohols during the reaction).[22,23] Hence, 2-propanol is one of the most frequently used donor species due to its being inexpensive, non-toxic, commercially available. This molecule has the advantage of acting as a solvent of a transfer reaction as well (Scheme **1**). Moreover, the huge excess of the donor species promotes the shift of the redox equilibrium in the direction of the desired product. The consequence of the hydrogen transfer is the formation of acetone, which can be easily removed from the reaction mixture, representing a further benefit of the system.

Formic acid (HCOOH) has been proposed as a potential liquid storage medium capable of releasing H_2 under mild conditions via catalytic decomposition.[24,28] For practical applications, suitable catalysts are essential to facilitate HCOOH decomposition via dehydrogenation

(HCOOH → H_2 + CO_2) as opposed to dehydration (HCOOH → H_2O + CO).

1.2.2 Formic acid as hydrogen donor

Formic acid (FA) is considered as one of the most promising materials for hydrogen storage today. Even though its production is mainly based on fossil feedstock,[29] recent developments indicate a large potential pool of renewable sources, namely biomass[30-32] and CO_2 hydrogenation.[33] Even though its hydrogen content (4.4 wt%) falls short of the milestones set by the US Department of Energy for 2010,[34] it surpasses that of most other state-of-the-art storage materials used today in terms of simplicity and useable/net capacity, especially where capacities at ambient temperature are concerned.[35]

The dehydration pathway (HCOOH → CO + H_2O) producing CO as the impurity, which is toxic for fuel cell catalysts, is an undesired side reaction and must be strictly controlled.[36,37] In the presence of gas phase CO in the reaction, carbon monoxide forms strong coordination bonds with transition metals, which could lead to catalyst poisoning (deactivation of the catalyst core). The selectivity and reactivity of FA decomposing to CO_2 and H_2 are crucial for FA-based hydrogen storage, in which CO_2 as the product, besides H_2, can be recycled to render a carbon-neutral cycle,[38-40] and they are strongly dependent on the catalysts used. The

commercially available formic acid/trimethylamine azeotrope (F/T) also shows a high solubility in various solvents at a wide range of temperatures (20 to 60 °C).

1.2.3 Isopropanol as hydrogen donor

Isopropanol is one of the best choices due to its ability to easily donate hydrogen. Isopropyl alcohol could often be used as both solvent and hydride source in the Meerwein-Ponndorf-Verley reduction and other TH reactions.

In 2016, the Paone group reported hydrogenolysis of benzyl phenyl ether at 240 ^{o}C with Pd/Fe_3O_4 as catalyst in the presence of isopropanol as hydrogen donor.[41]

The Guo group also found that the deoxygenation of p-cresol over Ru/Nb_2O_5 using isopropanol as a solvent/H-donor, to be feasible demonstrating that 84 % toluene could be produced via the catalytic transfer hydrogenolysis in 2017.[42]

The Wu group reported that the hydrogenolysis of various aromatic ether bonds over Ru/C with isopropanol, showing that the aromatic ether bonds were efficiently cleaved in 2018.[43]

1.2.4 Methanol as hydrogen donor

Methanol, with the formula CH_3OH, also named as methyl alcohol, and often abbreviated as MeOH, is the simplest aliphatic alcohol. It is a light, volatile, colourless, flammable liquid with a distinctive alcoholic similar to ethanol.

It was first produced by Sir Robert Boyle through the destructive distillation of buxus in 1661.[44] The composition of the new compounds was determined by Justus Von Liebig and J. B. A. Dumas in 1835.[45] French chemist Paul Sabatier presented the first process that could be used to produce methanol synthetically in 1905. This process suggested that carbon dioxide and hydrogen could be reacted to produce methanol. This process also became one of the mainly methods nowadays.[46]

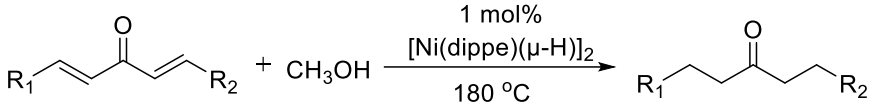
With a global production of ca. 110 million metric tons a year, methanol may be a cost-effective, easily available, and eco-friendly source of hydrogen.[47-48] However, in comparison with 2-propanol, MeOH is thermodynamically more difficult to undergo dehydrogenation to afford H_2 or metal hydride for TH.[49]

Consequently, its use as a hydrogen source for hydrogenation has been much less documented. Examples are known of the transfer

hydrogenation of C=C double bonds in α,β-unsaturated enones, alkenes and alkyne and ketones, with ruthenium, rhodium, iridium, or nickel complexes as catalysts.[50-60] With these catalysts, high temperatures (120-180 °C) are generally necessary to drive the hydrogenation.

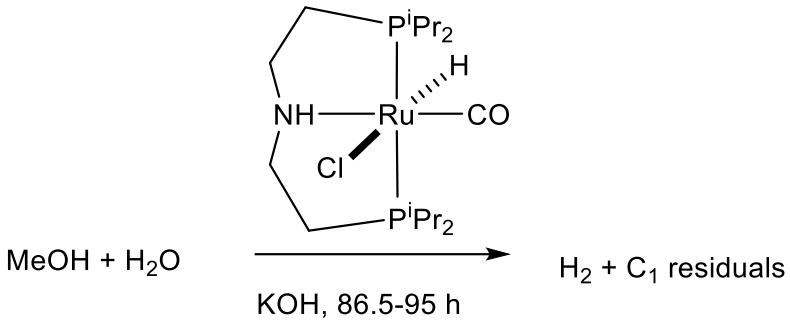
In 1985, the Maitlis group first reported catalytic reduction of ketone by ruthenium complexes with methanol at 150 °C. This work provides the possibility for subsequent intense research.[50]

Later, in 2012 Garcia and co-workers reported the reduction of α, β-unsaturated dienones into the corresponding saturated ketones with a nickel catalyst $[Ni(dippe)(\mu\text{-}H)]_2$ at 180 °C (Scheme **2**).[51]



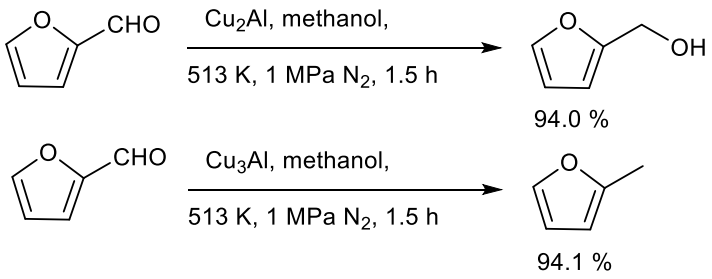
Scheme **2**. TH of α,β-unsaturated enones with methanol.

Then, Beller and co-workers reported that a Ru-PNP pincer has high activity and selectivity for dehydrogenation of MeOH and H_2O at 91 °C under strongly basic conditions in Nature in 2013 (Scheme **3**).[52] An iridium N-heterocyclic carbene complex was reported for TH of aromatic ketones and imines with methanol at 120 °C by the Crabtree group with the presence of 5 equivalents of a base in 2015.[53]



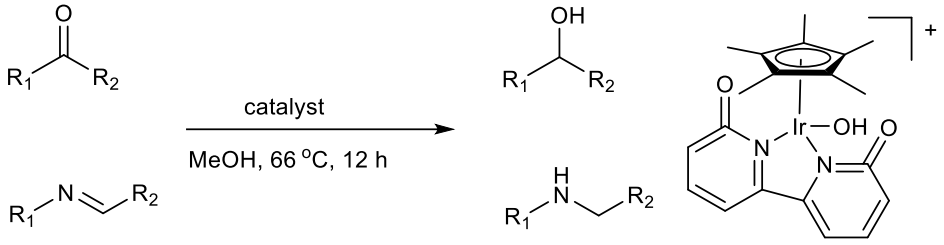
Scheme **3**. Ru-PNP catalyst reported by the Beller group.

In 2017, a series of inexpensive copper-based catalysts (Scheme **4**) were reported by Chen and co-workers, which were used for the selective TH of biomass-based furfural and 5-hydroxymethylfurfural with methanol.[54]



Scheme **4**. Copper-based catalysts for TH of furfural.

In 2020, an iridium-bipyridonate (Scheme **5**) was reported for low-temperature TH of ketones and imines with methanol by Li and co-workers.[55] Readily reducible or labile substituents were all tolerated by the complex without base.



Scheme **5**. Anionic bifunctional iridacycle catalysed TH of ketone and imines.

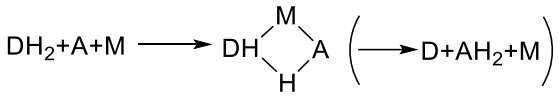
Although a few applications of methanol have been established, most of the catalytic systems still request complicated ligands or harsh reaction conditions. These all limit the development of the application of methanol. It is still challenging to achieve highly efficient usage of methanol with mild conditions. Meanwhile, in a future methanol economy, MeOH would also serve as a C1 building block for chemical synthesis. Currently, only few studies about methylation with methanol were reported with ruthenium and iridium compounds.[56-60]

1.2.5 Mechanistic study

The mechanism of catalytic TH reactions depends strongly on the particular metal and the starting material. Two main pathways could be differentiated, the direct and the indirect mechanisms. While in the direct transfer pathway, H is transferred directly (Scheme **6**, pathway **A**) from the donor to the acceptor molecule; in the case of an indirect mechanism

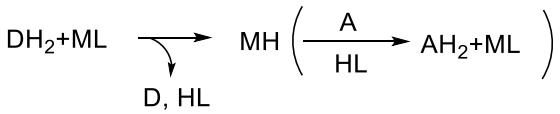
(Scheme **6**, pathway **B**) a metal hydride intermediate is formed. Generally, the most relevant representatives of the direct reaction type are strong Lewis acids such as Al^{III} and Ln^{III} ions. Compared with strong Lewis acids, weak Lewis acids such as Rh, Ru, and Ir, with high affinities for hydrides, are catalytically active.[61]

(**A**) Direct transfer pathway (A-substrate)

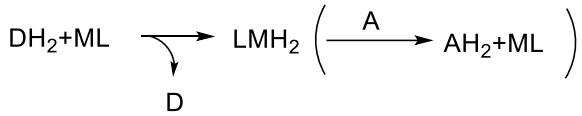


(**B**) Indirect transfer pathway

(**B1**) Formation of a monohydride



(**B2**) Formation of a dihydride



Scheme **6**. Transfer hydrogenation mechanisms.

Strong Lewis acid metal ions are able to coordinate the donor and the acceptor molecule, activate them via polarization, and promote an intramolecular H-shift (**A** pathway). For the indirect pathway, depending on the particular catalyst, the intermediate metal hydride complex formed can transfer one (Scheme **6**, pathway **B1**) or two hydrogen atoms (Scheme

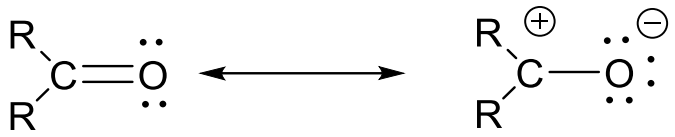
6, pathway **B2**) to the acceptor molecule (Scheme **6**). Hydrogen transfer reactions are equilibrium reactions. The dominance of the reduction/oxidation pathways are highly dependent on the concentration of the donor and acceptor molecules and the thermodynamic stability of the species involved in the redox equilibrium.

1.3 Transfer hydrogenation of carbonyl compounds

The symbol of the carbonyl group is C=O. The carbonyl group is formed by a carbon atom and an oxygen atom connected with a double bond. Ketones and aldehydes are the most common carbonyl compounds. For the reduction of ketones and aldehydes, alcohols are used most generally, while cyclic ethers and hydroaromatic components are frequently used to reduce alkenes and alkynes. The saturation of the carbon–carbon double bonded and carbon–carbon triple bonded molecules is generally preferred to be carried out with molecular hydrogen. However, the wide range of active and selective transfer hydrogenation catalysts and the practicality of the procedure makes transfer hydrogenation a fair competitor of pathways when using molecular hydrogen as the H-source. These transformations have relevance from mechanistic aspects and synthetic viewpoints as well.

Compared with C=C bonds in alkenes, the oxygen in carbonyl

compounds draw the electron density away from the carbon and makes the carbonyl group more polar. Thus, the carbon atom in the carbonyl group has a partial positive charge and the oxygen has a partial negative charge. The dipole-dipole interaction dramatically affects the boiling point of carbonyl compounds due to the charge separation (Scheme **7**). So, the carbonyl compounds are more active than alkenes based on the polarity of C=O bond.



Scheme **7**. The resonance structure of the carbonyl group.

The chemoselective hydrogenation of a carbonyl bond in multi-unsaturated aldehydes and ketones is a difficult task,[62-65] since thermodynamics favours C=C hydrogenation over C=O by ca. 35 kJ/mol.[66] The unsaturated alcohols are used as fragrances and drugs and thus this field has an industrial interest.

Selective reductions can be achieved using stoichiometric amounts of reducing agents such as metal hydrides.[67] Thus, cinnamaldehyde was reduced into cinnamic alcohol with a 99% selectivity of reduction of C=O bond.[68] The method is useful only for the small-scale production of highly priced products because they involve costly chemicals. Therefore,

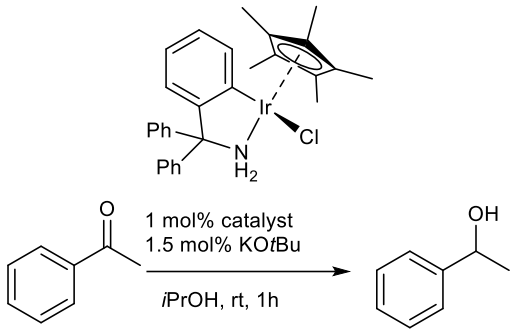
research efforts have been directed at developing hydrogenation processes based on heterogeneous or homogeneous catalysis. Among them, metal based catalytical hydrogenation of aldehyde and ketones is an efficient way to produce primary and secondary alcohols, which are valuable building blocks in fine chemicals and pharmaceutical industry. This type of transformation has been established using catalysts based on transition metals, such as iridium,[69] palladium,[70-71] titanium,[72-73] rhodium,[74-75] or ruthenium.[76-78] The reduction using simple organic molecules as hydrogen donors in the presence of a catalyst makes the hydrogenation process safer and environmentally friendly. Among them, iridium and rhodium-based catalysts have gained great attention due to their high activity.

1.3.1 Iridacycles catalysed TH reaction

Cyclometallated pentamethylcyclopentadienyl complexes have been used to catalyse a variety of organic transformations over the last decades. However, the huge potential of Cp* iridacycles has only been truly recognised in recent years due to its significant activities for a range of organic reactions such as hydrogenation, TH, reductive amination, dehydrogenation, hydrosilylation, oxidation, racemisation, etc.[79-80]

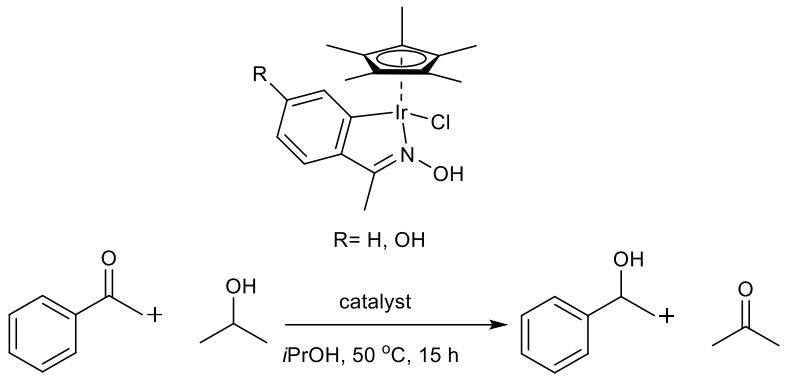
An iridacycle (Scheme **8**) was synthesised by Ikariya and co-workers

via reaction between $[Cp^*IrCl_2]_2$ and the appropriate benzylamines in CH_2Cl_2 at room temperature in the presence of NaOAc. The complex was tested in the TH of acetophenone with 1.5 mol% KO*t*Bu, and excellent yield (95-96%) of 1-phenylethanol was obtained with 1 mol% catalyst in 1 h.[81]



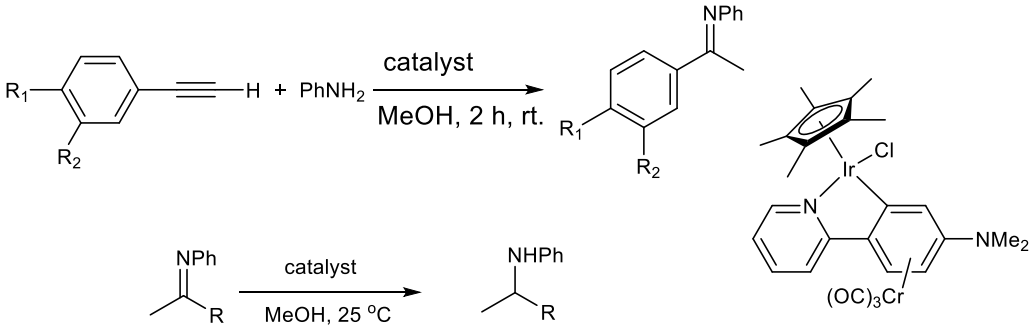
Scheme **8**. Iridacycle as catalyst in the TH of acetophenone.

A similar iridacycle (Scheme **9**) was prepared by Vein and co-workers, by reacting acetophenone oximes with $[Cp^*IrCl_2]_2$ and NaOAc in CH_2Cl_2 at room temperature.[82] The catalyst could be used for TH of substituted acetophenones with 5 mol% catalyst and 50 ^oC in 15 h. Various functionalised ketones with nitro, bromo, cyano, ester, and ether groups were reduced to the corresponding alcohols with these functional groups preserved.



Scheme **9**. Oxime-based iridacycles as catalysts for the TH of acetophenones.

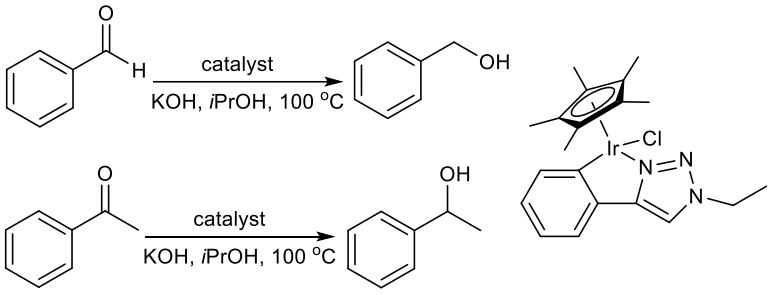
In the same year, Djukic et al. reported the catalytic activity of $Cr(CO)_3$-bound half-sandwich iridacycle (Scheme **10**) in tandem transformation of terminal alkynes into *N*-phenylamines, including hydroamination and hydrosilylation/protodesilylation reactions under mild one-pot conditions.[83]



Scheme **10**. Hydroamination catalysis by a tricarbonylchromium-bound iridacycle.

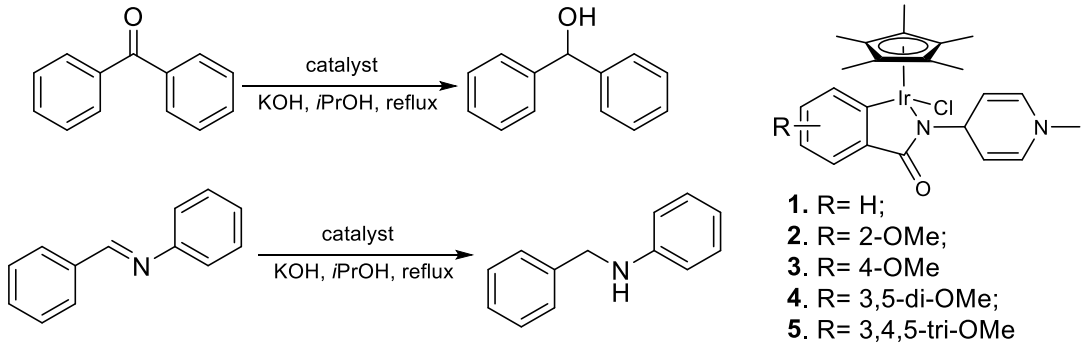
Sarkar et al. synthesised an iridacycle (Scheme **11**), which contains triazoles and mesoionic carbene. This iridacycle could catalyse TH of

benzaldehyde and acetophenone to form benzylalcohol in the presence of KOH as base and *i*PrOH as solvent at 100 °C, but the TH of acetophenone was slower under the same conditions.[84]



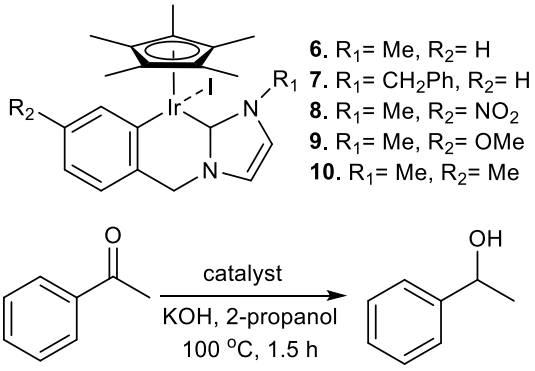
Scheme **11**. Hydrogenation of benzaldehyde and acetophenone by an iridacycle.

Albrecht and co-workers synthesised a set of iridacycles (Scheme **12**)[85] by introducing an N-methyl-1,4-dihydropyridylene substituent on the nitrogen atom. However, in doing so, the proton on the nitrogen atom that plays an important role in the outer sphere mechanism is sacrificed. As a result, these catalysts are much slower than previous iridacycles; however, they were highly active at ambient temperature. Complex **4** showed the best activity for the reduction of a small set of ketones comprising cyclohexanone, aryl-substituted acetophenones, and 2-, 3-, and 4-acetylpryridine with 1 mol% catalyst and isopropanol as reductant and solvent at 82 °C. All substrates could be fully reduced within 1–4 h with refluxing isopropanol.



Scheme **12**. Iridacycles catalysed TH of benzophenone.

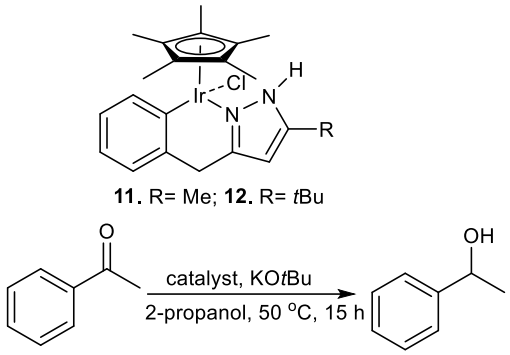
A series of iridacycles based on 1-aryl- or 1-benzyl-substituted N-heterocyclic carbenes (NHCs) were synthesized by Choudhoury and co-workers (Scheme **13**).[86] These complexes could also be used for TH of acetophenone. Among them, complexes **6**, **7**, **9**, **10** showed better activity with 20 mol% KOH at 100 °C for 1.5 h. The catalytic activity of the TH reaction with catalyst **8** was poor due to the strongly electron-withdrawing nature of the nitro group.



Scheme **13**. N-aryl and N-benzyl N-heterocyclic carbene-based iridacycles catalyzed TH of acetophenone.

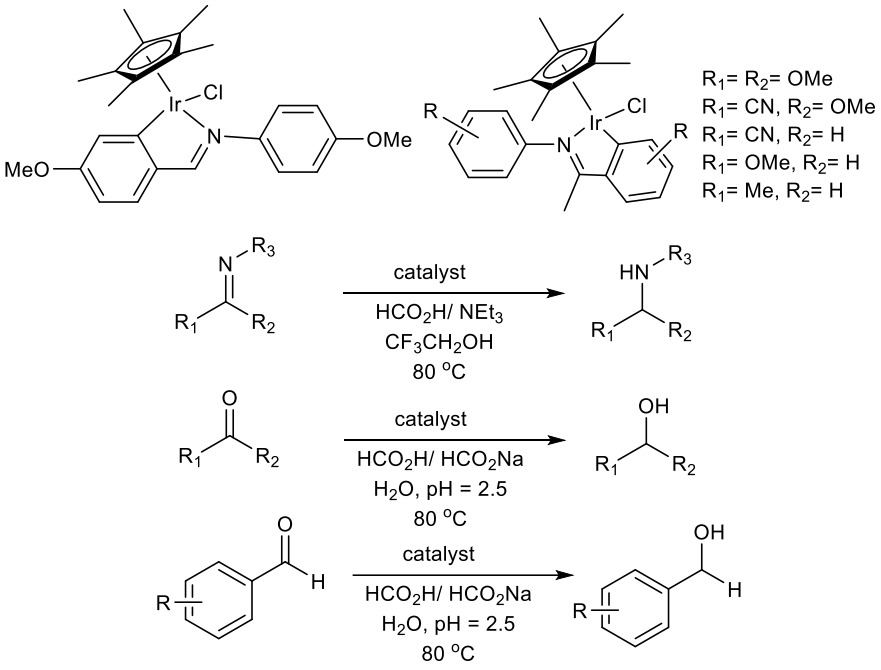
More recently, Kuwata and co-workers synthesised two new

iridacycles (Scheme **14**)[87] based on 5-alkyl-3-benzylpyrazoles in 2021. The chlorido complexes presented activity for TH of acetophenone with 2-propanol at 50 °C in 15 h. Experimental results showed that complex **12** is the faster catalyst.



Scheme **14**. TH of acetophenone catalysed by C-N chelate complexes.

Our group also synthesised a family of cyclometalated iridium complexes containing Cp* for TH processes (Scheme **15**).[79,88] These complexes showed highly efficient and selective TH with a wide range of substrates, such as imines, ketones, and aldehydes. Our studies also identified that the pH value is critical for the TH reactions.[79]



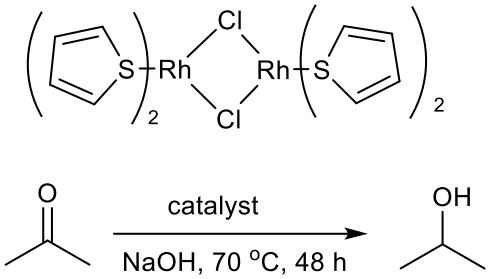
Scheme **15**. TH of various carbonyl compounds with iridacycle as catalyst.

1.3.2 Rhdacycles catalysed TH reaction

Compared with iridacycle catalysed TH, the application of rhodacycles in TH of carbonyl compounds has been very limited. So, we will focus on recent development of TH of carbonyl compounds with other rhodium catalysts.

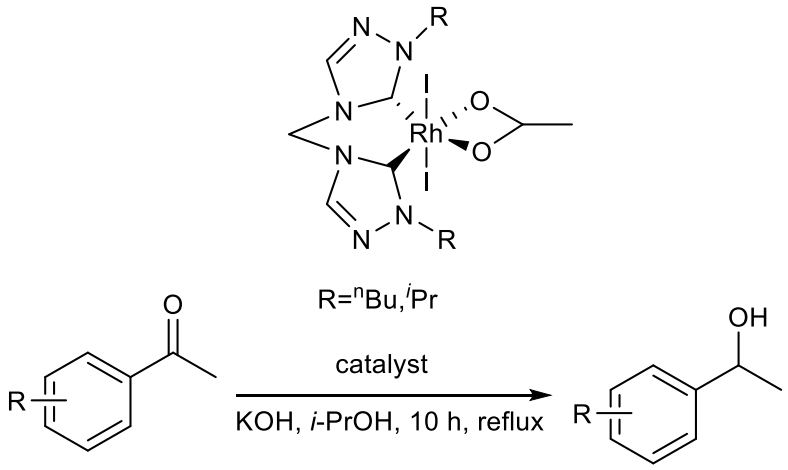
The most well-known hydrogenation catalyst is the Wilkinson complex $[Rh(PPh_3)_3Cl]$.[89,90] Meanwhile, it was also an excellent transfer hydrogenation catalyst with the presence of 2-propanol as the hydrogen source.[91] Some new complexes were produced based on Wilkinson

complex (Scheme **16**).[92] This complex provided better activity and more wide substrate scope.



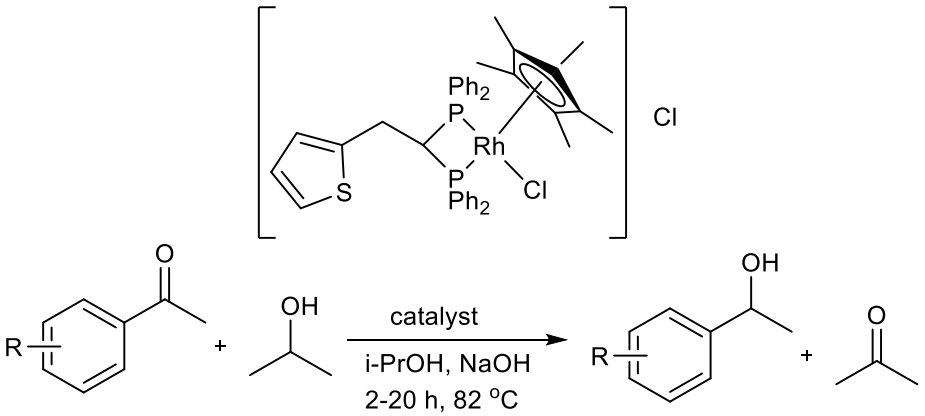
Scheme **16.** TH of ketones with further report of Wilkinson complex.

Aryl and alkyl carbonyls were converted in a hydrogen transfer reaction with good yields to the corresponding alcoholic species in the presence of air-stable [Rh(III)(bis-carbene)I_2(OAc)] complexes (hydrogen transfer of imines to amines was observed as well) (Scheme **17**).[93] The complex with the iso-propyl function hydrogenated the aliphatic substrates faster than the aromatic ones.



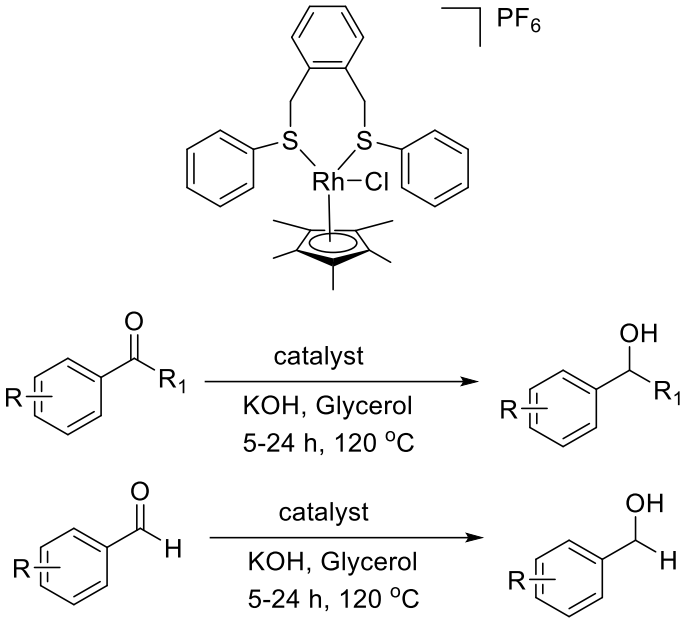
Scheme **17.** TH of ketones with chelating bis-carbene rhodium complexes.

The half-sandwich rhodium complexes are the most extensively used rhodium TH catalysts.[94-99] An easily accessible Rh(III)(η^5-Cp*)complex containing a bis-phosphine ligand catalysed TH of substituted acetophenones in 2-PrOH at 82 °C, and 94−99% conversions and 5−50 h^{-1} TOF values were obtained (Scheme **18**).[94]



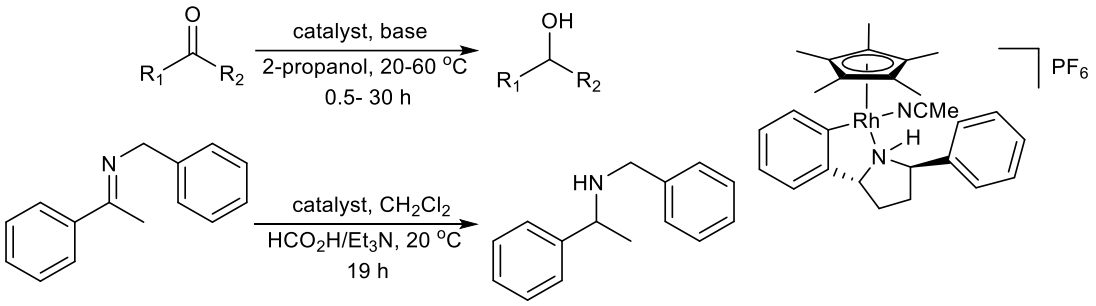
Scheme **18**. TH of ketones with bis-phosphine ligand rhodium complex.

The rhodium complex [Rh(η^5-Cp*)Cl(μ-Cl)]$_2$ with the ligand 1,2-bis-(phenylthiomethyl) benzene or 1,2-bis(phenylselenomethyl)-benzene (Scheme **19**) in the presence of NH_4PF_6 is the first rhodium catalyst for TH of carbonyls in glycerol, a cheap, nontoxic, biodegradable, and easily available by-product in biodiesel fuel production, obtained from the saponification of triglycerides of all natural fats and oils.[95]



Scheme **19**. TH of carbonyl compounds with rhodium complex.

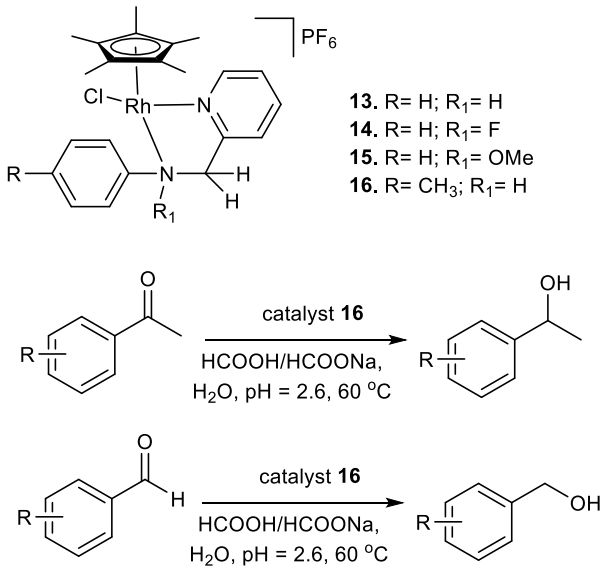
In 2011, a series cyclometalated rhodium complexes were synthesised and tested for TH of imines and ketones (Scheme **20**). The reaction was carried out in the presence of HCO_2H/Et_3N and CH_2Cl_2 as solvent more than 90 % yield was obtained.[97]



Scheme **20**. Rhodacycle catalysed TH of ketone.

Soon Later, Omondi and co-workers reported the synthesis and

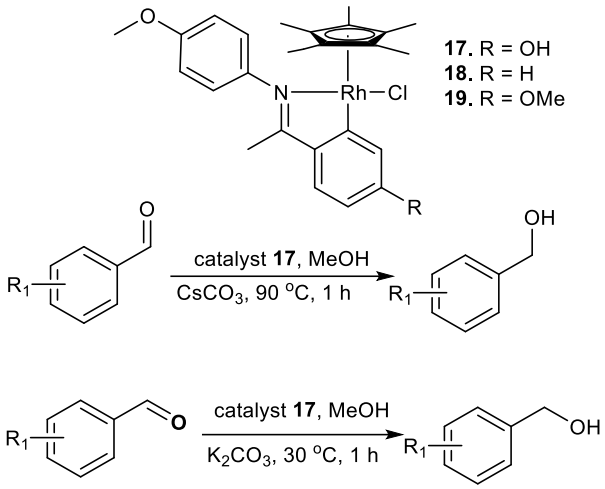
characterisation of new amine Rh(III) half-sandwich compounds with the metal centre coordinated to a N,N' chelated ligand (Scheme **21**).[98] The Ir(III) and Rh(III) amine compounds were compared in the catalytic transfer hydrogenation reaction. The Rh(III) compounds were found to be more versatile than the Ir(III) compounds. The Rh(III) compounds were particularly effective for the catalytic transfer hydrogenation of aromatic carbonyl groups in water with sodium acetate and formic acid as the hydrogen source under pH dependent acidic conditions.



Scheme **21**. TH of aromatic ketones and aldehydes by rhodacycles.

More recently, our group found that cyclometalated rhodium complexes (Scheme **22**) are highly active in the hydrogen transfer reaction of aldehydes to the corresponding alcohol in the presence of methanol as the hydrogen source.[96,99] More than 35 examples were reported, indicated the wide applicability of the system. Substituted aldehydes were

converted, with high yields (71–99 %) in methanol as hydrogen donor and solvent. It is worth noting that the TH of aldehydes could be achieved at near room temperature.



Scheme **22**. TH of aldehydes with half-sandwich cyclometalated rhodium complexes.

1.4 Conclusion and aims of the thesis

From the literature review, it is obvious that the catalytic hydrogenation processes play an indispensable role in contemporary synthetic chemistry, pharmaceutical chemistry, and other fields. Recently, a series of new catalytic hydrogenation systems have been created. Due to the application of green chemistry, replacement of the novel metal with abundant metal has gained wide concerning. At the same time, based on the characteristics of heterogeneous catalysts that are easy to separate and recycle, many more studies have been carried out and preliminary

results have been obtained. However, due to the excellent performance of novel molecular metal catalysts, homogeneous catalysis is still an important part in the field of catalytic hydrogenation. In this context, research has been focused on the improvement of the ligand and optimizing the catalytic process. Bearing this in mind, the core objective of this thesis was to develop new catalysts for TH of unsaturated compounds with the focus on the rhodium and iridium. In order to put this into practice, a series of ligands and metal complexes have been synthesised and investigated to find the suitable catalytic system where various carbonyl compounds and imines can be reduced to desired hydrogenated products.

As summarised in previous sections, there are limited catalysts and methods for the efficient TH of carbonyl compounds. The need for high catalyst loading and harsh reaction conditions limits the potential for industrial applications. In addition, the use of excessive amount of reducing agents may lead to abundant waste by-products and economic costs. In this context, the use of cheaper and greener hydrogen source like methanol are less explored.

The main aim of this thesis is to develop more efficient and greener methods for TH of carbonyls. Chapter 2 extends the previous study on TH

of unsaturated ketones to corresponding alcohols, with high activity and wide substrate scope in the presence of methanol as both solvent and hydrogen donor. Chapter 3 reports a different functional group-based rhodium catalyst for the TH and methylation of unsaturated carbonyl compounds, with methanol as hydrogen and methyl source as well as solvent.

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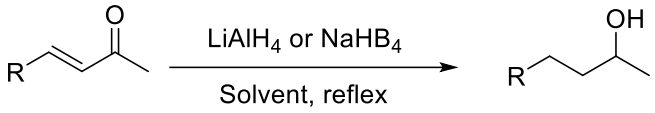
Chapter 2: Chemoselective Reduction of Unsaturated Ketones with Methanol

2.1 Introduction

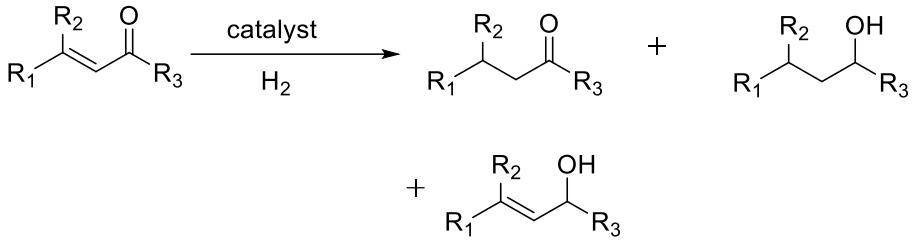
Reduction of carbonyl compounds to its corresponding alcohols and their derivatives is an important process in organic chemistry, with a number of applications in the fine chemical industry, laboratory, agrochemicals and pharmaceuticals industry.[1-5] Currently, hydrogenation is the key step in the preparation of ca. 25% of pharmaceutical drugs on the market.[3]

In the last decades, a number of methods have been reported for the reduction of carbonyl compounds. Among non-catalytic routes, reduction with lithium aluminium hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$) is widely used. Despite broad application of these agents, the reduction achieved is often lack of chemoselectivity (Scheme **1A**).[6] Among catalytic routes, reduction of carbonyl compounds is often carried out with heterogeneous catalysts using molecular hydrogen as reducing agent.[7-13] High efficiency in terms of reaction rates is usually achieved with these catalysts, although obvious limitations of this approach include low chemoselectivity and the hazards associated with the use of gaseous hydrogen. In addition, difficulty in the control of the stoichiometry of H_2 often results in substrate over-reduction (Scheme **1B**).

A. Reduction of α,β-unsaturated ketone by $LiAlH_4$ and $NaBH_4$



B. Hydrogenation of α,β-unsaturated ketone with heterogeneous catalysts using molecular hydrogen

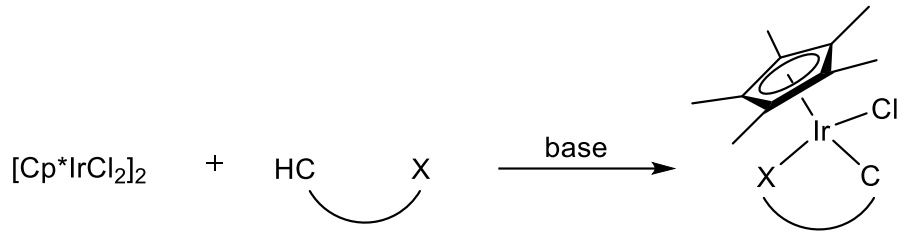


Scheme **1**. Reduction of α,β-unsaturated ketones.

Transfer hydrogenation (TH) is an attractive approach due to its operative simplicity and high selectivity. It provides a rational alternative for chemoselective reduction of the α,β-unsaturated ketones and other unsaturated compounds.[14-16] Higher molecular weight alcohols, formic acid and its salts have been described as a great hydrogen source in this method, with the reduction normally catalysed by transition metal complexes.[17-20]

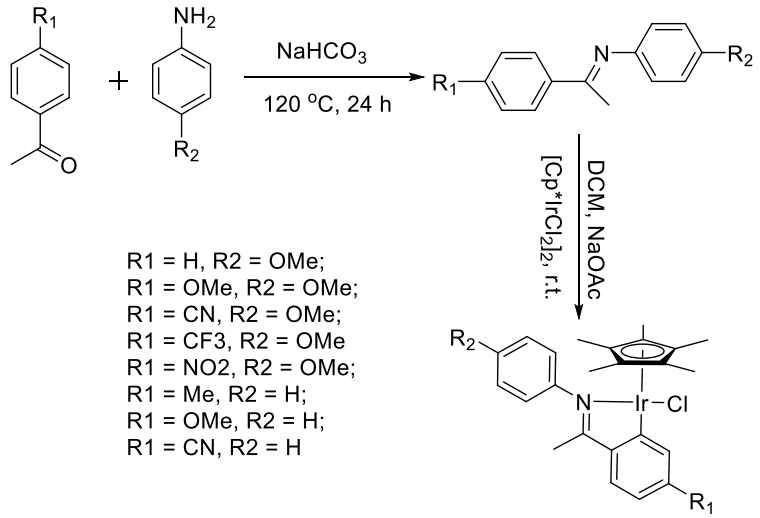
In the last decade, attention has been given to the catalytic TH with cyclometallated metal complexes as catalyst. Among this, the half-sandwich cyclometallated iridium complexes, *e.g.* [Cp*M(C^X)Cl] (M = Ir; X = C, N, O, P) are a common choice (Scheme **2**). These complexes can be easily prepared via the base promoted C–H activation of an H–C^X species

in the presence of $[Cp^*IrCl_2]_2$ under mild conditions. The prepared half-sandwich cyclometallated complexes have proven useful in hydrogenation, reductive amination, dehydrogenation, oxidation, alkylation, racemization, hydrosilylation, hydroamination, polymerization and related reactions.[19]



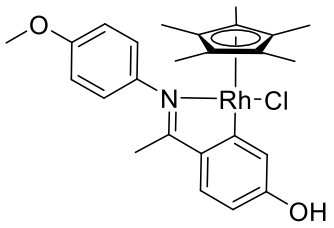
Scheme **2**. Preparation of iridacycles through the cyclometallation of H–C^X ligand.

Recently, our group reported on the preparation and application of a series of iridacycle compounds that showed activity for a range of catalytic processes.[21-22] Facile preparation of these air and moisture stable complexes makes easy their application in synthetic chemistry (Scheme **3**).



Scheme **3**. Preparation of iridacycles.

In 2018, Aboo of our group[21] introduced a new rhodacycle complex for the reduction of aldehydes with methanol as both the solvent and the hydrogen donor under mild conditions (Scheme **4**). It is noteworthy that methanol has always been considered as the securest source of hydrogen.[23] Success of these preliminary studies prompted us for further evaluation of rhodacycle complexes as catalysts in different reactions with methanol as the hydrogen source and solvent.



Scheme **4**. Rhodacycle reported by Aboo.

2.2 Aims of the project

Chemoselective reduction of α,β-unsaturated carbonyl compounds into allylic alcohols or saturated ketones are of importance to the preparation of fine chemicals, hardening of fats, pharmaceutical manufacturing processes and the synthesis of various organic intermediates and solvents.[3] Although the research in the area of TH of α,β-unsaturated carbonyl compounds has been developed for decades, the demand for cheap, efficient, and versatile catalysts is on the increase in both academia and industries.[14,16,17] Therefore, the main aim of this

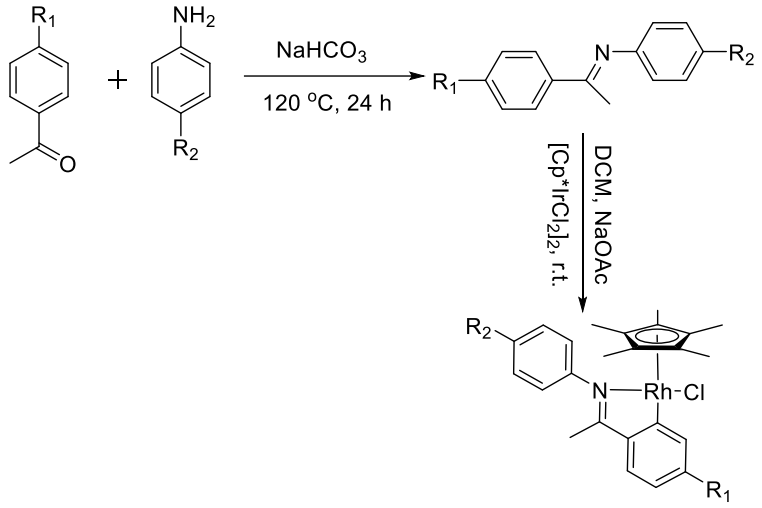
project is to develop more efficient and greener catalyst is for selective reduction of carbonyl compound using cheaper and abundant hydrogen sources.

Inspired by the success of the synthesised rhodacycle complex in TH of simple aldehydes and double bonds of various substituted conjugated aromatic ketones,[23] we would like to study it in the TH of both aromatic and aliphatic carbonyl compounds. In addition, we would like to explore these complexes further in the methylation of α,β-unsaturated ketones and other potential applications.

2.3 Result and discussion

2.3.1 Synthesis of rhodacycles

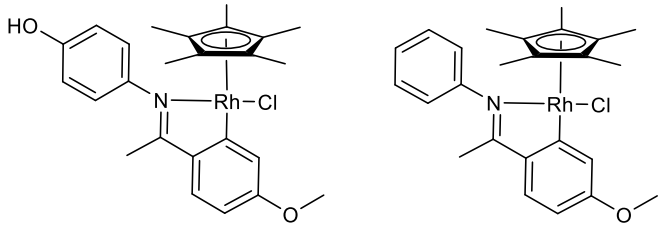
Synthesis of the cyclometallated Rh(III) metal complexes are shown in Scheme **5**. Preparation of imine species (used further as bidentate C, N-ligands) was achieved under the conditions described in the literature.[22] The imine species was derived from *p*-benzophenones and *p*-anilines. The imine species was then combined with the $[Cp^*RhCl_2]_2$ dimer in DCM at room temperature.



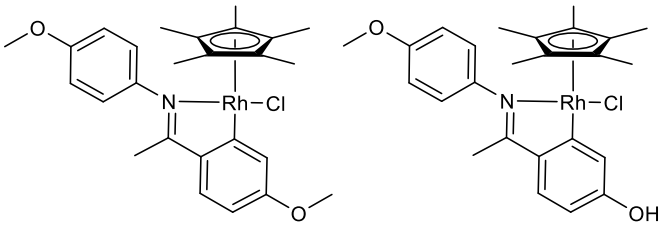
Scheme **5**. Formation of cyclometallated rhodium complexes.

Complexes **1**–**4** were synthesised, and their structures were established using ^{1}H NMR, ^{13}C NMR and ESI-mass-spectrometry. On comparison, complexes **1** and **4** are structural isomers, as they have similar imine ligand with only a difference in the position of the hydroxyl and methoxy group. Structures of **1**–**4** are schematically shown in Scheme **6**.

Complexes **1** and **4** were reported previously by other members of our group; complexes **2** and **3** were prepared by me in the similar fashion and were evaluated as potential catalysts for TH of carbonyl compounds.



1 (Yield= 80%) **2** (Yield=85%)



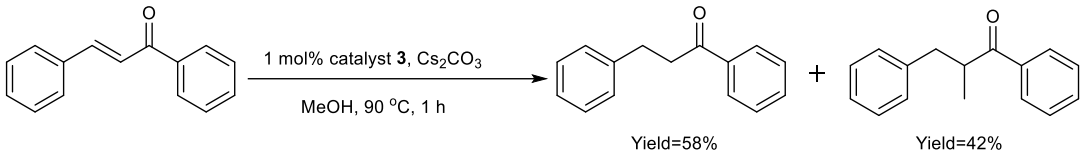
3 (Yield= 87%) **4** (Yield= 82%)

Scheme **6**. Schematic structures of rhodacycle species prepared.

2.3.2 Chemoselective reduction of unsaturated ketones

The reported procedure for the TH reaction of α,β-unsaturated ketone was used to examine the activity of complexes **1**-**4**.[20] 1,3-diphenyl-2-propenone was selected as a substrate. The substrate was expected to be reduced to the corresponding saturated ketone under these conditions: 1 mol% catalyst, 1 mol% base, 2.5 mL MeOH, at 90 °C for 1 h based on the previous report.[23] The composition of the reaction mixture was determined by GC-MS. Use of complexes **1**, **2** and **4** led to the chemoselective reduction of C=C double bond to give the expected saturated ketone. For **3**, two different products were obtained: one corresponds to the saturated ketone, while another presumably

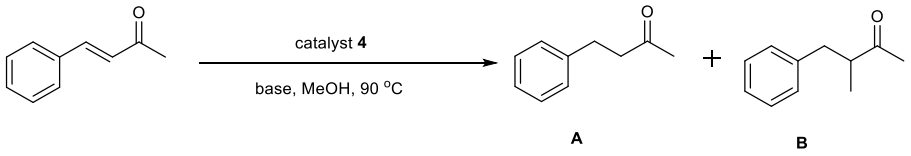
corresponds to the methylated saturated ketone (M = 224, Scheme **7**). The ratio between the products was ca. 1.4:1 (determined by ^{1}H NMR).



Scheme **7**. TH of α,β-unsaturated ketone catalysed by Rh complex **3**.

4-Phenyl-3-buten-2-one was also screened under the same conditions with rather similar outcome (Table **1**). Product yields were determined by ^{1}H NMR and composition of the reaction mixture was also confirmed by GC-MS. Among **1**–**4**, only catalyst **4** led to the selective reaction of the C=C bond in the vinylic α,β-unsaturated ketone without subsequent methylation of the saturated ketone formed (Table **1**, entry 4). The reason for this difference of the product is probably due to the presence of a hydroxyl group in the catalyst.

Table **1**. Hydrogenation of α,β-unsaturated ketone.



entry[a]	catalyst	**A** yield (%)	**B** yield (%)[b]
1	**1**	90	10

2	**2**	82	18
3	**3**	50	50
4	**4**	100	none

[a] Reaction conditions: 1 mol% catalyst, 0.25 mmol substrate, 0.5 equiv. of base, 1.5 mL MeOH, stirring at 90 °C for 1 h.

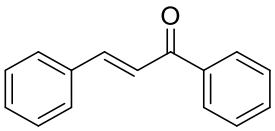
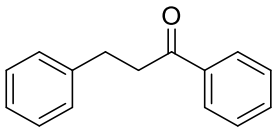
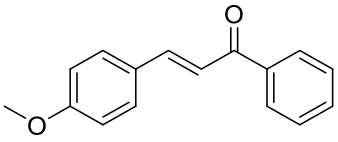
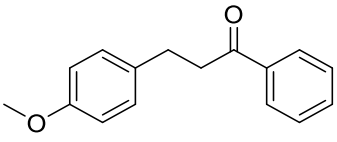
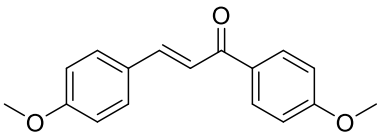
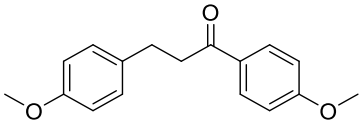
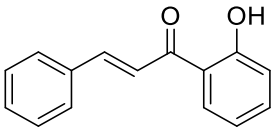
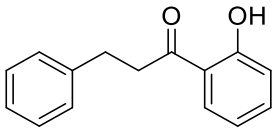
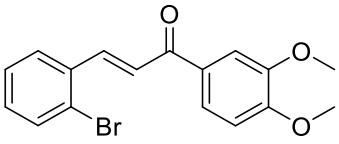
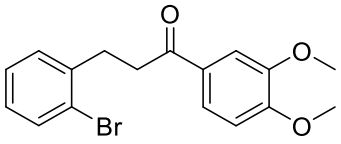
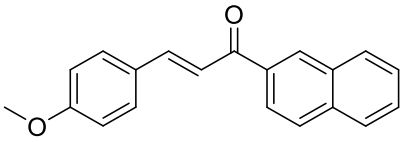
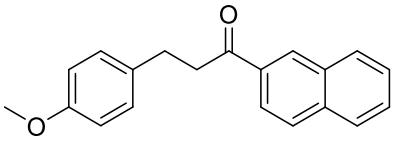
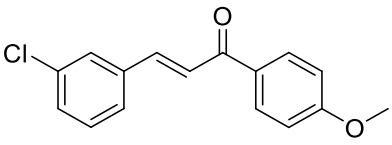
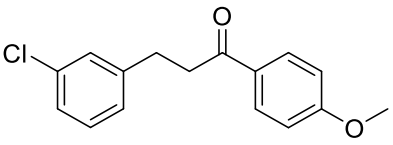
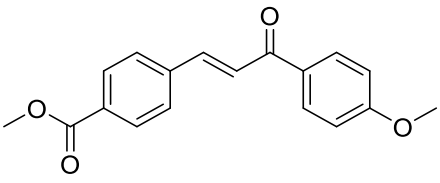
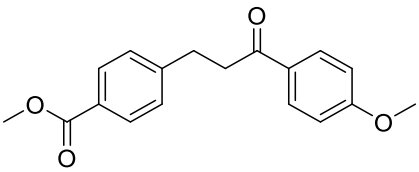
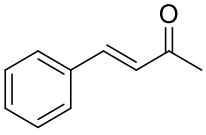
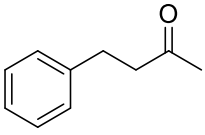
[b] The yield was determined by NMR.

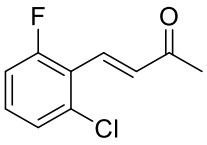
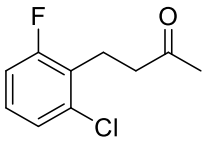
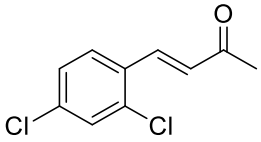
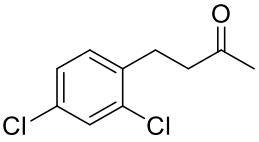
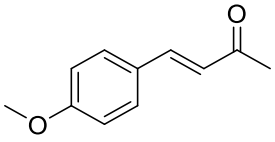
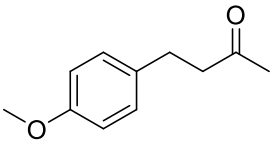
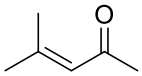
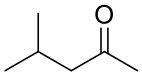
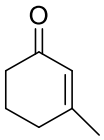
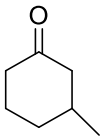
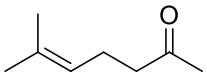
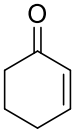
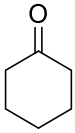
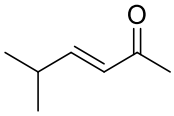
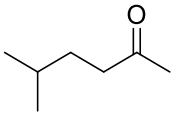
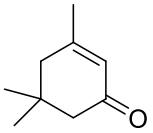
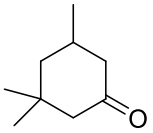
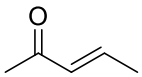
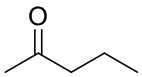
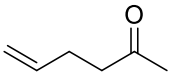
Inspection of the data above suggests that complex **4** shows excellent chemoselectivity in the reduction of carbonyl compounds to saturated ketones without any side products formed. The substrate scope of the reactions was subsequently extended to aromatic compounds with electron donating and withdraw groups and aliphatic species (Table **2**). Among them, entry 4-8 and 10-11 were finished by my collaborator Aboo. In the previous work of our group, the catalytic activity of this rhodacycle for the TH of saturated ketones was observed. In the current study, I extended the application of the catalyst to more aromatic ketones, styryl methyl ketones and aliphatic methyl vinyl ketones with different functional group. For the chalcones, both electron-donating and withdrawing substituents on the styryl side are tolerated (Table **2**, entry 1-

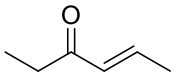
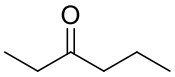
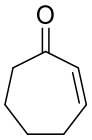
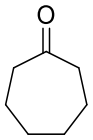
8). It is worth noting that chalcones having 2-sustituted or 2,6-disubstituted styryl units were all reduced with high yields (Table **2**, entry 5), considering that the hydride addition would take place at the β position of the C=C double bond. The rhodacycle **4** catalysed reduction with MeOH also works for styryl methyl ketones (Table **2**, entry 9-12). Again, the transfer hydrogenation is highly chemoselective, only affording the saturated ketones, and the reduction tolerates both electron-donating and withdrawing substituents on the styryl side (Table **2**, entry 11) and substrates bearing 2,6-disubstituted styryl units are equally viable (Table **2**, entry 10).

We also examined the reduction of aliphatic methyl vinyl ketones with **4** in MeOH. As can be seen below, these ketones including examples of cyclohexenone and cycloheptenone were also reduced, affording the corresponding saturated ketones in high yields (Table **2**, entry 13, 14, 16-19, 21, 22). Notably, α-disubstituted methyl vinyl ketone was reduced with no difficulty (Table **2**. entry 13). However, reduction of the substrates with non-conjugated C=C bonds was proven to be more difficult; there was no expected product formation (Table **2**, entry 15,20). The products yield of the reaction mixture was determined by isolation and/or GC.

Table **2**. Hydrogenation of carbonyl compounds with complex **4**.

Entry[a]	substrate	product	Yield (%)[b]
1			90
2			91
3			95[c]
4			86
5			95
6			90
7			94
8			97
9			86[b]

10			85
11			83
12			83[b]
13			98[c]
14			50[c]
15		N/A	N/A[d]
16			99[c]
17			94[c]
18			30[c]
19			97[c]
20		N/A	N/A[d]

22			97[c]
23			99[c]

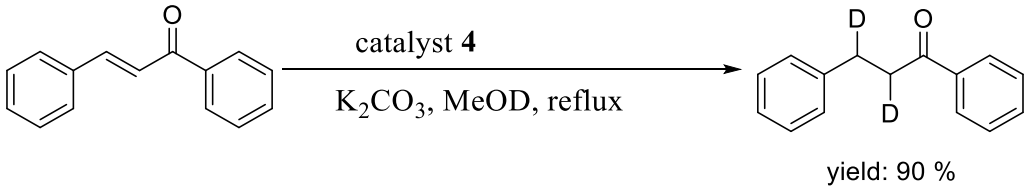
[a] Reaction Conditions: 1 mol% catalyst **4**, 0.25 mmol substrate, 0.5 equiv. of base, 1.5 mL MeOH, stirring at 90 °C for 1 h.

[b] The yield was calculated using isolated product.

[c] The yield was determined by GC or GC-MS.

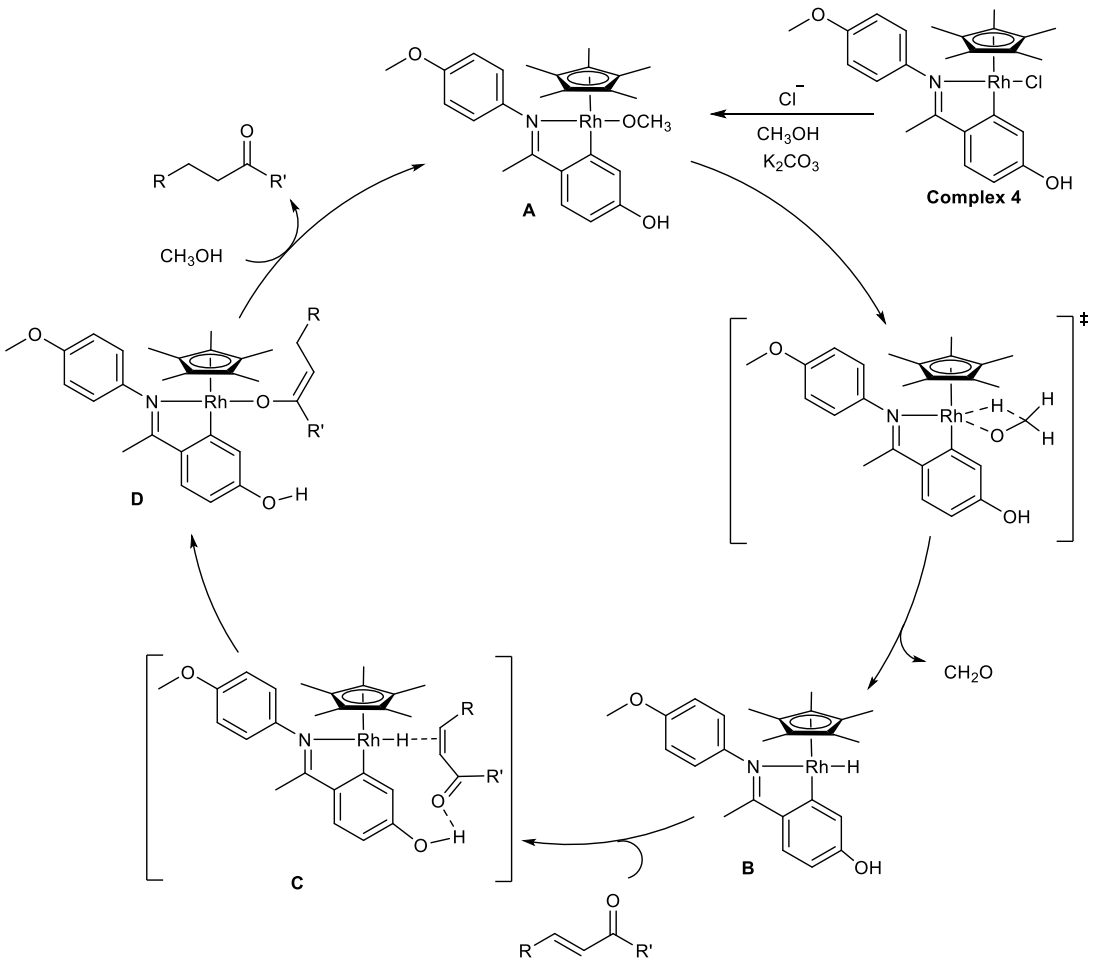
[d] No reaction.

To prove that the methanol is the only hydrogen source during the TH, the reduction of a model ketone in deuterated methanol (CD_3OD) was carried out. As shown in Scheme **9**, deuterium was found at both α and β position.



Scheme **9**. TH of α,β-unsaturated ketone with deuterated methanol.

2.4 Proposed Mechanism



Scheme **10.** A possible catalytic cycle for the rhodacycle **4** catalysed selective transfer hydrogenation of unsaturated ketones with MeOH.

On the basis of our group's previous study,[21] a plausible reaction mechanism for the **4** catalysed chemoselective reduction of unsaturated ketones with methanol is proposed in Scheme **10**. Under the basic reaction conditions employed, the alkoxide complex **A** is formed from the rhodacycle **4** in MeOH. Then the complex **A** undergoes β-hydrogen elimination, giving rise to the hydride complex **B** while releasing

formaldehyde, support for which was provided in our study of reduction of aldehydes with methanol.[21] The next step sees the hydride in complex **B** being transferred to the β-position of the C=C double bond, affording the species **D**. The hydride transfer may proceed via an intermediate **C**, in which the ligand hydroxyl group hydrogen-bonds with the ketone oxygen, rendering the C=C bond more electrophilic and thereby facilitating the hydride transfer. Such ligand-facilitated reduction has been well documented; however, the ligand-substrate interaction is usually confined to a smaller ring.[26,27] Finally, protonation of **D** with MeOH affords the saturated ketone while regenerating **A**.

2.5 Conclusion

Several rhodacycles have been synthesised and tested in transfer hydrogenation reactions. Rhodium complexes **1**–**4** were first used for reduction of an α,β-unsaturated carbonyl compound and complex **3** was found to give reduction/methylation product. In particulars, the rhodacycle **4** showed excellent chemselective transfer hydrogenation of α,β-unsaturated ketones under mild conditions in the presence of methanol as both a hydrogen donor and solvent. Only 1 mol% catalyst loading was applied during the reaction system. A variety of chalcones as substrates were hydrogenated into corresponding saturated ketones by

the catalyst. The process could also be applied to the aliphatic unsaturated ketones, but only a limited number of substrates were hydrogenated. The use of cheap, commercially available, green, and environmentally friendly methanol in this reaction reminds us that methanol could be a good alternative to other commonly used hydrogen sources, such as *i*PrOH and HCOOH.

2.6 Experimental

2.6.1 General information

All reactions were carried out with oven-dried glassware using standard Schlenk techniques under an inert atmosphere of dry argon. Chemicals, reagents and solvents were purchased commercially and used as received. Methanol was of HPLC grade. TLC silica gel 60F254 (Merck) plates were used for the analytical thin-layer chromatography and they were revealed under ultra-violet irradiation, potassium permanganate or iodine. Columns were run using a mixture of hexane/ethyl acetate and silica gel 60 Å (230-400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 400 MHz spectrometer using $CDCl_3$ as solvent with TMS as the internal standard at 25 ^{o}C. ^{1}H and ^{13}C NMR spectra were calibrated against the residual solvent signal at the corresponding central peak (^{1}H: $CDCl_3$ 7.26 ppm; ^{13}C: $CDCl_3$ 77.16 ppm). Chemical shift (δ) and coupling constants

(*J*) are given in ppm and in Hz, respectively.

Synthware® pressure tubes with front seal (25 mL) were used for the reaction.

Where appropriate analysis of reaction mixtures was undertaken on an Agilent 6890N/7890A gas chromatographic system equipped with a split/splitness injector and flame ionization detector. HP-5 capillary GC column (30m x 0.25mm i.d.) and helium as gas carrier were routinely used. Inject temperature 250 °C; detector temperature 300 °C; inlet pressure 15 psi; initial oven temperature 50 °C for 2 min, then ramp up to 300 °C (20 °C/ min), and 15 mins hold at 300 °C.

Substrates (chalcones) were prepared by aldol condensation according to the literature method.[24]

The rhodium complexes were prepared using the published procedures.[21]

2.6.2 General procedure for the imine ligand preparation

Imine ligands were prepared based on our previous work.[21] In a 250 mL round bottomed flask, ketone (5.0 mmol), amine (5.5 mmol) and $NaHCO_3$ (420 mg, 5 mmol) were dissolved in toluene (80 mL), and 4 Å

molecular sieves (1.2 g) were introduced. The resulting mixture was fitted with a Dean-Stark condenser and heated to reflux for 24 h. After completion, solid residues were removed, followed by removal of solvent in vacuo. The imine ligand was obtained from crystallization by using DCM/hexane.

2.6.3 General procedure for the rhodium complexes preparation

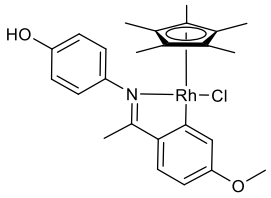
In a 50 mL round bottomed flask, $[Cp^*RhCl_2]_2$ dimer (100 mg, 0.16 mmol) (Cp* = pentamethylcyclopentadiene), imine ligand (2.2 eq.) and sodium acetate (10 eq.) were dissolved in DCM (10 mL). Then the reaction mixture was stirred overnight under a nitrogen atmosphere at room temperature. The resulting mixture was then filtered to remove insoluble materials, dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo. The crude solid product was then washed with diethyl ether/hexane to afford an air and moisture stable pure compound.

2.6.4 General procedures for TH of ketones

A Radleys tube was charged with an unsaturated ketone (0.3 mmol), catalyst (0.003 mmol) and K_2CO_3 (0.25 equiv.). MeOH (1.5 mL) was introduced, and then the reaction mixture was heated to reflux at 90 ^oC for 1 h. After cooling to room temperature, the solvent was evaporated

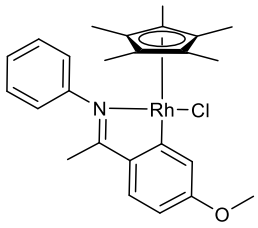
under vacuum and flash column chromatography using a hexane/ethyl acetate mixture was carried out to purify the product.

2.6.5 Analytic data of isolated products



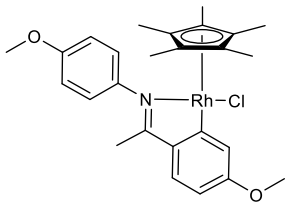
Rhodium complex 1:[21] ^{1}H NMR ($CDCl_3$, 400 MHz,298K) δ (ppm): 7.26 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 2.3 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.42 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.85 (s, 3H), 2.24 (s, 3H), 1.38 (s, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 185.32, 178.25, 157.97, 157.43, 143.66, 140.19, 129.11, 124.36, 122.98, 110.53, 99.99, 96.08, 96.01, 55.52, 17.02, 8.76; HRMS for $C_{25}H_{29}RhNO_2$ $[M\text{-}Cl]^+$: m/z calc.: 478.1236; found 478.1232.

Due to the fluxionality, two of the aromatic hydrogens in complex **1** appeared very broad and featureless at r.t. A better resolved spectrum was obtained in CD_2Cl_2 at a lower temperature (- 60 °C). ^{1}H NMR (CD_2Cl_2, 400 MHz, 298 K) δ (ppm): 7.47 (d, *J* = 8.5 Hz, 1H), 7.37 (s, 2H), 6.92 (d, *J* = 8.1 Hz, 2H), 6.64 (d, *J* = 8.5 Hz, 1H), 3.95 (s, 3H), 2.29 (s, 3H), 1.41 (s, 15H). ^{1}H NMR (CD_2Cl_2, 400 MHz, 213 K) δ (ppm): 7.65 (s, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.30 (s, 1H), 7.18 (s, 1H), 6.94 (s, 1H), 6.72 (s, 2H), 6.58 (d, *J* = 7.4 Hz, 1H), 3.88 (s, 3H), 2.22 (s, 3H), 1.33 (s, 15H).



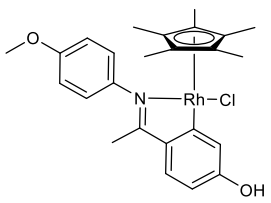
Rhodium complex 2:[21] ^{1}H NMR ($CDCl_3$, 400 MHz,298K) δ7.41 (dd, *J* = 7.4 Hz, 4H), 7.29 – 7.04 (m, 1H), 6.59 (d, *J* = 8.6 Hz, 1H), 3.92 (s, 3H), 2.28 (s, 3H), 1.38 (s, 15H). ^{13}C NMR ($CDCl_3$, 101 MHz,) δ 125.90, 120.72, 108.52, 96.12, 96.06, 77.33, 77.01, 76.70, 55.14, 8.71, HRMS for $C_{25}H_{29}ClRhNO$ [M + Na] $^{+}$: m/z calc.: 520.6232; found: 520.6263.

Due to the fluxionality, two of the aromatic hydrogens in complex **2** appeared very broad and featureless at r.t. A better resolved spectrum was obtained in CD_2Cl_2 at a lower temperature (- 60 °C). ^{1}H NMR (CD_2Cl_2, 400 MHz, 298 K) δ (ppm): 7.52 – 7.45 (m, 3H), 7.37 (d, *J* = 2.5 Hz, 1H), 7.28 (t, *J* = 8.4 Hz, 1H), 6.65 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.96 (s, 3H), 2.30 (s, 3H), 1.39 (s, 15H).^{1}H NMR (CD_2Cl_2, 400 MHz, 213 K) δ (ppm): 7.83 (d, *J* = 7.5 Hz, 1H), 7.49 (dd, *J* = 13.3, 7.8 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.33 – 7.21 (m, 2H), 6.91 (d, *J* = 7.2 Hz, 1H), 6.61 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 2.28 (s, 3H), 1.31 (s, 15H).



Rhodium complex 3:[21] 1H NMR ($CDCl_3$, 400 MHz, 298K) δ (ppm): 7.41 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 2.3 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.58 (dd, *J* = 8.5, 2.3 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 2.27 (s, 3H), 1.39 (s, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 182.38, 182.06, 178.06, 157.38, 156.64, 143.75, 140.18, 130.39, 124.45, 122.37, 118.21, 95.91, 95.85, 55.54, 53.42, 17.03, 15.69, 8.79; HRMS for $C_{26}H_{31}ClRhNO_2Na$ $[M + Na]^+$: m/z calc.: 550.0996; found 550.0988.

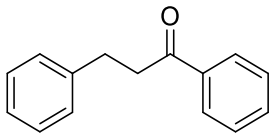
Due to the fluxionality, two of the aromatic hydrogens in complex **3** appeared very broad and featureless at r.t. A better resolved spectrum was obtained in CD_2Cl_2 at a lower temperature (- 60 °C). ^1H NMR (CD_2Cl_2, 400 MHz, 298 K) δ (ppm): 7.47 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 6.64 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.29 (s, 3H), 1.41 (s, 15H). ^1H NMR (CD_2Cl_2, 400 MHz, 213 K) δ (ppm):7.79 (d, *J* = 8.3 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.28 (s, 1H), 7.01 (s, 1H), 6.87 (d, *J* = 7.1 Hz, 2H), 6.60 (d, *J* = 8.2 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 2.26 (s, 3H), 1.33 (s, 15H).



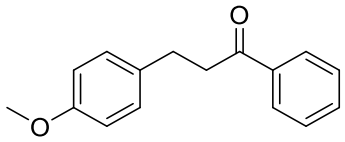
Rhodium complex 4:[21] ^1H NMR ($CDCl_3$, 400 MHz,298K) δ (ppm): 7.26 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 2.3 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.42 (dd, *J*

= 8.4, 2.4 Hz, 1H), 3.85 (s, 3H), 2.24 (s, 3H), 1.38 (s, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 185.32, 178.25, 157.97, 157.43, 143.66, 140.19, 129.11, 124.36, 122.98, 110.53, 99.99, 96.08, 96.01, 55.52, 17.02, 8.76; HRMS for $C_{25}H_{29}RhNO_2$ $[M\text{-}Cl]^+$: m/z calc: 478.1248; found 478.1255.

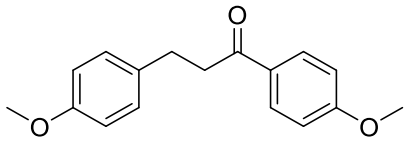
Due to the fluxionality, two of the aromatic hydrogens in complex **1** appeared very broad and featureless at r.t. A better resolved spectrum was obtained in CD_2Cl_2 at a lower temperature (- 60 °C). ^{1}H NMR (CD_2Cl_2, 400 MHz, 298 K) δ (ppm): 7.34 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 2.3 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 6.47 (dd, *J* = 8.3, 2.4 Hz, 1H), 3.88 (s, 3H), 2.27 (s, 3H), 1.40 (s, 15H).^{1}H NMR (CD_2Cl_2, 400 MHz, 213 K) δ (ppm): 7.77 (d, *J* = 8.3 Hz, 1H), 7.65 (s, 1H), 7.21 – 7.07 (m, 2H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.86 (d, *J* = 10.0 Hz, 2H), 6.26 (d, *J* = 7.8 Hz, 1H), 3.83 (s, 3H), 2.22 (s, 3H), 1.32 (s, 15H).



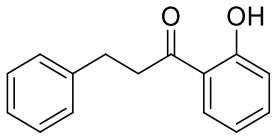
1,3-Diphenylpropan-1-one:[28] ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): 7.96 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.31-7.28 (m, 2H), 7.25-7.18 (m, 3H), 3.30 (t, *J* = 8.0 Hz, 2H), 3.07 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ (ppm): 199.23, 141.30, 136.87, 133.06, 128.5, 128.61, 128.53, 128.43, 128.04, 126.14, 40.45, 30.14; HRMS for $C_{15}H_{15}O$ $[M + H]^+$: m/z calc.: 211.1117; found: 211.1126.



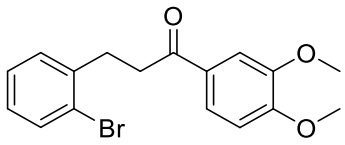
3-(4-Methoxyphenyl)-1-phenyl-1-propanone:[28] ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): δ 7.95 (d, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 3.78 (s, 3H), 3.26 (t, *J* = 8.0 Hz, 2H), 3.01 (t, *J* = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ (ppm): 199.4, 158.0, 136.92, 133.33, 133.03, 129.36, 128.6, 128.05, 113.95, 55.28, 40.71, 29.29.; HRMS for $C_{16}H_{17}O_2$ $[M + H]^+$: m/z calc.: 241.1223; found: 241.1225.



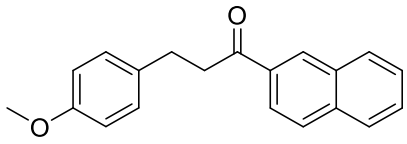
1,3-Bis(4-methoxyphenyl)-1-propanone:[28] ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): δ 7.93 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 3.21 (t, *J* = 7.2 Hz, 2H), 2.99 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ (ppm): 197.99, 163.44, 157.97, 133.49, 130.31, 130.02, 129.35, 113.92, 113.72, 55.46, 55.27, 40.37, 29.49; HRMS for $C_{17}H_{19}O_3$ $[M + H]^+$: m/z calc.: 271.1329; found: 271.1335.



1-(2-Hydroxyphenyl)-3-phenyl-1-propanone:[28] ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): 12.29 (s, 1H, 1H), 7.74 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45-7.43 (m, 1H), 7.32-7.28 (m, 2H), 7.25-7.21 (m, 3H), 6.98 (dd, *J* = 8.3, 0.88 Hz, 1H), 6.87 (td, *J* = 8.0, 1.1 Hz, 1H), 3.32 (t, *J* = 7.3 Hz, 2H), 3.00 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ (ppm): 205.39, 162.49, 140.73, 136.36, 129.83, 128.62, 128.40, 126.33, 119.29, 118.93, 118.58, 40.05, 30.04; HRMS for $C_{15}H_{15}O_2$ $[M + H]^+$: m/z calc.: 227.1067; found: 227.1076.

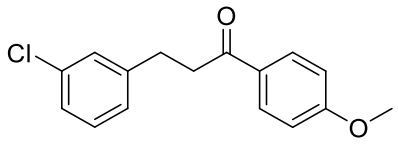


3-(2-Bromophenyl)-1-(3,4-dimethoxyphenyl)-1-propanone:[28] ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): 7.54 (d, J = 7.6 Hz, 1H), 7.49-7.48 (m, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.30-7.27 (m, 2H), 7.09 (d, *J* = 8.2, 1.8 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.21 (t, *J* = 7.2 Hz, 2H), 2.99 (t, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ (ppm): 199.21, 159.84, 156.66, 138.23, 132.78, 131.88, 130.06, 129.54, 120.70, 119.45, 112.62, 112.38, 111.92, 55.45, 38.64, 25.38; HRMS for $C_{17}H_{18}BrO_3$ $[M + H]^+$: m/z calc.: 349.0434; found: 349.0443.

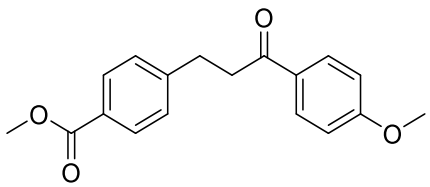


3-(4-Methoxyphenyl)-1-(naphthalen-2-yl)propan-1-one:[28] ^{1}H NMR

($CDCl_3$, 400 MHz, 298 K) δ (ppm): 8.43 (s, 1H), 8.02 (d, J = 8.6, 1.7 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.85 (t, *J* = 8.2 Hz, 2H), 7.59-7.50 (m, 2H), 7.20 (d, J = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 3.77 (s, 3H), 3.39 (t, *J* = 7.3 Hz, 2H), 3.06 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ (ppm): 199.33, 158.05, 135.58, 134.25, 133.39, 132.54, 129.7, 129.56, 129.41, 128.45, 128.43, 127.78, 126.77, 123.87, 113.99, 55.29, 40.83, 29.45; HRMS for $C_{20}H_{19}O_2$ $[M + H]^+$: m/z calc.: 291.138; found: 291.1392.

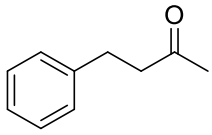


3-(3-Chlorophenyl)-1-(4-methoxyphenyl)propan-1-one:[28] ^1H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): 7.92 (d, *J* = 8.9 Hz, 2H), 7.25-7.11 (m, 4H), 6.91 (d, J= 8.8 Hz, 2H), 3.84 (s, 3H), 3.22 (t, *J* = 7.3 Hz, 2H), 3.02 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ (ppm): 197.24, 163.54, 143.55, 134.19, 130.29, 129.83, 129.75, 128.57, 126.72, 126.28, 113.78, 55.47, 39.63, 29.85; HRMS for $C_{16}H_{16}ClO_2$ $[M + H]^+$: m/z calc.: 275.0833; found: 275.0836.

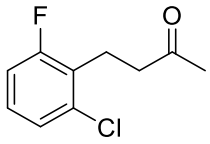


Methyl 4-(3-(4-methoxyphenyl)-3-oxopropyl)benzoate:[28] ^1H NMR

($CDCl_3$, 400 MHz, 298 K) δ (ppm): 7.96 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.26 (t, *J* = 7.8 Hz, 2H), 3.10 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.24, 167.04, 163.55, 147.00, 130.28, 129.84, 128.49, 128.09, 113.77, 55.47, 52.00, 39.44, 30.21; HRMS for $C_{19}H_{18}O_4$ $[M + H]^+$: m/z calc.: 299.1278; found: 299.1283.

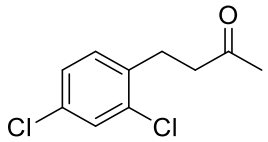


4-Phenylbutan-2-one:[28] ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): 7.30-7.28 (m, 2H), 7.21-7.17 (m, 3H), 2.90 (t, *J* = 7.6 Hz, 2H), 2.76 (t, *J* = 7.62 Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.00, 140.98, 128.50 and 128.28, 126.11, 45.18, 30.07 and 29.74; HRMS for $C_{10}H_{13}O$ $[M + H]^+$: m/z calc.: 149.0961; found: 149.0962.

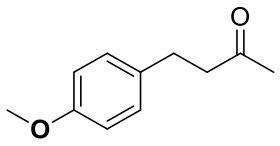


4-(2-Chloro-6-fluorophenyl)butan-2-one:[28] ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): 7.16-7.09 (m, 2H), 6.95 (t, *J* = 7.7 Hz, 1H), 3.04 (t, *J* = 7.7 Hz, 2H), 2.70 (t, *J* = 7.7 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ (ppm): 207.19, 161.34 (d, $J_{C\text{-}F}$ = 245.87 Hz), 135.04 (d, $J_{C\text{-}F}$ = 6.13 Hz), 127.91 (d, $J_{C\text{-}F}$ = 4.6 Hz), 126.73 (d, $J_{C\text{-}F}$ = 22.55 Hz), 125.22 (d, $J_{C\text{-}F}$ = 3.83

Hz), 113.94 (d, J_{C-F} = 22.9 Hz), 42.22, 29.72, 20.75 (d, J_{C-F} = 3.06 Hz); HRMS for $C_{10}H_{11}ClFO$ $[M + H]^+$: m/z calc.: 201.0477; found: 201.0483.

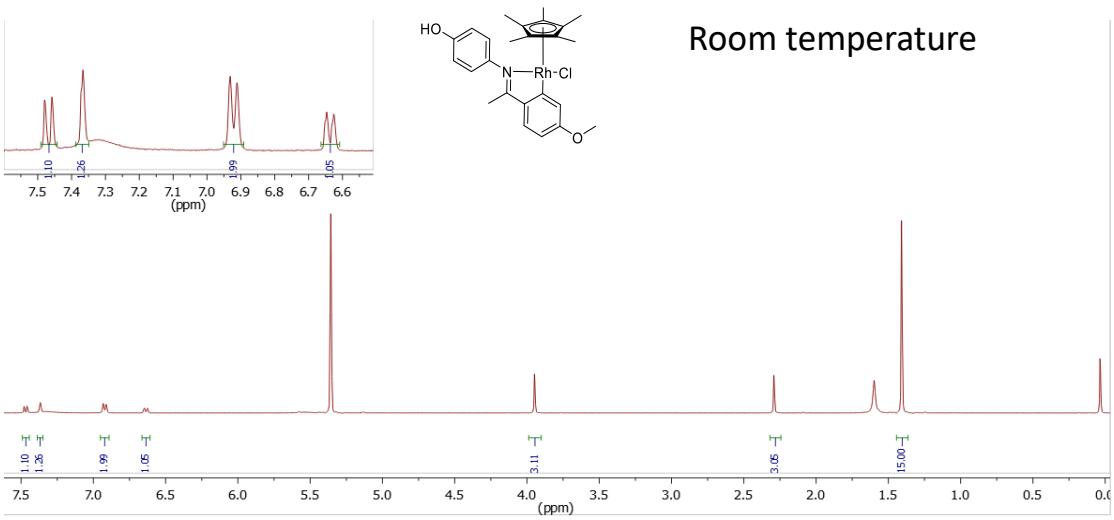


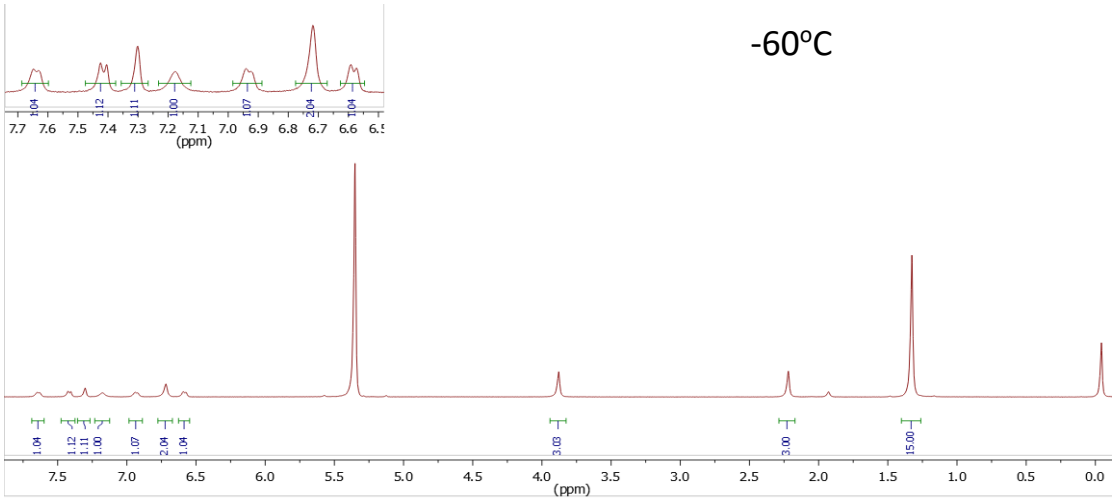
4-(2,4-Dichlorophenyl)butan-2-one:[28] ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): 7.35 (d, *J* = 1.7 Hz, 1H), 7.19-7.14 (m, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ (ppm): 207.16, 137.18, 134.47, 132.62, 131.49, 129.27, 127.15, 42.90, 29.97, 27.16; HRMS for $C_{10}H_{11}Cl_2O$ $[M + H]^+$: m/z calc.: 217.0181; found: 217.0188.

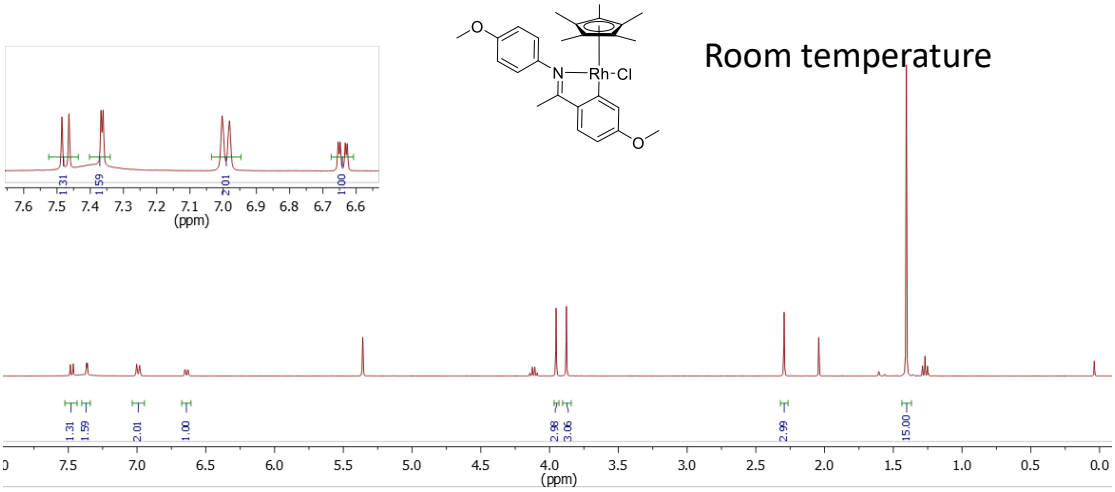


4-(4-Methoxyphenyl)butan-2-one:[28] ^{1}H NMR (CDCl3, 400 MHz, 298 K) δ (ppm): 7.10 (d, *J* = 8.11 Hz, 2H), 6.82 (d, *J* = 8.13 Hz, 2H), 3.78 (s, 3H), 2.84 (t, *J* = 7.45 Hz, 2H), 2.72 (t, *J* = 7.46 Hz, 2H), 2.13 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.15, 157.96, 133.01, 129.21, 113.91, 55.25, 45.45, 30.10 and 28.91; HRMS for $C_{11}H_{15}O_2$ $[M + H]^+$: m/z calc.: 179.1067; found: 179.1071.

2.6.6 NMR spectrum



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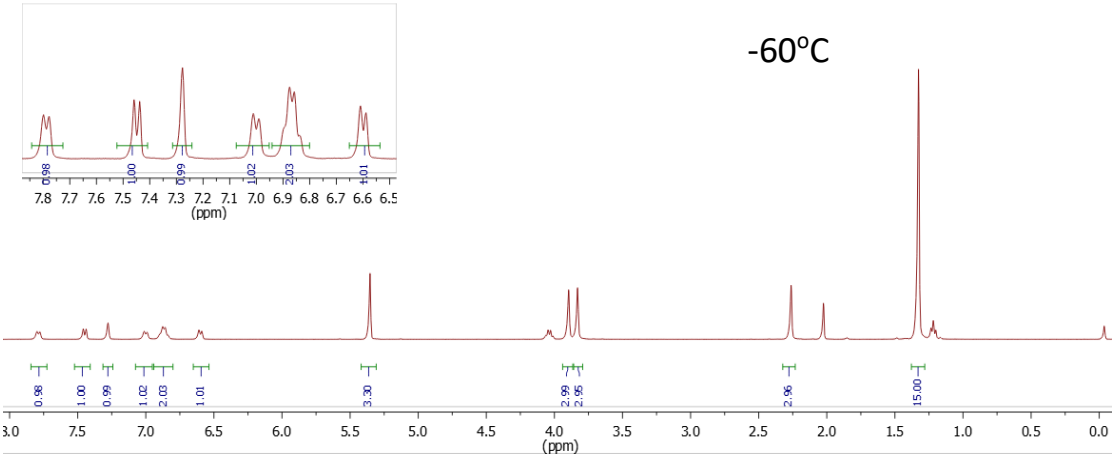
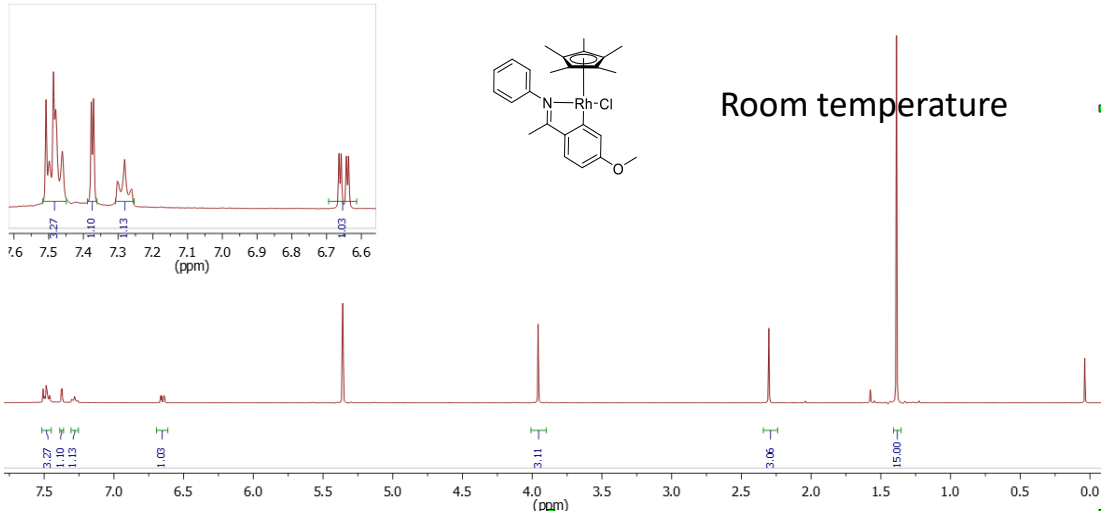
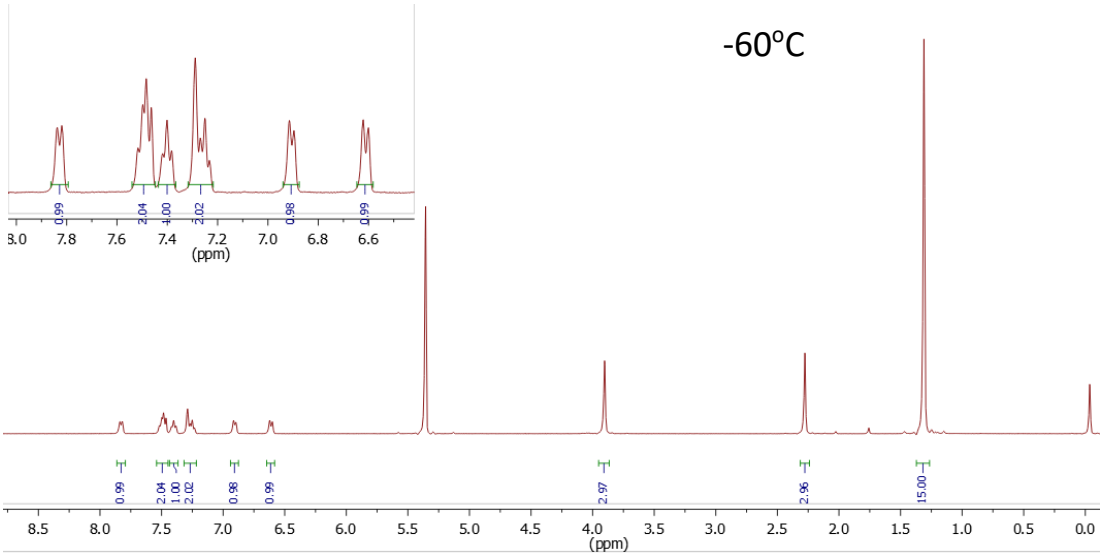
Room temperature
(ppm)


-60°C
(ppm)


Rh-Cl
N
O
Room temperature
(ppm)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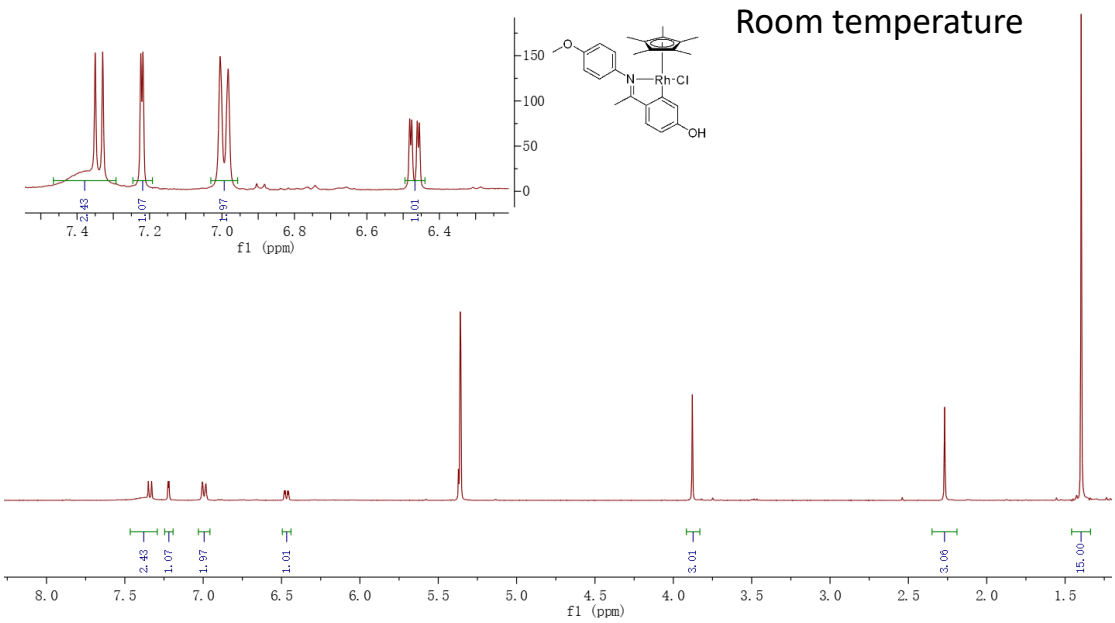
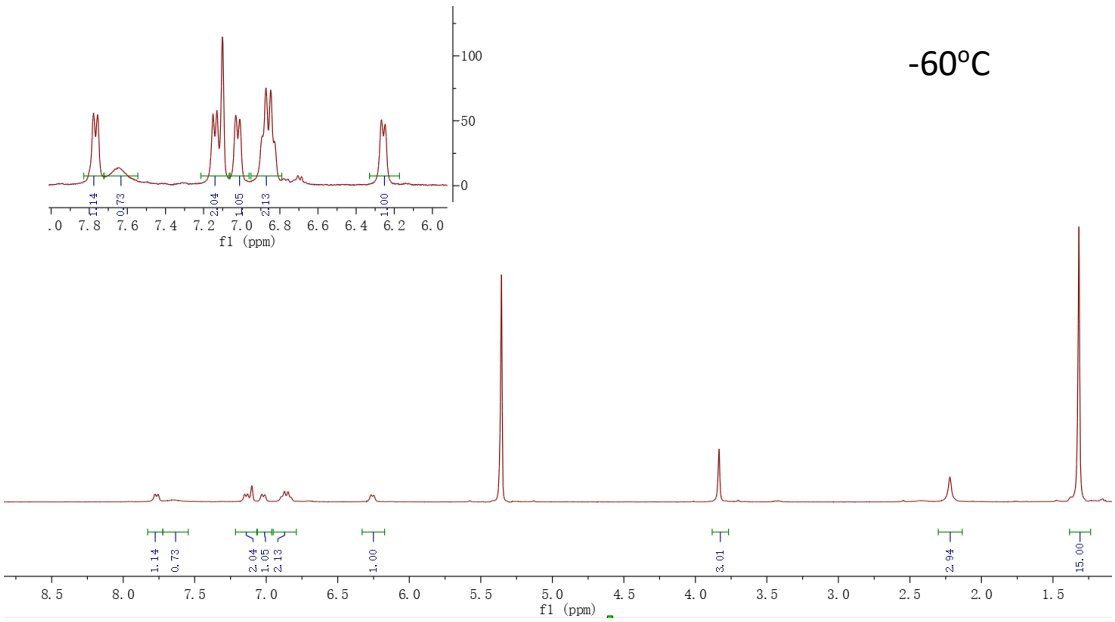

Room temperature
Rh-Cl
OH
f1 (ppm)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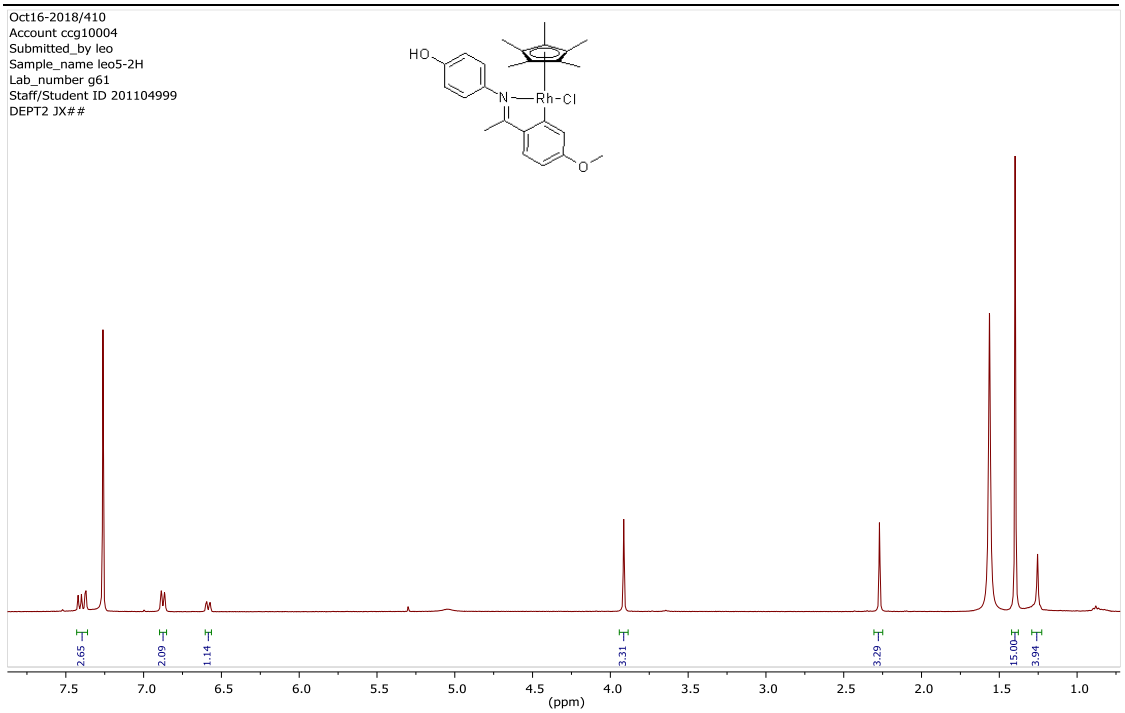
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Staff/Student ID 201104999
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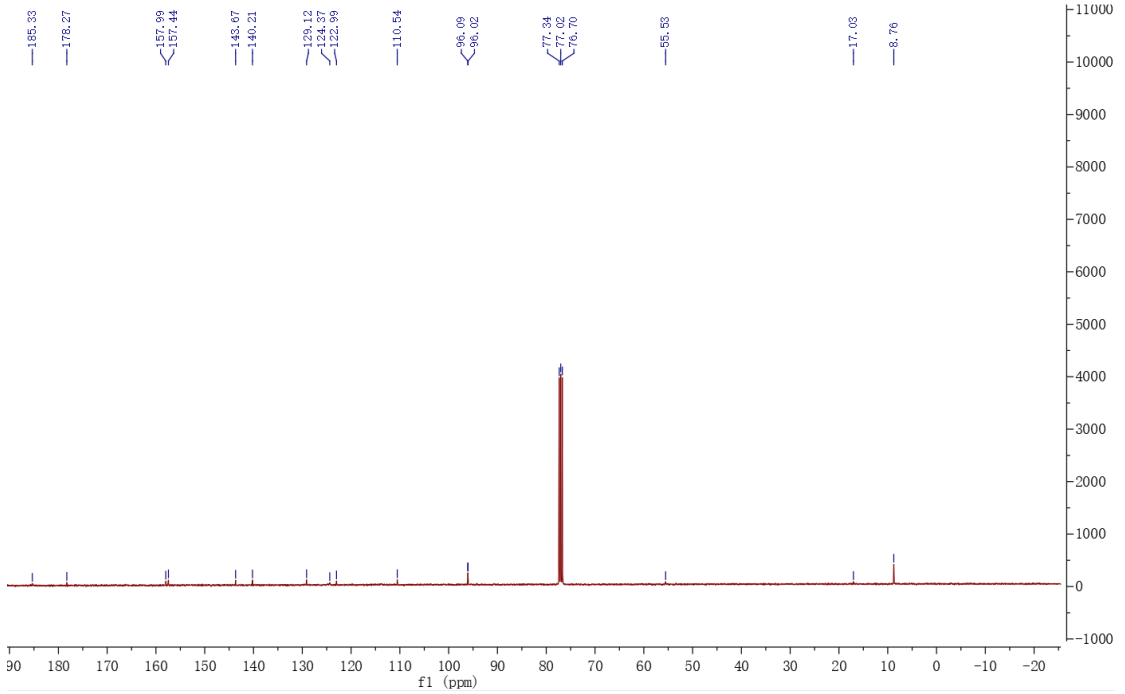
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77.02
76.70
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17.03
8.76
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7000
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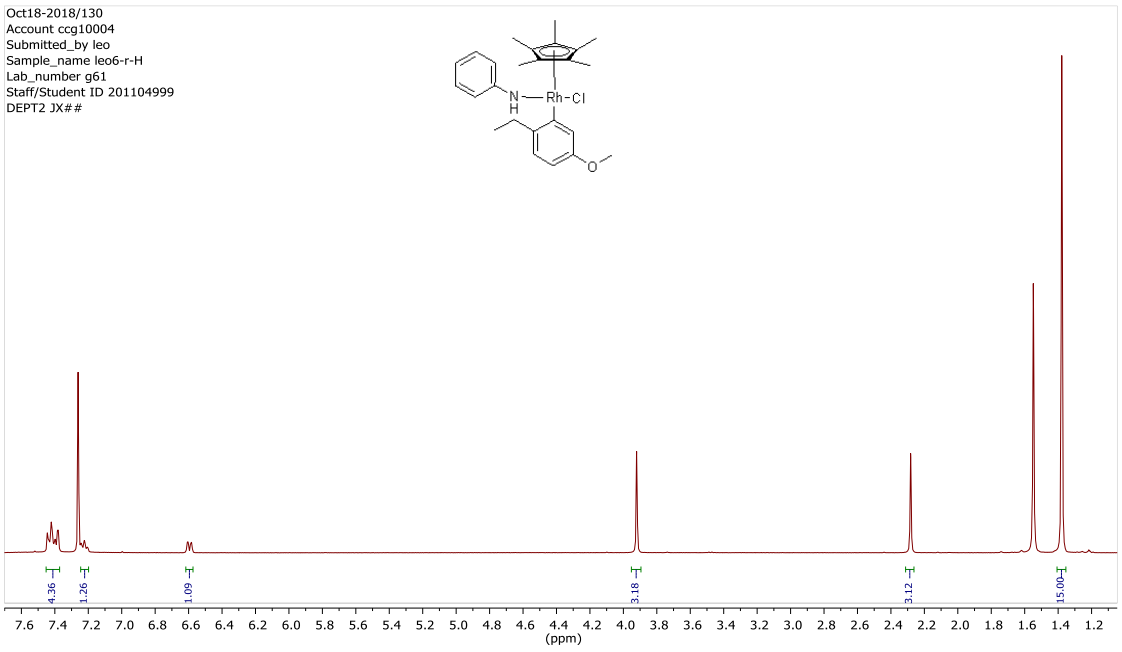
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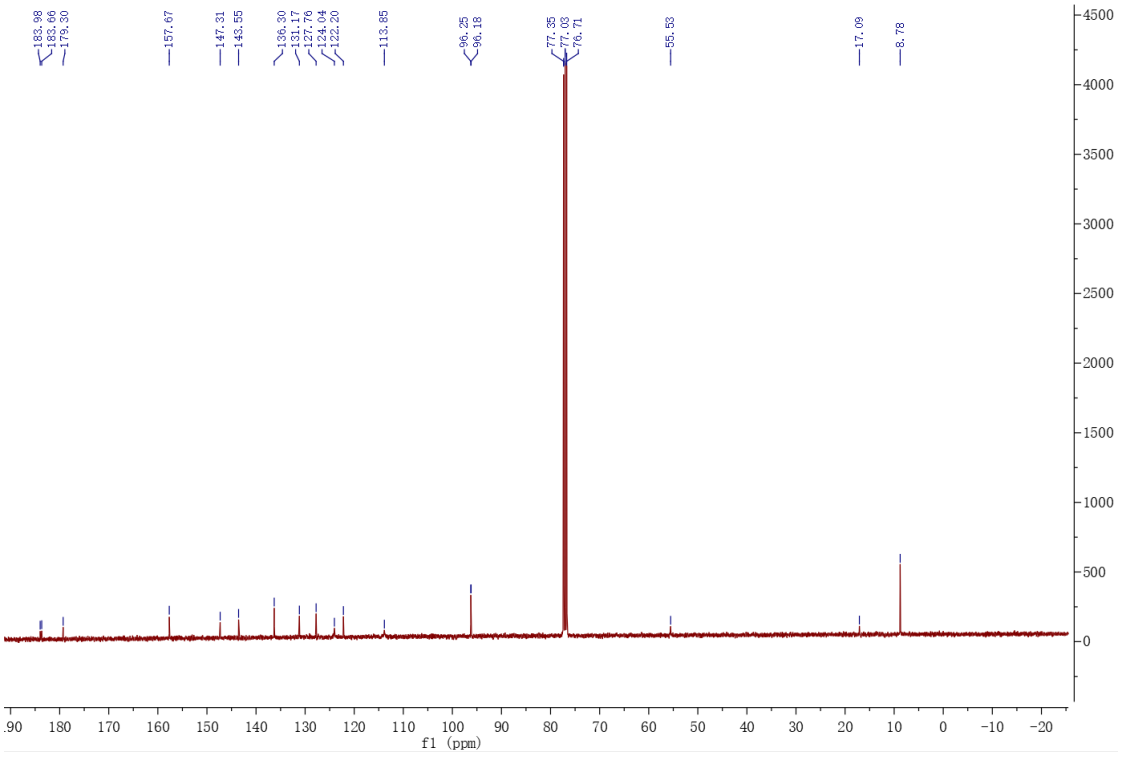
(ppm)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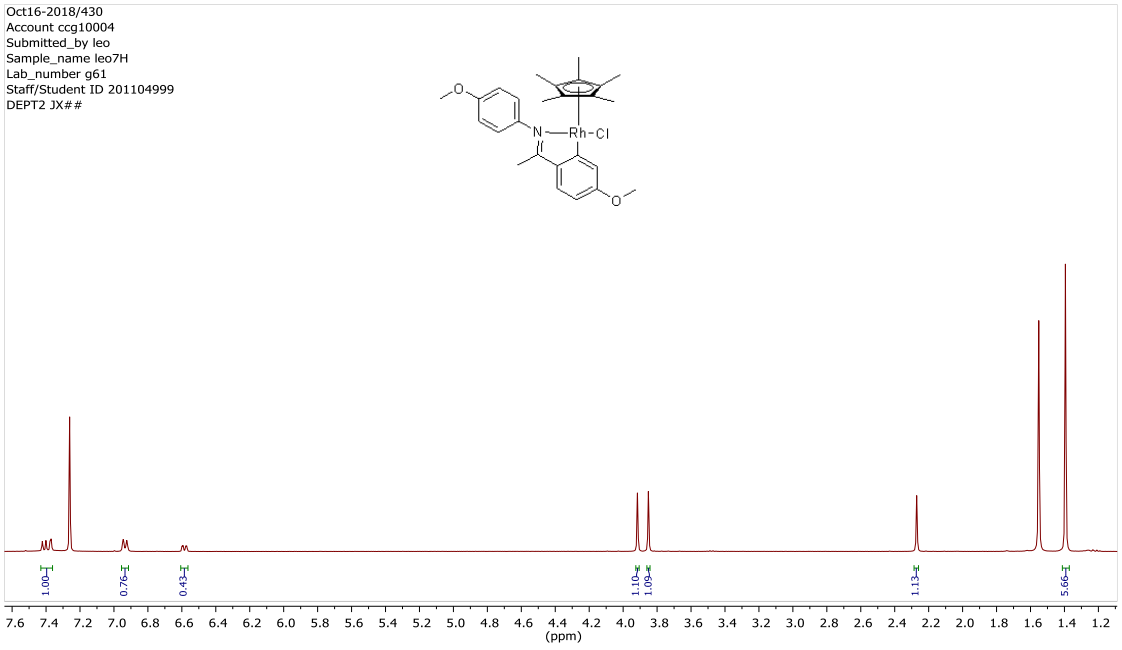
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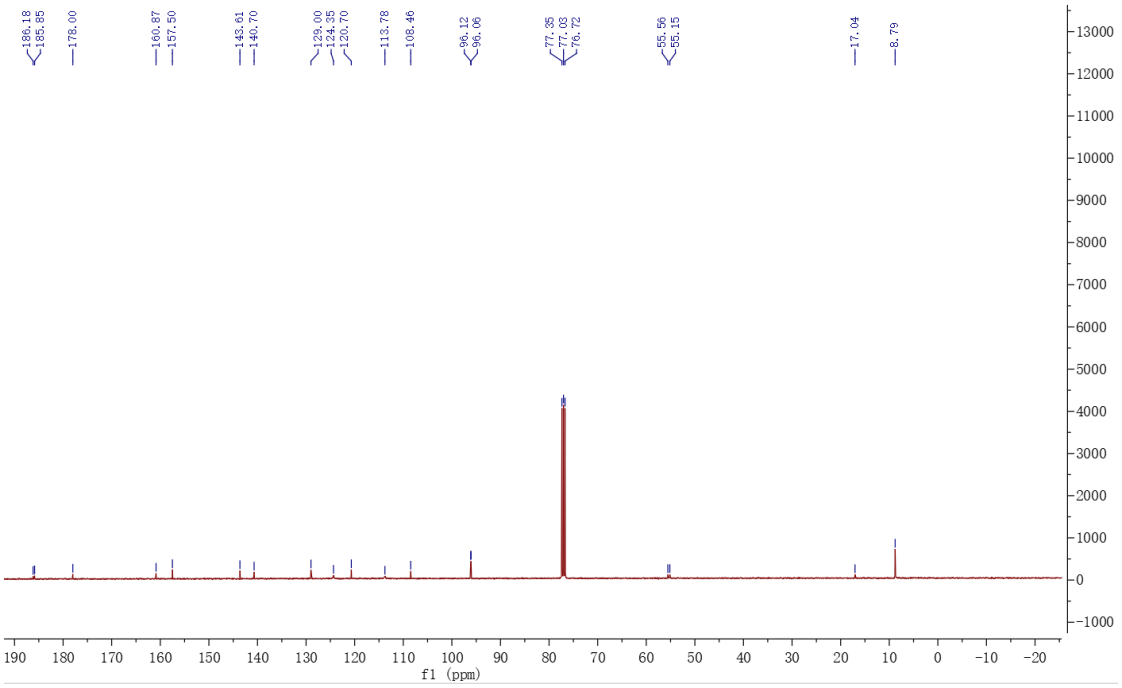
(ppm)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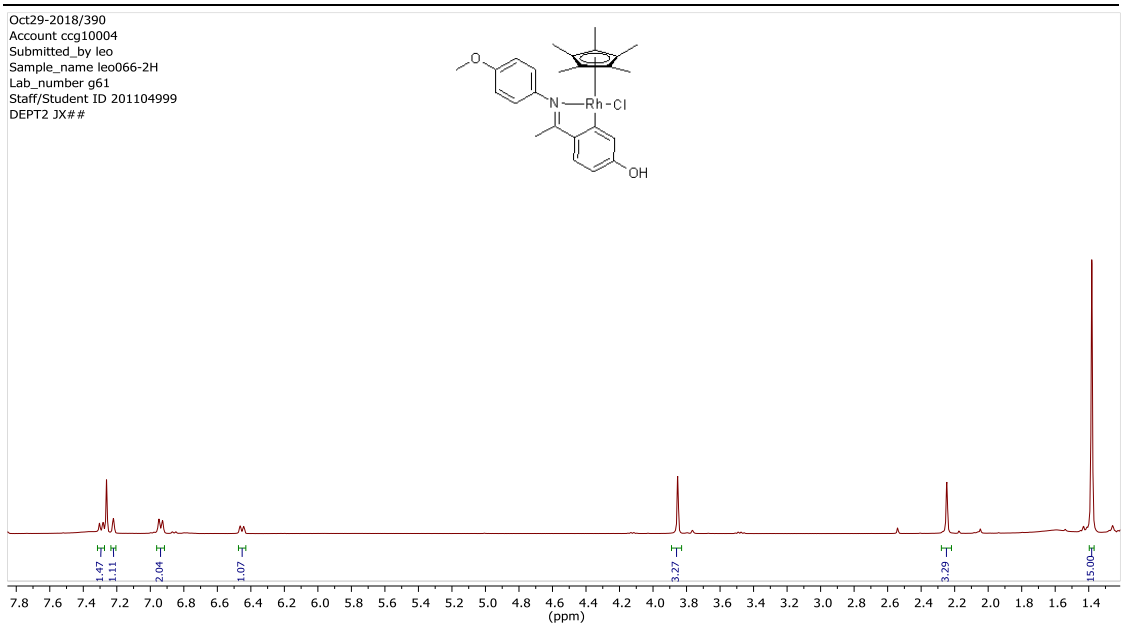
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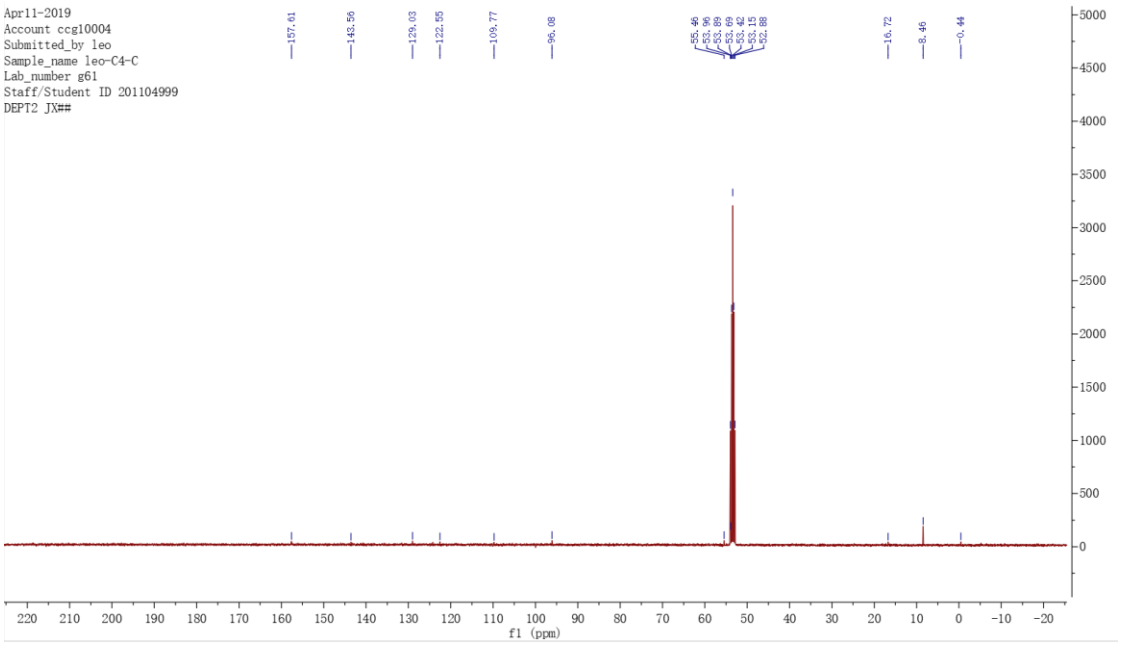
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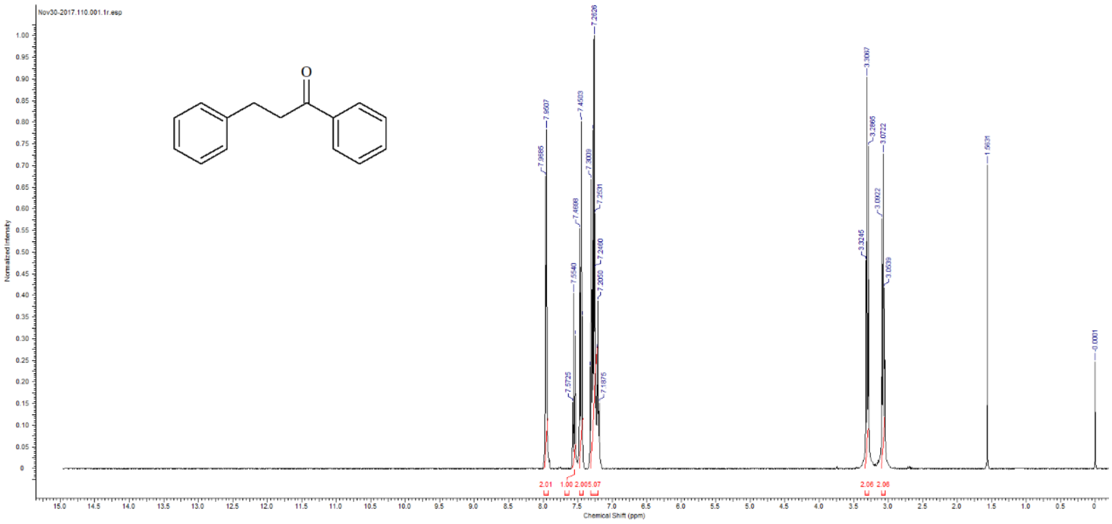
f1 (ppm)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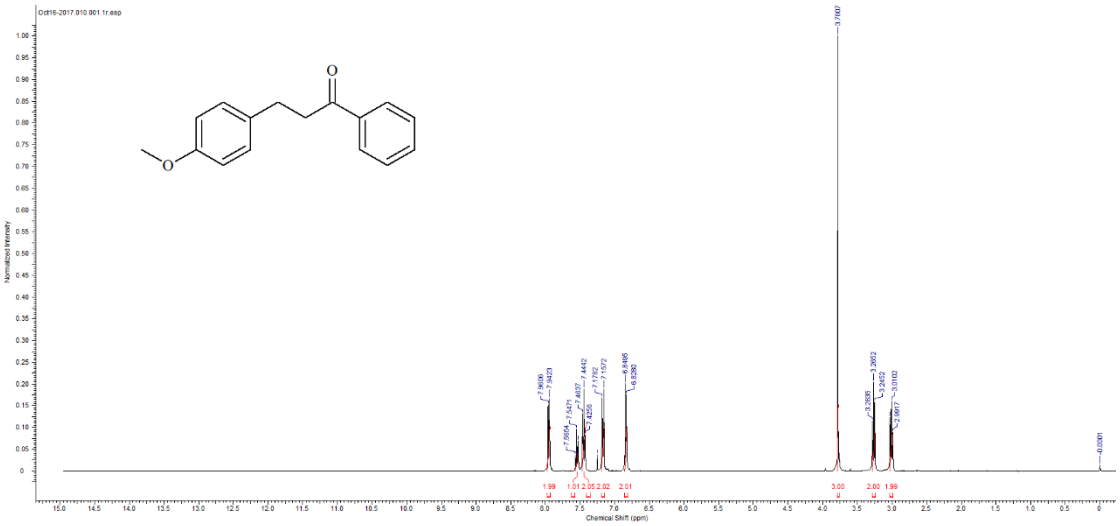
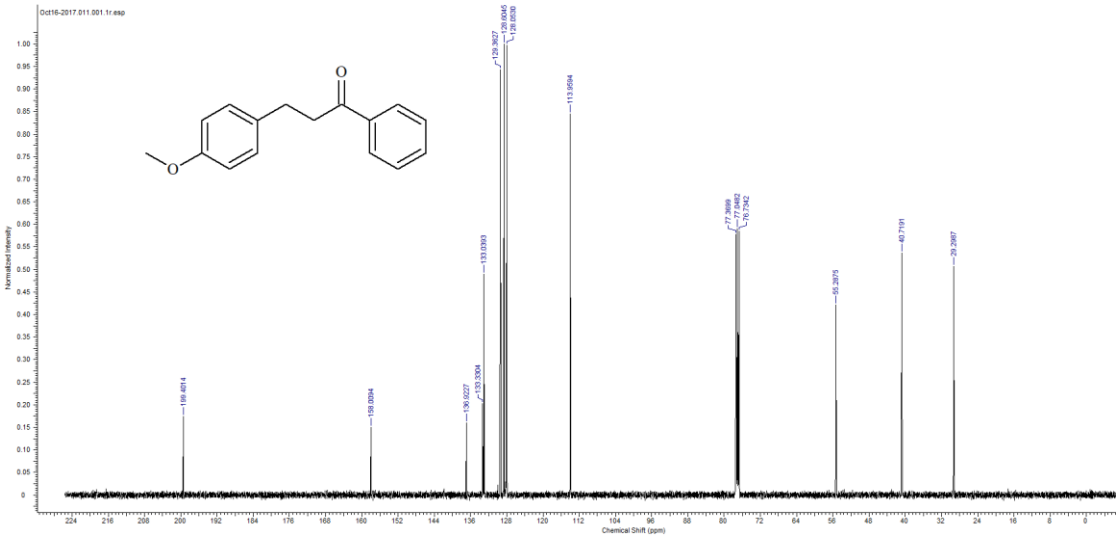
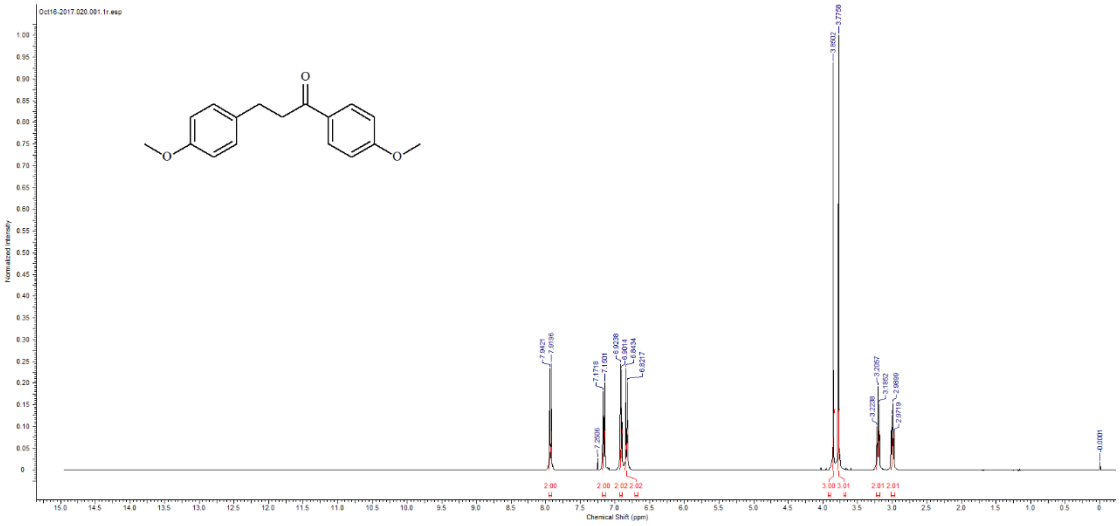
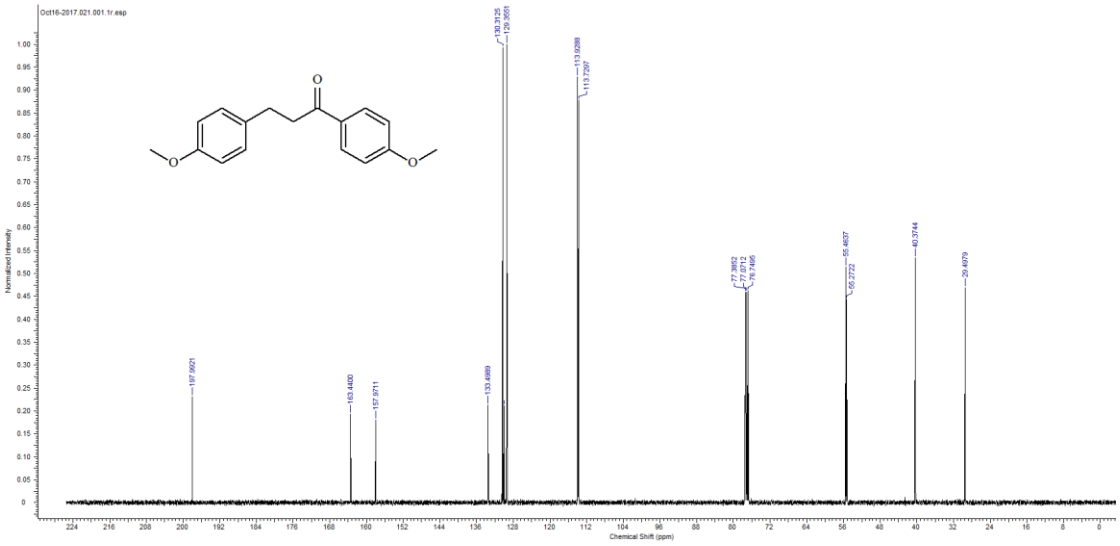
7.9695
7.5725
7.5543
7.4698
7.4503
7.3009
7.2626
7.2531
7.2460
7.2050
7.1875
3.3007
3.3245
3.2865
3.0722
3.0922
3.0539
1.5631
-0.0001
2.01
1.00
2.00
5.07
2.06
2.06
Normalized Intensity
Chemical Shift (ppm)

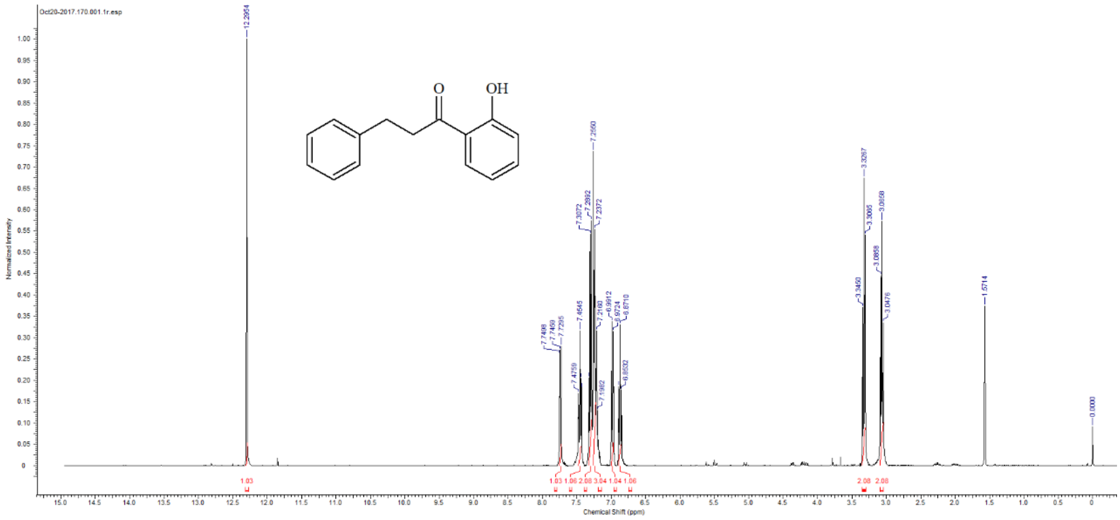

Nov30-2017.111.001.1r.esp
O
199.2329
141.3039
136.8767
133.0623
128.6121
128.5355
128.4359
128.0453
126.1457
77.3093
77.0252
76.7035
40.4587
30.1413
Normalized Intensity
Chemical Shift (ppm)

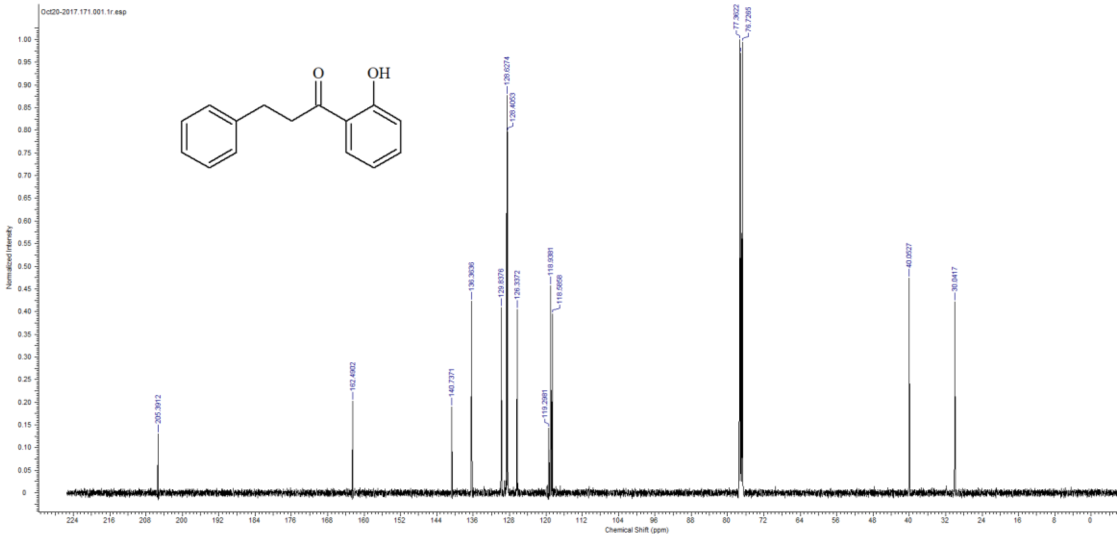

Oct16-2017.010.001.1r.esp
Normalised Intensity
Chemical Shift (ppm)
7.9606
7.9423
7.5471
7.4437
7.4442
7.4255
7.1572
7.1792
6.8496
6.8290
3.9307
3.3695
3.3052
3.2905
3.0102
2.9917
0.0001
1.99
1.01
2.05
2.02
2.01
3.00
2.00
1.99

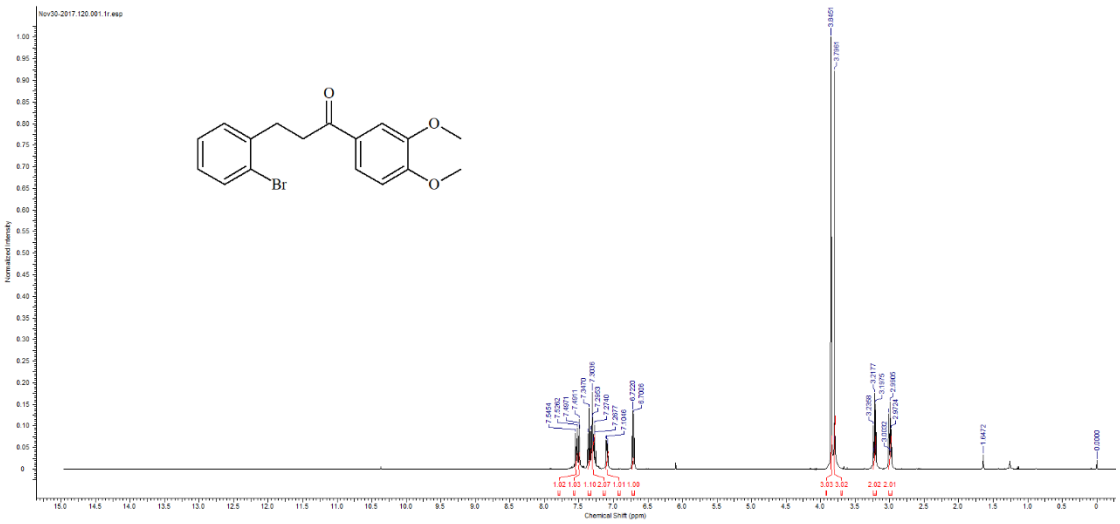

Oct16-2017.011.001.1r.esp
Normalised Intensity
Chemical Shift (ppm)
159.3627
129.6045
129.0830
113.9594
77.3689
77.0482
76.7342
55.2975
40.7191
29.2997
158.0094
133.0303
130.0227
129.5304

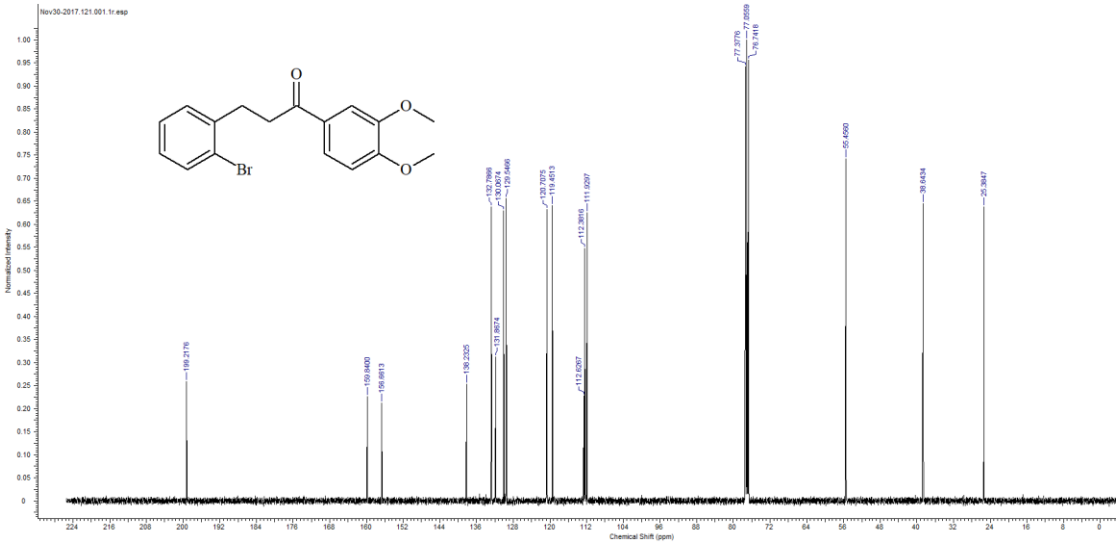

Oct16-2017.020.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)

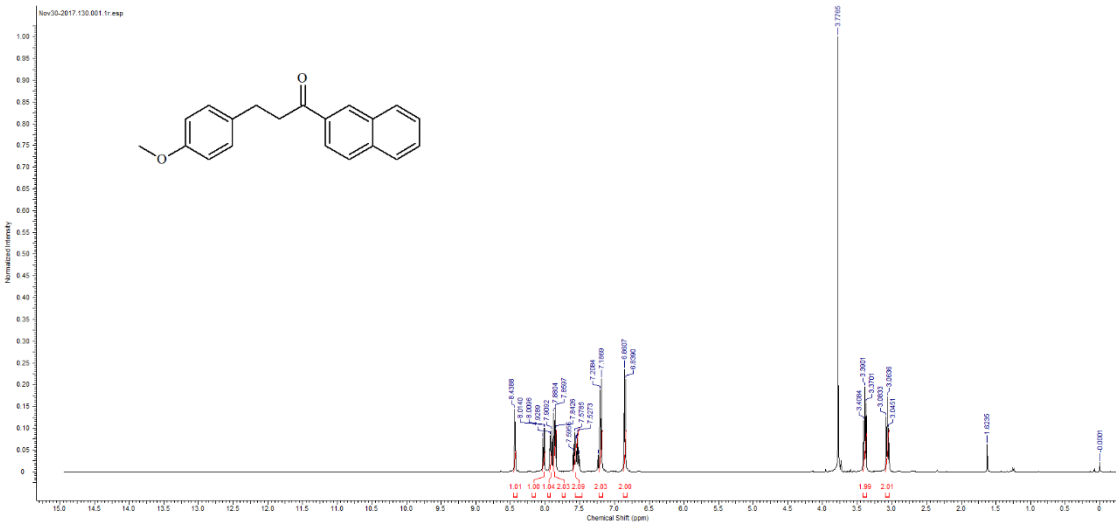

Oct16-2017.021.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)

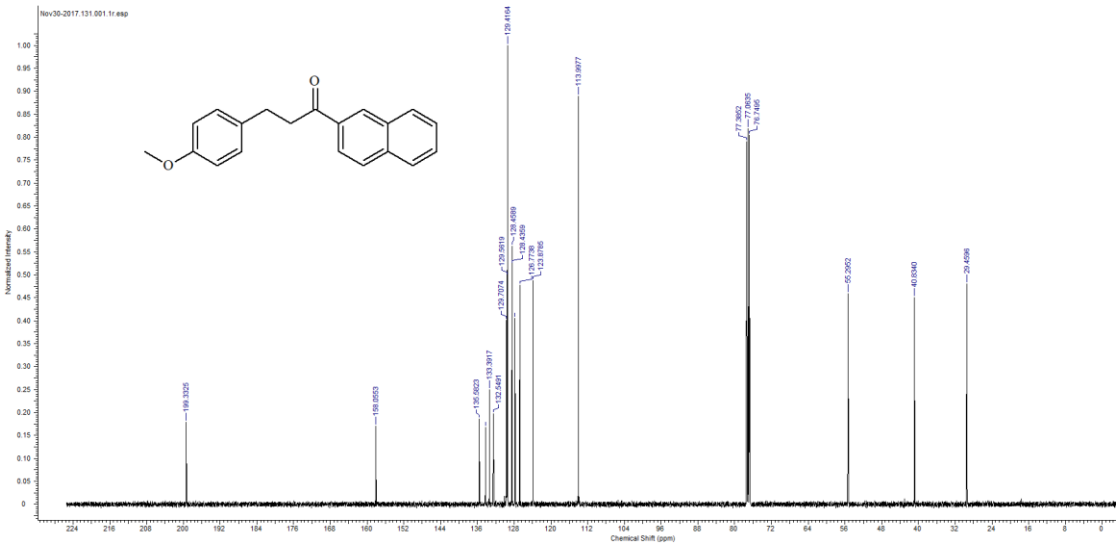

Oct20-2017.170.001.1r.esp
OH
O
Normalized Intensity
Chemical Shift (ppm)
12.2954
7.2560
3.3267
3.0659
1.5714
0.0000

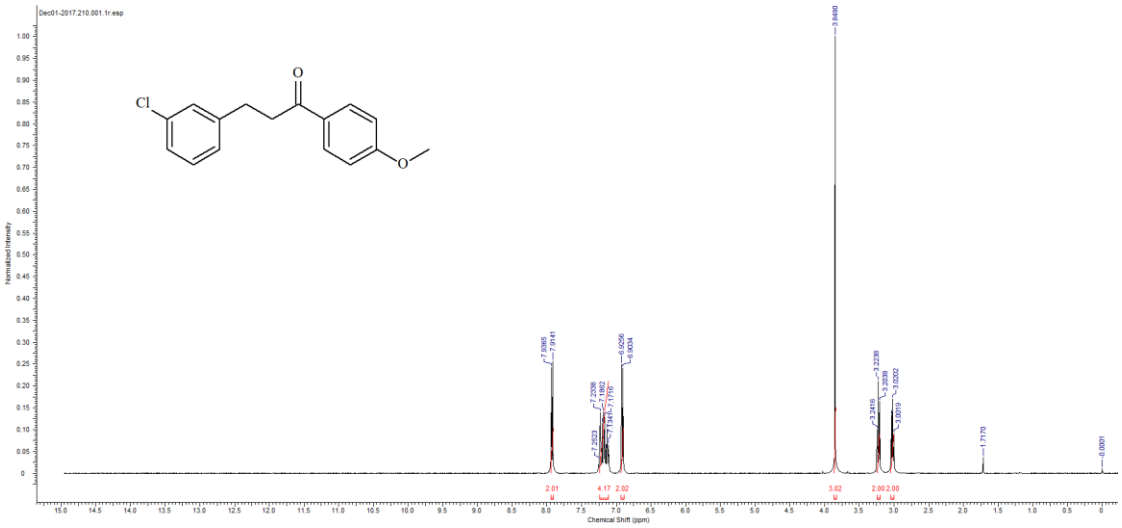

Oct20-2017.171.001.1r.esp
OH
O
Normalized Intensity
Chemical Shift (ppm)
205.3912
162.4902
140.7371
136.3636
129.8376
128.6274
128.4053
126.3372
118.9381
118.5958
119.2981
77.3622
76.7365
40.0527
30.0417

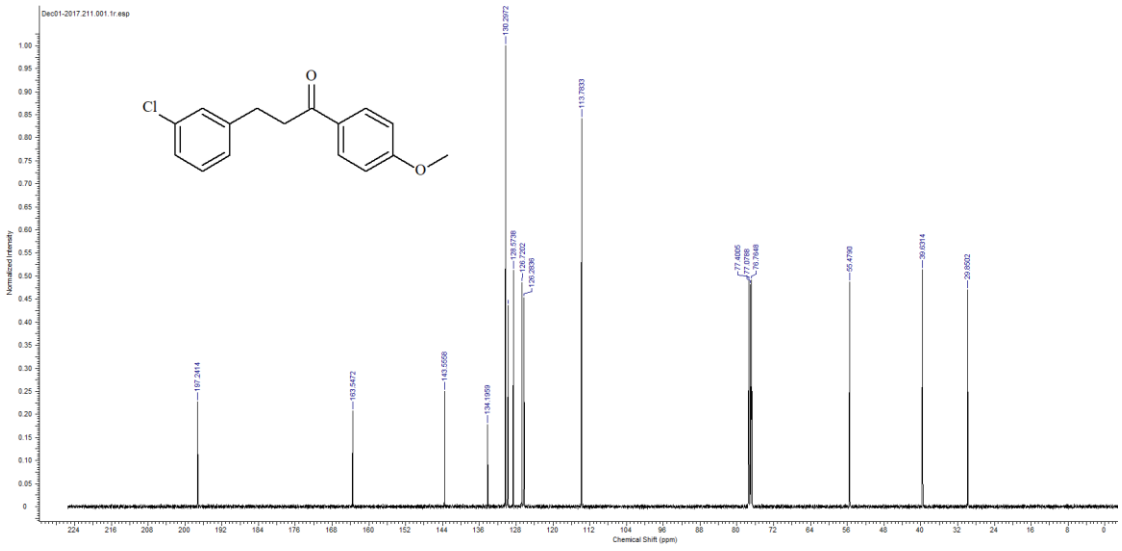

Nov30-2017.120.001.1r.esp
Br
O
O
O
Normalized Intensity
Chemical Shift (ppm)


Nov30-2017.121.001.1r.esp
Br
O
O
O
Normalized Intensity
Chemical Shift (ppm)

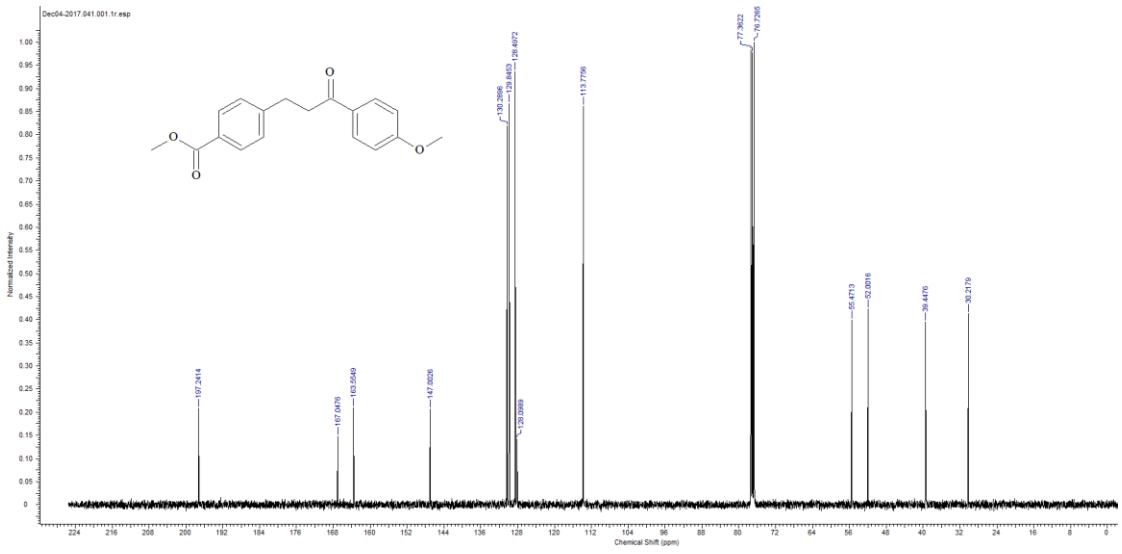

Nov30-2017.130.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)

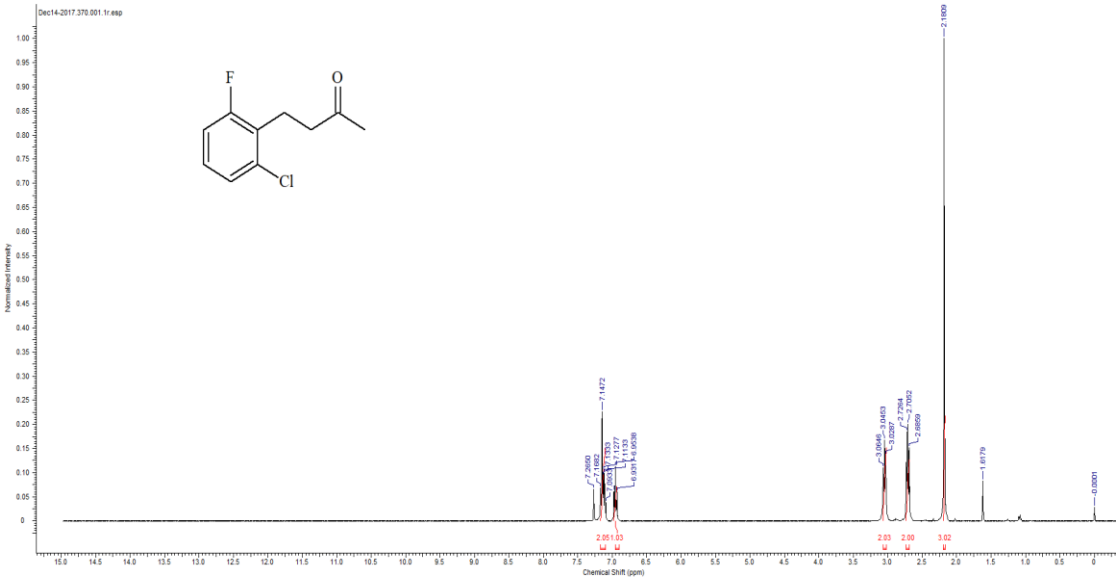

Nov30-2017.131.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)

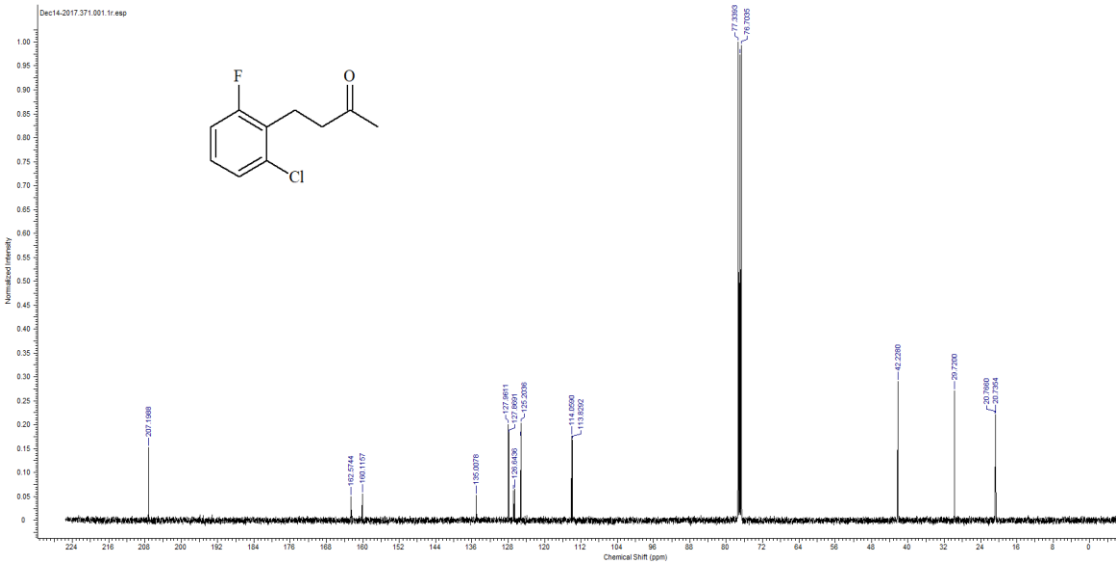

Dec01-2017.210.001.1r.esp
Cl
O
O
Normalized Intensity
Chemical Shift (ppm)

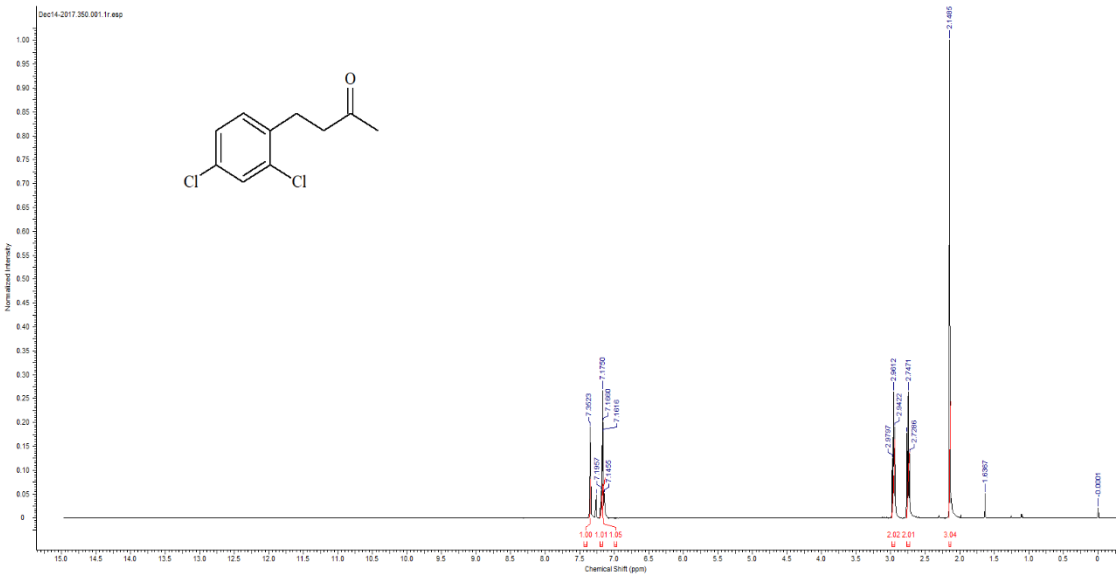

Dec01-2017.211.001.1r.esp
Cl
O
O
Normalized Intensity
Chemical Shift (ppm)

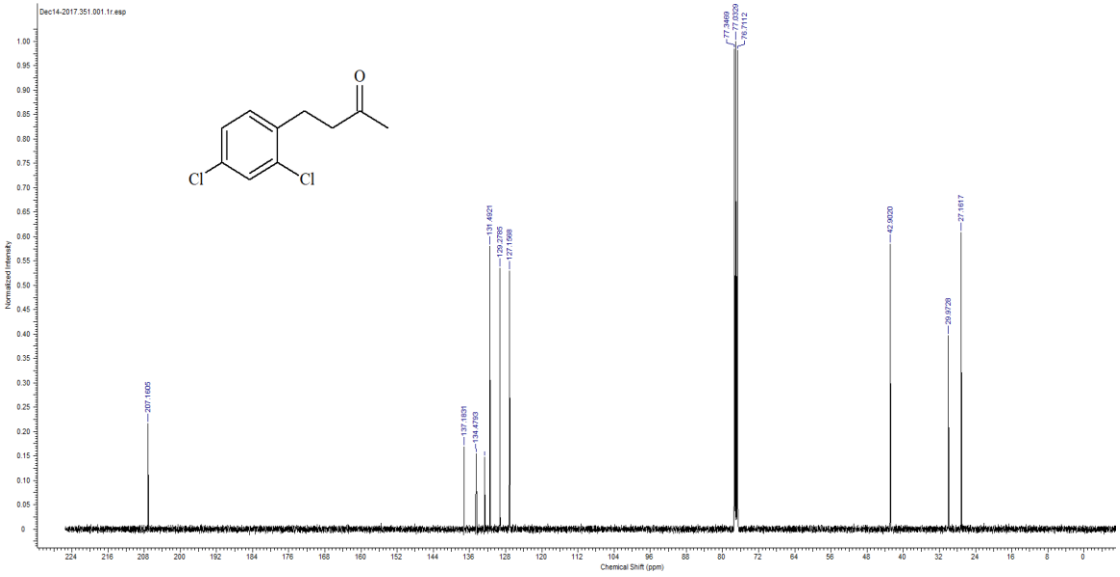

Dec04-2017.040.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
7.9730
7.9513
7.9492
7.8318
7.3279
7.3066
7.2594
6.9328
6.9196
3.8979
3.8821
3.2942
3.2811
3.1803
3.0915
1.0701
0.0802
2.03 2.04
2.02
2.00
3.03 3.03
2.01 2.00

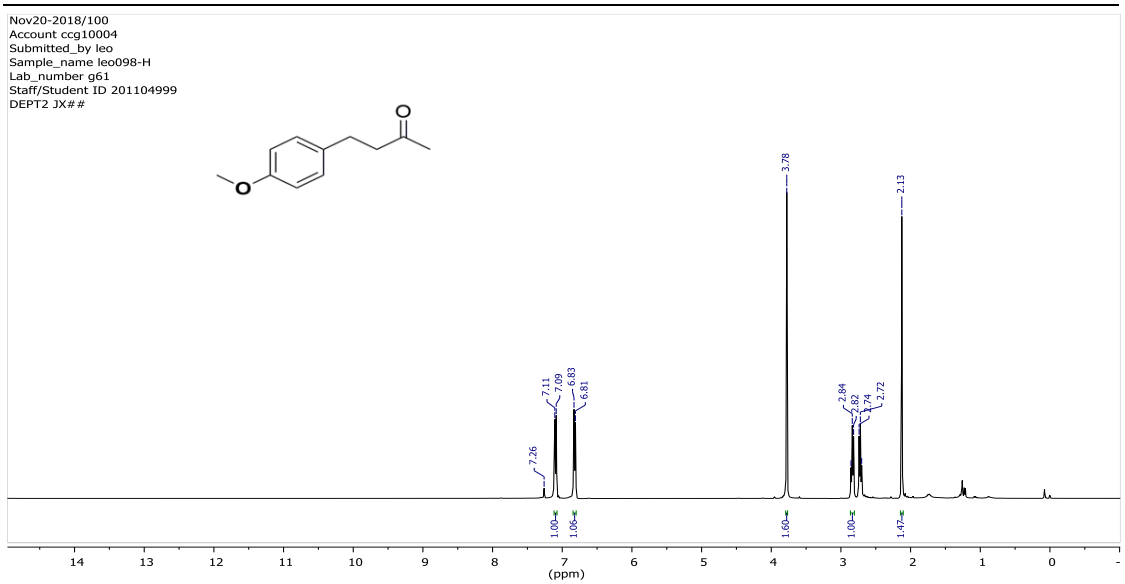

Dec04-2017.041.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
197.2414
167.0476
163.5549
147.8026
130.2896
129.8493
128.4972
128.0869
113.7756
77.3622
76.7265
55.4713
52.0016
39.4476
30.2179

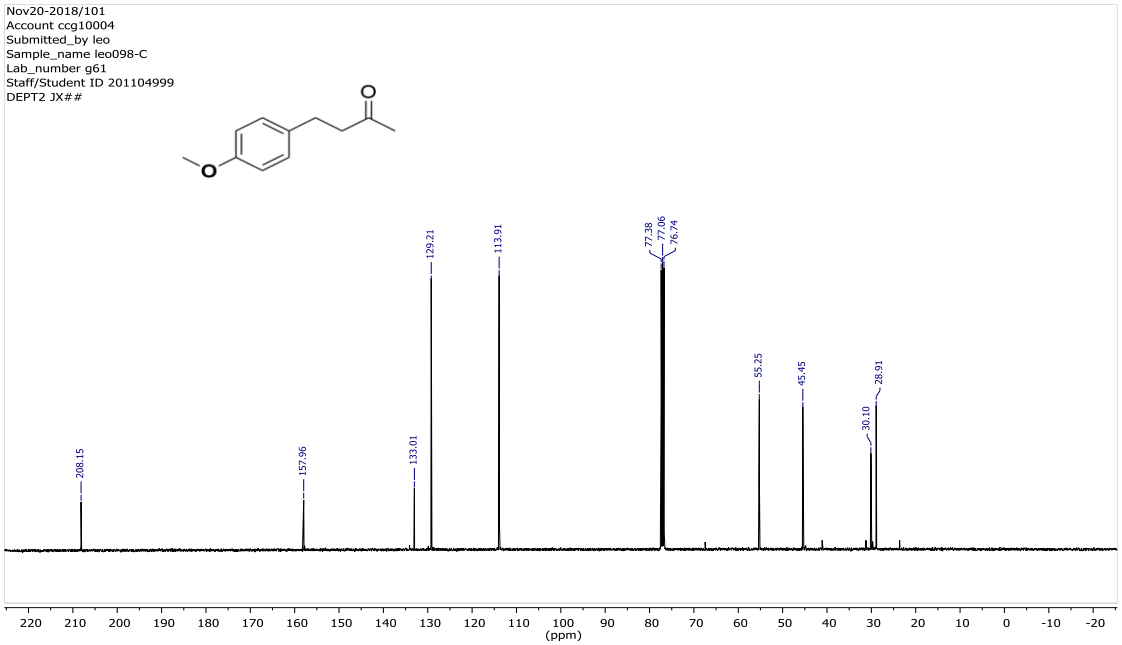

Dec14-2017.370.001.1r.esp
F
O
Cl
Normalized Intensity
Chemical Shift (ppm)

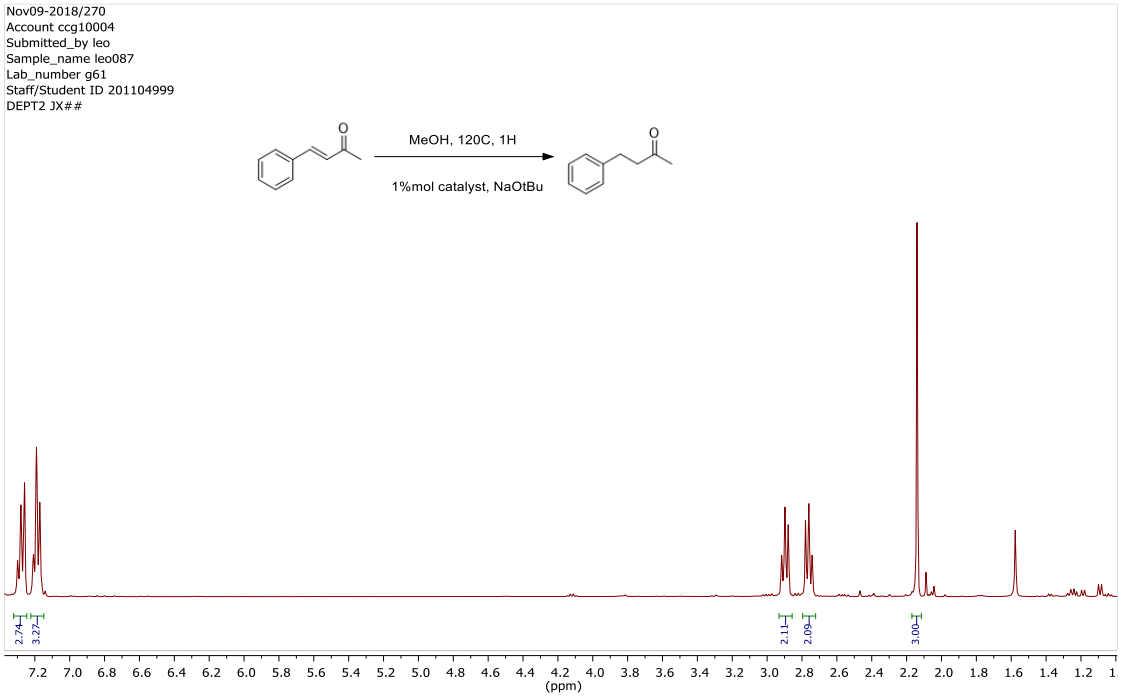

Dec14-2017.371.001.1r.esp
F
O
Cl
Normalized Intensity
Chemical Shift (ppm)

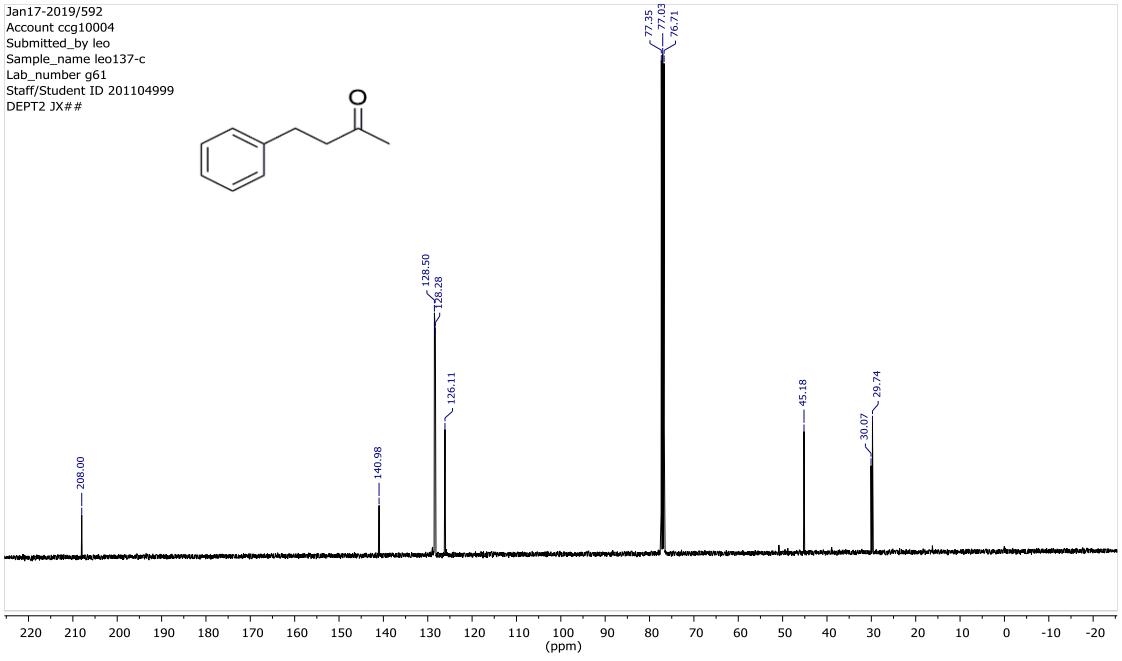

Dec14-2017.350.001.1r.esp
Cl
Cl
O
Normalized Intensity
Chemical Shift (ppm)
1.00 1.01 1.05
2.02 2.01
3.04


Dec14-2017.351.001.1r.esp
Cl
Cl
O
Normalized Intensity
Chemical Shift (ppm)


Nov20-2018/100
Account ccg10004
Submitted_by leo
Sample_name leo098-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##
7.26
7.11
7.09
6.83
6.81
3.78
2.84
2.82
2.74
2.72
2.13
1.00
1.06
1.60
1.00
1.47
(ppm)


Nov20-2018/101
Account ccg10004
Submitted_by leo
Sample_name leo098-C
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##
208.15
157.96
133.01
129.21
113.91
77.38
77.06
76.74
55.25
45.45
30.10
28.91
(ppm)


Nov09-2018/270
Account ccg10004
Submitted_by leo
Sample_name leo087
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##
MeOH, 120C, 1H
1%mol catalyst, NaOtBu
2.74
3.27
2.11
2.09
3.00
(ppm)


Jan17-2019/592
Account ccg10004
Submitted_by leo
Sample_name leo137-c
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##
77.35
77.03
76.71
128.50
128.28
126.11
208.00
140.98
45.18
30.07
29.74
(ppm)

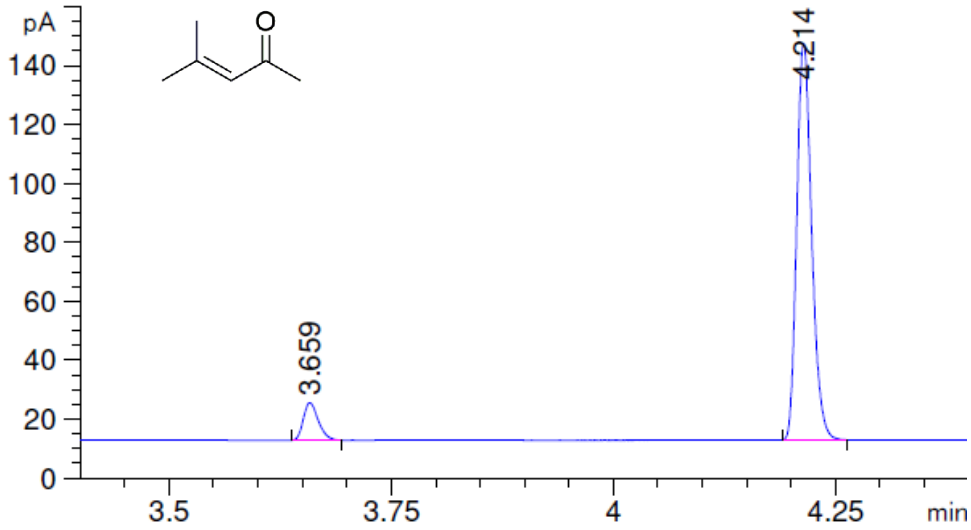
2.6.7 GC traces

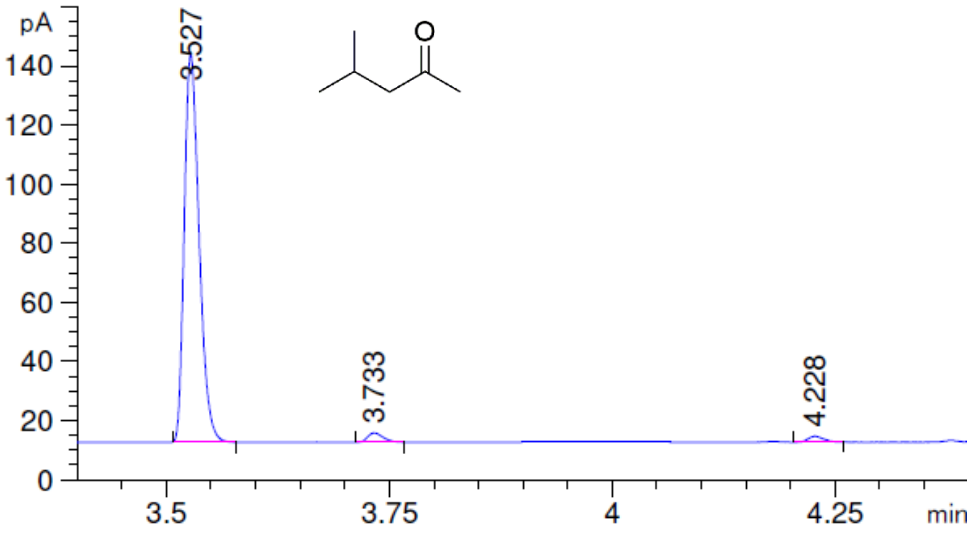
Analysis of reaction mixtures was undertaken on an Agilent 6890N/7890A gas chromatographic system equipped with a split/splitness injector and flame ionization detector. HP-5 capillary GC column (30m x 0.25mm i.d.) and helium as gas carrier were routinely used. Injector temperature was 250 °C; detector temperature was 300 °C; inlet pressure was 15 psi; oven temperature program: 50 °C for 2 min, then ramp up to 300 °C (20 °C/ min), and 15 mins hold at 300 °C.

Quantitative dodecane was used as internal standard, Chromatographic analysis was performed on the mixture of measured components and internal standard samples with a certain ratio, peak area was measured, and the curve of the relationship between concentration ratio and peak area ratio was made to obtain the calibration curve. The peak areas of the tested substance and internal standard substance were obtained through experiments, and then used in linear correlation formula, the concentrations of the tested substance in the mixture could be obtained respectively. And then the yield of the reactant was obtained.

4-Methylpentan-2-one

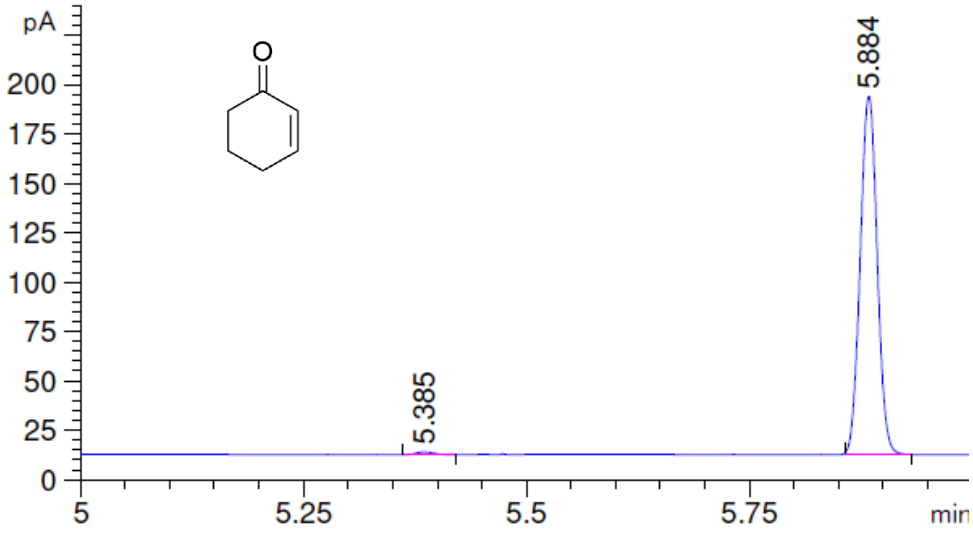
According to the general procedure, a volatile oil was obtained (98% yield by GC analysis).

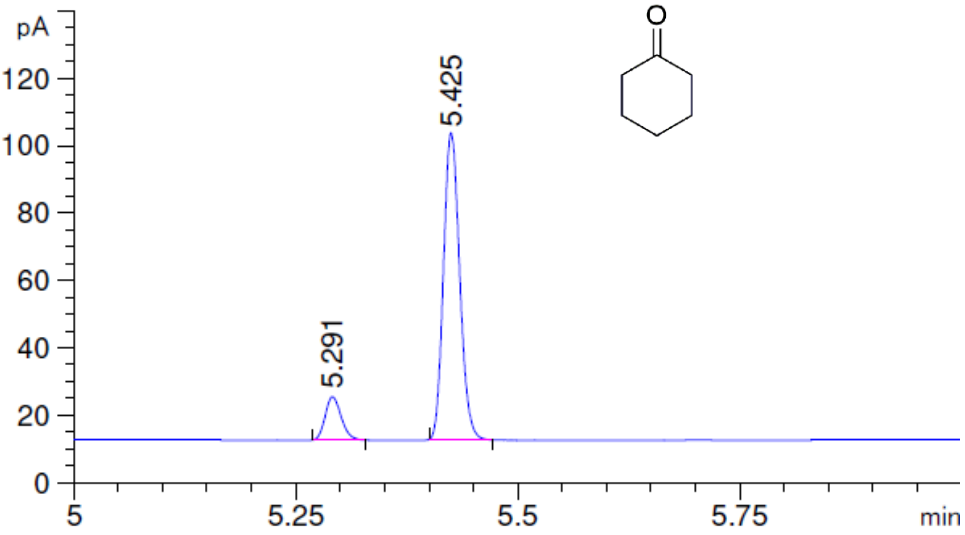




Cyclohexanone

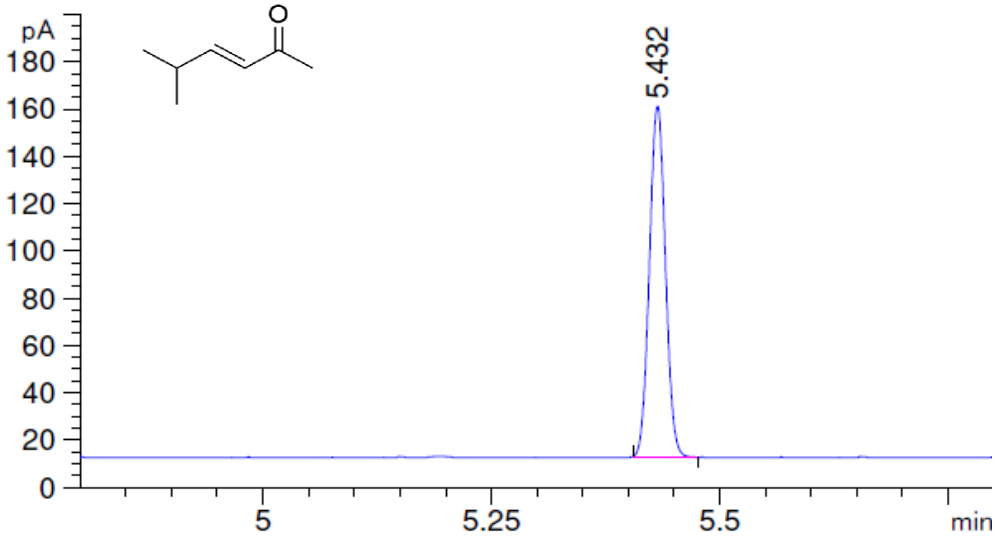
According to the general procedure, a volatile oil was obtained (99% by GC analysis).

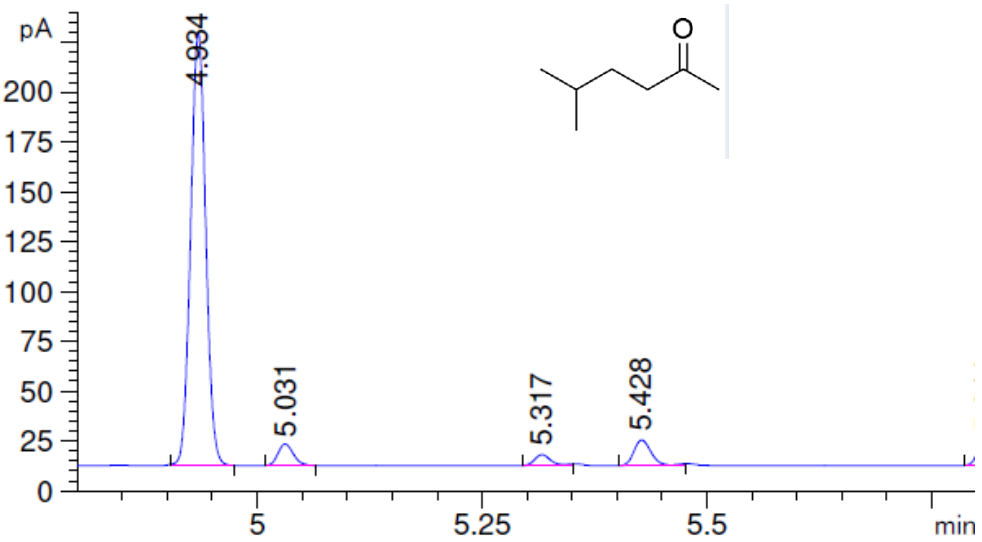




5-Methylhexan-2-one

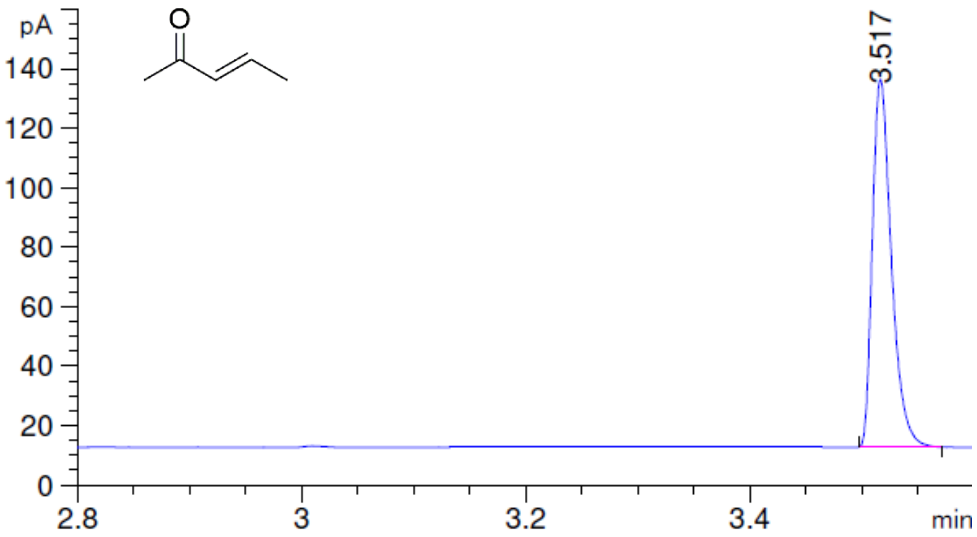
According to the general procedure, a volatile oil was obtained (94% by GC analysis).

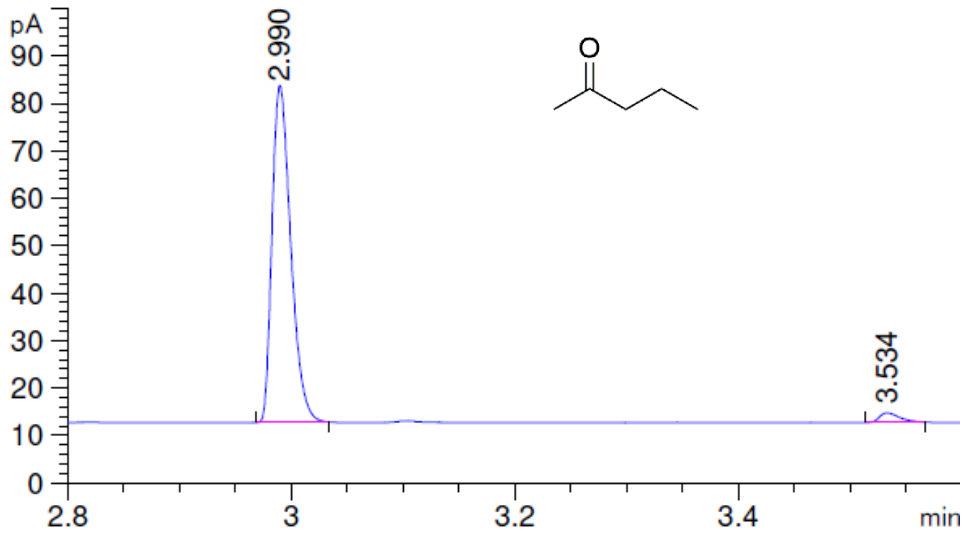




Pentan-2-one

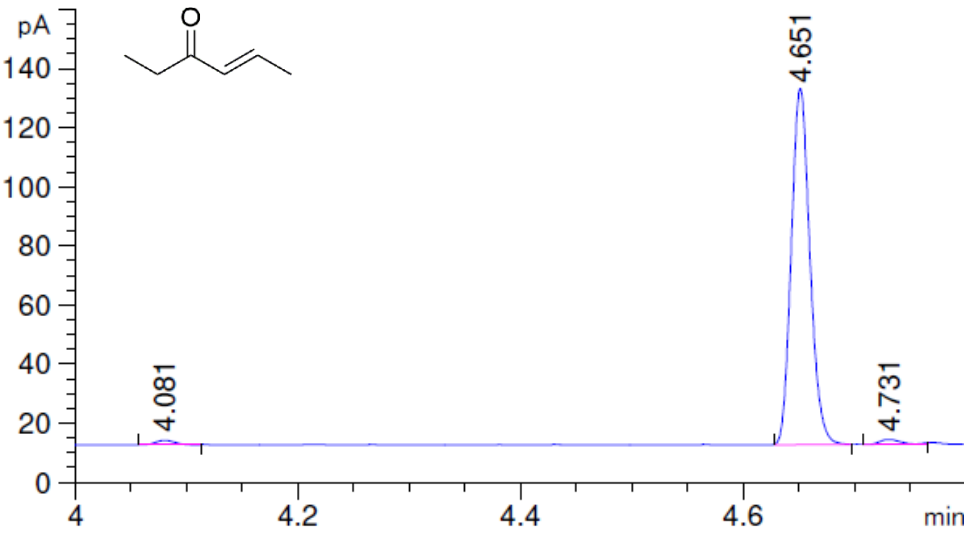
According to the general procedure, a volatile oil was obtained (97% by GC analysis).

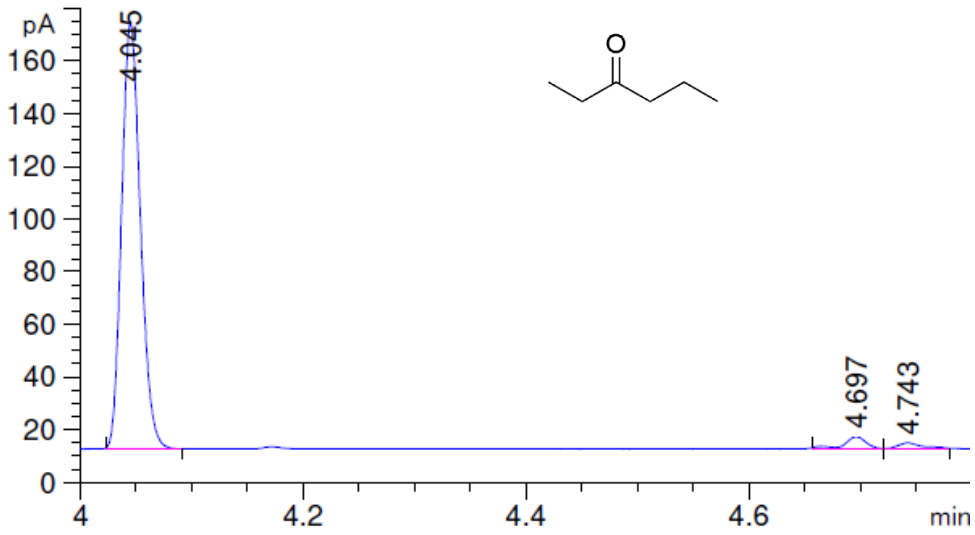




Hexan-3-one

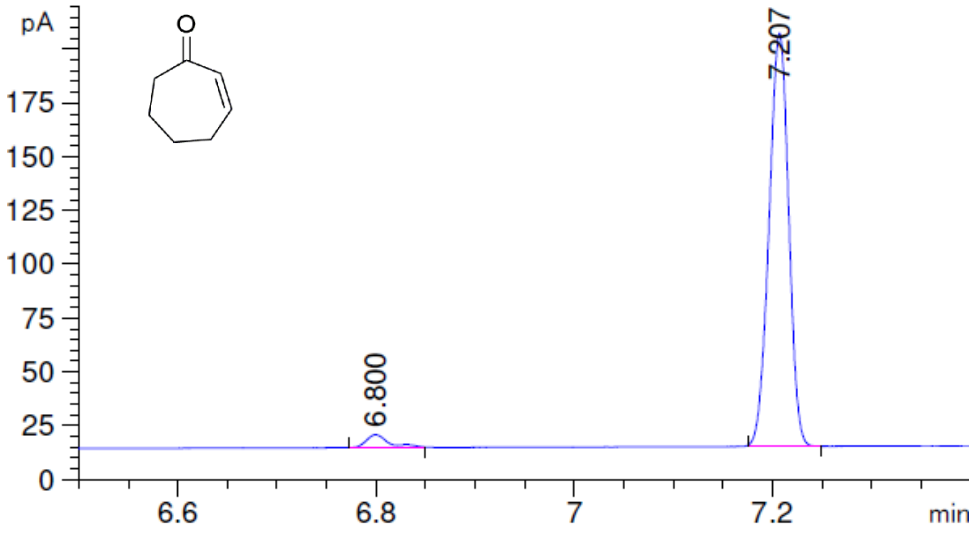
According to the general procedure, a volatile oil was obtained (97% by GC analysis).

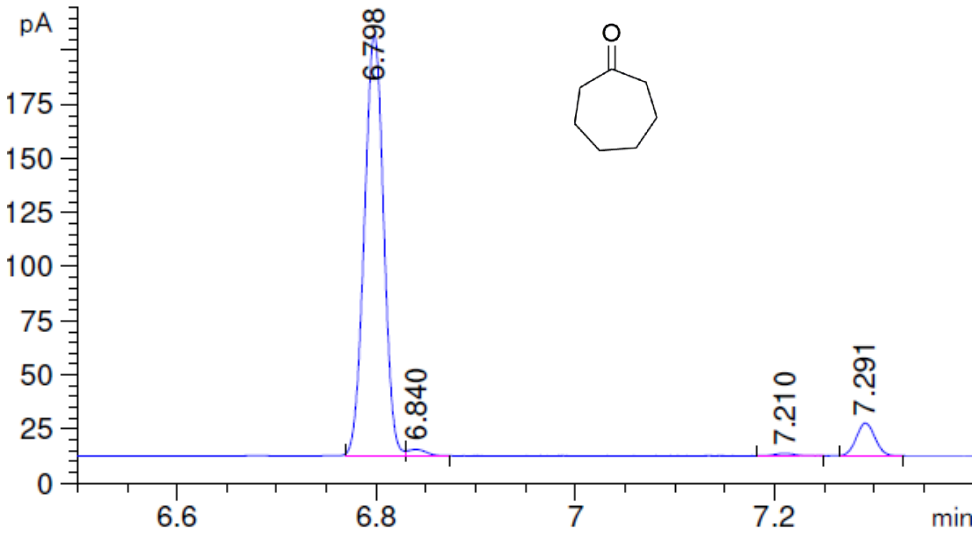




Cycloheptanone

According to the general procedure, a volatile oil was obtained (99% by GC analysis).





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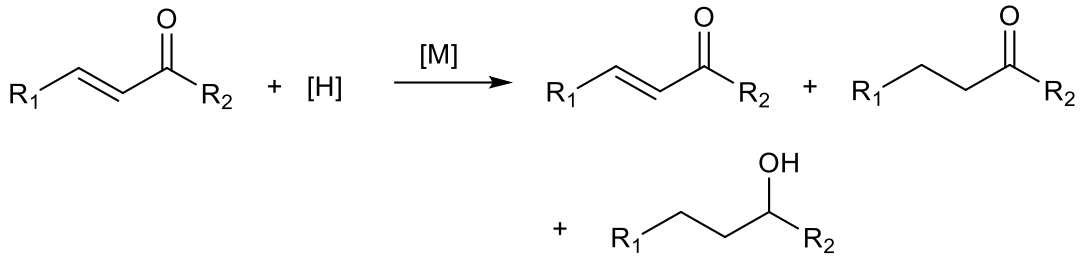
Chapter 3: Methanol as Both Hydrogen and α-Alkylation Source: Hydrogenation and Methylation of α,β-Unsaturated Ketones

3.1 Introduction

The selective hydrogenation of α,β-unsaturated ketones to produce their corresponding saturated ketones is of great significance for laboratory practice and the production of various valuable chemicals. This hydrogenated ketone has potential application value in the synthesis of food sweeteners, flavours, perfume products, pharmaceuticals and innovative functional materials.[1-3] However, mixtures of products are regularly gained, as various catalysts reduce both the C=O and C=C bonds, rather than exclusively either the C=O or C=C bond (Scheme **1**).[4-9] In particular, it has been difficult to reach overall chemoselective reduction of the carbon-carbon double bonds in the attendance of other simply reducible groups like C=O, although hydrogenation of a C=C double bond is normally thermodynamically more favourable compared with that of a C=O bond.[6-9] Although completely selective hydrogenation of carbonyl groups of α,β-unsaturated ketones has been well-developed with homogeneous catalysis,[10,11] the reduction of the olefinic group of unsaturated ketones is often carried out with heterogeneous catalysis with molecular hydrogen as reducing agent.[12-14] This is related with such issues as low chemoselectivity and the hazard of hydrogen gas, in addition to the requirement of specialized laboratory equipment.

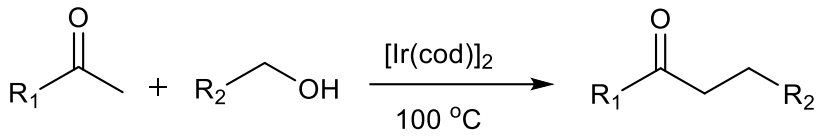


Scheme **1.** General pathway for hydrogenation of unsaturated carbonyl compounds.

The α-methylated ketones are often encountered in biologically active molecules.[15] The α-alkylation of ketone is usually carried out by the reaction of corresponding enolates with halides, thus producing stoichiometric amount of waste. In the perspective of sustainable chemistry, a new strategy of introducing methyl groups under catalytic conditions in an atomic-economical way from renewable resources is indeed very desirable.[16,17]

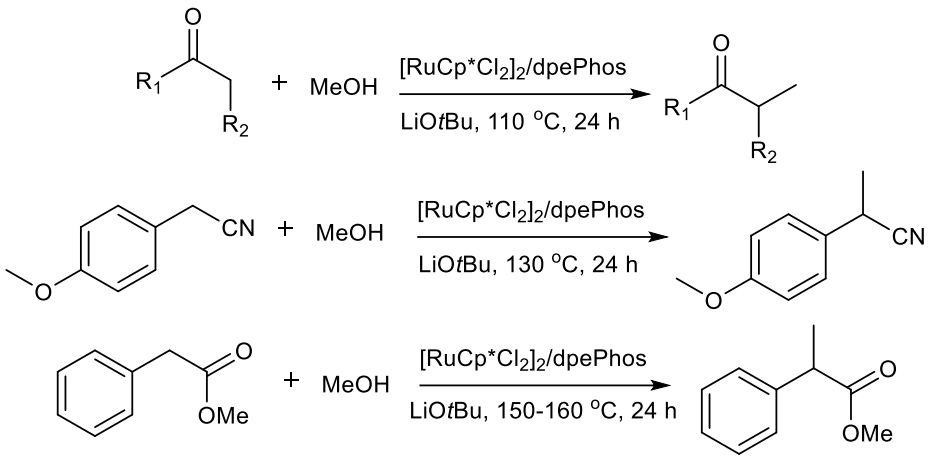
The methylation of ketones with alcohols in the presence of homogeneous catalysts based on novel metals is well established, which includes Ru, Rh, Ir, and Re.[18-22] The α-methylation with methanol remains challenging with the step of methanol dehydrogenation into aldehyde presents a higher activation barrier than that of heavier alcohols.[23,24]

In 2003, Ishill and co-workers[20] found that the selective α-alkylation with alcohols was achieved under the influence of catalytical amount of $[Ir(cod)Cl]_2$ in the presence of a base, such as KOH, which gave α-alkylation products in high yield (Scheme **2**). This method provided a novel route to α-alkylation ketones from ketones and alcohols without formation of any waste.



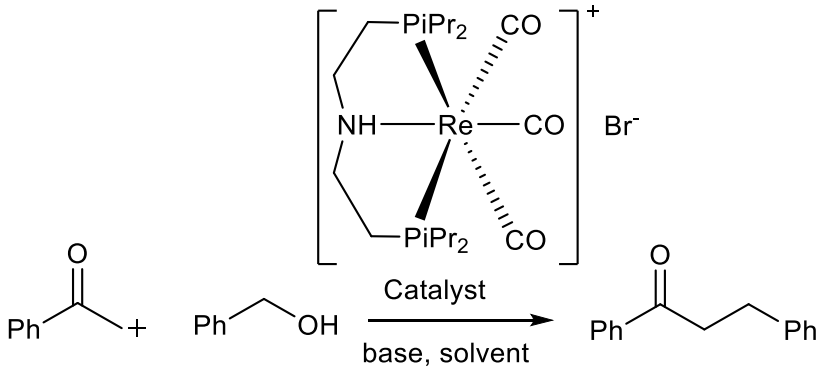
Scheme **2.** Methylation of ketones with alcohols catalysed by $[Ir(cod)Cl]_2$.

In 2016, an efficient ruthenium catalyst was reported by Seayad and co-workers (Scheme **3**),[21] which used for methylation of various ketones, nitrile, and esters in the presence of Li*O*t*Bu as base. It is worth noting that mono- or multi-methylation could be effectively controlled by temperature.



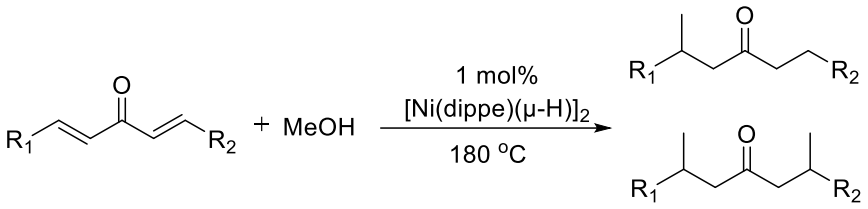
Scheme **3**. Ru-catalysed α-alkylation of ketone, nitrile and ester.

In 2017, Beller[22] and co-workers reported a rhenium pincer catalyst for α-alkylation of acetophenone with benzyl alcohol (Scheme **4**). These transformations take place in good to moderate yield in the presence of a very low amount of base.



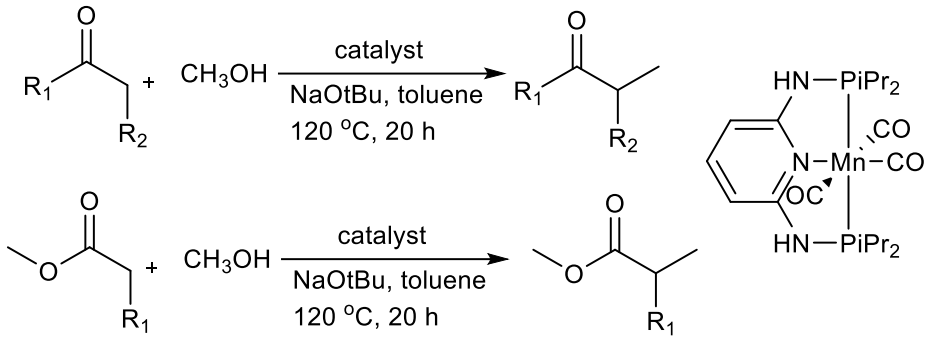
Scheme **4.** Rhenium-catalysed α-alkylation of acetophenone with benzyl alcohol.

With these catalysts, however high temperatures (120-180 °C) are generally necessary to drive the hydrogenation and methylation. For instance, using MeOH as the hydrogen donor, Garcia and co-workers reported the reduction of α,β-unsaturated dienones into the corresponding saturated ketones with a nickel catalyst $[Ni(dippe)(\mu\text{-}H)]_2$ at 180 °C (Scheme **5**).[25]



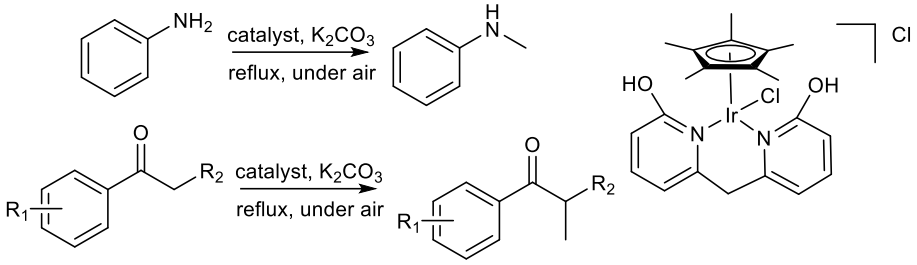
Scheme **5**. Catalytical hydrogenation and methylation by Ni complex.

α-Methylation with methanol was also reported by Antoine Bruneau-Voisine using a Mn complex as catalyst (Scheme **6**). The reaction proceeded with 3 mol% catalyst in the presence of NaO*t*Bu as base at 120 °C for 20 h.[26]



Scheme **6**. Catalytical methylation of ketones and esters by Mn complex.

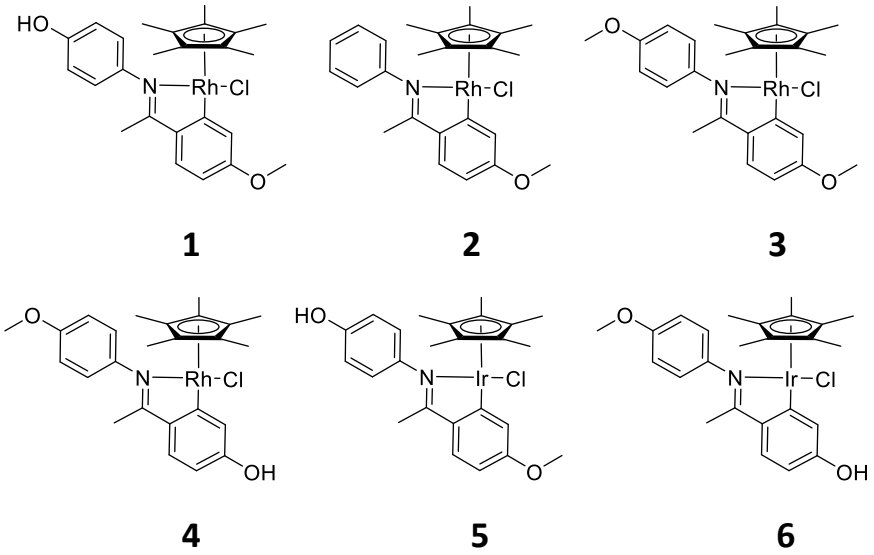
More recently, an iridium complex bearing 2-hydroxypridylmethylene fragment was synthesised by Deng and co-workers (Scheme **7**), which was used for methylation of amines and ketones with methanol as both C donor and solvent.[27]



Scheme **7**. Iridium complex catalysed methylation of amines and ketones.

In 2018, Aboo[28] of our group introduced a new rhodacycle complex **4** for the reduction of aldehydes with methanol as both the solvent and

the hydrogen donor under mild conditions (Scheme **8**). It is noteworthy that methanol has always been considered as the safest source of hydrogen.[29] Success of these preliminary studies prompted us for further evaluation of rhodacycle complexes as catalysts in different reactions with methanol as the hydrogen source and solvent.[30] Compared with previous report, milder reaction condition and lower catalyst loading were introduced in my research. And also, the catalyst could be prepared in an easier way.



Scheme **8**. Rhodacycles and iridacycles studied in this chapter.

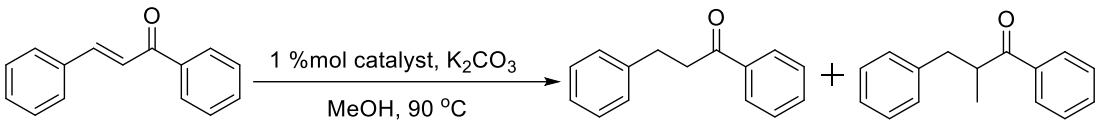
3.2 Results and discussion

The implementation of an efficient system based on a rhodium complex would constitute an additional accomplishment as simultaneous hydrogenation and methylation of ketones in a reaction system could be

achieved. Complementarily, industrial-scale production of methanol from a wide range of sources, including renewable resources, provides a very attractive C1 source and hydrogen source, which can be used as an environmentally friendly, inexpensive, and abundant alkylate.[31-34]

The condition for the optimization of the catalysts was adopted from previous research. We chose TH of 1,3-diphenyl-1-propen-3-one with methanol as the model reaction, in the presence of 1 mol% catalyst (complex **1-6**) and K_2CO_3 as base stirring in 90 ^oC for 1 h (Scheme **9,** table **1**). Compared with previous report from Aboo[31] the catalyst with OH group on the ligand could achieve TH of unsaturated ketones to its corresponding saturated ketones, but the catalyst could not obtain methylation product. During the catalytical process with catalyst **3**, the functional group OH is not needed in the reaction. This suggests that the presence of hydroxyl groups may inhibit the formation of methylation products. From entry 1 and 4, there was no target product **B** generated. Compared with entry 2 and 3**,** catalyst **3** showed better activities for the methylation product. Meanwhile, the iridium complexes show lower activity for the TH reaction. Hence, the complex **3** has the best catalytic activity for product **B** under current reaction condition. From entry 7-9, increasing the reaction temperature has positive consequence of methylation product until 120 ^oC. The methylated product was identified

by NMR. Compared with the NMR of pure hydrogenated product, a doublet peak was found in high field which is CH_3, and a multiplit peak replaced the triplet peak in high field which is H in α position. Thus, the new product could be identified as a methylated product. Later, serials of reactions were carried out based on the results.



A **B**

Scheme **9**. Hydrogenation of unsaturated ketone with MeOH.

Table **1**. Optimization of the catalysts for the hydrogenation of model substrate.

Entry	Catalyst	Base	Temperature °C	Conv. (%)	Yields (con. %)[a]	
					A	**B**
1	**1**	K_2CO_3	90	60	90	0
2	**2**	K_2CO_3	90	100	70	30
3	**3**	K_2CO_3	90	100	50	50
4	**4**	K_2CO_3	90	100	90	0
5	**5**	K_2CO_3	90	20	20	0
6	**6**	K_2CO_3	90	20	20	0
7	**3**	K_2CO_3	90	100	50	50

8	**3**	K_2CO_3	120	100	10	70
9	**3**	K_2CO_3	150	100	10	70

Reaction conditions: Under nitrogen atmosphere, ketone (0.25 mmol), MeOH (2 mL), rhodium complex (0.5 mol%), base (0.125 mmol), stirred at 90 °C for 1 h. [a] Isolated Yields.

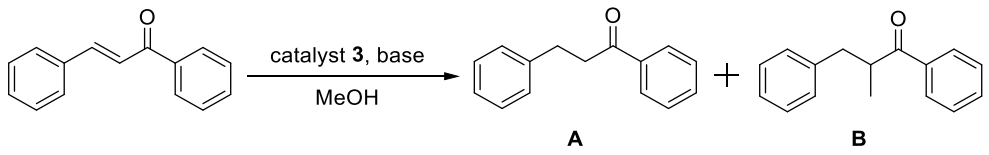
Further optimization of the reaction conditions was carried out considering the hydrogenation and methylation of 1,3-diphenyl-1-propen-3-one with methanol as the model reaction with the rhodacycle **3** as catalyst (Table **2**). Following the literature of the related rhodacycles, the chemoselectivity of the reduction of α,β-unsaturated ketones with formic acid in water was poor.[35] Pleasingly, using the conditions established for the transfer hydrogenation of aldehydes,[28] the substrate was completely reduced with MeOH in 1 h at 90 °C in the attendance of 1 mol% of **3** and K_2CO_3, but only small amount of methylation product being observed. It is worth noting that both hydrogenation and methylation could be completed in this single reaction system. Replacing the week base K_2CO_3 with the stronger KO*t*Bu and NaO*t*Bu increased the yield of methylation product under the conditions used. However, the yield of the reaction did not reach our expectation. Later, we tried to enhance the yield by increasing the reaction temperature from 90 °C to 120 °C. In the presence

of 0.5 mol% catalyst and KO*t*Bu (0.125 mmol) at 120 °C for 4 h, the best yield of methylation product was obtained.

The catalyst loading could be decreased from 1 mmol% to 0.25 mmol% while maintaining high conversion and yield (Table **2**, entry 5), but longer reaction time was required for full conversion. Further lowering the catalyst loading to 0.1 mmol% had a detrimental effect on conversion and yield of methylation product (Table **2**, entry 6).

Finally, after comprehensive consideration, our subsequent study of the methylation scope was therefore based on using **3** (0.5 mol%) as catalyst, KO*t*Bu (0.5 equipment) as base, and MeOH (2 mL) as both the reductant and solvent at 120 °C in 4 h.

Table **2.** Optimization of the parameters of the hydrogenation of model substrate with catalyst **3**.



Entry	Catalyst loading (%)	Base	Temperature, time (h, °C)	Conv. (%)	Yields[a]	
					A	**B**
1	1	K_2CO_3	1, 90	100	50	50
2	1	NaO*t*Bu	1, 90	100	30	70

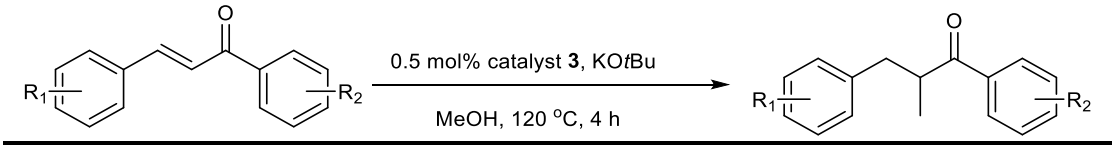
3	0.5	NaO*t*Bu	1, 120	100	25	75
4	0.5	KO*t*Bu	4, 120	100	8	92
5	0.25	KO*t*Bu	8, 120	100	12	88
6	0.1	KO*t*Bu	24, 120	20	20	trace

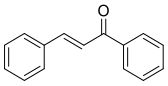
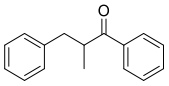
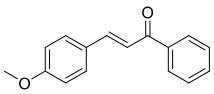
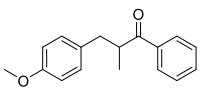
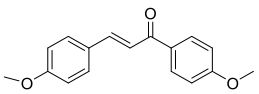
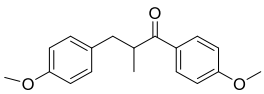
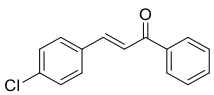
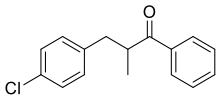
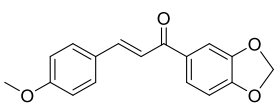
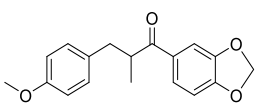
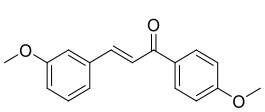
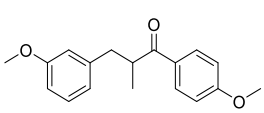
Reaction conditions: Under nitrogen atmosphere, ketone (0.25 mmol), MeOH (2 mL), rhodium complex, base (0.125 mmol), stirred at 90 ^{o}C for 4 h. [a] Yield determined by ^{1}H NMR of crude products and compared with GC/MS of the crude mixture.

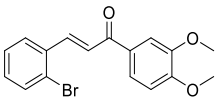
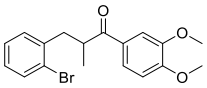
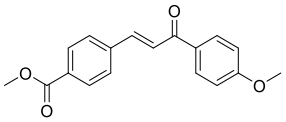
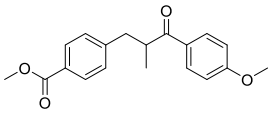
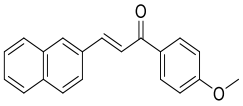
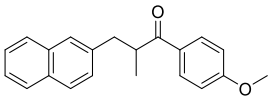
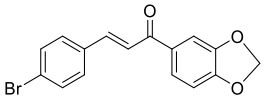
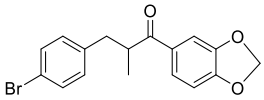
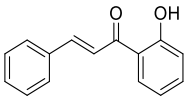
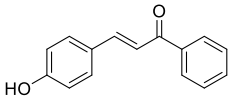
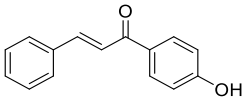
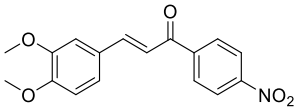
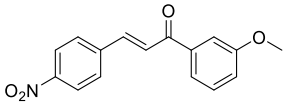
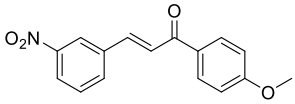
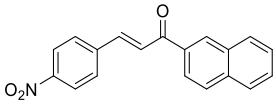
The applicability of the rhodacycle **3** towards the reduction with MeOH of the C=C double bonds of α,β-unsaturated ketones and α-methylation was examined under the optimized reaction conditions (Table **3**). As could be noticed, the catalyst is capable of highly chemo-selective transfer hydrogenation of a range of diversely substituted unsaturated ketones and also highly active for α-methylation of the substrates, allowing the methylated saturated ketones to be obtained with high yields in general in a quick reaction time of 4 h (Entry 1-10). For the chalcones, both electron-donating and withdrawing substituents on the styryl side are tolerated. Of special note is that chalcones having 2-sustituted or 4-disubstituted styryl units were all reduced with high yields,

considering that the hydride addition would take place at the β position of the C=C double bond (see below). However, with the presence of OH and NO_2 in the substrates (Entry 11-17), no target product was produced, and some intractable mixtures were generated. NO_2, a strong electron-withdrawing group, may actually participate in the reaction and react with the catalyst. The NO_2 group could be reduced to the corresponding amine, which could further react with the Rh catalyst, resulting in catalyst poisoning.

Table **3.** Scope of the methylation of ketones with methanol in the presence of **3** as a catalyst.



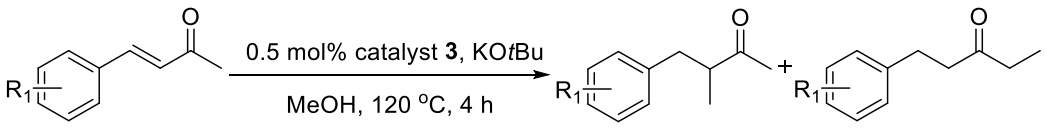
Entry	Substrate	Product	Yields (%)[a]
1			95
2			91
3			89
4			83
5			87
6			80

7			85
8			70
9			88
10			90
11		NA	
12		NA	
13		NA	
14		NA	
15		NA	
16		NA	
17		NA	

Reaction conditions: Under nitrogen atmosphere, ketone (0.25 mmol), MeOH (2 mL), rhodium complex (0.5 mol%), base (0.125 mmol), stirred at 120 ^{o}C for 1 h or 4 h. [a] Yield determined from isolated product.

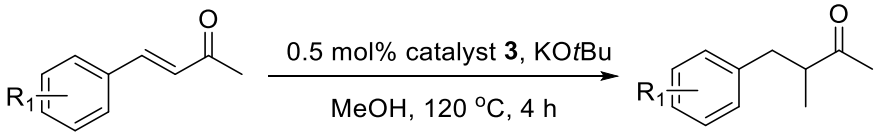
The methylation of α,β-unsaturated ketones was also applied to the

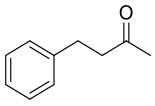
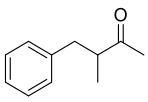
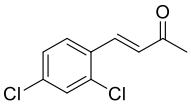
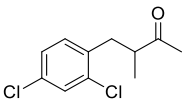
benzylideneacetone compounds (Table **4**). Obviously, the catalyst could also show excellent chemo-selective transfer hydrogenation of the benzylideneacetone substrates and high active for methylation of the substrates. Similar to the above results, it showed efficient activity toward the substrates with the same functional groups. However, when the F group was present, only 30 % yield was reached due to its strong electronegativity. Although high activity and excellent chemo-selectivity were achieved, the aliphatic part linked with the C=O brings a second possibility for methylation (Scheme **10**). Separation of these methylation products was difficult.

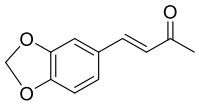
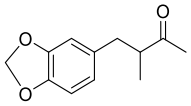
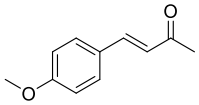
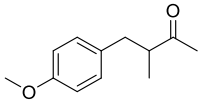
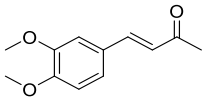
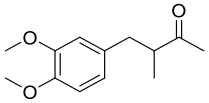
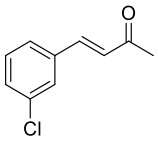
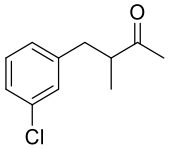


Scheme **10**. Possible methylated products.

Table **4**. Scope of the methylation of ketones with methanol in the presence of **3** as a catalyst.



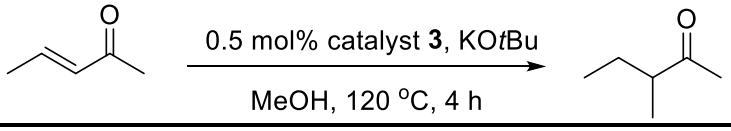
Entry	Substrate	Product	Yield (%)[a]
1			90
2			89

3			85
4			72
5			72
6			85

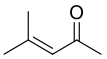
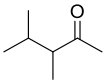
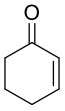
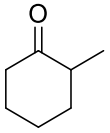
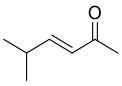
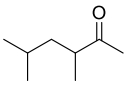
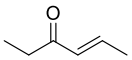
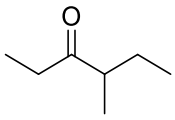
Reaction conditions: Under nitrogen atmosphere, ketone (0.25 mmol), MeOH (2 mL), rhodium complex (0.5 mol%), base (0.125 mmol), stirred at 120 ^{o}C for 4 h. [a] Yields were determined by ^{1}H NMR analysis of the crude mixture and confirmed by GC analysis.

Later, the catalytical process was also applied to aliphatic α,β-unsaturated ketones. Compared with aromatic substrates, the aliphatic substrates could also be hydrogenated and methylated, but with much lower yields (Table **5**). Similarly, since there are multiple positions that could be methylated, double methylation products were also found, but only the main product was list below.

Table **5**. Scope of the methylation of ketones with methanol in the presence of **3** as a catalyst.

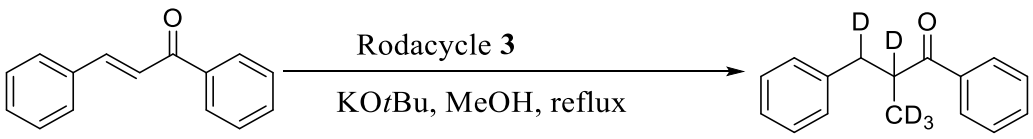


Entry	Substrate	Product	Yield (%)[a]

1			45
2			40
3			50
4			35

Reaction conditions: Under nitrogen atmosphere, ketone (0.25 mmol), MeOH (2 mL), rhodium complex (0.5 mol%), base (0.125 mmol), stirred at 120 ^{o}C for 4 h. [a] Yields were determined GC-MS and GC analysis.

To prove the methanol is the only hydrogen and methylation source during the reaction, the reduction of the model substrate in deuterated methanol (CD_3OD) was carried out. As shown in Scheme **11**, deuterium was found at both α and β position. The hydrogenation of the unsaturated ketone was proved in previous chapter. Furthermore, with the presence of the rhodium-deuteride, the formaldehyde reacted with saturated product, affording the deuterated methylation product.

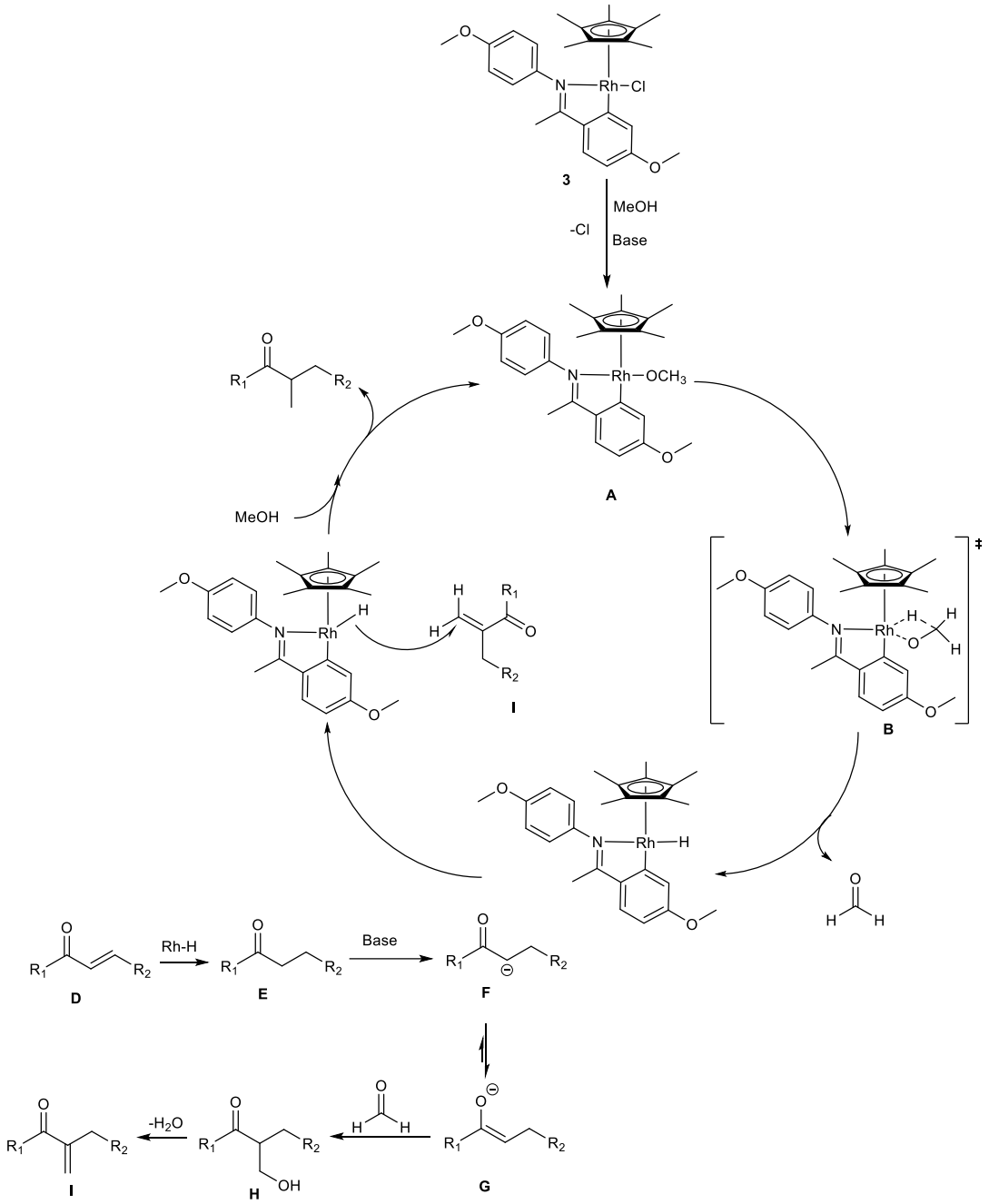


Scheme **11**. Hydrogenation and methylation of unsaturated ketone with deuterated MeOH.

3.3 Proposed Mechanism

Based on our research and study,[31] a plausible reaction mechanism for the hydrogenation and methylation of unsaturated ketones with methanol is proposed in Scheme **12**. Under the basic reaction conditions employed, the alkoxide complex **A** is formed from the rhodacyele in MeOH. Then the complex **A** undergoes β-hydrogen elimination, giving rise to the hydride complex **C** while releasing formaldehyde, support for which was provided in our study of reduction of aldehydes.[28] The mechanism from **D** to **E** was published by previous work. In the presence of a base, the intermediate **F** was formed from deprotonation of **E**. **G** the enoate form of **F** reacts with aldehyde producing **H**. Then the intermediate **H** undergoes dehydration, giving rise to the intermediate **I** while releasing H_2O. The next step sees the hydride in complex **C** being transferred to the position of the C=C double bond in **I**. Then, the protonation of **C** with MeOH affording the hydrogenation and methylation product while regenerating complex **A**. Compared with the mechanism from Chapter 2, OH group important therein does not induce a similar effect for the current process: when the respective catalyst contained OH group was evaluated, a significant drop in the catalytic activity was observed. We believe that due to the presence of a strong base and higher temperature of this process, the hydroxyl group could undergo deprotonation, thereby limiting the activity of the

catalyst and preventing the further reaction.



Scheme **12**. A possible catalytic cycle for the rhodacycle **3** catalysed hydrogenation and methylation of unsaturated ketones with MeOH.

3.4 Conclusions

In conclusion, the rhodium-catalysed alkylation of ketones using methanol as both a green alkylating reagent and hydrogen source was, for the first time, achieved. The process involves hydrogenation and methylation of ketones in a single reaction system. The system has been proved to be applicable to both aromatic and aliphatic α,β-unsaturated ketones. Catalysed by catalyst **3**, a wider variety of ketones with halogen, methoxy, ester, epoxy group were hydrogenated and methylated to its saturated and alkylated product in refluxing methanol in a short time under relatively mild conditions with methanol as solvent. Only 0.5 mol% catalyst loading was applied during the reaction system. The protocol could be extended to the even more challenging of alkylation of ketones using other alcohols and have the great potential in the field of C-alkylation. When formic acid was used as hydrogen and methylation source for the reaction system, there was no aimed product formed. Other alcohols such as isopropanol and ethanol were also evaluated for the reaction, reaction proceeded in a non-chemoselective manner leading to the mixture of products due to partial TH and alkylation. We also tried to reuse the catalyst by re-adding the substrates after the first catalytic run was complete. Although the reaction occurred in this case, significantly lower products yields were observed.

3.5 Experimental

3.5.1 General information

All reactions were carried out with oven-dried glassware using standard Schlenk techniques under an inert atmosphere of dry argon. Chemicals, reagents and solvents were purchased commercially and used as received. Methanol and ethanol were of HPLC grade. TLC silica gel 60F254 (Merck) plates were used for the analytical thin-layer chromatography and they were revealed under ultra-violet irradiation, potassium permanganate or iodine. Columns were run using a mixture of hexane/ethyl acetate and silica gel 60 Å (230-400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer using $CDCl_3$ as solvent with TMS as the internal standard at 25 ^{o}C and -60 ^{o}C. ^{1}H and ^{13}C NMR spectra were calibrated against the residual solvent signal at the corresponding central peak (^{1}H: $CDCl_3$ 7.26 ppm; ^{13}C: $CDCl_3$ 77.16 ppm). Chemical shift (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively.

Synthware® pressure tubes with front seal (25 mL) were used for the reaction. Analysis of reaction mixtures was undertaken on an Agilent 6890N/7890A gas chromatographic system equipped with a split/splitness injector and flame ionization detector. HP-5 capillary GC column (30m x

0.25mm i.d.) and helium as gas carrier were routinely used. Inject temperature 250 °C; detector temperature 300 °C; inlet pressure15 psi; initial oven temperature 50 °C for 2 min, then ramp up to 300 °C (20 °C/ min), and 15 mins hold at 300 °C. Substrates (chalcones) were prepared by aldol condensation according to the literature method.[37] The complex **3** was prepared using the published procedures.[28]

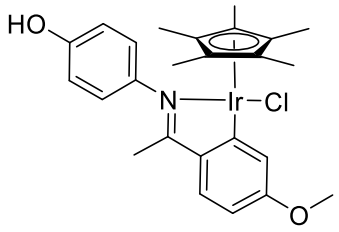
3.5.2 General procedure for the iridium complexes preparation

In a 50 mL round bottomed flask, $[Cp^*IrCl_2]_2$ dimer (100 mg, 0.16 mmol) (Cp* = pentamethylcyclopentadiene), imine ligand (2.2 eq.) and sodium acetate (10 eq.) were dissolved in DCM (10 mL). Then the reaction was stirred overnight under a nitrogen atmosphere at room temperature. The resulting mixture was then filtered to remove insoluble materials, dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo. The crude solid product was then washed with diethyl ether/hexane to afford an air and moisture stable pure compound.[28]

3.5.3 General procedure for the TH and methylation of unsaturated ketones in methanol

A 25 ml Synthware tube was charged with an unsaturated ketone (0.25 mmol), catalyst (0.003 mmol) and KOtBu (0.125 equiv.). MeOH (2 mL) was introduced, and then the reaction mixture was heated to reflux at 120 ^{o}C for 4 h. After cooling to room temperature, the solvent was evaporated under vacuum and flash column chromatography using a hexane/ethyl acetate mixture was carried out to purify the product.

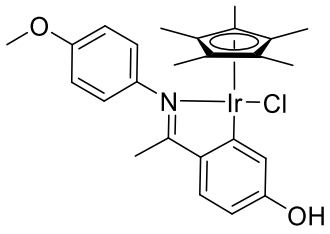
3.5.4 Analytical data of isolated products.



Iridium complex 5:[31] ^{1}H NMR ($CDCl_3$, 400 MHz, 298K) δ(ppm): 7.51 (d, *J* = 8.3 Hz, 2H), 7.35 (s, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 6.64 (dd, *J* = 8.5 Hz, 1H), 3.95 (s, 3H), 2.41 (s, 3H), 1.43 (s, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298K)δ(ppm): 177.97, 173.36, 160.86, 157.49, 143.60, 141.43, 128.99, 120.69, 108.45, 96.11, 55.13, 17.03, 8.80.HRMS for $C_{25}H_{29}IrNO_2$ $[M\text{-}Cl]^+$: m/z calc: 478.1248; found 478.1235.

Due to the fluxionality, two of the aromatic hydrogens in iridium complex **5** appeared very broad and featureless at r. t. A better resolved spectrum was obtained in CD_2Cl_2 at a lower temperature (- 60 ^{o}C). ^{1}H NMR (400 MHz, CD_2Cl_2, 298K) δ(ppm): 7.53 (d, *J* = 8.5 Hz, 3H), 7.35 (d, *J* = 2.5 Hz, 1H), 7.28

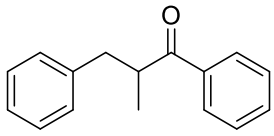
(d, *J* = 7.4 Hz, 1H), 6.64 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.95 (s, 3H), 2.41 (s, 3H), 1.43 (s, 15H). ^{1}H NMR (400 MHz, CD_2Cl_2, 213K) δ(ppm): 7.73 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 9.3 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.32 – 7.18 (m, 2H), 6.89 (d, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 3.90 (s, 3H), 2.38 (s, 3H), 1.35 (s, 15H).



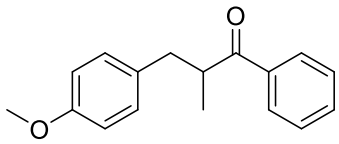
Iridium complex 6:[31] ^{1}H NMR ($CDCl_3$, 400 MHz,298K) δ(ppm): 7.42 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 2H), 6.51 (dd, *J* = 8.4, 2.3 Hz, 1H), 3.87 (s, 3H), 2.38 (s, 3H), 1.44 (s, 15H).^{13}C NMR ($CDCl_3$, 100 MHz, 298K)δ(ppm) 180.18, 170.49, 158.75, 157.54, 144.30, 141.16, 130.28, 121.25, 109.41, 88.92, 55.54, 16.80, 8.58.HRMS for $C_{25}H_{29}IrNO_2$ $[M\text{-}Cl]^+$: m/z calc: 478.1248; found 478.1242.

Due to the fluxionality, two of the aromatic hydrogens in iridium complex **6** appeared very broad and featureless at r. t. A better resolved spectrum was obtained in CD_2Cl_2 at a lower temperature (- 60 °C). ^{1}H NMR (400 MHz, CD_2Cl_2, 298K) δ(ppm): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.42 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 2H), 6.51 (dd, *J* = 8.4, 2.3 Hz, 1H), 3.87 (s, 3H), 2.38 (s, 3H), 1.44 (s, 15H). ^{1}H NMR (400 MHz, CD_2Cl_2, 213K) δ(ppm): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.66 (d, *J* = 8.5 Hz, 1H), 7.29

(d, *J* = 8.2 Hz, 2H), 7.16 (s, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.85 (dd, *J* = 26.3, 8.3 Hz, 2H), 6.37 (d, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 2.33 (s, 3H), 1.36 (s, 15H).

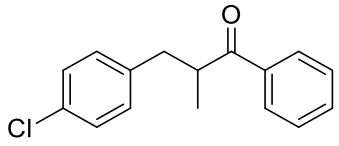


2-Methyl-1,3-diphenylpropan-1-one:[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ7.92 (d, *J* = 7.4 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.18 (dd, *J* = 14.0, 7.1 Hz, 3H), 3.74 (dd, *J* = 13.9, 6.9 Hz, 1H), 3.17 (dd, *J* = 13.6, 6.2 Hz, 1H), 2.69 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.74 (s), 139.98 , 136.49, 132.93, 129.11, 128.66, 128.40, 128.31, 126.22, 42.78, 39.40, 17.43. HRMS (ESI): calc. for $C_{16}H_{17}O$ $[M+H]^+$: 225.1093, found: 225.1097.

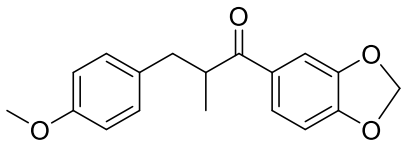


3.2.12. 3-(4-Methoxyphenyl)-2-methyl-1-phenylpropan-1one:[36]

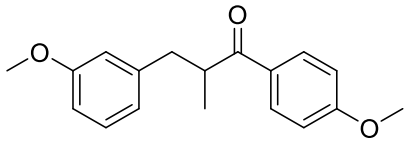
^{1}H NMR(400 MHz, $CDCl_3$) δ 7.92 (d, *J*=7.4 Hz, 2H), 7.54 (t, *J*=7.4 Hz, 1H), 7.44 (t, *J*=7.4 Hz, 2H), 7.10 (d, J=8.6 Hz, 2H), 6.80 (d, *J*=8.6 Hz, 2H), 3.76 (s, 3H), 3.70 (m, 1H), 3.13 (dd, *J*=13.8, 6.6 Hz, 1H), 2.63 (dd, *J*=13.8, 7.7 Hz, 1H), 1.19 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 202.78, 156.99, 135.48, 131.82, 130.90, 128.96, 127.57, 127.21, 112.73, 54.12, 41.91, 37.48, 16.29. HRMS (ESI): calc. for $C_{17}H_{19}O[M+H]^+$:239.1054,found:239.1151.



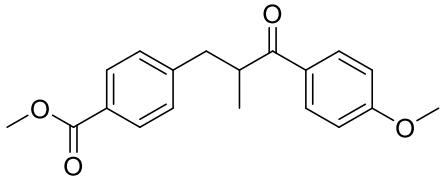
3-(4-chlorophenyl)-1-phenylbutan-1-one:[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.1 Hz, 2H), 7.54 (t, *J* = 7.1 Hz, 1H), 7.43 (t, *J* = 7.0 Hz, 2H), 7.25 (d, *J* = 6.9 Hz, 2H), 7.20 (d, *J* = 7.1 Hz, 2H), 3.49 (dd, *J* = 12.5, 6.1 Hz, 1H), 3.26 (m,1H), 3.17 (dd, *J* = 16.5, 7.4 Hz, 1H), 1.31 (dd, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.32, 137.39, 135.28,132.02, 130.94, 129.40, 127.65, 127.43, 127.21, 41.62, 37.55, 16.57. HRMS (ESI): calc. for $C_{16}H_{16}ClO$ $[M+H]^+$: 259.0704, found: 259.0708.



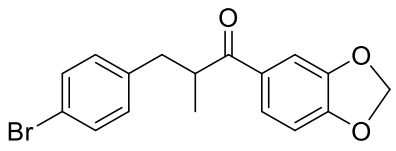
1-(benzo[d][1,3]dioxol-5-yl)-3-(4-methoxyphenyl)-2-methylpropan-1-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.39 (dd, J = 8.2, 1.6 Hz, 1H), 7.32 (s, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.72 (t, *J* = 15.1, 7.2 Hz, 3H), 5.93 (s, 2H), 3.67 (s, 3H), 3.51 (m,1H), 2.98 (dd, *J* = 13.8, 6.5 Hz, 1H), 2.53 (dd, *J* = 13.8, 7.6 Hz, 1H), 1.10 – 1.06 (d, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.96, 158.01, 151.67, 148.22, 132.03, 131.33, 129.99, 124.37, 113.76, 108.18, 107.86, 101.82, 55.22, 42.71, 38.74, 17.55. HRMS for $C_{18}H_{20}O_4$ $[M + H]^+$: m/z calc.: 300.1011; found: 300.103.



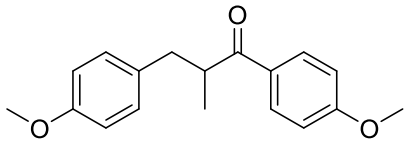
3-(3-methoxyphenyl)-1-(4-methoxyphenyl)-2-methylpropan-1-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.83 (d, *J*=8,2H), 7.11 – 7.07 (t, *J*=15.6, 1H), 6.84 – 6.82 (d, *J*=8.8, 2H), 6.72 – 6.70 (d, *J*=6, 1H), 6.66-6.62 (dd, *J*=11.2 2H), 3.77(s, 3H), 3.68 (s, 3H), 3.66-3.57(m, 1H), 3.04 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.57 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.24, 163.40, 159.66, 141.77, 130.58, 129.41, 129.31, 121.49, 114.92, 113.79, 111.39, 55.46, 55.13, 42.22, 39.54, 17.62. HRMS for $C_{18}H_{21}O_3$ $[M + H]^+$: m/z calc.: 285.1412; found: 285.1439.



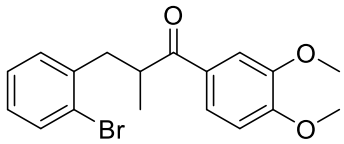
methyl 4-(3-(4-methoxyphenyl)-2-methyl-3-oxopropyl)benzoate: ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): 7.92 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 9.0 Hz, 2H), 7.27-7.25 (d, *J* = 8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.79 – 3.65 (m, 1H), 3.21 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.75 (dd, *J* = 13.6, 7.4 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), ^{13}C NMR (101 MHz, CDCl3) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.73, 167.06, 163.51, 145.71, 130.55, 129.70, 129.17, 128.14, 113.85, 55.48, 52.00, 42.06, 39.41, 17.87. HRMS for $C_{19}H_{21}O_4$ $[M + H]^+$: m/z calc.: 313.1362; found: 313.1520.



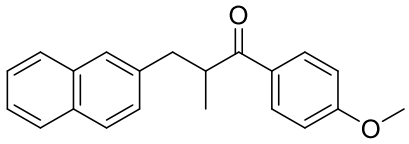
1-(benzo[d][1,3]dioxol-5-yl)-3-(4-bromophenyl)-2-methylpropan-1-one: ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): 7.44 (d, *J* = 1.7 Hz, 1H), 7.41 (d, *J* = 1.7 Hz, 1H), 7.32 (d, *J* = 1.7 Hz, 2H), 7.19 (s, 1H). 6.98 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.03 (s, 2H), 3.59 – 3.49 (m, 1H), 3.05 – 2.98 (dd, J=6.8, 7.2 Hz, 1H), 2.57 (dd, *J* = 13.7, 7.2 Hz, 1H), 1.11 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.31, 150.74, 147.28, 137.98, 130.38, 130.09, 129.78, 123.33, 118.97, 107.13, 106.89, 100.84, 41.33, 37.82, 16.88, HRMS for $C_{17}H_{16}BrO_3$ $[M + H]^+$: m/z calc.: 348.2080; found: 348.2078.



1,3-bis(4-methoxyphenyl)-2-methylpropan-1-one: ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): δ 7.93 (d, *J* = 9.2 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.70 – 3.59 (m, 1H), 3.08 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.62 (dd, *J* = 13.8, 7.7 Hz, 1H), 1.17 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.42, 163.36, 157.99, 132.18, 130.56, 130.01, 129.36, 113.76, 113.78, 55.46, 55.23, 42.56, 38.68, 17.51. HRMS for $C_{18}H_{21}O_3$ $[M + H]^+$: m/z calc.: 285.1412; found: 285.1419.

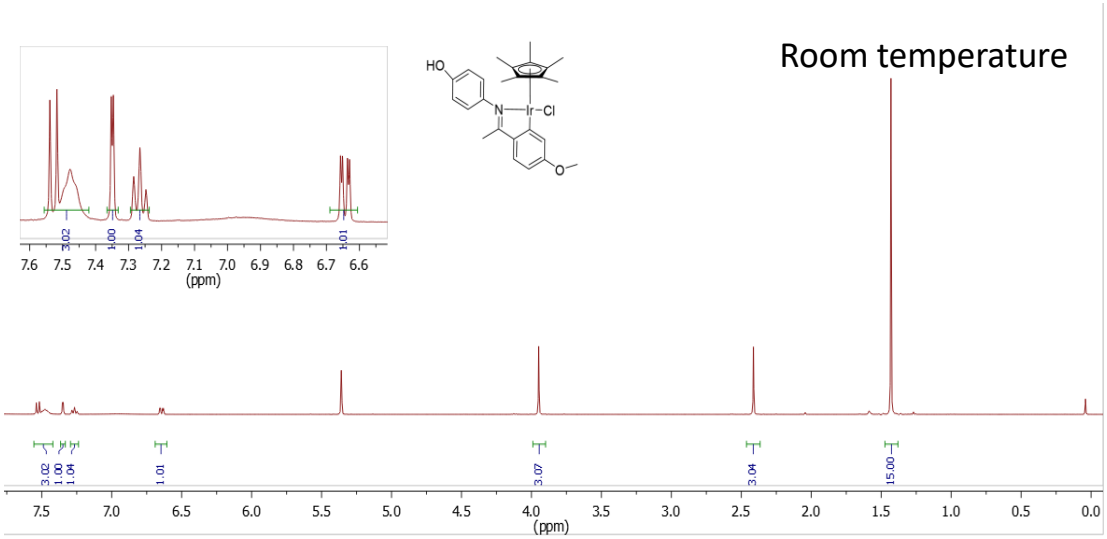


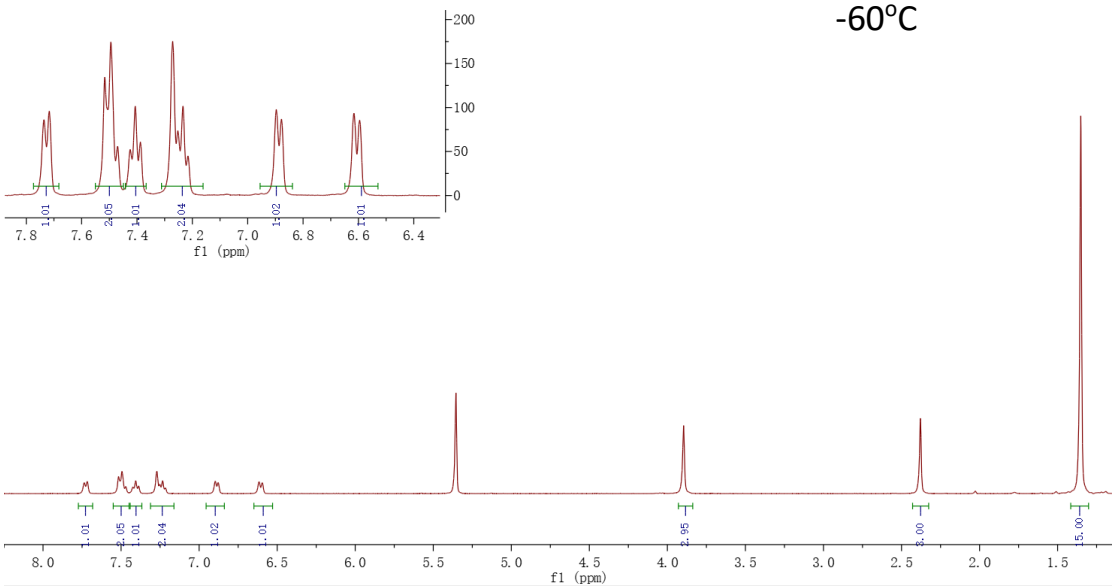
3-(2-bromophenyl)-1-(3,4-dimethoxyphenyl)-2-methylpropan-1-one: ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): 7.50 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 1.8 Hz, 1H), 7.15 – 7.04 (m, 2H), 6.96 (td, *J* = 7.9, 1.9 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 – 3.76 (m, 1H), 3.15 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.79 (dd, *J* = 13.5, 7.3 Hz, 1H), 1.14 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.39, 152.21, 147.99, 138.21, 131.78, 130.97, 128.63, 127.01, 126.29, 123.51, 121.78, 109.51, 108.97, 55.02, 54.91, 39.02, 38.62, 16.83, HRMS for $C_{18}H_{20}BrO_3$ $[M + H]^+$: m/z calc.: 364.2510; found: 364.2517.

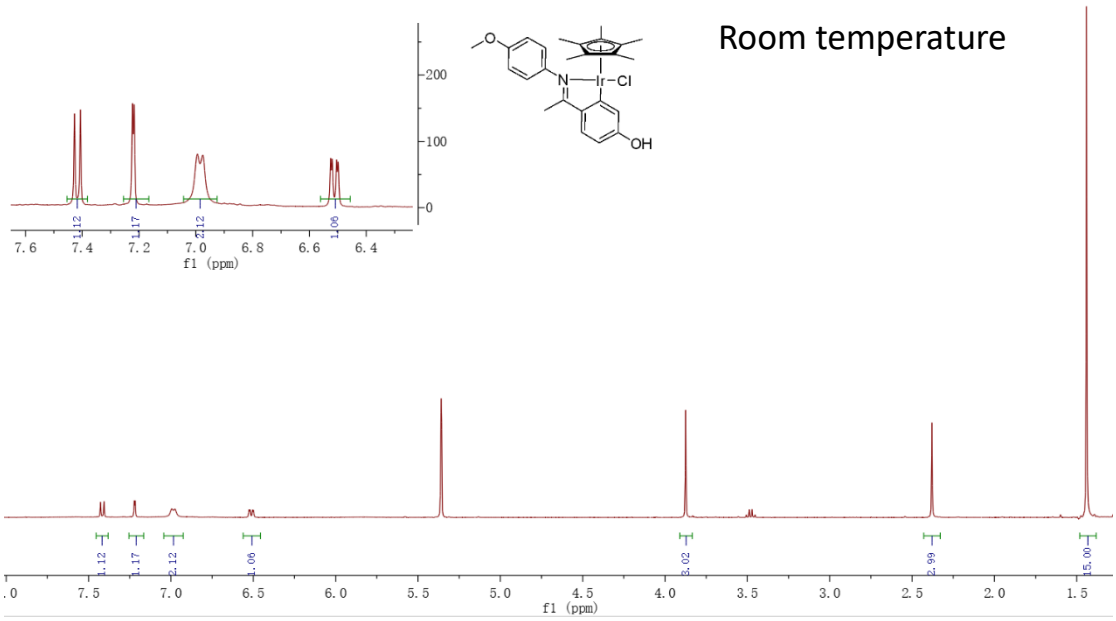


1-(4-methoxyphenyl)-2-methyl-3-(naphthalen-2-yl)propan-1-one: ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K) δ (ppm): 7.96 (d, *J* = 8.9 Hz, 2H), 7.79 (m, 3H), 7.68 (s, 1H), 7.46–7.38 (m, 3H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.79 (m, 1H), 3.33 (dd, *J* = 7.9 Hz, 1H), 3.21 (dd, *J* = 8.0 Hz, 1H), 1.28(d, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K) δ (ppm): 197.75, 163.47, 138.79, 133.64, 132.08, 130.33, 129.99, 128.09, 127.62, 127.46, 127.21, 126.48, 126.00, 125.28, 113.77, 55.47, 40.03, 30.48, 16.65, HRMS for $C_{21}H_{21}O_2$ $[M + H]^+$: m/z calc.: 305.3890; found: 305.3902.

3.5.5 NMR Spectrum



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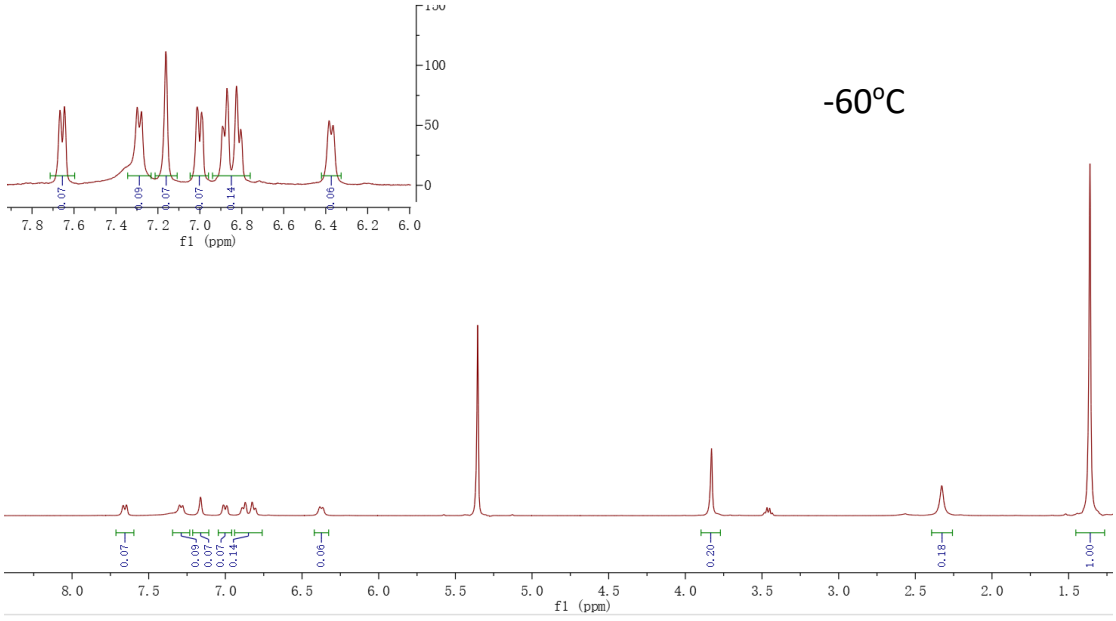
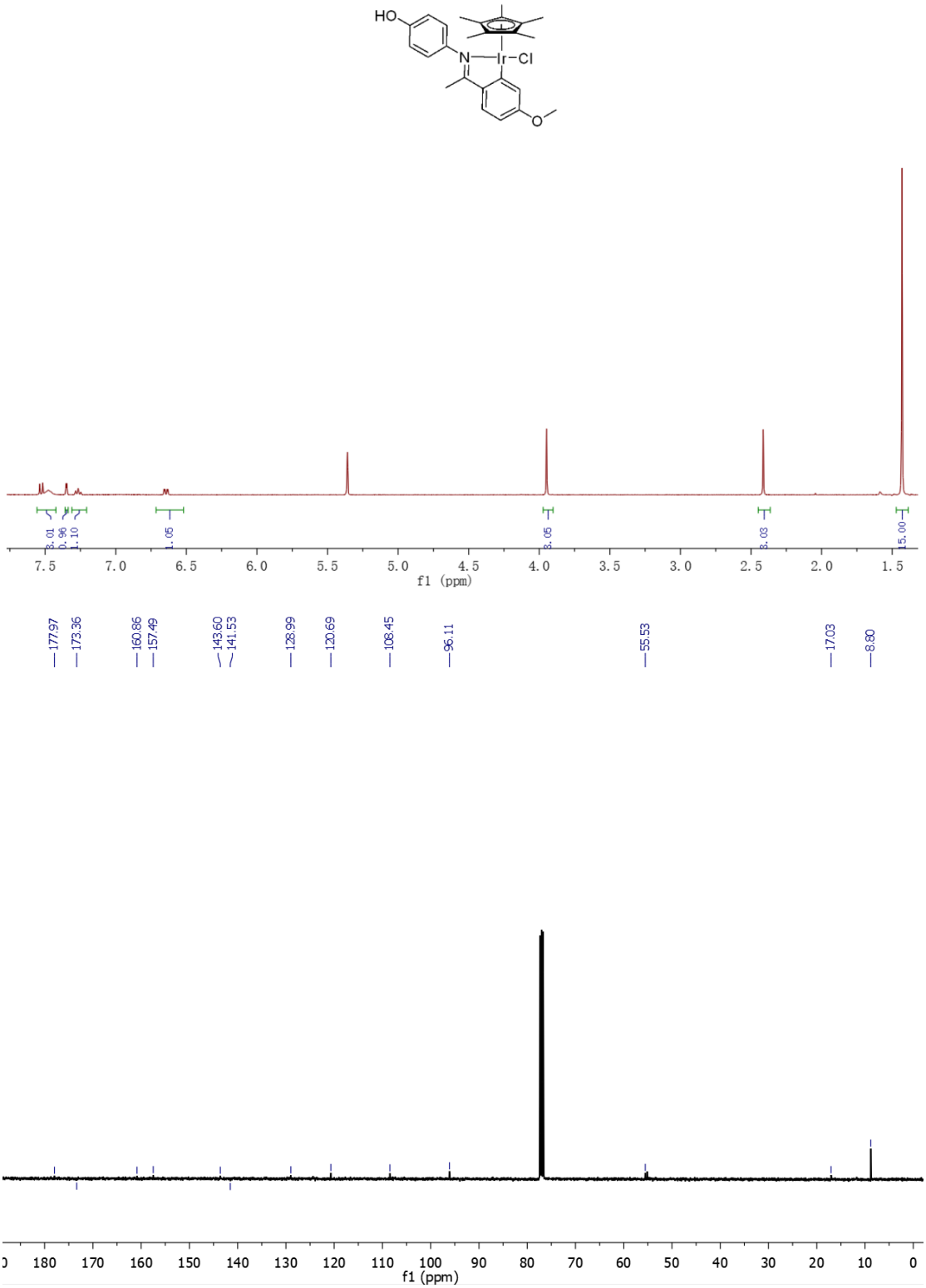
Ir
Cl
OH
f1 (ppm)


-60°C
f1 (ppm)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Ir
Cl
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3.05
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f1 (ppm)
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8.80
180
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50
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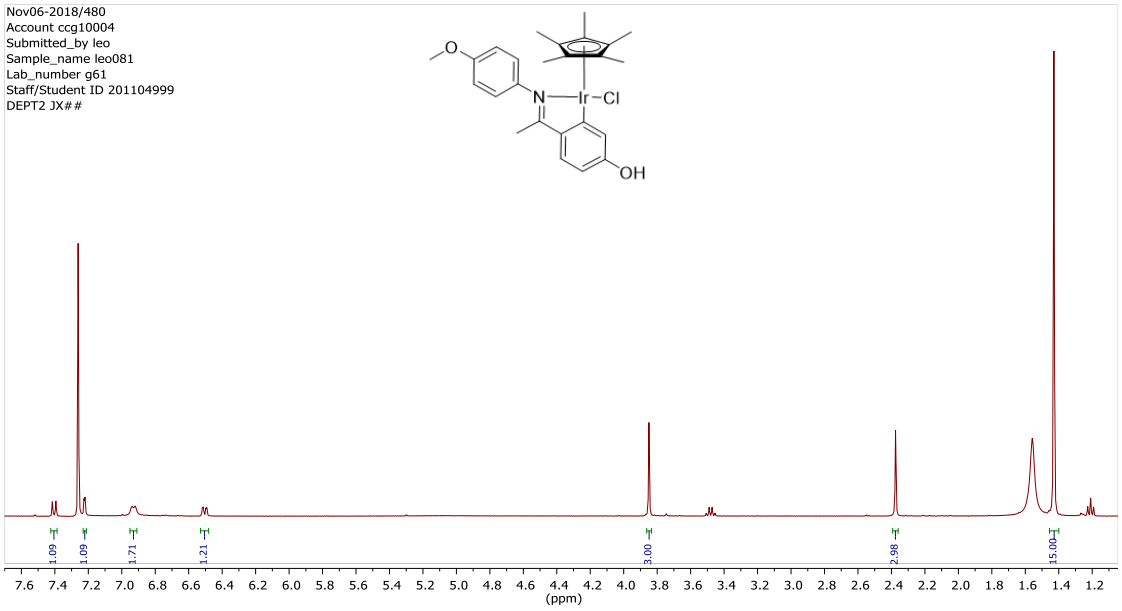
f1 (ppm)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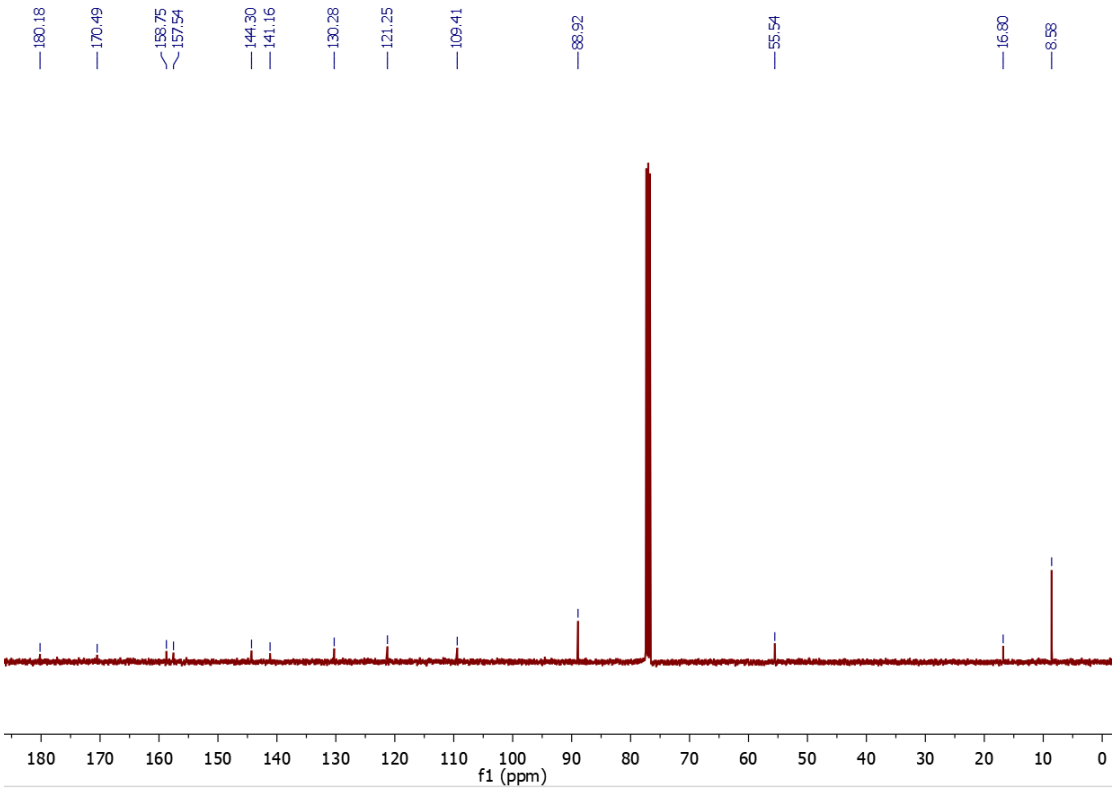
(ppm)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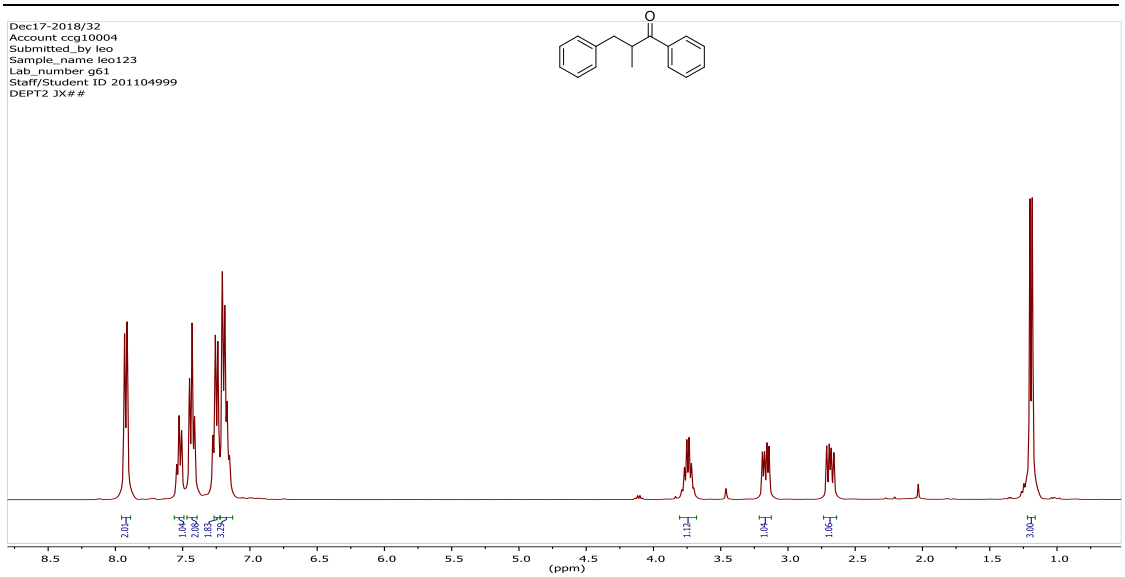
f1 (ppm)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Staff/Student ID 201104999
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2.08
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1.12
1.04
1.06
3.00
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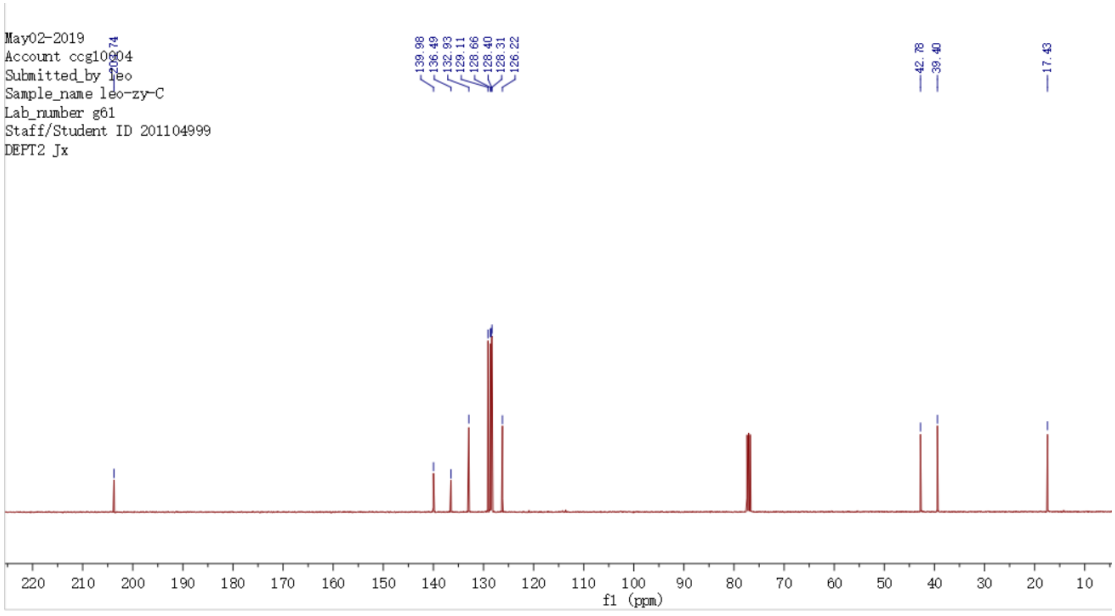
(ppm)


May02-2019
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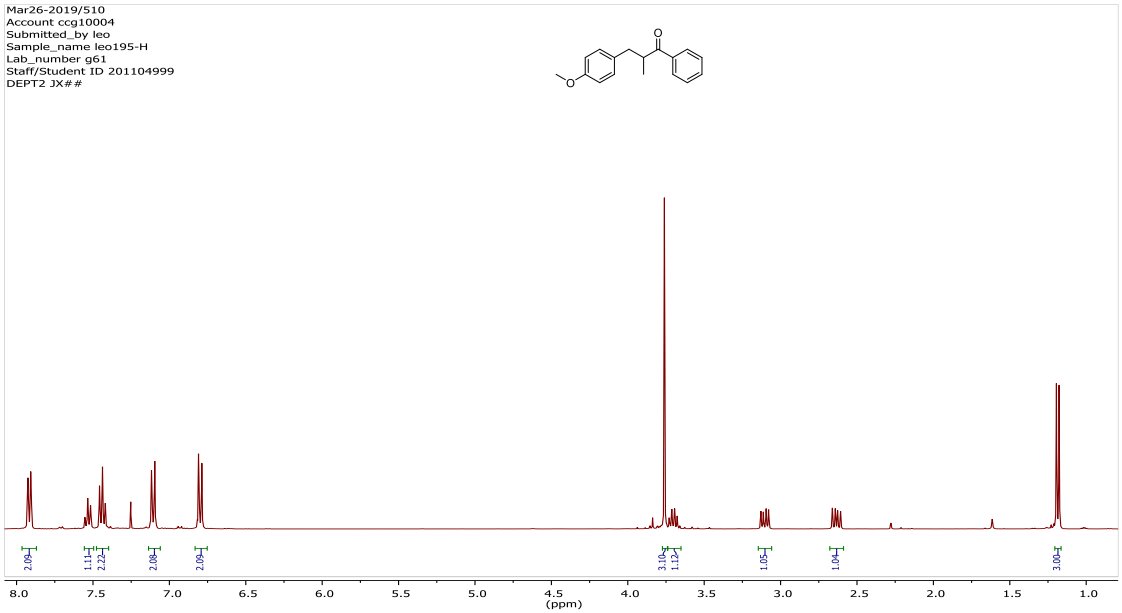
f1 (ppm)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3.10
1.12
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7.0
6.5
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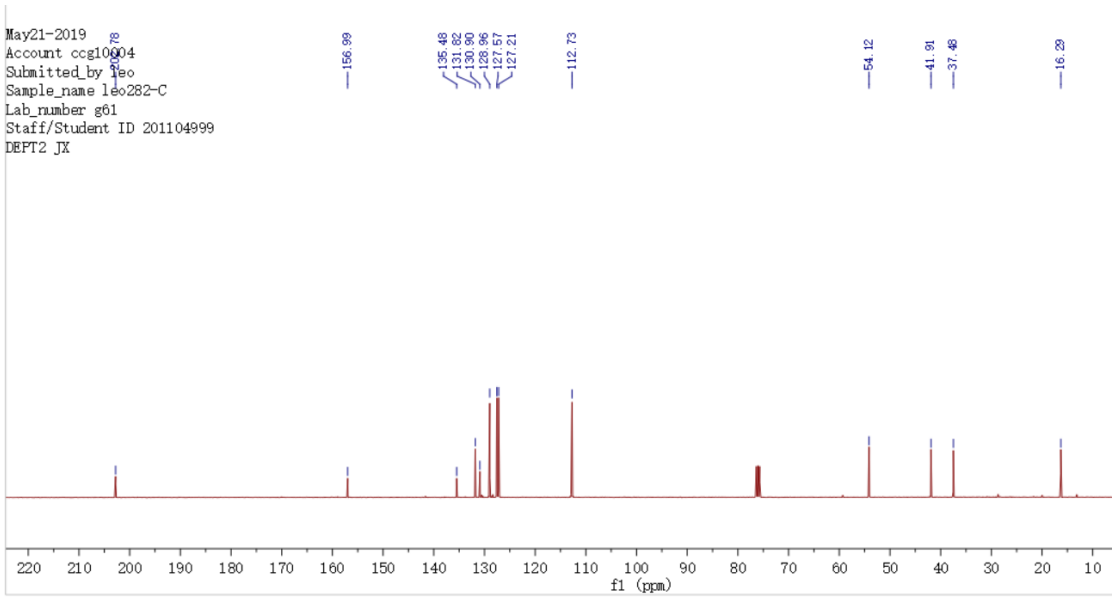
(ppm)


May21-2019
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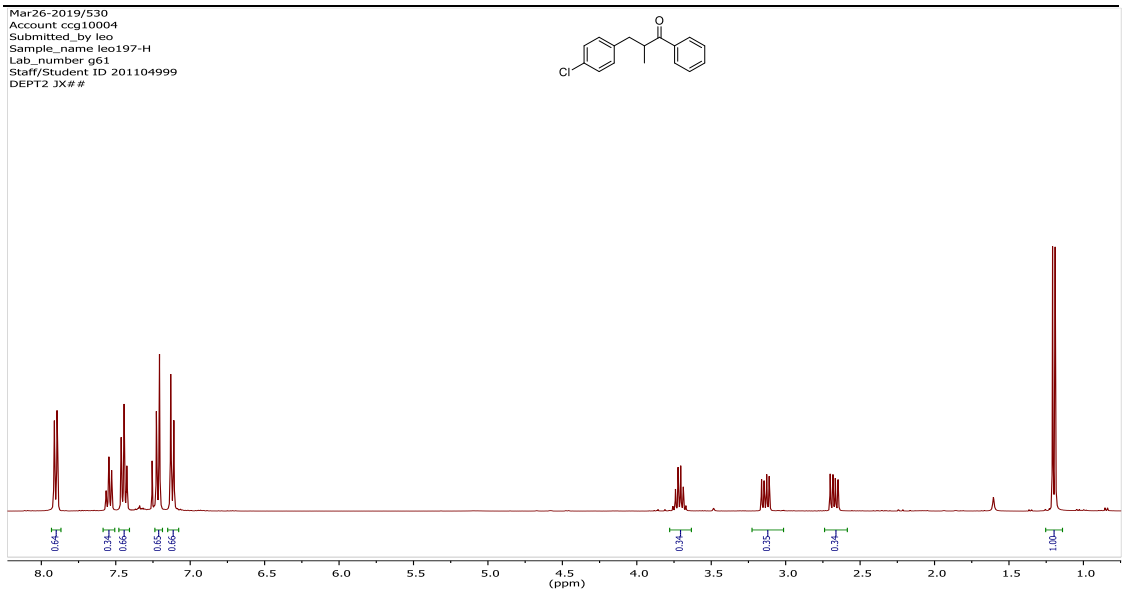
f1 (ppm)


Mar26-2019/530
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Staff/Student ID 201104999
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0.34
0.35
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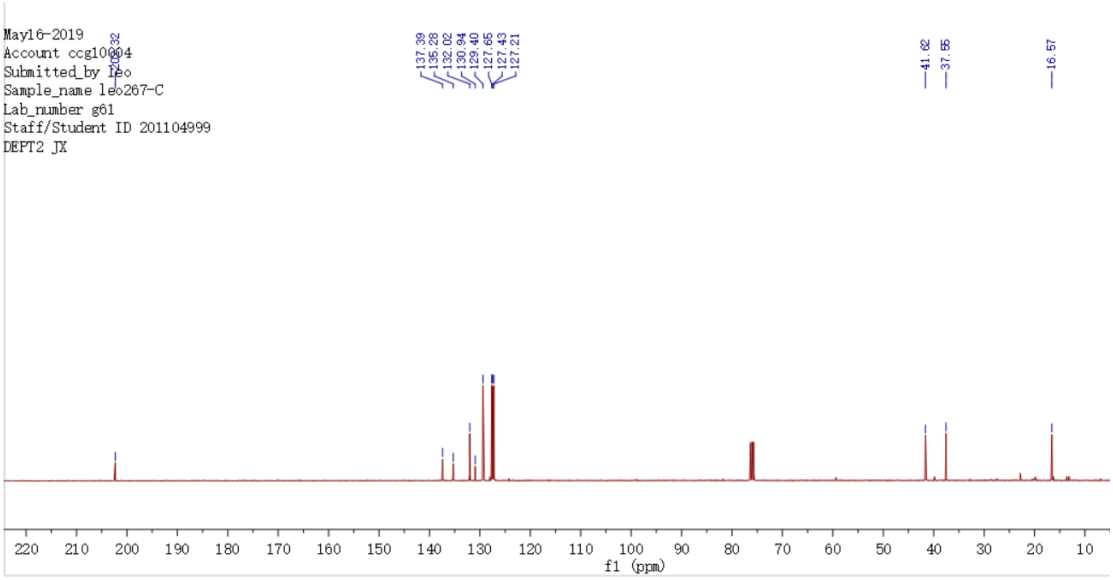
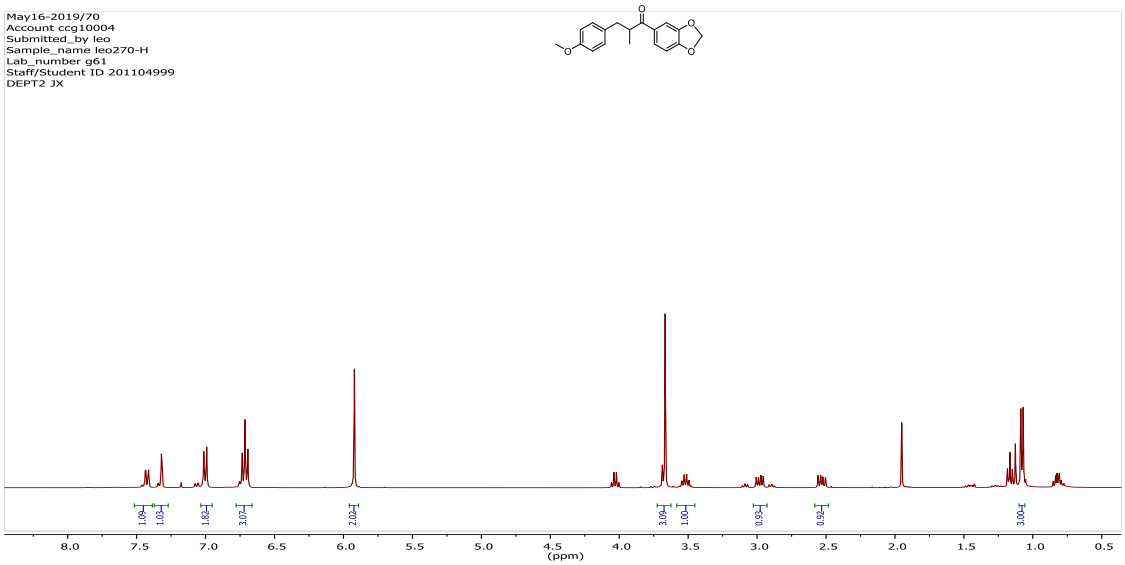
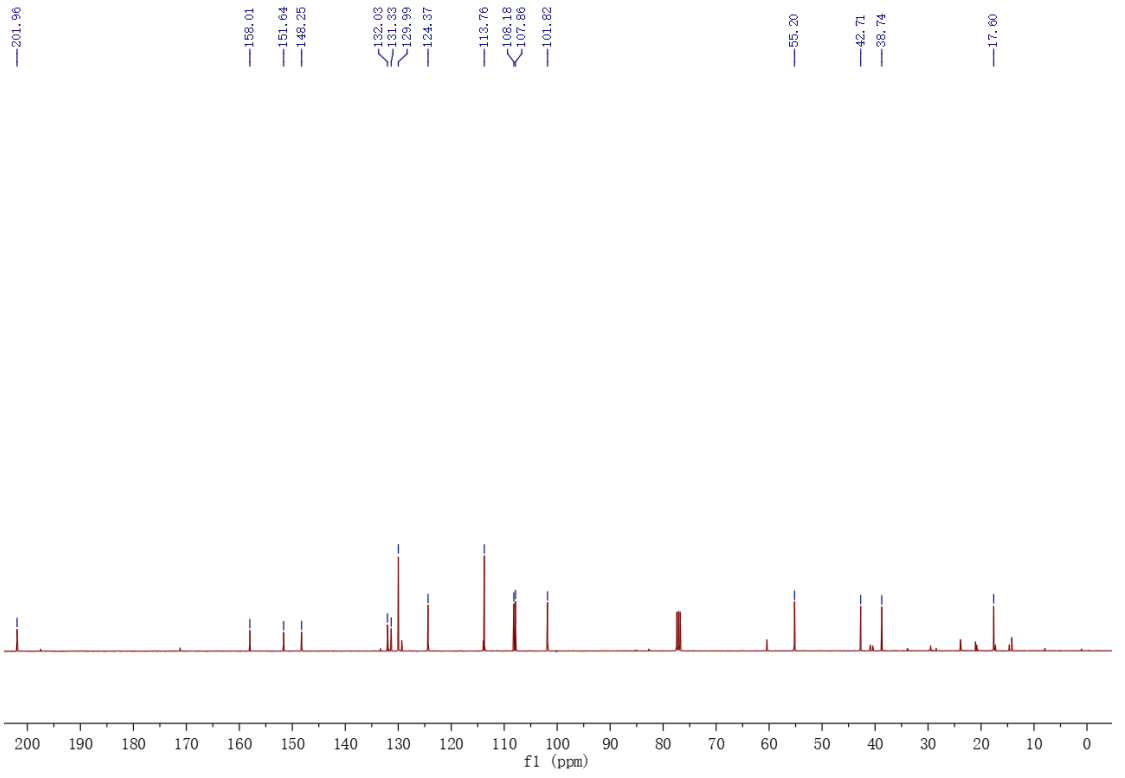
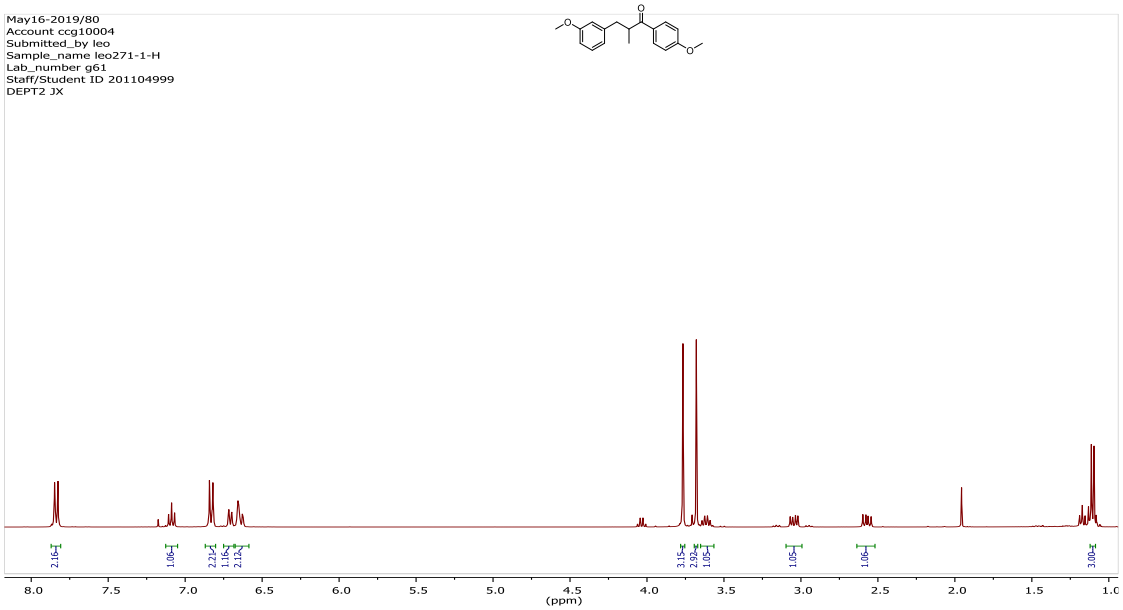
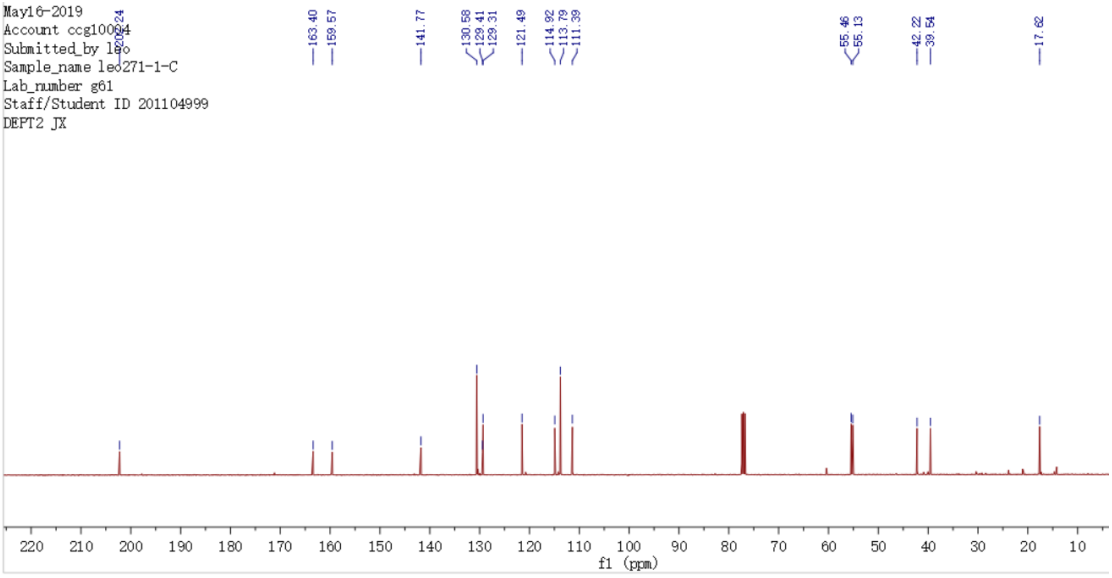
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

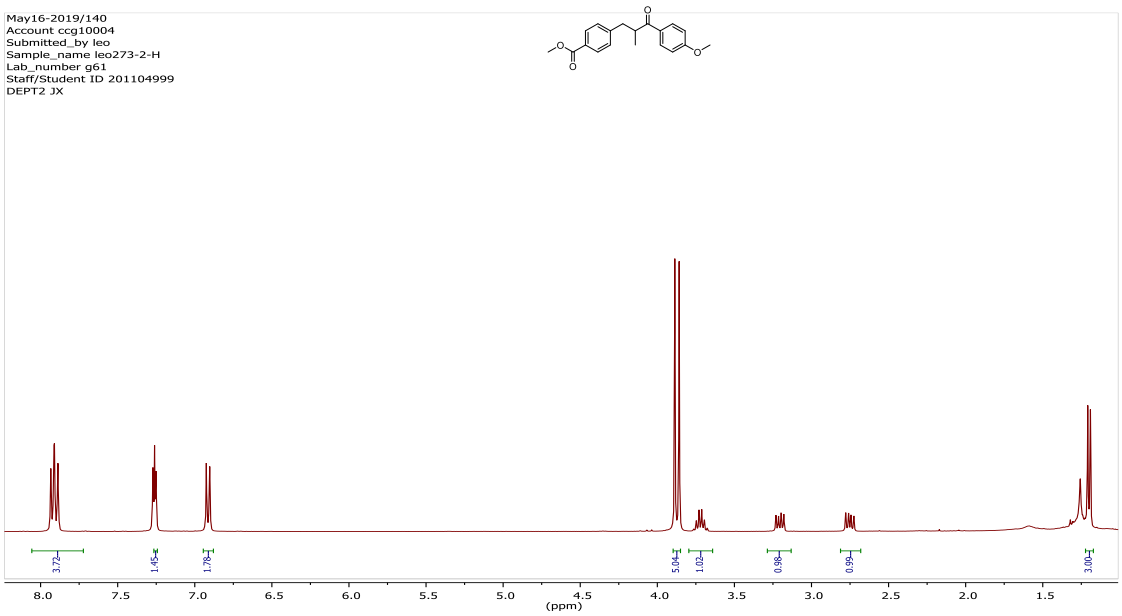

May16-2019
Account ccg10004
Submitted_by leo
Sample_name leo267-C
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX
197.32
137.39
135.28
135.02
130.94
129.40
127.65
127.43
127.21
41.62
37.55
16.57
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

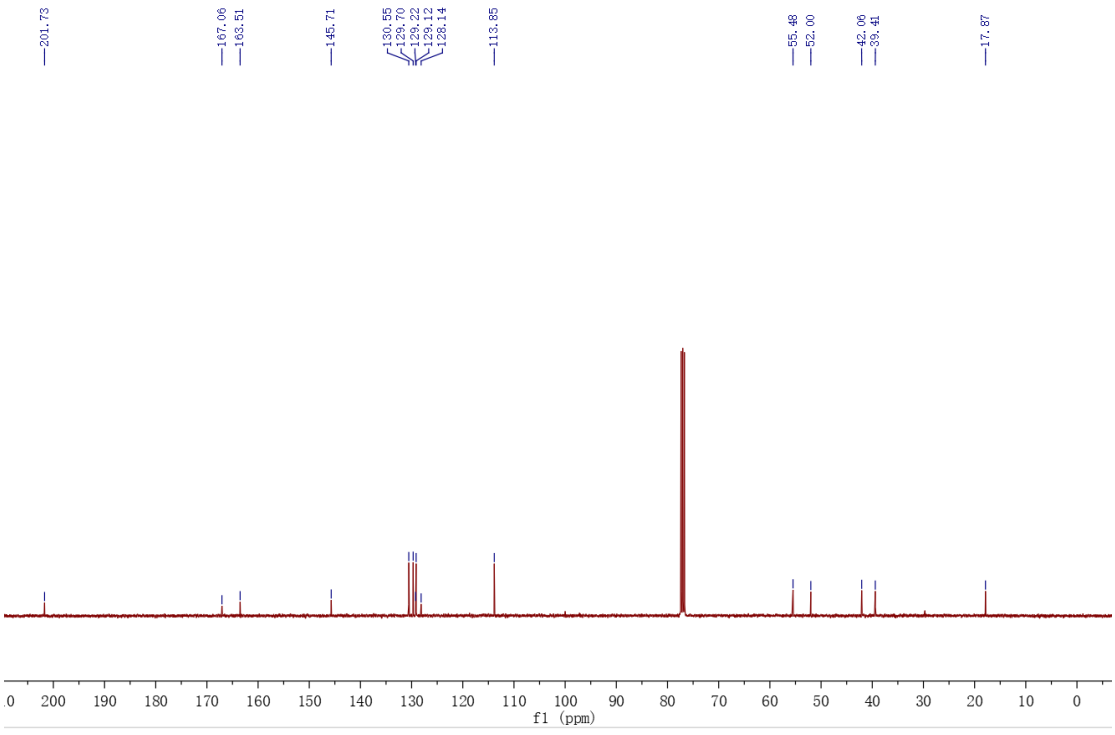

May16-2019/70
Account ccg10004
Submitted_by leo
Sample_name leo270-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX
1.09
1.03
1.82
3.07
2.02
3.09
1.00
0.93
0.92
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

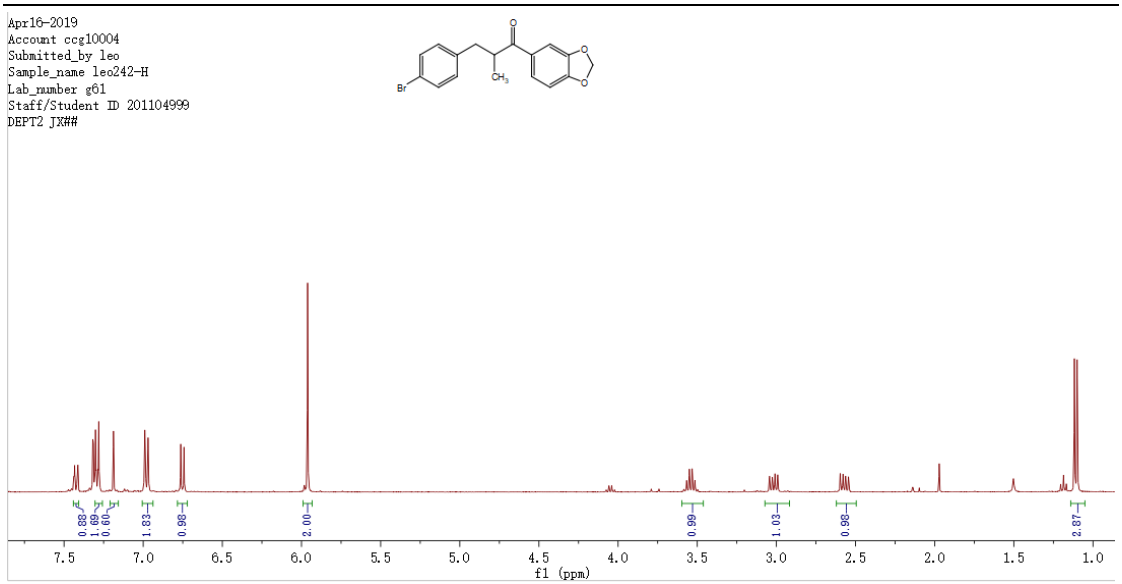

201.96
158.01
151.64
148.25
132.03
131.33
129.99
124.37
113.76
108.18
107.86
101.82
55.20
42.71
38.74
17.60
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

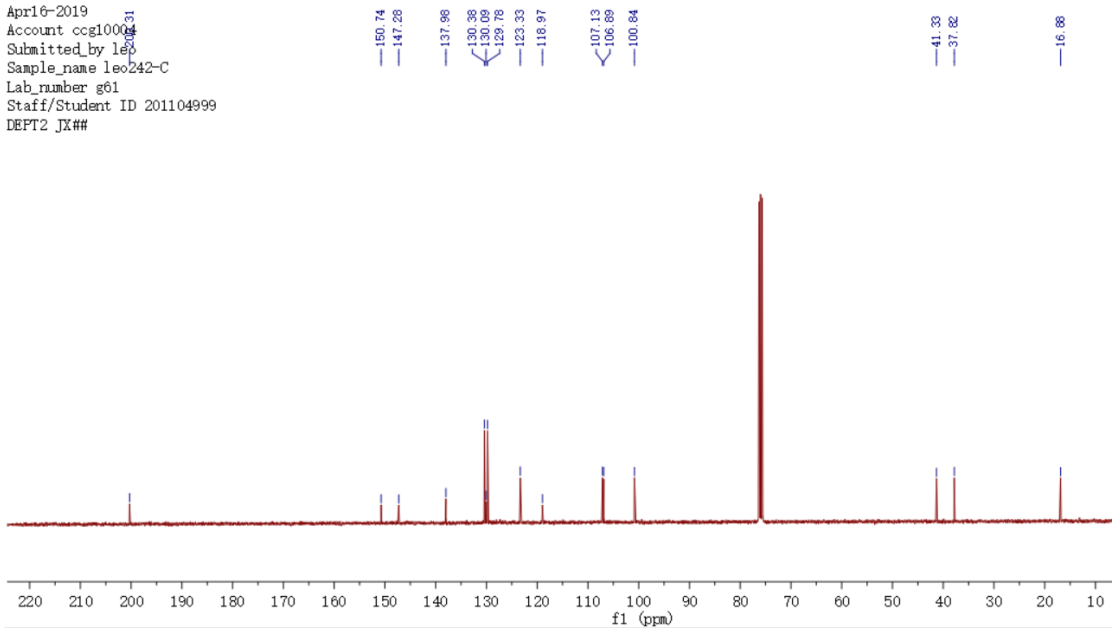

May16-2019/80
Account ccg10004
Submitted_by leo
Sample_name leo271-1-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX
(ppm)


May16-2019
Account ccg10004
Submitted_by leo
Sample_name leo271-1-C
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX
197.24
163.40
159.57
141.77
130.58
129.41
129.31
121.49
114.92
113.79
111.39
55.46
55.13
42.22
39.54
17.62
f1 (ppm)

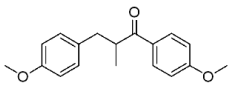

May16-2019/140
Account ccg10004
Submitted_by leo
Sample_name leo273-2-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX
3.72
1.45
1.78
5.04
1.02
0.98
0.99
3.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
(ppm)

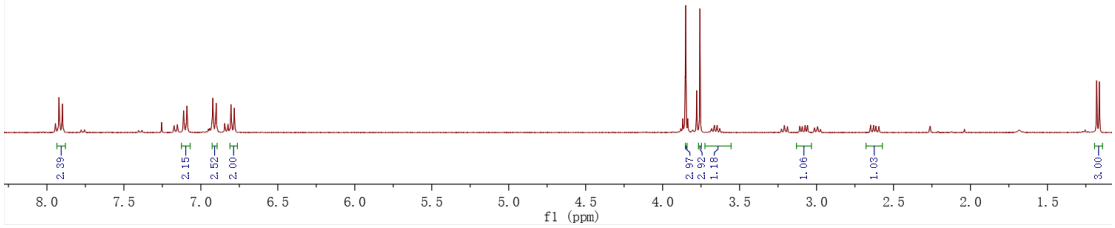

201.73
167.06
163.51
145.71
130.55
129.70
129.22
129.12
128.14
113.85
55.48
52.00
42.06
39.41
17.87
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

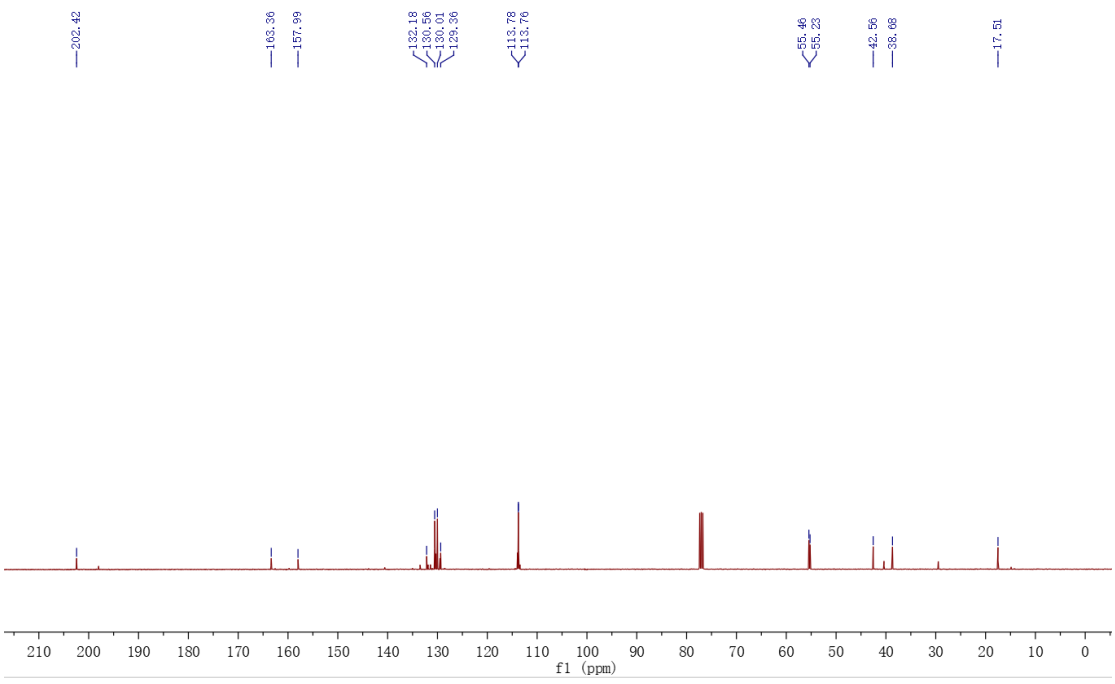

Apr16-2019
Account ccg10004
Submitted_by leo
Sample_name leo242-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##
Br
O
O
O
CH3
0.88
1.69
0.60
1.83
0.98
2.00
0.99
1.03
0.98
2.87
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

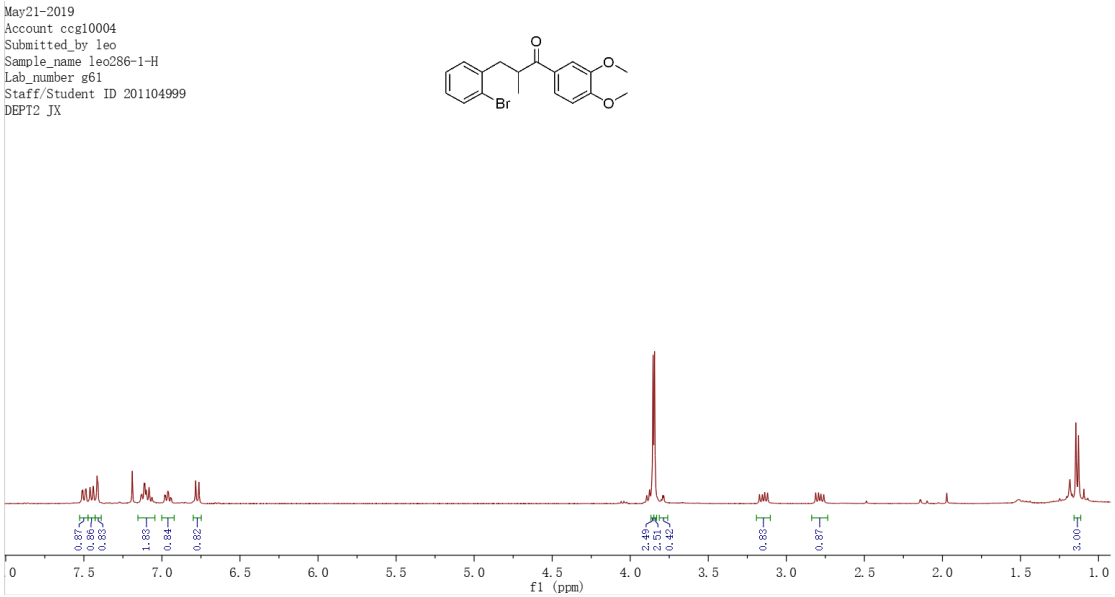

Apr16-2019
Account ccg10004
Submitted_by leo
Sample_name leo242-C
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##
199.31
150.74
147.28
137.98
130.38
130.09
129.78
123.33
118.97
107.13
106.89
100.84
41.33
37.82
16.88
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

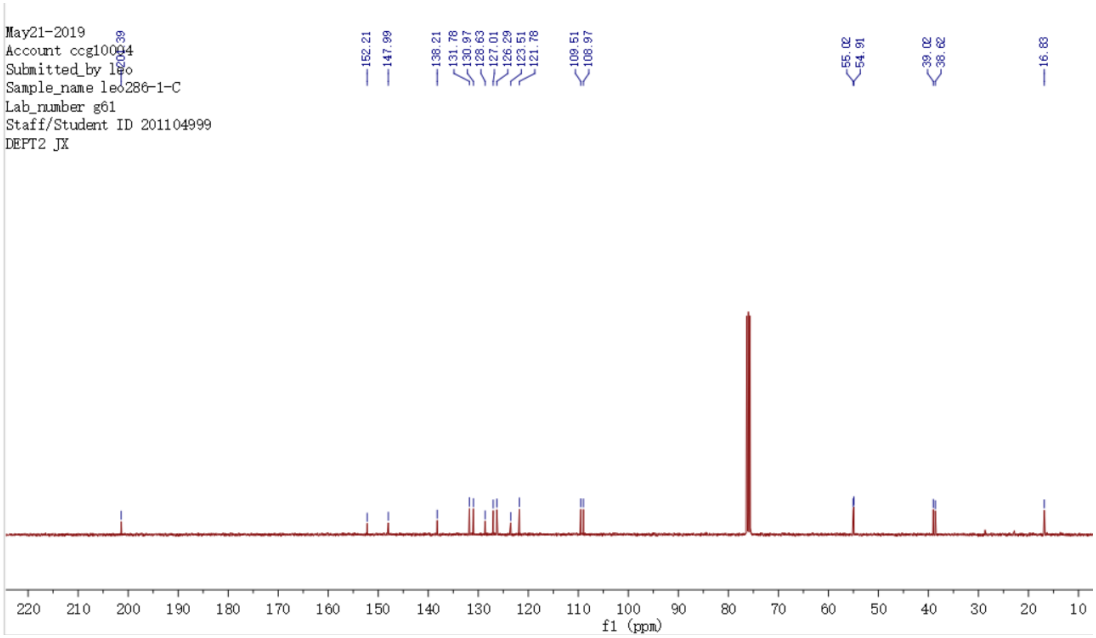
Mar27-2019
Account ccgl0004
Submitted_by leo
Sample_name leo201-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##

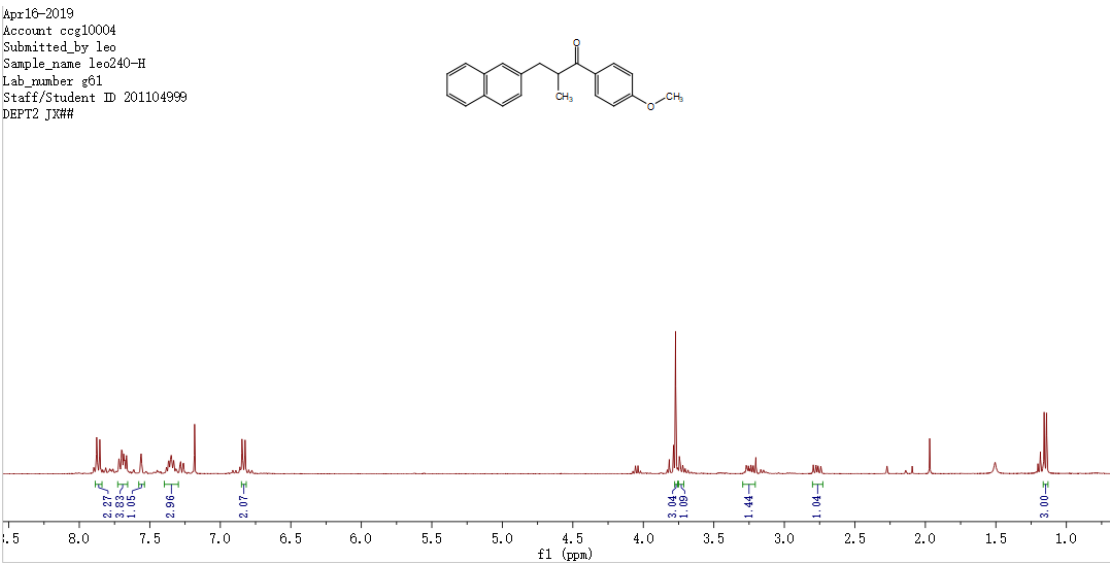


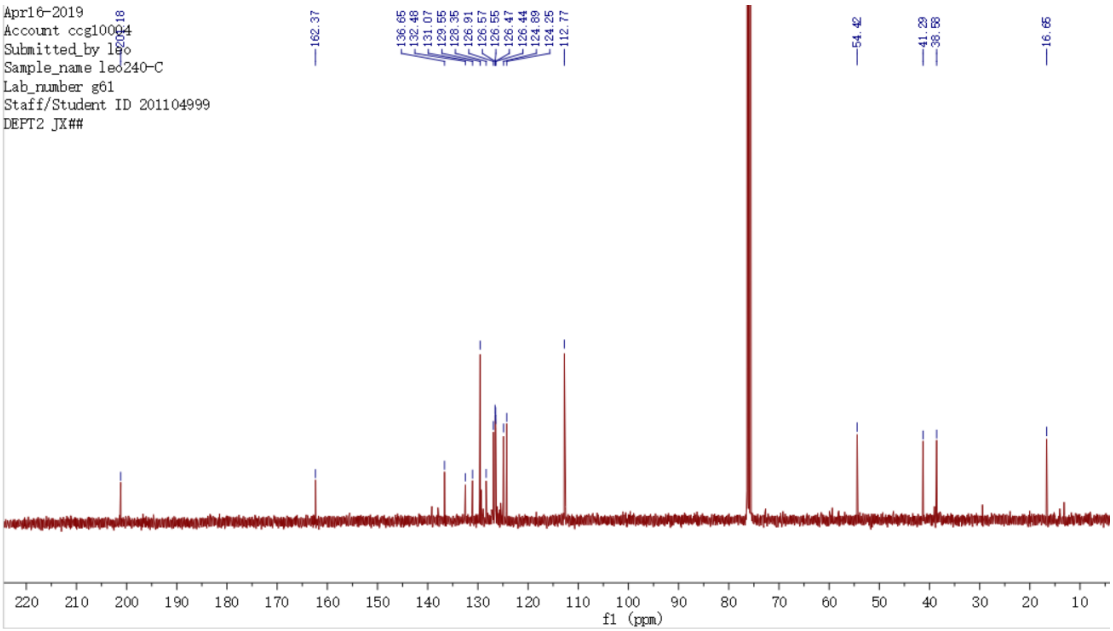




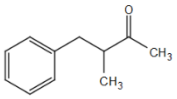

May21-2019
Account ccg10004
Submitted_by leo
Sample_name leo286-1-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX
Br
O
O
O
0.87
0.86
0.83
1.83
0.84
0.82
2.49
2.51
0.42
0.83
0.87
3.00
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

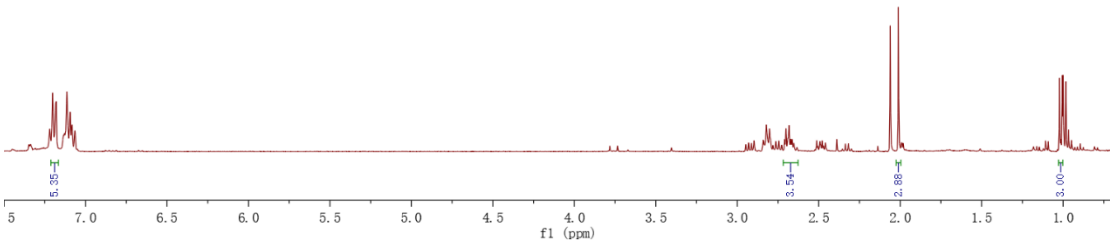

May21-2019
Account ccg10004
Submitted_by leo
Sample_name leo286-1-C
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX
39.39
152.21
147.99
138.21
131.78
130.97
128.63
127.01
126.29
123.51
121.78
109.51
108.97
55.02
54.91
39.02
38.62
16.83
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Apr16-2019
Account ccg10004
Submitted_by leo
Sample_name leo240-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##
2.27
3.83
1.05
2.96
2.07
3.04
1.09
1.44
1.04
3.00
f1 (ppm)

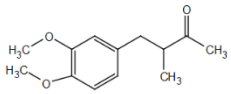

Apr16-2019
Account ccg10004
Submitted_by leo
Sample_name leo240-C
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##
200.18
162.37
136.65
132.48
131.07
129.55
128.35
126.91
126.57
126.55
126.47
126.44
124.89
124.25
112.77
54.42
41.29
38.68
16.65
f1 (ppm)

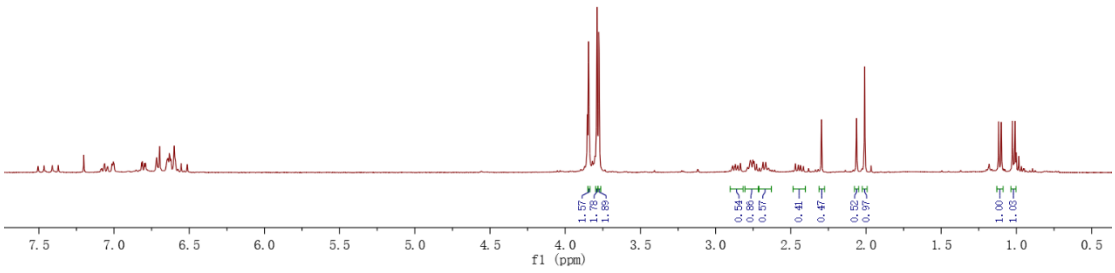
Apr26-2019
Account ccg10004
Submitted_by leo
Sample_name leo152-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##

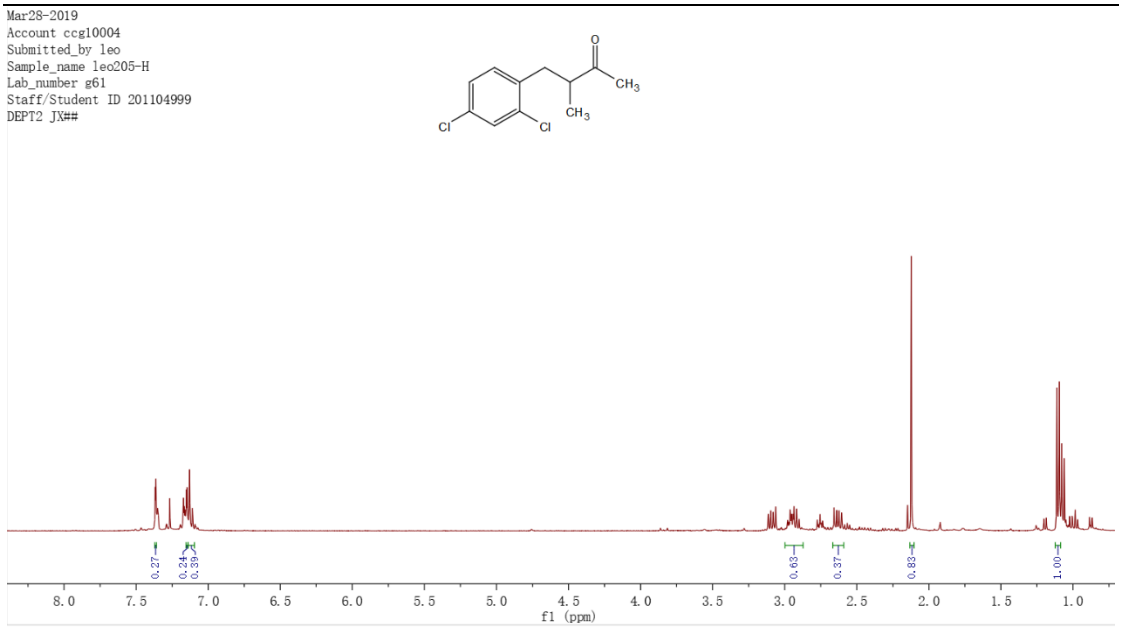


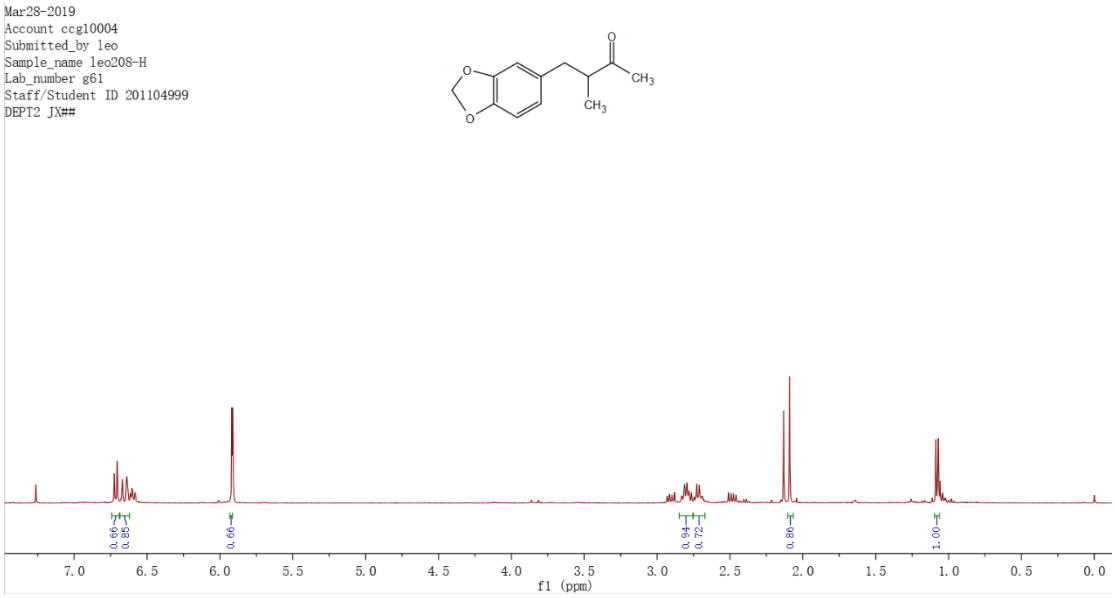


Mar27-2019
Account ccg10004
Submitted_by leo
Sample_name leo204-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##

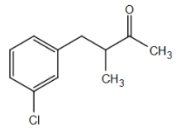


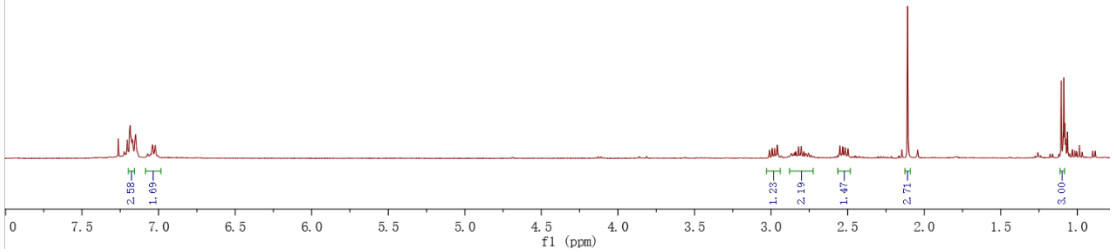



Mar28-2019
Account ccg10004
Submitted_by leo
Sample_name leo205-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##
O
CH3
CH3
Cl
Cl
0.27
0.24
0.39
0.63
0.37
0.83
1.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

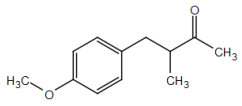

Mar28-2019
Account ccg10004
Submitted_by leo
Sample_name leo208-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##
O
CH3
CH3
O
O
0.66
0.85
0.60
0.94
0.72
0.86
1.00
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

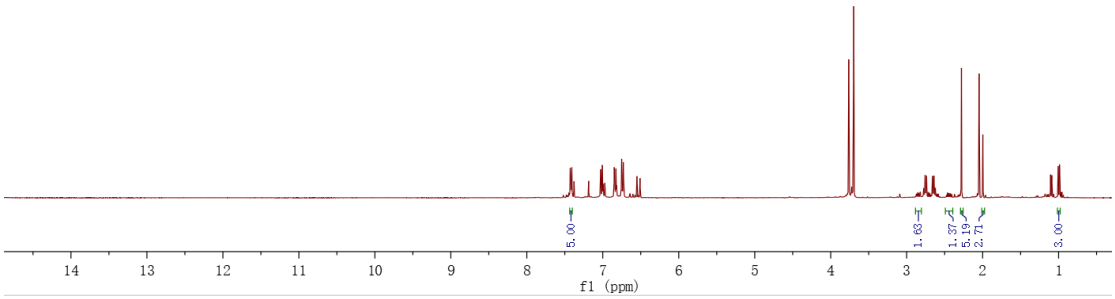
Mar28-2019
Account ccg10004
Submitted_by leo
Sample_name leo209-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##





Apr27-2019
Account ccg10004
Submitted_by leo
Sample_name leo254-H
Lab_number g61
Staff/Student ID 201104999
DEPT2 JX##





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Chapter 4: Conclusion

This thesis describes the investigation on rhodium-catalysed transfer hydrogenation and methylation. In Chapter 1, I summarised the status quo on the reduction of carbonyl compounds with different hydrogen donors. Although these types of reactions have been extensively studied by many research groups, a number of limitations and challenges still remain, such as the limited examples in the reduction process, and the reduction with the use of inexpensive and safe hydrogen sources that could perform under milder reaction conditions.

A cyclometalated rhodium complex has been found to be highly efficient and chemoselective for the TH of carbonyl compounds using methanol as hydrogen source. A wide range of substrates were screened in the reaction system with high yield and chemoselectivity using only 1 mol% catalyst loading. Few molecular catalysts are capable of dehydrogenating methanol under such mild conditions. Further studies showed the importance of the hydroxy functionality of the imino ligand.

In the field of hydrogen borrowing reactions, the advantage of this complex in methanol dehydrogenation may allow it to be used for methylation reactions. So, another cyclometalated rhodium complex **3** was prepared and introduced for TH and methylation of carbonyl compounds. A wider variety of ketones with halogen, methoxy, ester,

epoxy group were hydrogenated and methylated to its saturated and alkylated product in refluxing methanol in a short time under relatively mild conditions with methanol as hydrogen donor, C source and solvent. The catalyst loading could be reduced to 0.5 molCHEM286 Group 1 Workshop 2 %. It provided the possibility to achieve TH and chain growth of carbonyl compounds in one pot system.

During the thesis, we also find out that the possibility to replace methanol with heavy alcohols as both hydrogen donor and C source. Even the product was mixture, it still provides a new pathway for chain growth in future.

In the field of catalytic hydrogenation, catalysts based on non-noble metals, such as manganese[1-3], iron[4,5], cobalt[6-8], nickle[9-10], etc, have continued to be investigated over the last decade.[11] The search for more efficient metal catalysts could be a future direction of more environmentally friendly transfer hydrogenation and transamination processes.

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