Development of Ruthenium Based Catalytic Systems for C-H Bond Activation/Arylation of Aryl Pyridines

Ph.D. Thesis

by

Chinky Binnani

DISCIPLINE OF CHEMISTRY

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Development of Ruthenium Based Catalytic Systems for C-H Bond Activation/Arylation of Aryl Pyridines

A THESIS

Submitted in partial fulfillment of the requirements for the award of the degree
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by
Chinky Binnani

DISCIPLINE OF CHEMISTRY
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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled "**Development of Ruthenium Based Catalytic Systems for C-H Bond Activation/Arylation of Aryl Pyridines"** in the partial fulfillment of the requirements for the award of the degree of **DOCTOR OF PHILOSOPHY** and submitted in the **DISCIPLINE OF CHEMISTRY, Indian Institute of Technology Indore**, is an authentic record of my own work carried out during the time period from July 2014 to December 2019 under the supervision of Dr. Sanjay Kumar Singh, Associate Professor, Discipline of Chemistry, IIT Indore.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

Binnani 27/05/2020

signature of the student with date
(CHINKY BINNANI)

This is to certify that the above statement made by the candidate is correct to the best of my/our knowledge.

May 27, 2020
Signature of Thesis Supervisor with date
(Dr. SANJAY KUMAR SINGH)

CHINKY BINNANI has successfully given ~~his~~/her Ph.D. Oral Examination held on 27th May 2020.

Signature of Chairperson (OEB) Date: May 27, 2020	Signature of External Examiner Date:	Signature(s) of Thesis Supervisor(s) Date: May 27, 2020
Signature of PSPC Member #1 Date: May 27, 2020	Signature of PSPC Member #2 Date: May 27, 2020	Signature of Convener, DPGC Date: May 27, 2020

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I would like to express my sincere thanks to my loving families. I express my deep sense of gratitude to my parents ***Mr. Sanjeev Binnani*** *and* ***Mrs. Urmila Binnani*** *for their love and faith they kept in my dreams. My special thanks goes to all my mothers* ***Mrs. Prabha Totla****, my loving nani maa,* ***Mrs. Sudha Sharma****, my respectable mother-in-law and* ***Mrs. Pramila Maheshwari****, my beautiful chhoti maa for all their constant help, love, support in taking care of sweet, little, bundle of joy, Aarya in my absence so that I could follow the voice of my heart. I would like to extend my thanks to* ***Mr. Prahlad Das Totla****, nanaji,* ***Mr. Dharmesh Maheshwari****, mausaji,* ***Mr. Sumit Sharma****, brother-in-law and* ***Mrs. Ruchi Chitanya Sharma****, sister-in-law, for their strong faith in me and silent permission to fulfill my dreams. I cannot imagine that my thesis would be completed without receiving endless love, care, and encouragement of my mischievous brothers* ***Mr. Kushal Binnani*** *and* ***Mr. Priyesh Maheshwari****. and lovable company of my nephew* ***Devvrat Sharma****.*

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Words are short to express my deep sense of gratitude, but at the end of this journey, it is my great pleasure to thank them all who contributed in many ways to my success and made it an unforgettable experience for me.

Thank You!!!!!

Chinky Binnani

"Research is a journey with destination unknown"

This thesis is dedicated to

"My loving NANI MAA"

And

"My Beloved HUSBAND"

SYNOPSIS

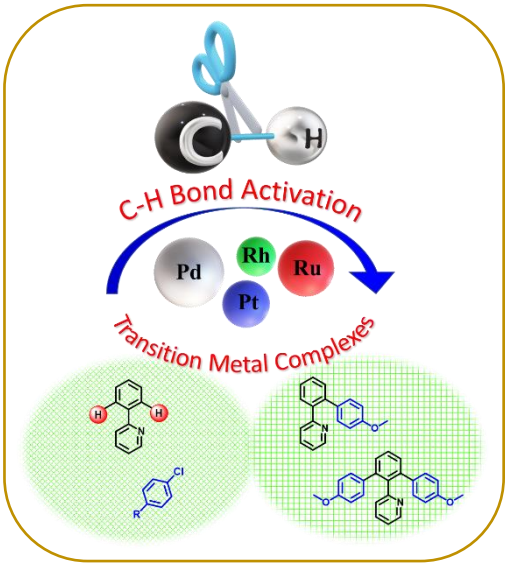
This thesis comprises of six chapters which deal with the designing and development of ruthenium based efficient catalytic systems for C-H bond activation of aryl pyridines. The first chapter of this thesis narrates the brief introduction of the research topic and extensive literature survey about the previous developments in the field of transition metal catalyzed C-H bond activation/functionalization reactions. The subsequent chapters illustrate the synthesis, characterization and catalytic activity of designed arene-ruthenium complexes based on *N,O*/*O,O* donor ligands. The main purpose of the thesis is to develop highly active and efficient catalytic system for *ortho* C-H bond activation/arylation of 2-phenylpyridines and to study the mechanistic pathways of catalyzed reaction using various instrumentation techniques. In the last chapter, concluding remarks along with the future speculations of the present research are briefly described.

The principal objectives of the present study are:

- To design and synthesize the highly efficient, competent, and robust catalytic system based on water soluble arene-Ru(II) complexes containing monodentate nitrogen-based ligands for *ortho* C-H bond arylation of 2-phenylpyridine.
- To synthesize water soluble Ru(II) based molecular catalysts coordinated with bidentate *N,O*/*N,N* donor ligands to study their structure activity relationship towards *ortho* C-H bond activation/arylation of 2-phenylpyridine.
- To develop an efficient catalytic system with readily available biomass derived *O,O* donor ligands, employed as additives, to achieve enhancement in the rate of Ru(II) catalyzed *ortho* C-H bond activation/arylation reaction.
- To establish a highly active catalytic system with *N,O* donor ligands such as 2-hydroxypyridine based ligands which acts as a promoter in achieving high selectivity and enhancement in the rate of Ru(II) catalyzed *ortho* C-H bond activation/arylation reaction of 2-phenylpyridine.
- To gain mechanistic insights into the reaction using various instrumentation techniques to deeply understand the reaction pathway.

The content of each chapter included in thesis are summarized as follows:

Chapter 1. Introduction: Transition metal catalyzed C-H bond activation and functionalization

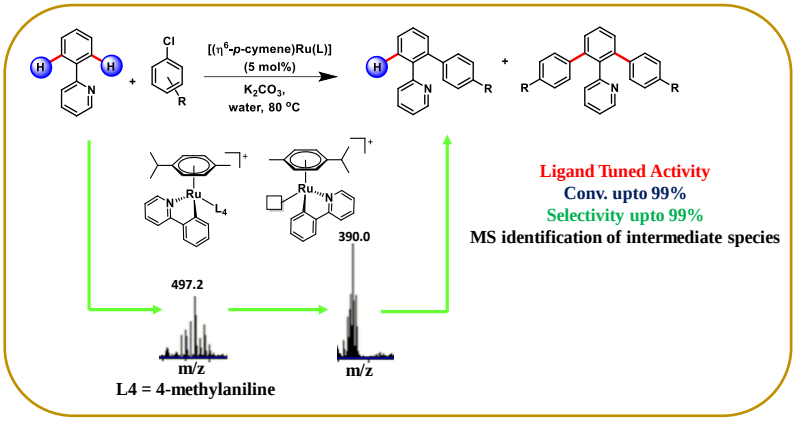


This chapter describes the gradual developments in the field of transition metal catalyzed C-H bond activation/functionalization. It summarizes the background and importance of *ortho* C-H bond activation of aryl pyridines in diverse fields like pharmaceuticals, material modifications and agricultural products. In this chapter, challenges in activating abundant but almost inert C-H bonds in organic molecules and probable solutions for this problem have been discussed. This chapter describes the brief history of advancement in the field of C-H bond activation by developing efficient catalytic systems and smart strategies to overcome the difficulties in achieving the goal. The gradual progress in the field of C-H bond activation/arylation has been accompanied with the use of various transition metals like Pt, Pd, Ir, Rh and Ru etc. Among the studied metals, Ru(II) proves to be the promising candidate to carry out the reaction. Various examples of Ru(II) catalyzed C-H bond activation/arylation have been taken into account along with the effect of various ligands on the catalytic activity.

Designing of ligand plays a crucial role in the catalytic reactions. The electronic and steric environment around metal center can be controlled by tuning the ligand

properties. In the last few decades, the designing of catalytic systems for C-H bond activation of aryl pyridines includes the use of phosphine-based ligands which suffers from many limitations. Gradual advancements in the field shift the interest of chemists towards more efficient, air stable, eco-friendly and easy to handle nitrogen and oxygen-based ligands. Based on the literature survey, we designed and developed phosphine free, water soluble, nitrogen/oxygen based arene-ruthenium complexes and their catalytic activity towards C-H bond arylation of 2-phenylpyridine has been presented in this thesis.

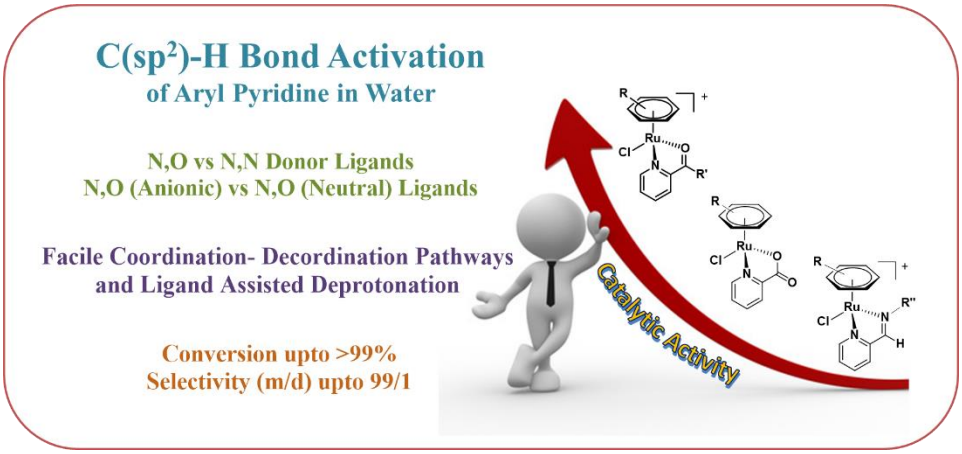
Chapter 2. C-H Bond activation/arylation catalyzed by arene-ruthenium-aniline complexes in water



In this chapter, we have designed and developed the phosphine free, water-soluble arene-ruthenium complexes having readily available substituted aniline ligands with varying electronic and steric effects. The synthesized complexes were successfully characterized by ^{1}H, ^{13}C NMR, mass, single crystal XRD and employed as high-performance catalysts towards *ortho* C-H bond activation/arylation of 2-phenylpyridine. Selectively corresponding monoarylated product was formed as major product during the reaction with various aryl halides. Furthermore, studies were carried out with structural analogues of aniline ligand to understand the structure activity relationship due to ligand substitution on the catalytic reaction. Different experimental observations including time-scaled ^{1}H NMR spectroscopy and mass spectrometry provides deep insight into the mechanistic pathway for catalytic *ortho* C-H bond arylation of 2-phenylpyridine. Mass spectral identification of the

cycloruthenated species, [(η^6-arene)Ru(κ^2-*C,N*-phenylpyridine)]$^+$, and several ligand coordinated cycloruthenated species, such as [(η^6-arene)Ru(4-methylaniline)(κ^2-*C,N*-phenylpyridine)]$^+$, during the reaction of 2-phenylpyridine and arene-ruthenium-aniline complexes, further authenticating the crucial role of these species in the observed highly selective and tuned catalytic activity. Further, structural identification of few of the active catalysts was also carried out by single crystal X-ray diffraction studies.

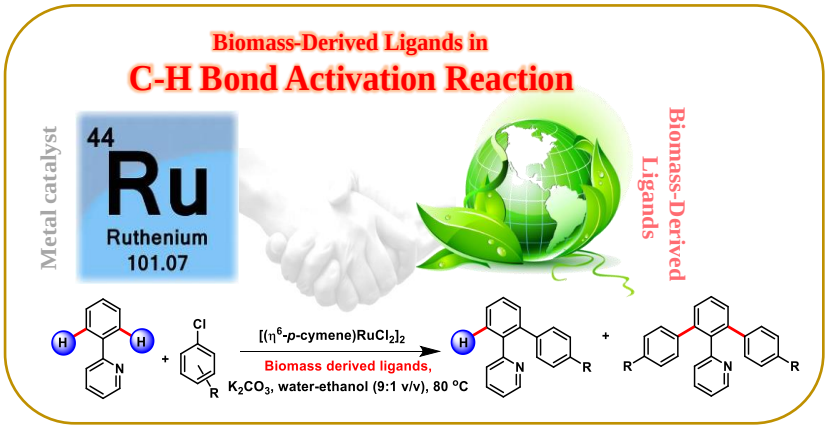
Chapter 3. Ligand-tuned C-H bond activation/arylation of 2-arylpyridines over pyridine-based *N,O/N,N* ligated arene-ruthenium complexes



Based on the previous results obtained with arene-ruthenium complexes containing monodentate aniline ligands, we assumed that complexes containing pyridine-based *N,O/N,N* donor bis-chelating ligands can also constitute an efficient catalytic system for C-H bond activation reactions. So, we have synthesized the half sandwich arene-ruthenium complexes containing pyridine-based *N,O/N,N* donor ligands which were successfully characterized by ^{1}H, ^{13}C, ^{31}P NMR spectroscopy, mass spectrometry and single crystal XRD and were further explored for the *ortho* C-H bond activation/arylation of 2-phenylpyridine in water-based condition. A remarkable structure activity relationship was observed with a series of *N,O/N,N* donor ligand based arene-ruthenium complexes. Results inferred that the complexes with bis-chelating *N,O* donor-based ligands (2-acetylpyridine and picolinate)

outperform those with *N,N* donor ligands (iminopyridine). Moreover, a unique behavior of *N,O* donor ligands was also observed towards *ortho* C-H bond activation/arylation of 2-phenylpyridine, depending upon the coordinating nature of oxygen atom. In this context, ruthenium-arene complexes having *N,O* donor ligands (2-acetylpyridine) with neutral oxygen-donor atoms exhibit enhanced catalytic activity over those with anionic oxygen-donor atoms (picolinate). The facile coordination-decoordination behavior and involvement of ligand in deprotonation step may be the reason of such unusual trend.

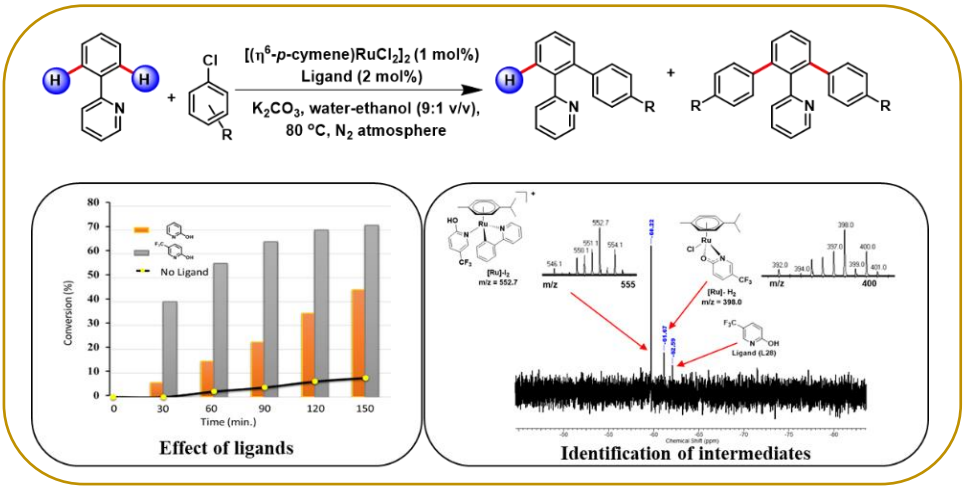
Chapter 4. Biomass derived ligands accelerated ruthenium catalyzed C-H bond activation/arylation



The previously observed facile coordination-decoordination behavior in the *N,O*/*N,N* donor ligand based arene-ruthenium complexes and role of acetyl group in deprotonation step encouraged us to explore abundantly available biomass derived *O,O* donor ligands as promoter with arene ruthenium(II) complex for C-H bond activation reaction. This chapter outlines the development of an efficient catalytic system for Ru(II) catalyzed *ortho* C-H bond activation/arylation of 2-phenylpyridine. Here we explored, several biomass derived ligands such as levulinic acid (LA), 2-acetylfuran, 2-furanaldehyde (furfural), 5-(hydroxymethyl)furan-2-carbaldehyde (5-HMF), 5-methylfuran-2-carbaldehyde (5-MF), furfuryl alcohol and 2-furoic acid as effective additives with arene-Ru(II) dimer for *ortho* C-H bond arylation of 2-phenylpyridine in a water-based condition. With the incremental effect of *O,O* donor biomass derived ligands, almost 7-fold enhancement has been achieved towards the

catalytic reaction than in the absence of ligand. Kinetic studies and mass spectral identification of ligand coordinated Ru(II) species and the well-established cyclometalated species under the catalytic and controlled reaction condition, evidenced the possible crucial role of the ligand in the observed accelerated catalytic activity. DFT calculations also infer that the ligand assisted route is more energetically favorable, where acetyl group is found to be involved in the deprotonation step.

Chapter 5. Ruthenium(II) catalyzed C-H bond activation/arylation: Mechanistic investigation for 2-hydroxypyridine-based ligands as promoter



Based on the previous results with biomass derived *O,O* donor ligands containing arene-ruthenium complexes, which shows the active participation of acetyl group in the deprotonation step, we decided to study the role of *N,O* donor 2-hydroxypyridine based systems for C-H bond activation. We systematically explored the role of 2-hydroxypyridine based *N,O* donor ligands such as pyridine-2-methanol, 2-methoxypyridine, 2-hydroxypyridine, 6-chloro-2-hydroxypyridine, 5-chloro-2-hydroxypyridine, 5-trifluoromethyl-2-hydroxypyridine, in the acceleration of reaction rate for Ru(II) catalyzed *ortho* C-H bond activation/arylation of 2-phenylpyridine. The *N,O* donor ligands such as 2-hydroxypyridine can quickly undergo tautomerism and effectively acts as an additive for catalytic reaction. Our studies demonstrated that 5-trifluoromethyl-2-hydroxypyridine, with strong electron withdrawing substitution, outperformed over all the studied ligands. Further, the extensive mass studies revealed

the crucial role of pendent group of 2-pyridone tautomer in the enhancement of rate of reaction. During the extensive mechanistic studies ligand coordinated cycloruthenated species [(η^6-*p*-cymene)Ru(κ^1-2-hydroxypyridine)(κ^2-*C,N*-2-phenylpyridine)]$^+$ and [(η^6-*p*-cymene)Ru(κ^1-5-trifluoromethyl-2-hydroxypyridine)(κ^2-*C,N*-2-phenylpyridine)]$^+$ has also been identified as key intermediates during the reaction along with the well-established intermediate [(η^6-*p*-cymene)Ru(κ^2-*C,N*-2-phenylpyridine)]$^+$.

Chapter 6. Conclusion and future scope

6.1. Conclusions

We developed phosphine-free water-soluble arene-ruthenium complexes with substituted aniline-based and bis chelating *N,O/N,N* donor pyridine-based ligands for the *ortho* C-H bond arylation of 2-phenylpyridine. Our studies revealed that the aniline ligands with varying electronic and steric properties significantly influenced the observed catalytic activity by enhancing the rate of reaction. The identification of several intermediates, including those with ligand-coordinated cycloruthenated species, further authenticate the crucial role of these species and provide better understanding of mechanistic pathway for the catalytic C-H bond activation reaction.

Our experimental findings with pyridine-based *N,O/N,N* ligated arene-ruthenium catalysts demonstrated that among all of the synthesized complexes, arene-ruthenium complexes ligated with *N,O* donor pyridine ligands outperform those containing *N,N* donor pyridine ligands. The observed trend in the ligand tuned catalytic activity of complexes can be attributed to the coordination-decoordination interconversion pathway and involvement of ligand in deprotonation step. Further, mechanistic insights were provided by mass spectral identification of various intermediate species.

Along with the exploration of monodentate and bidentate nitrogen-based ligands containing arene-ruthenium complexes, the role of several biomass-derived *O,O* donor ligands as active additives for Ru(II) catalyzed C-H bond arylation reaction was also investigated. Among the studied ligands such as levulinic acid (LA), 2-acetylfuran, 2-furanaldehyde (furfural), 5-(hydroxymethyl)furan-2-carbaldehyde (5-HMF), 5-methylfuran-2-carbaldehyde (5-MF), furfuryl alcohol and 2-furoic acid, levulinic acid (LA) outperformed with Ru(II) catalyst. Results attained on utilizing biomass-derived

ligands as promoter, remarkably showed the 7-fold enhancement in the catalytic activity for C-H bond activation/arylation. The crucial involvement of acetyl group in the deprotonation step has also been confirmed experimentally by mass analysis and theoretically by density functional theory calculations. DFT calculations also revealed that the C-H bond activation of 2-phenylpyridine is energetically more favorable (by 8.9 kcal/mol) in the presence of levulinic acid as compared to the ligand-free reaction which suggests the crucial role of ligand in the reaction pathway.

Further, our systematic study with 2-hydroxypyridine based *N,O* donor ligands towards the ligand accelerated Ru(II) catalyzed *ortho* C-H bond activation/arylation of 2-phenylpyridine demonstrated that 5-trifluoromethyl-2-hydroxypyridine with strong electron withdrawing substitution, outperformed the studied ligands. Time dependent ^{1}H NMR studies suggests the enhancement in the rate of reaction and extensive mass studies identified the ligand coordinated cycloruthenated species [(η^6-*p*-cymene)Ru(κ^1-2-hydroxypyridine)(κ^2-*C,N*-2-phenylpyridine)]$^+$ and [(η^6-*p*-cymene)Ru(κ^1-5-trifluoromethyl-2-hydroxypyridine)(κ^2-*C,N*-2-phenylpyridine)]$^+$ as key intermediates during the reaction along with the well-established intermediate [(η^6-*p*-cymene)Ru(κ^2-*C,N*-2-phenylpyridine)]$^+$ which may be due to involvement of pendent oxygen group of 2-pyridone form in the deprotonation of 2-phenylpyridine.

6.2. Future Scope: The relevant future scope of the work, included in thesis has been discussed briefly.

Publications included in thesis

1. **Binnani C.**, Tyagi D., Rai R. K.; Mobin S. M., Singh S. K.* (2016), C-H bond activation/arylation catalyzed by arene-ruthenium-aniline complexes in water, *Chem. Asian J.*, 11, 3022-3031 (DOI: 10.1002/asia.201600954)**.**
2. **Binnani C.**, Rai R. K., Tyagi D., Mobin S. M., Singh S. K.* (2018), Ligand-tuned C-H bond activation/arylation of 2-arylpyridines over pyridine-based *N,O/N,N* ligated ruthenium-arene complexes, *Eur. J. Inorg. Chem.*, 1435-1445 (DOI: 10.1002/ejic.201701446).
3. **Binnani C.**, Mandal S. C., Pathak B., Singh S. K.* (2019)**,** Ruthenium-catalyzed C-H bond activation/arylation accelerated by biomass-derived ligands, *Eur. J. Inorg. Chem.*, 2844-2854 (DOI: 10.1002/ejic.201900218).
4. **Binnani C.**, Singh S. K.* (2019), 2-Hydroxypyridine-based ligands as promoter in ruthenium(II) catalyzed C-H bond activation/arylation reactions in water, (*Manuscript submitted*)

Publications other than included in thesis

1. Dwivedi A. D., **Binnani C.,** Tyagi D., Rawat K. S., Li P. -Z., Zhao Y., Mobin S. M., Pathak B., Singh S. K.* (2016), Troponate-/aminotroponate ruthenium-arene complexes: Synthesis, structure and ligand tuned mechanistic pathway for direct C-H bond arylation with arylchlorides in water" *Inorg. Chem.*, 55, 6739-6749 (DOI: 10.1021/acs.inorgchem.6b01028).
2. Tyagi D., **Binnani C.**, Rai R. K., Dwivedi A. D., Gupta K., Li P. -Z., Zhao Y., Singh S. K.* (2016), Ruthenium catalyzed oxidative homocoupling of arylboronic acids in water: Ligand tuned reactivity and mechanistic study, *Inorg. Chem.*, 55, 6332-6343 (DOI: 10.1021/acs.inorgchem.6b01115).

Conferences and workshops

1. Poster presentation at ***10th Mid-Year CRSI National Symposium in Chemistry (CRSI-NSC-2015),*** NIT-T (Trichy), India (July 2015). **Binnani C**., Tyagi D., Singh S. K.*, Ruthenium catalyzed selective C(sp^2)-H bond arylation in water.

2. Attended ***Researcher Connector Program*** organized by ***Willey at IIT Indore***, India (Oct 2015).

3. Attended ***GIAN Course: "Catalysis by metal complexes"*** (Course Instructor: **Prof. Pierre H. Dixneuf**, CNRS-Université de Rennes, France) at IIT Indore, India (November 2016).

4. Poster presentation at ***20th CRSI National Symposium in Chemistry (CRSI-NSC-2017)***, Guwahati University (Guwahati, Assam), India (July 2017). **Binnani C**., Tyagi D., Singh S. K.*, Ru(II) catalyzed *ortho* C(sp^2)-H bond arylation in water.

5. Attended ***RSC-IIT Indore Symposium in Chemical Science*** organized by Indian Institute of Technology (IIT) Indore & Royal Society of Chemistry, at Indian Institute of Technology (IIT) Indore (January 2018).

6. Attended ***GIAN Course: "Metal-Ligand Interplay in Advanced Coordination Chemistry"*** (Course Instructor: **Prof. Pierre Braunstein**, CNRS-Université de Strasbourg, France) at IIT Indore, India (February 2018).

7. Poster presentation at ***"International Conference on Emerging Trends in Chemistry"***, IIT Indore (Indore, M. P.), India (July 2019). **Binnani C**., Singh S. K.*, Biomass derived ligands accelerated ruthenium-catalyzed C-H bond activation/arylation.

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Chapter 3. Ligand-tuned C-H bond activation/arylation of 2-arylpyridines over pyridine-based N,O/N,N ligated arene-ruthenium complexes

various (hetero)aryl halides over Ru(II) catalyst in water-ethanol

NOMENCLATURE

α	Alpha
β	Beta
λ	Gamma
Å	Angstrom
λ	Wavelength
μ	Micro
σ	Sigma
π	Pi
η	Eta
δ	Delta
κ	Kappa
J	Coupling constant
Hz	Hertz
MHz	Mega hertz
K	Kelvin
D	Density
V	Volume
mM	Milli Molar
μM	Micro Molar
cm	Centimeter
°	Degree
°C	Degree centigrade
mL	Milliliter
μL	Microliter
a. u.	Arbitrary Unit
min	Minute
mL	Milliliter
mm	Millimeter

ACRONYMS

Arene-Ru(II)	Arene ruthenium (II) complexes
[Ru]-A	[(η^6-*p*-cymene)$RuCl_2$}$_2$]
[Ru]-B	[(η^6-benzene)$RuCl_2$}$_2$]
[Ru]-1	[(η^6-*p*-cymene)$RuCl_2$(aniline)]
[Ru]-2	[(η^6-*p*-cymene)$RuCl_2$(2-methylaniline)]
[Ru]-3	[(η^6-*p*-cymene)$RuCl_2$(2,6-dimethylaniline)]
[Ru]-4	[(η^6-*p*-cymene)$RuCl_2$(4-methylaniline)]
[Ru]-5	[(η^6-*p*-cymene)$RuCl_2$(4-chlorolaniline)]
[Ru]-6	[(η^6-benzene)$RuCl_2$(aniline)]
[Ru]-7	[(η^6-benzene)$RuCl_2$(2-methylaniline)]
[Ru]-8	[(η^6-benzene)$RuCl_2$(2,6-dimethylaniline)]
[Ru]-9	[(η^6-benzene)$RuCl_2$(4-meyhylaniline)]
[Ru]-10	[(η^6-benzene)$RuCl_2$(4-chloroaniline)]
[Ru]-11	[(η^6-*p*-cymene)RuCl(κ^2-*N*,*O*-pyridine-2-carboxylate)]
[Ru]-12	[(η^6-*p*-cymene)RuCl(κ^2-*N*,*O*-2-acetylpyridine)]PF_6
[Ru]-13	[(η^6-*p*-cymene)RuCl(κ^2-*N*,*O*-2-methylpicolinate)]PF_6
[Ru]-14	[(η^6-*p*-cymene)RuCl(κ^2-*N*,*N*-(N-benzylpyridylimine)]PF_6
[Ru]-15	[(η^6-*p*-cymene)RuCl(κ^2-*N*,*N*-(N-butylpyridylimine)]PF_6
[Ru]-16	[(η^6-benzene)RuCl(κ^2-*N*,*O*-pyridine-2-carboxylate)]
[Ru]-17	[(η^6-benzene)RuCl(κ^2-*N*,*O*-2-acetylpyridine)]PF_6
[Ru]-18	[(η^6-benzene)RuCl(κ^2-*N*,*O*-2-methylpicolinate)]PF_6
[Ru]-19	[(η^6-benzene)RuCl(κ^2-*N*,*N*-(N-benzylpyridylimine)]PF_6
[Ru]-20	[(η^6-benzene)RuCl(κ^2-*N*,*N*-(N-butylpyridylimine)]PF_6
L1	Aniline
L2	2-methylaniline
L3	2,6-dimethylaniline
L4	4-methylaniline
L5	4-chloroaniline
L6	Pyridine-2-carboxylic acid

L7	2-acetylpyridine
L8	Methyl Picolinate
L9	*N*-benzyl-pyridylimine
L10	*N*-butyl-pyridylimine
L11	Levilinic acid
L12	2-acetylfuran
L13	2-furfural
L14	5-hydroxymethylfurfural
L15	5-methylfuran
L16	Furfuryl alcohol
L17	2-Furoic Acid
L18	2,5-hexanedione
L19	2,3-butanedione
L20	1-butanoic acid
L21	1-hexanoic acid
L22	1,6-hexanoic acid
L23	Pyridine-2-methanol
L24	2-methoxypyridine
L25	2-hydroxypyridine
L26	6-chloro-2-hydroxypyridine
L27	5-chloro-2-hydroxypyridine
L28	5-trifluoromethyl-2-hydroxypyridine
DFT	Density Functional Theory
NMR	Nuclear Magnetic Resonance
UV-vis	UV-visible Spectroscopy
ESI-MS	Electrospray Ionization- Mass Spectrometry
GC-MS	Gas Chromatography-Mass Spectrometry
TGA	Thermogravimetric Analysis
TLC	Thin Layer Chromatography
SCXRD	Single crystal X-ray Diffraction
GOF	Goodness of fit

$CDCl_3$	Chloroform-*d*
D_2O	Deuterium oxide
DMSO-d_6	Dimethylsulphoxide-d_6
Ar	Argon
O_2	Oxygen
H_2	Dihydrogen
N_2	Nitrogen
o	*ortho*
m	*meta*
p	*para*
HMF	5-hydroxymethylfurfural
Py	Pyridine
Mes	Mesityl
NHC	*N*-heterocyclic carbene
PCy_3	Tricyclohexylphosphine
PPh_3	Triphenylphosphine
KOAc	Potassium acetate
$KOPr^i$	Potassium Propionate
KO-^{iso}Bu	Potassium Isobutyrate
KOPiv	Potassium Pivalate
s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	Multiplet
br	Broad
ppm	Parts per million
r.t.	Room temperature
temp	Temperature
TMS	Trimethylsilane
TON	Turnover number

TTN	Total turnover number
TOF	Turnover frequency
Abs	Absorption
calc.	Calculated
cat.	Catalyst
cm^3	Cubic centimeter
Cy	Cyclohexane
Et	Ethyl
Me	Methyl
^{i}Pr	*iso*-propyl
Ph	Phenyl
equiv.	Equivalents
g	Gram
h	Hour
EtOH	Ethanol
DMF	Dimethylformamide
MeOH	Methanol
DCM	Dichloromethane
DCE	Dichloroethane
AcOH	Acetic acid
CH_3CN	Acetonitrile
Et_2O	Diethyl ether
NEt_3	Triethylamine
Atm	Atmospheres (pressure)

Chapter 1

Introduction: Transition metal catalyzed C-H bond activation and functionalization

1.1. Introduction

The ubiquitous nature of C-H bonds is an important feature of hydrocarbons, yet it is quite difficult to exploit them directly as a functional group for an organic transformation. Stability of these unreactive hydrocarbons can also be attributed to the high energy empty molecular orbitals (LUMOs) or low lying filled molecular orbitals (HOMOs). The larger HOMO-LUMO gap further adds to the kinetic stability of the hydrocarbon C-H bonds. Another reason for unreactive nature of hydrocarbons is the high bond dissociation energy[1] which requires harsh reaction conditions, such as high temperature and strong reagents to activate and functionalize the otherwise inert C-H bonds. Such difficulties restrict the implementation of even effective methodology for utilizing naturally abundant, low cost feedstocks as raw material for the production of synthetically useful compounds. In order to exploit and transform the abundant C-H bond present in the natural feedstock, the development of efficient methodology is very much required. In this context, catalytic C-H bond activation and functionalization strategy is proved to be an effective way to synthesize a wide variety of organic compounds.

Nature also has its own way to carry out C-H functionalization of organic substances. Some of the best examples of biological catalysts to carry out C-H bond activation for important transformation are methane monooxygenase enzyme in methanotropic bacteria, cytochrome P-450 in photosynthetic process and vitamin B12 in living bodies (Figure 1.1). Methane monooxygenase and cytochrome P-450 enzymes are unique in their ability to oxidize the C-H bond of methane and unactivated alkene respectively.[2,3] The necessary energy to carry out these reactions are provided by sacrificial reductants (NADPH or another source). The structure elucidation of these enzymes revealed that the active site in the sMMO and cytochrome P-450 are consists of iron metal center.[4] Vitamin B12, having cobalt metal center catalyzes the C-H bond

activation of organic molecules followed by 1,2-functional group shifts through a non-organometallic pathway.[5]

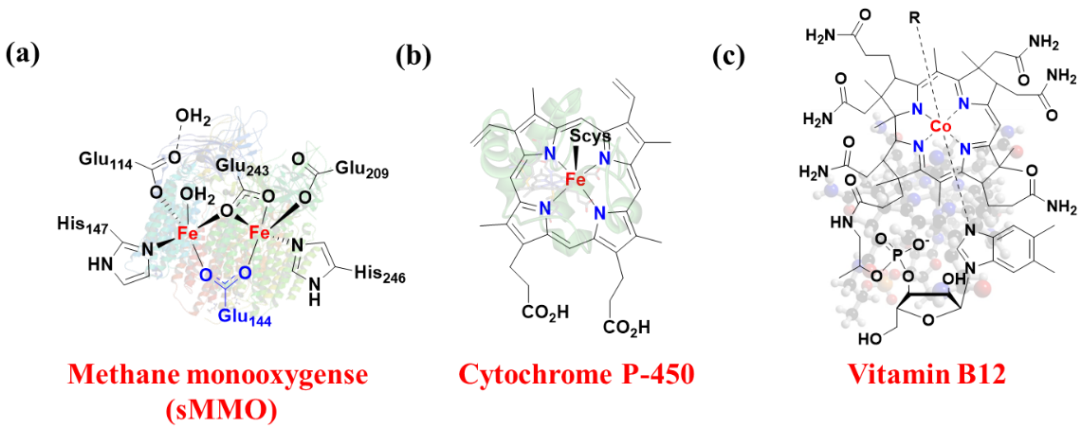


Figure 1.1. *Naturally occurring C-H bond activation catalysts (a) soluble methane monooxygenase enzymes (sMMO) (b) cytochrome P-450 and (c) vitamin B12.*

Inspired by the above examples of natural catalytic systems for C-H bond activation/functionalization, various researchers have attempted to mimic the enzyme structures and developed various catalytic systems based on transition metals as a prominent tool for C-H bond the activation/functionalization reactions.

1.2. C-H bond activation/functionalization

C-H bond activation/functionalization methodology has high potential to transform the field of organic synthesis by building-up a vast number of organic compounds, ranging from small biologically active molecules to the macromolecular organic material in a very energy efficient way.[6] The traditional ways of making new bonds in organic synthesis by utilizing the existing functionalized organic compounds are comparatively less atom economical. C-H bond activation/functionalization technique not only provides a shorter route but is an atom economical protocol to synthesize a wide range of organic molecules. The two terminologies, C-H bond activation and C-H bond functionalization have different meanings and can be defined separately.

In the organometallic perspective, the term "C-H bond activation" can be defined as the breakage of strong, comparatively inert C-H bond using some transition metal complexes accompanied by the formation of M-C (metal-carbon) bond. This can be

followed by functionalization step in which the substrate is transformed into a C-H functionalized product. Literature revealed that C-H bond activation/functionalization reaction may involve through different mechanistic pathways (Electrophilic activation, oxidative addition, concerted metalation-deprotonation pathway and σ-bond metathesis).[7] These mechanistic pathways depend upon the choice of transition metal, steric and electronic environment around metal center, and the nature of substrate involved in the process. Formation of reactive intermediates during the reaction pathways are generally studied with the help of different instrumentation techniques such as mass spectrometry, nuclear magnetic resonance (NMR) spectroscopy, UV-vis, infrared spectroscopy and so on. Identification of intermediate species further enables the elucidation of reaction pathway for better mechanistic understanding.

1.3. Application of C-H bond activation/functionalization strategy

In the last few decades, it has been established that the C-H bond activation/functionalization methodology acts as a complementary tool in organic transformations. C-H bond activation/functionalization methodology is not only limited to organic synthesis, but it can be extensively exploited in different fields of science to achieve various late stage diversifications for preparation of industrially important substances. C-H functionalization reactions have emerged as a potential path to access novel building blocks that would be otherwise difficult to access using traditional methodologies. For instance, construction of functional material for organic light emitting diodes (OLEDs) and other applications, synthesis of medicinally relevant molecules, total synthesis of various important organic molecules, are some of the important areas where C-H bond activation/functionalization can be implemented as a powerful strategy (Figure 1.2). Various examples showing the potential applications of the methodology in the diverse fields have been briefly discussed in the subsequent sections:

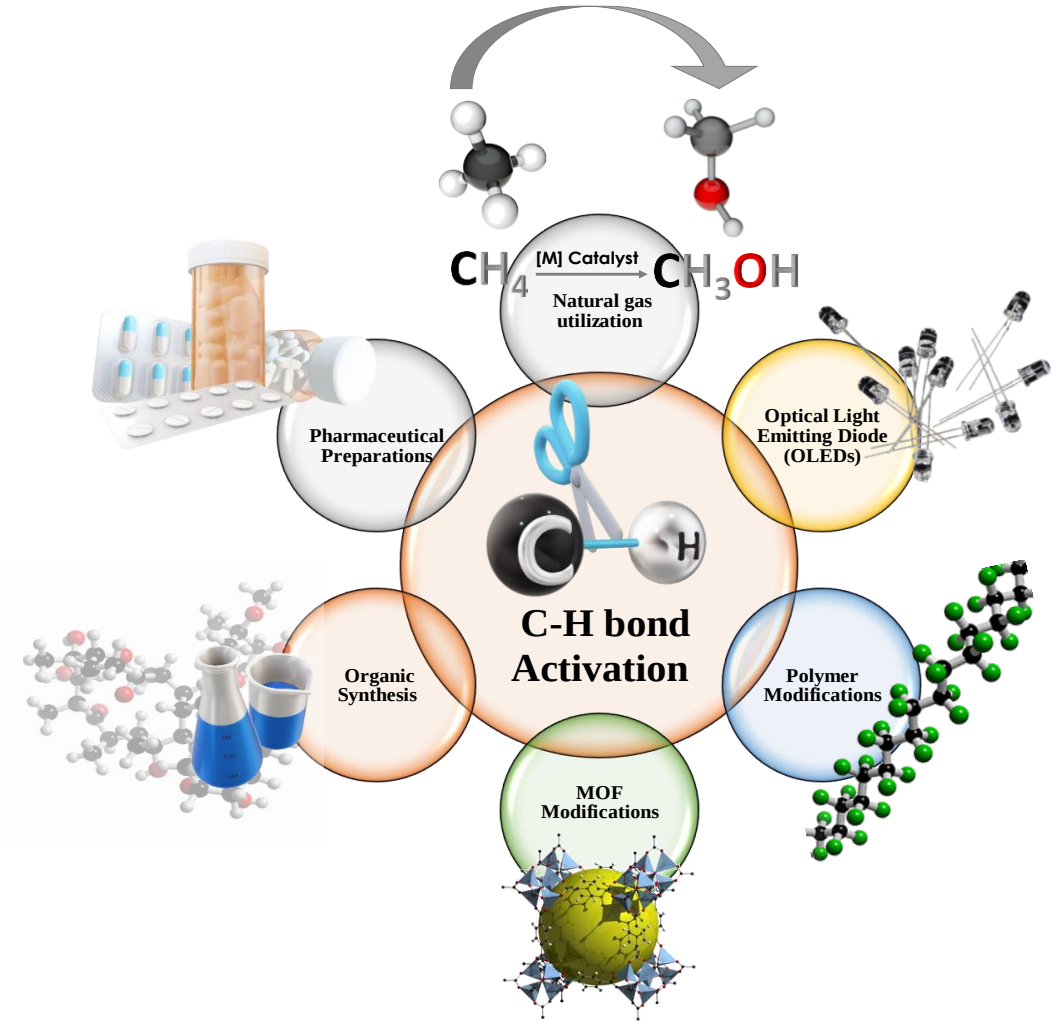


Figure 1.2. *Application of C-H bond activation reactions in late stage diversification of several industrially important compounds.*

1.3.1. Natural product synthesis

Various complex organic compounds found in the nature has incredible biological or pharmaceutical properties, but their tedious extraction from natural sources and multi-step synthetic routes restricts their large-scale synthesis. C-H bond activation strategy has made this task comparatively easier by providing direct access to the total synthesis of various important natural products (Figure 1.3).[8] For instance, Lithospermic acid is a naturally occurring compound, isolated from a perennial herb *Lithospermum ruderale* and can be used in various cardiovascular diseases. The synthesis of (+)-lithospermic acid

which is a potent HIV-integrase inhibitor,[9b] was achieved by Bergman, Ellman and co-workers via rhodium(II) catalyzed C-H bond activation.[9]

Another example includes the synthesis of calothrixin A and B, which are heterocyclic quinones exhibiting the potent antimalarial properties, and can be isolated naturally from *Calothrix cynobacteria*. Synthesis of this drug also included Pd(II) catalyzed C-H bond activation reaction for the construction of quinoline ring from a substituted carbazole moiety.[10] C-H bond activation/functionalization not only shortens the route of synthesis but also avoids the unnecessary waste generation. The broad scope, utility and ease of methodology inspires the organic chemists to develop and explore catalytic C-H bond activation/functionalization reaction as an efficient tool in organic synthesis.

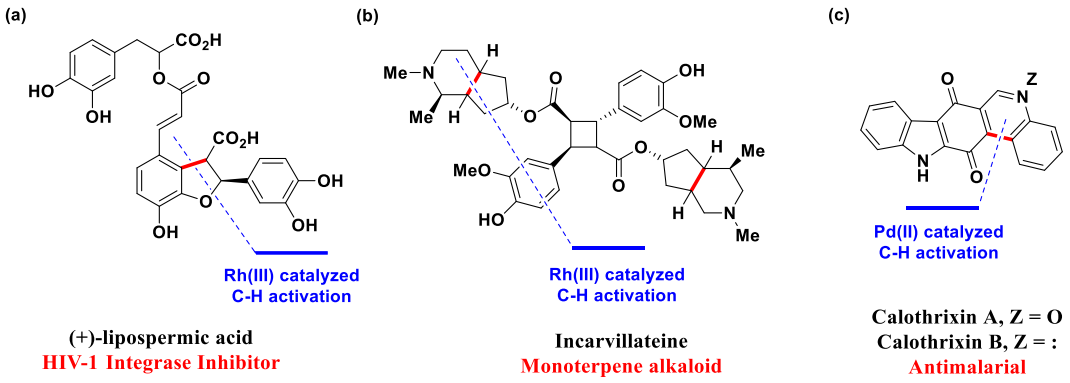


Figure 1.3. *Synthesis of a few important natural products via metal catalyzed C-H bond activation strategy.*

1.3.2. Utilization of naturally available feedstocks

The abundantly available natural gas (methane) serves as the cheapest and the best chemical feedstock for the synthesis of various value-added chemicals such as methanol, formaldehyde or formic acid. Practically, the direct utilization of natural gas is difficult due to high stability, high bond dissociation energy and pKa value of alkane C-H bond. The current technologies to convert methane into industrially useful compounds includes the production of syngas, the mixture of CO_2 and H_2, which further can be used in Fischer-Tropsch process for large scale production of methanol. The major breakthrough in the transition metal catalyzed C-H bond activation of methane came with the work of Periana

et al. They employed Pt(II) catalysts with bidentate *N,N* donor bipyrimidine ligand for C-H bond activation of the natural gas.[11] Here, platinum complex reacts with methane in H_2SO_4 at 200 °C to produce methyl bisulfide and constitutes a highly stable catalytic system. Reported C-H bond activation of methane proceeds through the electrophilic C-H bond activation pathway as shown below in Figure 1.4:

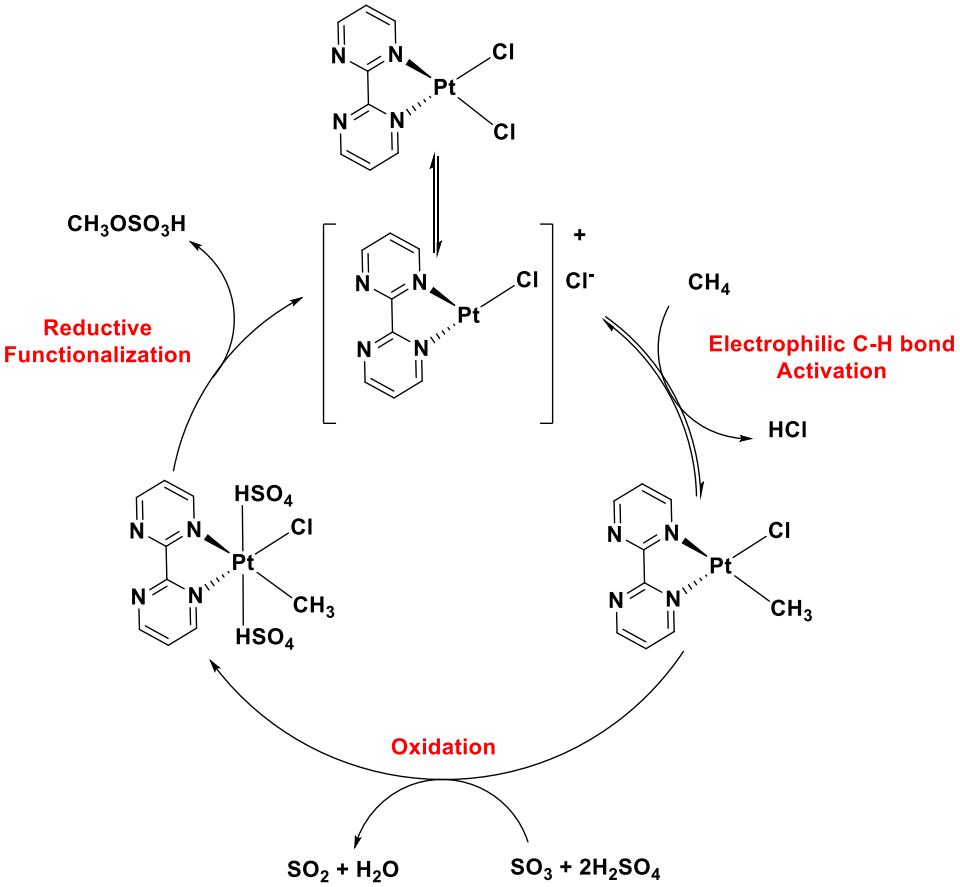


Figure 1.4. *Plausible mechanism of C-H bond activation of methane using Pt(II) bipyrimidine complexes in Periana system. Reproduced from ref. (11) with permission of Science.*

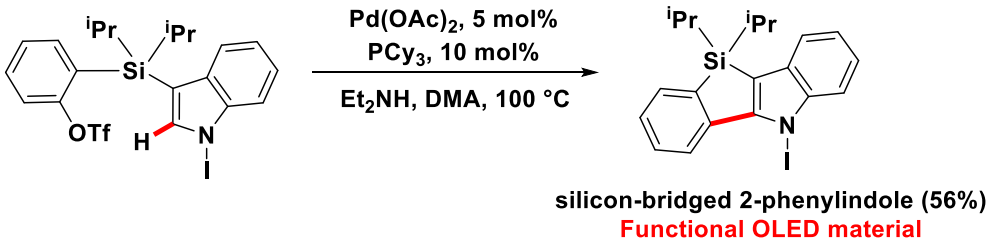
Though this method possesses high productivity and selectivity still it suffers from several limitations such as high reaction temperature and the use of H_2SO_4 which reduces the practical importance of this process. Neverthless, this report highlighted the importance of metal catalyzed C-H bond activation to utilize natural gas feedstocks for practical utility.

1.3.3. Modification of complex drug molecules via C-H bond activation

The development of drug molecules is generally based on the identification of "Lead" compound and its modification for structure-activity-relationship studies in the search for the most effective analogue exhibiting improved properties than the lead compound. Traditional synthetic methods impede the direct transformations of such compounds for fine tuning of the biological activity and improved performance. C-H bond activation strategy offers the best solution for such problem for carrying out modifications in the basic structure of lead compound for tuned activity. Some pioneering work by Yu and co-workers for the late stage diversification of an anti-inflammatory drug "celecoxib" was a breakthrough in this area.[12] They reported the *ortho* C-H bond activation of aryl ring selectively in single step, which paved the path for various organic transformations. In their recent reports, they developed *ortho*-C(sp^2)-H functionalization of benzaldehyde substrates, using the transient directing group strategy for the preparation of analogues of celecoxib.[13] Reports from Itami *et al.* revealed that they have prepared a series of structural analogues of σ_1 receptor containing a spirocyclic thiophene scaffold with control of regioselectivity by employing different ligands during Pd(II) catalyzed C-H bond activation of thiophene ring.[14] The introduction of non-polar aryl ring in the spirocyclic thiophene moiety as a structural modification, increases the hydrophobic character of the drug which in turn shows enhanced σ_1 affinity and improved performance.

1.3.4. Post-synthetic modifications in functional molecules

In addition to the synthesis and late stage diversification of complex organic molecules, C-H bond activation also provides opportunities for the construction of various industrially important chemicals. For example, a class of materials known as organic light emitting diodes (OLEDs), can be benefited through the structural modifications by taking advantage of C-H bond activation strategy. Shimizu and co-workers[15] in 2008 reported an efficient Pd(II) catalyzed C-H activation method to perform the intramolecular direct coupling between two aromatic substituents for the preparation of dibenzosilole, a functional organic molecule, to be used in OLEDs, thin layer transistors and solar cells (Scheme 1.1)

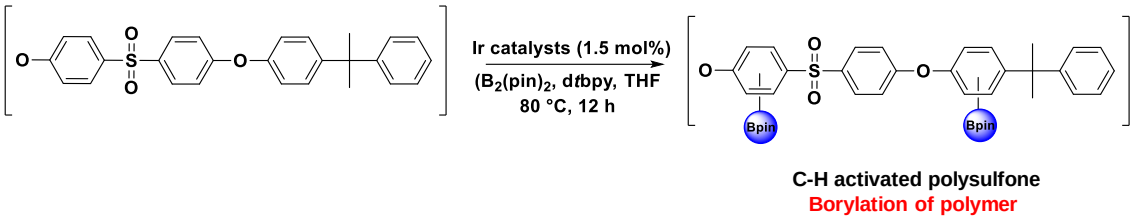


Scheme 1.1. *Synthesis of silicon bridged 2-phenylindole for applications in the field of optoelectronic devices, OLEDs and solid-state organic lasers. Adapted from ref. 15 with permission of Wiley VCH.*

Another example of post synthetic modification is the arylation of metal organic framework (MOF) by transition metal catalyzed C-H bond activation reported by Glorius *et al.*[16] MOF constitutes a new class of highly porous materials having applications in various fields like gas storage, catalysis, drug delivery and so on. Slight modifications in these materials can lead to the drastic alterations in their physical and chemical properties. For instance, the structural modification in the linker molecules (benzene-1,3,5-triyl-tribenzoate and 1-methylindole-4,7-dicarboxylic acid) of UMCM-1-indole MOF, obtained by employing the Pd(II) catalysts under mild reaction conditions leads to the 4 times better activity in N_2 gas uptake. Despite its novelty and efficiency, this method suffers from various limitations. Therefore, a more general and better optimal method is needed for C-H bond activation of MOF, because enormous scope of improvement has been lying in this area.

Scope of the C-H bond activation methodology is not restricted to the synthetic chemistry, but also has its extension in various aspects of science. Polymers are the special class of materials which play essential and important role in everyday life. Tremendous efforts are being made to improve their properties to get the best performance. Post-synthetic C-H functionalization of monomer units provides the best solution for all the difficulties encountered during functional group transformation of monomers. In this context, Bae *et al*. reported the controlled and efficient iridium catalyzed C-H bond activation method for borylation followed by Suzuki-Miyaura coupling, that enables the installation of various functional groups on polymeric aromatic ring (Scheme 1.2).[17] This highly efficient and mild post-functionalization method

efficiently synthesized a new class of functionalized polysulfones, with broader applications as the new high-performance plastic materials.



Scheme 1.2. *Structural modification of monomer units of polysulfones by C-H bond borylation. Adapted from ref. 17 with the permission of American Chemical Society.*

Despite the advantages offered by the C-H bond activation/functionalization strategy for late stage diversification, this methodology suffers from many limitations which can be overcome by employing the correct countermeasures as discussed in the subsequent sections.

1.4. Overcoming the challenges in C-H bond activation/functionalization

Alkane or hydrocarbons are considered as the most unreactive species, because of their reluctance to donate or accept electrons. Further, because of the lack of polarity and π-electrons, bond breaking can only be done with homolytic cleavage which requires harsh reaction conditions such as high temperature and strong reagents. Also, it is difficult to achieve selective transformations for unreactive alkanes to produce fine chemicals under these harsh conditions. Developing efficient homogeneous metal catalysts for selective C-H bond functionalization has gathered attention in the last few decades as a potential tool in synthetic organic chemistry.

One of the most efficient and widely adapted strategies to achieve regioselective C-H bond functionalization involves the installation of directing group, containing some Lewis base heteroatom for chelation with the transition metal species. During the past decades, a variety of functionalities have been identified as powerful directing groups for site selective C-H bond activation/functionalization (Figure 1.5).[18] This approach mainly works on the principle of proximity-induced reactivity in which transition metal upon coordination with the heteroatom, efficiently activates the proximal C-H bond to the directing group. However, the scope of these kinds of directing groups is limited to

certain kind of molecules and activation of *ortho* position that one generally targeted. Such drawbacks impede the practical application of this kind of effective methodology for distant C-H bond activation.

The solution for this problem has come with the development of easily removable and/or modifiable organic templates that serves as a promising solution to control the selectivity by applying either steric or electronic approach or by using end-on templates. [19] Despite significant utility of these organic templates in distant C-H bond functionalization, the additional step to install and deconstruct the directing groups/templates generate undesired waste, and thus compromising the atom economic nature of the C-H bond activation methodology.

Further to the trail of advancement, the concept of *in-situ* generated transient directing group has been developed, which is becoming more popular due to its potential to transform even a weakly coordinating functional motif through synergistic C-H bond activation/functionalization. [20] Transient directing groups are the organic moieties which reversibly bind with the substrate in order to generate a particular functional group to support the chelation assisted binding with metal center for site selective C-H bond functionalization.

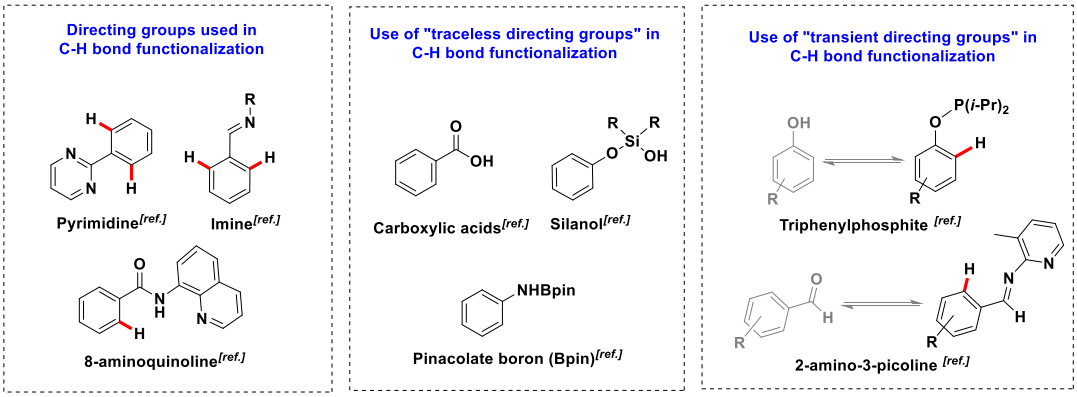


Figure 1.5. *Examples of various directing groups used for C-H bond functionalization.*

1.5. Importance of aryl pyridines in nature and pharmaceuticals

The organic compounds containing at least one hetero atom in their carbon skeleton are generally termed as “heterocyclic compounds”. The presence of heterocyclic compounds is much more common in the natural products. Various important bioactive

natural products are also enriched by the heterocyclic constitution. Many of the vitamins (thiamine (B_1), riboflavin (B_2), nicotinamide (B_3), ascorbic acid (C) etc.), nucleic acids (adenine, guanine, thymine, cytosine, uracil), amino acids (proline, (pyrrolidine), tryptophan (indole) and histidine (imidazole)) and pigments (chlorophyll (pyrrole)) contains heterocycles as essential part for their functioning. Importance of such compounds can not be underestimated as they are the main constitution of many of the potent antibiotics and drug molecules such as penicillin (antibiotic, β-lactam, ring), cephalosporin (antibiotic, β-lactam ring), zolimidine (gastroprotective, imidazopyridine ring), diazepam (anxiolytic, benzodiazepine ring), oxaprozin (NSAID, oxazole ring), sulfaphenazole (antibacterial, pyrazole ring) etc.

Pyridine ring has a very prominent place in the heterocyclic drug molecules. For instance, a heterocyclic compound "Atazanavir" containing 2-phenylpyridine motif, sold under the trade name "Reyataz", has proved to be a promising candidate as antiretroviral medication to prevent HIV-AIDS (Figure 1.6).[21] This drug acts on the virus by blocking the active site of protease enzyme and is very effective to cure the infection caused by needlestick injury in its initial stages. Another drug named as "Vismodegib" has been approved for the treatment of basal-cell carcinoma (BCC),[22] and also has 2-phenylpyridine moiety, which might play crucial role on activity of the drug. Similarly, "(R)-DRF053", has been reported with pyridine heterocyclic ring acting as an anticancer, enzyme inhibitor drug (Figure 1.6).

Due to widespread therapeutic uses of the above-mentioned drugs, their synthesis has gained much attention and importance. Notably, aryl pyridines such as 2-phenylpyridine has also attracted tremendous interest as the starting material for highly fluorescent materials are used as organic light emitting diode (OLEDs) in electronic industries.[23] Some other important areas where aryl pyridines can serve as functional moiety, includes food coloring, dyes, photographic materials, food additives and cosmetics and perfume industries.[24]

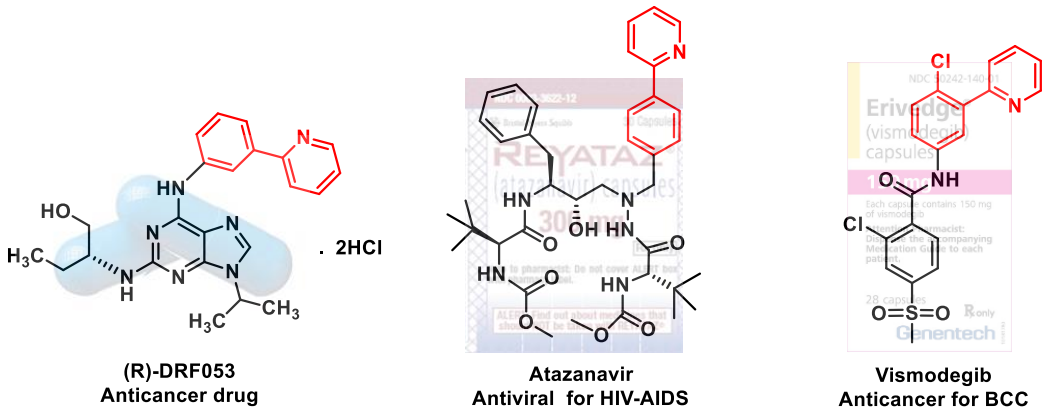


Figure 1.6. *Presence of aryl pyridines in various drug molecules and bioactive natural compounds.*

1.6. Transition metal catalyzed C-H bond activation of aryl pyridines

Transition metal catalyzed C-H bond activation has become an indistinguishable part in the toolbox of organic synthesis. Due to vast importance of aryl pyridines in various bioactive organic compounds, drug molecules, natural products and various industrially important compounds, much attention has been paid for the development of efficient catalytic system for C-H bond activation/functionalization of 2-phenylpyridine, which is the simplest and the most suitable substrate to examine and screen the activity of a catalyst for C-H bond activation reactions.

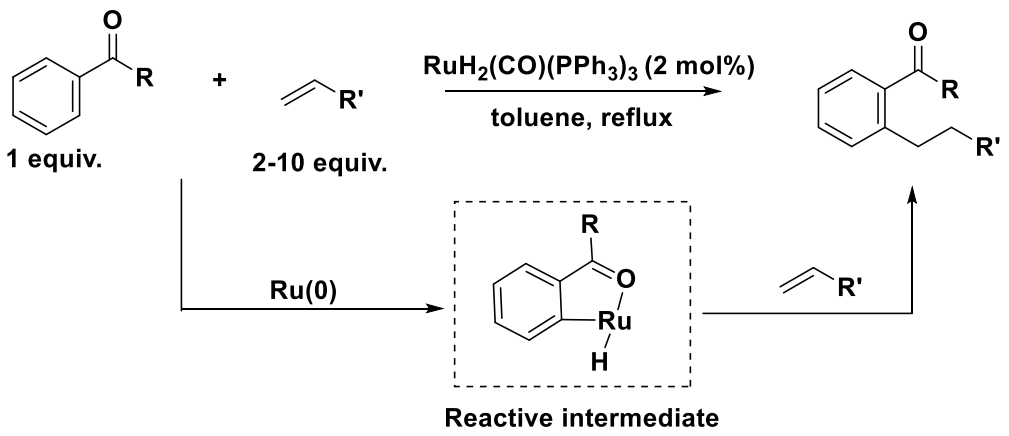
It is well reported in literature that transition metals such as Ir,[25] Pd, Pt[26] and Rh can undergo cyclometallation under stoichiometric conditions, therefore most of the early work on catalytic C-H functionalization reactions was carried out with Pd[27] and Rh[28] catalysts. Although many groups have reported palladium-catalyzed direct C-H bond activation/arylation of aromatic substrates with organometallic compounds, especially organoboronic acids, organotin and organosilane compounds etc.[29] for coupling, but aryl halides were proved to be the most suitable, readily available and cost-effective substrate as coupling partners. In case of palladium catalyts, ligand-directed C-H activation takes place at Pd(II) centers to afford cyclometalated intermediates, but Sanford *et al.* extensively studied and suggested that *ortho* C-H bond arylation of aryl pyridines proceed via Pd(II)/Pd(IV) catalytic cycle.[30] On the basis of these assumptions, several reports on C-H bond activation were published in the subsequent years. However,

in spite of great potential to catalyze the C-H bond activation reactions and cost effectiveness in comparison to palladium, the rhodium came into scene after a long time. Both Rh(I)[31] and Rh(III)[32] complexes have been extensively employed in catalytic C-H functionalization of aryl pyridines, but some reports have also appeared featuring Rh(II) [33]as active species.

Although, Pd and Rh transition metals showed remarkable activity towards C-H bond activation/functionalization reactions, still an alternative solution is needed to replace these expensive metal catalysts to make the catalytic C-H activation/functionalization process more cost effective and practically applicable. Among various transition metals investigated, Ru metal complexes have been identified as a promising catalyst for C-H bond activation reaction because of its high versatility and reactivity, compatibility with air and water, diversity in oxidation states and cost effectiveness over the other metals (Rh, Pd). With the significant contribution made by Murai, Oi and Inoue,[35] ruthenium based new catalytic systems were developed in the field of sp^2 C-H bond activation/arylation reactions.

1.7. Ruthenium(II) catalyzed C-H bond activation/arylation reactions

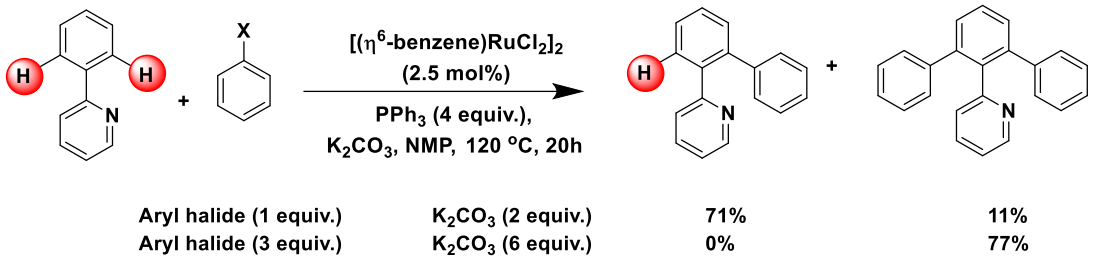
After the discovery of ruthenium catalysts as the most suitable catalyst for C-H bond functionalization reactions, various catalytic cycles including Ru(II)/Ru(IV), Ru(II)/Ru(0) and Ru(0)/Ru(II) have been systematically studied. In the initial stages of development, ruthenium metal in the form of Ru(0) gained popularity after the pioneering work initiated by Murai and co-workers[34] to achieve *ortho* C-H bond activation (Scheme 1.3). This is the first example of chelation assisted C-H bond alkenylation of aromatic ketones with $RuH_2(CO)(PPh_3)_3$ precursor, which *in situ* generates the active Ru(0) catalyst during the reaction to achieve the excellent regioselectivity for monoarylated product.



Scheme 1.3. *Ru(0) catalyzed C-H bond alkenylation of aromatic ketones via cyclometalated intermediate. Reproduced from ref. 34 with the permission of Nature.*

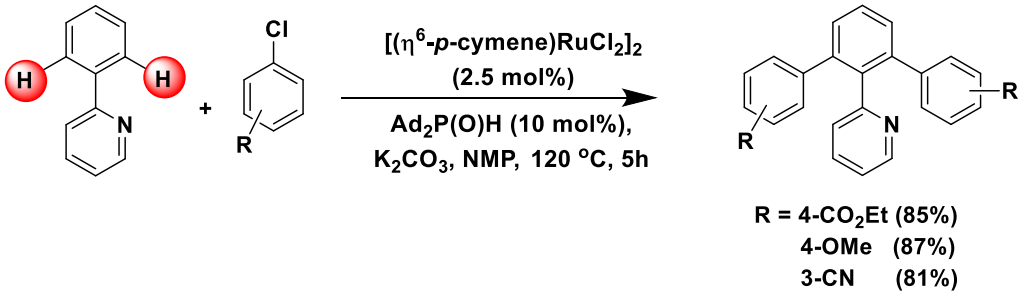
In addition to the above example of ruthenium(0) complexes, a wide range of non-arene ruthenium(II) complexes such as $RuCl_2(PPh_3)_3$,[36] $[RuH(codyl)_2]BF_4$ (codyl = η^5-cyclooctadienyl) [37] Ru_3CO_{12}[38] and some ligand free catalysis with complexes such as $RuCl_3.xH_2O$[39] has also been extensively investigated for C-H bond arylation reactions. Also, the arene-ruthenium(II) complexes in combination with various ligands, either as an additive or as integral part of the complex are proved to be the promising candidates for C-H arylation reactions.

It all started with the pioneering work of Oi and Inoue in 2001, when they reported the Ru (II) catalyzed *ortho* C-H bond arylation of 2-phenylpyridine with aryl halide in the presence of excess of triphenylphosphine (Scheme 1.4). With 2.5 mol% of arene-ruthenium complex as catalyst and 2 equiv. of K_2CO_3 as base, selective monoarylation of 2-phenylpyridine was achieved in 20 h at 120 °C in NMP. When equimolar amount of aryl halide was used, but excess of aryl halide led to the formation of biarylated product in good yield. Other ruthenium precursors, such as $RuCl_2(PPh_3)_3$ and $[RuCl_2(COD)]_n$ also found to exhibit comparable activity.[35]



Scheme 1.4. *Pioneering work of Oi and Inoue in the field of Ru(II) catalyzed C-H bond activation of 2-phenylpyridine.*

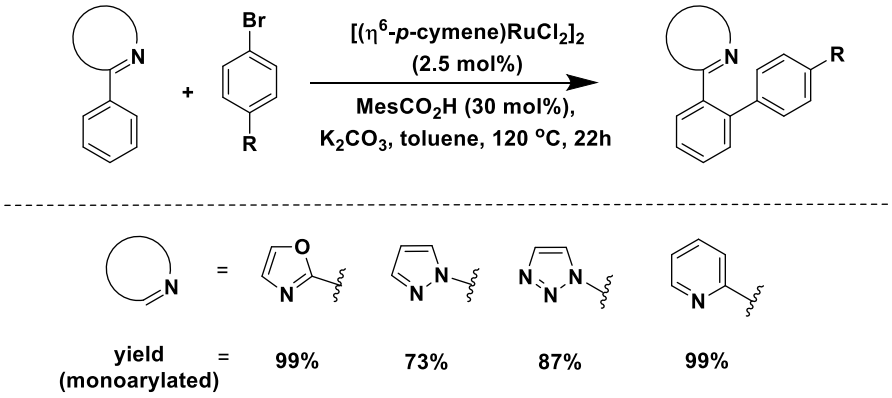
Further advancement in the field of phosphorus-based ligands for ruthenium(II) catalyzed C-H arylation reaction was brought by Ackermann in 2005 by the introduction of phosphine oxide $R_2P(O)H$ ligands which works efficiently with comparatively cheaper and readily available aryl chlorides as coupling partner (Scheme 1.5). [40] The performance of phosphine oxide preligand, $(adamantly)_2P(O)H$ was found to be better than other phosphorus-based ligands employed to afford biarylated product in C-H arylation reaction over $[(\eta^6\text{-}p\text{-cymene})\ RuCl_2]_2$ (2.5 mol%) with K_2CO_3 as base in NMP at 120 °C within 5 h (72%)/ 24 h (98%).



Scheme 1.5. *Phosphine oxides as an effective additive used for C-H bond activation/arylation of aryl pyridines by Ackermann.*

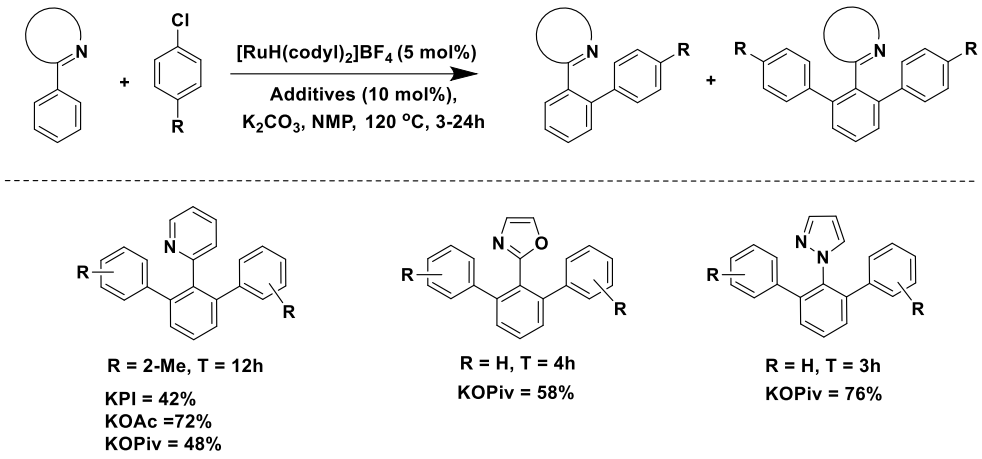
Further, the replacement of phosphine ligands took place to ease of handling of ligands when Ackermann studied the beneficial effects of carboxylic acids as a co-catalyst.[41] The investigation of a variety of cocatalysts including the use of phosphoric acid with ruthenium(II) catalyst (2.5 mol%) in the presence of K_2CO_3 in apolar solvent where the activity of sterically bulky mesitylic acid was found to be best among all. A wide range of N-heteroarenes with different functional groups such as oxazoline,

pyrazole, pyridine, triazole and others were efficiently and selectively monoarylated with aryl bromides (Scheme 1.6).



Scheme 1.6. *Ruthenium(II) catalyzed ortho C-H bond activation using carboxylic acids as cocatalyst.*

During investigation it has been found that such reaction conditions are not compatible for aryl chlorides, and the formation of biaryl as side product was observed which decreases the yield of the product. So, later, in the search of the efficient catalytic system for C-H bond activation of aryl pyridines which is compatible with aryl chlorides, Dixneuf *et al.* [37] developed a novel method using $[RuH(codyl)_2]BF_4$ complex to generate Ru(II) species in the presence of a base. They achieved complete biarylation of aryl heteroarenes by employing 5 mol% Ru(II) catalyst with K_2CO_3 as base in the presence of various carboxylate additives at 120 °C in NMP. The best results were obtained by employing potassium phthalimidate (KPI) as carboxylate additive under the optimized reaction conditions. The reaction condition was also compatible for various aryl chlorides as coupling partners bearing electron donating and electron withdrawing substituents (Scheme 1.7).

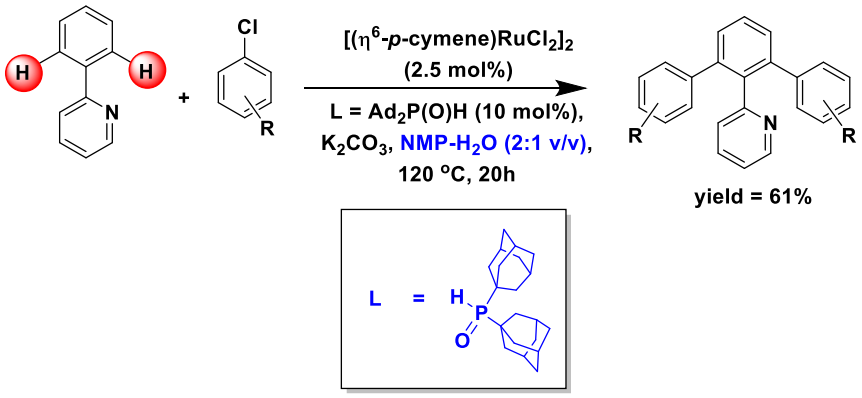


Scheme 1.7. *Ruthenium(II) catalyzed selective biarylation of aryl heteroarene using carboxylate additives.*

Despite extensive development in this area most of the literature known for C-H bond activation reactions of aryl pyridines suffered from many limitations, such as use of organic solvents and high reaction temperature. Hence extensive efforts were made to replace to avoid the use of hazardous organic solvents such as NMP, toluene, dichloroethane and perform reactions under environmentally and economically friendly alternatives. In this direction, Dixneuf *et al.* in 2009 demonstrated that Ru(II) catalyzed C-H bond arylation can be effectively performed in diethylcarbonate (DEC) at comparatively lower temperature.[42] DEC proved to be the best choice to carry out the C-H bond activation reaction because of its relatively non-toxic nature, availability of abundant renewable sources and easily degradable by natural cycles which makes it an appropriate reaction medium for such reactions. Although, reaction takes a longer time for completion in DEC, but addition of small amount of NMP dramatically increases the rate of reaction which encourages to study the effect of several other amide additives, such as acetamide, pivalamide etc. on the formation of biarylated product in DEC.

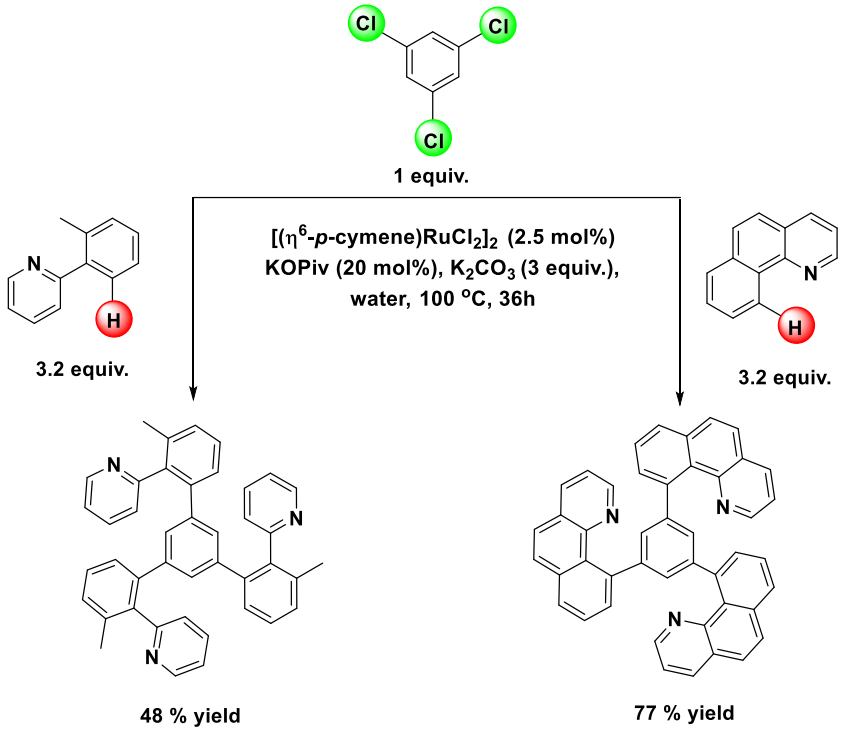
Similarly, Ackermann *et al.* also performed extensive investigation to explore easy to handle and more environment-tolerant solvent as reaction medium for such reactions. In this regard, they were the first to use water as a co-solvent with *N*-methylpyrrolidone (NMP/H_2O, 1:2 v/v) for the C-H bond arylation of 2-phenylpyridine in the presence of ruthenium(II) catalyst with $(adamantyl)_2P(O)H$ and demonstrated that Ru catalysts can also work efficiently even in water.[40] This report from Ackermann *et*

al. open new avenues for the use of water as reaction medium in ruthenium catalyzed C-H bond activation of aryl pyridines. The excellent aqueous solubility and stability of ruthenium complexes also offers the use of water as a solvent for the reactions performed at low temperature (80-100 °C) (Scheme 1.8).



Scheme 1.8. *Incremental effect of water in ruthenium(II) catalyzed C-H bond arylation of 2-phenylpyridine with aryl chloride.*

In the presence of carbonate/carboxylates additives Dixneuf and co-workers have successfully achieved the ruthenium(II) catalyzed *ortho* C-H bond arylation of aryl pyridine in water. They demonstrated the selective biarylation of 2-phenylpyridine can be achieved with Ru(II) catalyst using carboxylate additives (KOPiv) at 100 °C in 2 h.[43] They also extended the scope of reaction to arylation of 2-(2-pyridyl)toluene and benzoquinoline with 1,3,5-trichlorobenzene for the synthesis of functional materials used in OLEDs. The better performance of this catalytic system using water as compared to that of NMP, clearly demonstrated the fact that C-H bond arylation can be carried out efficiently in water with stable ruthenium complexes (Scheme 1.9).



Scheme 1.9. *Synthesis of functional material for OLEDs via Ru(II) catalyzed C-H bond arylation in water.*

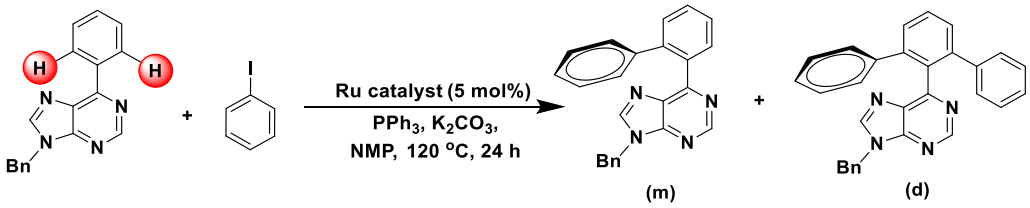
After establishing green conditions for reaction, further advancement in the field of C-H bond activation/arylation of aryl pyridine includes the screening of efficient ligands having various Lewis acid heteroatom such as *N,O/N,N* donor ligands and their effect on the catalytic reaction. Experimental and theoretical studies were also performed to understand the mode of action and involvement of different ligands in mechanistic cycle of reaction. Subsequent sections will discuss the direct or indirect role of the ligands in tuning the catalytic activity for C-H bond activation/functionalization reactions.

1.8. Role of ligands in ruthenium(II) catalyzed C-H bond arylation reactions

Extensive efforts were made to design new and efficient ligands to develop active catalysts for enhanced catalytic performance for C-H bond activation/functionalization reactions. Ligands containing various heteroatoms such as phosphorus, nitrogen, oxygen play a central role in tuning the catalytic activity of transition metal complex based catalysts. Electronic and steric properties of the transition metal complex can be fine

tuned by using appropriate ligand. Interestingly, the role of various phosphorus-based ligands in the development of efficient catalytic systems for C-H activation reactions was found to be crucial and provided a wide scope for further advancement. Transition metals such as ruthenium and palladium often form stable complexes by utilizing the phosphine ligands. These ligands are very good σ-donor and poor π-acceptors and often act as a spectator ligand. Such interesting properties of phosphine ligands make them an ideal choice of ligand for cross-coupling and C-H bond activation reactions.

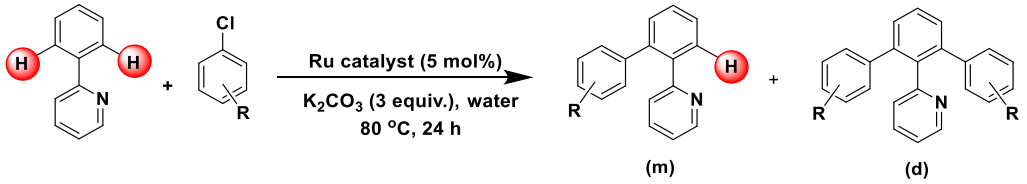
The effect of phosphine ligands on the catalytic reaction has been extensively studied by various researchers in the initial stages of development of C-H bond functionalization reactions. For instance, Oi and Inoue, in 2001, demonstrated that PPh_3 with good σ-donation capacity, facilitates the oxidative addition of aryl halides.[35] Further, evidence for this fact comes from the study by Lakshman *et al*. showing the influence of PPh_3 in the Ru(II) catalyzed *ortho* arylation of 6-phenylpurine for the modification of nucleosides.[44] They observed an increase in the reactivity and high selectivity for monoarylated product with the increasing amount of PPh_3. These finding demonstrated the crucial role of electronic and steric properties of phosphine ligands in promoting the oxidative addition and favoring the monoarylation for C-H bond activation reaction (Scheme 1.10).



Catalyst (5 mol%)	Amount of PPh_3 (mol%)	Conversion (%)	Yield (%) (m/d)
$[(\eta^6\text{-benzene})RuCl_2)]_2$	20	37	34/3
$[(\eta^6\text{-}p\text{-cymene})RuCl_2)]_2$	40	97	84/13
$[(\eta^6\text{-benzene})RuCl_2)]_2$	40	>99	76/17

Scheme 1.10. *Selectivity control by the use of triphenylphosphine ligands in Ru(II) catalyzed ortho arylation of 6-phenylpurine.*

Profitable role of PPh_3 in tuning the selectivity of the monoarylated products in Ru(II) catalyzed *ortho* C-H bond activation/arylation reaction was also demonstrated by Dixneuf and co-workers, when they performed the reaction in green solvent.[43] A remarkable control on the selectivity for monoarylated product was observed in the presence of PPh_3 either as a ligand additive with Ru(II) catalyst or as preformed complex [(η^6-*p*-cymene)$RuCl_2(PPh_3)$] (Scheme 1.11).



Catalyst (5 mol%)	Conversion (%)	Selectivity (%) (m/d)
[(η^6-*p*-cymene)$Ru(OPiv)_2$]	98	78/22
[(η^6-*p*-cymene)$Ru(OPiv)_2$] + 2 equiv. PPh_3	>99	82/12
[(η^6-*p*-cymene)$RuCl_2(PPh_3)$]	>99	89/11

Scheme 1.11. *Selectivity control by the use of triphenylphosphine ligands in Ru(II) catalyzed ortho arylation of 2-phenylpyridine in water.*

Subsequent studies with Ru(II) complexes, containing phosphorus-based ligands, further demonstrated the influence of these ligands in tuning the activity and selectivity for the C-H arylation products. For instance, secondary phosphine oxide (SPO) $R_2P(O)H$ ligands were efficiently used due to their advantage over the traditional phosphines for being bulkier, more air and moisture stable.[40] Later, Ackermann *et al*. proposed that SPO ligands displayed considerable acceleration in the rate of the reaction by assisting the Ru(II) catalyst in deprotonation step.[41] Analogously, single component phosphinous acid (PA) Ru(II) complexes were also proved to be crucial for PA-assisted C-H ruthenation step.[45]

In the subsequent years, carbonates and carboxylates were also studied for their potential to enhance the catalytic activity and their assistance in the C-H bond cleavage step. The role of carbonate in Ru(II) catalyzed C-H bond activation of 2-phenylpyridine was also investigated using Ru(II)-NHC complex and then well studied with density

functional theoretical (DFT) calculations.[46] Results showed that carbonate coordinates with the ruthenium center and effectively participate in the deprotonation of *ortho* C-H bond of 2-phenylpyridine. DFT calculations also favors the fact that activation of C(sp^2)-H bond with a Ru(II) site to give the expected metallacycle, which is actually a C-H bond deprotonation assisted by the concerted action of the coordinated base and the Ru(II) center.

Analogously, the influence of carboxylates in addition to the base is also found to be crucial in tuning the selectivity of the reaction. Ackermann *et al.*, for the first time, employed carboxylate additives to replace the phosphine ligands.[41] The Ru-carboxylate complex, [(η^6-*p*-cymene)($O_2CMes)_2$Ru] readily forms the cyclometalated product with 2-phenylpyridine in the presence of carbonate base. This further confirms that the presence of carbonate is crucial for the reaction to proceed. Subsequently, various researchers efficiently achieved the selective diarylation of a wide range of (hetero)aryl halides either with Ru-carboxylates catalysts or using carboxylates as additives, in green solvents such as water[43] and diethylcarbonate (DEC).[42]

The ligand acceleration effect exhibited by Ru-carboxylate catalyst was further established from the work from Jutand and co-workers. They performed detailed kinetic studies to better establish the combined effect of carbonate and carboxylates in the C-H bond activation reaction of 2-phenylpyridine.[47] When reaction was performed with Ru-carboxylate catalyst in acetonitrile using 2-phenylpyridine as a substrate, surprisingly, an autocatalytic process was found to takes place at room temperature. It is demonstrated that during the formation of cycloruthenated species from [(η^6-*p*-cymene)($OAc)_2$Ru] catalyst, 1 equiv. of AcOH was generated as a co-product, which indeed enhances the rate of reaction by accelerating the decordination process of acetate ligand. Interestingly, kinetic results showed that the addition of carbonate base strongly retards the formation of cycloruthenated species, probably due to deprotonation of co-catalyst AcOH which disfavors the interaction of Ru(II) center with 2-phenylpyridine (Figure 1.7).

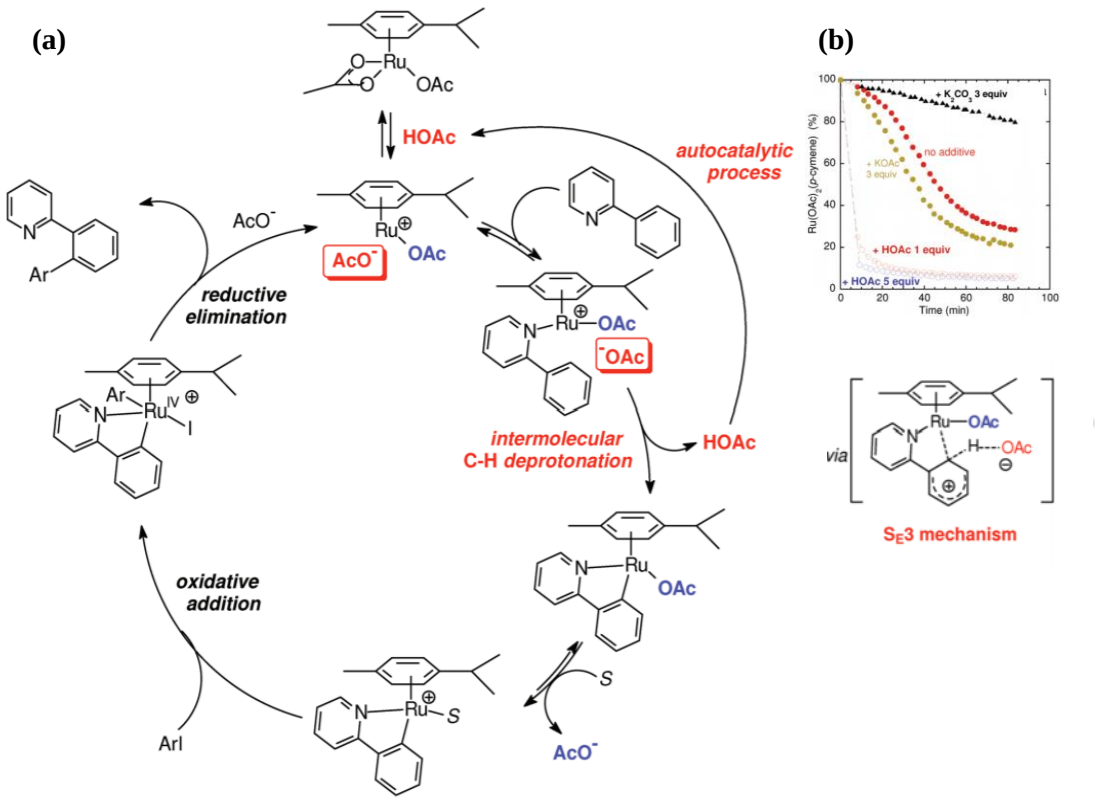


Figure 1.7. *(a) Ruthenium(II) catalyzed autocatalysis for C-H Bond activation by AcOH. (b) Influence of carbonate on carboxylate accelerated C-H bond activation of 2-phenylpyridine. Reproduced from ref. 47 with the permission of American Chemical Society.*

1.9. Mechanistic studies for C-H bond activation reactions

It is well established in the literature that the directing group strategy associated with the use of various transition metals to catalyze the activation of otherwise inert C-H bond generally are accompanied with the formation of cyclometalated intermediates. Depending upon the nature of the transition metal used for the catalytic reaction along with the other factors such as substrate, solvent, additives, ligands and others, C-H bond activation reaction can proceed via following pathways (Figure 1.8):

1. Oxidative addition
2. σ-bond metathesis
3. Electrophilic activation
4. Concerted metalation-deprotonation

Oxidative addition is an important reaction pathway in organometallic chemistry, which causes the change in oxidation state and coordination number by 2 units. To proceed through this pathway, the reactive complex must possess an empty σ-type molecular orbital (MO) and a high energy MO with a pair of electrons that can be transferred from the metal to the σ* orbital of the C-H bond during the reaction. It is the most common reaction pathway for C-H bond activation of aryl pyridines, which are well studied for the formation of five membered cyclometalated species as reactive intermediates.[48]

In contrast to oxidative addition, which is observed with electron rich metal centers, electrophilic C-H activation generally occurs with the late transition metals with high oxidation states. Further, the concerted metalation-deprotonation (CMD) pathway involves the intramolecular deprotonation of C-H bond, when a base is employed to the reaction. CMD pathway for C-H activation is generally facilitated by the coordination of free base, often a carbonate or carboxylate ligand, which can accept the leaving proton.

Further, σ-bond metathesis mechanism is rarely observed approach in organic synthesis. If reaction proceeds via σ-bond metathesis pathway, the reactive species must fulfill the requirement of having vacant acceptor MOs for stabilization of transferred electron pair in the transition state. This reaction pathway is generally observed with the metals having d^0 electronic configuration which cannot undergo oxidative addition.

In brief, C-H bond activation/functionalization reactions can proceed through any of these pathways, but the nature of transition metal used to catalyze the reaction plays a very crucial role.

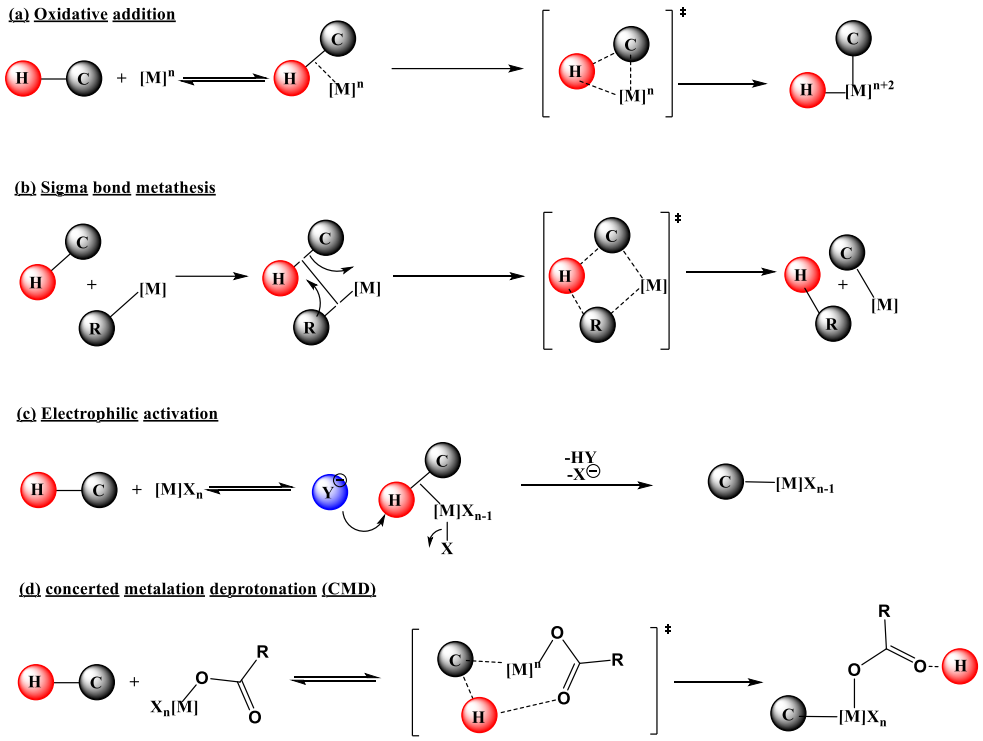


Figure 1.8. *Type of mechanisms involved in C-H activation/functionalization.*

Mechanistic investigation of a particular catalytic reaction is a powerful technique to understand the pathway of the reaction and add to the further improvements of the catalytic performance. To accomplish this goal, following experimental techniques have been extensively used to characterize the formation of active catalytic species intermediates during the catalytic reaction.

1. Mass spectrometry
2. Nuclear magnetic resonance (NMR) spectroscopy
3. Infrared (IR) absorption spectroscopy
4. Ultra-violet and visible absorption spectroscopy (UV-vis)
5. Single crystal X-ray diffraction technique (SC-XRD)
6. Kinetic studies (by mass, NMR or UV)

1.10. Objectives of thesis

C-H activation methodology has tremendous potential to synthesize and transform organic molecules via comparatively shorter and economic pathways by employing various metal catalysts. Inspired by the extensive literature survey and wide

scope for the advancement in the field, this thesis attempts to explore some new and efficient catalytic systems to carry C-H activation/arylation of 2-arylpyridines and to explore new pathways to enhance the catalytic performance. To fulfil the motive, various Ru(II) complexes with different nitrogen and oxygen-based ligands were designed and developed to thoroughly study the mode of action of such ligands and complexes in C-H bond activation reaction. Previous reports suggest that not only *O,O* donor ligands, but a variety of *N,N/N,O* donor ligands can also be applied to enhance the activity of metal catalysts. Therefore, the main aim of thesis is mainly targeted to achieve the following mentioned goals:

- To synthesize the arene-Ru(II) based robust catalytic systems, using a variety of ligands, which can provide high productivity and selectivity using mild reaction conditions for C-H bond activation/arylation of 2-phenylpyridine.
- To develop the efficient catalytic system for C-H bond activation/arylation reactions in water.
- To explore the mechanistic insights of the catalytic C-H bond arylation reactions, to establish the role of ligands and metal complex in C-H bond activation reactions.

1.11. Organization of thesis

In ***chapter 1***, relevant literature survey for the background of C-H bond activation reactions, transition metal catalyzed *ortho* C-H bond activation/functionalization, especially of aryl pyridines, application of the strategy to prepare industrially important compounds and development of new catalytic systems, have been presented along with a brief discussion on the scope of mechanistic investigations.

Chapter 2 discusses the synthesis, characterization and catalytic activity of water soluble arene-Ru(II) complexes having nitrogen-based ligands for *ortho* C-H bond activation/arylation of 2-phenylpyridine.

Chapter 3 discuss the synthesis of a series of arene-Ru(II) complexes containing bidentate *N,O* donor ligands and the role of different ligand in tuning the catalytic activity towards *ortho* C-H bond activation/arylation of 2-phenylpyridine.

Chapter 4 demonstrates the ligand acceleration effect of biomass derived ligands in Ru(II) catalyzed *ortho* C-H bond activation/arylation of 2-phenylpyridine.

Chapter 5 illustrates the role of *N,O* donor ligands such as (2-hydroxypyridine and its derivatives) in tuning the catalytic activity of arene-ruthenium(II) catalysts for *ortho* C-H bond activation/arylation of 2-phenylpyridine.

Chapter 6 presents a brief summary of the present thesis, including the findings, limitations and future scope of the was discussed in this thesis.

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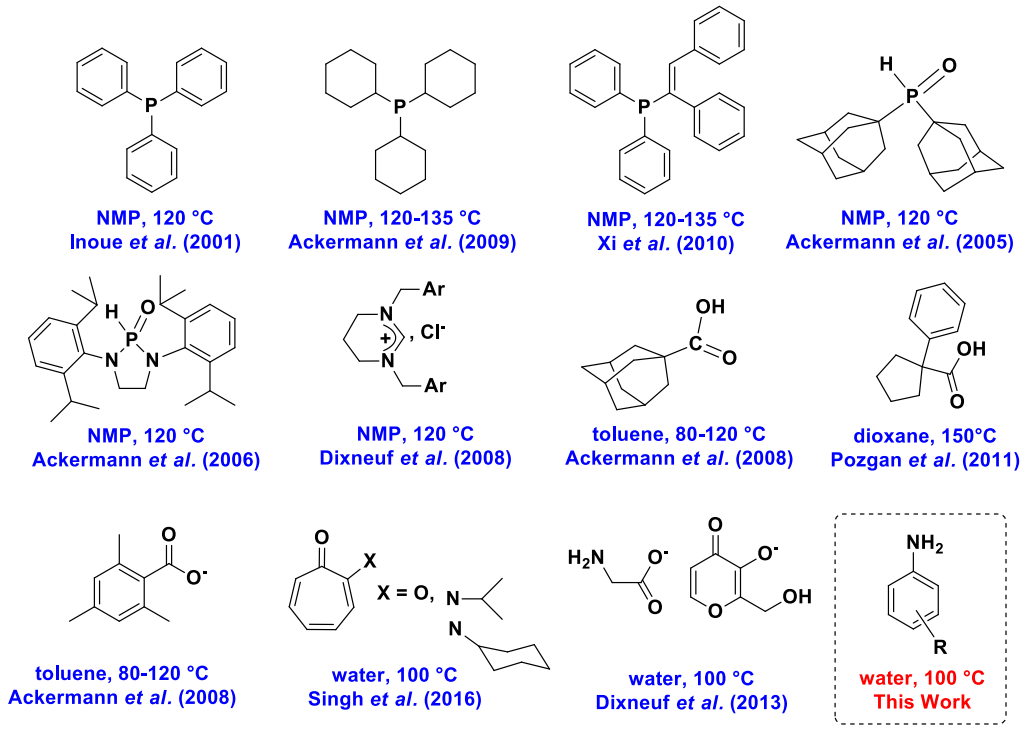
Chapter 2

C-H bond activation/arylation catalyzed by arene-ruthenium-aniline complexes in water

2.1. Introduction

Transition metal catalyzed C-H bond activation reactions have received extensive attention because these reactions provide a shorter and atom economic way to synthesize a wide range of compounds by activating the C-H bond.[1] One of the most explored C-H bond activation strategies includes those involving a directing group as it proceed via the formation of an active 5-membered cyclometalated species. Among the several transition metals based catalysts explored for C-H bond activation, ruthenium complexes being highly active, with a wide range of active and stable oxidation states, high stability in air and water, have gained advantages over others.[2-6] Hence a wide range of ruthenium complexes such as $RuCl_2(PPh_3)_3$, $[RuCl_2(cod)]_n$, $RuCl_3.xH_2O$ and others were extensively investigated for C-H bond activation reaction.[5,6] Among these, $RuCl_3.xH_2O$ was the first ligand-free catalytic system reported by Ackermann *et al.* for C-H bond activation of aryl pyridine.[5b,5f] However, arene-ruthenium complexes, for example $[\{(\eta^6\text{-arene})RuCl_2\}_2]$ and their analogues, were identified as one of the most promising and extensively explored ruthenium catalysts for C-H bond activation/functionalization.[5,6] Recently, double C-H bond activation using rhodium and ruthenium catalysts was also reported to achieve analogous C-H bond functionalization.[6e]

In particular, C-H bond activation using arene-ruthenium complexes in the presence of a wide range of phosphine bound ligands/ additives has been well studied and explored (Scheme 2.1).[7-14] For instance, Ackermann *et al*. used phosphoric acids with arene-ruthenium catalyst to enable efficient C-H bond functionalization in toluene.[8b] Recently, C-H bond activation/arylation over a well-defined arene-ruthenium-phosphinous acid catalyst was reported where phosphinous acids acts as a deprotonating agent.[7e]



Scheme 2.1. *Various ligands associated with arene-ruthenium catalyzed C-H bond activation/functionalization.*

Moreover, reports inferred that performing water based catalytic reactions does not only provide a non-toxic greener condition, but also there are several incremental effects of water on the catalytic reaction. Ackermann *et al* first used water as a co-solvent with NMP (1:2 v/v) for the C-H bond arylation of 2-phenylpyridine in the presence of Ru-*p*-cymene dimer catalyst with $(adamantyl)_2P(O)H$ and observed that Ru catalysts are active even in water.[8c] Further, Dixneuf *et al.* investigated the sequential arylation of 2-phenylpyridine with aryl halides over $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ complexes in the presence of various phosphine based ligands at 80 ºC in water and reported that in water better catalytic activity and yields can be achieved.[9] Also, for low temperature reactions (<100 °C), water is considered even as a more efficient solvent than other organic solvents (e.g. NMP).[9] Contrary to phosphine based ligands, carboxylates being both a ligand and deprotonating agent displayed more potential to achieve high catalytic activity and to tune the selectivity for arene-ruthenium catalyzed C-H bond activation reaction.[9c,10] We also developed water-soluble arene-ruthenium complexes using troponate/aminotroponate ligands to achieve superior catalytic activity for C-H bond arylation with arylchlorides in water at 100 ºC.[12] Our investigations evidenced that having strongly coordinating

chelating ligands arene-ruthenium complexes may led to the release of arene ligand in contrast to the well-established arene-ruthenium cyclometalated species.

During our studies, we also focused on the development of water-soluble arene-ruthenium complexes containing aniline ligands inferred that these complexes could be used for the catalytic synthesis of biaryls *via* an oxidative homocoupling reaction of arylboronic acids in water.[15a] Our investigations evidenced the formation of (di-σ-aryl)Ru species as a possible active intermediate species.[15a] Interestingly, anilines which are considered as a weakly coordinating ligand exerts substantial role to tune the activity and selectivity towards homocoupling of arylboronic acids. Notably, [(η^6-arene)$RuCl_2$(aniline)] complexes displayed comparable or even higher activity than their structurally analogous phosphine containing complex [(η^6-arene)$RuCl_2(PPh_3)$].[9,15] We envisioned that being a weak ligand, aniline, in contrary to strongly coordinating phosphine ligand, can be easily displaced by the reacting substrate under catalytic reaction conditions. Encouraged by these findings, herein we systematically explored the catalytic activity of arene-ruthenium complexes containing aniline based ligands for *ortho*-C-H bond activation and arylation of 2-phenylpyridine with arylchlorides in water. We also investigated the influence of having aniline-based ligands of varying electronic and steric behavior, on the catalytic activity of the resulting arene-ruthenium-aniline complexes. Time-scaled NMR and mass spectral investigation were also performed to monitor the reaction progress and to identify the reactive intermediate species formed during the C-H bond activation reactions.[5g,15a,16] All the synthesized arene-ruthenium complexes was well characterized using spectro-analytical techniques and structural identity of few of the representative complexes was established by single crystal X-ray diffraction also.

2.2 Results and Discussion

2.2.1 Synthesis and structure of water soluble arene-ruthenium-aniline based complexes. Aniline ligands, with varying steric and electronic properties ((**L** = aniline (**L1**), 2-methylaniline (**L2**), 2,6-dimethylaniline (**L3**), 4-methylaniline (**L4**), 4-chloroaniline (**L5**)), reacts readily with arene-ruthenium precursors to synthesize water soluble arene-ruthenium-aniline based complexes.[15a,17] Therefore, [(η^6-*p*-

cymene)Ru(L)Cl_2)] (**[Ru]-1**−**[Ru]-5**) are obtained in excellent yields by reacting [(η^6-*p*-cymene)RuCl_2]$_2$ **[Ru]-A**, with aniline based ligands (where **L1** = Aniline, **L2** = 2-methylaniline, **L3** = 2,6-dimethylaniline, **L4** = 4-methylaniline, **L5** = 4-chloroaniline) in methanol under refluxing condition (Figure 2.1).

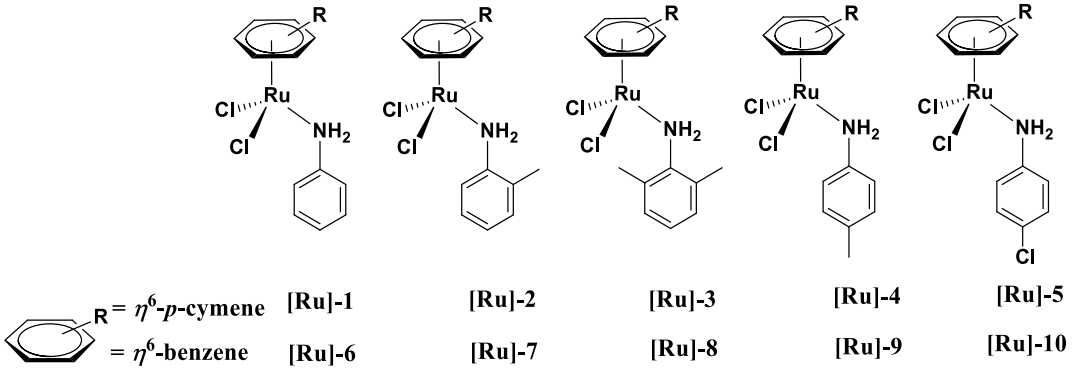


Figure 2.1. *Schematic representation of arene-Ru(II) complexes* ***[Ru]-1 – [Ru]-10.***

Structural identity of complexes **[Ru]-1–[Ru]-5** was confirmed by ^{1}H NMR, ^{13}C NMR and ESI mass spectrometry. The analogous [(η^6-benzene)Ru(L)Cl_2)] ((L = L1 (**[Ru]-6**), L2 (**[Ru]-7**), L3 (**[Ru]-8**), L4 (**[Ru]-9**) and L5 **([Ru]-10**)) were also synthesized.[15a,17] As expected all the complexes showed a downfield shift for the protons of aniline ligands in comparison to the free ligand, suggesting the coordination of aniline ligands with the ruthenium metal. Moreover, ^{1}H NMR resonances for protons corresponding to ruthenium coordinated η^6-*p*-cymene ring were also observed in the expected region, further supports the proposed structural formulation of these complexes. Stability of the catalysts **[Ru]-1**−**[Ru]-5** were confirmed by thermal gravimetric analysis (TGA) experiments. TGA results inferred that all of the catalysts exhibit good thermal stability up to ca. 160 °C (Figure 2.2). Moreover, all the catalysts (**[Ru]-1** to **[Ru]-10**) are air stable and no decomposition or structural change of these catalysts have been observed on exposure to air.

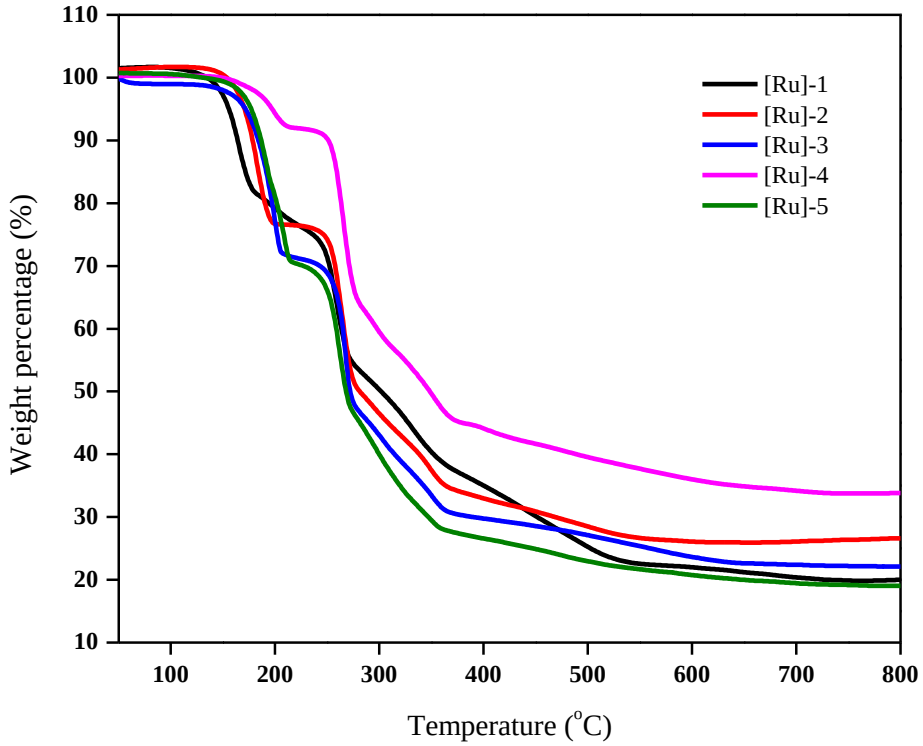


Figure 2.2. *Thermal gravimetric analysis (TGA) data of complexes* ***[Ru]-1 – [Ru]-5****.*

Single crystals of complexes **[Ru]-1**, **[Ru]-4** and **[Ru]-5** were grown by the slow evaporation of a methanol-dichloromethane solution of the respective complexes and their molecular structures were confirmed by single-crystal X-ray diffraction studies (Figure 2.3). The molecular structure of the complex **[Ru]-2** was also confirmed by single-crystal X-ray diffraction studies but unfortunately, diffraction data was weak and therefore complete data refinement could not be retrieved. Nevertheless, based on the obtained un-refined X-ray data, there is a clear information about the coordination of 2-methylaniline to the ruthenium centre (Figure 2.4).

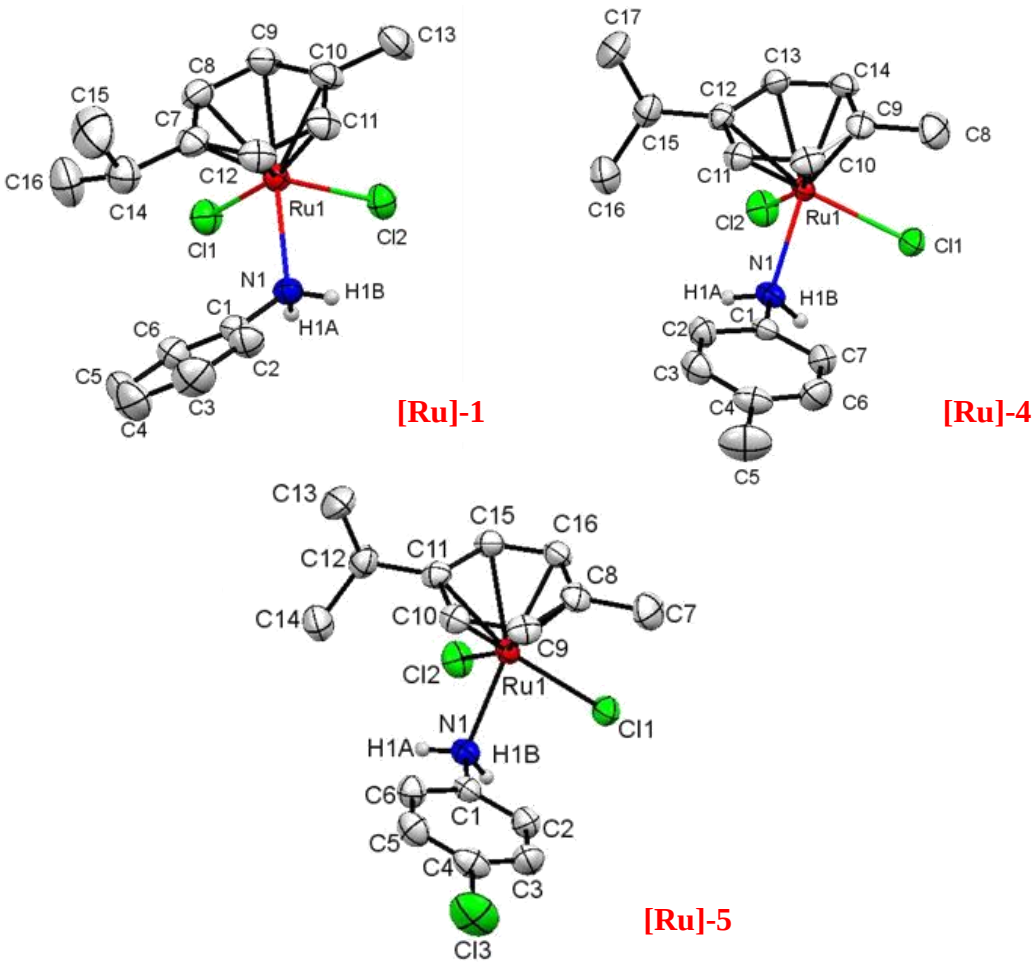


Figure 2.3. *Single crystal X-ray structures of the representative complexes* ***[Ru]-1****,* ***[Ru]-4*** *and* ***[Ru]-5*** *assessed for the catalytic C-H bond activation reaction. (30% thermal ellipsoids; hydrogen atoms (except those on nitrogen atoms) are omitted for clarity).*

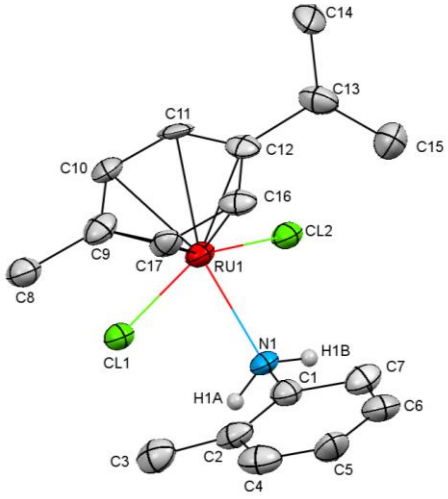


Figure 2.4*. Single crystal X-ray structure of the complex* ***[Ru]-2****. Ellipsoids are set at 30% probability. All hydrogen atoms, except those on nitrogen, are omitted for clarity.*

As shown in Figure 2.3, all the complexes, **[Ru]-1**, **[Ru]-4** and **[Ru]-5**, adapted the *pseudo*-octahedral geometry where η^6-*p*-cymene ring occupied the top position and the aniline ligand along with two -Cl groups occupied the three legs respectively. Complex **[Ru]-1** crystallizes in the triclinic crystal system with P-1 space group, whereas complexes **[Ru]-4** and **[Ru]-5** attain the monoclinic crystal system with P21/n space group. In agreement with the proposed formulation shown in Figure 2.3, molecular structures confirmed the co-ordination of aniline ligands (**L1**, **L4** and **L5**) through the nitrogen atom to the ruthenium centre.[15a,17] Interestingly, the Ru-N distance is slightly shorter (2.1632(19) Å) for electronically rich 4-methylaniline containing complex **[Ru]-4,** than those for complexes **[Ru]-5** (2.178(2) Å) and **[Ru]-1** (2.180(3) Å) containing 4-chloroaniline and aniline, respectively. Phenyl ring of aniline ligands are placed away from the metal centre, as depicted from the Ru-N-C angles of 120.5°–122.0° for complexes **[Ru]-1**, **[Ru]-4** and **[Ru]-5**.[15a,17] Angles between the legs, Cl-Ru-Cl (87.7°–89.0º) and Cl-Ru-N (80.1°–83.7°) and those between the legs and the centroid of η^6-*p*-cymene ring (127.4°–132.4°) are also in good agreement with earlier reported analogous complexes.[15a,17,18] η^6-*p*-cymene ring is displaced at a distance of 1.65 Å from the ruthenium center. Ru-Cl bond distances are in the range of 2.163-2.180 and 2.406–2.421 Å and are comparable to those for analogous η^6-benzene complexes.[15a,17] Crystal refinement data and selected bond parameters for complexes **[Ru]-1**, **[Ru]-4** and **[Ru]-5** are provided in following tables.

Table 2.1. *Crystal data and structure refinement for complex* ***[Ru]-1****, complex* ***[Ru]-4*** *and complex* ***[Ru]-5****.*

crystal parameter	**complex [Ru]-1**	**complex [Ru]-4**	**complex [Ru]-5**
Empirical formula	$C_{16}H_{21}Cl_2N$ Ru	$C_{17}H_{23}Cl_2$ N Ru	C_{16} $H_{20}Cl_3N$ Ru
Formula weight	399.31	413.33	433.75
Temperature (K)	150 (2)	150 (2)	293(2)
Wavelength (Å)	1.54184	1.54184	0.71073
Crystal system, space group	Triclinic, $P1^-$	Monoclinic, $P2_1/n$	Monoclinic, $P2_1/n$
a (Å)	7.9112 (5)	8.9820 (10)	8.8940 (4)
b (Å)	9.0981 (8)	12.4077 (14)	12.4578 (4)
c (Å)	12.6300 (12)	15.6385 (18)	15.5966 (6)

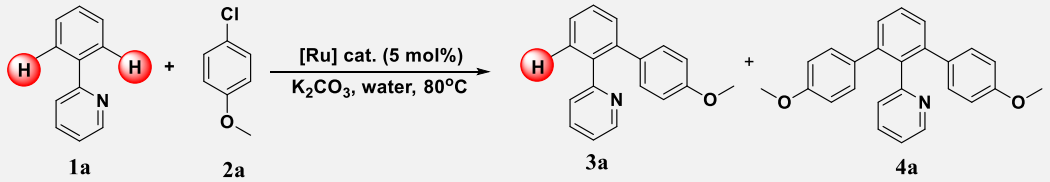
α (°)	87.499 (7)	90	90
β (°)	85.297 (6)	90.80	91.468 (3)
γ (°)	69.365 (7)	90	90
Volume ($Å^3$)	847.78(12)	1742.7(3)	1727.53 (12)
Z, calculated density (mg/m^3)	2, 1.564	4, 1.575	4, 1.668
μ (mm^{-1})	10.287	10.030	1.364
F (000)	404	840	872
Crystal size (mm^3)	0.33 × 0.26 × 0.21	0.28 × 0.24 × 0.22	0.23 × 0.18 × 0.13
Theta range for data collection (°)	5.20 to 71.40	5.65 to 71.51	3.07 to 32.23
Index ranges	-9<=h<=7; -11<=k<=11; -15<=l<=14	6<=h<=10; -14<=k<=15; -19<=l<=18	-12<=h<=11 -18<=k<=17 -22<=l<=22
Reflections collected	5180 / 3182 [R(int) = 0.0373]	10688 / 3348 [R(int) = 0.0204]	20254 / 5745 [R(int) = 0.0503]
Completeness to theta (%)	96.4 (θ = 71.40°)	98.8 (θ = 71.51°)	99.8 (θ = 25.24°)
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.29294	0.2163 and 0.1656	1.00000 and 0.82150
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/ restraints/ parameters	3182 / 0 / 184	3348 / 0 / 194	5745 / 0 / 193
Goodness-of-fit on F^2	1.062	1.059	1.084
Final R indices [I > 2sigma(I)]	R1 = 0.0443, wR2 = 0.1208	R1 = 0.0271, wR2 = 0.0743	R1 = 0.0417 wR2 = 0.0951
R indices (all data)	R1 = 0.0449, wR2 = 0.1222	R1 = 0.0275, wR2 = 0.0747	R1 = 0.0557 wR2 = 0.1033
Largest diff. peak and hole ($eÅ^{-3}$)	1.130 and -1.692	0.592 and -1.012	1.168 and -0.997
CCDC numbers	1491603	1491612	1491613

2.2.2 Catalytic *ortho*-C-H bond arylation of 2-phenylpyridine with arylchlorides

At the outset of our investigations towards C-H bond activation reactions, the catalytic reaction was performed using 2-phenylpyridine **(1a)** and 4-chloroanisole (**2a**, as

arylation agent) in the presence of **[Ru]-1** (5 mol%) in water at 80 ºC. Results as summarized in Table 2.2, inferred that monoarylated product **(3a)** by *ortho*-C-H arylation of 2-phenylpyridine **(1a)** was formed as the major product (88%), along with diarylated product **(4a)** as minor component (12%). Preliminary results suggested that (η^6-*p*-cymene)Ru complex (**[Ru]-1**) showed higher selectivity for monoarylated product (**3a**) than the (η^6-benzene)Ru complex (**[Ru]-6**) (Table 2.2, entries 1 and 2).

Table 2.2. *Catalytic ortho-C-H bond arylation of 2-phenylpyridine with 4-chloroanisole in water* [a][b]



1a 2a 3a 4a

Entry	Catalyst	Conv (%)	Sel. (%) (3a/4a)	TON/ TOF (h^{-1})
1.	[(η^6-*p*-cymene)$RuCl_2$(aniline)] (**[Ru]-1**)	94	88/12	18.8/4.7
2.	[(η^6-benzene)$RuCl_2$(aniline)] (**[Ru]-6**)	96	86/14	19.2/4.8
3.	[(η^6-*p*-cymene)$RuCl_2$(2,6-dimethylaniline)] (**[Ru]-3**)	85	92/8	17/4.2
4.	**[(η^6-*p*-cymene)$RuCl_2$(4-methylaniline)] ([Ru]-4)**	**>99**	**93/7**	**20/5**
5.	[(η^6-*p*-cymene)$RuCl_2$(4-chloroaniline)] (**[Ru]-5**)	89	90/10	17.8/4.4
6.	[(η^6-*p*-cymene)$RuCl_2$]$_2$	90	89/11	18/4.5
7. [c]	[(η^6-*p*-cymene)$RuCl_2(PPh_3)$]	88	96/4	17.6/2.2

[a]Reaction Conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), K_2CO_3 (3 equiv.), **[Ru]** catalyst (5 mol%) in water (2 mL) at 80 ºC for 4 h. [b]Conversion and selectivity were determined by ^{1}H NMR with TMS as internal standard. [c]8 h.[9]

To further investigate the effect of various aniline ligands (**L1, L3, L4 and L5**) having different steric and electronic properties on the C-H bond activation of 2-phenylpyridine, catalytic reactions were performed with complexes **[Ru]-1** to **[Ru]-5**

under the optimized reaction conditions (Table 2.2 and Figure 2.5). Results inferred that having sterically bulky 2,6-dimethylaniline ligand, **[Ru]-3** displayed lower conversion (85%) in 4 h as compared to **[Ru]-1** complex containing aniline ligand (94%) (Table 2.2, entries 1 and 3). Interestingly, amongst all the ruthenium complexes investigated, **[Ru]-4** having 4-methyl aniline ligand outperform with complete C-H bond arylation of 2-phenlpyridine (**1a**) achieved in 4 h with 93% selectivity for *ortho*-C-H bond activated monoarylated product, **3a** (Table 2.2, entry 4). Contrary to the above, **[Ru]-5** having 4-chloroaniline ligand also showed lower conversion (90%) (Table 2.2, entry 5). Notably, under analogous reaction conditions, the precursor (arene)Ru dimer, [(η^6-*p*-cymene)$RuCl_2$]$_2$ (**[Ru]-A**), also showed lower conversion (90%). It is worth mentioning that the structural analogue of [(η^6-*p*-cymene)$RuCl_2$(4-methylaniline)] (**[Ru]-4**), the phosphine containing complex [(η^6-*p*-cymene)]$RuCl_2(PPh_3)$] was reported to display only 88% conversion towards C-H bond arylation of 2-phenylpyridine under analogous reaction conditions.[9] Further, the presence of inert atmosphere was found to be crucial to achieve high catalytic conversions, as no reaction was occurred in the absence of inert atmosphere. Notably, analogous to argon atmosphere, nitrogen atmosphere also worked well to achieve comparable catalytic conversions (Table 2.3).

Table 2.3. *Catalytic C-H bond arylation of 2-phenylpyridine with 4-chloroanisole over* ***[Ru]-4*** *catalyst*[a][b]

Entry	Catalyst	Conv. (%)	Sel. (%) (3a/4a)
1.	Under argon	>99	93/7
2.	Open air	0	N.R.
3.	Under N_2	>99	89/11
4.	Without base	0	N.R.

[a]Reaction Conditions: 2-phenylpyridine (0.6 mmol), 4-chloroanisole (0.5 mmol), K_2CO_3 (3 equiv.), **[Ru]-4** catalyst (5 mol%) in water (2 mL) at 80 ºC, 8 h. [b]Conversion and selectivity were determined by ^{1}H NMR with TMS as internal standard.

Further, it is important to mention that the catalytic reactions performed using **[Ru]-A** with aniline ligands (**L1**/**L4**/**L5**) added, resulted in lower activity, suggesting that the presence of a pre-formed structure of ruthenium coordinated aniline ligand structure is crucial to achieve higher catalytic activity (Table 2.4).

Table 2.4. *Effect of externally added aniline ligands on conversion and selectivity for C-H arylation of 2-phenylpyridine*

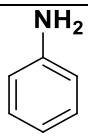
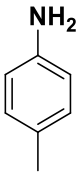
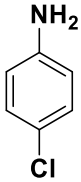
Entry	Ligand	Conv. % (2a)	Sel. % (3a)
1.	 L1 = Aniline	67%	85%
2.	 L4 = 4-methylaniline	67%	84%
3.	 L5 = 4-chloroaniline	63%	80%

Figure 2.5 displayed the comparative TOF (h^{-1}) of the arene-ruthenium complexes studied towards the C-H bond activation of 2-phenylpyridine. It is evident from figure 2.5 that [Ru]-4 is the best performing complex among all the Ru(II) complexes studied.

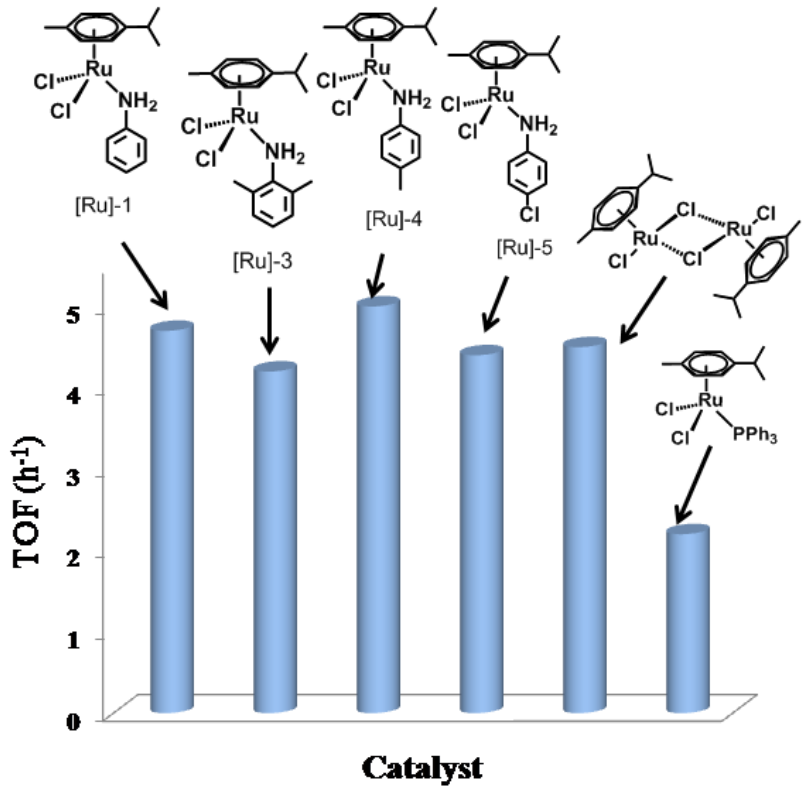


Figure 2.5. *Comparative catalytic efficacy (as TOF h^{-1}) of various (η^6-p-cymene)ruthenium complexes for ortho-C-H bond arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**) at 80 °C in water.*

Time-scaled ^{1}H NMR experiments were performed over a period of 2-8 h, to understand the effect of different substituents of aniline based ligands on the catalytic reaction. As inferred from the Figure 2.6, **[Ru]-4** was found to be highly active among all the complexes studied, as with **[Ru]-4** complete conversion can be achieved in 4 h. Notably, **[Ru]-4** was fo5nd to exhibit the higher rate (3.22×10^{-4} sec^{-1}) for the initial 4 h of reaction (Figure 2.7). Contrary to **[Ru]-4**, complexes having bulky 2,6-dimethyl aniline (**[Ru]-3**) and the 4-chloroaniline complex, **[Ru]-5,** showed relatively lower activity (1.60×10^{-4} sec^{-1} and 1.86×10^{-4} sec^{-1}, respectively for **[Ru]-3** and **[Ru]-5**) under analogous reaction conditions (Figure 2.7). The observed results suggesting a crucial role of aniline ligands to achieve high catalytic activity towards C-H bond activation/arylation reaction.

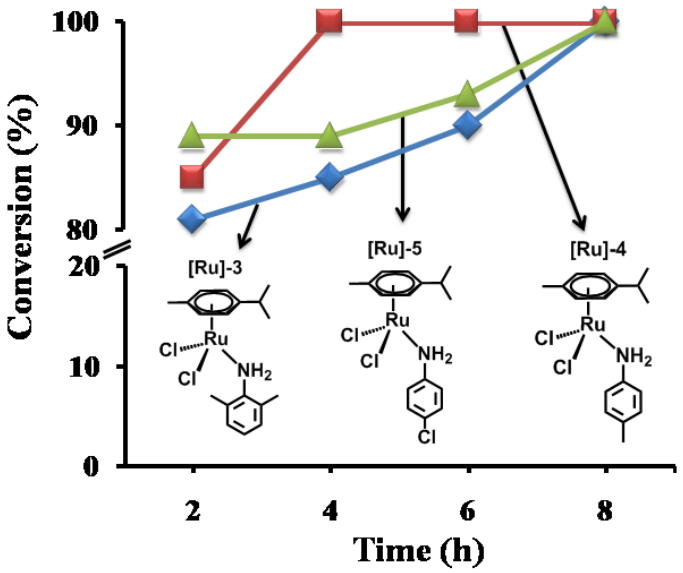
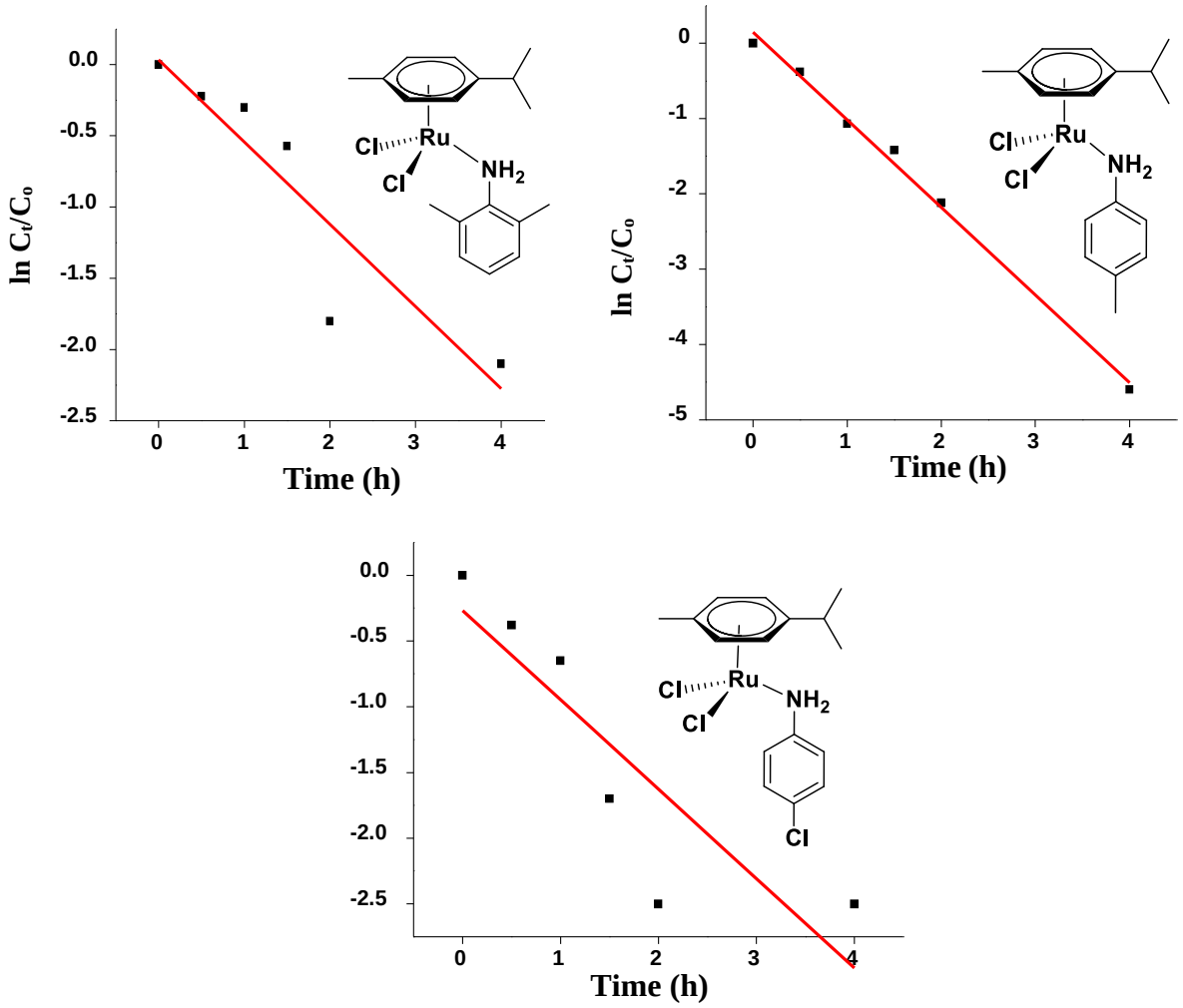


Figure 2.6. *Influence of ligands on the reaction progress for the catalytic ortho-C-H bond arylation of 2-phenylpyridine with 4-chloroanisole over complexes* ***[Ru]-3***, ***[Ru]-4*** *and* ***[Ru]-5****.*

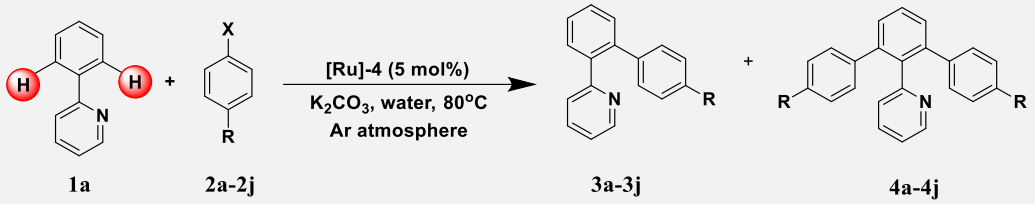


Catalysts	[Ru]-3	[Ru]-4	[Ru]-5
Rate constant (k)	1.60×10^{-4} sec^{-1}	3.22×10^{-4} sec^{-1}	1.86×10^{-4} sec^{-1}

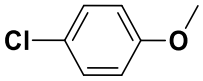
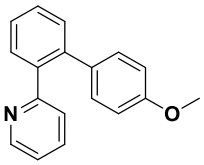
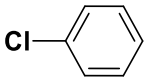
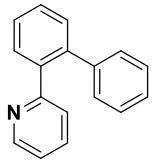
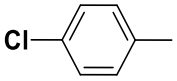
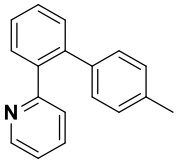
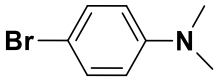
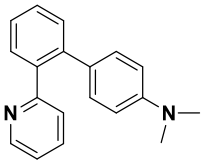
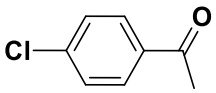
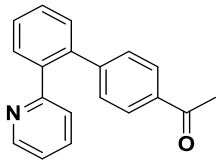
Figure 2.7*. Kinetics of the C-H bond activation/arylation of 2-phenylpyridine with 4-chloroanisole over complexes* ***[Ru]-3****,* ***[Ru]-4*** *and* ***[Ru]-5****.*

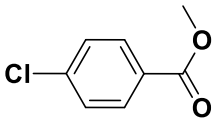
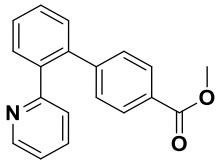
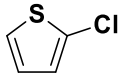
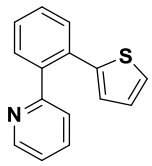
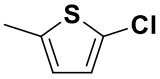
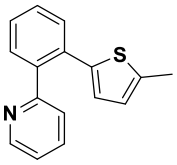
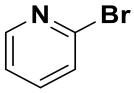
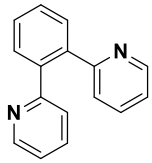
Further exploration using a wide range of arylchlorides for the *ortho*-C-H bond arylation of 2-phenylpyridine was conducted over the highly active **[Ru]-4** complex at 80 ºC in water. A range of arylchlorides having electron donating and electron withdrawing substituents were used for the C-H bond arylation of 2-phenylpyridine. Results are summarized in Table 2.5. Notably, the monoarylated product was found to be the major product for most of the arylchlorides used. Chlorobenzene (**2b**), which is considered as most inactive aryl halide due to lack of any substitution, gave complete conversion in 8 h with 87% selectivity for the monoarylated product (**3b**) (Table 2.5, entry 2). Similar to 4-chloroanisole (**2a**), electron donating substituted arylchlorides, such as 4-chlorotoluene (**2c**) and 4-bromo-*N*,*N*-dimethylaniline **(2d)**, also resulted in complete conversion in 4 h and 8 h, respectively to their corresponding C-H arylated products **3c** and **3d** in 90% and 65% selectivities (Table 2.5, entries 3 and 4). Contrary to arylchlorides with electron donating groups, those having electron withdrawing groups, such as 4-chloroacetophenone **(2e)** and 4-chloromethylbenzoate (**2f**) exhibited moderate activities towards C-H arylation with 45% (6 h) and 92% (8 h) conversion respectively to obtain (**3e**) and **(3f)** in 53% and 87% selectivities respectively (Table 2.5, entries 5 and 6). (Hetero)arylchlorides such as 2-chlorothiophene (**2g**) and 5-methyl 2-chlorothiophene (**2h**) were also used for *ortho*-C-H bond arylation of 2-phenylpyridine, where high conversion was achieved towards respective C-H arylated products (**3g**) and (**3h**) in 82% and 80% selectivities, respectively (Table 2.5, entries 7 and 8). Analogous thiophene containing poly(hetero)aryls (**3h**) may also be prepared by double C-H activation using rhodium or ruthenium catalysts.[6e] However, the reaction performed with 2-bromopyridine (**2i**) resulted in poor conversion (Table 2.5, entry 9).

Table 2.5. *Catalytic ortho-C-H bond arylation of 2-phenylpyridine using various (hetero)aryl halides over* ***[Ru]-4*** *catalyst in water*[a][b][c]



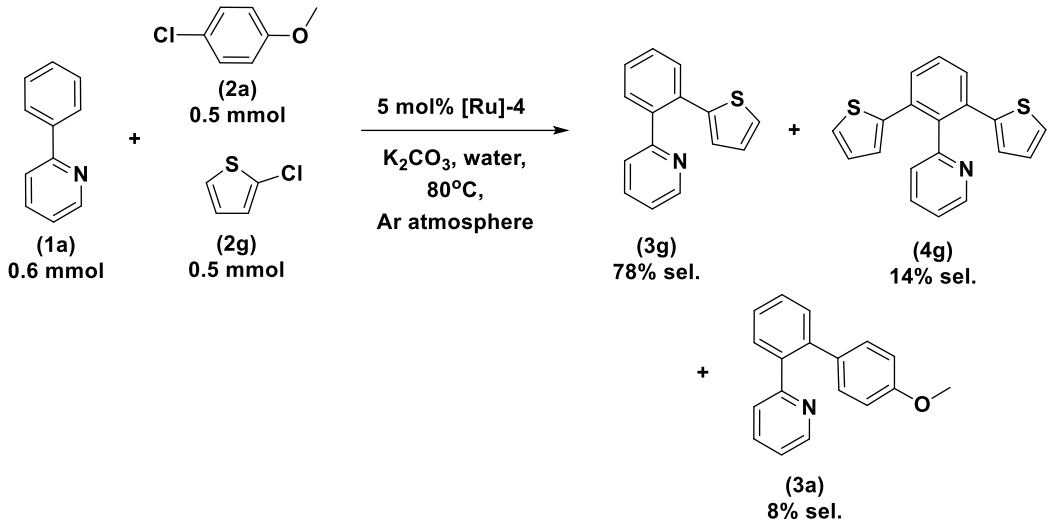
1a **2a-2j** **3a-3j** **4a-4j**

Entry	Substrate	Time (h)	Conv. (%)	Sel. (%)	Product (Yield %)
1.	 **2a**	8	>99	90/10 (**3a**:**4a**)	 **3a** (60%)
2.	 **2b**	8	>99	87/13 (**3b**:**4b**)	 **3b** (45%)
3.	 **2c**	4	>99	90/10 (**3c**:**4c**)	 **3c** (73%)
4.	 **2d**	8	86	65/35 (**3d**:**4d**)	 **3d** (42%)
5.	 **2e**	6	45	53/47 (**3e**:**4e**)	 **3e** (20%)

6.	 **2f**	8	92	87/13 (**3f**:**4f**)	 **3f** (58%)
7.	 **2g**	4	>99	82/18 (**3g**:**4g**)	 **3g** (62%)
8.	 **2h**	8	80	80/20 (**3h**:**4h**)	 **3h** (53%)
9.	 **2i**	8	38	79/21 (**3i**:**4i**)	 **3i** (23%)

[a]Reaction conditions: 2-phenylpyridine (0.6 mmol), (hetero)aryl halide (0.5 mmol), K_2CO_3 (3 equiv.), [Ru]-4 (5 mol%) in water (2 mL) at 80 °C. [b]Conversion and selectivity were determined by ^{1}H NMR with TMS as internal standard. [c]Isolated yield are given in parenthesis.

Further, to compare the chemoselectivity towards C–H arylated products, competitive C-H bond arylation reaction of 2-phenypyridine (**1a**) was performed using an equimolar ratio of 4-chloroanisole (**2a**) and 2-chlorothiophene (**2g**) under the optimized reaction conditions over complex **[Ru]-4** (Scheme 2.2). Selectivities of different C-H arylated products were determined by the ^{1}H NMR. Results inferred that the formation of monoarylated product (**3g**, 78% selectivity) of 2-chlorothiophene (**2g**) was dominated over the monoarylated product (**3a**, 8% selectivity) of 4-chloroanisole during the competitive arylation. Notably, biarylated product of 2-chlorothiophene was also formed (**4g**, with 14% selectivity), but cross-biarylation was not observed.



Scheme 2.2. *Competitive C-H bond arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**) and 2-chlorothiophene (**2g**) over **[Ru]-4** catalyst.*

It is well established that ruthenium catalyzed C-H bond activation of 2-phenylpyridine is expected to proceed via a five-membered cycloruthenated species.[12,19] In this context, our experimental findings, including extensive mass spectral studies, inferred that the formation of analogous cycloruthenated species during the catalytic C-H bond arylation reaction over **[Ru]-4** complex. Mass spectral analysis of stoichiometric reaction of **[Ru]-4** and 2-phenylpyridine (in 1:2 molar ratio) in acetonitrile with added triethylamine (Et_3N) as base showed a prominent peak appeared at m/z = 390.07 corresponding to the expected cycloruthenated species [(η^6-*p*-cymene)Ru(κ^2-*C*,*N*-phenylpyridine)]$^+$ (**[Ru]-C**) (Figure 2.8). As the reaction was performed in acetonitrile, acetonitrile coordinated peak was also observed at m/z = 431.10 (Figure 2.8). The observed m/z position and mass patterns are in good agreement with the calculated mass pattern of [(η^6-*p*-cymene)Ru(κ^2-*C*,*N*-phenylpyridine)]$^+CH_3CN$ (Figures 2.9). Notably, mass spectral studies of the stoichiometric reaction performed in water, analogous to the catalytic reaction conditions, with complex **[Ru]-4** and 2-phenylpyridine (**1a**) (in 1:2 molar ratio) in the presence of K_2CO_3 (3 equiv.), also showed the formation of analogous cycloruthenated species (**[Ru]-C**). Moreover, cycloruthenated species (**[Ru]-C**) was isolated and characterized by ^{1}H NMR and MS.[12,19] Hence the formation of the

cycloruthenated species **[Ru]-C**, inferred that the studied arene-ruthenium-aniline complexes also followed the analogous reaction pathway for the C-H bond activation by initial *ortho*-C-H bond activation of 2-phenylpyridine in water.

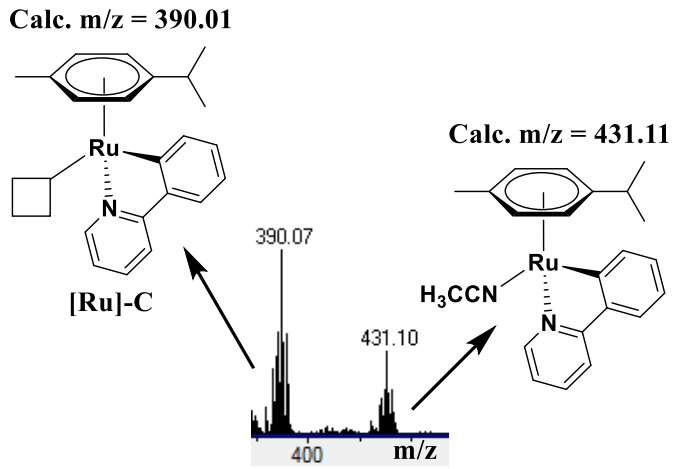
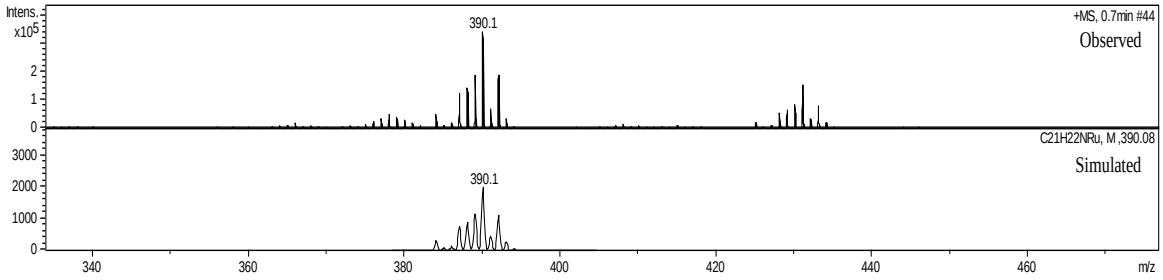


Figure 2.8. *Mass spectral identification of cycloruthenated species for the reaction of* ***[Ru]-4*** *and 2-phenylpyridine (with 1:2 molar ratio) in water.*

(A) [(η⁶-p-cymene)Ru(κ²-C,N-phenylpyridine)]⁺.



(B) [(η⁶-p-cymene)Ru(κ²-C,N-phenylpyridine)(CH₃CN)]⁺.

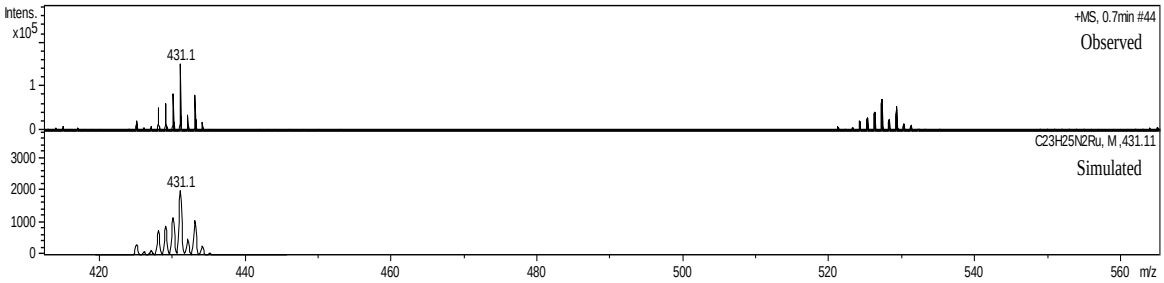
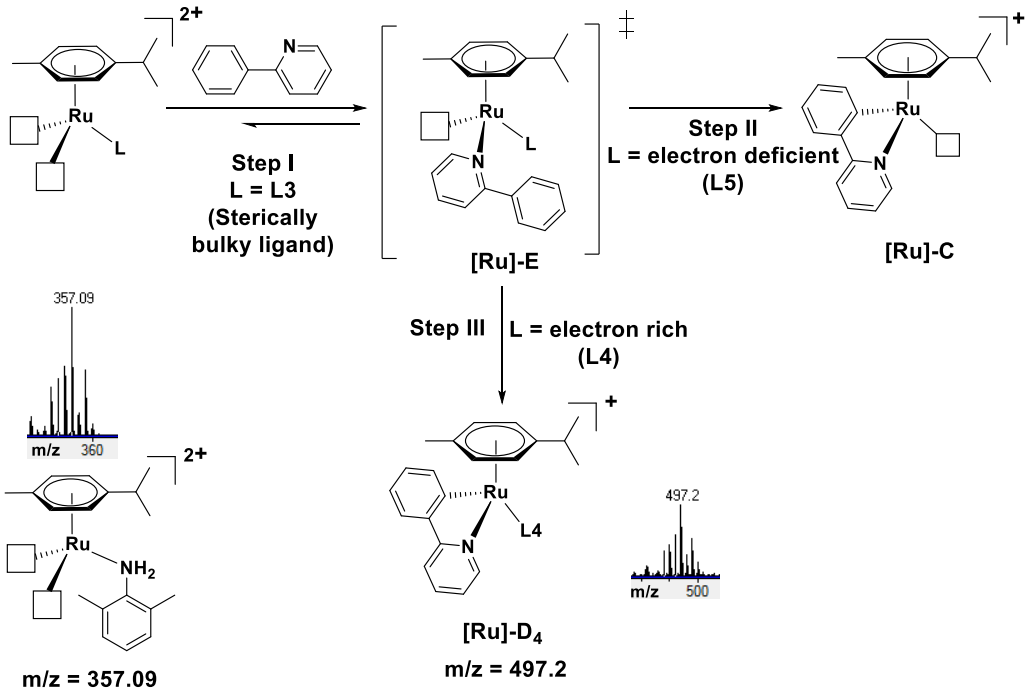


Figure 2.9*. Observed and simulated pattern of cycloruthenated species* ***(A)*** *[(η⁶-p-cymene)Ru(κ²-C,N-phenylpyridine)]⁺ and* ***(B)*** *[(η⁶-p-cymene)Ru(κ²-C,N-phenylpyridine)(CH₃CN)]⁺.*

^{1}H NMR studies inferred that there is a distinct influence of the substituents of the aniline ligands on the catalytic activity of the resulting complexes. To further authenticate this, we performed mass spectral analysis during catalytic C-H bond activation reaction (0-8 h) over **[Ru]-3**, **[Ru]-4** and **[Ru]-5** complexes. In agreement with **[Ru]-4**, analogous cycloruthenated species [(η^6-*p*-cymene)Ru(κ^2-*C,N*-phenylpyridine)]$^+$ was also observed for the complex **[Ru]-3** and **[Ru]-5**. Interestingly, the m/z intensity ratio of cyclometalated species [(η^6-*p*-cymene)Ru(κ^2-*C,N*-phenylpyridine)]$^+$ (**[Ru]-C**, m/z = 390.01) to the molecular ion peak of **[Ru]-5** catalyst [(η^6-*p*-cymene)Ru(**L5**)Cl]$^+$ m/z = 398.11) was found to be 7 and 22 times higher than that observed with **[Ru]-4** and **[Ru]-3** complexes respectively. Interestingly, a ligand bonded cycloruthenated species [(η^6-*p*-cymene)Ru**(L4)**(κ^2-*C,N*-phenylpyridine)]$^+$ **([Ru]-D$_4$)** was also observed for **[Ru]-4**, however an analogous species was not observed for **[Ru]-3** or **[Ru]-5**. These findings suggested that the removal of electron deficient 4-chloroaniline was very facile over 4-methylaniline and 2,6-dimethylaniline from their respective complex under catalytic reaction conditions.

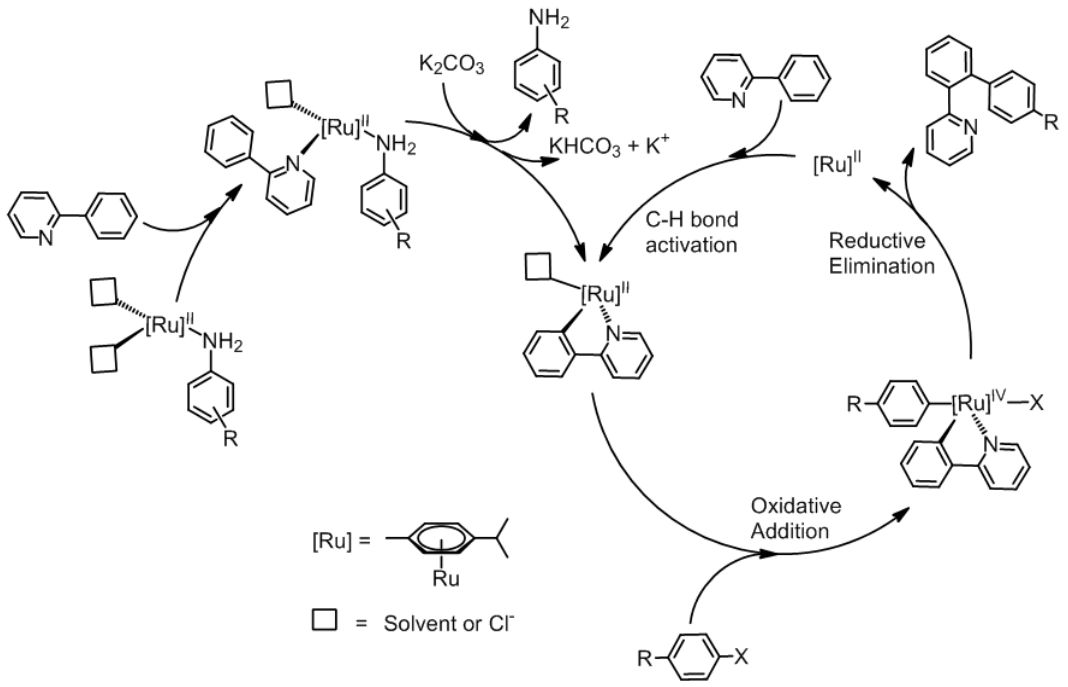
Amongst the studied complexes, removal of sterically bulky, 2,6-dimethylaniline (**L3**) ligand from **[Ru]-3** was appeared to be least favorable which was further supported by the appearance of a peak at m/z = 357.09 corresponding to [(η^6-*p*-cymene)Ru(**L3**)]$^{2+}$. We anticipated that the initial interaction of 2-phenylpyridine with ruthenium catalyst led to the formation of a short-lived intermediate [(η^6-*p*-cymene)Ru(κ^1-*N*-phenylpyridine)(L)]$^{2+}$ (**[Ru]-E**) by following step I (Scheme 2.3). This step is presumably least favorable for **[Ru]-3** having a sterically demanding, 2,6-dimethylaniline (**L3**) ligand, as mass spectral data inferred the formation of cyclometalated species was slowest for **[Ru]-3** compared to **[Ru]-4** and **[Ru]-5**. Further the intermediate such as, **[Ru]-E** undergoes facile transformation to cyclometalated species **[Ru]-C**. Notably, a ligand bounded cycloruthenated species **[Ru]-D** may also form via step III as observed for **[Ru]-4** (Scheme 2.3). Thus, electronic and steric behavior of the coordinating aniline ligands exerts crucial role to tune the catalytic activity of the studied arene-ruthenium-aniline based complexes towards C-H bond activation/arylation of 2-phenylpyridine with aryl halides. It is worthy to mention that the Ru-aniline ligand bonds in the studied complexes displayed high stability towards dissociation in heating in water. As inferred from the

mass spectral analysis, peaks corresponding of the complexes with added solvent molecules, water and/or methanol (as methanol was used for the dilution of the solution) were only observed with no sign of the dissociation of Ru-aniline bond.



Scheme 2.3. *Mass spectral investigation of the formation of cyclometalated species during the ortho-C-H bond activation.*

Notably, reaction of the isolated **[Ru]-C** species with 4-chloroanisole under the optimized reaction conditions afforded the formation of C-H arylated products (**3a** and **3b**) with 49% conversion. Consistent with earlier reports, these results also inferred that the cycloruthenated species **[Ru]-C** is indeed the active species participating in the C-H arylation reaction. [9b, 12, 19, 21] On the basis of experimental and extensive mass spectral investigations a plausible reaction mechanism of *ortho*-C-H bond arylation of 2-phenylpyridine is elaborated in Scheme 2.4.



Scheme 2.4. *Plausible mechanism of ortho-C-H bond arylation of 2-phenylpyridine with (hetero)aryl halides.*

2.3. Conclusions

We developed a new class of phosphine-free water-soluble arene-ruthenium complexes obtained with readily available aniline-based ligands, and successfully employed these complexes for the *ortho*-C-H bond activation and arylation of 2-phenylpyridine with a wide range of (hetero)aryl halides in water. Results inferred that monoarylated products were preferred over biarylated products, where moderate to good yields of the corresponding monoarylated products were achieved. Time-scaled NMR and mass spectral investigation evidenced that aniline ligands, of varying electronic and steric behavior, exerts significant influence on the observed catalytic activity. Moreover, NMR and mass spectral identification of several cycloruthenated species, including those with ligand coordinated cycloruthenated species, further authenticated the crucial role of these species in the catalytic C-H bond activation reaction. Moreover, after spectro-analytical characterization, structural identity of some representative complexes was further confirmed by single crystal X-ray diffraction studies. We believe the findings of the

present work will significantly contribute towards the investigation and development of highly active phosphine-free and water-soluble new catalytic systems for C-H bond activation and functionalization reactions. Further investigations in this direction are underway.

2.4. Experimental Section

2.4.1. Materials and Instrumentations.

All reactions for catalyst preparation were performed without inert gas protection and all the catalytic reactions for C-H bond arylation of 2-phenylpyridine with aryl halides were carried out in Ar atmosphere using chemicals of high purity purchased from Sigma Aldrich and Alfa Aesar. Arene-ruthenium precursors, $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ **[Ru]-A** and $[(\eta^6\text{-benzene})RuCl_2]_2$ **[Ru]-B**, were synthesized according to the literature procedures.[22,23] ^1H NMR(400 MHz), ^{13}C NMR (100 MHz), and ^{19}F NMR (376.5 MHz) spectra were recorded at 298 K using $CDCl_3$ or DMSO-d_6 as the solvent on a Bruker Avance 400 spectrometer. Tetramethylsilane (TMS) was used as an external standard and the chemical shifts in ppm are reported relative to the center of the singlet at 7.26 ppm for $CDCl_3$ and 2.50 ppm for DMSO-d_6 in ^1H NMR and to the center of the triplet at 77.0 ppm for $CDCl_3$ and 39.50 ppm for DMSO-d_6 in ^{13}C NMR. Coupling constants, J values are reported in Hertz (Hz), and the splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br., broad, sept, septet. Single-crystal X-ray structural studies of complexes were carried out using Agilent Technologies Supernova CCD system. Elemental analysis was carried out using a Thermo Scientific FLASH 200 elemental analyzer. High-resolution mass spectra (HRMS) were recorded on amicrOTF-Q II mass spectrometer. Thermal gravimetric analyses (TGA) were performed on the Mettler Toledo thermal analysis system.

2.4.2. Single crystal X-ray diffraction structure determination.

Single crystal X-ray diffraction structural studies of the complexes **[Ru]-1**, **[Ru]-2**, **[Ru]-4** and **[Ru]-5**, from the suitably grown crystals of the complexes by the slow evaporation of methanol-dichloromethane solution of the respective complexes, were carried out using Agilent Technologies Supernova CCD system. Using graphite-monochromated

CuKα radiation (λ = 1.54184 Å) based diffraction, data were collected by the standard 'phi-omega' scan techniques and were scaled and reduced using CrysAlisPro RED software. The extracted data was evaluated using the CrysAlisPro CCD software. Structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares with SHELXL-97, refining on *F2*.[20] The positions of all the atoms were determined by direct methods. All non-hydrogen atoms were refined anisotropically. The remaining hydrogen atoms were placed in geometrically constrained positions, and refined with isotropic temperature factors, generally 1.2*Ueq* of their parent atoms. Unfortunately, X-ray diffraction data for complex **[Ru]-2** was found to be abnormal and could not be further refined to obtain suitable parameters to report. Crystallographic data and bond parameters for the complexes **[Ru]-1**, **[Ru]-4** and **[Ru]-5** are listed in Tables 2.1 – 2.5. CCDC deposition numbers of the complexes **[Ru]-1**, **[Ru]-4** and **[Ru]-5** are 1491603, 1491612 and 1491613, respectively. This data can be obtained free of charge via www.ccdc.cam.ac.uk (or from the Cambridge Crystallographic Data Centre, 12 union Road, Cambridge CB21 EZ, UK; Fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

2.4.3. General procedure for the synthesis of arene-ruthenium-aniline complexes ([Ru]-1 – [Ru]-5.

Dichloro bridged arene-ruthenium precursors [(η^6-*p*-cymene)$RuCl_2$]$_2$ **[Ru]-A**, (0.5 mmol) and the suitable aniline based ligand (1.05 mmol) in methanol (100 mL) were refluxed for 24 h.[15a,17] The resulting solution was filtered, and solvent was removed under reduced pressure. Resulting complexes were characterized using ^{1}H NMR, ^{13}C NMR, ESI-Mass spectrometry, CHN elemental analysis and single crystal X-ray diffraction studies.

(a) Preparation of complex [(η^6-p-cymene)$RuCl_2$(aniline)] ([Ru]-1). Synthesized using [(η^6-*p*-cymene)$RuCl_2$]$_2$ (**[Ru]-A**) (0.306 g, 0.5 mmol) and aniline (95 µL, 1.05 mmol). Orange brown. Yield: 85% (0.339 g). **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 7.37 (s, 5H), 7.22 (br., 1H), 5.02 (d, 2H, *J* = 5.5Hz), 4.91 (d, 2H, *J* = 5.5Hz), 4.88 (br., 1H), 2.86-2.79 (m, 1H), 2.11 (s, 3H), 1.20 (d, 6H, *J* = 8Hz). **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 145.36, 129.51, 125.55, 120.40, 103.51, 95.68, 81.74, 79.67, 30.49, 22.02, 18.58. **Elemental analysis (CHN)** Calculated: C: 48.2; H: 5.30; N: 3.51, Observed: C: 47.7; H: 5.27; N: 3.64. **MS (ESI) m/z** Calculated: 364.040 $[M-Cl]^+$, Observed 364.034 $[M-Cl]^+$.

(b) Preparation of complex [(η^6-p-cymene)$RuCl_2$(2-methylaniline)] ([Ru]-2). Synthesized using [(η^6-*p*-cymene)$RuCl_2$]$_2$ (**[Ru]-A**) (0.306 g, 0.5 mmol) and 2-methylaniline (112 µL, 1.05 mmol). Orange-brown. Yield: 87% (0.279 g). **^{1}H NMR (400 MHz, DMSO)** δ (ppm) = 6.89-6.84 (m, 2H), 6.57 (d, 1H, *J* = 8.0 Hz), 6.45-6.42 (m, 1H), 5.80 (d, 2H, *J* = 4.0 Hz), 5.76 (d, 2H, *J* = 8.0 Hz), 4.75 (bs, 2H, NH_2), 2.84-2.80 (sept, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.19 (d, 6H, *J* = 8.0 Hz). **^{13}C NMR (100 MHz, DMSO)** δ (ppm) = 146.45, 129.82, 126.36, 120.92, 115.99, 113.90, 106.38, 100.08, 86.34, 85.49, 29.96, 21.48, 17.84, **Elemental analysis (CHN)** Calculated: C: 49.40, H: 5.61, N: 3.39, Observed: C: 49.40, H: 5.28, N: 2.71, **MS (ESI) m/z** Calculated: 378.1341 $[M\text{-}Cl]^+$, Observed: 378.0580 $[M\text{-}Cl]^+$.

(c) Preparation of complex [(η^6-p-cymene)$RuCl_2$(2,6-dimethylaniline)] ([Ru]-3). Synthesized using [(η^6-*p*-cymene)$RuCl_2$]$_2$ (**[Ru]-A**) (0.306 g, 0.5 mmol) and 2,6-dimethylaniline (130 µL, 1.05 mmol). Orange color, Yield: 89% (0.267 g).**^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 7.12-7.06 (m, 3H), 5.02 (d, 2H, *J* = 8.0 Hz), 4.83 (d, 2H, *J* = 4.0 Hz), 4.63 (bs, 2H, NH_2), 2.99-2.88 (sept, 1H), 2.43 (s, 6H), 2.01 (s, 3H), 1.31 (d, 6H, *J* = 8.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 141.72, 128.99, 127.79, 125.05, 105.37, 94.38, 82.76, 77.84, 30.82, 22.28, 18.33. **Elemental analysis (CHN)** Calculated: C: 50.59, H: 5.90, N: 3.28, Observed: C: 49.69, H: 5.65, N: 3.70. **MS (ESI) m/z** Calculated: 392.0715 $[M\text{-}Cl]^+$, Observed: 391.0866 $[M\text{-}Cl]^+$.

(d) Preparation of complex [(η^6-p-cymene)$RuCl_2$(4-methylaniline)] ([Ru]-4). Synthesized using [(η^6-*p*-cymene)$RuCl_2$]$_2$ (**[Ru]-A**) (0.306 g, 0.5 mmol) and 4-methylaniline (112 µL, 1.05 mmol). Orange color, Yield: 86% (0.276 g). **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 7.19 (s, 4H), 5.02 (d, 2H, *J* = 8.0 Hz), 4.87 (d, 2H, *J* = 8.0 Hz), 4.67 (bs, 2H, NH_2), 2.95-2.88 (sept, 1H), 2.36 (s, 3H), 2.15 (s, 3H), 1.26 (d, 6H, *J* = 8.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 142.48, 135.32, 130.05, 119.76, 103.50, 95.53, 81.79, 79.56, 30.55, 22.02, 18.55. **Elemental analysis (CHN)** Calculated: C: 49.40, H: 5.61, N: 3.39, Observed: C: 49.99, H: 5.47, N: 3.35, **MS (ESI) m/z** Calculated: 378.0558 $[M\text{-}Cl]^+$, Observed: 378.0593 $[M\text{-}Cl]^+$.

(e) ***Preparation of complex [(η^6-p-cymene)$RuCl_2$(4-chloroaniline)] ([Ru]-5).*** Synthesized using [(η^6-*p*-cymene)$RuCl_2$]$_2$ (**[Ru]-A**) (0.306 g, 0.5 mmol) and 4-chloroaniline (0.134 g, 1.05 mmol). Orange-brown color, Yield: 84% (0.287 g). **^{1}H NMR**

(400 MHz, $CDCl_3$) δ (ppm) = 7.35-7.31 (m, 4H), 5.05 (d, 2H, J = 8.0 Hz), 4.91 (d, 2H, J = 4.0 Hz), 4.79 (bs, 2H, NH_2), 2.92-2.87 (sept, 1H), 2.14 (s, 3H), 1.25 (d, 6H, J = 8.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 129.67, 121.27, 103.75, 95.97, 81.51, 79.52, 30.65, 22.05, 18.59. **Elemental analysis (CHN)** Calculated: C: 44.30, H: 4.65, N: 2.45, Observed C: 44.82, H: 4.62, N: 3.14. **MS (ESI) m/z** Calculated: 398.0009 $[M-Cl]^+$, Observed: 398.0034 $[M-Cl]^+$.

2.4.4. General procedure for C-H bond activation/arylation reaction.

In a two necked reaction flask containing 2-phenylpyridine (0.6 mmol, 86 µL), K_2CO_3 (3 equiv., 1.5 mmol, 0.207 g) and 5 mol % Ru catalysts in 2 mL water, was added 0.5 mmol of arylchloride. Reaction mixture was further degassed using a vacuum pump and then filled with Argon. Reaction mixture was stirred at 80 ºC for the specified reaction time under Argon, after completion of the reaction, it was cooled to room temperature. Crude reaction mixture was extracted with ethyl acetate (3 × 10 mL) and dried over Na_2SO_4. The obtained solid, after removal of solvent under vacuum, was further analyzed by ^{1}H NMR. Products were further separated and purified by column chromatography (ethyl acetate/ hexane 99:1, v/v).

2.4.5. Typical procedure to study the effect of externally added aniline based ligands (L1, L4 and L5) on C-H activation and arylation of 2-phenylpyridine.

Reaction flask containing $[(\eta^6$-*p*-cymene)$RuCl_2]_2$ (**[Ru]-A**) (2.5 mol%) along with 5 mol% ligands (**L1/L4/L5**) in 2 mL water was added K_2CO_3 (1.5 mmol, 0.207 g), and reaction mixture was stirred for 30 min. To this, 2-phenylpyridine (0.6 mmol, 86 µL) and 4-chloroanisole (0.5 mmol, 61 µL) was added and reaction mixture was heated at 80 ºC for 8 h under argon atmosphere. After which, reaction mixture was cooled to room temperature, and the crude reaction mixture was extracted with ethyl acetate (3×10 mL). Combined organic fraction was dried over Na_2SO_4 and volume was reduced in vacuum to obtain the solid reaction product for ^{1}H NMR studies.

2.4.6. Typical procedure for the competitive C-H bond arylation reaction.

In a two necked reaction flask containing 2-phenylpyridine (0.6 mmol, 86 µL), K_2CO_3 (3 equiv.) and 5 mol % **[Ru]-4** catalyst in 2 mL water, was added 0.5 mmol each of 4-

chloroanisole (61 µL) and 2-chlorothiophene (49 µL). Reaction mixture was further degassed with vacuum pump, and then filled with Argon. Reaction mixture was stirred at 80 ºC for 8 h under Argon, and after the specified reaction time, reaction mixture was cooled to room temperature. Crude reaction mixture was extracted with ethyl acetate (3 × 10 mL) and dried over Na_2SO_4. The obtained solid, after removal of solvent under vacuum, was further analyzed by ^1H NMR.

2.4.7. Typical stoichiometric reaction for the identification of cycloruthenated species.

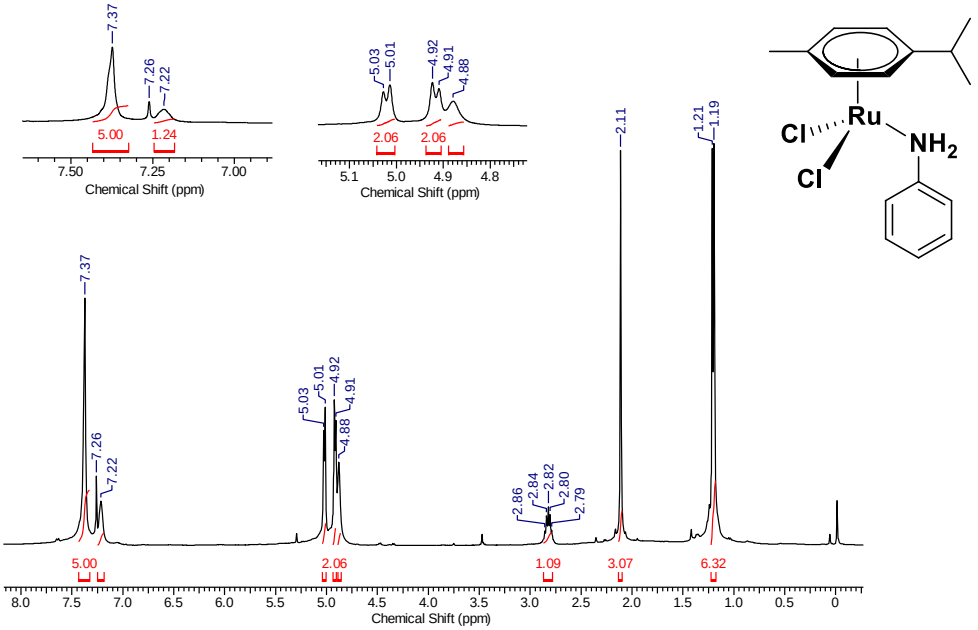
[Ru]-4 (0.03 mmol, 0.0123 g) and 2-phenylpyridine (0.06 mmol, 8.6 µL) in 5 mL acetonitrile were taken in a reaction flask, which was added 2 µL of Et_3N (triethylamine). Reaction flask was degassed with vacuum pump and then filled up with Argon. Reaction mixture was then stirred at 80 ºC for 3 h, and then was cooled to room temperature. Crude reaction mixture was diluted with acetonitrile and analyzed by ESI-MS in positive mode. For reaction performed in water, potassium carbonate (1.5 mmol, 0.207 g) was used instead of triethylamine.

2.4.8. Time-scaled mass spectrometric analysis of the cycloruthenated species.

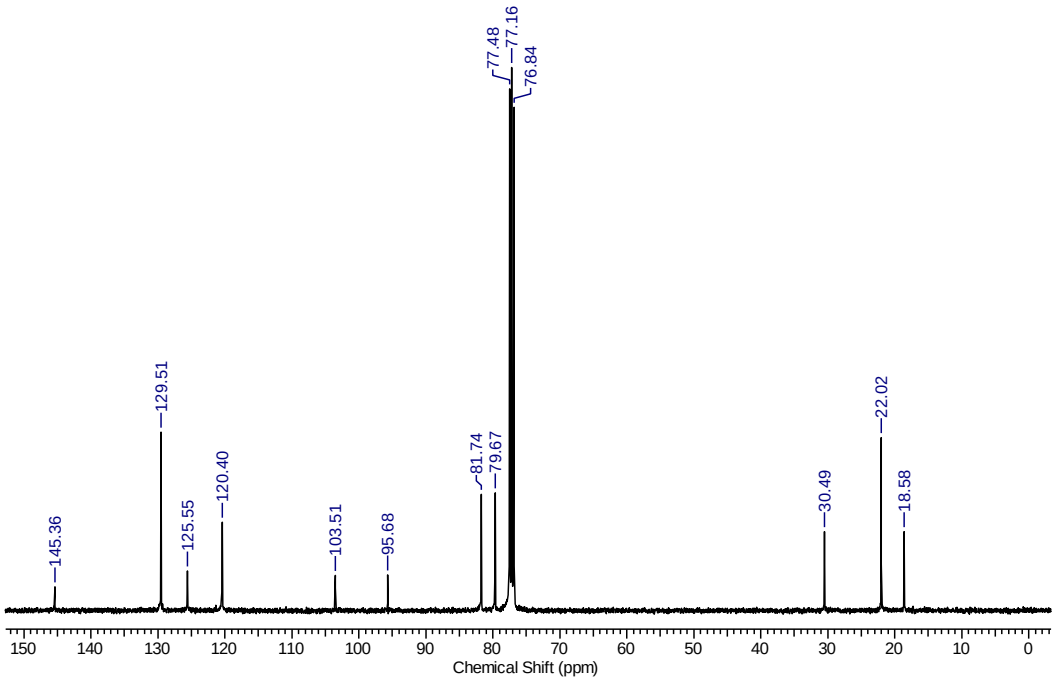
Reaction flask containing **[Ru]-4** (0.025 mmol, 0.0103 g) in 2 mL water was added 2-phenylpyridine (0.6 mmol, 86 µL) and 4-chloroanisole (0.5 mmol, 61 µL). Reaction mixture was heated at 80 ºC under argon for 8 h. 100 µL of aliquot from the reaction mixture was taken out at different intervals of reaction time (2, 4, 6 and 8 h), which was diluted with acetonitrile and ESI-MS was recorded in positive mode. Analogous reactions were also performed using **[Ru]-1**, **[Ru]-3** and **[Ru]-5** complexes.

2.4.9. Characterization of metal complexes

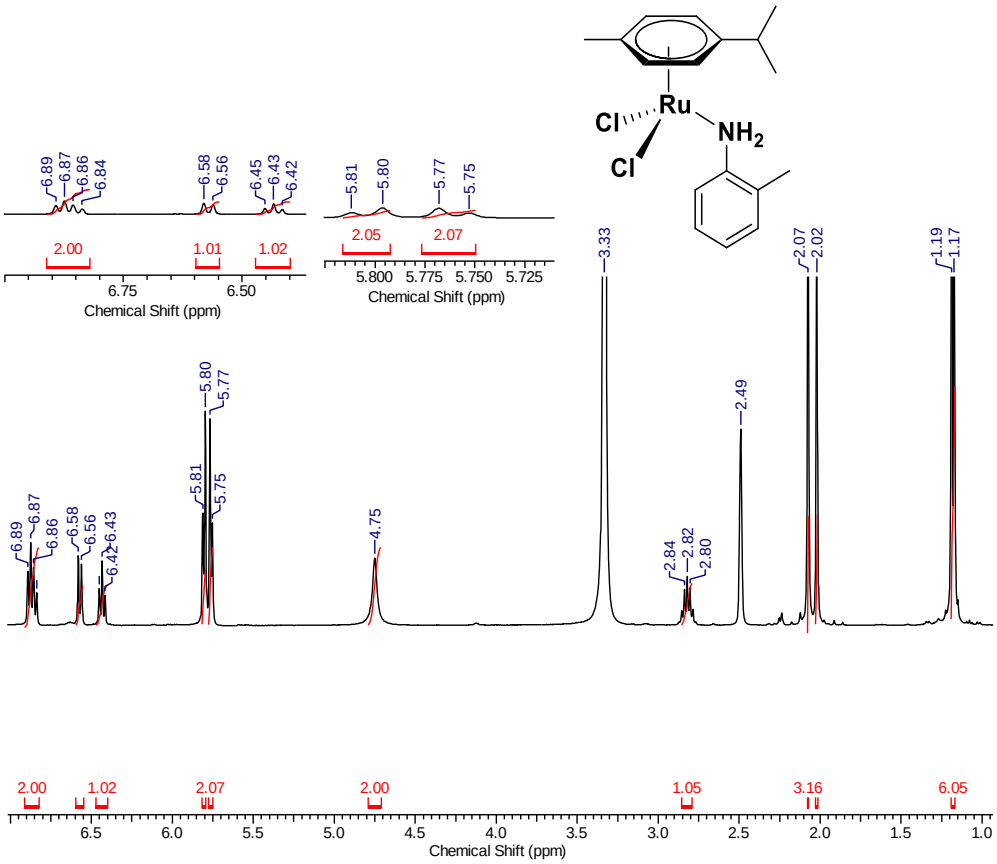
NMR spectra of arene-ruthenium complexes [Ru]-1 to [Ru]-5.



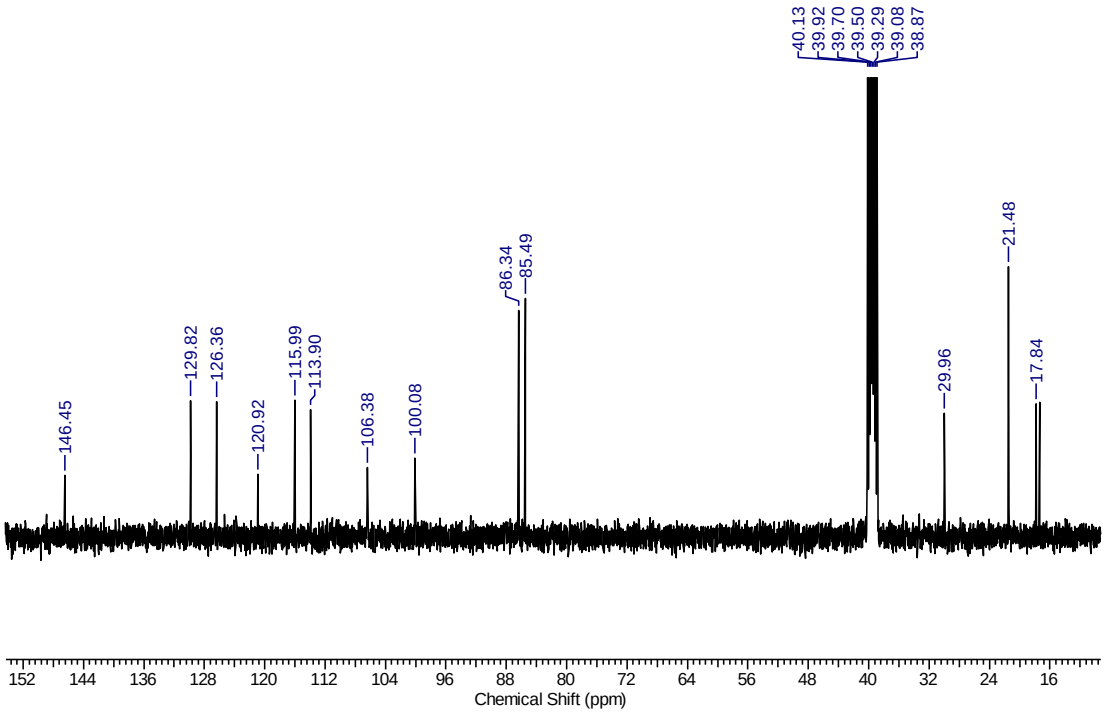
^{1}H NMR of [Ru]-1



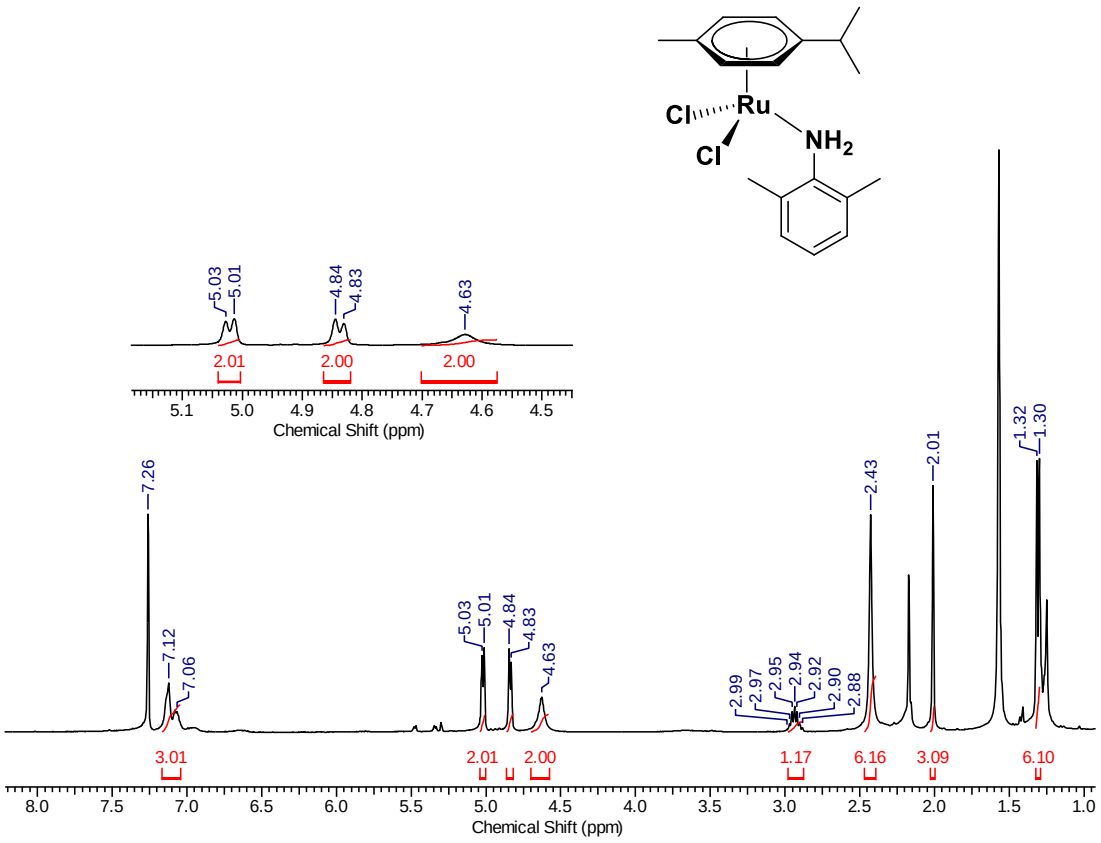
^{13}C NMR of [Ru]-1



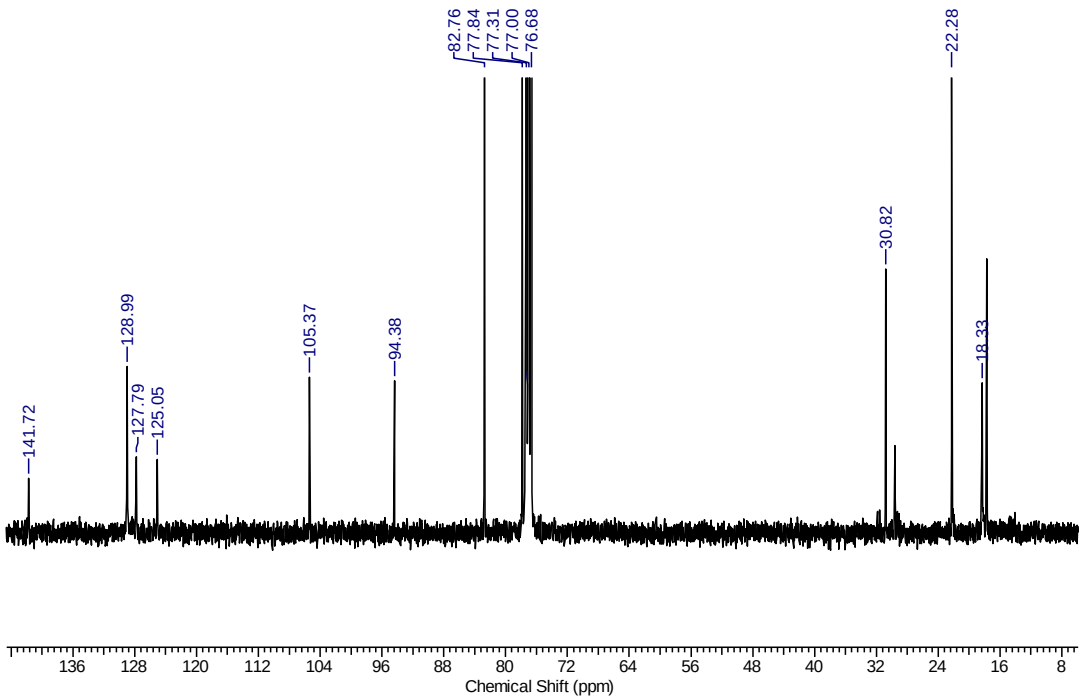
^{1}H NMR of [Ru]-2



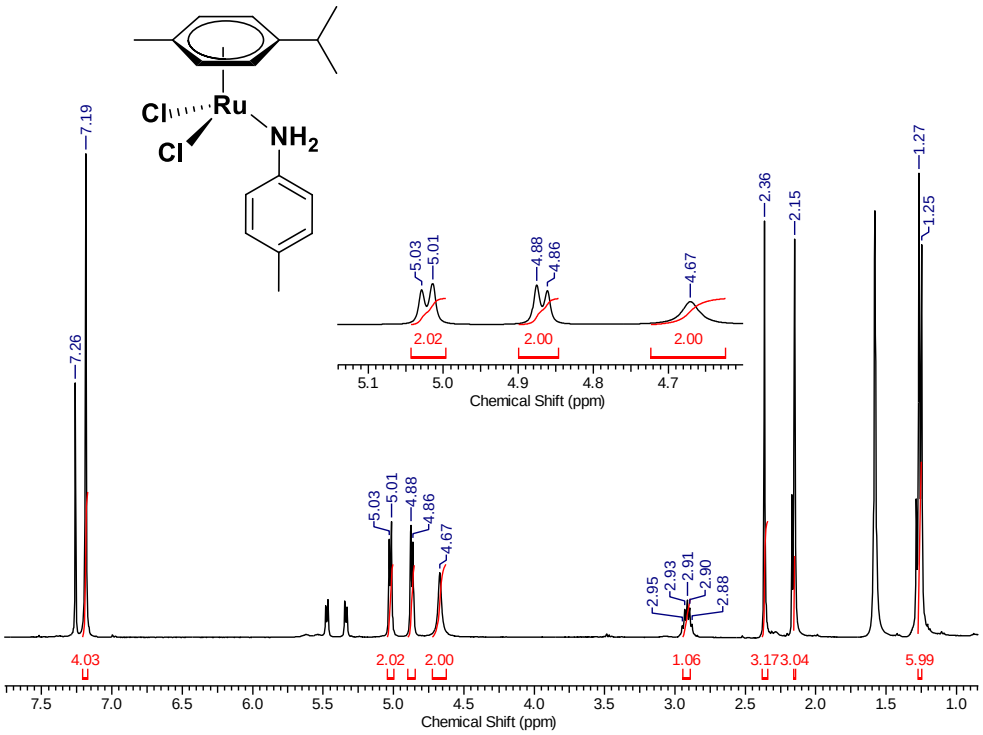
^{13}C NMR of [Ru]-2



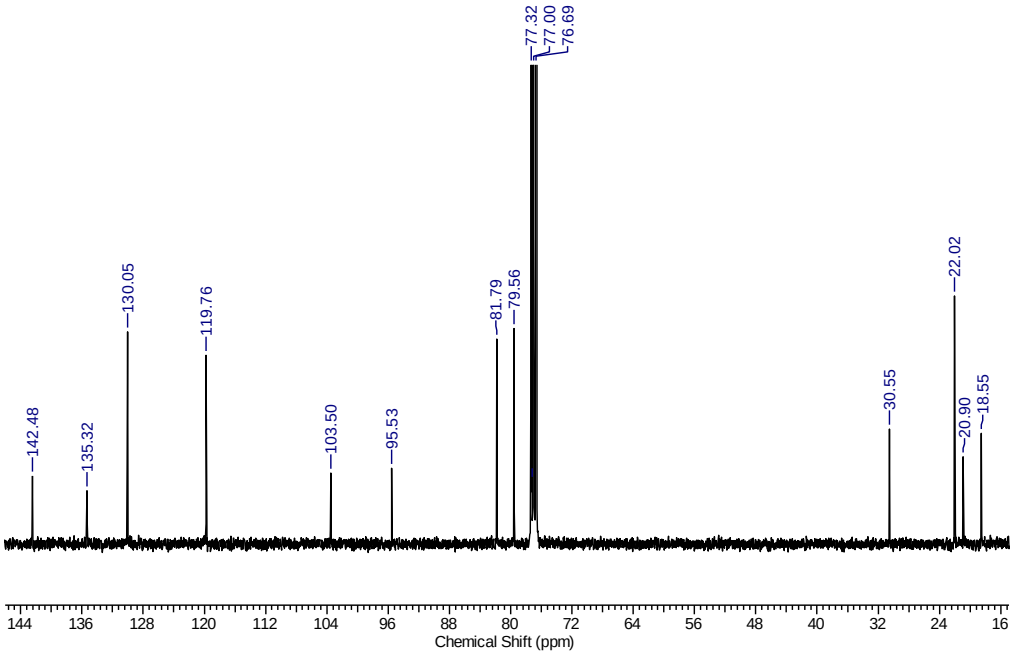
^{1}H NMR of [Ru]-3



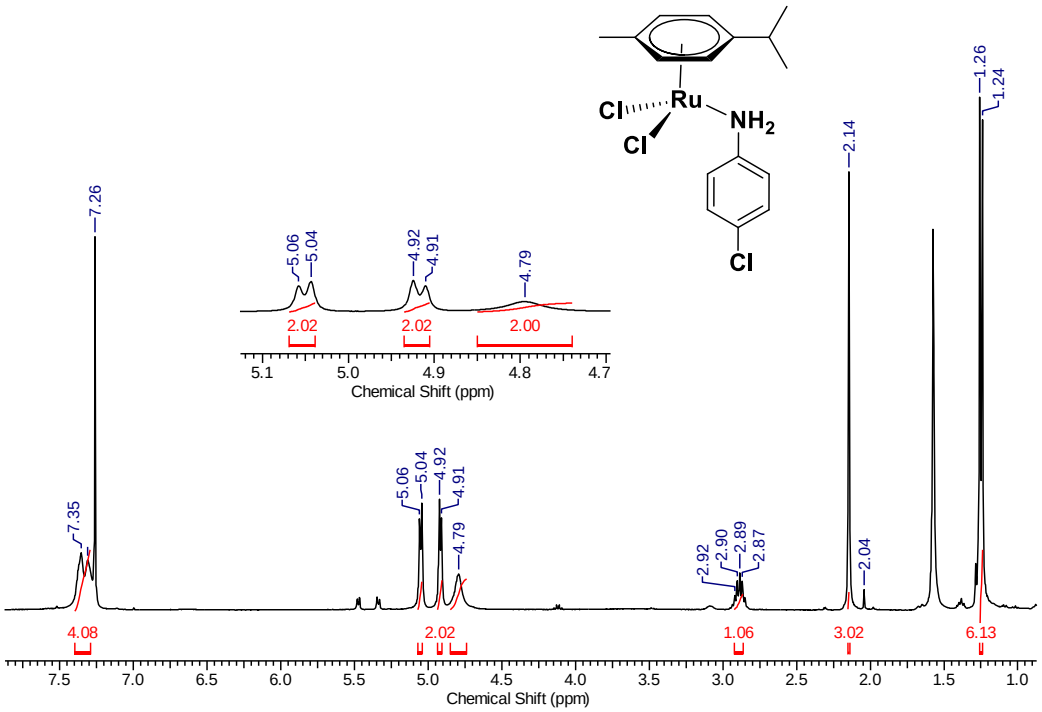
^{13}C NMR of [Ru]-3



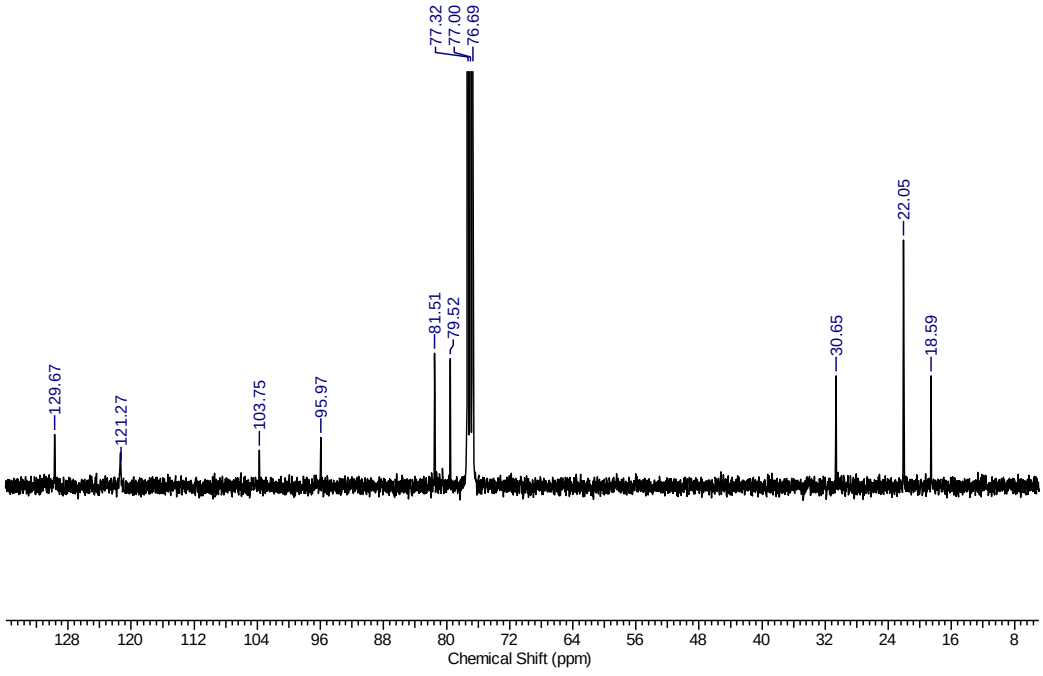
^{1}H NMR of [Ru]-4



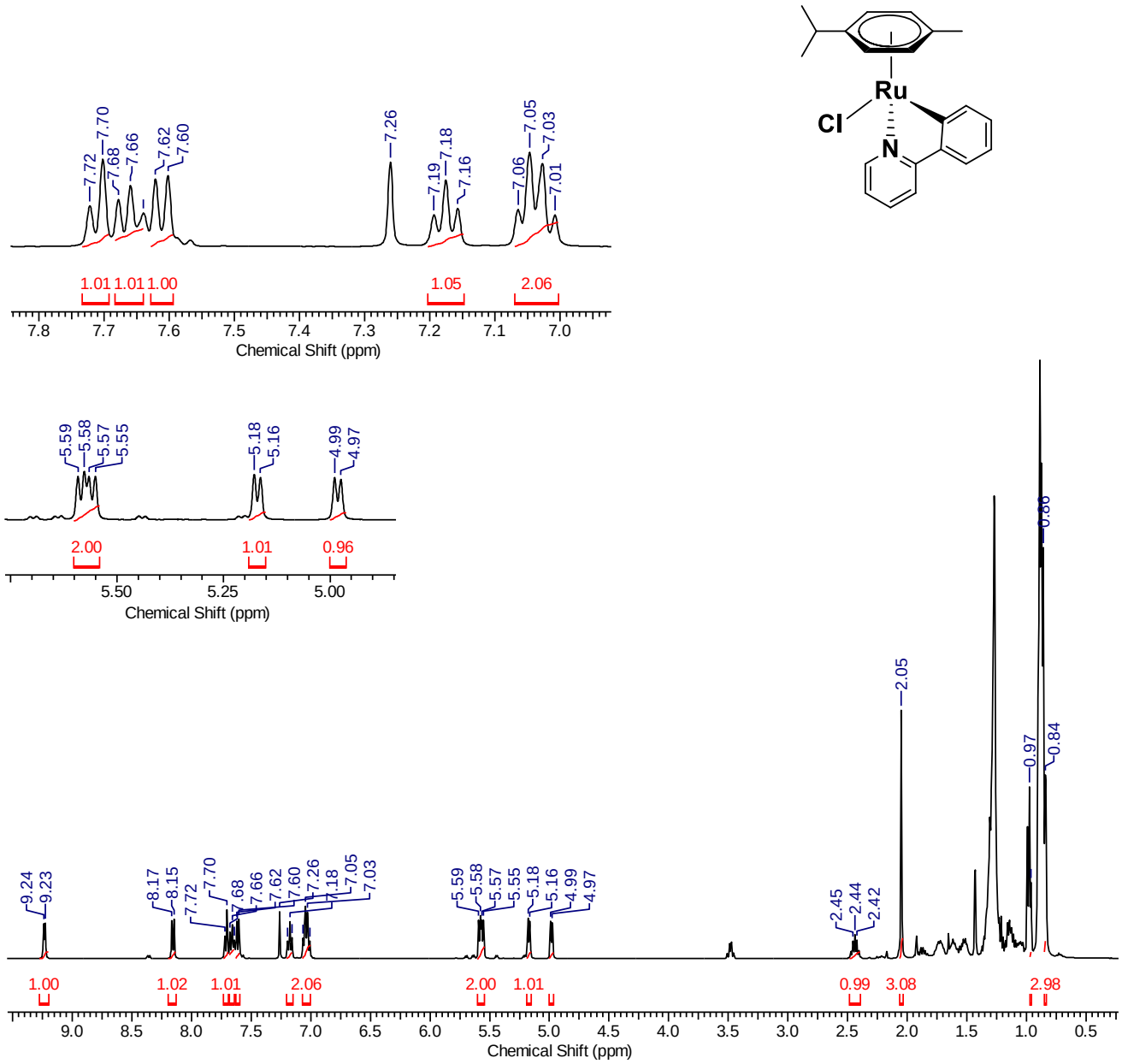
^{13}C NMR of [Ru]-4



^{1}H NMR of [Ru]-5

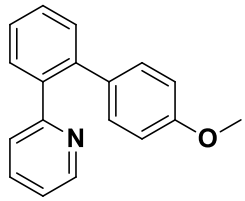


^{13}C NMR of [Ru]-5



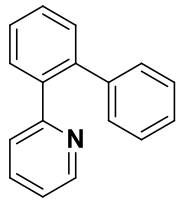
^{1}H NMR of [(η^6-*p*-cymene)Ru(κ^2-*C,N*-2-phenylpyridine)Cl] ([Ru]-C)

2.4.10. Spectral data for the C-H bond arylated products



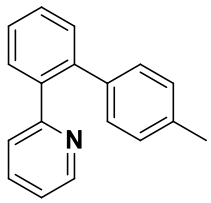
3a

2-(4'-methoxy[1,1'-biphenyl]-2-yl)pyridine (3a).[9a] Yield 76% (198 mg), 8 h. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 8.63 (d, 1H, *J* = 4.0 Hz), 7.68-7.66 (m, 1H), 7.45-7.38 (m, 4H), 7.10 (d, 1H, *J* = 8.0 Hz), 7.07 (d, 2H, *J* = 8.0 Hz), 6.90 (d, 1H, *J* = 8.0 Hz), 6.77 (d, 2H, *J* = 8.0 Hz), 3.78 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 159.4, 158.4, 149.3, 140.1, 139.3, 135.1, 133.6, 130.7, 130.4, 130.3, 128.4, 127.2, 125.3, 121.2, 113.4, 55.1. **HRMS (ESI) m/z** Calculated: 262.1226 ($C_{18}H_{15}NO$ + H), Observed: 262.1276 ($C_{18}H_{15}NO$ + H).



3b

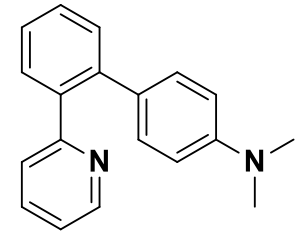
2-([1,1'-biphenyl]-2-yl)pyridine (3b).[9a] Yield 45% (10 mg), 8 h.**^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 8.64 (d, 1H, *J* = 8.0 Hz), 7.71-7.69 (m, 1H), 7.48-7.44 (m, 3H), 7.39-7.36 (m, 1H), 7.23 (d, 3H, *J* = 8.0 Hz), 7.17-7.15 (m, 2H), 7.12-7.09 (m, 1H), 6.89 (d, 1H, *J* = 8.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 159.2, 149.3, 40.6, 135.1, 130.4, 129.7, 128.0, 127.6, 126.6, 125.4, 121.3, **HRMS (ESI) m/z** Calculated: 232.1124 ($C_{17}H_{13}N$ + H), Observed: 232.1121 ($C_{17}H_{13}N$ + H).



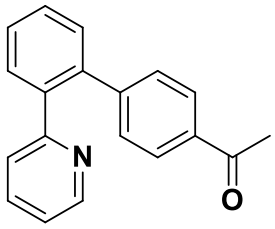
3c

2-(4'-methyl[1,1'-biphenyl]-2-yl)pyridine (3c).[24] Yield 73% (178 mg), 4 h. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 8.63 (d, 1H, *J* = 4.0 Hz), 7.69-7.66 (m, 1H), 7.44-7.39 (m, 3H), 7.38-7.33 (m, 1H), 7.08 (d, 1H, *J* = 8.0 Hz), 7.03 (t, 4H, *J* = 8.0 Hz), 6.89 (d, 1H, *J* = 8.0 Hz), 2.30 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) =159.3, 149.3, 140.5, 139.3, 138.3, 136.2, 135.1, 130.4, 129.5, 128.7, 128.4, 127.3, 125.3, 121.2, 21.0. **HRMS (ESI) m/z** Calculated: 246.1283 ($C_{18}H_{15}N$ + H), Observed: 246.1277 ($C_{18}H_{15}N$ + H).

***N,N*-dimethyl-2'-(pyridin-2-yl)-[1,1'-biphenyl]-4-amine (3d)**.[25] Yield 42% (115 mg), 8 h. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 8.65 (d, 1H, *J* = 4.0 Hz), 7.67 (d, 2H, *J* = 8.0 Hz), 7.43-7.39 (m, 4H), 7.12-7.09 (m, 1H), 7.02 (d, 2H, *J* = 8.0 Hz), 6.94 (d, 1H, *J* = 8.0 Hz), 6.60 (d, 2H, *J* = 16.0 Hz) 2.93 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 159.7, 149.3, 149.3, 140.6, 139.2, 135.1, 130.5, 130.4, 130.3, 129.2, 128.4, 126.7, 125.5, 121.1, 114.0, 112.1. **HRMS (ESI) m/z** Calculated: 275.1511 ($C_{19}H_{18}N_2$ + H), Observed: 275.1543 ($C_{19}H_{18}N_2$ + H).

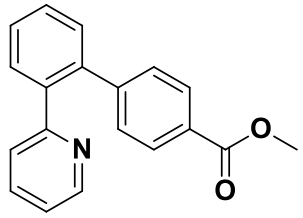


3d



3e

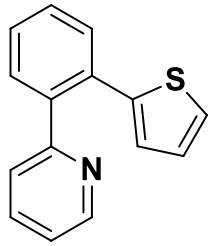
1-(2'-(pyridin-2-yl)-[1,1'-biphenyl]-4-yl)ethanone (3e).[26] Yield 20% (54 mg), 6 h. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 8.63 (d, 1H, *J* = 8.0 Hz), 7.83 (d, 2H, *J* = 8.0 Hz), 7.72-7.69 (m, 1H), 7.52-7.49 (m, 2H), 7.45 (d, 2H, *J* = 8.0 Hz), 7.25 (d, 2H, *J* = 8.0 Hz), 7.17-7.14 (m, 1H), 6.94 (d, 1H, *J* = 8.0 Hz), 2.58 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 197.8, 158.6, 149.1, 139.5, 135.3, 130.6, 129.8, 128.8, 128.1, 125.3, 121.7, 26.5. **HRMS (ESI) m/z** Calculated: 274.1226 ($C_{19}H_{15}NO$ + H), Observed: 274.1268 ($C_{19}H_{15}NO$ + H).



3f

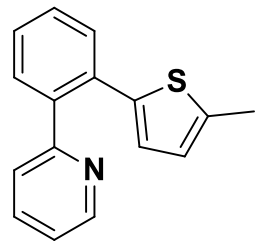
Methyl 2'-(pyridin-2-yl)-[1,1'-biphenyl]-4-carboxylate (3f).[9a] Yield 58% (167 mg), 8 h. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) = 8.60 (d, 1H, *J* = 4.0 Hz), 7.90 (d, 2H, *J* = 8.0 Hz), 7.70-7.68 (m, 1H), 7.50-7.48 (m, 2H), 7.44 (d, 1H, *J* = 8.0 Hz), 7.40 (d, 1H, *J* = 8.0 Hz), 7.22 (d, 2H, *J* = 8.0 Hz) 7.13-7.10 (m, 1H), 6.90 (d, 1H, *J* = 8.0 Hz), 3.89 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) = 171.1, 166.9, 158.7, 149.4, 146.1, 139.5, 139.4, 135.5, 130.5, 129.6, 129.3, 128.6, 128.2, 125.2, 121.5, 52.0. **HRMS (ESI) m/z** Calculated: 290.1176 ($C_{19}H_{15}NO_2$ + H), Obsreved: 290.1145 ($C_{19}H_{15}NO_2$ + H).

2-(2-(2-thienyl)phenyl)pyridine (3g).[9a] Yield 62% (146 mg), 4 h. **^{1}H NMR (400 MHz, CDCl$_3$)** δ (ppm) = 8.67 (d, 1H, *J* = 4.0 Hz), 7.62-7.60 (m, 1H), 7.56-7.50 (m, 2H), 7.45-7.43 (m, 2H), 7.22-7.17 (m, 2H) 7.14 (d, 1H, *J* = 8.0 Hz), 6.91-6.88 (m, 1H), 6.70 (d, 1H, *J* = 4.0 Hz). **^{13}C NMR (100 MHz, CDCl$_3$)** δ (ppm) = 159.2, 149.3, 142.8, 139.7, 139.2, 135.5, 130.6, 130.5, 128.5, 128.0, 127.0, 126.4, 125.6, 124.9, 121.7, **HRMS (ESI) m/z** Calculated: 238.0685 ($C_{15}H_{11}NS$ + H), Observed: 238.0755 ($C_{15}H_{11}NS$ + H).



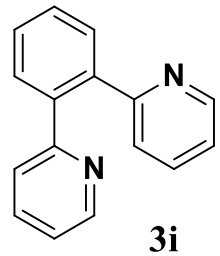
3g

2-(2-(5-methylthiophen-2-yl)phenyl)pyridine (3h).[9a] Yield 53% (133 mg), 4 h. **^{1}H NMR (400 MHz, CDCl$_3$)** δ (ppm) = 8.69 (d, 1H, *J* = 4.0 Hz), 7.58 (d, 1H, *J* = 8.0 Hz), 7.55-7.50 (m, 2H), 7.42 (d, 2H, *J* =8.0 Hz), 7.23-7.18 (m, 2H) 6.52 (d, 1H, *J* = 4.0 Hz), 6.45 (d, 1H, *J* = 4.0 Hz), 2.42 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ (ppm) = 159.1, 148.7, 140.3, 140.2, 135.9, 133.4, 130.6, 130.5, 128.6, 127.2, 126.9, 125.4, 15.2, 14.1. **HRMS (ESI) m/z** Calculated: 252.0841 ($C_{16}H_{13}NS$ + H), Observed: 252.0862 ($C_{16}H_{13}NS$ + H).

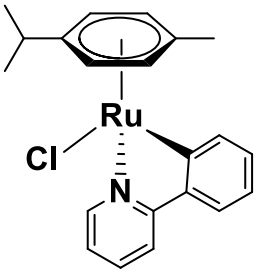


3h

1,2-di(pyridin-2-yl)benzene (3i).[9a] Yield 23% (53 mg), 8 h. **^{1}H NMR (400 MHz, CDCl$_3$)** δ (ppm) =8.61 (d, 1H, *J* = 4.0 Hz), 7.69-7.67 (m, 1H), 7.53-7.51 (m, 1H), 7.48-7.44 (m, 1H), 7.15-7.12 (m, 1H), 6.99 (d, 2H, *J* = 8.0 Hz). **^{13}C NMR (100 MHz, CDCl$_3$)** δ (ppm) = 159.1, 149.2, 139.5, 135.6, 130.3, 128.6, 125.5, 121.5. **HRMS (ESI) m/z** Calculated: 233.1073 ($C_{16}H_{12}N_2$ + H), Observed: 233.1158 ($C_{16}H_{12}N_2$ + H).

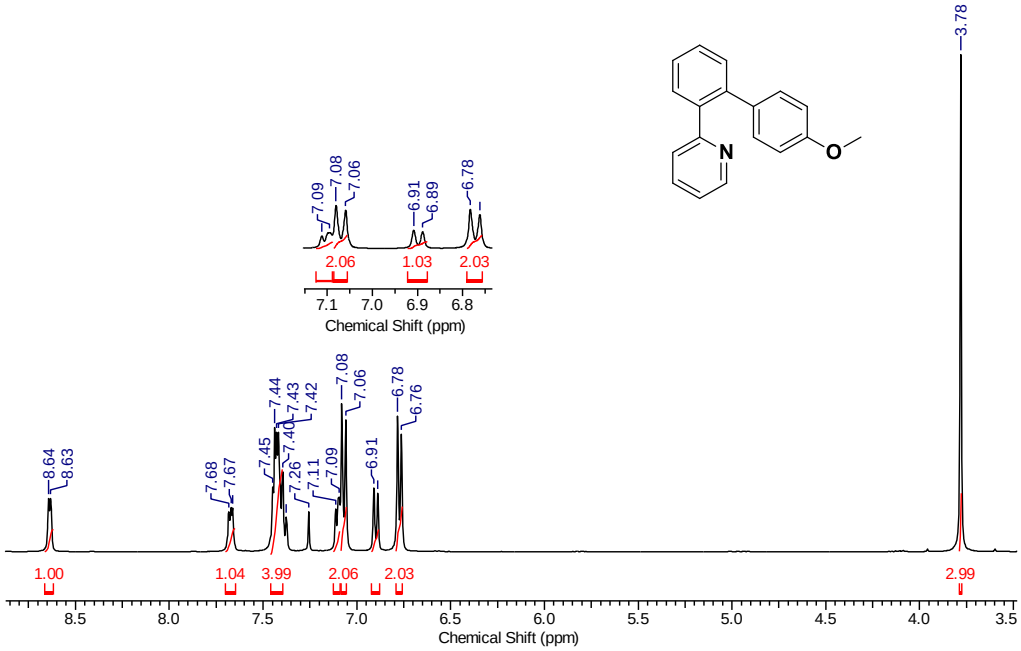


3i

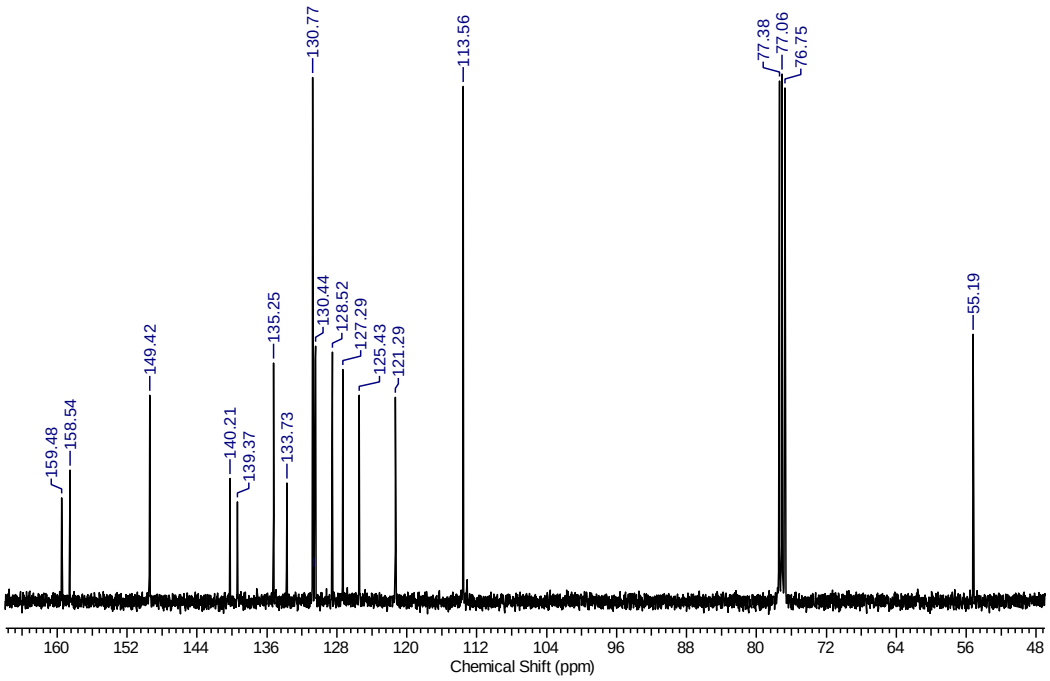


[(η^6-*p*-cymene)Ru(κ^2-*C,N*-phenylpyridine)Cl] ([Ru]-C)[27]. ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) = 9.24 (d, 1H, *J* = 4.0 Hz), 8.16 (d, 1H, *J* = 8.0 Hz), 7.71 (d, 1H, *J* = 8.0 Hz), 7.68-7.64 (m, 1H), 7.62 (d, 1H, *J* = 8.0 Hz), 7.19-7.17 (m, 1H), 7.06-7.01 (m, 2H), 5.59-5.55 (m, 2H), 5.17 (d, 1H, *J* = 8.0 Hz), 4.98 (d, 1H, *J* = 8.0 Hz), 2.45-2.42 (m, 1H), 2.05 (s, 3H), 0.97 (d, 3H, *J* = 4.0 Hz), 0.85 (d, 3H, *J* = 8.0 Hz).

2.4.11. NMR spectra of C-H activated monoarylated product 3a



^{1}H NMR spectra of compound 3a



^{13}C NMR spectra of compound 3a

Table 2.6. *Selected bond lengths [Å] of ruthenium(II) complexes.*

	[Ru]-1	**[Ru]-4**	**[Ru]-5**
Ru(1)-C(12)	2.128(3)	2.187(2)	-
Ru(1)-C(8)	2.153(4)	-	2.206(3)
Ru(1)-N(1)	2.180(3)	2.1632(19)	2.178(2)
Ru(1)-C(7)	2.180(4)	-	-
Ru(1)-C(11)	2.189(4)	2.159(2)	2.192(3)
Ru(1)-C(9)	2.189(4)	2.195(2)	2.172(3)
Ru(1)-C(10)	2.231(3)	2.165(2)	2.155(2)
Ru(1)-Cl(1)	2.4068(9)	2.4184(6)	2.4243(7)
Ru(1)-Cl(2)	2.4171(9)	2.4182(6)	2.4210(7)
N(1)-C(1)	1.437(4)	1.440(3)	1.440(3)
N(1)-H(1A)	0.9200	0.9200	0.8900
N(1)-H(1B)	0.9200	0.9200	0.8900
C(1)-C(6)	1.380(5)	-	1.383(4)
C(1)-C(2)	1.388(5)	1.387(3)	1.381(4)
C(2)-C(3)	1.394(6)	1.384(3)	1.377(4)
C(3)-C(4)	1.373(8)	1.376(4)	1.382(5)
C(4)-C(5)	1.385(7)	1.511(4)	1.371(4)
C(4)-Cl(3)	-	-	1.744(3)
C(5)-C(6)	1.385(6)	-	1.389(4)
C(7)-C(8)	1.418(6)	-	1.501(4)
C(7)-C(12)	1.421(6)	-	-
C(7)-C(14)	1.510(6)	-	-
C(8)-C(9)	1.414(6)	1.503(3)	1.417(4)
C(9)-C(10)	1.405(6)	1.409(3)	1.426(4)
C(10)-C(11)	1.414(5)	1.420(3)	1.416(4)
C(10)-C(13)	1.498(5)	-	-
C(11)-C(12)	1.411(6)	1.407(3)	1.511(4)
C(14)-C(15)	1.521(6)	-	-

Table 2.7. *Selected bond angles [deg] of complex* ***[Ru]-1****.*

C(12)-Ru(1)-C(8)	68.44(15)	C(1)-N(1)-H(1B)	107.2
C(12)-Ru(1)-N(1)	91.82(13)	Ru(1)-N(1)-H(1B)	107.2
C(8)-Ru(1)-N(1)	139.36(14)	H(1A)-N(1)-H(1B)	106.8
C(12)-Ru(1)-C(7)	38.48(15)	C(6)-C(1)-C(2)	120.6(3)
C(8)-Ru(1)-C(7)	38.19(15)	C(6)-C(1)-N(1)	119.5(3)
N(1)-Ru(1)-C(7)	105.50(13)	C(2)-C(1)-N(1)	119.9(3)
C(12)-Ru(1)-C(11)	38.11(15)	C(1)-C(2)-C(3)	118.7(4)
C(8)-Ru(1)-C(11)	80.84(15)	C(4)-C(3)-C(2)	121.2(4)
N(1)-Ru(1)-C(11)	105.68(13)	C(3)-C(4)-C(5)	119.2(4)
C(7)-Ru(1)-C(11)	69.46(16)	C(4)-C(5)-C(6)	120.6(4)
C(12)-Ru(1)-C(9)	80.30(15)	C(1)-C(6)-C(5)	119.6(4)
C(8)-Ru(1)-C(9)	38.02(15)	C(8)-C(7)-C(12)	116.0(4)
N(1)-Ru(1)-C(9)	172.04(13)	C(8)-C(7)-C(14)	123.8(4)
C(7)-Ru(1)-C(9)	68.92(15)	C(12)-C(7)-C(14)	120.2(4)
C(11)-Ru(1)-C(9)	67.33(14)	C(8)-C(7)-Ru(1)	69.9(2)
C(12)-Ru(1)-C(10)	68.01(15)	C(12)-C(7)-Ru(1)	68.8(2)
C(8)-Ru(1)-C(10)	68.06(15)	C(14)-C(7)-Ru(1)	132.5(3)
N(1)-Ru(1)-C(10)	138.26(13)	C(9)-C(8)-C(7)	121.6(4)
C(7)-Ru(1)-C(10)	81.55(15)	C(9)-C(8)-Ru(1)	72.4(2)
C(11)-Ru(1)-C(10)	37.32(14)	C(7)-C(8)-Ru(1)	72.0(2)
C(9)-Ru(1)-C(10)	37.05(14)	C(10)-C(9)-C(8)	121.0(4)
C(12)-Ru(1)-Cl(1)	136.26(11)	C(10)-C(9)-Ru(1)	73.1(2)

C(8)-Ru(1)-Cl(1)	87.15(11)	C(8)-C(9)-Ru(1)	69.6(2)
N(1)-Ru(1)-Cl(1)	83.74(9)	C(9)-C(10)-C(11)	118.8(4)
C(7)-Ru(1)-Cl(1)	101.15(11)	C(9)-C(10)-C(13)	120.6(4)
C(11)-Ru(1)-Cl(1)	167.99(12)	C(11)-C(10)-C(13)	120.6(4)
C(9)-Ru(1)-Cl(1)	102.71(10)	C(9)-C(10)-Ru(1)	69.9(2)
C(10)-Ru(1)-Cl(1)	136.22(10)	C(11)-C(10)-Ru(1)	69.7(2)
C(12)-Ru(1)-Cl(2)	134.43(11)	C(13)-C(10)-Ru(1)	130.1(3)
C(8)-Ru(1)-Cl(2)	138.94(11)	C(12)-C(11)-C(10)	119.4(3)
N(1)-Ru(1)-Cl(2)	80.23(8)	C(12)-C(11)-Ru(1)	68.6(2)
C(7)-Ru(1)-Cl(2)	169.79(11)	C(10)-C(11)-Ru(1)	72.9(2)
C(11)-Ru(1)-Cl(2)	101.02(11)	C(11)-C(12)-C(7)	123.1(3)
C(9)-Ru(1)-Cl(2)	104.46(12)	C(11)-C(12)-Ru(1)	73.3(2)
C(10)-Ru(1)-Cl(2)	88.57(11)	C(7)-C(12)-Ru(1)	72.7(2)
Cl(1)-Ru(1)-Cl(2)	87.76(3)	C(7)-C(14)-C(15)	109.4(4)
C(1)-N(1)-Ru(1)	120.5(2)	C(7)-C(14)-C(16)	114.1(4)
C(1)-N(1)-H(1A)	107.2	C(15)-C(14)-C(16)	110.3(5)
Ru(1)-N(1)-H(1A)	107.2		

Table 2.8. *Selected bond angles [deg] of complex* ***[Ru]-4****.*

C(11)-Ru(1)-C(13)	68.34(8)	Ru(1)-N(1)-H(1B)	106.8
C(11)-Ru(1)-N(1)	92.62(8)	H(1A)-N(1)-H(1B)	106.7
C(11)-Ru(1)-C(10)	38.33(9)	C(7)-C(1)-C(2)	119.6(2)
C(13)-Ru(1)-C(10)	80.78(9)	C(7)-C(1)-N(1)	120.0(2)
N(1)-Ru(1)-C(10)	100.07(8)	C(2)-C(1)-N(1)	120.4(2)

C(11)-Ru(1)-C(14)	80.90(9)	C(3)-C(2)-C(1)	120.2(2)
C(13)-Ru(1)-C(14)	37.60(9)	C(4)-C(3)-C(2)	121.2(2)
N(1)-Ru(1)-C(14)	167.32(8)	C(3)-C(4)-C(6)	117.4(2)
C(10)-Ru(1)-C(14)	68.13(9)	C(3)-C(4)-C(5)	120.8(3)
C(11)-Ru(1)-C(12)	37.77(8)	C(6)-C(4)-C(5)	121.7(3)
C(13)-Ru(1)-C(12)	38.30(9)	C(7)-C(6)-C(4)	122.0(2)
N(1)-Ru(1)-C(12)	112.26(8)	C(1)-C(7)-C(6)	119.5(2)
C(10)-Ru(1)-C(12)	68.83(9)	C(10)-C(9)-C(14)	118.7(2)
C(14)-Ru(1)-C(12)	68.76(8)	C(10)-C(9)-C(8)	121.1(2)
C(11)-Ru(1)-C(9)	68.75(9)	C(14)-C(9)-C(8)	120.2(2)
C(13)-Ru(1)-C(9)	68.33(9)	C(10)-C(9)-Ru(1)	70.00(12)
N(1)-Ru(1)-C(9)	129.49(8)	C(14)-C(9)-Ru(1)	70.63(13)
C(10)-Ru(1)-C(9)	37.71(9)	C(8)-C(9)-Ru(1)	129.66(17)
C(14)-Ru(1)-C(9)	37.90(9)	C(9)-C(10)-C(11)	120.7(2)
C(12)-Ru(1)-C(9)	81.60(9)	C(9)-C(10)-Ru(1)	72.29(13)
C(11)-Ru(1)-Cl(2)	123.94(6)	C(11)-C(10)-Ru(1)	70.60(12)
C(13)-Ru(1)-Cl(2)	89.77(6)	C(12)-C(11)-C(10)	121.0(2)
N(1)-Ru(1)-Cl(2)	80.15(5)	C(12)-C(11)-Ru(1)	72.19(12)
C(10)-Ru(1)-Cl(2)	162.16(7)	C(10)-C(11)-Ru(1)	71.07(12)
C(14)-Ru(1)-Cl(2)	112.52(7)	C(11)-C(12)-C(13)	117.8(2)
C(12)-Ru(1)-Cl(2)	94.41(6)	C(11)-C(12)-C(15)	122.3(2)
C(9)-Ru(1)-Cl(2)	149.43(7)	C(13)-C(12)-C(15)	119.9(2)
C(11)-Ru(1)-Cl(1)	145.52(6)	C(11)-C(12)-Ru(1)	70.04(12)

C(13)-Ru(1)-Cl(1)	127.41(7)	C(13)-C(12)-Ru(1)	69.80(12)
N(1)-Ru(1)-Cl(1)	82.61(6)	C(15)-C(12)-Ru(1)	131.10(17)
C(10)-Ru(1)-Cl(1)	108.76(7)	C(14)-C(13)-C(12)	121.7(2)
C(14)-Ru(1)-Cl(1)	96.54(6)	C(14)-C(13)-Ru(1)	72.16(13)
C(12)-Ru(1)-Cl(1)	165.10(6)	C(12)-C(13)-Ru(1)	71.89(13)
C(9)-Ru(1)-Cl(1)	88.08(6)	C(13)-C(14)-C(9)	120.1(2)
Cl(2)-Ru(1)-Cl(1)	89.01(2)	C(13)-C(14)-Ru(1)	70.25(13)
C(1)-N(1)-Ru(1)	122.08(13)	C(9)-C(14)-Ru(1)	71.47(13)
C(1)-N(1)-H(1A)	106.8	C(16)-C(15)-C(12)	114.0(2)
Ru(1)-N(1)-H(1A)	106.8	C(16)-C(15)-C(17)	110.4(2)
C(1)-N(1)-H(1B)	106.8	C(12)-C(15)-C(17)	107.8(2)

Table 2.9. *Selected bond angles [deg] of complex* ***[Ru]-5****.*

C(10)-Ru(1)-C(15)	68.40(11)	C(1)-N(1)-H(1B)	107.1
C(10)-Ru(1)-C(9)	38.48(11)	H(1A)-N(1)-H(1B)	106.8
C(15)-Ru(1)-C(9)	80.70(11)	C(2)-C(1)-C(6)	119.8(3)
C(10)-Ru(1)-N(1)	92.28(10)	C(2)-C(1)-N(1)	119.3(2)
C(15)-Ru(1)-N(1)	147.81(10)	C(6)-C(1)-N(1)	120.9(2)
C(9)-Ru(1)-N(1)	100.35(10)	C(3)-C(2)-C(1)	120.0(3)
C(10)-Ru(1)-C(16)	81.09(11)	C(2)-C(3)-C(4)	119.6(3)
C(15)-Ru(1)-C(16)	37.50(11)	C(5)-C(4)-C(3)	121.3(3)
C(9)-Ru(1)-C(16)	68.17(12)	C(5)-C(4)-Cl(3)	120.1(3)
N(1)-Ru(1)-C(16)	167.84(10)	C(3)-C(4)-Cl(3)	118.6(3)

C(10)-Ru(1)-C(11)	38.00(10)	C(4)-C(5)-C(6)	118.7(3)
C(15)-Ru(1)-C(11)	38.22(11)	C(1)-C(6)-C(5)	120.5(3)
C(9)-Ru(1)-C(11)	69.07(11)	C(9)-C(8)-C(16)	118.6(3)
N(1)-Ru(1)-C(11)	111.77(10)	C(9)-C(8)-C(7)	120.4(3)
C(16)-Ru(1)-C(11)	68.77(11)	C(16)-C(8)-C(7)	120.9(3)
C(10)-Ru(1)-C(8)	68.92(11)	C(9)-C(8)-Ru(1)	69.84(16)
C(15)-Ru(1)-C(8)	68.08(11)	C(16)-C(8)-Ru(1)	70.32(16)
C(9)-Ru(1)-C(8)	37.77(11)	C(7)-C(8)-Ru(1)	129.2(2)
N(1)-Ru(1)-C(8)	130.18(10)	C(8)-C(9)-C(10)	120.5(3)
C(16)-Ru(1)-C(8)	37.79(11)	C(8)-C(9)-Ru(1)	72.40(16)
C(11)-Ru(1)-C(8)	81.64(11)	C(10)-C(9)-Ru(1)	70.13(14)
C(10)-Ru(1)-Cl(2)	124.67(8)	C(11)-C(10)-C(9)	121.1(3)
C(15)-Ru(1)-Cl(2)	89.70(7)	C(11)-C(10)-Ru(1)	72.40(14)
C(9)-Ru(1)-Cl(2)	162.94(8)	C(9)-C(10)-Ru(1)	71.40(14)
N(1)-Ru(1)-Cl(2)	80.34(6)	C(10)-C(11)-C(15)	117.3(3)
C(16)-Ru(1)-Cl(2)	111.81(8)	C(10)-C(11)-C(12)	121.8(3)
C(11)-Ru(1)-Cl(2)	94.70(8)	C(15)-C(11)-C(12)	120.9(3)
C(8)-Ru(1)-Cl(2)	148.48(9)	C(10)-C(11)-Ru(1)	69.60(14)
C(10)-Ru(1)-Cl(1)	144.73(8)	C(15)-C(11)-Ru(1)	69.75(15)
C(15)-Ru(1)-Cl(1)	127.75(8)	C(12)-C(11)-Ru(1)	131.1(2)
C(9)-Ru(1)-Cl(1)	107.94(8)	C(11)-C(12)-C(14)	113.8(3)
N(1)-Ru(1)-Cl(1)	82.94(6)	C(11)-C(12)-C(13)	108.3(3)
C(16)-Ru(1)-Cl(1)	96.56(8)	C(14)-C(12)-C(13)	111.1(3)

C(11)-Ru(1)-Cl(1)	165.22(8)	C(16)-C(15)-C(11)	122.2(3)
C(8)-Ru(1)-Cl(1)	87.66(8)	C(16)-C(15)-Ru(1)	72.15(16)
Cl(2)-Ru(1)-Cl(1)	89.09(3)	C(11)-C(15)-Ru(1)	72.03(16)
C(1)-N(1)-Ru(1)	120.77(17)	C(15)-C(16)-C(8)	120.3(3)
Ru(1)-N(1)-H(1A)	107.1	C(15)-C(16)-Ru(1)	70.35(17)
C(1)-N(1)-H(1A)	107.1	C(8)-C(16)-Ru(1)	71.89(17)
Ru(1)-N(1)-H(1B)	107.1		

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2.5 References

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Chapter 3

Ligand-tuned C-H bond activation/arylation of 2-arylpyridines over pyridine-based *N,O/N,N* ligated arene-ruthenium complexes

3.1. Introduction

C-H bond activation and functionalization is a promising and efficient strategy to synthesize a wide range of organic compounds in a step economical way.[1] C-H bond activation/functionalization reactions not only reduce time and efforts in long and tedious organic transformations, but also generate less waste and undesired side products. Therefore, to serve this purpose, several methodologies have been developed to activate the otherwise un-reactive C-H bonds. Among these methodologies, the functional group directed C-H bond activation and functionalization has emerged as an efficient way to achieve tuned regioselectivity.[1-2] The key feature of this strategy is to exploit the Lewis basic site of substrate to bring the transition metal in the close proximity of the targeted C-H bond to facilitate deprotonation – *a concerted metalation and deprotonation mechanistic pathway*.[1-3] In recent years, reactions proceeded through the directed C-H bond activation have been illustrated by the formation of cyclometalated intermediates, an important intermediate of C-H bond activation reactions.[2-3] Along with a variety of transition metals including palladium,[4] iridium[5] and rhodium[6] which form cyclometalated species, ruthenium based complexes have also shown appreciable reactivity towards the formation of cyclometalated species.[7] Moreover, ruthenium complexes offers excellent water solubility which provides the opportunity to perform catalytic C-H bond activation/functionalization under environmentally benign condition using of water as a solvent.[8,9,12,13]

In particular, catalytic systems based on ruthenium-arene complexes for C-H bond activation/functionalization of various heteroarenes have also been vastly explored, where the role of ligands was found to be a crucial factor.[7-14] For instance, bulky phosphines have been used to tune the selectivity of monoarylated product during the

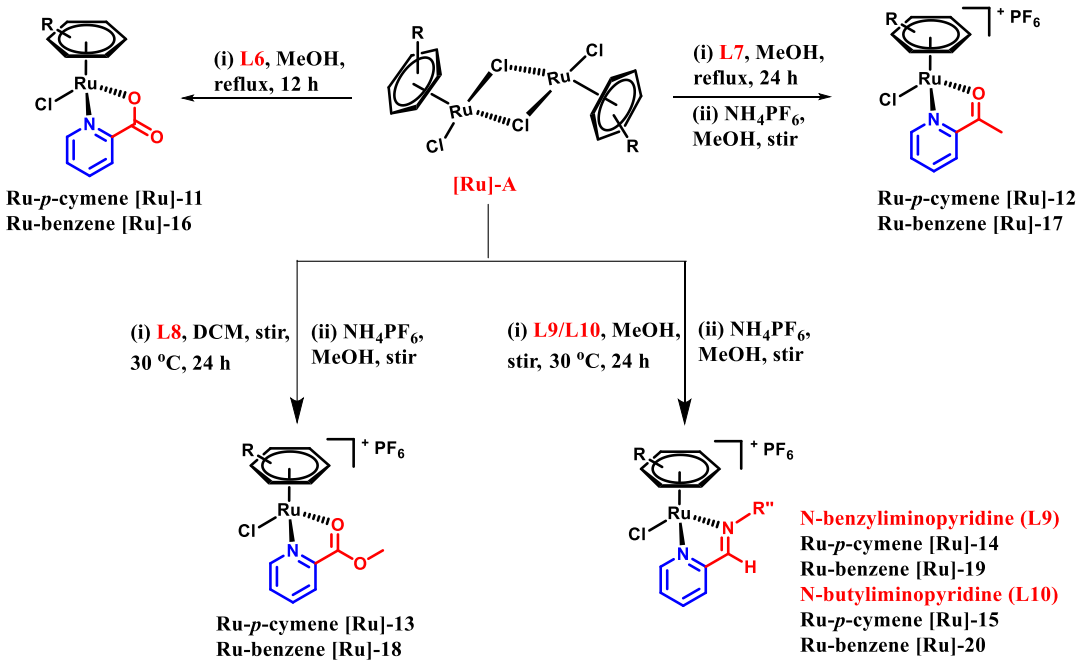
ortho arylation of heteroarenes by Inoue *et al*.[11a] Contrary to phosphine based ligands, carboxylates, as a ligand and deprotonating agent explored by various researchers and displayed high potential to achieve enhanced catalytic activity with tunable selectivity for ruthenium catalyzed C-H bond activation reaction.[12] Extensive kinetic studies by Jutand *et al.* also evidenced the active role of carboxylates as deprotonating agents, which enhances the catalytic efficiency of reaction by autocatalytic process.[12g] A remarkable example of robust ruthenium(II) catalyzed carboxylate assisted C-H arylation of amino acids and peptides has recently been reported by Ackermann *et al.* which also suggests the crucial role of carboxylates in C-H activation reaction.[12i] In our recent studies with ruthenium-arene complexes containing *O,O* and *O,N* donor tropolone/ aminotropolone ligands for C-H bond arylation of 2-phenylpyridine in water, we also investigated the interesting role of carboxylate additives, driven by steric bulkiness, in tuning the selectivity of C-H arylation products.[13] Later, we also explored aniline based ruthenium-arene complexes for C-H bond arylation in water, where the strength of aniline-ruthenium bond and the substitution on aniline ligand was found to be the crucial factors to tune the selectivity of mono v/s biarylated products during the reaction.[14]

Further, in our deliberate efforts to develop efficient catalytic system for C-H activation/functionalization reactions,[13,14] herein we synthesized a series of ruthenium(II)-arene complexes containing pyridine based *N,O* and *N,N* donor ligands and systematically investigated their catalytic performance for *ortho* C-H bond activation/arylation of 2-phenylpyridine with several aryl halides in water. Synthesized ruthenium-arene complexes were well characterized using NMR, mass spectral analysis and the molecular structure for few of the representative complexes were authenticated by single crystal X-ray diffraction studies. Attempts were also made to establish a relation between the pattern of bonding of ligands to the ruthenium metal center and the observed catalytic activity of these complexes for *ortho* C-H bond activation/arylation reaction using time-scaled ^{1}H NMR spectroscopy.

3.2. Results and Discussion

3.2.1. Synthesis of water-soluble ruthenium(II)-arene complexes [Ru]-11 to [Ru]-20:

Water-soluble ruthenium-arene complexes (**[Ru]-11–[Ru]-20**) containing pyridine based *N,O* and *N,N* donor ligands were synthesized in good yield by reacting respective ruthenium(II)-arene dimer with the readily available *ortho* substituted pyridine based *N,O*/*N,N* donor bidentate ligands with substituents ranging from carboxylic (pyridine-2-carboxylic acid (**L6**)), acetyl (2-acetylpyridine (**L7**)), ester (2-methylpicolinate (**L8**)) and imino groups (N-benzyl-pyridylimine (**L9**) and N-butyl-pyridylimine (**L10**)) as shown in the Scheme 3.1.



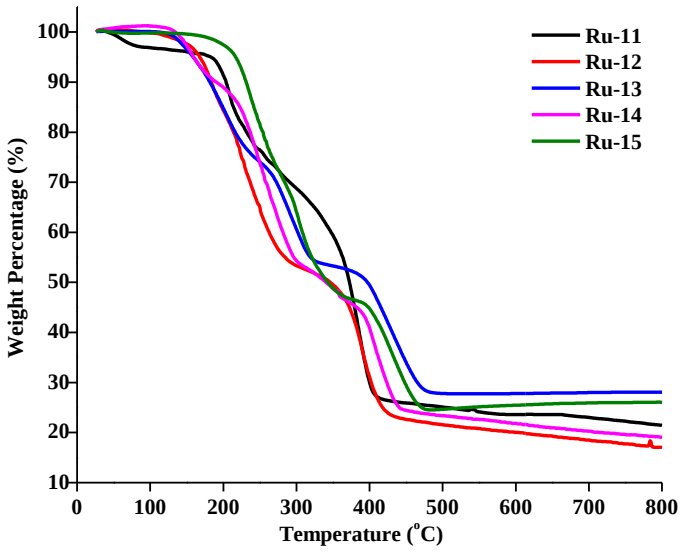
Scheme 3.1. *Synthesis of ruthenium-arene complexes* ***[Ru]-11*** *–* ***[Ru]-20*** *containing pyridine-based N,O and N,N donor ligands.*

Ligand **L8** was prepared by acid catalyzed esterification of **L6** in methanol under refluxing condition.[15a] Iminopyridine ligands **L9** and **L10** were prepared by the condensation of pyridine-2-carboxyladehyde with benzylamine and *n*-butylamine respectively.[15b-15d] Identity and purity of the synthesized ligands **L8 – L10** were confirmed by ^{1}H and ^{13}C NMR.[15] Complexes **[Ru]-11 – [Ru]-12**, **[Ru]-14 – [Ru]-17**, **[Ru]-19** and **[Ru]-20**, with general formula [(η^6-arene)RuCl(κ^2-L)]$^{n+}$, where η^6-arene =

C_6H_6 or $C_{10}H_{14}$, L = **L6 – L7**, **L9** and **L10** and n = 0, +1, were obtained by treating respective [{(η^6-arene)$RuCl_2$}$_2$] with ligands **L6 – L7**, **L9** and **L10** in methanol.[15d,16] Complexes **[Ru]-13** and **[Ru]-18** were obtained by stirring ligand **L8** with [{(η^6-arene)$RuCl_2$}$_2$] (η^6-arene = η^6-$C_{10}H_{14}$ and η^6-C_6H_6) in dichloromethane at room temperature. The synthesized complexes were well characterized by various spectro-analytical techniques, which further authenticated the proposed structure as shown in the Scheme 3.1.

^{1}H NMR spectra of the complexes **[Ru]-11** – **[Ru]-20** depicted an analogous trend, where a downfield shift in the chemical shifts of the protons associated with ligands was observed compared to the free ligands, suggesting the coordination of ligand to the ruthenium metal center. ^{1}H NMR resonances for protons corresponding to ruthenium coordinated η^6-arene ring were also observed in the expected region for all the complexes.[13,14,15-18] FTIR and UV-visible spectra recorded for the synthesized complexes were also in accordance with the previous reports.[16,18] The ESI mass spectra of the complexes **[Ru]-11** and **[Ru]-16** showed peaks corresponding to the $[M\text{-}Cl]^+$ ions, while rest of the cationic complexes displayed peaks for $[M]^+$ ions with the characteristic Ru isotopic patterns. Moreover, the synthesized complexes also exhibited appreciably good thermal stability (up to 250 ºC), as inferred from TGA studies (Figure 3.1).

(a)



(b)

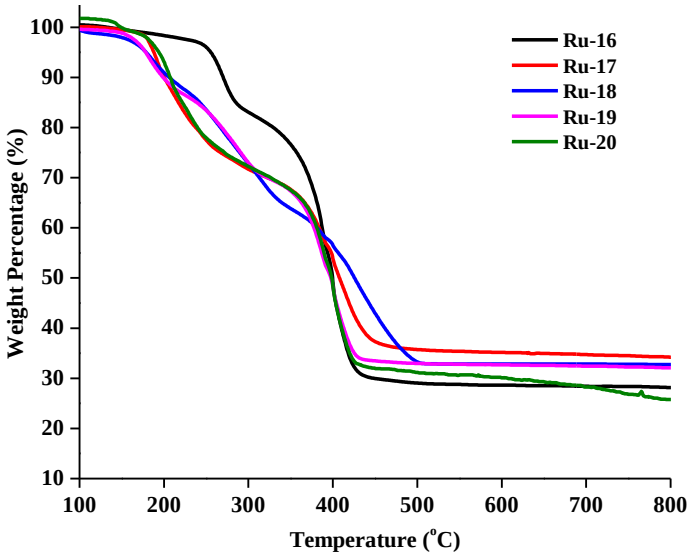


Figure 3.1. *Thermal gravimetric analysis (TGA) of* ***(a)*** *complexes* ***[Ru]-11*** *to* ***[Ru]-15****,* ***(b)*** *complexes* ***[Ru]-16*** *to* ***[Ru]-20****.*

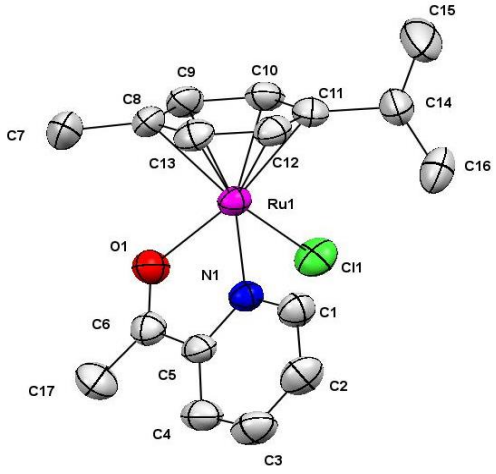
Further, molecular structure of the representative complexes **[Ru]-12**, **[Ru]-14** and **[Ru]-15** was also confirmed by single crystal X-ray diffraction studies. Crystals suitable for X-ray diffraction of the complexes **[Ru]-12**, **[Ru]-14** and **[Ru]-15** were grown by the diffusion of diethyl ether into the methanolic solution of these complexes at room temperature. Complexes **[Ru]-12** and **[Ru]-14** crystallized in monoclinic crystal system with *P*21/c space group, whereas **[Ru]-15** crystallized in triclinic crystal system with *P*-1 space group. The geometry around the ruthenium metal center was pseudo-octahedral, where the η^6-arene ring occupied the top of the *piano-stool*, and three legs were occupied by the bidentate *N*,*O* or *N*,*N* donor ligands and one chloride ligand. The η^6-arene ring centroid was displaced from the Ru(II) center by 1.671, 1.693 and 1.695 Å for the complexes **[Ru]-12**, **[Ru]-14** and **[Ru]-15** respectively, which is comparable to the similar arene-Ru(II) complexes.[16-18] For complex **[Ru]-12**, the ligand 2-acetylpyridine (**L7**) was coordinated with the ruthenium metal in bidentate fashion involving the nitrogen atom of pyridine ring and oxygen atom of acetyl. Similarly, for complexes **[Ru]-14** and **[Ru]-15**, iminopyridine ligands **L9** and **L10** were coordinated with the ruthenium metal in κ^2-mode through N_{py} and N_{imine}. Ru-N_{py}(1) and Ru-O(1) bond distances 2.107 and 2.117 Å respectively of complex **[Ru]-12** were within the permissible ranges for analogous ruthenium-arene complexes.[18] Angles between the legs of the

complex, N(1)-Ru-Cl(1) and O(1)-Ru-Cl(1), were 83.9º and 83.8º respectively, whereas bond angle between the legs and the centroid of the η^6-arene ring (C_t) were in the range of 129.6 - 133.9º for complex **[Ru]-12**. The N(1)-Ru-O(1) bite angle was 76.2º for complex **[Ru]-12**. Ru-N_{py} and Ru-N_{imine} bond distances were 2.079 and 2.094 Å respectively for the complex **[Ru]-14** and those for **[Ru]-15** were 2.0871 and 2.0708 Å respectively. Bite angles N(1)-Ru-N(2) for the complexes **[Ru]-14** and **[Ru]-15** were 76.6º and 76.8º. Angles between legs of these *piano-stool* complexes were in the range of 83.3º-86.1º for complex **[Ru]-14** and 85.1º - 85.9º for complex **[Ru]-15**. The observed bond parameters are comparable to the previous reports for related complexes.[16,18] Detailed crystal refinement data is given in the Table 3.1.

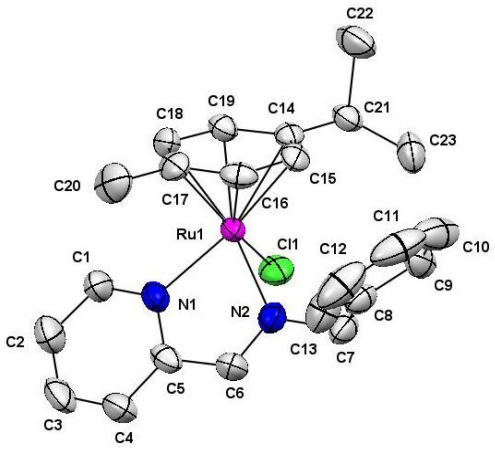
Table 3.1. *Crystal refinement details for complexes* ***[Ru]-12****,* ***[Ru]-14*** *and* ***[Ru]-15****.*

crystal parameters	**[Ru]-12**	**[Ru]-14**	**[Ru]-15**
Empirical formula	$C_{17}H_{21}ClF_6NOPRu$	$C_{23}H_{26}ClF_6N_2PRu$	$C_{20}H_{28}ClF_6N_2PRu$
Formula weight	536.84	611.95	577.93
Temperature (K)	293(2)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system, space group	Monoclinic, P21/c	Monoclinic, P21/c	Triclinic, P-1
a (Å)	13.4675(8)	11.7384(2)	9.3186(3)
b (Å)	6.5219(4)	11.6248(2)	9.9357(2)
c (Å)	24.2390(13)	18.7059(3)	12.8352(5)
α (deg)	90	90	83.203(3)
β (deg)	105.022(6)	104.3960(10)	77.803(3)
γ (deg)	90	90	84.522(2)
Volume ($Å^3$)	2056.2(2)	2472.39(7)	1150.34(6)
Z, calculated density (mg/m^3)	4, 1.734	4, 1.644	2, 1.669
μ (mm^{-1})	1.031	0.867	0.926
F (000)	1072	1232	584
Crystal size (mm^3)	0.290 x 0.260 x 0.210	0.290 x 0.230 x 0.170	0.230 x 0.180 x 0.130
Theta range for data collection (deg)	3.132 to 32.276	2.923 to 25.000	3.023 to 32.312
Index ranges	-19<=h<=20, -9<=k<=8, -33<=l<=36	-13<=h<=13, -13<=k<=13, -22<=l<=22	-13<=h<=13, -13<=k<=14, -18<=l<=19
Reflections collected	26724 / 6868 [R(int)=0.1047]	19349 / 4341 [R(int)=0.2648]	14725 / 7471 [R(int)=0.0399]
Completeness to θ (%)	99.9	99.8	99.8
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.51448	1.00000 and 0.67738	1.00000 and 0.67738

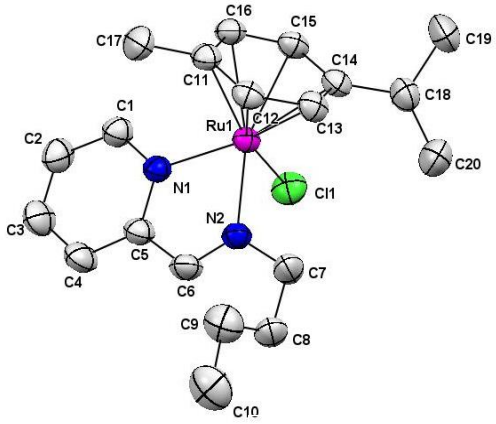
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/ restraints/ parameters	6868 / 0 / 257	4341 / 0 / 310	7471 / 0 / 285
Goodness-of-fit on F^2	1.037	1.186	1.188
Final R indices [I > 2sigma(I)]	R1 = 0.0767, wR2 = 0.1946	R1 = 0.1075, wR2 = 0.2791	R1 = 0.0442, wR2 = 0.1178
R indices (all data)	R1 = 0.1075, wR2 = 0.2222	R1 = 0.1310, wR2 = 0.3212	R1 = 0.0526, wR2 = 0.1359
Largest diff. peak and hole ($eÅ^{-3}$)	1.565 and -2.667	2.707 and -2.459	1.471 and -1.236
CCDC	**1515543**	**1518468**	**1515545**



[Ru]-12



[Ru]-14

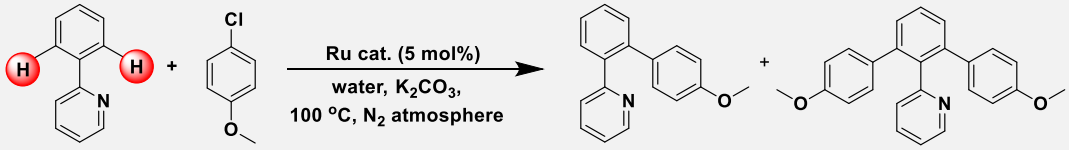


[Ru]-15

Figure 3.2. *Single crystal X-ray structure of complex* ***[Ru]-12, [Ru]-14, and [Ru]-15****. Ellipsoids are set at 30% probability. Counter ion* PF_6 *and all hydrogen atoms are omitted for clarity.*

3.2.2 Ruthenium-arene catalyzed *ortho* C-H bond arylation of 2-phenylpyridines with aryl halides. At an outset, 2-phenylpyridine (**1a**) and 4-chloroanisole (**2a**) were chosen as model substrates for *ortho* C-H bond arylation over **[Ru]-11 – [Ru]-20** catalysts. The reaction of **1a** (0.5 mmol) and **2a** (1.25 mmol)[13,19] over **[Ru]-11** catalyst (5 mol %) in the presence of 3 equiv. of K_2CO_3 showed a conversion of 82% with 86% selectivity (63% yield) for the monoarylated product (**3a**) in 8 h at 100 °C in water (Table 3.2, entry 1). Further, a remarkably high conversion of 98% was achieved over **[Ru]-12** with 73% selectivity for **3a** (65% yield) in 8 h under analogous reaction conditions. Moreover, extending the catalytic reaction to 10 h, complete conversion of 2-phenylpyridine can be achieved over **[Ru]-12** catalyst. Notably, **[Ru]-13** catalyst also resulted in 93% conversion with 61% yield of **3a** (Table 3.2, entry 3). In contrary to the higher catalytic activity of **[Ru]-11 – [Ru]-13** catalysts (ruthenium-arene with *N,O* donor ligands), ruthenium-arene-iminopyridine complexes (**[Ru]-14 – [Ru]-15**) exhibited only moderate conversions (Table 3.2, entries 4 and 5).

Table 3.2. *Catalytic activity of ruthenium-arene complexes for ortho C-H bond arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**)*[a]



1a **2a** **3a** **4a**

Entry	Catalyst	Conv. (%)[d]	Sel. (%)[d] (3a/4a)	Yield (%) (3a)	TON/TOF
1.	[(η^6-*p*-cymene)Ru(κ^2-*N,O*-pyridine-2-carboxylate)Cl] **[Ru]-11**	82	86/14	63%	16.4/2.05
2.	**[(η^6-*p*-cymene)Ru(κ^2-*N,O*-2-acetylpyridine)Cl]PF_6 [Ru]-12**	**98 (100)[b]**	**73/27 (68/22)[b]**	**65% (60%)[c]**	**19.6/2.45**
3.	[(η^6-*p*-cymene)Ru(κ^2-*N,O*-2-methylpicolinate)Cl]PF_6 **[Ru]-13**	93	76/24	61%	18.6/2.32
4.	[(η^6-*p*-cymene)Ru(κ^2-*N,N*-(N-benzyl-pyridylimine)Cl]PF_6 **[Ru]-14**	42	86/14	28%	8.4/1.05

5.	[(η^6-*p*-cymene)Ru(κ^2-*N*,*N*-(N-butyl-pyridylimine)Cl]PF_6 **[Ru]-15**	45	88/12	33%	9.0/1.12
6.	[(η^6-benzene)Ru(κ^2-*N*,*O*-pyridine-2-carboxylate)Cl] **[Ru]-16**	80	89/11	63%	16.0/2.0
7.	[(η^6-benzene)Ru(κ^2-*N*,*O*-2-acetylpyridine)Cl]PF_6**[Ru]-17**	97	87/13	72%	19.4/2.42
8.	[(η^6-benzene)Ru(κ^2-*N*,*O*-2-methylpicolinate)Cl]PF_6 **[Ru]-18**	88	84/16	65%	17.6/2.2
9.	[(η^6-benzene)Ru(κ^2-*N*,*N*-(N-benzyl-pyridylimine)Cl]PF_6 **[Ru]-19**	62	80/20	40%	12.4/1.55
10.	[(η^6-benzene)Ru(κ^2-*N*,*N*-(N-butyl-pyridylimine)Cl]PF_6 **[Ru]-20**	45	86/14	32%	9.0/1.12

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), K_2CO_3 (3 equiv.), [Ru] catalyst (5 mol%) in water (5 mL) at 100 ºC for 8 h. [b]Reaction time = 10 h. [c]Isolated yield in 10 h. [d]Conversion and selectivity were determined by ^{1}H NMR with TMS as internal standard. Yield (%) represents the isolated yield of the purified product (**3a**). TON = Turn Over Number. TOF = Turn Over Frequency (h^{-1}).

Consistent with the higher catalytic activity observed with (η^6-*p*-cymene)Ru complexes (**[Ru]-11 – [Ru]-13**), analogous (η^6-benzene)Ru complexes (**[Ru]-16 – [Ru]-18**) also exhibited enhanced catalytic conversion, where the (η^6-benzene)Ru-acetylpyridine complex (**[Ru]-17**) showed 97% conversion of **1a** (Table 3.2, entry 6). Moreover, (η^6-benzene)Ru complexes containing iminopyridine based ligands (**[Ru]-19** and **[Ru]-20**) were also observed to be less active than the complexes with *N*,*O* donor ligands (Table 3.2, entries 9,10). Therefore, it is evident from the above results, that ruthenium-arene complexes with *N*,*O* donor pyridine-based ligands displayed superior catalytic performance over those ligated with *N*,*N* donor ligands for the *ortho* C-H bond arylation of **1a**. Moreover, amongst *N*,*O* donor ligands, the ruthenium-arene complexes having *N*,*O* donor ligands with neutral oxygen donor group (acetylpyridine ligated ruthenium-arene complexes (**[Ru]-12**, **[Ru]-13**, **[Ru]-17** and **[Ru]-18**) outperformed over those coordinated with anionic oxygen donor group (picolinate ligated ruthenium-arene complexes **[Ru]-11** and **[Ru]-16**), under analogous reaction condition. The above results suggesting a crucial role of ligand in the observed trend in the catalytic C-H bond

activation reaction. Moreover, most of the ionic ruthenium catalysts (**[Ru]-12**, **[Ru]-13**, **[Ru]-17** and **[Ru]-18**) exhibited superior catalytic activity than the electroneutral catalysts (**[Ru]-11** and **[Ru]-16**),[20] but the poor performance of other ionic catalysts (**[Ru]-14**, **[Ru]-15**, **[Ru]-19** and **[Ru]-20**) suggesting that presumably the effect of solvation was superseded by the dominating and crucial role of the ligands.

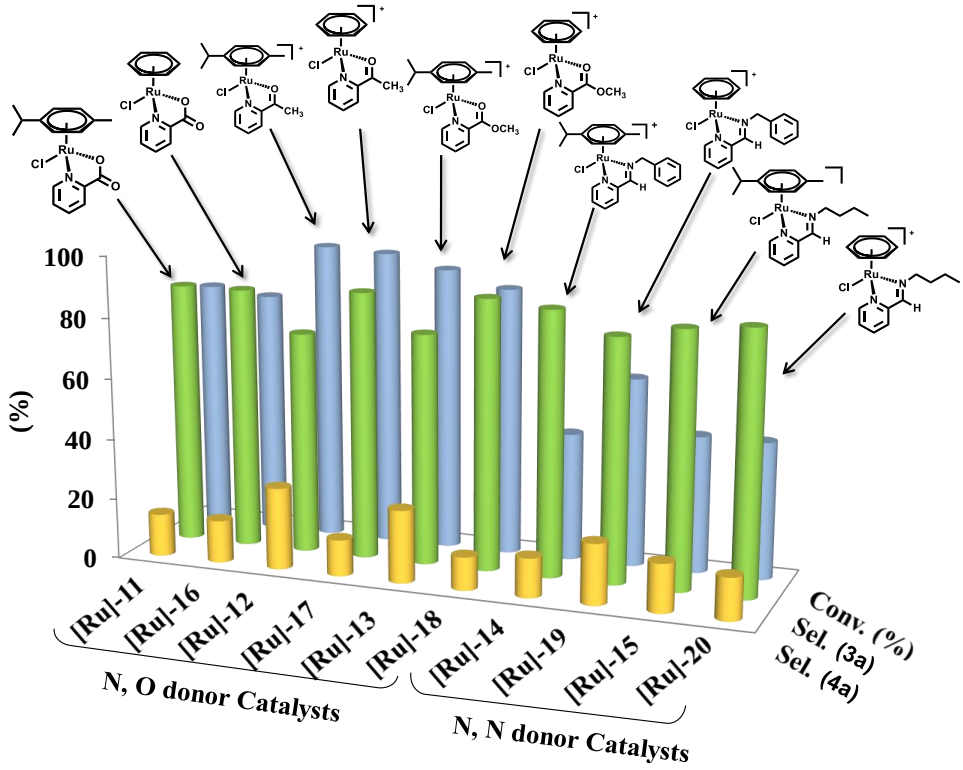


Figure 3.3. *Structure-activity relationship for ortho C-H bond arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**) over **[Ru]-11 – [Ru]-20** catalysts.*

Notably, carboxylate additives are considered as efficient deprotonating agents in C-H bond activation reactions, where its deprotonating properties increases with the increase in bulkiness/ basicity and on its availability in the solution.[12, 13] Therefore, the effect of carboxylate salts, with increasing bulkiness on α-carbon, were explored over the best catalyst (**[Ru]-12**) under the optimized reaction conditions: Cat. 5 mol%, 100 ºC, K_2CO_3 (3 equiv.) (Table 3.3, Figure 3.4). Results inferred that with the increase in bulkiness of the carboxylate salts (acetate → pivalate), a gradual decrease in the conversion of **1a** was observed over ruthenium-arene-acetylpyridine **[Ru]-12** catalyst (Table 3.3, entries 9-12).

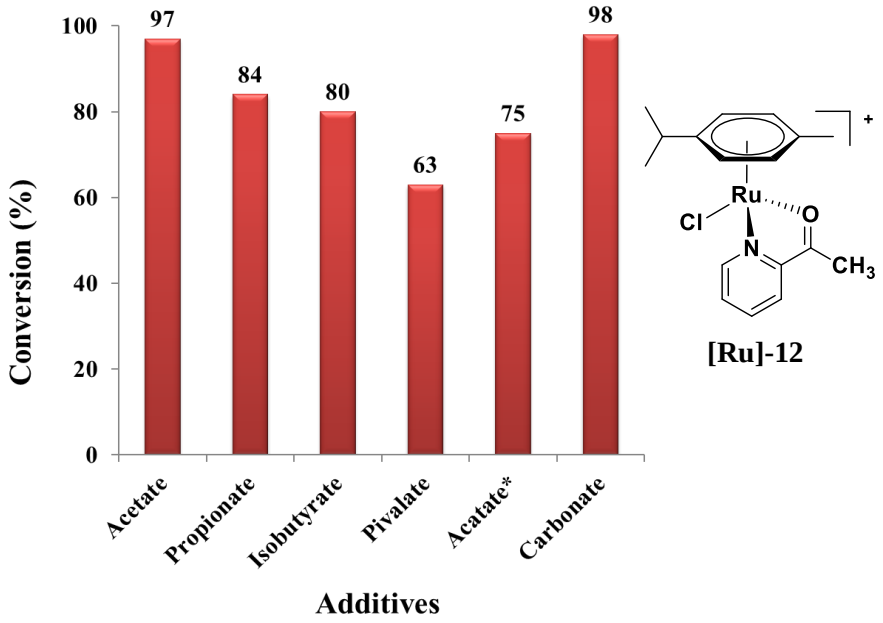


Figure 3.4*. Effect of carboxylate additives on ortho C-H bond arylation of 2-phenylpyridine with 4-chloroanisole over* ***[Ru]-12*** *catalyst.*Reaction performed with KOAc in absence of* K_2CO_3*.*

Interestingly, the ruthenium-arene picolinate catalyst **[Ru]-11** showed a reverse pattern, where an increase in the catalytic activity was observed with bulky carboxylates (acetate → pivalate) (Figure 3.5).

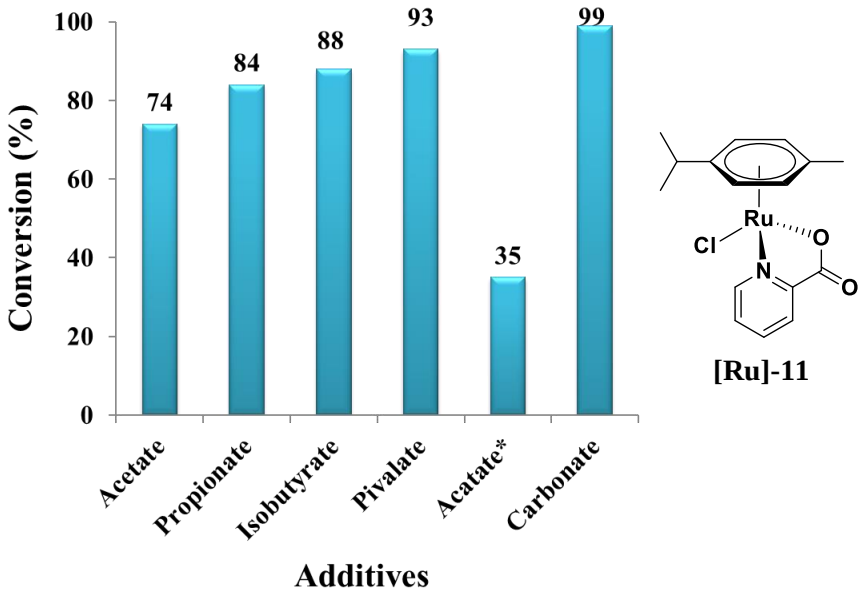
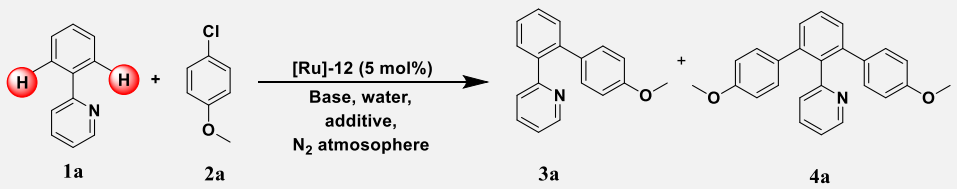


Figure 3.5. *Effect of carboxylate additives on ortho C-H bond arylation of 2-phenylpyridine with 4-chloroanisole over* ***[Ru]-11*** *catalyst.*Reaction performed with KOAc in absence of* K_2CO_3*.*

The observed trend can be attributed to the competitive coordination of the acetylpyridine/ picolinate and the carboxylate additives to the ruthenium center. The strong coordinating nature of pivalate compared to acetylpyridine, under catalytic reaction condition unless otherwise mentioned, resulted in the decreases in the availability of free carboxylate in the solution, whereas picolinate showed stronger coordination behavior than carboxylate additives and hence ensured greater availability of carboxylate additives in the solution. Though the observed conversion with a range of carboxylate salts (with or without K_2CO_3) was found to be lower than the conversion observed with only K_2CO_3 base (in the absence of any carboxylate additives) in case of both catalysts, the above observations are worth noting as it inferred the crucial role of the ligand in controlling the catalytic activity in the studied ruthenium-arene complexes. Therefore, further optimization experiments were performed using only K_2CO_3 base, without carboxylate additives. Notably, reaction could not occur in the absence of base or catalyst (Table 3.3, entries 7-8). Moreover, performing the reaction at lower temperature < 100 ºC resulted in poor conversion over **[Ru]-12** catalyst (Table 3.3, entries 5-6).

Table 3.3. *Optimization table for catalytic ortho C-H bond arylation of 2-phenylpyridine over complex* ***[Ru]-12****.*[a]



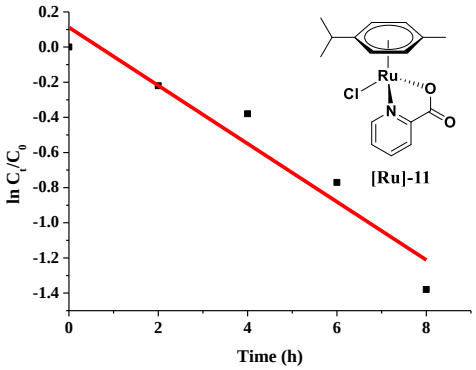
1a 2a 3a 4a

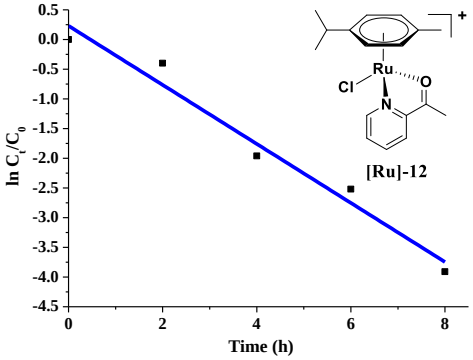
Entry	Temp. (ºC)	Time (h)	Base	Additive	Conv. (%)	Sel.(%) (3a/4a)
1.	100	2	K_2CO_3	-	33	>99/<1
2.	100	4	K_2CO_3	-	86	83/17
3.	100	6	K_2CO_3	-	92	75/25
4.	100	8	K_2CO_3	-	98	73/27
5.	70	8	K_2CO_3	-	12	>99/<1
6.	80	8	K_2CO_3	-	37	>99/<1
7.	100	8	-	-	n.r.	-

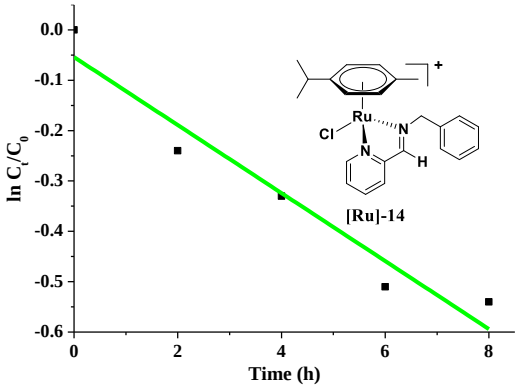
8.[b]	100	8	K_2CO_3	-	n.r.	-
9.	100	8	K_2CO_3	CH_3COOK	97	57/43
10.	100	8	K_2CO_3	CH_3CH_2COOK	84	76/24
11.	100	8	K_2CO_3	$(CH_3)_2CH_2COOK$	80	81/19
12.	100	8	K_2CO_3	$(CH_3)_3CHCOOK$	63	89/11

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), base (3 equiv., 1.5 mmol), **[Ru]-12** (5 mol%), additives (0.05 mmol) in water (5 mL). Conversion and selectivity were determined by ^{1}H NMR with TMS as internal standard.[b]without catalyst. n.r. = No reaction.

Further, time-dependent ^{1}H NMR experiments for C-H bond arylation reaction were conducted over the high performance **[Ru]-12** catalyst, and the results were compared with those of the analogous picolinate (**[Ru]-11**) and iminopyridine (**[Ru]-14**) complexes (Figure 3.6 and 3.7). Among all the complexes studied, **[Ru]-12** exhibited higher rates (6.12×10^{-4} sec^{-1}) during the 0-8 hours of the catalytic reaction (Figure 3.6 and 3.7). Contrary to **[Ru]-12**, complexes **[Ru]-11** and **[Ru]-14** displayed relatively lower kinetics 3.50×10^{-5} sec^{-1} and 2.63×10^{-5} sec^{-1}, respectively (Figure 3.6). The above results clearly evidenced the crucial role of the coordination environment around the Ru center, due to *N,O*/*N,N* donor ligands, on the catalytic efficiency of the resulting ruthenium-arene complexes.







Catalyst	[Ru]-11	[Ru]-12	[Ru-4
Rate constant (k)	3.50×10^{-5} sec^{-1}	**6.12×10^{-4} sec^{-1}**	2.63×10^{-5} sec^{-1}

Figure 3.6. *Kinetics of the C-H bond activation/arylation reaction of 2-phenylpyridine with 4-chloroanisole over complexes* ***[Ru]-11***, ***[Ru]-12*** *and* ***[Ru]-14.***

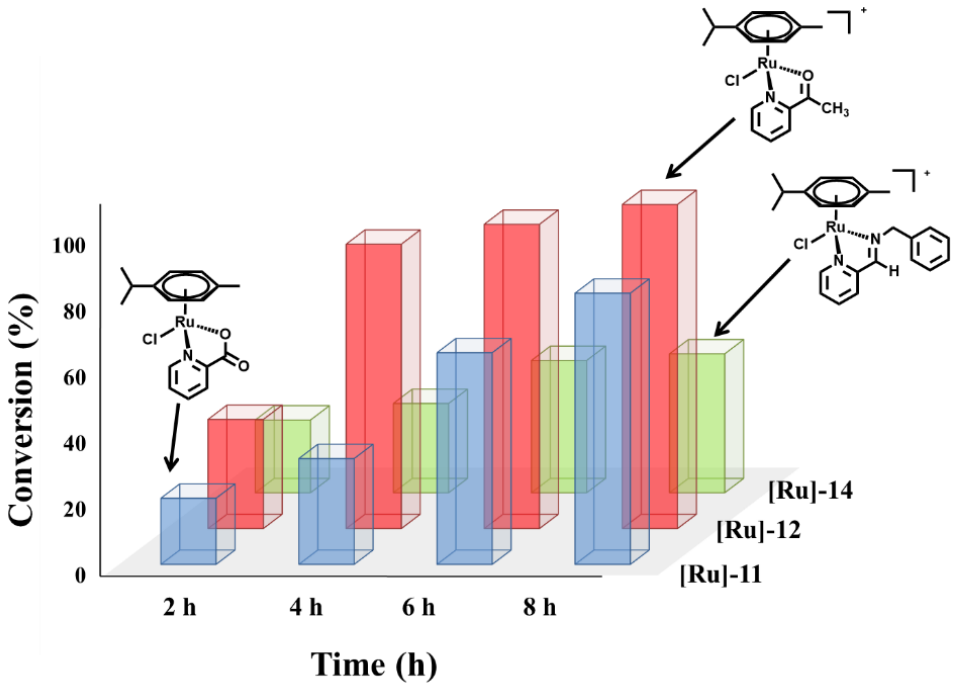


Figure 3.7. *Time dependent reaction profile with N,O/N,N donor ligated complexes* ***[Ru]-11***, ***[Ru]-12*** *and* ***[Ru]-14***.

Further, the time-dependent reaction profile over **[Ru]-12** catalyst showed >90% consumption of **1a** over a period of 6 h. Though the selectivity for monoarylated product (**3a**) remains dominated throughout the reaction (2-10 h), the selectivity for the biarylated product (**4a**) increases gradually with the increase in the reaction time, suggesting the consumption of **3a** to form **4a** (Figure 3.8).

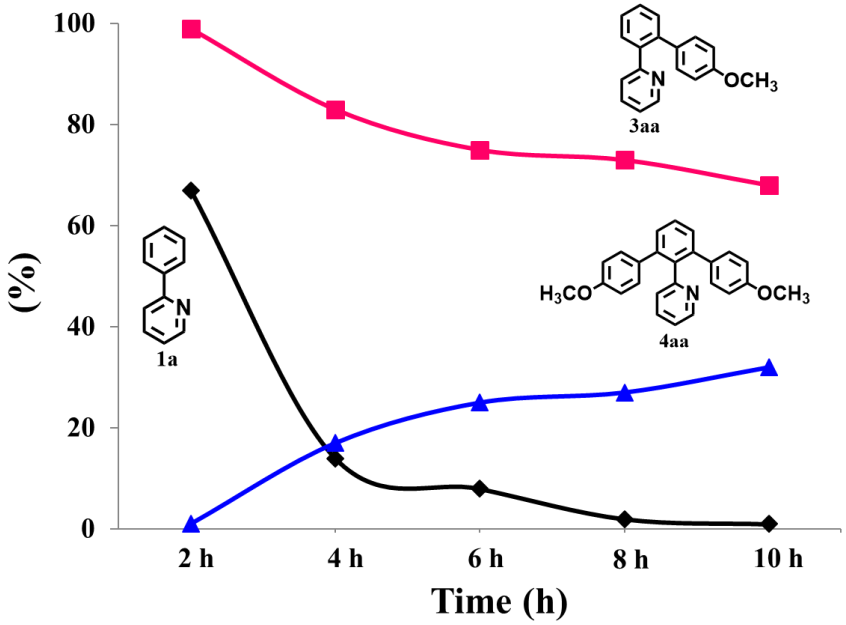
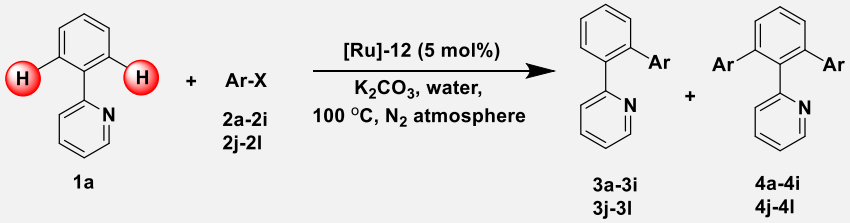


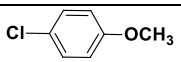
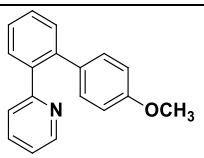
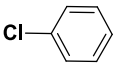
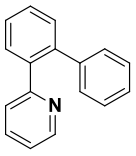
Figure 3.8. *Products, monoarylated (**3a**) and biarylated (**4a**), distribution over **[Ru]-12** for ortho C-H bond arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**) at 100 °C in water.*

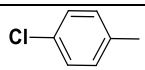
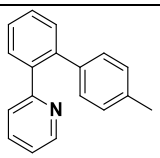
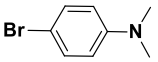
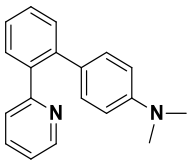
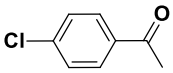
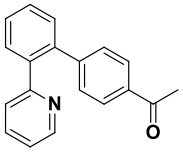
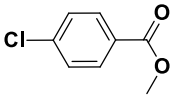
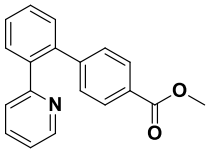
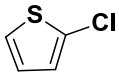
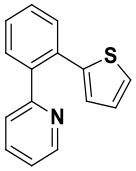
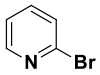
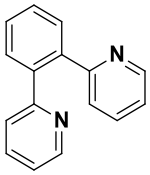
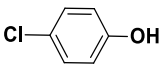
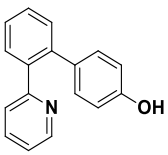
Further, the scope and generality for **[Ru]-12** catalyzed C-H bond arylation of 2-phenylpyridine (**1a**) using several aryl halides (**2a-2l**) was explored under the optimized reaction condition (Table 3.4). Notably, both electron donating and electron withdrawing aryl halides were proved to be efficient arylating agents for *ortho* C-H bond arylation of **1a** to afford corresponding monoarylated products as major component, with moderate to high selectivity and yield in 8 h. The unsubstituted chlorobenzene (**2b**) afforded 82% conversion for the arylation of **1a** with 78% selectivity for the monoarylated product (**3b**) (Table 3.4, entry 2). Analogous to 4-chloroanisole (**2a**), reaction with electron donating aryl halides such as 4-chlorotoluene (**2c**) afforded the respective monoarylated products with high selectivity, (70% for **3c**) (Table 3.4, entry 3). Further, 4-bromo *N*,*N*-dimethylaniline (**2d**) also exhibited moderate conversion, but with high selectivity of 82%

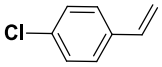
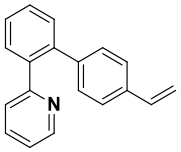
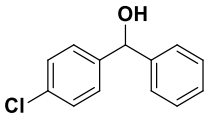
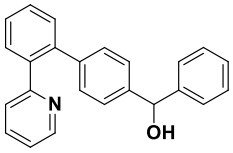
for the monoarylated products (**3d**) (Table 3.4, entry 4). Electron withdrawing aryl halides, 4-chloroacetophenone (**2e**) and 4-chloromethylbenzoate (**2f**), also exhibited excellent conversion of 80% and 96%, respectively with selectivities of 80% and 45% for (**3e**) and (**3f**) (Table 3.4, entries 5,6). However, (hetero)aryl halides, 2-chlorothiophene (**2g**) and 2-bromopyridine (**2i**), showed only poor conversion, presumably due to the strong coordination of Lewis basic heteroatoms to the ruthenium center (Table 3.4, entries 7,8).[21] Another electron donating aryl halide, 4-chlorophenol (**2j**), also afforded the respective monoarylated products with high selectivity, 75% for (**3j**) (Table 3.4, entry 9). Notably, 4-chlorostyrene (**2k**) showed sluggish reaction, presumably due to the coordination of vinyl group to the catalyst and thus retarded the reaction progress. Nevertheless, 91% selectivity for the monoarylated product (**3k**) was achieved with **2k** (Table 3.4, entry 10). Further, 4-chlorobenzhydrol (**2l**) also exhibited moderate conversion, but with high selectivity of 99% for the monoarylated products (**3l**) (Table 3.4, entry 11).

Table 3.4. *Catalytic ortho-C-H bond arylation of 2-phenylpyridine (**1a**) using various aryl halides (**2a-2k**).*[a]



Entry	(Hetero)aryl halide	Conv. (%)/ Time (h)	Sel. (%)	Yield (%)
1.	 **2a**	98 (8 h) >99 (10 h)	73/27 68/32 (**3a**/**4a**)	 **3a** (63%)
2.	 **2b**	82	78/22 (**3b**/**4b**)	 **3b** (58%)

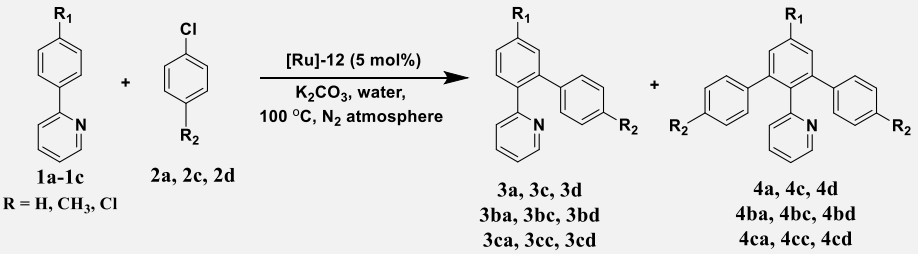
3.	 **2c**	86	70/30 (**3c**/**4c**)	 **3c** (53%)
4.	 **2d**	37	82/18 (**3d**/**4d**)	 **3d** (20%)
5.	 **2e**	80	80/20 (**3e**/**4e**)	 **3e** (58%)
6.	 **2f**	96	45/55 (**3f**/**4f**)	 **3f** (36%)
7.	 **2g**	40	80/20 (**3g**/**4g**)	 **3g** (24%)
8.	 **2i**	15	45/55 (**3i**/**4i**)	 **3i** (nd)[b]
9.	 **2j**	>99	75/25 (**3j**/**4j**)	 **3j** (63%)

10.	 **2k**	52	91/9 (**3k**/**4k**)	 **3k** (40%)
11.	 **2l**	65	99/1 (**3l**/**4l**)	 **3l** (56%)

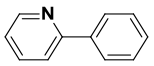
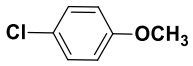
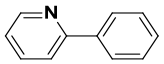
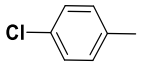
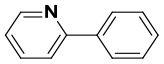
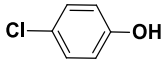
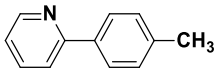
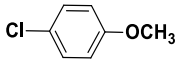
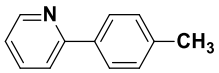
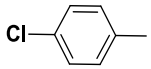
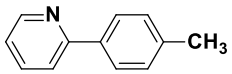
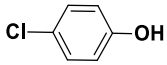
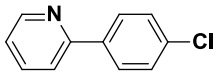
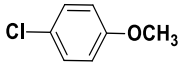
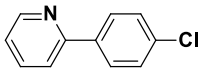
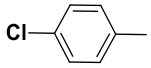
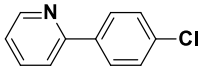
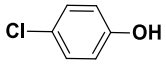
[a]Reaction conditions: **1a** (0.5 mmol), **2a-2l** (1.25 mmol), K_2CO_3 (3 equiv.), **[Ru]-12** (5 mol%) in water (5 mL) at 100 ºC for 8 h. Conversion and selectivity were determined by ^{1}H NMR with TMS as internal standard. Yield (%) represents the isolated yield of the purified product. [b]nd = Not determined.

Moreover, the effect of the substituted 2-phenylpyridines (**1a-1c**) on *ortho* C-H bond arylation was also investigated (Table 3.5). Results inferred that having an electron donating substituent, 2-(*p*-tolyl)pyridine (**1b**) showed enhanced reactivity with >80% conversion and appreciably good selectivity for the monoarylated products was achieved (Table 3.5, entries 4-6). In contrary, 2-(4-chloro)phenylpyridine (**1c**) bearing electron withdrawing chloro substituent resulted in lower conversion for *ortho* C-H bond arylation (Table 3.5, entries 7-9). Nevertheless, monoarylated products remain the dominating product for all the reactions.

Table 3.5. *Catalytic ortho C-H bond arylation of substituted 2-phenylpyridines (**1a-1c**) using selected aryl halides*[a]



Entry	Phenylpyridine	Aryl halide	Conv. (%)	Sel. m/d (%) (Yield (%))

1	 **1a**	 **2a**	>99%[b]	68/22 [b] (**3a,** 60%)[c]
2	 **1a**	 **2c**	82%	78/22 (**3c,** 58%)[c]
3	 **1a**	 **2d**	>99%	75/25 (**3d,** 53%)[c]
4	 **1b**	 **2a**	98%	53/47 (**3ba,** 40%)[c]
5	 **1b**	 **2c**	95%	70/30 (**3bc,** 55%)[c]
6	 **1b**	 **2d**	>99%	68/32 (**3bd,** nd) [e]
7	 **1c**	 **2a**	62%	80/20 (**3ca,** 40%)[d]
8	 **1c**	 **2c**	39%	86/14 (**3cc,** 23%)[c]
9	 **1c**	 **2d**	55%	49/51 (**3cd,** 20%)[d]

[a]Reaction conditions: **1a-1c** (0.5 mmol), aryl halide (1.25 mmol), K_2CO_3 (3 equiv.), **[Ru]-12** (5 mol%) in water (5 mL) at 100 ºC for 8 h. Conversion and selectivity for monoarylated (**m**) and biarylated product (**d**) were determined by ^{1}H NMR with TMS as internal standard. [b]Time = 10 h. [c]Isolated yield. [d]Combined yield for monoarylated and biarylated product. [e]nd = Not determined.

To investigate and identify the possible organometallic species, which may be involved in one or many steps of the catalytic *ortho* C-H bond arylation reaction, several controlled experiments were performed. ^{1}H NMR analysis of the reaction mixture using

the stoichiometric ratio of catalyst **[Ru]-12** and substrate (**1a**) (C:S = 1:5) after 3 h, showed the formation of 2-phenylpyridine coordinated cyclometalated species [(η^6-*p*-cymene)Ru(κ^2-*C,N*-phenylpyridine)]$^+$ **[Ru]-C**. Earlier reports inferred that such organometallic species **[Ru]-C** are indeed a crucial species involved in several ruthenium-arene catalyzed *ortho* C-H bond activation reactions.[8,12,14] The presence of cycloruthenated species (**[Ru]-C**) was also confirmed by mass spectrometric investigation (m/z 390.1) of the stoichiometric reaction of complex **[Ru]-12** with 2-phenylpyridine (**1a**), even in the absence of base K_2CO_3 (Figure 3.7), suggesting the possible role of the ruthenium coordinated 2-acetylpyridine in C-H activation reaction. Therefore, the above NMR and mass spectral investigations along with the reaction kinetics and carboxylate effect experiments substantially accounted for the observed superior catalytic activity of *N,O* donor ligated ruthenium-arene complexes over those with *N,N* donor ligands,[21] and the order of catalytic activity of the studied complexes was found as (η^6-arene)Ru(κ^2-*N,O*-2-acetylpyridine) > (η^6-arene)Ru(κ^2-*N,O*-2-methylpicolinate) > (η^6-arene)Ru(κ^2-*N,O*-picolinate) >> (η^6-arene)Ru(κ^2-*N,N*-iminopyridine). The observed trend is indeed in accordance with the previous studies, which evidenced the crucial role of bis-chelating ligands in tuning the catalytic C-H activation reaction pathway *via* coordination/decoordination mechanism and by participating in deprotonation step.[22,23] For instance, the crucial role of Pd-coordinated picolinate in the deprotonation of arene was reported over a Pd-catalyzed C-H acetoxylation of arenes, where interestingly, picolinate/picolinic acid remains coordinated to the Pd during this deprotonation step.[23a] Moreover, compared to the picolinate ligated Pt metal complexes, those having *N,N* donor ligands exhibited lower activity.[23b] In contrary to the picolinate and *N,N* donor ligands, studies revealed that the acetyl group participated actively in the deprotonation of the C-H bond activation, while remain uncoordinated.[22] Moreover, literature also revealed that proton abstraction by a carbonate base requires less energy (-13.7 kcal/mol) and comparatively favorable over hydride abstraction pathway (+28.2 kcal/mol).[24]. Hence, we anticipated that the remarkable catalytic activity of 2-acetylpyridine ligated ruthenium-arene complexes for C-H activation/arylation is presumably due to the active participation of the ligand in

facile deprotonation of C-H bond and efficient coordination-decoordination interconversion process (Figure 3.9).

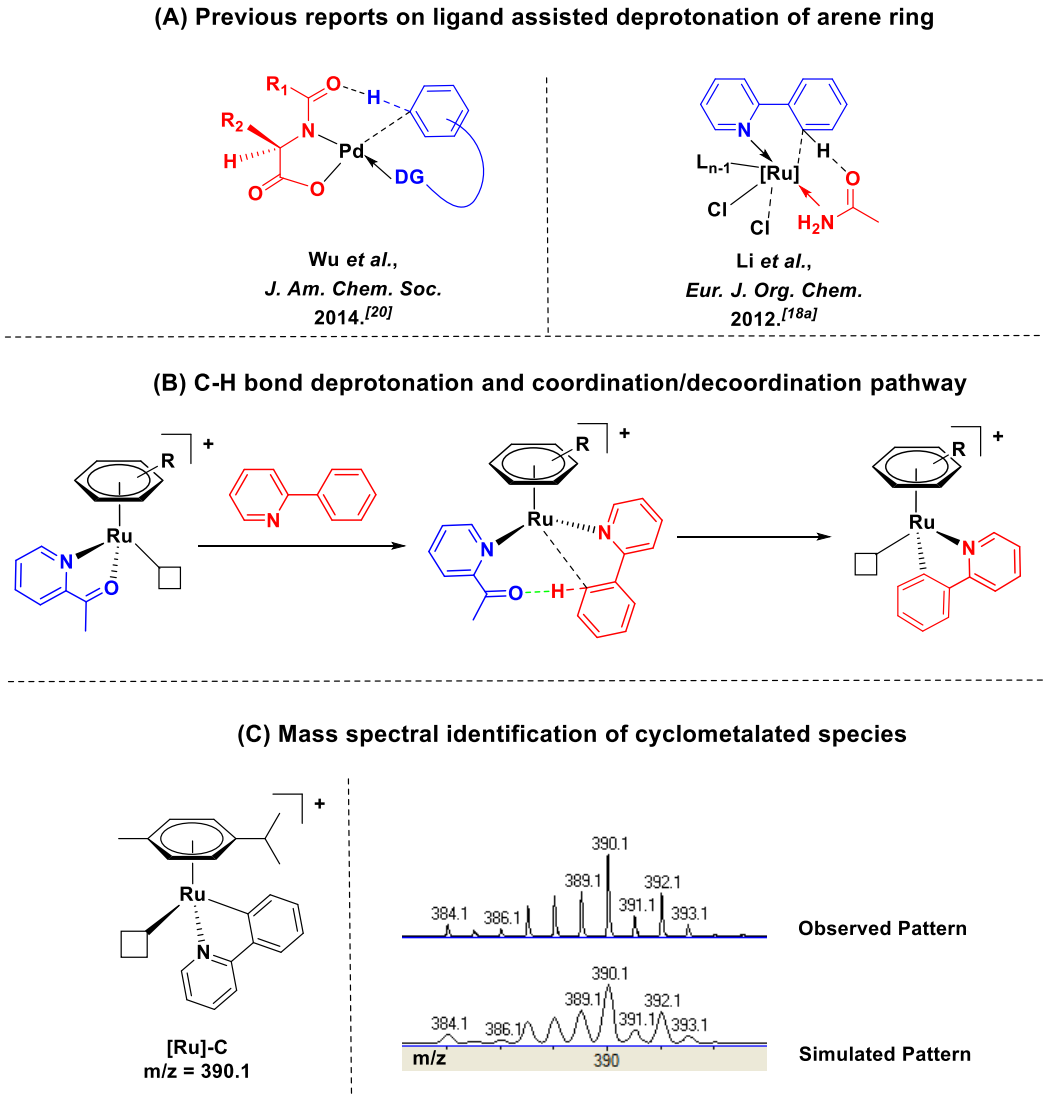
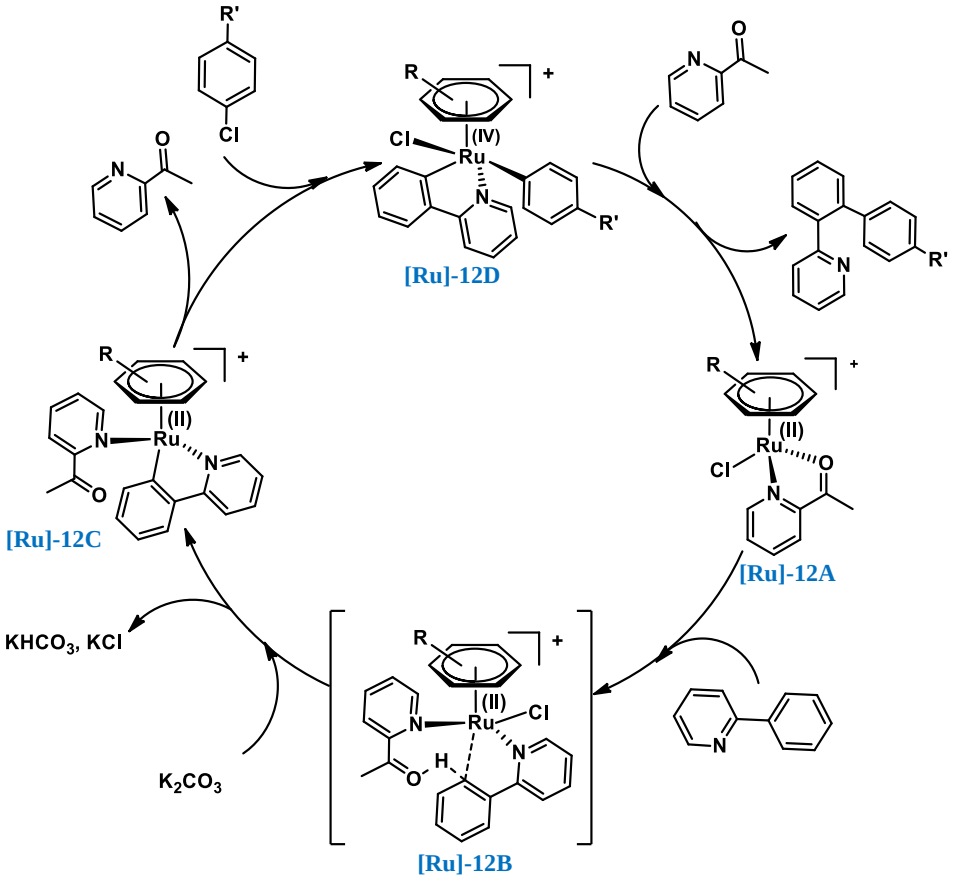


Figure 3.9. (A) *Ligand assisted remote C-H bond deprotonation of various arene rings with transition metal (Ref. 18a, 20)* ***(B)*** *C-H bond deprotonation of 2-phenylpyridine and coordination and decoordination of carbonyl oxygen of N,O donor ligand for the formation of deprotonated cycloruthenated species.* ***(C)*** *Mass spectral identification of cycloruthenated species for the reaction of* ***[Ru]-12*** *with 2-phenylpyridine (with 1:5 molar ratio) in absence of base.*

On the basis of above experimental observations a plausible reaction pathway for the *ortho* C-H bond arylation of 2-phenylpyridine is illustrated in Scheme S1.



Scheme 3.2. *Plausible mechanism for 2-acetylpyridine assisted ruthenium-catalyzed ortho C-H bond arylation of 2-phenylpyridine with aryl halides.*

3.3. Conclusions

To summarize, we systematically investigated the ligand-tuned catalytic performance of ruthenium(II)-arene complexes ligated with *N,O* and *N,N* donor pyridine-based ligands for the *ortho* C-H bond arylation of 2-phenylpyridine with a variety of aryl halides in water. Our findings demonstrated that among all the synthesized complexes, ruthenium-arene complexes ligated with *N,O* donor pyridine ligands, **[Ru]-11** – **[Ru]-13** and **[Ru]-16** – **[Ru]-18**, outperformed with good to moderate yields (61-77%) for the C-H bond arylated products, over those containing *N,N* donor pyridine ligands (28-40%). Moreover, the time-dependent ^{1}H NMR studies inferred higher rate constant for **[Ru]-12** (ruthenium-acetylpyridine) ($k = 6.12 \times 10^{-4}$ sec^{-1}) over **[Ru]-13** (ruthenium-picolinate) ($k = 3.50 \times$

10^{-5} sec^{-1}) and **[Ru]-14** (ruthenium-iminopyridine) ($k = 2.63 \times 10^{-5}$ sec^{-1}). The observed trend in the ligand-tuned catalytic performance of the studied complexes inferred the crucial role of the coordinating ligands (nitrogen *vs* oxygen and neutral *vs* anionic) to establish the structure-activity relationship for the catalytic C-H activation/arylation reactions, where the facile ligand to Ru center coordination-decoordination interconversion and deprotonation of C-H bond played crucial role in the observed trend. Moreover, the mass spectral and ^{1}H NMR studies showed the formation of the crucial cycloruthenated species, [(η^6-arene)Ru(κ^2-*C*,*N*-phenylpyridine)]$^+$ (**[Ru]-A**) during the C-H bond activation of 2-phenylpyridine. In addition, molecular structures for few of the representative complexes, **[Ru]-12**, **[Ru]-14** and **[Ru]-15**, were also authenticated by single crystal X-ray diffraction studies. Specifically, we demonstrated ligand-tuned efficient ruthenium catalyzed C-H activation/arylation reactions, which will be helpful in exploring new possibilities in this field.

3.4. Experimental Section

3.4.1 Materials and instrumentation. All the reactions for catalyst preparation were performed without inert gas protection and all the catalytic reactions for C-H bond arylation of 2-phenylpyridine with aryl halides were performed under N_2 atmosphere using chemicals of high purity purchased from Sigma Aldrich and Alfa Aesar. Ruthenium-arene precursors [(η^6-*p*-cymene)$RuCl_2$]$_2$ **([Ru]-A)** and [(η^6-benzene)$RuCl_2$]$_2$ **([Ru]-B)** were synthesized according to the literature procedures. *[25,26]* ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{31}P NMR (161.98 MHz) spectra were recorded at 298 K using $CDCl_3$, Acetone-d_6 or DMSO-d_6 as the solvent on a Bruker Avance 400 spectrometer. The chemical shifts in ppm are reported relative to the center of the singlet at 7.26 ppm for $CDCl_3$, 2.04 ppm for Acetone-d_6 and 2.49 ppm for DMSO-d_6 in ^{1}H NMR and to the center of the triplet at 77.0 ppm for $CDCl_3$, singlet at 206.0 ppm for Acetone-d_6 and multiplet at 39.50 ppm for DMSO-d_6 in ^{13}C NMR. Coupling constants, *J* values are reported in Hertz (Hz), and the splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; sept, septet. Single-crystal X-ray structural studies of complexes were carried out using Agilent Technologies Supernova CCD system. FTIR for complexes was recorded on Perkin Elmer STD10 FTIR spectrometer and UV-visible

spectra of all the complexes was recorded in methanol at room temperature on Carry-60 UV-visible spectrophotometer with concentration of 5×10^{-5} M. Elemental analysis was carried out using a Thermo Scientific FLASH 200 elemental analyzer. High-resolution mass spectra (HRMS) were recorded on amicrOTF-Q II mass spectrometer. Thermal gravimetric analyses (TGA) were performed on the Mettler Toledo thermal analysis system. CCDC deposition numbers of the complexes **[Ru]-12, [Ru]-14** and **[Ru]-15** are **1515543**, **1518468** and **1515545** respectively.

3.4.2. General procedure for the synthesis of pyridine-based ligands (L8, L9 and L10)

Synthesis of 2-methylpicolinate (L8).

Ligands **L8** was prepared by the esterification of 2-picolinic acid. Pyridine-2-carboxylic acid (1.23 g, 10 mmol) in methanol (50 mL) and conc. H_2SO_4 (2 mL) was refluxed for 8 h in a round bottom flask. After completion of the reaction, reaction mixture was cooled down to room temperature. All the volatiles were removed under vacuum and residue was extracted with dichloromethane (4 × 10 mL) after addition of 10 mL water. Organic phases were further washed with brine solution (20 mL) and dried over Na_2SO_4. The obtained product was analyzed by ^{1}H and ^{13}C NMR.*[18,15c]*

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.75 (d, 1H, J = 4.0 Hz), 8.14 (d, 1H, J = 8.0 Hz), 7.87-7.83 (m, 1H), 7.50-7.47 (m, 1H), 4.01 (s, 3H). ^{1}H NMR (400 MHz, Acetone-d_6) δ (ppm) = 8.67 (d, 1H, J = 4.0 Hz), 8.04 (d, 1H, J = 8.0 Hz), 7.94 (d, 1H, J = 8.0 Hz), 7.59-7.56 (m, 1H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 165.5, 149.6, 147.5, 136.9, 126.8, 125.0, 52.7.

Synthesis of N-benzyl-pyridylmethyleneamine (L9). Ligands **L9** was prepared by following the reported literature method with slight modification. Pyridine-2-carboxyaldehyde (478 µL, 5 mmol) with benzylamine (595 µL, 5 mmol) was stirred at room temperature in THF (25 mL) for 24 h. All the volatiles are removed under vacuum and obtained product was analyzed by ^{1}H and ^{13}C NMR. *[18,15c]*

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.64 (d, 1H, J = 4.0 Hz), 8.48 (s, 1H), 8.05 (d, 1H, J = 8.0 Hz), 7.73 – 7.70 (m, 1H), 7.33 (s, 5H), 7.32-7.28 (m, 1H), 4.87 (s, 2H). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.65 (d, 1H, J = 8.0 Hz), 8.49 (s, 1H), 7.99 (d, 1H, J = 8.0 Hz), 7.87-7.83 (m, 1H), 7.46-7.44 (m, 1H), 7.34 (s, 5H), 4.83 (s, 2H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ (ppm) = 162.7, 154.4, 149.3, 138.6, 136.5, 128.5, 128.1, 127.1, 124.7, 121.3, 64.8.

Synthesis of N-butyl-pyridylmethyleneamine (L10). Above procedure was used for the synthesis of **L10** using pyridine-2-carboxyaldehyde (478 µL, 5 mmol) and *n*-butyl amine (522 µL, 5 mmol) in THF (25 mL) at room temperature. All the volatiles are removed under vacuum and the obtained product was analyzed by ^{1}H and ^{13}C NMR. *[18,15c]*

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.63 (d, 1H, J = 8.0 Hz), 8.37 (s, 1H), 7.98 (d, 1H, J = 8.0 Hz), 7.74-7.70 (m, 1H), 7.31-7.28 (m, 1H), 3.69-3.65 (m, 2H), 1.74-1.67 (sept, 2H, J = 8.0 Hz), 1.42-1.37 (sept, 2H, J = 8.0 Hz), 0.96-0.92 (m, 3H). ^{1}H NMR (400 MHz, Acetone-d_6) δ (ppm) = 8.57 (d, 1H, J = 8.0 Hz), 8.29 (s, 1H), 7.97 (d, 1H, J = 8.0 Hz), 7.80-7.77 (m, 1H), 7.37-7.34 (m, 1H), 3.62-3.59 (m, 2H), 1.66-1.60 (sept, 2H, J = 4.0 Hz), 1.39-1.31 (sept, 2H, J = 8.0 Hz), 0.91-0.85 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 161.6, 154.5, 149.3, 136.4, 124.5, 121.0, 61.1, 32.6, 20.3, 13.7.

3.4.3. Procedure for the synthesis of arene-Ru(II) complexes ([Ru]-11-[Ru]-20) containing pyridine-based ligands.

Synthesis of [(η^6-p-cymene)Ru(κ^2-N,O-pyridine-2-carboxylate)Cl] ([Ru]-11). Complex **[Ru]-11** was prepared by the modified procedure.*[16]* [(η^6-*p*-cymene)$RuCl_2$]$_2$ **([Ru]-A)** (0.306 g, 0.5 mmol) was suspended in methanol (25 mL) and stirred for 30 minute at room temperature, and was added pyridine-2-carboxylic acid (0.135, 1.1 mmol). After refluxing the reaction mixture for 12 h, all volatiles were removed on rotavaporator and the residue obtained was dissolved in a minimum amount of dichloromethane. Upon addition of excess of diethyl ether in the above dichloromethane solution, yellow solid was precipitated out. Yield: 85% (0.260 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.99 (d, 1H, J = 8.0 Hz), 7.98-7.94 (m, 2H), 7.59 (d, 1H, J = 8.0 Hz), 5.63 (d, 2H, J = 4.0 Hz), 5.47 (d, 2H, J = 8.0 Hz), 2.88 (m, 1H), 2.28 (s, 3H), 1.23 (d, 6H, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) =171.2, 153.1 151.1, 139.4, 128.4, 127.0, 102.6, 98.6, 83.2, 83.0, 82.1, 81.1, 31.1, 22.5, 22.49, 19.1. IR (cm^{-1}) = 1634 ($\upsilon_{C=O}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 252 (5400), 320 (2400), 410 (400). MS (ESI) m/z calculated: 358.02 $[M-Cl]^+$ $[C_{16}H_{18}NO_2Ru]$, Found: 358.03 $[M-Cl]^+$ $[C_{16}H_{18}NO_2Ru]$.

Synthesis of [(η^6-p-cymene)Ru(κ^2-N,O-2-acetylpyridine)Cl]PF_6 ([Ru]-12). Complex **[Ru]-12** was synthesized following modified procedure,[16] by refluxing [(η^6-*p*-cymene)$RuCl_2$]$_2$ **([Ru]-A)** (0.306 g, 0.5 mmol) and 2-acetylpyridine (124 μL, 1.1 mmol) in methanol (25 mL) for 24 h. Upon cooling to room temperature, 3 equiv. of NH_4PF_6 (0.489 g) was added and the solution was stirred for 4 h at room temperature. Then, solvent was removed on rotavapour and the obtained residue was dissolved in a minimum amount of dichloromethane. To the filtered dichloromethane solution, excess of diethyl ether was added to precipitate out a green solid. Yield: 89% (0.272 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.26 (d, 1H, *J* = 8.0 Hz), 8.25 (d, 1H, *J* = 8.0 Hz), 8.20-8.16 (m, 1H), 7.90-7.86 (m, 1H), 6.02 (d, 1H, *J* = 8.0 Hz), 5.90 (d, 1H, *J* = 4.0 Hz), 5.82 (d, 1H, *J* = 8.0 Hz), 5.76 (d, 1H, *J* = 8.0 Hz), 3.02-2.97 (sept, 1H, *J* = 8.0 Hz), 2.95 (s, 3H), 2.31 (s, 3H), 1.39 (d, 6H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 211.0, 154.4, 151.1, 140.2, 131.9, 130.4, 103.7, 99.4, 85.7, 83.4, 83.3, 82.5, 31.3, 30.9, 22.5, 22.1, 18.3. ^{31}P NMR (161.97 MHz, $CDCl_3$) δ (ppm) = -144.6. IR (cm^{-1}) = 1615 ($\upsilon_{C=O}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 270 (4800), 370 (1400), 437 (1100). MS (ESI) m/z calculated: 392.03 $[M]^+$ [$C_{17}H_{21}ClNORu$], Found: 392.03 $[M]^+$ [$C_{17}H_{21}ClNORu$].

Synthesis of [(η^6-p-cymene)Ru(κ^2-N,O-2-methylpicolinate)Cl]PF_6 ([Ru]-13). Complex **[Ru]-13** was synthesized by stirring [(η^6-*p*-cymene)$RuCl_2$]$_2$ **([Ru]-A)** (0.306 g, 0.5 mmol) and 2-methylpicolinate (0.150 mg, 1.1 mmol) in dichloromethane (25 mL) at room temperature for 24 h. Volume was then reduced and 10 mL methanol was added followed by the addition of 3 equiv. of NH_4PF_6 (0.489 g). The resulting mixture was stirred for 4 h at room temperature. Volume of solution was again reduced to 5 mL under vacuum and complex was dissolved in minimum amount of dichloromethane. An excess of NH_4PF_6 was removed and complex was precipitated out with excess of diethyl ether as an orange colored solid. Yield: 80% (0.244 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.21 (d, 1H, *J* = 8.0 Hz), 8.12-8.09 (m, 2H), 7.92-7.89 (m, 1H), 6.04 (d, 1H, *J* = 8.0 Hz), 5.89 (d, 1H, *J* = 4.0 Hz), 5.83 (d, 2H, *J* = 4.0 Hz), 4.30 (s, 3H), 3.00-2.96 (sept, 1H, *J* = 8.0 Hz), 2.30 (s, 3H), 1.38 (d, 6H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 202.0, 152.8, 145.1, 139.4, 128.7, 127.1, 102.6, 98.7, 82.7, 82.5, 81.7, 80.7, 31.0, 29.6, 22.23, 22.21, 18.6. ^{31}P NMR (161.97 MHz, $CDCl_3$) δ (ppm) = -144.6. IR (cm^{-1}) = 1599 ($\upsilon_{C=O}$). UV/vis

(MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 250 (5000), 316 (2600), 415 (600). MS (ESI) m/z calculated: 408.03 $[M]^+$ $[C_{17}H_{21}ClNO_2Ru]$, Found: 408.03 $[M]^+$ $[C_{17}H_{21}ClNO_2Ru]$.

Synthesis of [(η^6-p-cymene)Ru(κ^2-N,N-(N-benzyl-pyridylmethyleneamine))Cl]PF_6 ([Ru]-14). Complex **[Ru]-14** was synthesized following the analogous procedure as used for complex **[Ru]-12**, by stirring $[(\eta^6$-*p*-cymene)$RuCl_2]_2$ **([Ru]-A)** (0.306 g, 0.5 mmol) and N-benzyl-pyridylmethyleneamine (0.215 mg, 1.1 mmol) in methanol (25 mL) at room temperature for 24 h. Brown solid. Yield: 89% (0.272 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.32 (d, 1H, *J* = 8.0 Hz), 8.04 (s, 1H), 7.99-7.95 (m, 1H), 7.82 (d, 1H, *J* = 8.0 Hz) 7.67-7.63 (m, 1H), 7.47 (s, 5H), 5.84 (d, 1H, *J* = 4.0 Hz), 5.68-5.64 (m, 2H), 5.60 (d, 1H, *J* = 4.0 Hz), 2.74-2.67 (sept, 1H, *J* = 8.0 Hz), 2.13 (s, 2H), 1.59 (s, 3H), 1.15-1.07 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 166.0, 155.6, 154.3, 139.3, 133.2, 130.1, 129.6, 129.5, 129.0, 128.6, 106.9, 102.1, 86.1, 85.3, 85.0, 84.7, 69.5, 31.1, 22.1, 21.8, 18.4. ^{31}P NMR (161.97 MHz, $CDCl_3$) δ (ppm) = -149.3. IR (cm^{-1}) = 1598 ($\upsilon_{C=N\ imine}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 264 (3600), 330 (2200), 427 (1000). MS (ESI) m/z calculated: 467.08 $[M]^+$ $[C_{23}H_{26}ClN_2Ru]$, Found: 467.08 $[M]^+$ $[C_{23}H_{26}ClN_2Ru]$.

Synthesis of [(η^6-p-cymene)Ru(κ^2-N,N-(N-butyl-pyridylmethyleneamine))Cl]PF_6 ([Ru]-15). **[Ru]-15** was synthesized following the above procedure as used for complex **[Ru]-12** by stirring $[(\eta^6$-*p*-cymene)$RuCl_2]_2$ **([Ru]-A)** (0.306 g, 0.5 mmol) and N-butyl-pyridylmethyleneamine (0.178 mg, 1.1 mmol) in methanol (25 mL) at room temperature for 24 h. Brown solid. Yield: 85% (0.260 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.26 (d,1H, *J* = 8.0 Hz), 8.37 (s, 1H), 8.03-7.99 (m, 1H), 7.94 (d, 1H, *J* = 8.0 Hz), 7.65-7.63 (m, 1H), 5.83 (d, 1H, *J* = 4.0 Hz), 5.79 (d, 1H, *J* = 8.0 Hz), 5.70 (d, 1H, *J* = 4.0 Hz), 5.62 (d, 1H, *J* = 4.0 Hz), 4.45-4.31 (m, 2H), 2.76-2.73 (sept, 1H, *J* = 8.0 Hz), 2.21 (s, 3H), 1.09-1.96 (m, 2H), 1.44-1.41 (m, 2H), 1.15 (d, 3H, *J* = 8.0 Hz), 1.10 (d, 3H, *J* = 8.0 Hz), 0.99-0.96 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 165.8, 155.4, 154.4, 139.4, 128.6, 128.5, 106.9, 102.1, 86.2, 85.4, 85.3, 84.9, 67.0, 31.3, 31.1, 22.0, 21.9, 20.0, 18.5, 13.6. ^{31}P NMR (161.97 MHz, $CDCl_3$) δ (ppm) = -149.4. IR (cm^{-1}) = 1599 ($\upsilon_{C=N\ imine}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 272 (6400), 357 (2400), 415 (1800). MS (ESI) m/z calculated: 433.09 $[M]^+$ $[C_{20}H_{28}ClN_2Ru]$, Found: 433.10 $[M]^+$ $[C_{20}H_{28}ClN_2Ru]$.

Synthesis of [(η^6-benzene)Ru(κ^2-N,O-pyridine-2-carboxylate)Cl] ([Ru]-16). Complex **[Ru]-16** was synthesized by following the analogous procedure used for the synthesis of complex **[Ru]-11** by refluxing [(η^6-benzene)$RuCl_2$]$_2$ **([Ru]-B)** (0.250 g, 0.5 mmol) and pyridine-2-carboxylic acid (0.135, 1.1 mmol) in methanol (25 mL) for 12 h. Brown solid. Yield: 80% (0.200 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 9.38 (d, 1H, J = 4.0 Hz), 8.08 (d, 1H, J = 8.0 Hz), 7.75 (d, 2H, J = 8.0 Hz), 5.93 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 170.3, 154.1, 150.3, 139.7, 127.9, 125.3, 83.2. IR (cm^{-1}) = 1655 ($\upsilon_{C=O}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 250 (2200), 312 (1000), 391 (200). MS (ESI) m/z calculated: 301.97 $[M\text{-}Cl]^+$ $[C_{12}H_{10}NO_2Ru]$, Found: 301.97 $[M\text{-}Cl]^+$ $[C_{12}H_{10}NO_2Ru]$.

Synthesis of [(η^6-benzene)Ru(κ^2-N,O-2-acetylpyridine)Cl]PF_6 ([Ru]-17). Complex **[Ru]-17** was synthesized by following the analogous procedure used for the synthesis of complex **[Ru]-12** by refluxing [(η^6-benzene)$RuCl_2$]$_2$ **([Ru]-B)** (0.250 g, 0.5 mmol) and 2-acetylpyridine (124 µL, 1.1 mmol) in methanol (25 mL) for 24 h. Green solid. Yield: 87% (0.217 g). ^{1}H NMR (400 MHz, Acetone-d_6) δ (ppm) = 8.96 (d, 1H, J = 8.0 Hz), 7.91 (d, 1H, J = 8.0 Hz), 7.69-7.65 (m, 1H), 7.31-7.28 (m, 1H), 5.48 (s, 6H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6) δ (ppm) = 213.0, 157.2, 152.0, 142.2, 133.2, 132.2, 86.4, 30.4. ^{31}P NMR (161.97 MHz, Acetone-d_6) δ (ppm) = -139.9. IR (cm^{-1}) = 1567 ($\upsilon_{C=O}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 268 (3000), 380 (600), 435 (400). MS (ESI) m/z calculated: 335.97 $[M]^+$ $[C_{13}H_{13}ClNORu]$, Found: 335.97 $[M]^+$ $[C_{13}H_{13}ClNORu]$.

Synthesis of [(η^6-benzene)Ru(κ^2-N,O-2-methylpicolinate)Cl]PF_6 ([Ru]-18). Complex **[Ru]-18** was synthesized by following the analogous procedure used for the synthesis of complex **[Ru]-13** by stirring [(η^6-benzene)$RuCl_2$]$_2$ **([Ru]-B)** (0.250 g, 0.5 mmol) and 2-methylpicolinate (0.150 mg, 1.1 mmol) in dichloromethane (25 mL) at room temperature for 24 h. Orange solid. Yield: 83% (0.207 g). ^{1}H NMR (400 MHz, Acetone-d_6) δ (ppm) = 8.70 (d, 1H, J = 4.0 Hz), 7.45-7.41(m, 1H), 7.31 (d, 1H, J = 8.0 Hz), 7.13-7.10 (m, 1H), 5.30 (s, 6H), 3.37 (s, 3H). ^{13}C NMR (100 MHz, Acetone-d_6) δ (ppm) = 206.8, 157.1, 145.7, 142.2, 133.0, 129.0, 85.2, 58.3. ^{31}P NMR (161.97 MHz, Acetone-d_6) δ (ppm) = -144.6. IR (cm^{-1}) = 1596 ($\upsilon_{C=O}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 260 (5000), 320 (1600), 394 (600). MS (ESI) m/z calculated: 351.96 $[M]^+$ $[C_{13}H_{13}ClNO_2Ru]$, Found: 351.97 $[M]^+$ $[C_{13}H_{13}ClNO_2Ru]$.

Synthesis of [(η^6-benzene)Ru(κ^2-N,N-(N-benzyl-pyridylmethyleneamine))Cl]PF_6 ([Ru]-19). Complex **[Ru]-19** was synthesized following a modified procedure,[15d] analogous to that used for synthesis of complex **[Ru]-14** by stirring [(η^6-benzene)$RuCl_2$]$_2$ **([Ru]-B)** (0.250 g, 0.5 mmol) and N-benzyl-pyridylmethyleneamine (0.215 mg, 1.1 mmol) in methanol (25 mL) at room temperature for 24 h. Brown solid. Yield: 88% (0.220 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 9.62 (d, 1H, J = 8.0 Hz), 8.38 (s, 1H), 8.19 (d, 2H, J = 8.0 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.49-7.44 (m, 5H), 6.10 (s, 6H), 3.31 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 167.2, 156.0, 154.5, 139.7, 134.4, 129.7, 129.1, 128.7, 128.3, 121.9, 87.8, 68.5. ^{31}P NMR (161.97 MHz, DMSO-d_6) δ (ppm) = -148.9. IR (cm^{-1}) = 1601 ($\upsilon_{C=N\ imine}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 270 (4600), 350 (1600), 576 (40). MS (ESI) m/z calculated: 411.01 [M]$^+$ [$C_{19}H_{18}ClN_2Ru$], Found: 411.03 [M]$^+$ [$C_{19}H_{18}ClN_2Ru$].

Synthesis of [(η^6-benzene)Ru(κ^2-N,N-(N-butyl-pyridylmethyleneamine))Cl]PF_6 ([Ru]-20). Complex **[Ru]-20** was synthesized by following the analogous procedure used for synthesis of complex **[Ru]-15** by stirring [(η^6-benzene)$RuCl_2$]$_2$ **([Ru]-B)** (0.250 g, 0.5 mmol) and N-butyl-pyridylmethyleneamine (0.178 mg, 1.1 mmol) in methanol (25 mL) at room temperature for 24 h. Brown solid. Yield: 82% (0.205 g). ^{1}H NMR (400 MHz, Acetone-d_6) δ (ppm) = 9.63 (d, 1H, J = 8.0 Hz), 8.76 (s, 1H), 8.26 (d, 1H, J = 8.0 Hz), 8.21 (d, 1H, J = 8.0 Hz), 7.81 (d, 1H, J = 4.0 Hz), 6.23 (s, 6H), 4.75-4.71 (m, 1H), 4.49-4.43 (m, 1H), 2.03-1.97 (m, 2H), 1.44-1.40 (m, 2H), 0.96-0.92 (m, 3H). ^{13}C NMR (100 MHz, Acetone-d_6) δ (ppm) = 168.2, 157.3, 156.4, 141.1, 130.0, 129.3, 88.6, 68.1, 32.8, 21.2, 14.3. ^{31}P NMR (161.97 MHz, Acetone-d_6) δ (ppm) = -144.2. IR (cm^{-1}) = 1634 ($\upsilon_{C=N\ imine}$). UV/vis (MeOH, λ_{max}/nm) (ε_{max}/M^{-1} cm^{-1}) = 272 (5200), 348 (2200), 410 (1200). MS (ESI) m/z calculated: 377.03 [M]$^+$ [$C_{16}H_{20}ClN_2Ru$], Found: 377.04 [M]$^+$ [$C_{16}H_{20}ClN_2Ru$].

3.4.4. General procedure for catalytic ortho C−H bond arylation of 2-phenylpyridine with aryl halides.

All the reactions were carried out under N_2 atmosphere. C-H bond arylation reactions of 2-phenylpyridine were performed in a two necked round bottom flask. Flask was charged with ruthenium catalyst (5 mol %, 0.025 mmol) and K_2CO_3 (3 equiv., 1.5 mmol, 0.207 g)

with distilled water (5 mL). Solution was stirred for 15 minutes and then added 2-phenylpyridine (0.5 mmol) and aryl halide (1.25 mmol). The reaction was continued to stir at 100 ºC for specified duration and then cooled down to room temperature. Further, the reaction mixture was extracted with ethyl acetate (3×10 mL) and the combine organic fractions was washed with 10 mL of brine solution and dried over Na_2SO_4. All the volatiles were removed under vacuum to obtain the crude product. Conversion and selectivity of the mono and biarylated products were determined by ^{1}H NMR. Products were purified and isolated from the crude reaction mixture by using column chromatography on silica gel with ethyl acetate/*n*-hexane as eluents.

3.4.5. General procedure to study the effect of carboxylate additives on ortho C-H bond arylation reaction.

To investigate the effect of carboxylate additives on *ortho* C-H bond arylation reaction, experiments were performed under the optimized reaction condition using 2-phenylpyrdine and 4-chloroanisole as substrates over the ruthenium catalysts **([Ru]-11/[Ru]-12)** with 3 equiv. of carboxylate salt (acetate, propionate, isobutyrate or pivalate) and 3 equiv. of K_2CO_3 under optimized reaction condition for 8 h. Reaction mixture was then cooled down to room temperature and extracted with ethyl acetate (3×10 mL) and the organic layer was dried over Na_2SO_4. The combined organic fraction was washed with the 10 mL of brine solution, and the solvent volume was reduced under pressure to recover the C-H arylated product. Conversion and selectivity for mono- and diarylated products were determined by ^{1}H NMR.

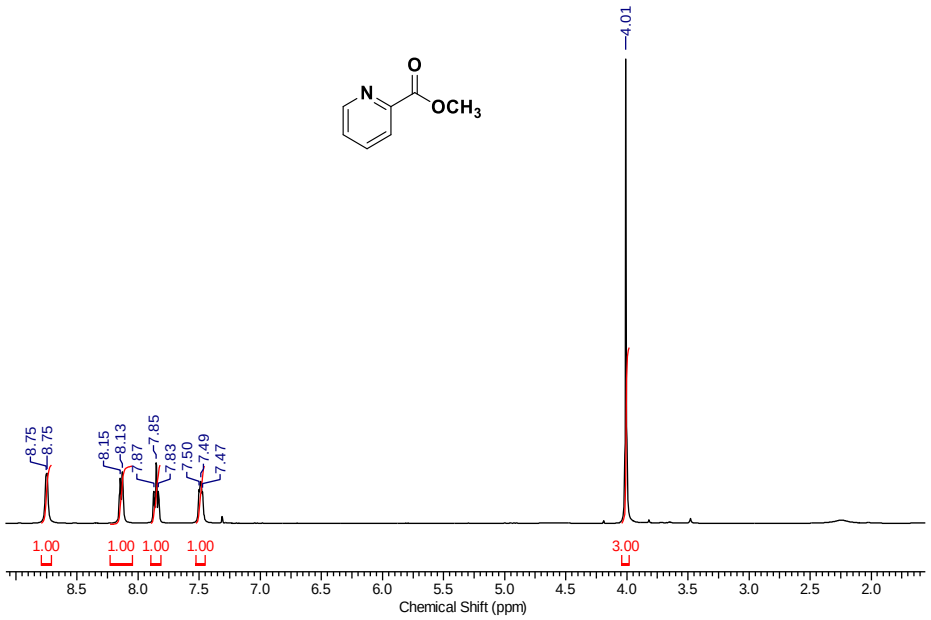
3.4.6. Typical procedure for stoichiometric reaction for the identification of cycloruthenated species

Mass studies were also carried out in a two necked reaction flask containing **[Ru]-12** (0.025 mmol, 0.0107 g) and 2-phenylpyridine (0.25 mmol, 36 µL) in 5 mL water keeping catalyst substrate ratio constant (C:S = 1:5) in the presence (3 equiv. K_2CO_3) or absence of base. Reaction mixture was then heated at 100 ºC under nitrogen atmosphere for 3 h. 100 µL of aliquot from the reaction mixture was withdrawn at different intervals of reaction time (0, 60, 120 and 180 minutes) which was diluted with methanol and ESI-MS

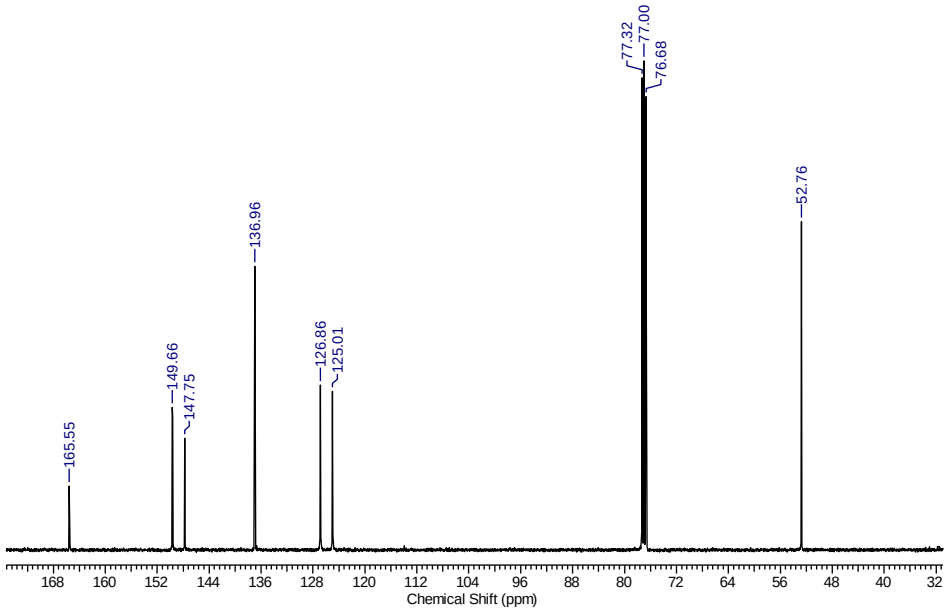
was recorded in positive mode. Mass spectra were analyzed, and active intermediates generated during the reaction have been identified.

3.4.7. Characterization of metal complexes

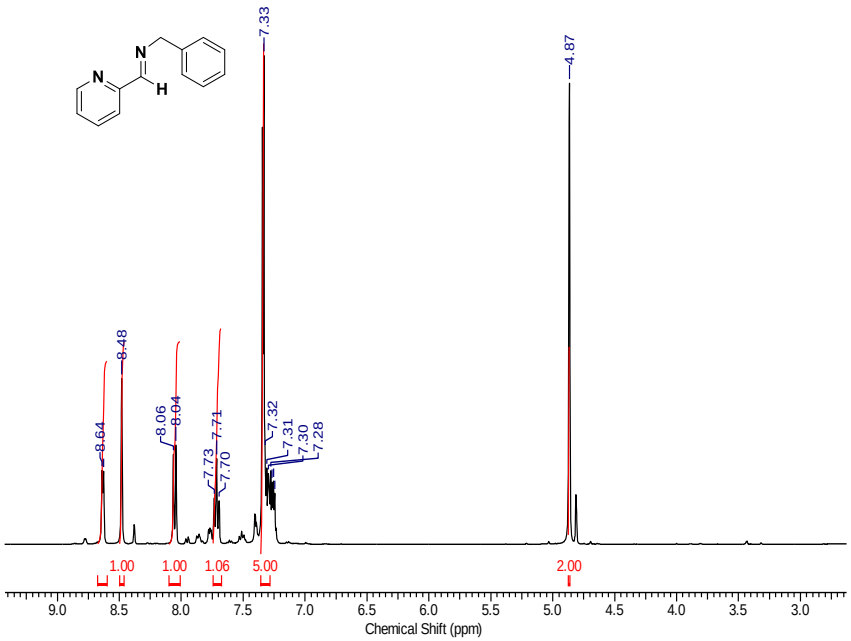
NMR spectra of synthesized ligands L8, L9 and L10.



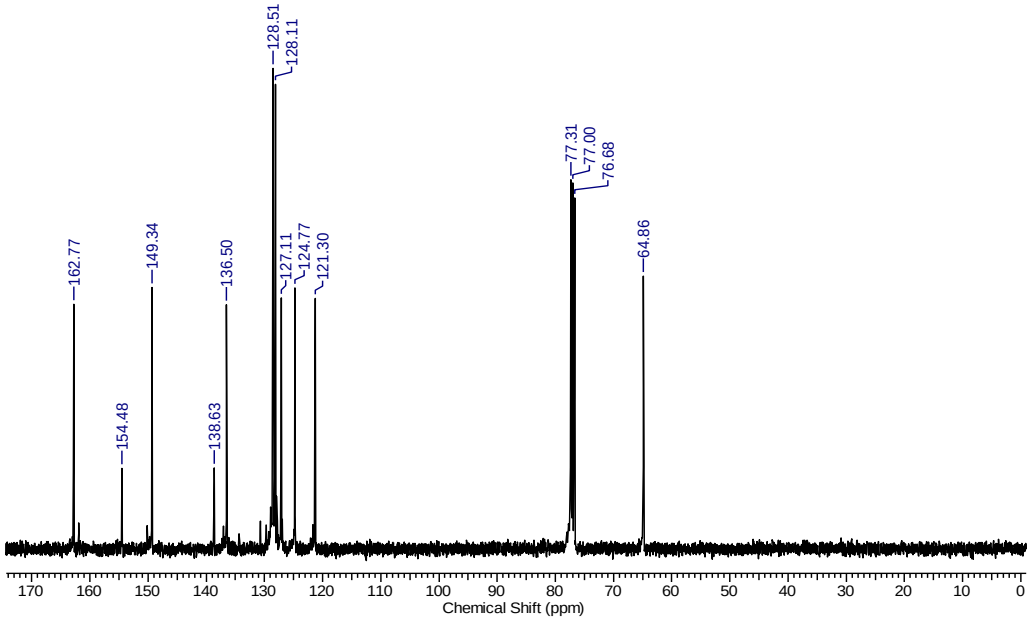
^{1}H NMR of L8 in $CDCl_3$



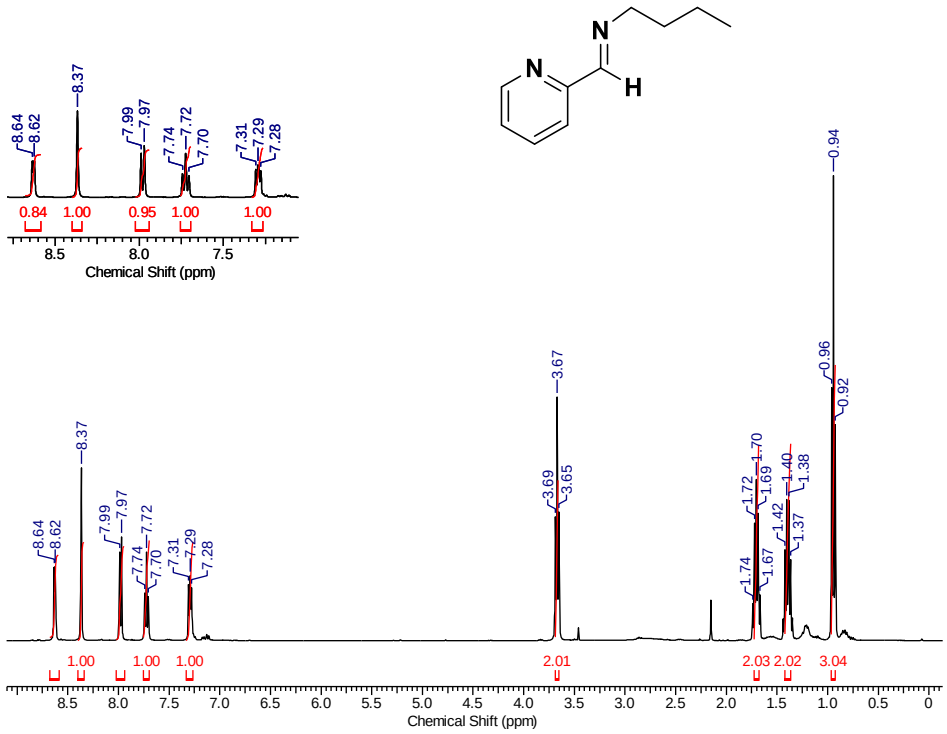
^{13}C NMR of L8 in $CDCl_3$



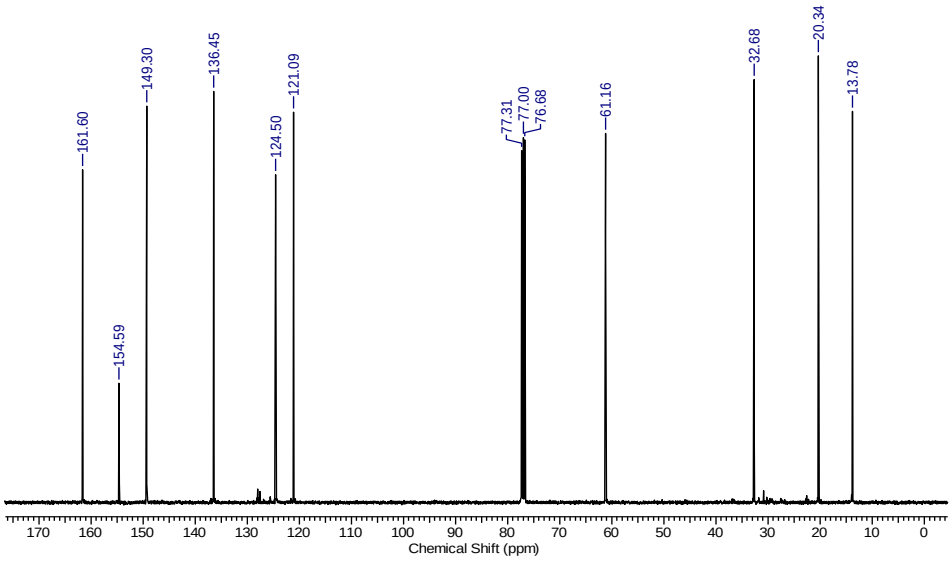
^{1}H NMR of L9 in $CDCl_3$



^{13}C NMR of L9 in $CDCl_3$

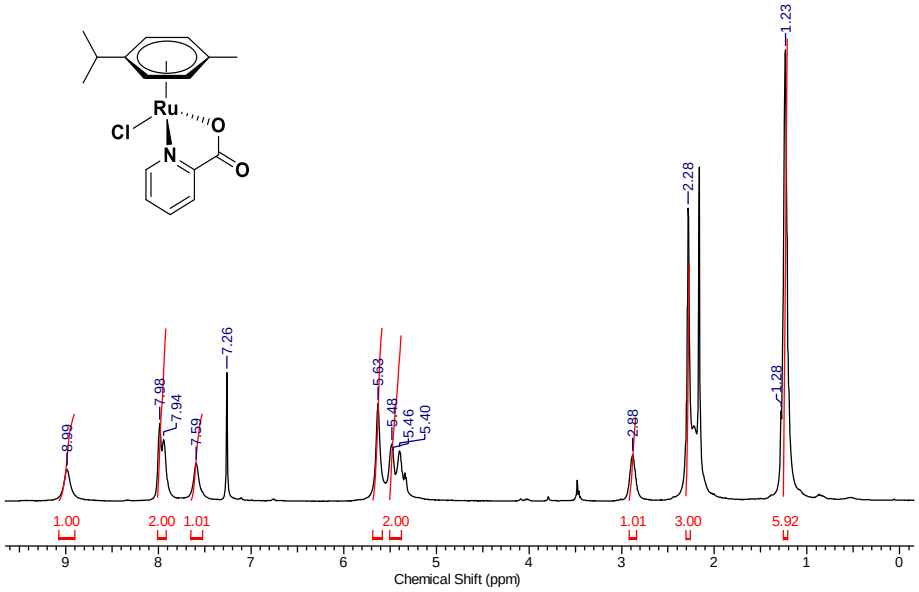


^{1}H NMR of L10 in $CDCl_3$

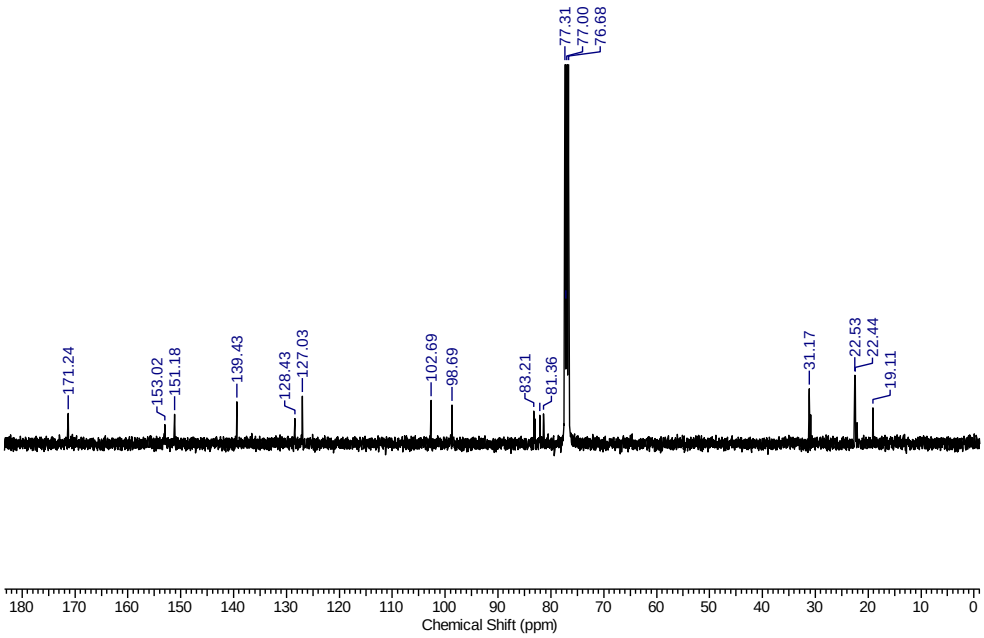


^{13}C NMR of L10 in $CDCl_3$

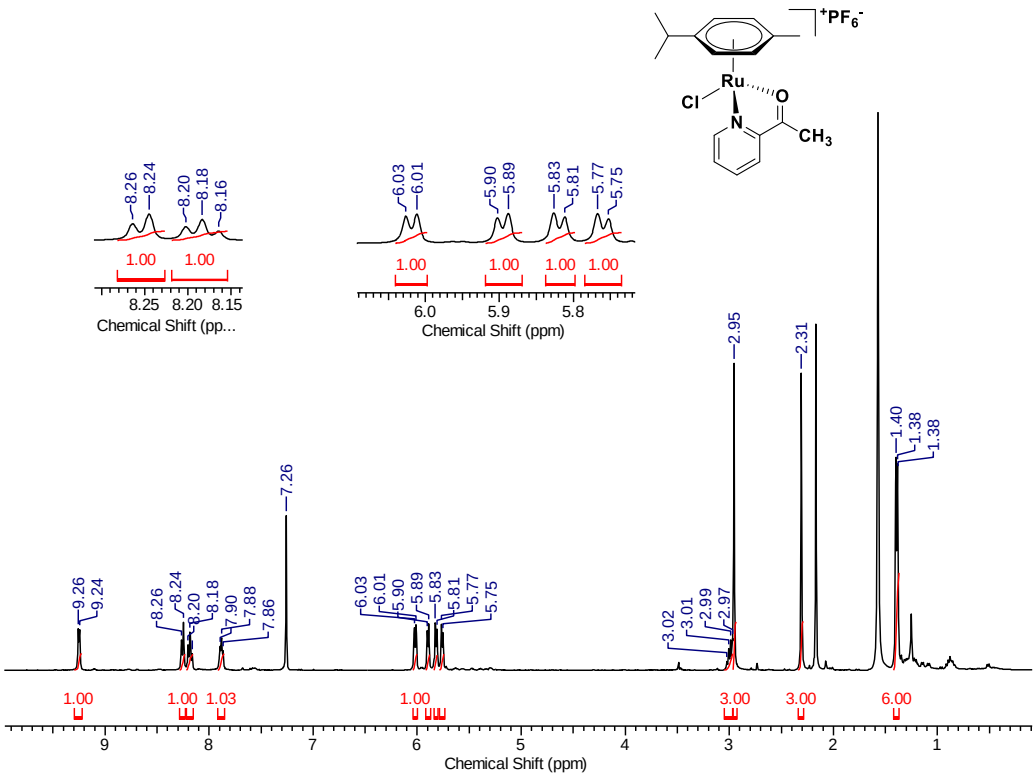
NMR spectra of arene-ruthenium complexes [Ru]-11 to [Ru]-20



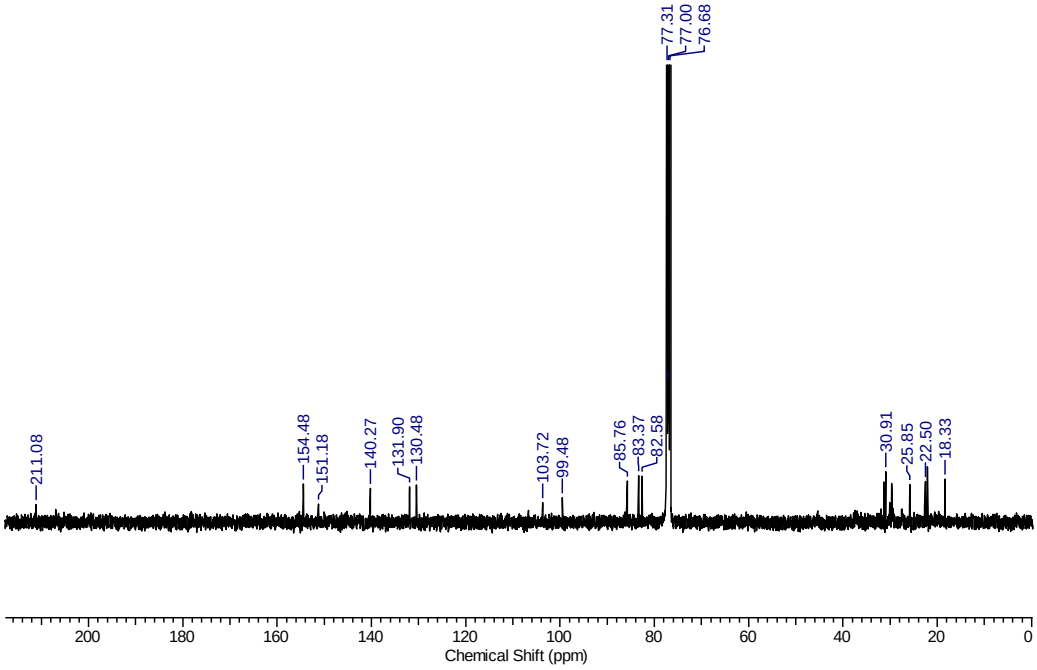
^{1}H NMR of [Ru]-11 in $CDCl_3$



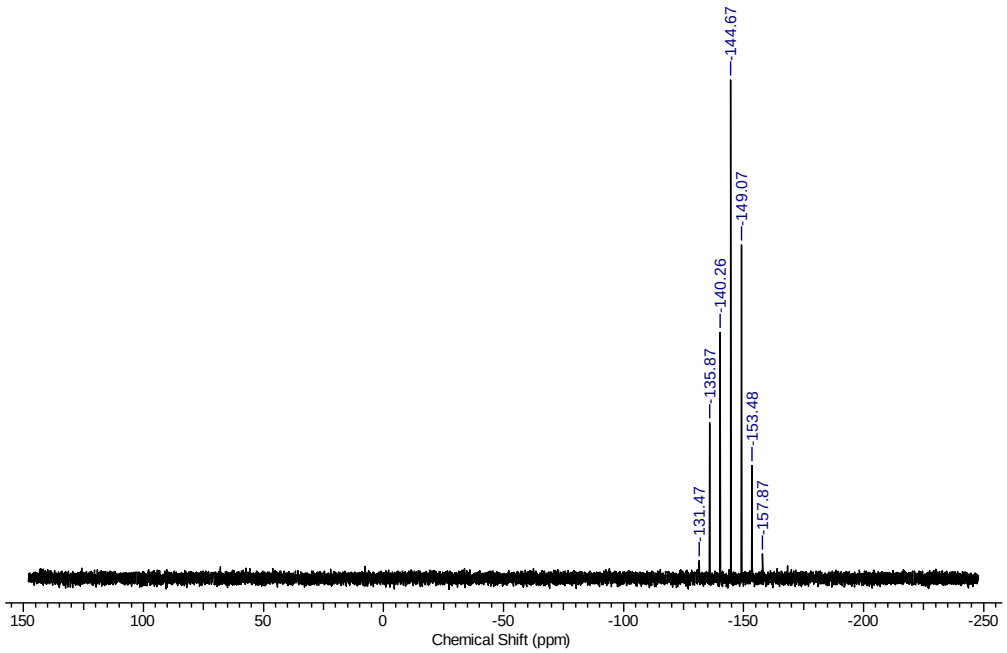
^{13}C NMR of [Ru]-11 in $CDCl_3$



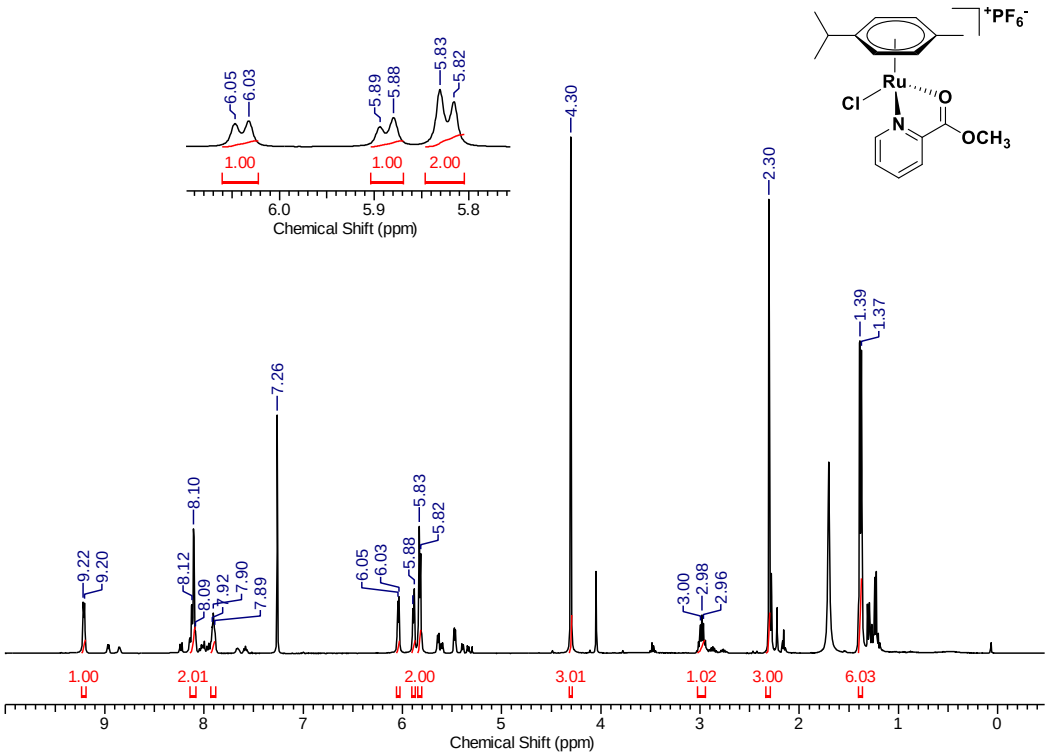
^{1}H NMR of complex [Ru]-12 in $CDCl_3$



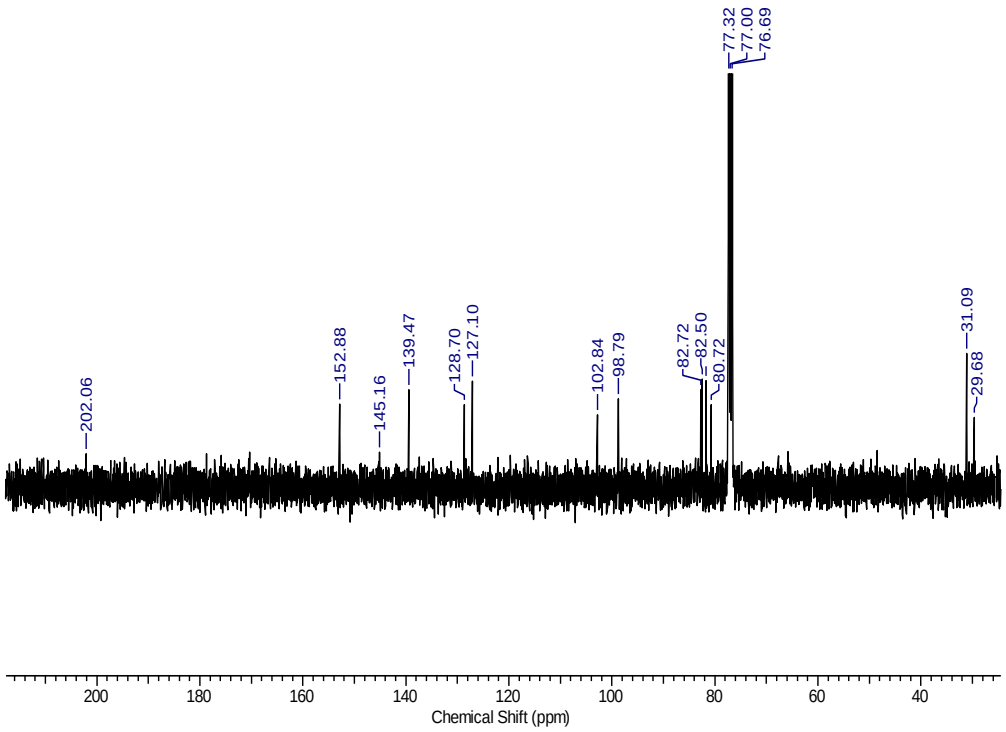
^{13}C NMR of complex [Ru]-12 in $CDCl_3$



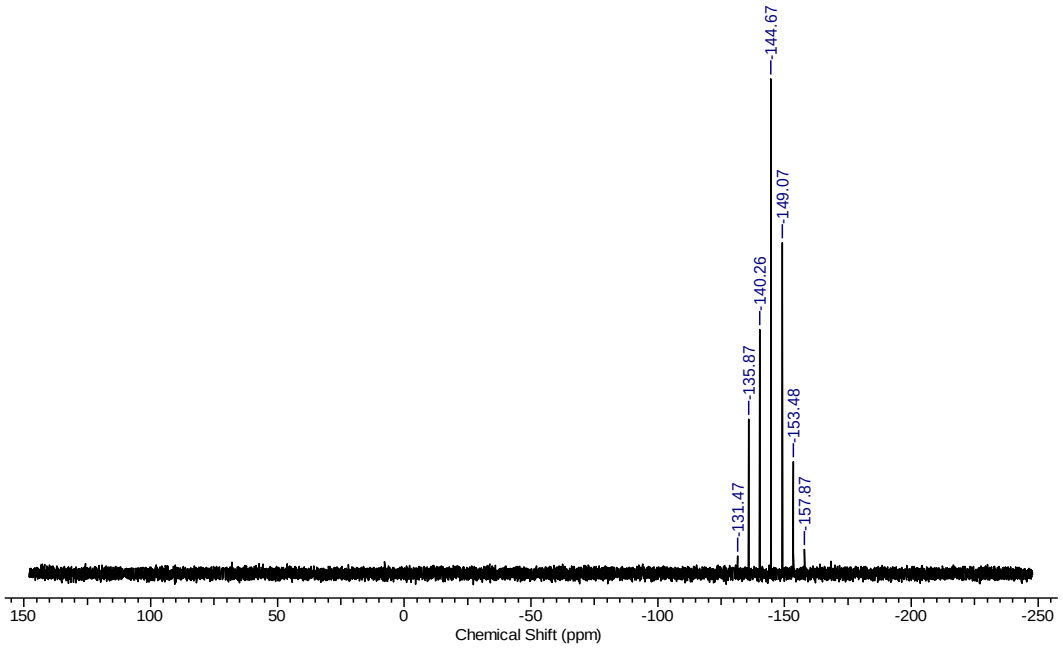
^{31}P NMR of complex [Ru]-12 in $CDCl_3$



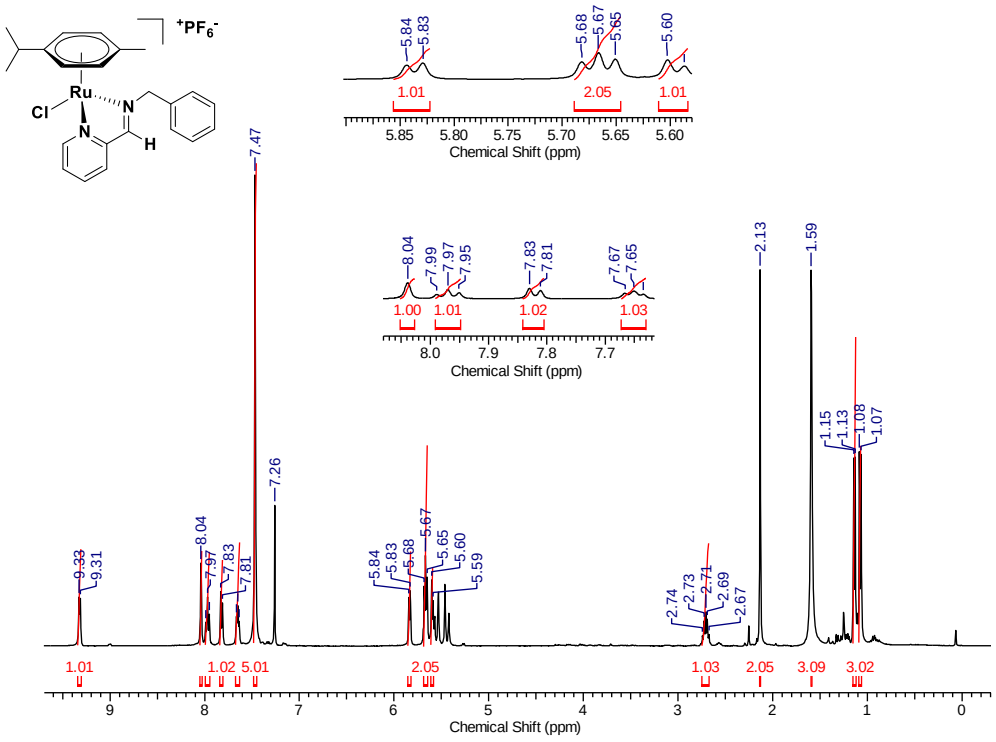
^{1}H NMR of complex [Ru]-13 in $CDCl_3$



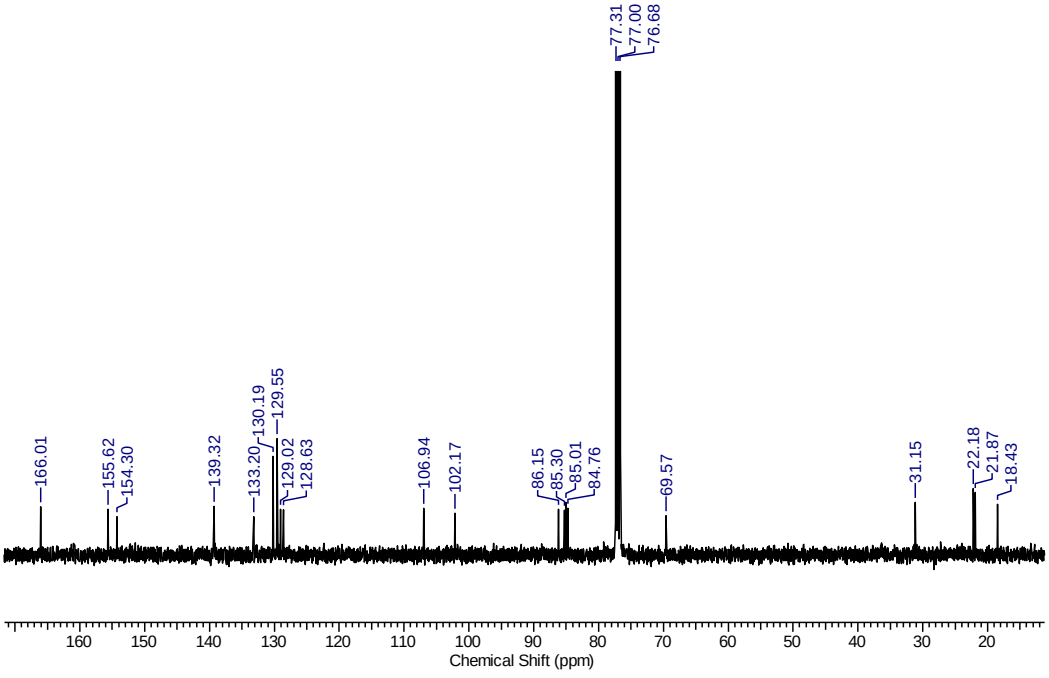
^{13}C NMR of complex [Ru]-13 in $CDCl_3$



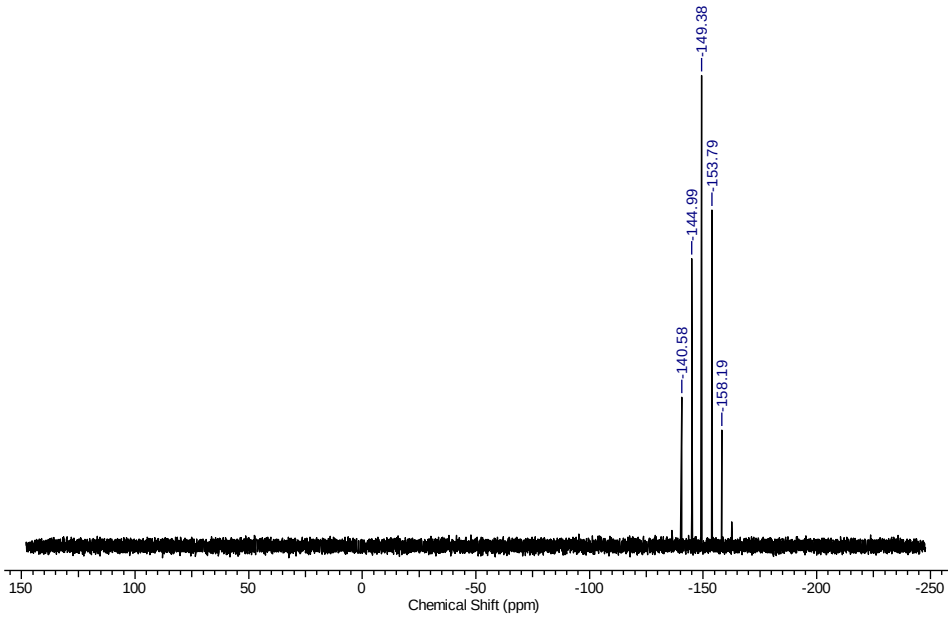
^{31}P NMR of complex [Ru]-13 in $CDCl_3$



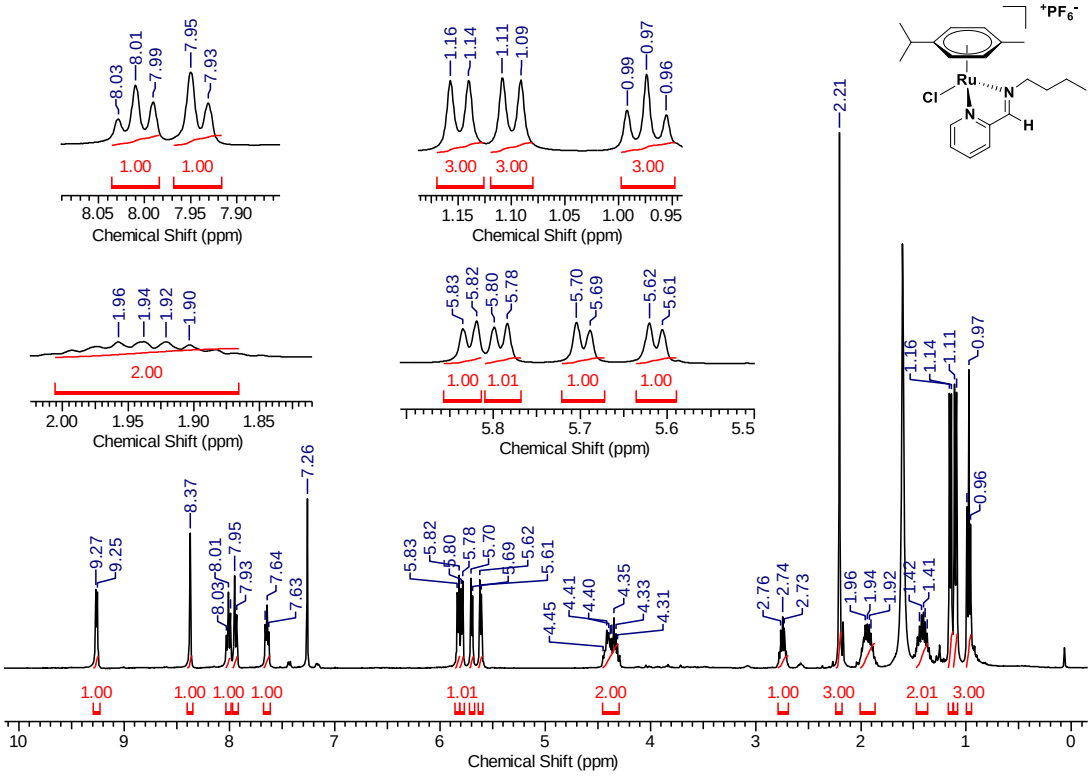
^{1}H NMR of complex [Ru]-14 in $CDCl_3$



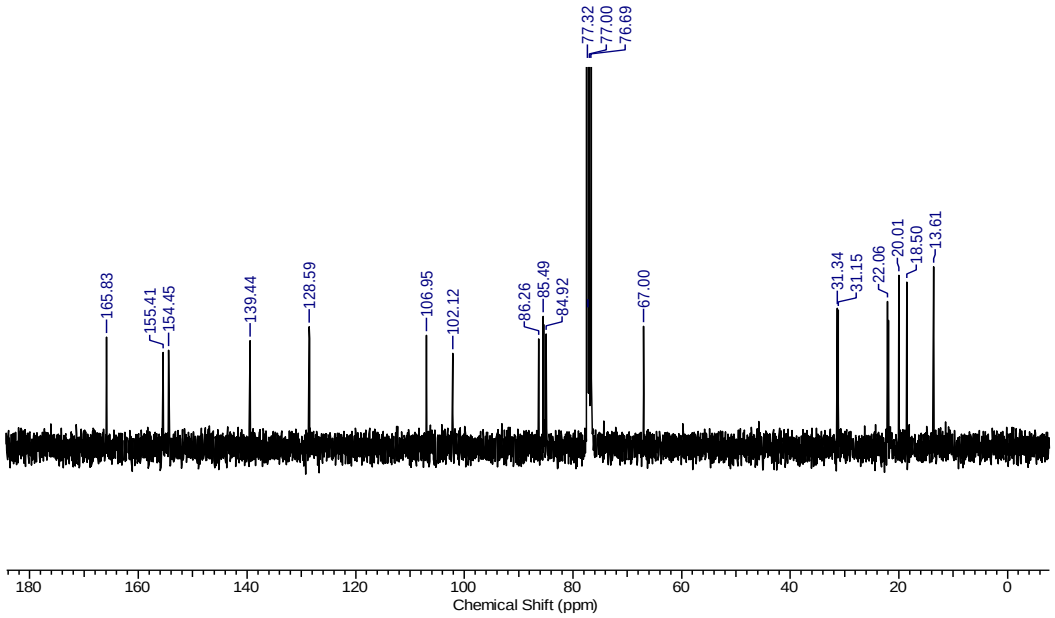
^{13}C NMR of complex [Ru]-14 in $CDCl_3$



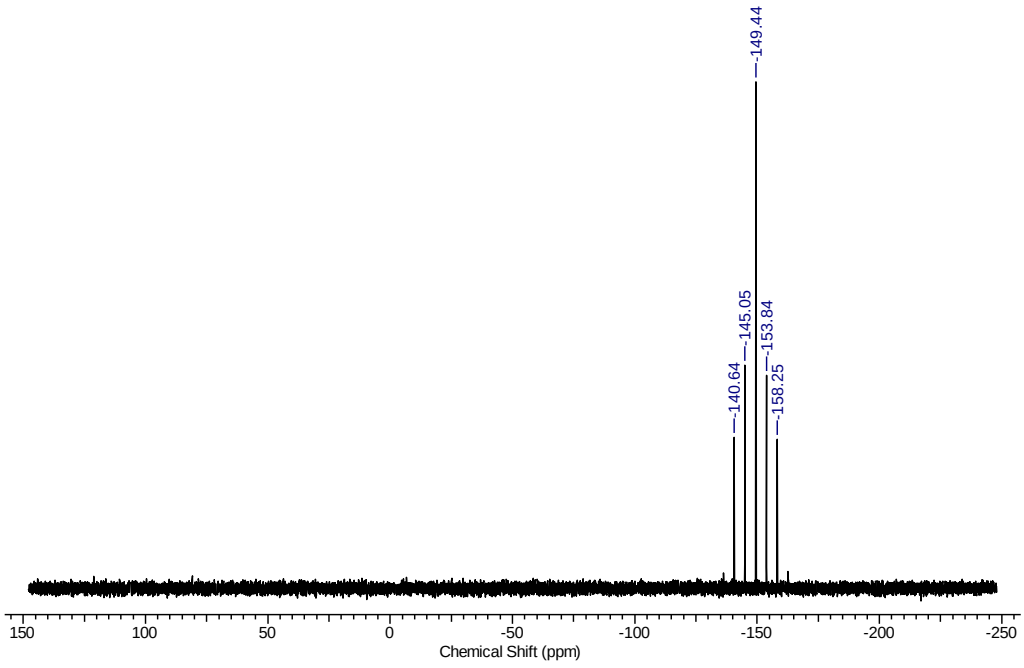
^{31}P NMR of complex [Ru]-14 in $CDCl_3$



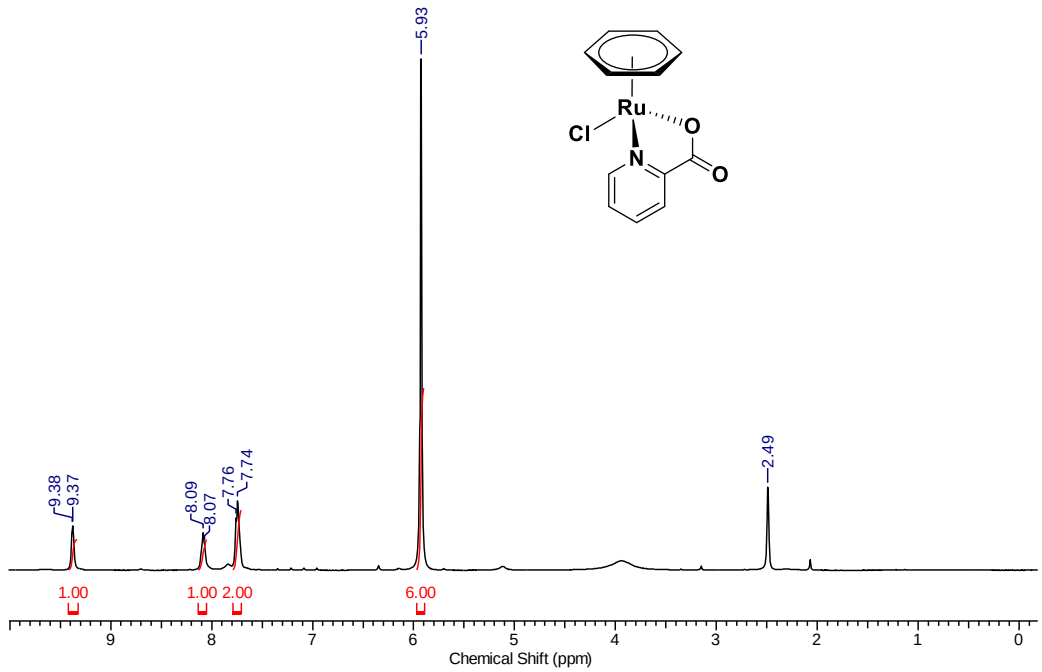
^{1}H NMR of complex [Ru]-15 in $CDCl_3$



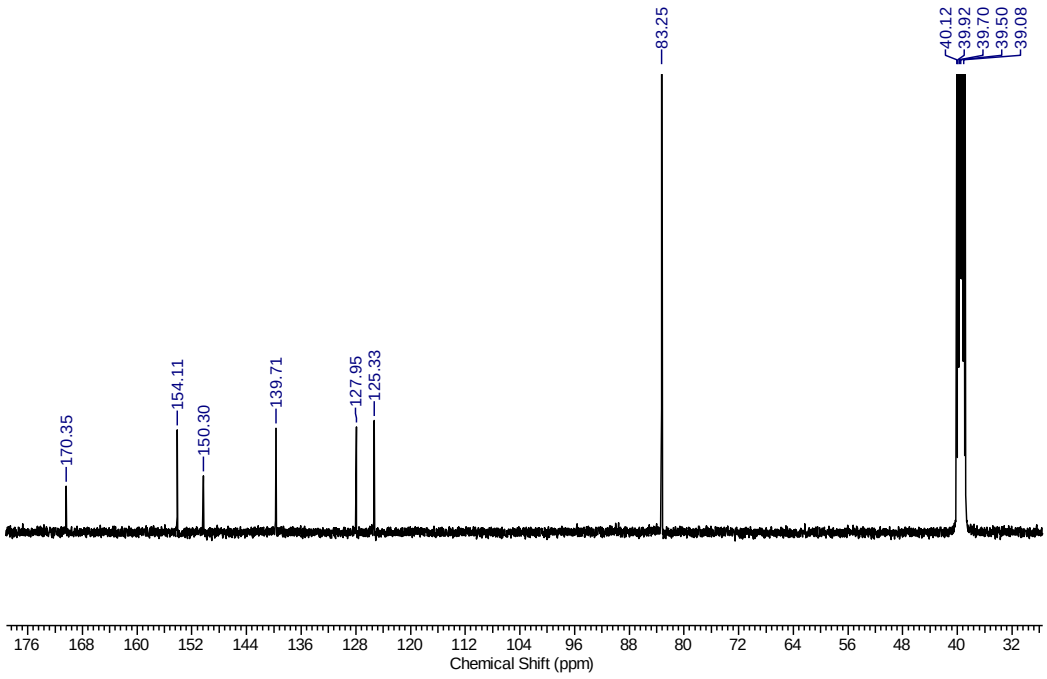
^{13}C NMR of complex [Ru]-15 in $CDCl_3$



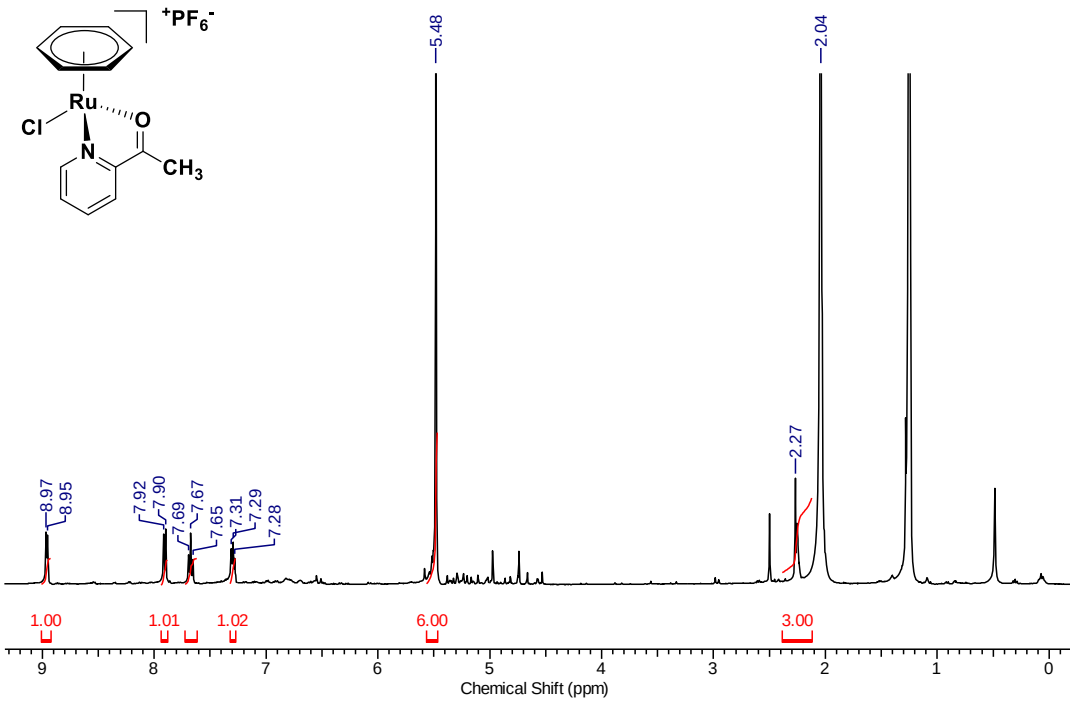
^{31}P NMR of complex [Ru]-15 in $CDCl_3$



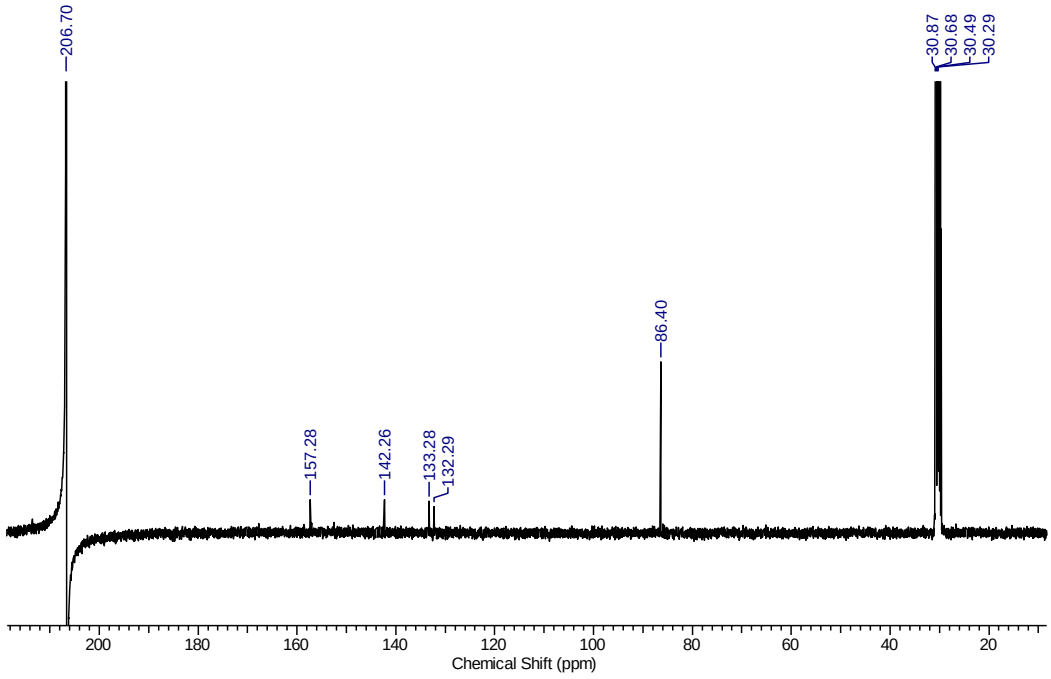
^{1}H NMR of complex [Ru]-16 in DMSO-*d*$_6$



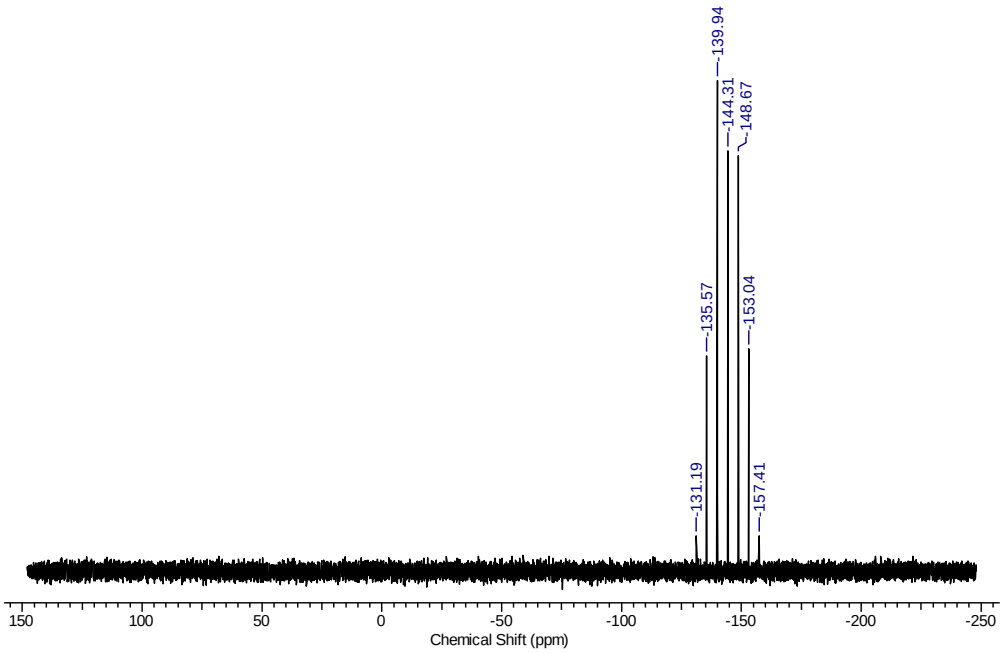
^{13}C NMR of complex [Ru]-16 in DMSO-*d*$_6$



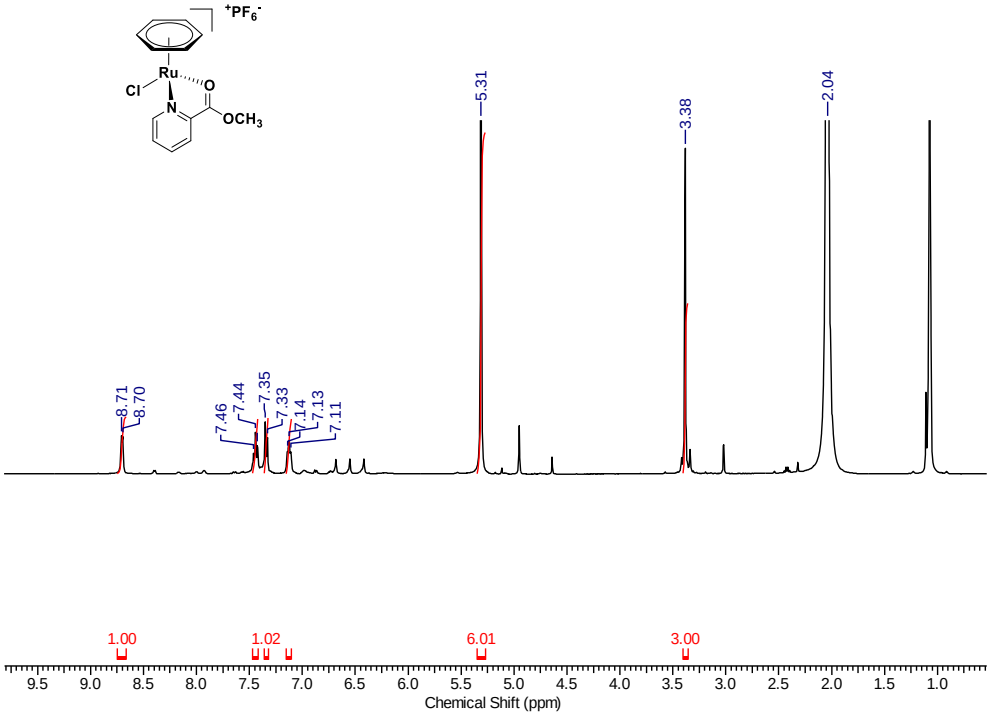
^{1}H NMR of complex [Ru]-17 in acetone-*d*$_6$



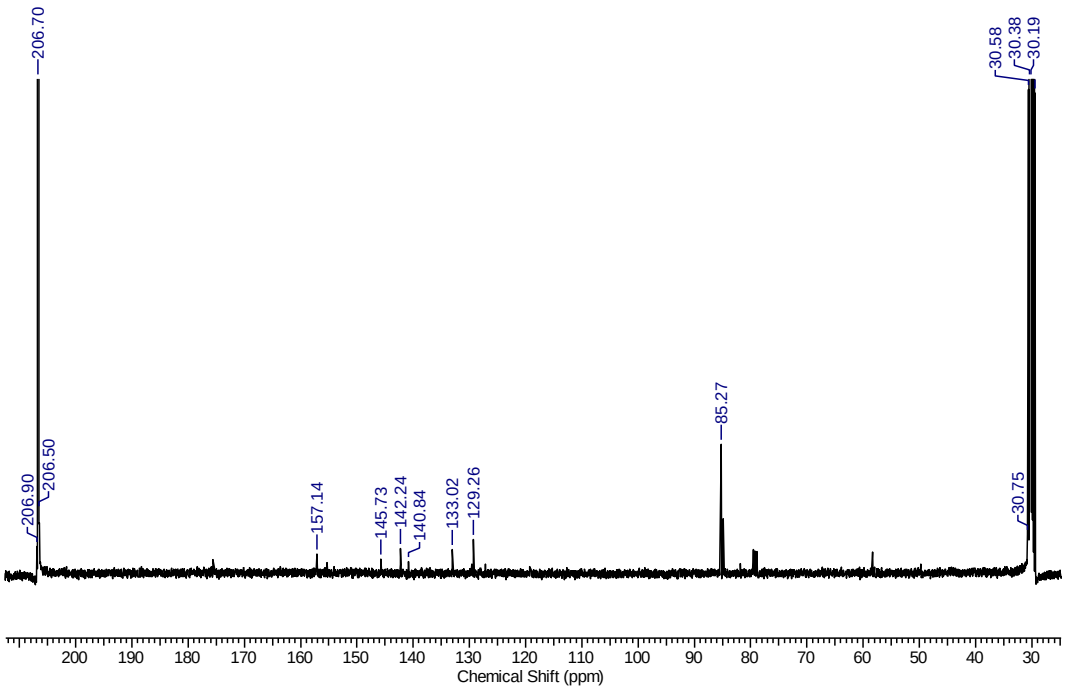
^{13}C NMR of complex [Ru]-17 in acetone-*d*$_6$



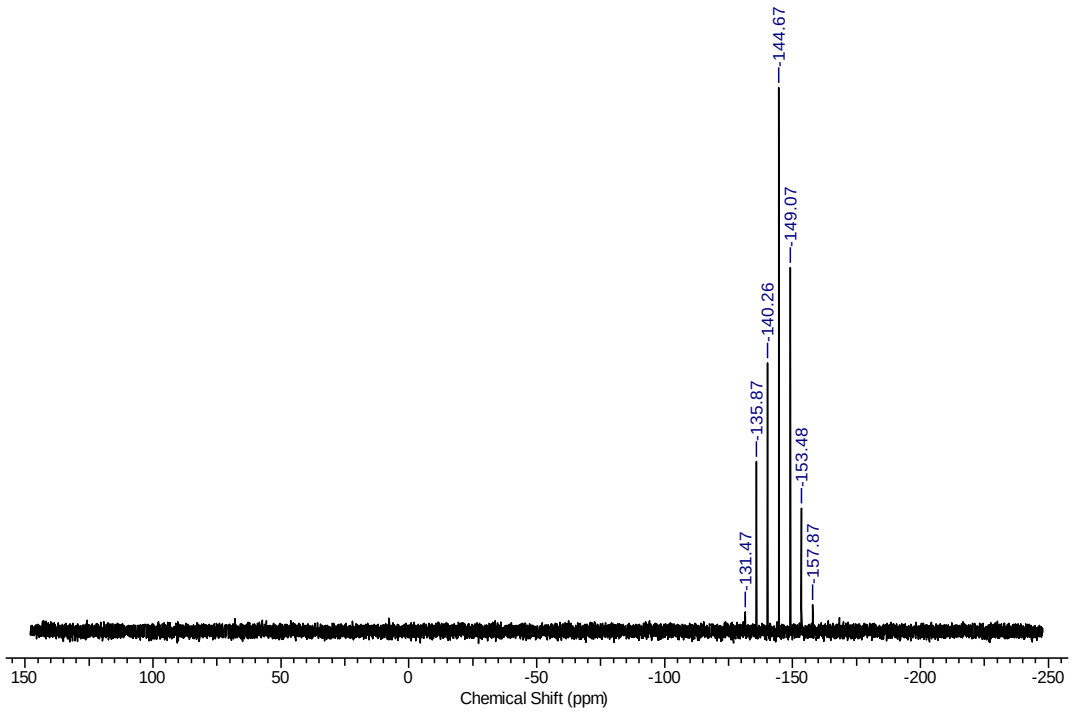
^{31}P NMR of complex [Ru]-17 in acetone-*d*$_6$



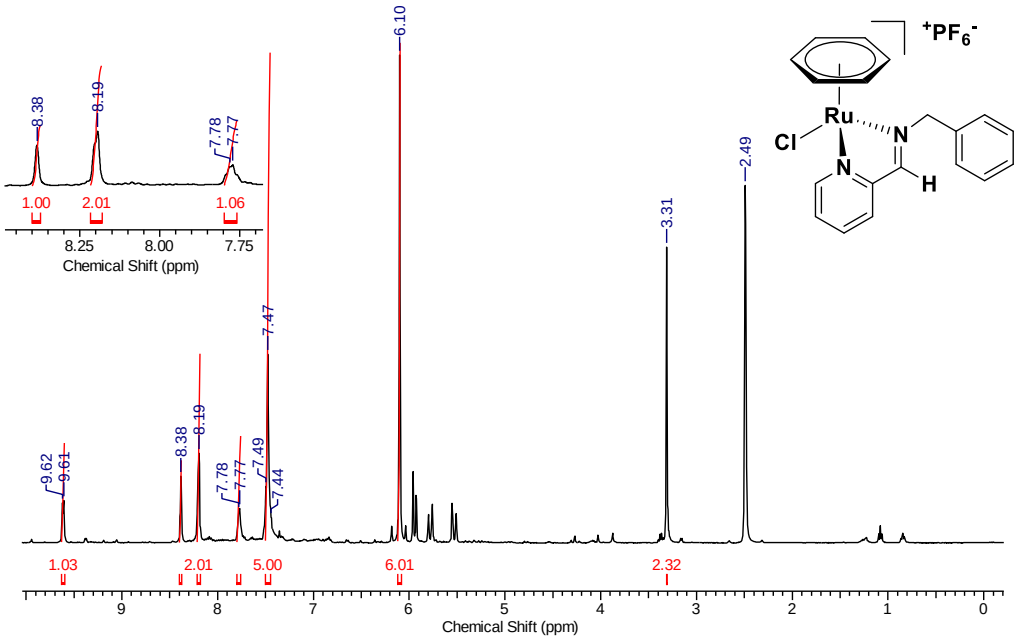
^{1}H NMR of complex [Ru]-18 in acetone-*d*$_6$



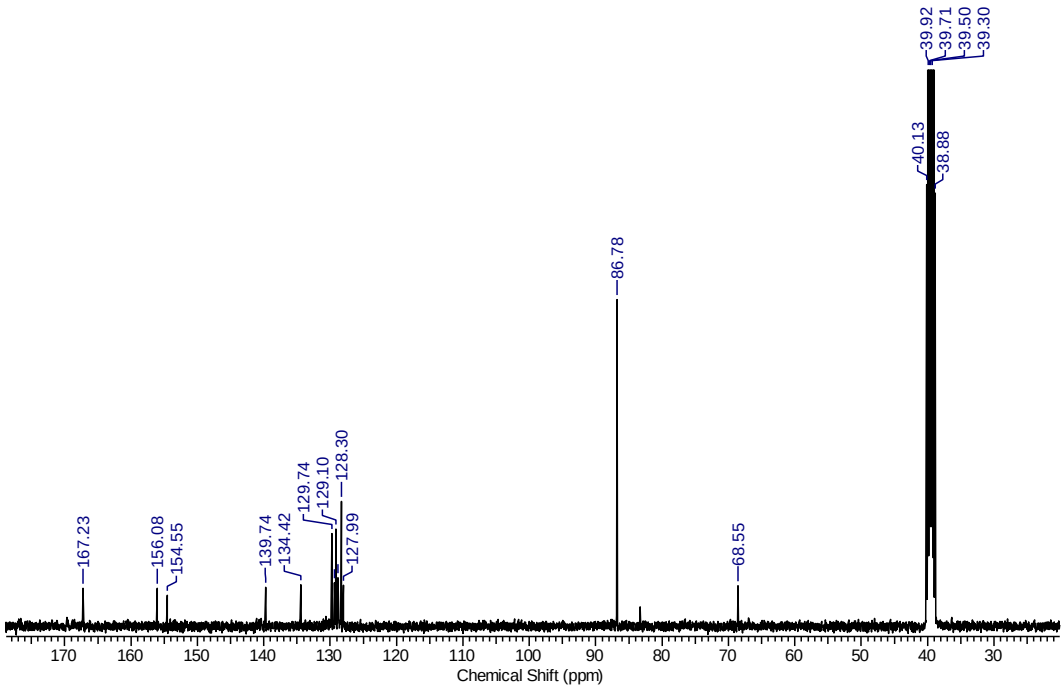
^{13}C NMR of complex [Ru]-18 in acetone-*d*$_6$



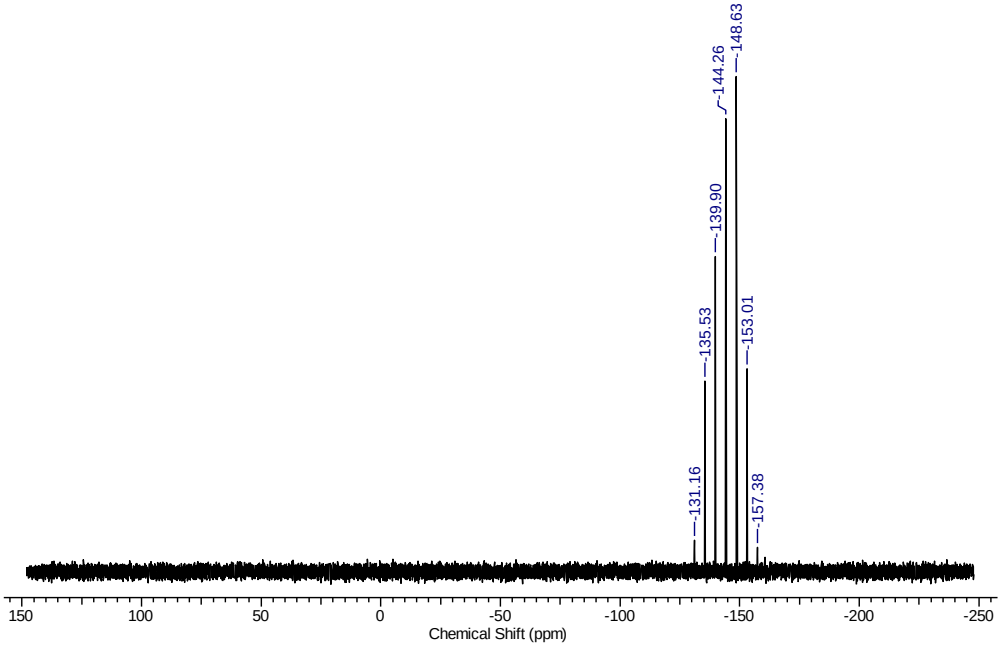
^{31}P NMR of complex [Ru]-18 in acetone-*d*$_6$



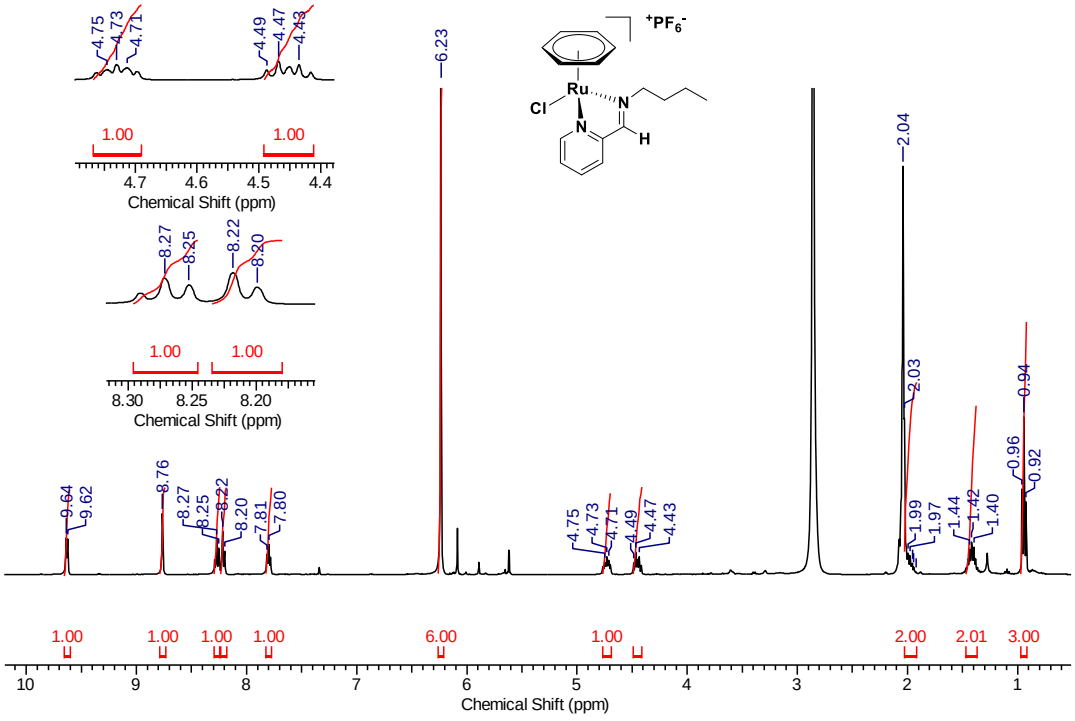
^{1}H NMR of complex [Ru]-19 in DMSO-*d*$_6$



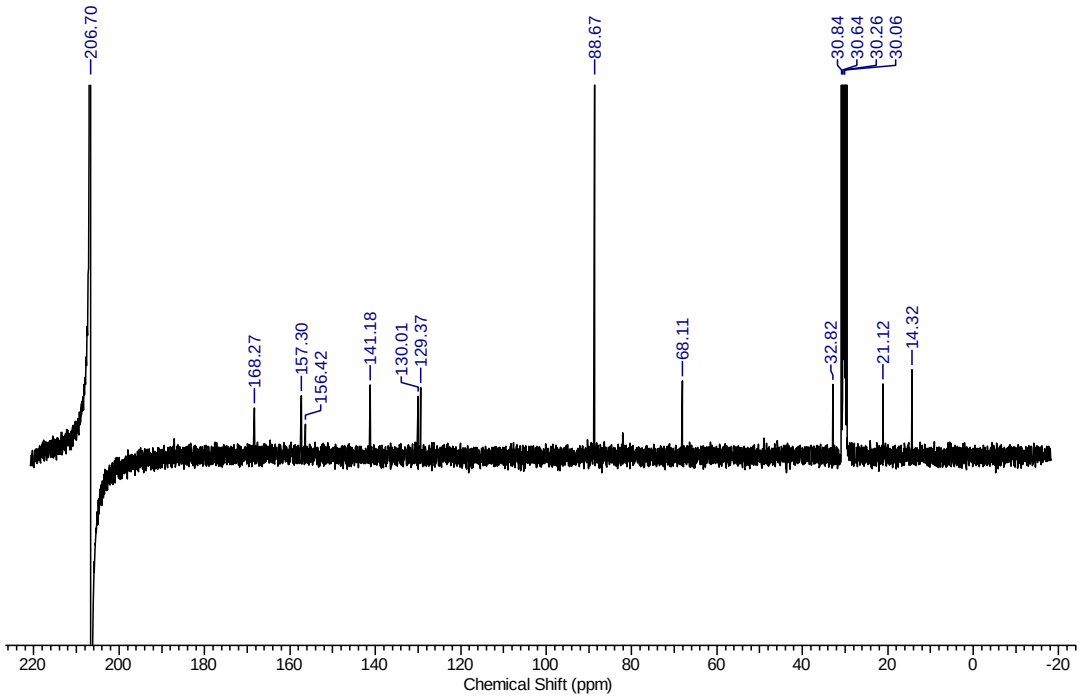
^{13}C NMR of complex [Ru]-19 in DMSO-*d*$_6$



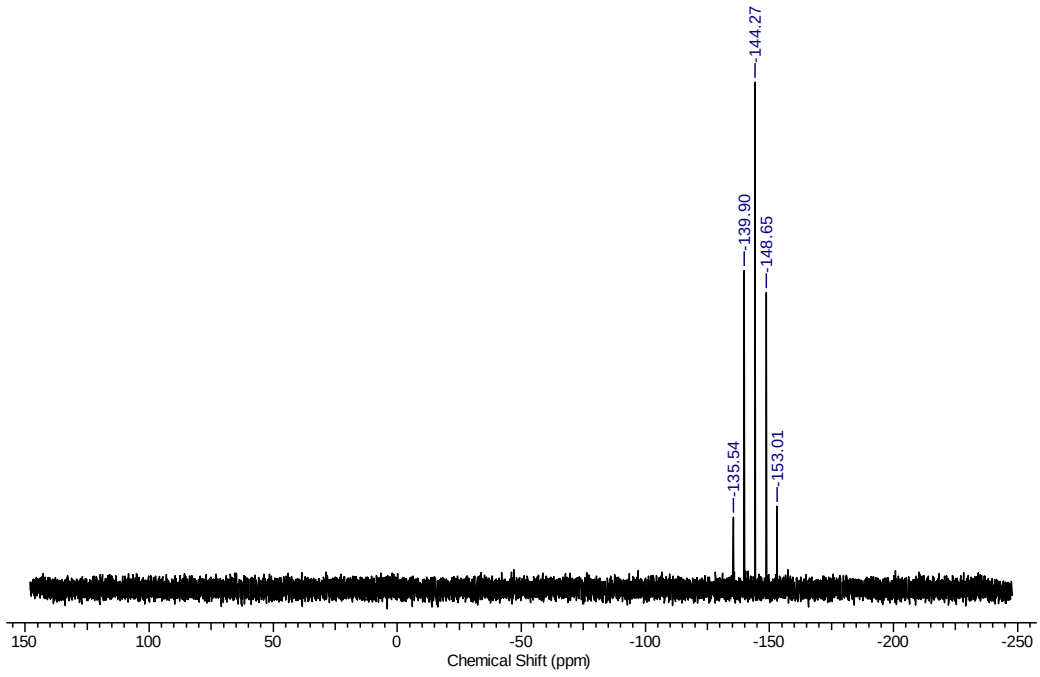
^{31}P NMR of complex [Ru]-19 in DMSO-*d*$_6$



^{1}H NMR of complex [Ru]-20 in acetone-*d*$_6$

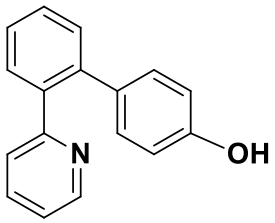


^{13}C NMR of complex [Ru]-20 in acetone-d_6

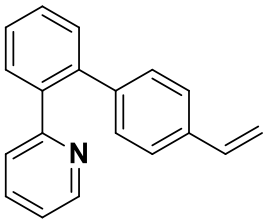


^{31}P NMR of complex [Ru]-20 in acetone-d_6

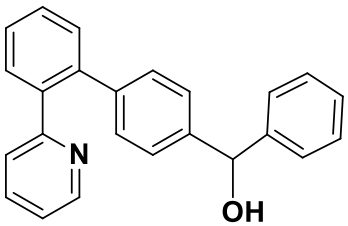
3.4.8. Spectral data for the C-H arylated products



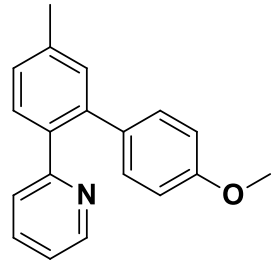
2'-(pyridin-2-yl)-[1,1'-biphenyl]-4-ol (3ad). Yield 63% (155 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.68 (d, 1H, *J* = 4.0 Hz), 7.92 (d, 2H, *J* = 8.0 Hz), 7.78-7.82 (m, 1H), 7.73 (d, 1H, *J* = 8.0 Hz), 7.41-7.48 (m, 3H), 7.26-7.29(m, 1H), 7.12 (d, 2H, *J* = 8.0 Hz), 6.72 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) =171.6, 157.6, 155.0, 149.1, 138.8, 137.4, 129.2, 128.8, 127.1, 124.7, 122.3, 121.4, 116.7, 80.5, 29.6, 21.0, 14.1. HRMS (ESI) m/z calculated: 247.0996 ($C_{17}H_{13}NO$ + H), Found: 247.1125 ($C_{17}H_{13}NO$ + H).



2-(4'-vinyl-[1,1'-biphenyl]-2-yl)pyridine (3ae). Yield 40% (102 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.63 (d, 1H, *J* = 4.0 Hz), 7.69-7.67 (m, 1H), 7.48-7.37 (m, 5H), 7.27 (d, 2H, *J* = 8.0 Hz), 7.11-7.08 (m, 3H), 6.91 (d, 1H, *J* = 8.0 Hz), 6.70-6.63 (dd, 1H, *J* = 12.0 Hz,), 5.71 (d, 1H, *J* = 16.0 Hz), 5.21 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) =159.2, 149.4, 140.8, 139.3, 136.4, 135.8, 135.3, 130.5, 130.3, 129.8, 128.7, 128.5, 127.6, 126.8, 125.9, 125.3, 121.3, 113.7, HRMS (ESI) m/z calculated: 258.1277 ($C_{19}H_{15}N$ + H), Found: 258.1283 ($C_{19}H_{15}N$ + H).

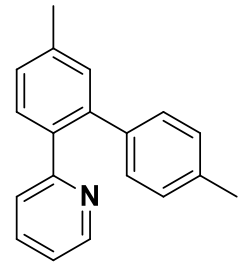


Phenyl(2'-(pyridin-2-yl)-[1,1'-biphenyl]-4-yl)methanol (3af). Yield 56% (188 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.71 (d, 1H, *J* = 4.0 Hz), 7.99 (d, 2H), 7.73-7.78 (m, 3H), 7.60 (d, 1H, *J* = 8.0 Hz), 7.50-7.44 (m, 4H, *J* = 8.0 Hz), 7.35-7.31 (m, 7H), 5.82 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) =157.4, 149.5, 143.4, 142.2, 139.2, 136.9, 133.2, 132.6, 131.4, 129.9, 129.0, 128.7, 128.6, 128.5, 128.4, 127.8, 127.2, 127.1, 126.9, 126.5, 122.1, 75.6, 29.6. HRMS (ESI) m/z calculated: 246.1283 ($C_{18}H_{15}N$ + H), Found: 246.1287 ($C_{18}H_{15}N$ + H).

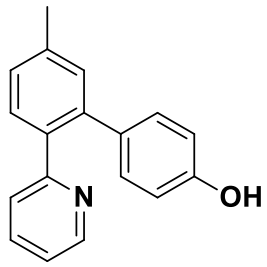


2-(4'-methoxy-5-methyl-[1,1'-biphenyl]-2-yl)pyridine (3ba). Yield 40% (110 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.63 (d, 1H, *J* = 4.0 Hz), 7.59 (d, 1H, *J* = 8.0 Hz), 7.39-7.36 (m, 1H), 7.26-7.22 (m, 1H), 7.07 (d, 1H, *J* = 8.0Hz), 6.87 (d, 1H, *J* = 8.0 Hz), 6.77 (d, 1H, *J* = 8.0 Hz), 3.78 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 159.4, 158.4,

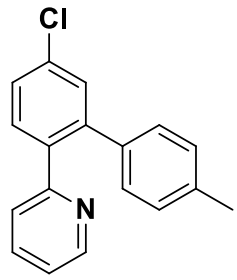
149.3, 140.0, 138.2, 136.6, 135.1, 133.8, 131.1, 130.7, 130.4, 128.0, 125.3, 121.0, 113.4, 113.0, 55.1, 21.2. HRMS (ESI) m/z calculated: 276.1383 ($C_{19}H_{17}NO$ + H), Found: 276.1375 ($C_{19}H_{17}NO$ + H).



2-(4',5-dimethyl-[1,1'-biphenyl]-2-yl)pyridine (3bc). Yield 55% (142 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.86 (d, 1H, *J* = 4.0 Hz), 7.83 (d, 1H, *J* = 8.0 Hz), 7.64-7.60 (m, 2H), 7.50-7.46 (m, 4H), 7.34-7.32 (m, 2H), 7.10 (d, 2H, *J* = 8.0 Hz), 2.66 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 159.1, 148.8, 143.8, 140.4, 138.5, 138.3, 136.1, 136.2, 136.0, 135.5, 131.2, 130.4, 129.5, 128.7, 128.2, 127.3, 125.6, 121.1, 21.2, 21.0. HRMS (ESI) m/z calculated: 260.1434 ($C_{19}H_{17}N$ + H), Found: 260.1450 ($C_{19}H_{17}N$ + H).

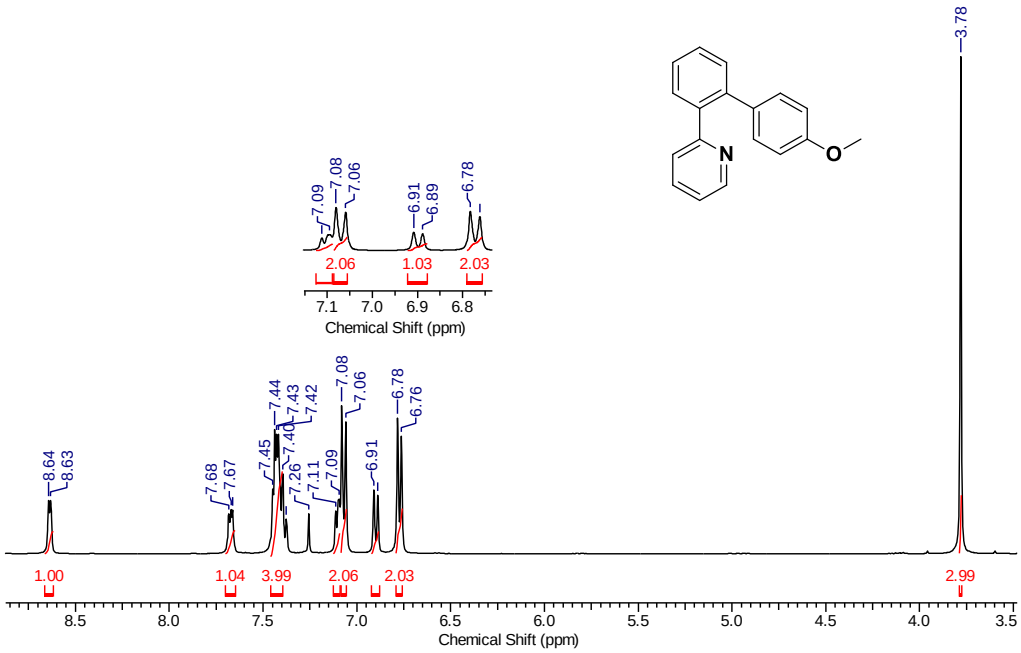


5'-methyl-2'-(pyridin-2-yl)-[1,1'-biphenyl]-4-ol (3bd). Yield (not determined). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.70 (d, 1H, *J* = 4.0 Hz), 7.97-7.89 (m, 2H), 7.75-7.64 (m, 3H), 7.53-7.47 (m, 3H), 6.91 (d, 1H, *J* = 8.0 Hz), 6.70 (d, 1H, *J* = 4.0 Hz). HRMS (ESI) m/z calculated: 262.1226 ($C_{18}H_{15}NO$ + H), Found: 262.1206 ($C_{18}H_{15}N$ + H).

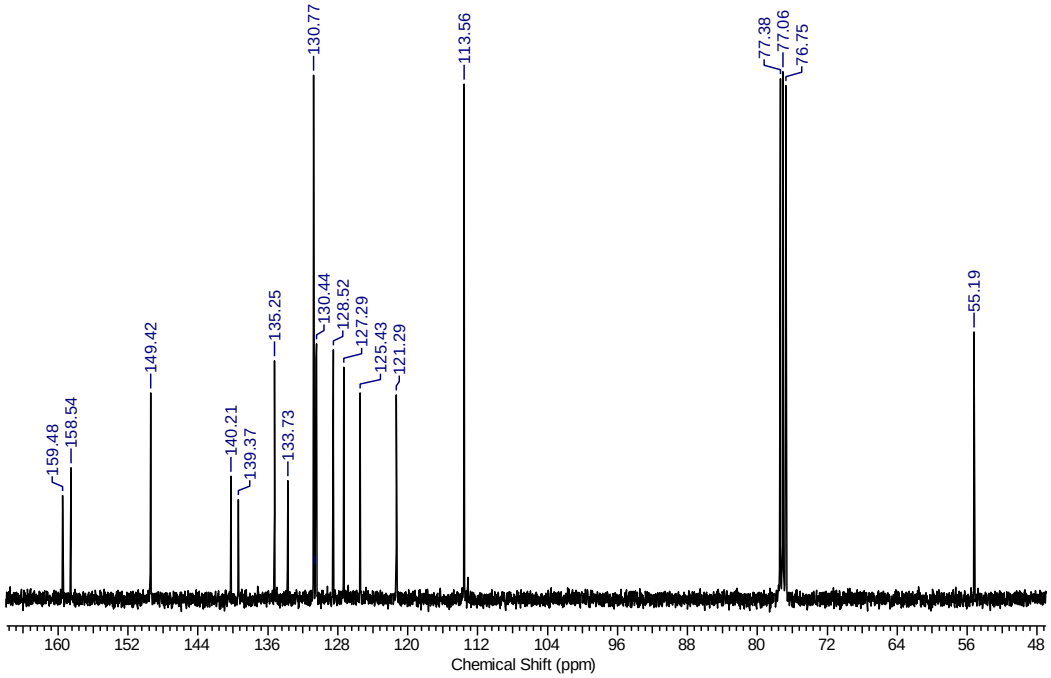


2-(5-chloro-4'-methyl-[1,1'-biphenyl]-2-yl)pyridine (3cc). Yield (not determined). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.63 (d, 1H, *J* = 4.0 Hz), 7.90 (d, 2H, *J* = 8.0 Hz), 7.78-7.69 (m, 3H), 7.49-7.47 (m, 1H), 7.46-7.39 (m, 2H), 7.15-7.12 (m, 1H), 6.92 (d, 1H, *J* = 8.0 Hz), 1.25 (s, 3H). HRMS (ESI) m/z calculated: 302.0707 ($C_{18}H_{14}ClN$ + Na), Found: 302.1441 ($C_{18}H_{14}ClN$ + Na).

3.4.9. NMR spectra of C-H activated monoarylated product 3a



^{1}H NMR spectra of compound 3a



^{13}C NMR spectra of compound 3a

Table 3.6. *Selected bond lengths (Å) for complex* ***[Ru]-12.***

Ru(1)-N(1)	2.107(4)
Ru(1)-O(1)	2.117(4)
Ru(1)-C(12)	2.179(5)
Ru(1)-C(13)	2.186(5)
Ru(1)-C(9)	2.187(5)
Ru(1)-C(10)	2.188(5)
Ru(1)-C(11)	2.196(5)
Ru(1)-C(8)	2.201(5)
Ru(1)-$C_{centroid}$	1.671
Ru(1)-Cl(1)	2.3911(14)
O(1)-C(6)	1.235(6)
N(1)-C(1)	1.327(7)
N(1)-C(5)	1.358(7)
C(1)-C(2)	1.384(8)
C(2)-C(3)	1.359(9)
C(3)-C(4)	1.383(9)
C(4)-C(5)	1.389(7)
C(5)-C(6)	1.476(8)

Table 3.7. *Selected bond angles (deg) for complex* ***[Ru]-12.***

N(1)-Ru(1)-O(1)	76.21(16)
N(1)-Ru(1)-C(12)	97.31(18)

O(1)-Ru(1)-C(12)	150.60(19)
N(1)-Ru(1)-C(13)	98.13(19)
O(1)-Ru(1)-C(13)	114.24(19)
C(12)-Ru(1)-C(13)	37.4(2)
N(1)-Ru(1)-C(9)	159.4(2)
O(1)-Ru(1)-C(9)	95.96(18)
C(12)-Ru(1)-C(9)	80.1(2)
C(13)-Ru(1)-C(9)	67.3(2)
N(1)-Ru(1)-C(10)	157.97(19)
O(1)-Ru(1)-C(10)	124.91(18)
C(12)-Ru(1)-C(10)	67.5(2)
C(13)-Ru(1)-C(10)	79.6(2)
C(9)-Ru(1)-C(10)	37.8(2)
N(1)-Ru(1)-C(11)	120.70(19)
O(1)-Ru(1)-C(11)	162.95(19)
C(12)-Ru(1)-C(11)	37.7(2)
C(13)-Ru(1)-C(11)	68.1(2)
C(9)-Ru(1)-C(11)	68.9(2)
C(10)-Ru(1)-C(11)	38.0(2)
N(1)-Ru(1)-C(8)	122.5(2)
O(1)-Ru(1)-C(8)	90.82(18)
C(12)-Ru(1)-C(8)	68.2(2)

C(13)-Ru(1)-C(8)	37.7(2)
C(9)-Ru(1)-C(8)	37.5(2)
C(10)-Ru(1)-C(8)	68.1(2)
C(11)-Ru(1)-C(8)	81.7(2)
N(1)-Ru(1)-Cl(1)	83.91(12)
O(1)-Ru(1)-Cl(1)	83.85(12)
C(12)-Ru(1)-Cl(1)	124.47(15)
C(13)-Ru(1)-Cl(1)	161.81(16)
C(9)-Ru(1)-Cl(1)	114.61(18)
C(10)-Ru(1)-Cl(1)	91.73(16)
C(11)-Ru(1)-Cl(1)	95.23(15)
C(8)-Ru(1)-Cl(1)	151.02(17)
C(6)-O(1)-Ru(1)	117.2(3)
O(1)-C(6)-C(5)	117.5(5)
O(1)-C(6)-C(17)	121.2(5)

Table 3.8. *Selected bond lengths (Å) for complex* ***[Ru]-14.***

Ru(1)-N(1)	2.079(5)
Ru(1)-N(2)	2.094(5)
Ru(1)-C(16)	2.165(6)
Ru(1)-C(19)	2.205(6)
Ru(1)-C(18)	2.207(6)

Ru(1)-C(15)	2.210(5)
Ru(1)-C(17)	2.223(6)
Ru(1)-C(14)	2.237(5)
Ru(1)-$C_{centroid}$	1.693
Ru(1)-Cl(1)	2.3985(15)
N(2)-C(6)	1.276(8)
N(2)-C(7)	1.496(7)
C(7)-C(8)	1.514(9)
C(5)-C(6)	1.438(9)
C(7)-C(8)	1.514(9)

Table 3.9. *Selected bond angles (deg) for complexes* ***[Ru]-14.***

N(1)-Ru(1)-N(2)	76.65(19)
N(1)-Ru(1)-C(16)	119.1(2)
N(2)-Ru(1)-C(16)	95.8(2)
N(1)-Ru(1)-C(19)	120.1(2)
N(2)-Ru(1)-C(19)	162.7(2)
C(16)-Ru(1)-C(19)	79.9(2)
N(1)-Ru(1)-C(18)	94.5(2)
N(2)-Ru(1)-C(18)	154.4(2)
C(16)-Ru(1)-C(18)	67.3(2)
C(19)-Ru(1)-C(18)	37.4(2)

N(1)-Ru(1)-C(15)	156.8(2)
N(2)-Ru(1)-C(15)	99.9(2)
C(16)-Ru(1)-C(15)	37.9(2)
C(19)-Ru(1)-C(15)	66.4(2)
C(18)-Ru(1)-C(15)	78.7(2)
N(1)-Ru(1)-C(17)	93.8(2)
N(2)-Ru(1)-C(17)	117.7(2)
C(16)-Ru(1)-C(17)	36.8(2)
C(19)-Ru(1)-C(17)	68.2(2)
C(18)-Ru(1)-C(17)	38.0(3)
C(15)-Ru(1)-C(17)	67.1(2)
N(1)-Ru(1)-C(14)	157.3(2)
N(2)-Ru(1)-C(14)	125.39(19)
C(16)-Ru(1)-C(14)	68.4(2)
C(19)-Ru(1)-C(14)	37.49(19)
C(18)-Ru(1)-C(14)	67.8(2)
C(15)-Ru(1)-C(14)	37.0(2)
C(17)-Ru(1)-C(14)	80.9(2)
N(1)-Ru(1)-Cl(1)	86.15(16)
N(2)-Ru(1)-Cl(1)	83.30(14)
C(16)-Ru(1)-Cl(1)	153.99(18)
C(19)-Ru(1)-Cl(1)	93.26(15)

C(18)-Ru(1)-Cl(1)	120.50(17)
C(15)-Ru(1)-Cl(1)	116.52(16)
C(17)-Ru(1)-Cl(1)	158.5(2)
C(14)-Ru(1)-Cl(1)	90.87(14)
C(1)-N(1)-Ru(1)	126.3(5)
C(5)-N(1)-Ru(1)	115.7(4)
C(6)-N(2)-C(7)	118.5(5)
C(6)-N(2)-Ru(1)	115.7(4)
C(7)-N(2)-Ru(1)	125.5(4)

Table 3.10. *Selected bond lengths (Å) for complex* ***[Ru]-15.***

Ru(1)-N(1)	2.0871(19)
Ru(1)-N(2)	2.0708(19)
Ru(1)-C(12)	2.187(2)
Ru(1)-C(15)	2.201(2)
Ru(1)-C(13)	2.209(2)
Ru(1)-C(11)	2.216(2)
Ru(1)-C(16)	2.217(2)
Ru(1)-C(14)	2.232(2)
Ru(1)-$C_{centroid}$	1.695
Ru(1)-Cl(1)	2.3997(6)
N(2)-C(6)	1.275(3)
N(2)-C(7)	1.484(3)

C(7)-C(8)	1.513(4)
C(8)-C(9)	1.522(5)
C(9)-C(10)	1.504(5)

Table 3.11. *Selected bond angles (deg) for complex* ***[Ru]-15.***

N(2)-Ru(1)-N(1)	76.80(8)
N(2)-Ru(1)-C(12)	95.17(9)
N(1)-Ru(1)-C(12)	117.38(9)
N(2)-Ru(1)-C(15)	158.44(9)
N(1)-Ru(1)-C(15)	124.23(8)
C(12)-Ru(1)-C(15)	79.71(9)
N(2)-Ru(1)-C(13)	96.32(9)
N(1)-Ru(1)-C(13)	154.59(9)
C(12)-Ru(1)-C(13)	38.03(9)
C(15)-Ru(1)-C(13)	66.74(9)
N(2)-Ru(1)-C(11)	119.83(9)
N(1)-Ru(1)-C(11)	94.02(8)
C(12)-Ru(1)-C(11)	37.45(9)
C(15)-Ru(1)-C(11)	67.63(9)
C(13)-Ru(1)-C(11)	67.89(9)
N(2)-Ru(1)-C(16)	156.99(9)
N(1)-Ru(1)-C(16)	97.75(9)
C(12)-Ru(1)-C(16)	67.16(9)

C(15)-Ru(1)-C(16)	36.96(9)
C(13)-Ru(1)-C(16)	78.96(9)
C(11)-Ru(1)-C(16)	37.51(9)
N(2)-Ru(1)-C(14)	120.86(9)
N(1)-Ru(1)-C(14)	161.87(9)
C(12)-Ru(1)-C(14)	68.10(9)
C(15)-Ru(1)-C(14)	37.82(9)
C(13)-Ru(1)-C(14)	36.83(9)
C(11)-Ru(1)-C(14)	80.85(9)
C(16)-Ru(1)-C(14)	67.65(9)
N(2)-Ru(1)-Cl(1)	85.93(6)
N(1)-Ru(1)-Cl(1)	85.10(6)
C(12)-Ru(1)-Cl(1)	157.19(7)
C(15)-Ru(1)-Cl(1)	90.92(7)
C(13)-Ru(1)-Cl(1)	119.17(7)
C(11)-Ru(1)-Cl(1)	153.40(7)
C(16)-Ru(1)-Cl(1)	116.17(7)
C(14)-Ru(1)-Cl(1)	91.76(7)
C(6)-N(2)-C(7)	121.4(2)
C(6)-N(2)-Ru(1)	116.91(16)
C(7)-N(2)-Ru(1)	121.57(16)
C(5)-N(1)-Ru(1)	115.46(15)

Note 1: Spectral copies and NMR data for some of the substrates has been given in the previous chapters (Chapter 2).

Note 2: The contents of this chapter has been published as Binnani et al., Eur. J. Inorg. Chem. 2018, 1435-1445 (DOI:10.1002/ejic.20170144) and reproduced with the permission from Wiley VCH with license number 4601810701530.

3.5. References

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Chapter 4

Biomass derived ligands accelerated ruthenium-catalyzed C-H bond activation/arylation

4.1. Introduction

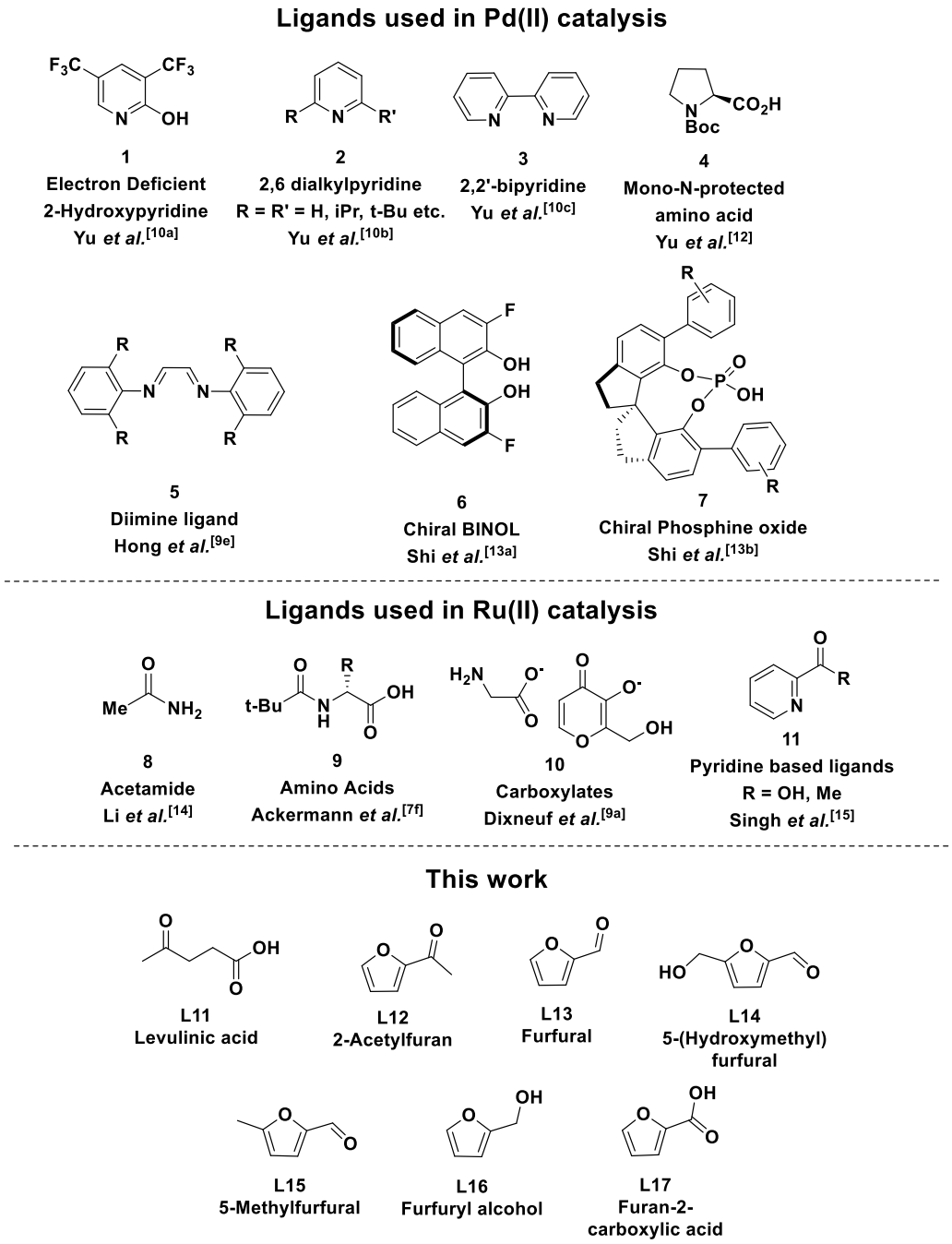
Metal catalyzed C-H bond activation and functionalization methodologies are of significant importance in the field of synthetic organic transformations.[1] It is evident that several metal catalysts based on Rh,[2] Pd,[3] Ir,[4] and Ru[5] have been extensively explored for C-H bond functionalization reactions. With further advancement in the field, the earth abundant 3d transition metals (Mn, Co, Fe) are also seeking attention as active catalysts for C-H bond activation and functionalization reactions in a very efficient, selective and cost-effective manner.[6] Among the various metals explored for C-H activation/functionalization reactions, the ruthenium-based catalysts, particularly arene-Ru(II) complexes have shown several advantages over others due to its non-toxic nature, stability in air and water, high aqueous solubility and therefore these catalysts are considered as one of the most promising catalytic system for C-H activation/functionalization reactions. Among several strategies, designing and utilizing efficient ligand to induce accelerated C-H bond activation reactions has contributed remarkably to enhance the practical usability of C-H activation/functionalization reactions. In this context, a variety of ligands such as carboxylates,[7] phosphorus-based ligands[8] and several *N,O*/*O,O* donor ligands,[9] either as additives or pre-coordinated with the metal center, have been extensively studied to achieve enhanced catalytic activity. In general, carboxylate additives facilitate the initial deprotonation of *ortho* C-H bond while phosphine-based ligands play crucial role in stabilizing the active catalytic species.

The other set of ligands, which are rather weakly coordinating, also found to significantly tune the catalytic activity in C-H bond functionalization reactions. For instance, Yu *et al*. employed bulky pyridine ligands for the challenging C-H activation of electron deficient arenes catalyzed on Pd catalyst.[10] They showed that sterically bulky

2,6-dialkylpyridines induced a significant enhancement in the catalytic activity, which was attributed to the facile replacement of bulky pyridine by reactant. We also observed an accelerated Ru(II) catalyzed C-H bond arylation in the presence of weakly coordinating electron deficient aniline ligands.[11] Apart from several monodentate ligands, various bidentate ligands have also been explored to achieve enhance catalytic activity. For instance, Pd(II) catalyzed *ortho* C-H bond alkylation was accelerated by N-protected amino acid ligands, where it was proposed that the coordination/de-coordination mode of one of the coordinating group of these ligands presumably tune the catalytic activity.[12] However, no direct role of these ligands in deprotonation step was observed. The designing and development of various chiral ligands for enantioselective Pd(II) catalyzed C-H bond activation/functionalization has also revolutionized the synthesis of several chiral organic compounds with excellent enantioselectivity.[13] Furthermore, accelerated Ru(II) catalyzed C-H bond arylation has also been achieved in the presence of acetamide ligand where the pendent acyl group of Ru-coordinated acetamide facilitated the deprotonation of C-H bond.[14] In a recent report, we have also explored several pyridine based bidentate ligands and observed that 2-acetylpyridine ligand greatly enhanced the catalytic activity for C-H bond arylation reaction.[15] The observed ligand-induced enhancement in the catalytic activity was attributed to the involvement of acetyl group in the deprotonation step due to its close proximity to the *ortho* C-H bond of 2-phenylpyridine (Scheme 4.1).

Envisioned by the recent advancement and our continuous efforts towards ligand assisted C-H bond activation reaction, herein we investigated in detail a wide range of ligands, which can be readily derived from biomass, for arene-Ru(II) catalyzed C-H bond arylation in water-based reaction condition (Scheme 4.1). As these ligands such as levulinic acid (**L11**), 2,5-hexanedione (**L18**) and other furan-based ligands, contain acetyl, formyl or carboxylate groups, these groups may play an important role in accelerating the catalytic activity for C-H bond arylation of 2-phenylpyridine with several aryl chlorides over arene-Ru(II) catalyst. We also probed mass investigations to elucidate the involvement of these ligands in the C-H bond activation reactions by identifying reaction intermediates such as ligand coordinated Ru species and cyclometalated species under the catalytic and controlled reaction conditions. Density functional theoretical

(DFT) calculations provided substantial support to our experimental findings and the active role of the studied ligands in accelerating the catalytic activity for C-H activation reactions.



Scheme 4.1. *Various ligands explored for C-H bond activation reactions.*

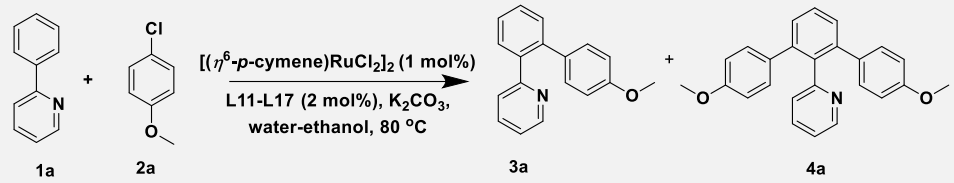
4.2. Results and discussion

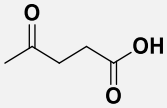
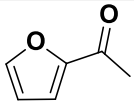
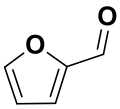
At an outset, we evaluated the ligands **L11 − L17** (2 mol%) for C-H arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**), as model substrates, catalyzed by [(η^6-*p*-cymene)$RuCl_2$]$_2$ (**[Ru]-A**, 1 mol%) catalyst at 80°C in water-ethanol (9:1 v/v) solution. After evaluating various biomass-derived ligands (**L11 − L17**), we found that levulinic acid (**L11**), greatly accelerated the catalytic activity with 70% yield of monoarylated product (**3a**) in 4 h (**3a/4a** selectivity = 93/7) (Table 4.1, entry 2). Yield for **3a** was further improved to 87% by extending the reaction for 8 h under analogous reaction condition. The remarkable activity shown by Ru(II) catalyst in the presence of the acyclic ligand **L11**, can be attributed to the conformational freedom of **L11** which further facilitated its orientation to promote the deprotonation of *ortho* C-H bond of 2-phenylpyridine.

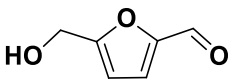
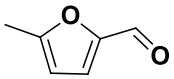
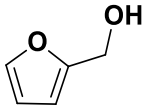
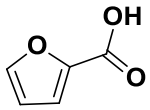
In contrary to the excellent activity achieved in the presence of levulinic acid (**L11**) ligand, other furan-based ligands (**L12 − L17**) showed relatively lower activity for the product **3a** (35-75% conv.) (Table 4.1). After levulinic acid (**L11**), 2-acetylfuran (**L12**) showed the highest yield (65%) for **3a**, (Table 4.1, entry 3) while furfural (**L13**), 5-HMF (**L14**), 5-methylfurfural (**L15**), furfuryl alcohol (**L16**) and furan-2-carboxylic acid (**L17**) could not efficiently accelerated the catalytic activity of ruthenium catalyzed C-H arylation reaction (Table 4.1, entries 4-8). It is noteworthy to mention here that comparatively lower temperature, shorter reaction duration or using aryl halide as a limiting agent may favor higher selectivity for monoarylation over biarylation of 2-phenylpyridine.[7g, 8g, 16] It is also evident from the previous reports that using excess of aryl halide (>2 equiv.) resulted in the higher selectivity of biarylated product.[8c] Hence we optimized the reactions with slight excess of 2-phenylpyridine (1.1 equiv.) at 80 °C for 4 h to achieve higher selectively for the monoarylated product. As a result, high selectivity for monoarylated product (**3a**) over biarylated product (**4a**) was maintained for all the conducted reactions. The lower activity for ruthenium catalyzed C-H bond arylation of **1a** in the presence of furan-based ligands can be attributed to the tendency of these ligands to polymerize in aqueous solvent.[17] Reports also revealed that the polymerization of 5-HMF (**L14**) is lower than the furfuryl alcohol (**L16**), which is in line with the lower yield for **3a** observed with **L16** (38%) as compared to the moderate yield (53%) achieved with **L14**. It is evident from the results that *O,O* donor furan-based

ligands having neutral oxygen donor groups (**L12 − L16**) outperformed over furan-2-carboxylic acid (**L17**) with anionic oxygen donor (Table 4.1). These findings can be attributed to the strong coordination behavior of **L17** with the Ru(II) metal center. Previous studies also demonstrated enhanced catalytic activity for C-H bond arylation reaction over 2-acetylpyridine ligated Ru(II) complex as compared to 2-picolinate ligated Ru(II) complex.[15] Notably, carboxylate additives, such as acetates and pivalates are well explored for the Ru(II) catalyzed C-H bond activation reactions,[7,18] where these carboxylates facilitated the deprotonation of C-H bond by coordinating with the Ru center.

Table 4.1. Catalytic *ortho* C-H bond arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**) over $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ **([Ru]-A)** catalyst in the presence of various biomass-derived ligands[a]



Entry	Ligand	Conv. (%)	Sel. (%) (3a/4a)	Yield[c] (%) (3a)
1.	**ligand free**	12%	93/7	n.d.
2.	 **(L11)**	**83%** **>99%**[b]	**93/7** **90/10**[b]	**70%** **87%**[b]
3.	 **(L12)**	75%	94/6	65%
4.	 **(L13)**	70%	91/9	58%

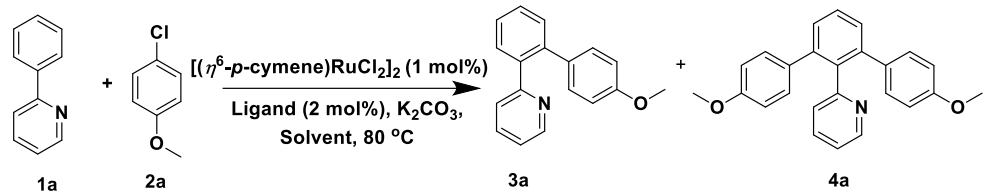
5.	 **(L14)**	65%	94/6	53%
6.	 **(L15)**	52%	93/7	42%
7.	 **(L16)**	44%	96/7	38%
8.	 **(L17)**	35%	90/10	27%

[a]Reaction Condition: [(η^6-*p*-cymene)$RuCl_2$]$_2$ **([Ru]-A)** (1 mol%), **L11-L17** (2 mol %.), K_2CO_3 (3 equiv.), 2-phenylpyridine (**1a**) (0.6 mmol), 4-chloroanisole (**2a**) (0.5 mmol), water-ethanol (9:1 v/v, 2 mL), 80 ºC, 4 h, N_2 atmosphere, [b]time = 8 h, [c]isolated yield, conversion and selectivity were determined by ^{1}H NMR with TMS as internal standard, n.d. = not determined.

Based on the above findings, levulinic acid (**L11**) was identified as the best performing ligand to induce 7-fold enhancement in the catalytic activity of [(η^6-*p*-cymene)$RuCl_2$]$_2$ catalyst. Notably, in the absence of the ligand, [(η^6-*p*-cymene)$RuCl_2$]$_2$ displayed only poor catalytic conversion under analogous reaction condition (Table 4.1, entry 1). Further, optimization of reaction condition inferred that performing the catalytic reaction with lower amount of K_2CO_3 base (3 equiv.) significantly deteriorated the conversion. Moreover, reaction could not proceed in the absence of base or performing the catalytic reaction at lower temperature (Table 4.2). Notably, in the absence of ligand, Ru(II) catalyst showed negligible conversion of **1a** under analogous reaction condition (Table 1, entry 1). Further optimization showed that the catalytic activity deteriorates with lower amount of base and reaction failed to occur in the absence of K_2CO_3. Lowering the reaction temperature could not result in the reaction

Table 4.2. *Optimization of reaction conditions for Ru(II) catalyzed C-H bond activation/arylation of 2-phenylpyridine(**1a**).*

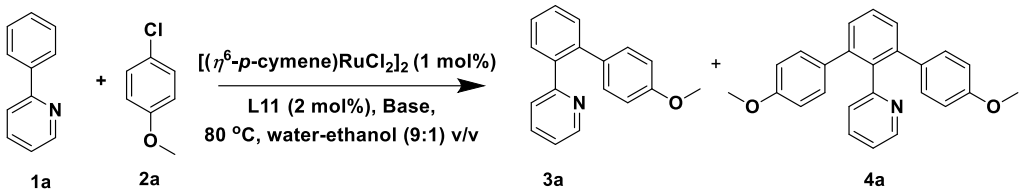
(a) Effect of solvent[a]



Water				Water-ethanol (9:1) v/v			
Entry	**Ligand**	**Conv. (%)**	**Sel. (3a/4a)**	**Entry**	**Ligand**	**Conv. (%)**	**Sel. (3a/4a)**
1.	**L11**	40%	85/15	5.	**L11**	83%	93/7
2.	**L12**	44%	90/10	6.	**L12**	73%	94/6
3.	**L13**	53%	93/7	7.	**L13**	69%	95/5
4.	**L16**	50%	>99/1	8.	**L16**	44%	96/4

[a]Reaction condition: $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ **([Ru]-A)** (1 mol%), Ligand (2 mol%), K_2CO_3 (3 equiv.), 2-phenylpyridine (0.6 mmol), 4-chloroanisole (0.5 mmol), solvent (2 mL), 80 °C, 4 h, N_2 atmosphere.

(b) Loading of base and effect of temperature[a]



Loading of base (K_2CO_3)[b]				Effect of temperature[c]			
Entry	**Base**	**Conv. (%)**	**Sel. (3a/4a)**	**Entry**	**Temp.**	**Conv. (%)**	**Sel. (3a/4a)**
1.	0 equiv.	n.r.	-	1.	60 °C	n.r.	-
2.	1 equiv.[d]	n.r.	-	2.	80 °C	83%	93/7
3.	2 equiv.	50%	92/8				
4.	3 equiv.	83%	93/7				

[a]Reaction condition: $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ **([Ru]-A)** (1 mol%), **L11** (2 mol%), 2-phenylpyridine (0.6 mmol), 4-chloroanisole (0.5 mmol), water-ethanol (9:1) v/v (2 mL), 4 h, N_2 atmosphere, n.r. = no reaction. [b]Temp.= 80 °C, [c]K_2CO_3 (3 equiv.), [d]Intermediate observed in ^1H NMR.

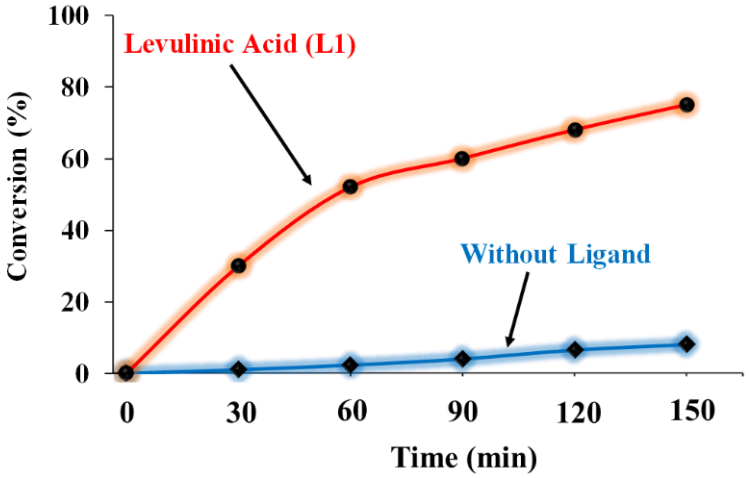
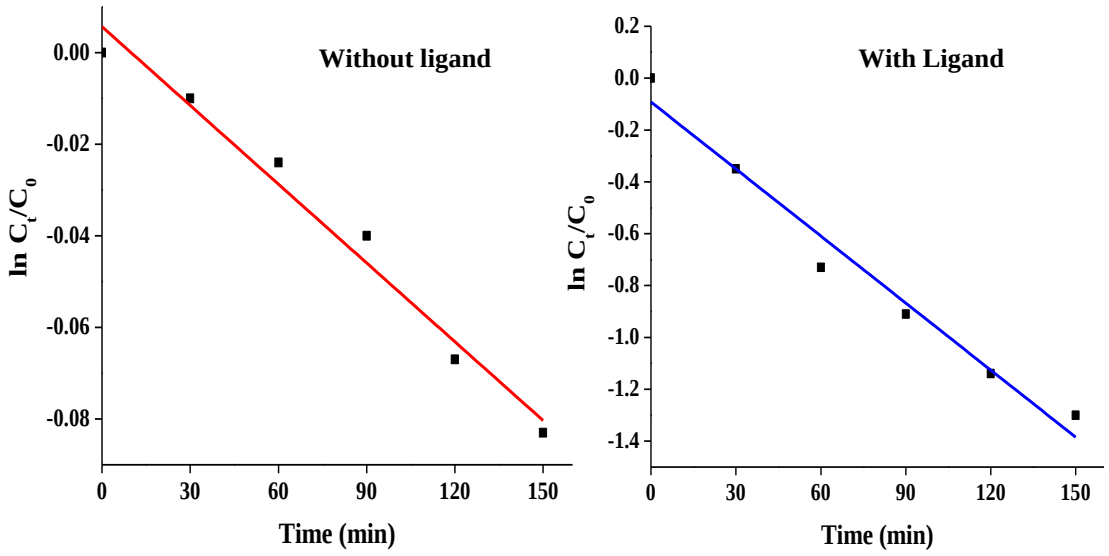


Figure 4.1. *Time dependent reaction profile for C-H arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**) over [(η^6-p-cymene)RuCl$_2$]$_2$* **([Ru]-A)** *catalyst in ligand-free condition and in the presence of ligand **L11** under the optimized reaction condition.*

Further, to understand the influential effect of biomass derived *O,O* donor ligands on C-H arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**) over Ru(II) catalyst, time-dependent ^{1}H NMR studies were conducted over the period of 1.5 h. As evident from the time dependent reaction profile (Figure 4.1), when reaction was performed in the absence of any ligand, very slow reaction rate (4.89×10^{-4} sec^{-1}) was observed. Contrary to the base-free condition, significantly increased kinetics with relatively very high rate constant (1.02×10^{2} sec^{-1}) was observed in the presence of levulinic acid (**L11**) (Figure 4.1 and 4.2), suggesting that the enhancement in the catalytic reaction was probably due to the involvement of levulinic acid (**L11**) in the C-H bond cleavage step.



Catalyst	Without ligand	With ligand (L11)
Rate constant (k)	4.89×10^{-4} sec^{-1}	**1.02×10^{2} sec^{-1}**

Figure 4.2. *Rate constants (k) for ortho C-H bond activation/arylation of 2-phenylpyridine(**1a**) with 4-chloroanisole (**2a**) over [(η^6-p-cymene)$RuCl_2$]$_2$* **([Ru]-A)** *catalyst in ligand-free condition and in the presence of ligand **L11** under the optimized reaction condition.*

To further support this hypothesis, we probed mass investigations, under the catalytic and controlled reaction condition, to identify possible reaction intermediates for the Ru(II) catalyzed *ortho* C-H bond arylation of **1a** with **2a** in the presence of the ligand **L11** (Figure 4.3). Notably, levulinate coordinated arene-Ru species (**[Ru]-F**, m/z = 351, [M]-Cl) was observed upon the treatment of [(η^6-*p*-cymene)$RuCl_2$]$_2$ **([Ru]-A)** with levulinic acid (Ru:**L11** = 1:2) in water-ethanol (9:1 v/v) in the presence of K_2CO_3 at 80 ºC for 1.5 h (Figure 4.3).

(a) Ligand coordinated arene-Ru species [(η^6-*p*-cymene)Ru(**L11**)]$^+$ **[Ru]-F**

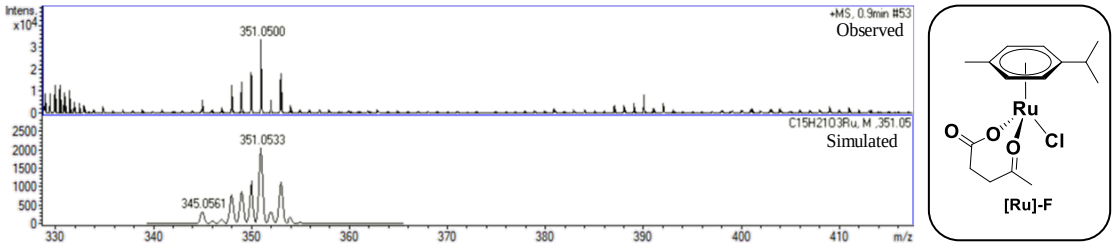


Figure 4.3. *Observed and simulated pattern of levulinic acid (**L11**) coordinated arene-Ru species [(η^6-p-cymene)RuCl(**L11**)]$^+$ [M-Cl]$^+$ **[Ru]-F**.*

Further, upon addition of 2-phenylpyridine (**1a**) (Ru:**1a** = 1:5), mass peak corresponding to the crucial cyclometalated species [(η^6-*p*-cymene)RuCl(κ^2-*C,N*-2-phenylpyridine)] (**[Ru]-C**, m/z = 390, [M]-Cl) was appeared as prominent peak (Figure 4.4).

(b) Cycloruthenated species [(η^6-*p*-cymene)Ru(κ^2-*C*,*N*-phenylpyridine)]$^+$ (**[Ru]-C**).

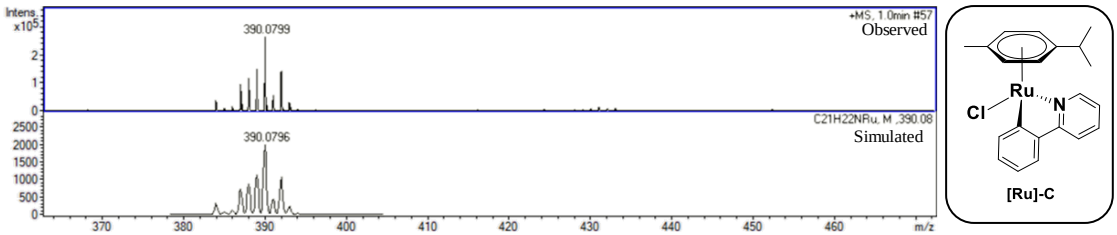


Figure 4.4. *Observed and simulated pattern of cycloruthenated species [(η^6-p-cymene)Ru(κ^2-C,N-phenylpyridine]$^+$ (**[Ru]-C**).*

The ligand coordinated arene-Ru species **[Ru]-F**, was also observed under the base free condition, which was possibly formed *via* an initial aqua-coordinated arene-Ru species ([(η^6-*p*-cymene)Ru(OH_2)Cl_2] (m/z = 288, [M]-Cl) (Figure 4.5).

(c) *Water coordinated ruthenium species [(η^6-p-cymene)Ru(OH_2)Cl]$^+$ (**[Ru]-G**).*

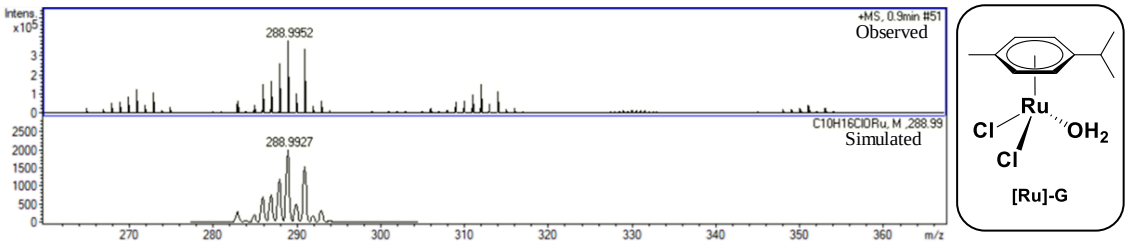


Figure 4.5. *Observed and simulated pattern of water coordinated ruthenium species [(η^6-p-cymene)Ru(OH_2)Cl_2] [M-Cl]$^+$ (**[Ru]-G**).*

Notably, presence of the prominent mass peak at m/z 390 corresponding to the cyclometalated species **[Ru-C]** under base free condition upon the treatment of [(η^6-*p*-cymene)RuCl_2]$_2$ **([Ru]-A)** with 2-phenylpyridine (Ru:**1a** = 1:5) in the presence of levulinic acid (**L11**) at 80 ºC, substantiate the crucial role of levulinic acid (**L11**) in achieving high catalytic activity. Earlier reports also inferred the presence of analogous cyclometalated species **[Ru-C]** as one of the key intermediates in several Ru(II) catalyzed C-H bond activation reactions.[19]

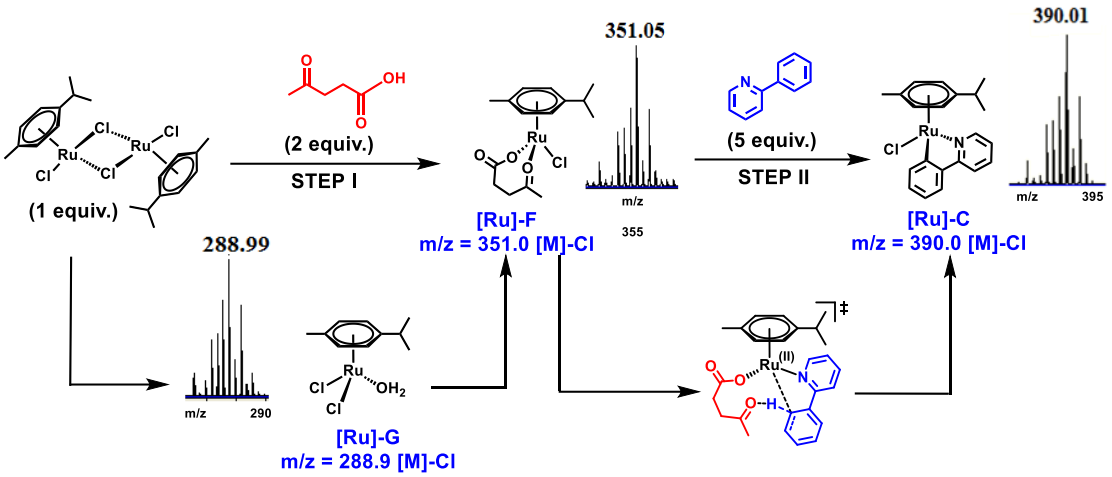
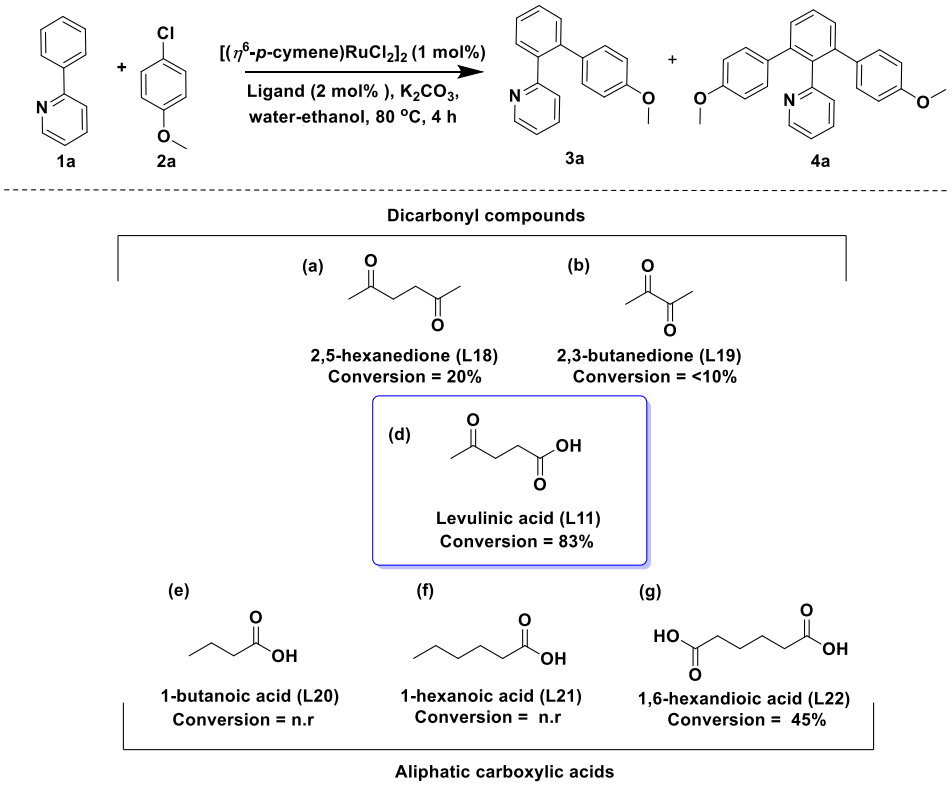


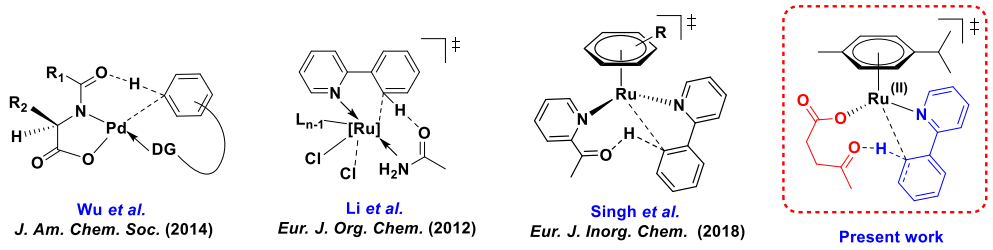
Figure 4.6. *Mass spectral identification of several intermediate species formed during the ortho C-H bond activation/arylation of* ***1a*** *over Ru catalyst under stoichiometric reaction conditions in the presence of levulinic acid (**L11**). Step I: water-ethanol (9:1 v/v), 80 ℃, 1.5 h, N_2 atmosphere. Step II: K_2CO_3, water-ethanol (9:1 v/v), 80 ℃, 1.5 h, N_2 atmosphere.*

Further to investigate the role of acetyl and carboxylate groups, we performed the catalytic reaction by replacing levulinic acid (**L11**) with dicarbonyl compounds (2,5-hexanedione (**L18**) and 2,3-butanedione (**L19**)) and aliphatic carboxylic acids (1-butanoic acid (**L20**), 1-hexanoic acid (**L21**), 1,6-hexanedioic acid (**L22**)) (Scheme 4.2). Results inferred that the dicarbonyl ligands (**L18** and **L19**) could not enhance the catalytic performance, attributed to their poor coordination with the metal center and hence could not efficiently participated in the ligand assisted deprotonation step. Moreover, controlled experiments performed using aliphatic carboxylic acid (**L20 – L22**) also inferred no significant enhancement in the catalytic reaction, presumably due to the strong coordination behavior of these ligands with the metal center.



Scheme 4.2. *Comparative catalytic activity of ortho C-H bond activation/arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**) over [(η^6-p-cymene)RuCl$_2$]$_2$ catalyst in the presence of various dicarbonyl compounds (**L18 − L19**) and aliphatic carboxylic acids (**L20 − L22**), under the optimized reaction condition.*

The above findings inferred that the facile coordination of the ligand **L11** in a bidentate manner with the ruthenium center *via* acetyl and carboxylate-O$^-$ groups, as also evidenced by the presence of levulinate coordinated arene-Ru species (**[Ru]-F**) (m/z = 351, [M]-Cl) during mass studies, is presumably responsible for the observed accelerated catalytic activity. In this context, previous studies also revealed that analogous bis-chelating ligands may display coordination/de-coordination behavior during the catalytic reaction and hence significantly tune the catalytic reactivity (Scheme 4.3).[14,15,20]



Scheme 4.3. *Previously reported catalytic systems showing the involvement of acetyl group in the deprotonation step for C-H bond bond of 2-phenylpyridine or benzene.*

It is also evident from our previous report that the enhanced catalytic activity in Ru-picolinate systems was due to the involvement of acetyl group in C-H deprotonation, while remain coordinated with metal center with strongly coordinating pyridine.[15]

To further support our experimental findings, we performed DFT calculations (computational details given in supporting information)[21] for C-H bond activation/arylation of 2-phenylpyridine(**1a**) and calculated reaction free energies (ΔG) for the formation of the crucial cycloruthenated species [Ru(η^6-*p*-cymene)(κ^2-*C*,*N*-2-phenylpyridine)(H_2O)]$^+$ (**5**), in the presence and absence of ligand **L11**. As mass studies evidenced the presence of a water coordinated ruthenium species [(η^6-*p*-cymene)$RuCl_2(OH_2)$] (m/z 288, [M]-Cl) in the absence of ligand, we considered this as active catalytic species for DFT calculations under ligand-free condition. The reaction free energy profile, Figure 4.7, suggested that the formation of the crucial cycloruthenated species (**5**) is energetically favorable (ΔG = 14.0 kcal/mol) in the presence of the ligand **L11** compared to that for ligand-free condition (ΔG = 22.9 kcal/mol).

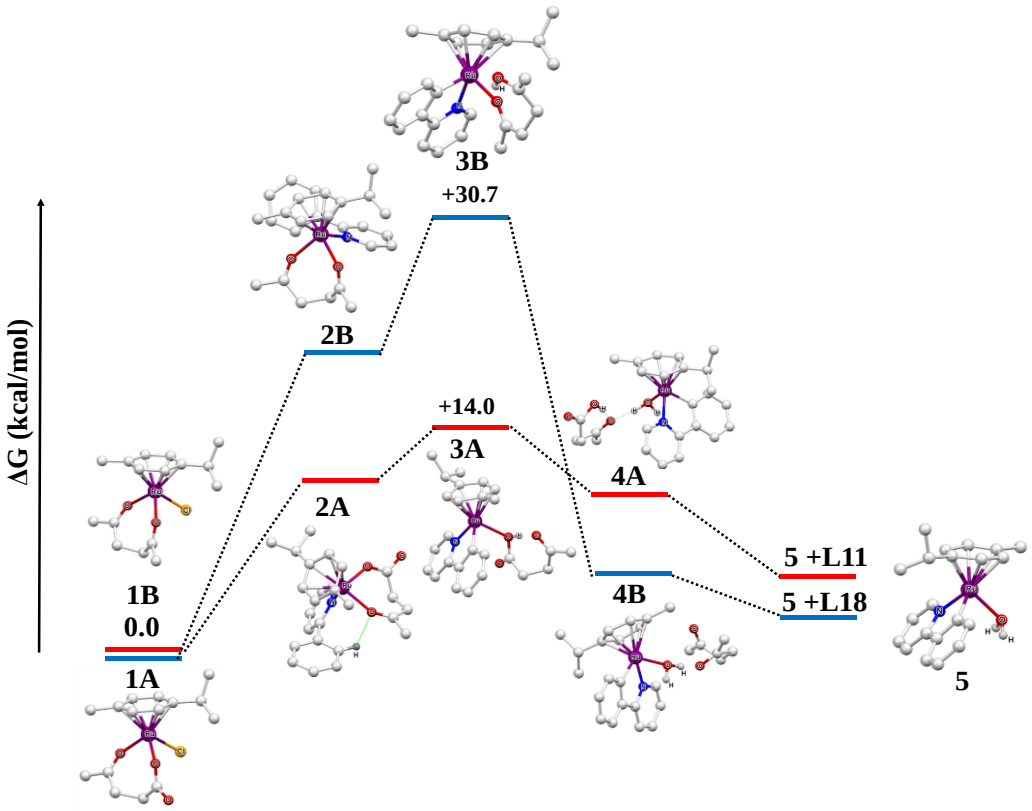


Figure 4.7*. Reaction free energy profile, as calculated by DFT, to study the role of ligands, levulinic acid (**L11**) and 2,5-hexanedione (**L18**), in ruthenium catalyzed ortho C-H bond activation/arylation of 2-phenylpyridine (**1a**).*

These results further evidenced the crucial role of the ligand **L11** in the C-H activation of 2-phenylpyridine. Further, it was also evident from the DFT calculations that the species **2A-I** having acetyl group in the close proximity of *ortho* proton of 2-phenylpyridine was stable by 2.7 kcal/mol than the species **2A-II** having carboxylate group in that place. These results are in concurrence with earlier reports,[14,15,20] suggesting that presumably the acetyl group was involved in the C-H bond activation of 2-phenylpyridine (Figure 4.8).

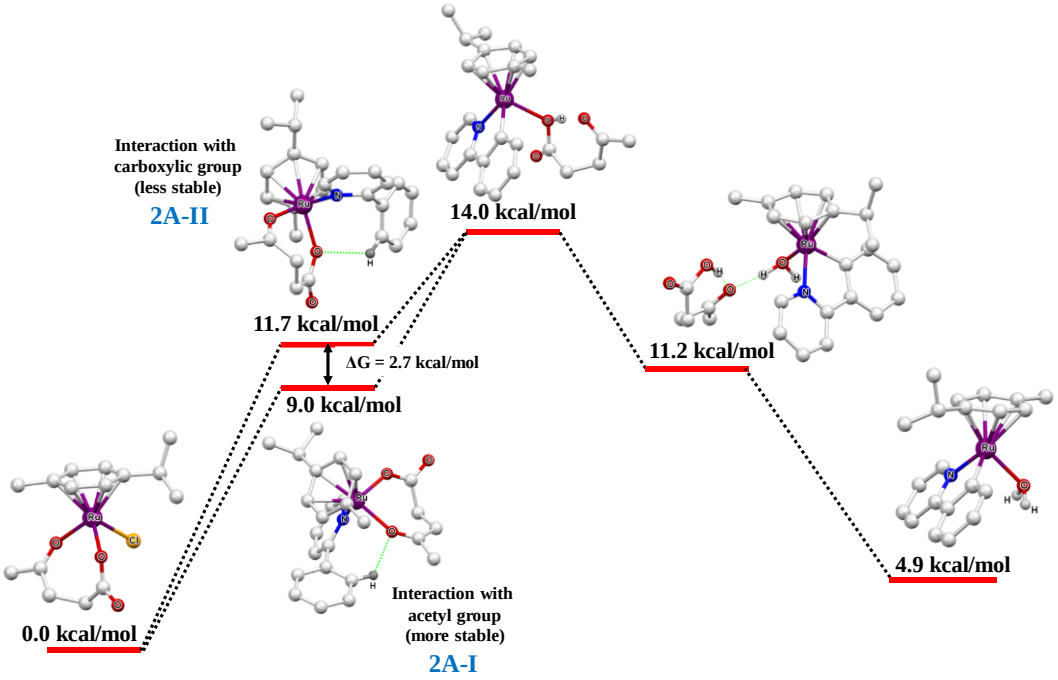
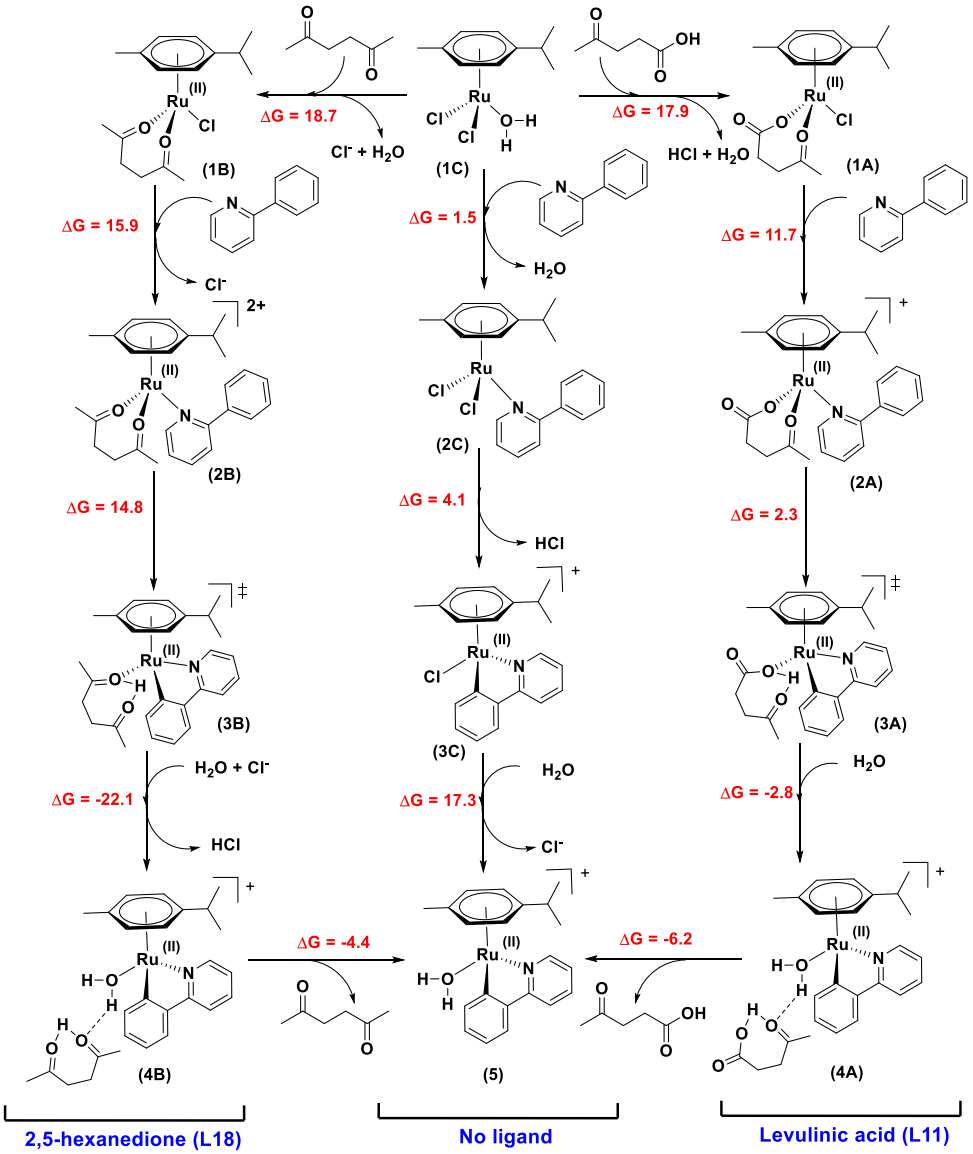


Figure 4.8. *Theoretical evidence (based on reaction free energy profile calculations) for involvement of acetyl group in the deprotonation step of ruthenium catalyzed ortho C-H bond activation/arylation reaction.*

Further, upon replacing the ligand **L11** with 2,5-hexanedione (**L18**), free energy calculations revealed that the C-H activation reaction was highly unfavorable in the presence of **L18** (ΔG = 30.7 kcal/mol) (Scheme 4.4). These results inferred that presumably the anionic carboxylate ensured the strong anchoring of ligand with the metal center, while the acetyl group facilitated C-H deprotonation via a facile coordination-decoordination inter-conversion pathway (Figure 4.7).



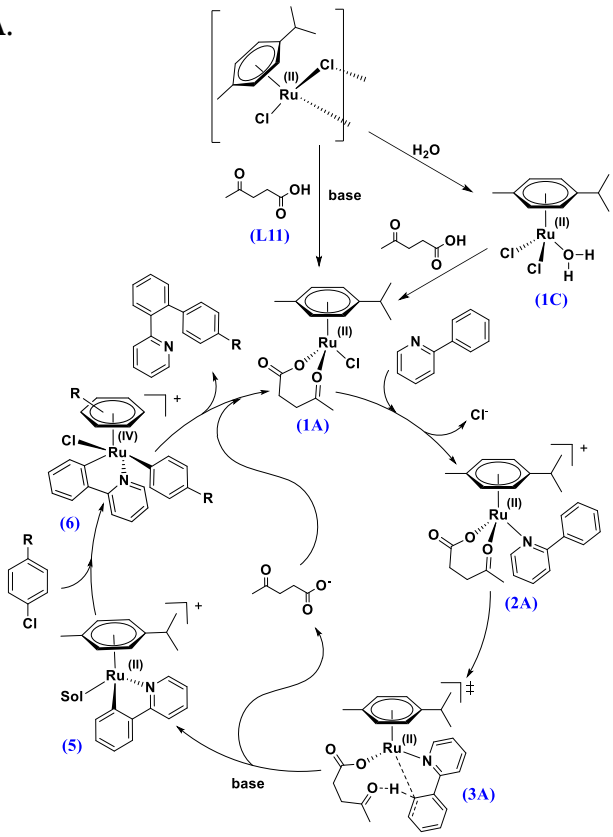
No ligand					
Mechanism Steps	1C→2C	2C→3C	3C→5	ΔΔG‡	
ΔG (kcal/mol)	1.5	4.1	17.3	22.9	
With ligand					
Mechanism Steps	1A/B→2A/B	2A/B→3A/B	3A/B→4A/B	4A/B→5	ΔΔG‡
ΔG (kcal/mol) **L11**	11.7	2.3	-2.8	-6.3	14.0
ΔG (kcal/mol) **L18**	15.9	14.8	-22.1	-4.4	30.7

* ΔΔG‡ represents the overall free energy of reaction.

Scheme 4.4. *Reaction free energy (kcal/mol) for ortho C-H bond activation/arylation of 2-phenylpyridine (**1a**) in the absence and presence of the ligands **L11**/**L18**.*

Therefore, based on the above findings, we anticipated that the significantly enhanced catalytic activity of $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ **([Ru]-A)** in the presence of levulinic acid (**L1**) for C-H bond arylation of **1a** is presumably due to the involvement of acetyl group of **L1** in C-H bond deprotonation.

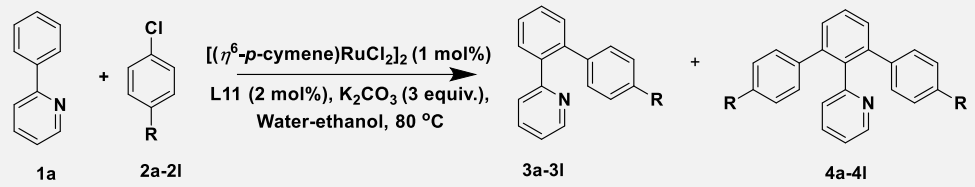
Based on our experimental findings and DFT calculations, a plausible reaction mechanism for biomass derived ligand accelerated *ortho* C-H bond activation/arylation of 2-phenylpyridine is depicted in Scheme 4.5. In the first step, the precatalyst $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ generates the active catalytic species **1A** by the direct coordination of ligand **L1** either to the precatalyst or via a water coordinated species **1C**. Subsequently, upon coordination of 2-phenylpyridine, species **2A** was generated. Further, the species **2A** was transformed to a cyclometalated species **5** *via* a ligand (**L1**)-accelerated concerted metalation deprotonation (CMD) step, and the ligand **L1** was released. Finally, the oxidative addition of aryl halide over the species **5**, and subsequently the release of the monoarylated product (**3a**) *via* reductive elimination step (**6→1A**) generated the active catalytic species **1A**.

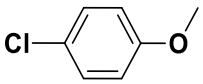
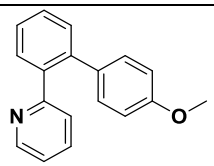
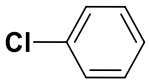
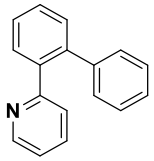
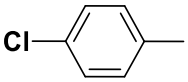
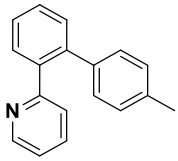
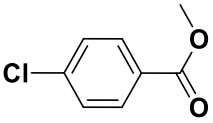
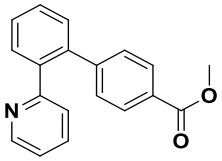
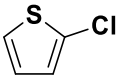
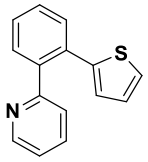
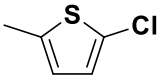
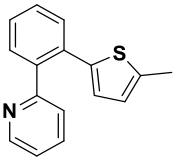


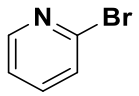
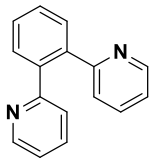
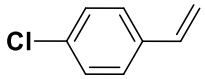
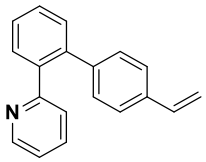
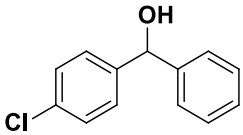
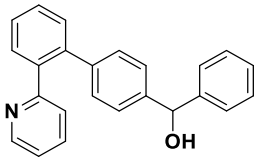
Scheme 4.5. *The plausible reaction pathway for the ruthenium catalyzed ortho C-H activation/arylation of 2-phenylpyridine in the presence of biomass-derived ligand* ***L11****.*

After establishing that the ligand levulinic acid (**L11**) substantially accelerated the activity of ruthenium catalyzed C-H bond activation/arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**2a**), C-H arylation of 2-phenylpyridine (**1a**) with other arylating agents was further explored under the optimized reaction conditions. As summarized in Table 4.3, a wide range of aryl chlorides (**2a-2l**) as coupling partners of 2-phenylpyridine (**1a**) delivered high yields for the monoarylated products (**3a-3l**), while biarylated products (**4a-4l**) were formed as minor products. C-H arylation of 2-phenypyridine (**1a**) with 4-chloroanisole (**2a**) afforded monoarylated product **3a** with 93% selectivity and 87% isolated yield (Table 4.3, entry 1). The unsubstituted aryl halide, chlorobenzene (**2b**) showed >99% conversion with 85% yield for **3b** (Table 4.3, entry 2)**.** Electron rich (**2a, 2c, 2k-2l**) and electron deficient (**2f**) aryl chlorides both exhibited high yield for the corresponding monoarylated products (**3a, 3c, 3k-3l**) of 2-phenylpyridine (**1a**). 4-chlorotoluene (**2c**) also afforded high conversion of 2-phenylpyridine (**1a**) to the corresponding monoarylated product (**3c**) with high selectivity (**3c:4c** = 96:4) and 89% yield (Table 4.3, entry 3). Further, the electron deficient 4-chloromethylbenzoate (**2f**) also exhibited high selectivity (88%) and yield (65%) for **3f** (Table 4.3, entry 4). Notably, the sulphur containing (hetero)aryl halides, 2-chlorothiophene (**2g**) and 5-methyl-2-chlorothiophene (**2h**) also resulted in remarkably high conversion with high yields for the corresponding monoarylated products **3g** (90%) and **3h** (83%) (Table 4.3, entries 5-6). In contrary to 2-chlorothiophene (**2g**), reaction with nitrogen containing heterocycle, 2-bromopyridine (**2i**) was found to be quite sluggish and only 20% conversion was observed in 4 h and 52% conversion, even after 24 h, with poor yield for the monoarylated product (**3i**) (Table 4.3, entry 7). 4-Chlorostyrene (**2k**) and 4-chlorobenzhydrol (**2l**) also afforded appreciably very high selectivity (99:1) for the corresponding monoarylated products (**3k** and **3l,** Table 4.3, entries 8-9).

Table 4.3. *Catalytic ortho C-H bond arylation of 2-phenylpyridine (**1a**) with various (hetero)aryl halides (**2a-2l**) over [(η^6-p-cymene)$RuCl_2$]$_2$ catalyst in the presence of levulinic acid (**L11**) ligand*[a]



Entry	Substrate	Conv. (%)	Sel. (%)	Yield (%)[d]
1.	 **2a**	83% >99%[b] (8 h)	93/7 90/10[b] (**3a**:**4a**)	 **3a (87%)**[b]
2.	 **2b**	>99%	93/7 (**3b**:**4b**)	 **3b (85%)**
3.	 **2c**	>99%	96/4 (**3c**:**4c**)	 **3c (89%)**
4.	 **2f**	80%	88/12 (**3f**:**4f**)	 **3f (65%)**
5.	 **2g**	>99%	93/7 (**3g**:**4g**)	 **3g (90%)**
6.	 **2h**	>99%	89/11 (**3h**:**4h**)	 **3h (83%)**

7.	 **2i**	20% 52%[c] (24 h)	99/1 80/20 (**3i**:**4i**)	 **3i** (32%)[c]
8.	 **2k**	90%	99/1 (**3k**:**4k**)	 **3k (83%)**
9.	 **2l**	73%	99/1 (**3l**:**4l**)	 **3l (67%)**

[a]Reaction Conditions: [(η^6-*p*-cymene)$RuCl_2$]$_2$ (1 mol%), **L11** (2 mol %.), K_2CO_3 (3 equiv.), 2-phenylpyridine (**1a**) (0.6 mmol), aryl halide (**2a-2l**) (0.5 mmol), water-ethanol (9:1 v/v, 2 mL), 80 ºC, 4 h, N_2 atmosphere, [b]time = 8 h, [c]time = 24 h, [d]isolated yield. Conversion and selectivity were determined by ^{1}H NMR with TMS as internal standard.

4.3. Conclusion

In summary, we investigated in detail the role of several biomass-derived ligands as active additives for accelerated Ru(II) catalyzed C-H bond arylation reaction. Among the studied ligands, levulinic acid (**L11**) ligand afforded an excellent enhancement in the catalytic activity of [(η^6-*p*-cymene)$RuCl_2$]$_2$ for C-H bond arylation of 2-phenylpyridine (**1a**) with 4-chloroanisole (**1b**) in a water-based reaction condition. We achieved high compatibility of the studied Ru(II)-levulinate catalytic system for C-H bond arylation of 2-phenylpyridine (**1a**) with a wide range of electron rich and electron deficient aryl halides and heteroaryl halides. Kinetic studies and mass spectral identification of ligand coordinated Ru(II) species (**[Ru]-F**) and the crucial cyclometalated species (**[Ru]-C**) under the catalytic and controlled reaction condition evidenced the possible crucial role of the ligand **L11** in the observed accelerated catalytic activity. In concurrence with the experimental findings, DFT calculations also revealed that the C-H bond activation of 2-phenylpyridine (**1a**) is energetically more favorable (by 8.9 kcal/mol) in the presence of ligand **L11** as compared to the ligand-free reaction. Our experimental findings and DFT

calculations evidenced the involvement of acetyl group of the ligand **L11** in the deprotonation step and suggesting that the anionic carboxylate group facilitated the strong anchoring of ligand to the metal center. Therefore, we believe that the present study utilizing biomass-derived ligands to achieve remarkably 7-fold enhanced catalytic activity for C-H bond activation/arylation over arene-Ru(II) catalyst is significant, and such systems will also help in the development of other ligand-tuned highly active catalytic system. Further investigations in this direction are underway in our laboratory.

4.4. Experimental section

4.4.1. Materials and instrumentation

All the catalytic reactions for C-H bond arylation of 2-phenylpyridine with aryl halides were performed under N_2 atmosphere using chemicals of high purity purchased from Sigma Aldrich and Alfa Aesar. Ruthenium-arene precursor $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ **([Ru]-A)** was synthesized according to the literature procedures. [22,23] ^{1}H NMR (400 MHz), and ^{13}C NMR (100 MHz), spectra were recorded at 298 K using $CDCl_3$ as the solvent on a Bruker Advance 400 spectrometer. The chemical shifts in ppm are reported relative to the center of the singlet at 7.26 ppm for $CDCl_3$ in ^{1}H NMR and to the center of the triplet at 77.0 ppm for $CDCl_3$ in ^{13}C NMR. Coupling constants, *J* values are reported in Hertz (Hz), and the splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. DFT calculations have been carried out using Gaussian 09 D.01 package.[21] B3LYP functional has been used for geometry optimization of the intermediates.[24] Furthermore, Pople 6-31++G(d, p) basis set [25] has been used for non-metals (C, H, N, O and Cl) and LANL2DZ-ECP (effective core potential) has been used for Ru metal(52). Grimme's dispersion correction (DFT-D3) has also been included with the B3LYP functional to incorporate the non-covalent interactions.[26] In the experimental condition we have used water as a solvent. Therefore, conductor-like polarizable continuum model (C-PCM) has been used to incorporate solvent effect (ε= 78.3553 for water) in the calculation.[27] All the reaction free energies have been calculated at 298.15 K and 1 atm pressure. The zero-point energy and thermal corrections have been included with the electronic energies to get the reaction free energy. The reaction free energies

(ΔG) have been calculated from the energy difference between the final and initial state of the intermediates.

4.4.2. Typical Procedure for the synthesis of biomass-derived ligands (L14 and L17)

Synthesis of 5-hydroxymethyl furfural (5-HMF) (L14). The biomass derived furan derivative 5-hydroxymethyl furfural (5-HMF) was prepared by slight modification in the previously reported method.[28] D-fructose (1 mmol, 0.180 g) was dissolved in 2 mL of 2-propanol followed by the addition of 0.5 mmol (0.027 g) of NH_4Cl. The reaction mixture was continued to stir at 120 ºC for 12 h and the progress of the reaction was monitored by thin-layered chromatography. After completion, 2-propanol was removed by evaporation under reduced vacuum. Then, 5 mL water was added in the remaining fraction and extracted with diethyl ether (3 × 10 mL) and dried over anhydrous Na_2SO_4. All the volatiles were removed under vacuum to obtain the crude product. Product was purified by using column chromatography and confirmed by ^1H and ^{13}C NMR.

Synthesis of furan-2-carboxylic acid (2-furoic acid) (L17). The biomass derived furan derivative, furan-2-carboxylic acid (2-furoic acid) was prepared by following the reported procedure using $Ni_{0.90}Pd_{0.10}$ nanoparticles as a catalyst.[29] A two-neck round-bottom flask was charged with freshly prepared 5 mol % $Ni_{0.90}Pd_{0.10}$ nanoparticles followed by the addition of furan 2-carboxyaldehyde (1 mmol, 82.8 µL). The reaction mixture was stirred at 80 ºC with a continuous flow of air for 1 h. The progress of the reaction was monitored by thin-layered chromatography. After the completion of the reaction, the catalyst was recovered from the reaction mixture by centrifugation and brine solution (5 mL) was added with the 1.2 M HCl (3 mL). The crude reaction mixture was extracted by using diethyl ether (5 × 10 mL) and combined organic layer was dried over anhydrous Na_2SO_4. Then all the volatiles were removed under vacuum to obtain the crude product. Then the product was purified by using column chromatography and confirmed by ^1H and ^{13}C NMR.

4.4.3. General procedure for catalytic ortho C-H bond arylation of 2-phenylpyridine with aryl halides

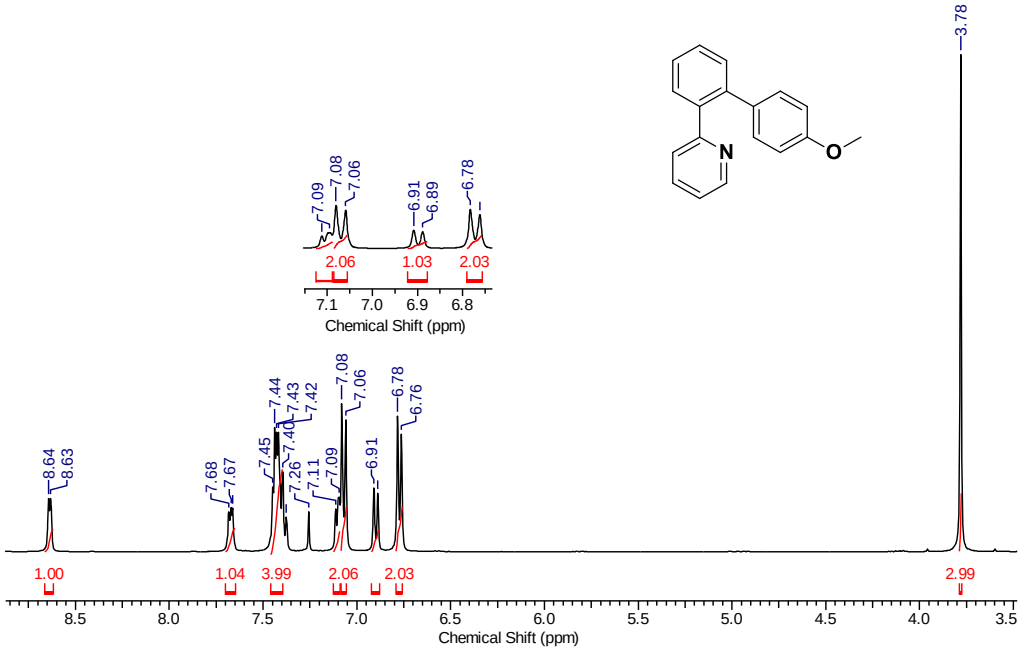
All the reactions were carried out under N_2 atmosphere. C-H bond arylation reactions of 2-phenylpyridine were performed in a two necked round bottom flask. Flask was charged with ruthenium catalyst, $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ **([Ru]-A)** (1 mol %, 0.005 mmol, 0.00306

g), ligand (2 equiv., 2 mol%) and K_2CO_3 (3 equiv., 1.5 mmol, 0.207 g) with water-ethanol (2 mL) in 9:1 v/v ratio. Water-ethanol solvent medium was chosen in order to avoid decomposition/polymerization of furan-based ligands. Solution was stirred for 15 minutes and then 2-phenylpyridine (0.6 mmol, 86 µL) and aryl halide (0.5 mmol) was added. The reaction was continued to stir at 80 ºC for 4 h under N_2 atmosphere and then cooled down to room temperature. Further, the reaction mixture was extracted with ethyl acetate (3×10 mL) and dried over anhydrous Na_2SO_4. All the volatiles were removed under vacuum to obtain the crude product. Conversion and selectivity of the mono and biarylated products were determined by ^{1}H NMR. Products were purified and isolated from the crude reaction mixture by using column chromatography on silica gel with ethyl acetate/*n*-hexane as eluents.

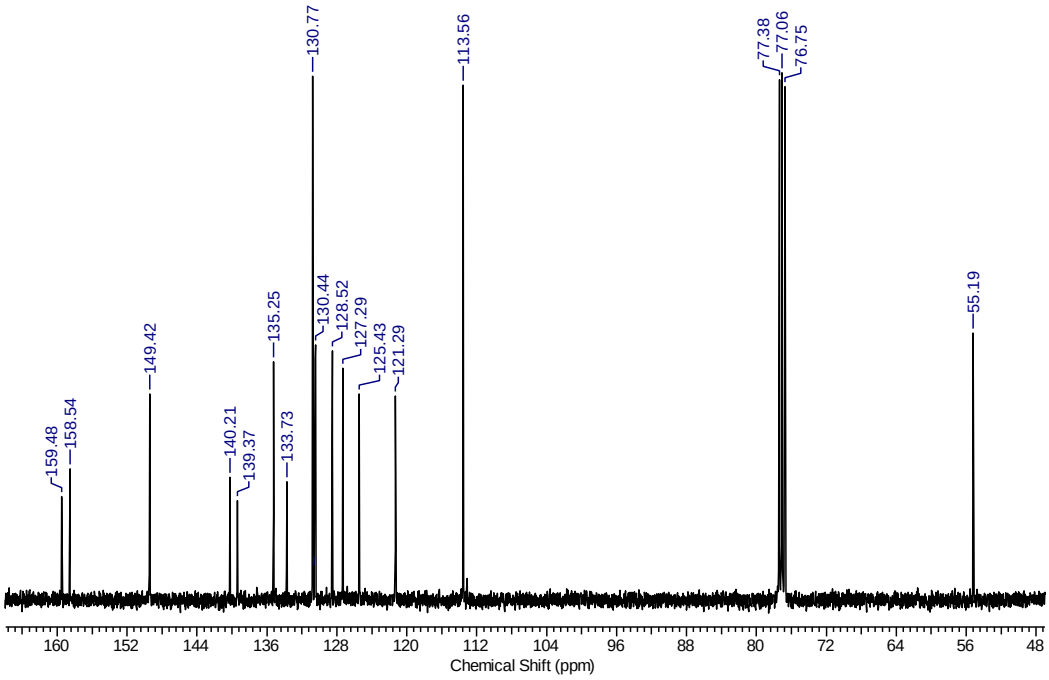
4.4.4. Typical procedure for mass spectrometric analysis for the identification of reactive intermediate species

Mass studies were also carried out in a two necked reaction flask containing [(η^6-*p*-cymene)$RuCl_2$]$_2$ **([Ru]-A)** (1 mol%, 0.005 mmol, 0.00306 g) in 2 mL water-ethanol [(9:1) v/v] with or without base. Then ligand (2 mol%) and 2-phenylpyridine (0.025 mmol, 3.6 µL) was added for maintaining the catalyst: ligand: substrate ratio i.e. C:L:S = 1:2:5. Reaction mixture was heated at 80 ºC under nitrogen atmosphere for 1.5 h. 100 µL of aliquot from the reaction mixture was withdrawn at different intervals of reaction time (0, 30, 60, 90 and 120 minutes) which was diluted with methanol and ESI-MS was recorded in positive mode. Mass spectra were analyzed, and active intermediates generated during the reaction have been identified.

4.4.5. NMR spectra of C-H activated monoarylated product 3a



^{1}H NMR spectra of compound **3a**



^{13}C NMR spectra of compound **3a**

Note 1: Spectral copies and NMR data for substrate has been given in the previous chapters (Chapter 2 and 3).

Note 2: The contents of this chapter is published as Binnani et al., Eur. J. Inorg. Chem. 2019, 2844- 2852 (DOI: 10.1002/ejic.201900218) and reproduced with the permission from Wiley VCH with license number 4615211492391.

4.5. References

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Chapter 5

Ruthenium(II) catalyzed C-H bond activation/arylation: Mechanistic investigation for 2-hydroxypyridine-based ligands as promoter

5.1. Introduction

C-H bond activation and functionalization has become an intensively studied strategy in the past decades, due to its potential application in economically and ecologically friendly organic synthesis.[1] Apart from transition metals including Pd[2], Rh[3] and Ir,[4] which are the promising options for C-H bond activation and functionalization reactions, various 3d transition metals,[5] such as Mn, Co, Fe etc. have also attracted the attention of researchers for such reactions. Among various transition metals investigated, Ru metal complexes have been employed as an outstanding and attractive catalyst for C-H bond activation reaction, due to its high versatility and reactivity, compatibility with air and water, diversity in oxidation states and cost effectiveness over the other metals.[6] Metal catalyzed C-H bond activation and functionalization reactions generally accompanied by the use of suitable ligands, either as an additive or as integral part of complex, to accelerate the rate of reaction. Role of a ligand in ruthenium catalyzed C-H bond activation and functionalization reactions is crucial and affect the activity and efficiency of a ruthenium catalyst by tuning the surrounding environment around the metal center.[7]

For instance, phosphine ligands has extensively been studied by various researchers and they found to be of key importance in facilitating the oxidative addition steps for ruthenium(II) catalyzed C-H bond activation/functionalization reactions.[8] Further studies also demonstrated that phosphine ligands have very strong influence on controlling the selectivity for C-H arylated products.[8b] Although, in subsequent years, various ligands ranging from weakly coordinating *O,O* donor carboxylates to strongly coordinating nitrogen-based donor ligands have also been extensively explored and studied for C-H bond activation reactions. For instance, Ackermann *et al.* explored

variety of carboxylates as co-catalyst[9a] and phosphine oxides as ligands[9b] with arene-ruthenium complex which displayed the high potential as deprotonating agent and also plays crucial role to tune the selectivity of the reaction. Our recent results also showed that with Ru(II) complexes having troponate/aminotroponate ligands, there is a gradual increase in the selectivity for biarylated product with increasing bulkiness of carboxylate additives from acetate, propionate to isobutyrate and pivalate for C-H bond activation/arylation.[10]

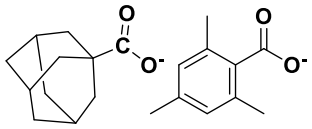
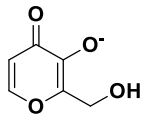
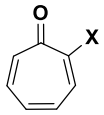
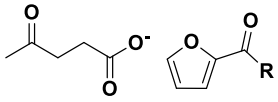
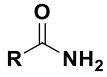
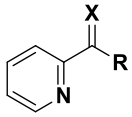
Dixneuf also demonstrated that the role of bulky carboxylates such as pivalate[11] is crucial to achieve higher catalytic activity and selectivity for C-H arylated product of heteroarene in Ru(II) catalyzed C-H bond activation/arylation reactions. Our recent results also support the previous reports by showing 7-fold enhancement in the catalytic activity for Ru(II) catalyzed C-H bond activation/arylation in the presence of biomass derived *O,O* donor ligands in water-based condition.[12] Our finding suggesting that the biomass derived *O,O* donor ligands having neutral acyl oxygen outperformed over those having anionic oxygen exhibiting the carboxylates type weak interaction of ligand with metal which further facilitates the enhancement in the catalytic activity.

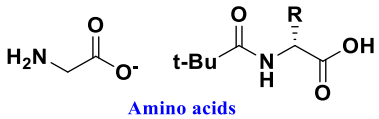
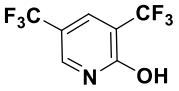
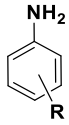
Along with the widely explored *O,O* donor ligands, *N,O* donor ligands also constitutes an important class of ligands which are efficiently catalyze the C-H bond activation reactions. Recently, Li et al. used acetamide ligand to display enhanced catalytic activity due to involvement of acetyl group in C-H deprotonation step in ruthenium (II) catalyzed C-H bond arylation reaction.[13] In our recent report, we also demonstrated that the involvement of acetyl group of 2-acetylpyridine ligand is vital for promoting the facile deprotonation of 2-arylpyridine in ruthenium(II) catalyzed C-H bond activation reactions.[14]

Rather than ruthenium, other metals such as palladium has also been accompanied with the use of *N,O* donor ligands such as mono N-protected amino acid ligands to accelerate the C-H deprotonation step.[15] Further, Yu *et al.* reported the Pd(II) catalyzed ligand accelerated C-H bond activation of unactivated arene using electron deficient 2-hydroxypyridine-based ligands.[16] They proposed the active participation of substituted 2-pyridone ligands which is a tautomeric form of 2-hydroxypyridne, which further gets coordinated with the palladium center and undergo concerted metalation-deprotonation

pathway. DFT calculations also supported the involvement of 2-pyridone ligand in deprotonation step. Several previous reports also suggested the crucial role of bis-chelating *N,O* donor ligands in tuning the catalytic C-H activation reaction pathway via coordination/decoordination mechanism and by participating in deprotonation step.[17] We also observed an accelerated Ru(II) catalyzed C-H bond arylation in the presence of weakly coordinating electron deficient aniline ligands (Table 5.1).[18]

Table 5.1. *N,O/O,O donor ligands investigated previously for C-H bond activation/arylation reactions.*

Entry	Ligand	Metal catalyst	Reference
1.	 Carboxylates	Ru(II)	Ref. *[9]*
2.	 Kojoic acid	Ru(II)	Ref. *[10]*
3.	 Tropolone/ aminotropolone X = O, -NR	Ru(II)	Ref. *[11]*
4.	 Biomass derived ligands R = -H, -Me, -OH	Ru(II)	Ref. *[12]*
5.	 Amides	Ru(II)	Ref. *[13]*
6.	 Pyridine based ligands X = O, -NR R = -H, -Me	Ru(II)	Ref. *[14]*

7.	 Amino acids	Ru(II) Pd(II)	Ref. *[15]*
8.	 Substituted 2-hydroxypyridine	Pd(II)	Ref. *[16]*
9.	 Aniline	Ru(II)	Ref. *[18]*

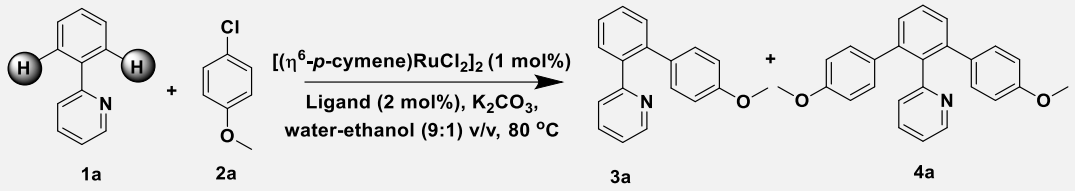
Encouraged by above findings and in our continuing efforts to develop efficient catalytic system for C-H bond activation/arylation reaction, we systematically studied the series of 2-hydroxypyridine based ligands for ruthenium catalyzed C-H bond activation. 2-hydroxypyridine based ligands (**L23 – L28**) emerged as an efficient tool for various catalytic reactions as it can quickly undergo tautomerization to form 2-pyridone depending upon the various reaction conditions and it may serve as an internal base in *ortho* C-H bond deprotonation of 2-phenylpyridine. Mass spectrometric investigations also revealed the crucial role of 2-hydroxypyridine or 2-pyridone ligands in enhancement of the reaction rate by the identification of various intermediate species during the reaction.

5.2. Results and discussion

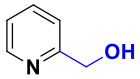
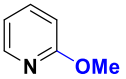
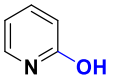
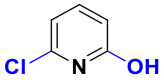
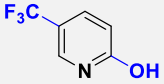
At an outset of our investigations, we conducted *ortho* C-H bond activation/arylation reaction using 2-phenylpyridine (**1a**) as model substrate along with the 4-chloroanisole (**2a**) as coupling partner over $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ **([Ru]-A)** catalyst (1 mol%) at 80 °C in water-ethanol solution in the presence of 3 equiv. of K_2CO_3 as base. The preliminary evaluation of various 2-substituted pyridine-based ligands (**L23 – L25**) for *ortho* C-H bond activation/arylation of **1a** inferred that 2-hydroxypyridine ligand (**L25**) outperformed over pyridine-2-methanol (**L23**) and 2-methoxypyridine (**L24**) ligands with 65% conversion and 52% yield for monoarylated product (**3a**) in 4 h (**3a**/**4a** selectivity = 92/8) (Table 5.2, entry 4). In contrary, other ligands, **L23** and **L24**,

showed comparatively lower yield for monoarylated product (**3a**) (36% and 48% respectively) under optimized reaction condition (Table 5.2, entry 2, 3).

Table 5.2. *Effect of various 2-hydroxypyridine-based ligands on ruthenium (II) catalyzed ortho C-H bond activation/arylation of heteroarenes with aryl halide* [a]



1a 2a 3a 4a

Entry	Ligand	Conv. (%)	Sel. (3a/4a)	Yield[b] (%) (3a)	TON/TOF (h^{-1})
1.	**No ligand**	12%	93/7	n.d.	24/6
2.	 **Pyridine-2-methanol (L23)**	45%	92/8	36%	45/11.25
3.	 **2-methoxypyridine (L24)**	54%	96/4	48%	54/13.5
4.	 **2-hydroxypyridine (L25)**	65%	92/8	52%	65/16.25
5.	 **6-chloro-2-hydroxypyridine (L26)**	70%	92/8	58%	70/17.5
6.	 **5-chloro-2-hydroxypyridine (L27)**	73%	93/7	65%	73/18.25
7.	 **5-trifluoromethyl-2-hydroxypyridine (L28)**	**90%**	**93/7**	**75%**	**90/22.5**

[a]**Reaction Condition:** $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ **([Ru]-A)** (1 mol%), **L23-L28** (2 mol %.), K_2CO_3 (3 equiv.), 2-phenylpyridine (**1a**) (0.6 mmol), 4-chloroanisole (**2a**) (0.5 mmol), water-ethanol (9:1 v/v, 2 mL), 80 °C, 4 h, N_2 atmosphere, [b]isolated yield, conversion and selectivity were determined by ^1H NMR with TMS as internal standard, TON = Turn over number, TOF (h^{-1}) = Turn over frequency, n.d. = not determined.

Previous reports evidenced that 2-hydroxypyridine based ligands serves as a pyridone ligand to coordinate with the metal center through the pyridine nitrogen and may act as an internal base to facilitate the C-H bond cleavage/ activation.[19] It is evident from the structure of the ligands **L23 – L25**, only the ligand **L25** can exist in pyridone form, thus accelerated the C-H bond arylation of 2-phenylpyridine **1a** to **3a**. To further explore the role of 2-hydroxypyridine based ligands, we employed several 5 or 6 substituted 2-hydroxypyridine ligands such as 6-chloro-2-hydroxypyridine (**L26**), 5-chloro-2-hydroxypyridine (**L27**) and 5-trifluoromethyl-2-hydroxypyridine (**L28**) for [(η^6-*p*-cymene)$RuCl_2$]$_2$ catalyzed C-H bond arylation of **1a** with **2a** to afford **3a**/**4a** under the optimized reaction conditions (Table 5.2, entries 5-7). Results inferred that 2-hydroxypyridine ligands with electron-deficient substituents (**L26 – L28**) exhibited more prominent effect to accelerate the C-H bond arylation of **1a** over **[Ru]-A** catalyst. In particular, 5-trifluoromethyl-2-hydroxypyridine (**L28**) significantly accelerated the C-H bond arylation of **1a** under the optimized reaction conditions. Notably, in the absence of ligand, **[Ru]-A** catalyst showed negligible conversion of **1a** under analogous reaction condition (Table 5.2, entry 1).

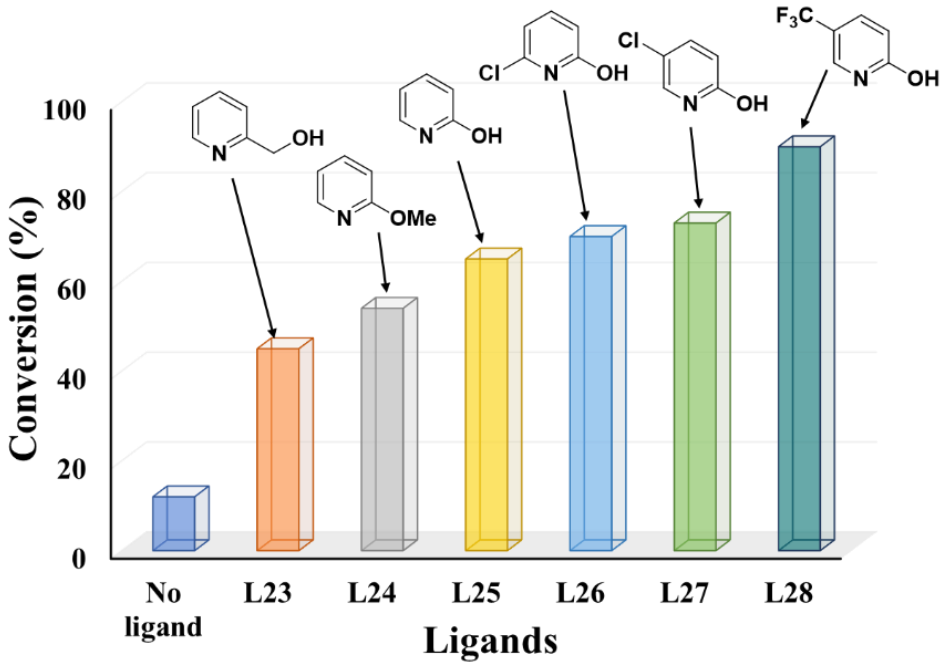
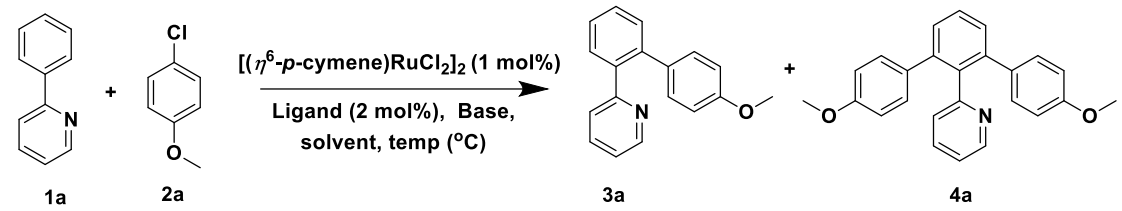


Figure 5.1. *Comparison of activity of various 2-hydroxypyridine based ligands for ortho C-H bond activation/arylation of 2-phenylpyridne (**1a**) over Ru(II) catalyst.*

Further optimization showed that the catalytic activity deteriorates with lower amount of base and reaction failed to occur in the absence of K_2CO_3. Lowering the reaction temperature could not result in the reaction of **1a** (Table 5.3 (a) and (b)).

Table 5.3. *Optimization of reaction conditions for Ru(II) catalyzed C-H bond activation/arylation of 2-phenylpyridine with aryl halide.*[a]



(a) Loading of base effect of temperatutre[a]

Entry	Base	Conv. (%)	Sel. (3a/4a)
1.	0 equiv.	n. r.	-
2.	1 equiv.	n. r.	-
3.	2 equiv.	38%	90/10
4.	3 equiv.	90%	93/7
5.	3 equiv.[b]	n. r.	-

[a]**Reaction condition:** [Ru(η^6-*p*-cymene)Cl_2]$_2$ (1 mol%), **L28** (2 mol%), 2-phenylpyridine (0.6 mmol), aryl halide (0.5 mmol), water-ethanol (9:1) v/v (2 mL), 80 °C, [b]temp. 60 °C, 4 h, N_2 atmosphere, n.r. = no reaction.

Further, time-dependent ^{1}H NMR experiments were performed over a period of 2.5 h under analogous reaction condition to understand the effect of 2-hydroxypyridine-based ligands on the catalytic reaction. As inferred from the Figure 5.1, **L28** was found to show the enhanced the catalytic activity for the Ru(II) catalyzed *ortho* C-H bond arylation of 2-phenylpyridine. Notably, ruthenium catalyst in the presence of electron deficient ligand **L28**, was found to exhibit the highest reaction rate (12.1×10^3 sec^{-1}) for initial 2.5 h as compared to reaction performed with ligand **L25** (2.94×10^3 sec^{-1}) under the analogous reaction condition (Figure 5.2 and 5.3). Contrary to this, when reaction was performed with Ru(II) catalyst, in the absence of any ligand, poor catalytic activity was observed (4.59×10^{-4} sec^{-1}) resulting into very slow rate of reaction (Figure 5.2 and 5.3).

The observed results suggesting a crucial role of 2-hydroxypyridine-based ligands to achieve high catalytic activity towards C-H bond activation/arylation reaction (Figure 5.2 and 5.3).

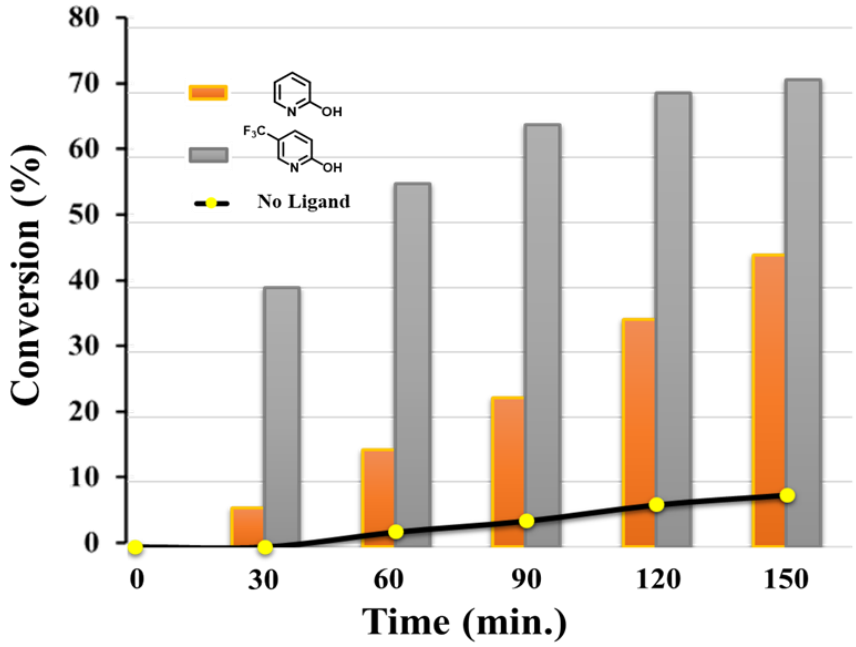
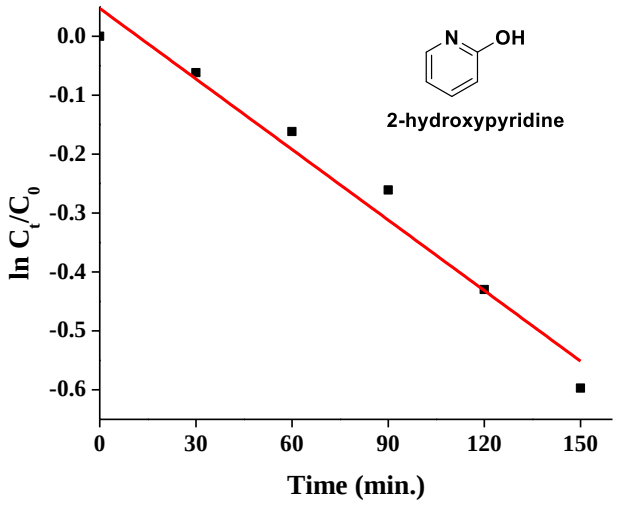
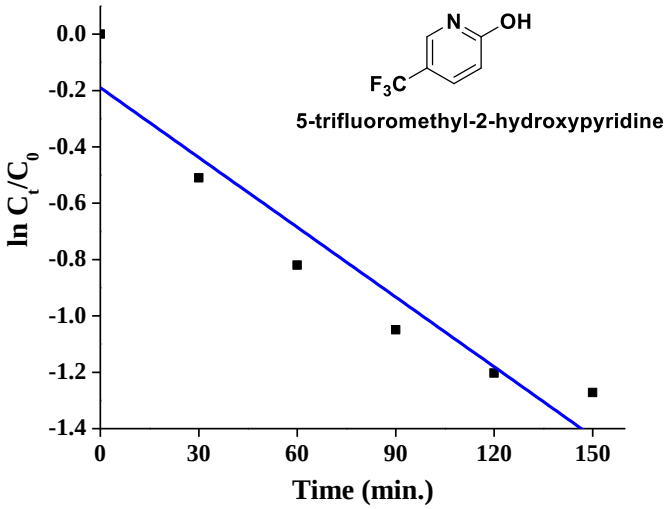


Figure 5.2. *Time dependent ^{1}H NMR studies for the investigation of influence of ligands* ***L25*** *and* ***L28*** *for ortho C-H bond activation/arylation reaction over [(η^6-p-cymene)$RuCl_2$]$_2$ catalyst.*

Calculation of rate constant (k) for the *ortho* C-H bond activation/arylation of 2-phenylpyridine in the presence and absence of 2-hydroxypyridine based ligands is as follows (Figure 5.3):





Calculation of rate constant (k) for the first order reaction:

$$k = \frac{1}{t} ln \frac{[C_o]}{[C_t]}$$

Catalyst	Without ligand	With ligand (L25)	With ligand (L28)
Rate constant (k)	4.89×10^{-4} sec^{-1}	**2.94×10^{3} sec^{-1}**	**12.1×10^{3} sec^{-1}**

Figure 5.3*. Calculation of rate constant for Ru(II) catalyzed C-H bond activation/arylation of 2-phenylpyridine to understand of effect of ligands (**L25** and **L28**).*

To further, identify the important intermediate species involves in the 2-hydroxypyridine promoted *ortho* C-H bond arylation reaction of 2-phenylpyridine, extensive mass spectral studies have been performed in the presence of ligands **L25** and **L28**, under stoichiometric condition. Controlled experiments were performed with stoichiometric ratio of 1:2 (Catalyst : Ligand (**L25/L28**)) in water-ethanol (9:1, v/v) at 80 °C for 1.5 h in the absence of base. The mass spectral analysis of reaction mixture showed the prominent peak at m/z = 330.0 and m/z = 398.0, corresponding to the species [(η^6-*p*-cymene)RuCl(**L25/L28**)] ($[M\text{-}Cl]^+$) (**[Ru]-H_1/H_2**) (Figure 5.4 (a) and (b)).

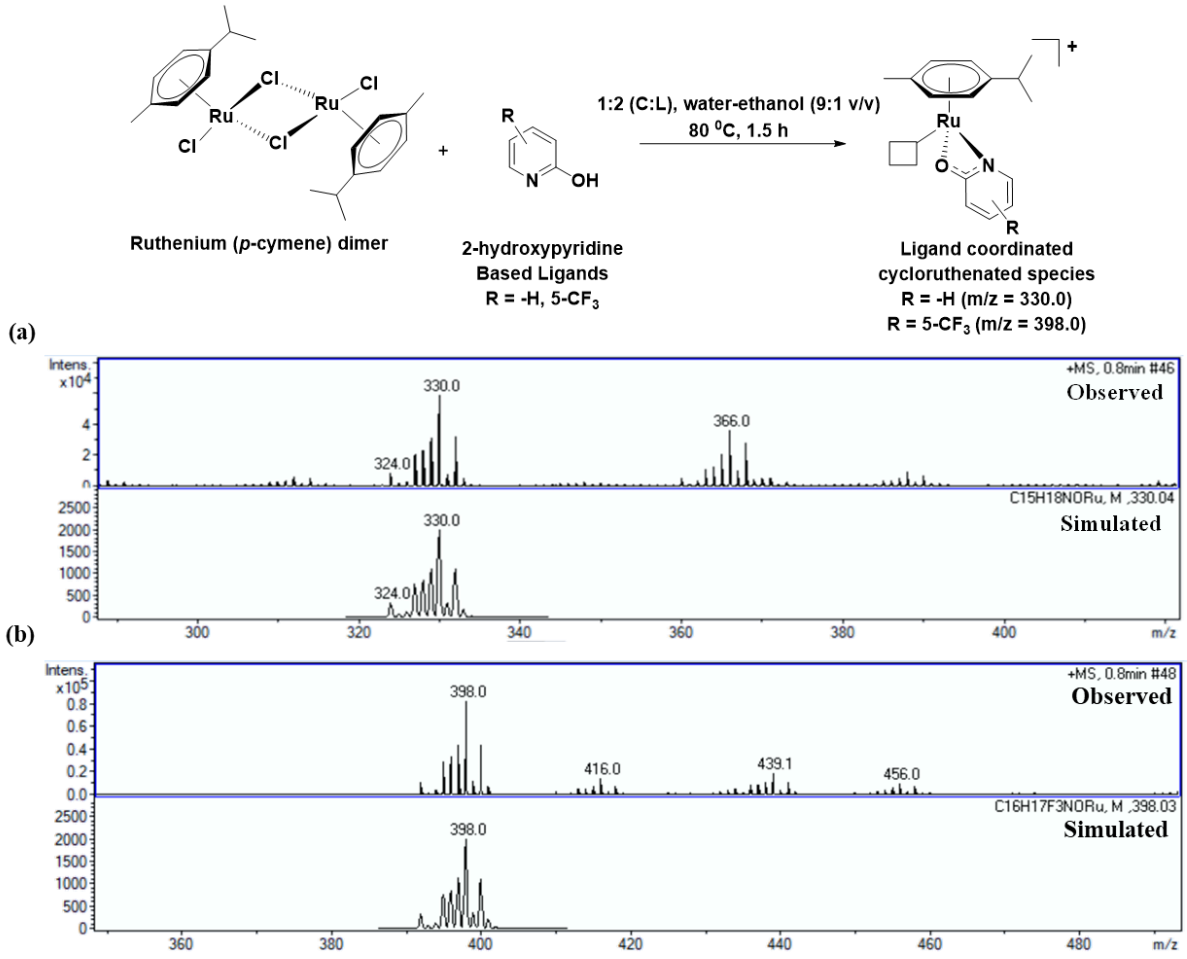


Figure 5.4. *Observed and simulated pattern of* ***(a)*** *2-hydroxypyridine (**L25**) coordinated arene-Ru species [(η^6-p-cymene)Ru(**L25**)]$^+$ **[Ru]-H$_1$**.* ***(b)*** *5-trifluoromethyl-2-hydroxypyridine (**L28**) coordinated arene-Ru species [(η^6-p-cymene)Ru(**L28**)]$^+$ **[Ru]-H$_2$**.*

Further, the addition of 2-phenylpyridine in the above reaction mixture resulted into the appearance of a significant peak which can be attributed to the ligand coordinated cycloruthenated species [(η^6-*p*-cymene)Ru(**L25/L28**)(κ^2-*C,N*-2-phenylpyridine)]$^+$ ([M]$^+$] (**[Ru]-I$_1$/I$_2$**), at m/z = 485 and m/z = 552.0 respectively (Figure 5.5 (a) and (b)).

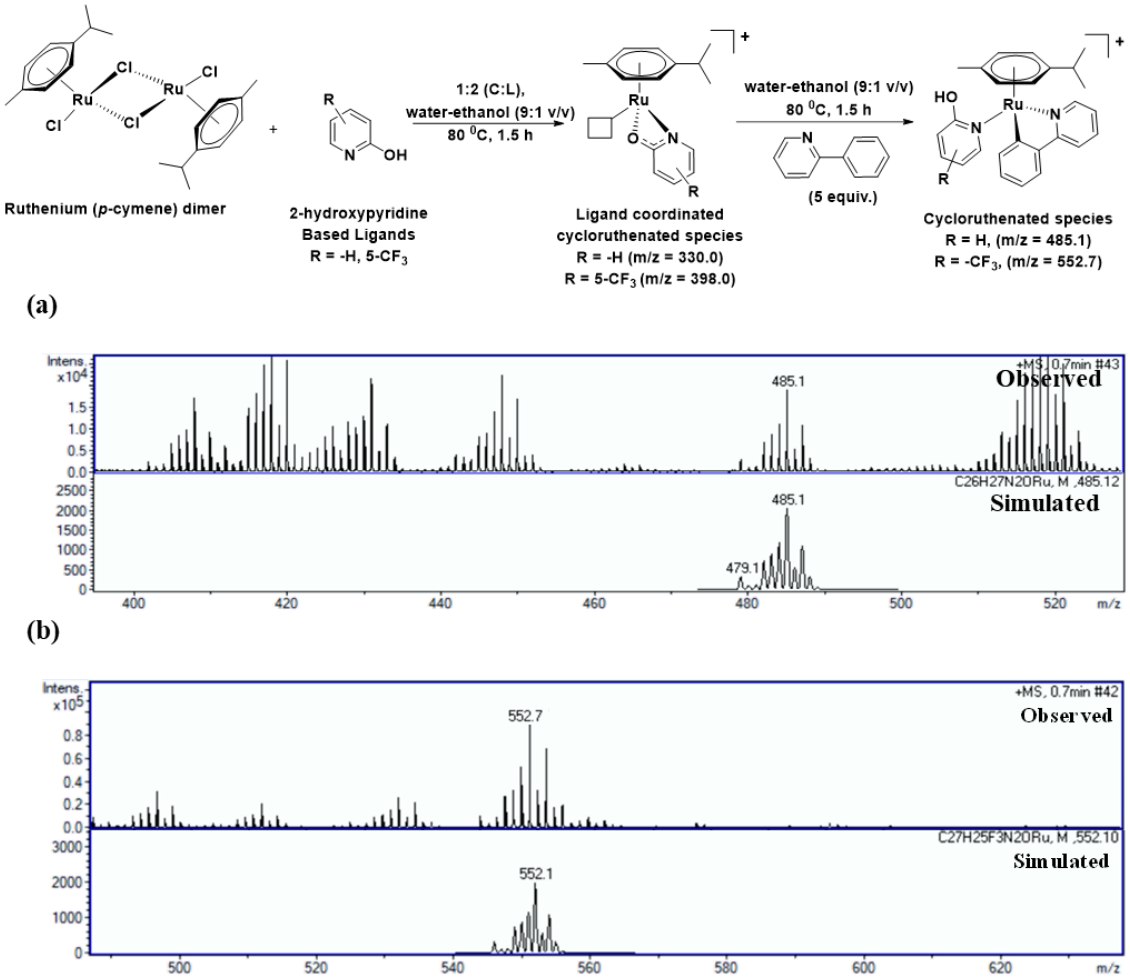


Figure 5.5. *Observed and simulated pattern of (a) 2-hydroxypyridine (**L25**) coordinated arene-Ru species [(η^6-p-cymene)Ru(**L25**)(κ^2-C,N-2-phenylpyridine)]$^+$* ***[Ru]-I$_1$. (b)*** *5-trifluoromethyl-2-hydroxypyridine (**L28**) coordinated arene-Ru species [(η^6-p-cymene)Ru(**L28**)(κ^2-C,N-2-phenylpyridine)]$^+$* ***[Ru]-I$_2$.***

Further, the decoordination of ligand, leads to the formation of cycloruthenated intermediate species [(η^6-*p*-cymene)RuCl(κ^2-*C,N*-2-phenylpyridine)] (**[Ru]-C**) (Figure 5.6), observed at m/z = 390.1 ([M-Cl]$^+$], which is a crucial intermediate, very well reported in literature for *ortho* C-H bond activation/arylation of 2-phenylpyridine.

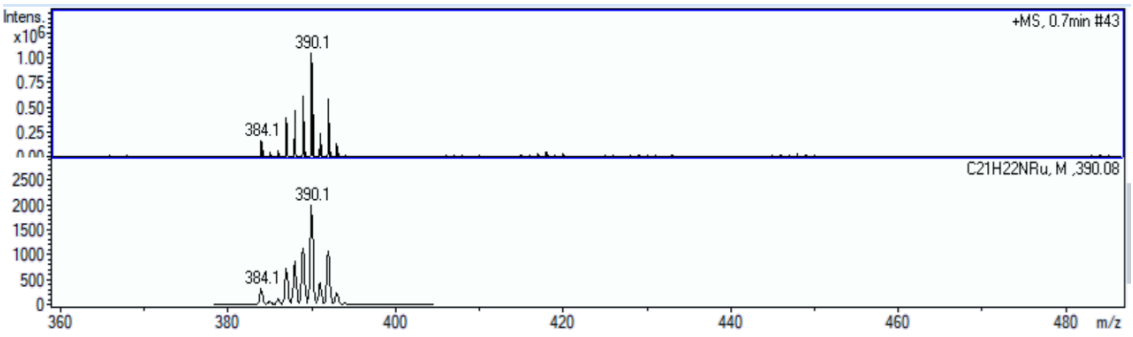


***Figure 5.6**. Observed and simulated pattern of cycloruthenated species {(η^6-p-cymene)Ru(κ^2-C,N-phenylpyridine)}$^+$ **([Ru]-C)**.*

In addition, we probed ^{19}F NMR to identify **L28** coordinated arene-Ru(II) species **[Ru]-H$_2$** and cycloruthenated species **[Ru]-I$_2$**. The presence of a peak at 61.74 ppm in the ^{19}F NMR (in $CDCl_3$) of the reaction mixture obtained by stirring [(η^6-*p*-cymene)$RuCl_2$]$_2$ and **L28** (in 1:2 molar ratio) in dichloromethane at room temperature for 24 h, is corresponding to the [(η^6-*p*-cymene)Ru(κ^2-**L28**)]$^+$ (**[Ru]-H$_2$**) species (m/z = 398.0). Further upon addition of 5 equivalents of 2-phenylpyridine (**1a**) in the above reaction mixture, another prominent peak at 60.22 ppm appeared corresponding to the ligand coordinated cycloruthenated species [(η^6-*p*-cymene)Ru(κ^1-**L28**)(κ^2-*C,N*-2-phenylpyridine)]$^+$ **[Ru]-I$_2$** (m/z = 552.7) (Figure 5.7).

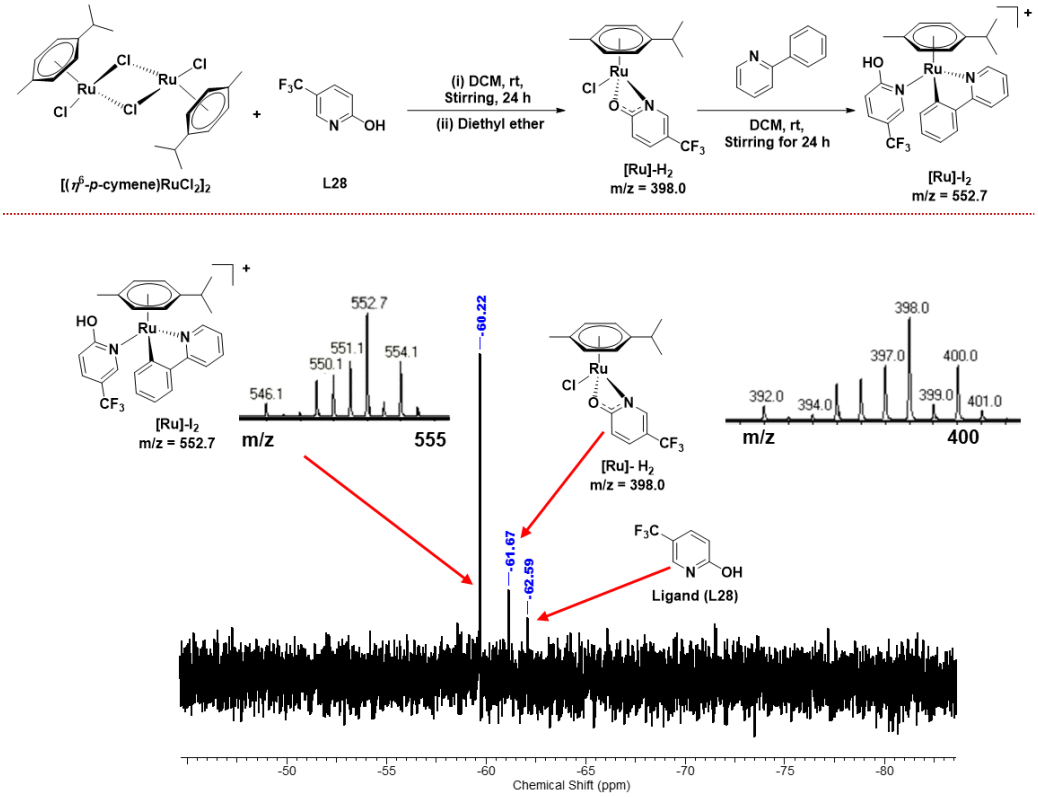
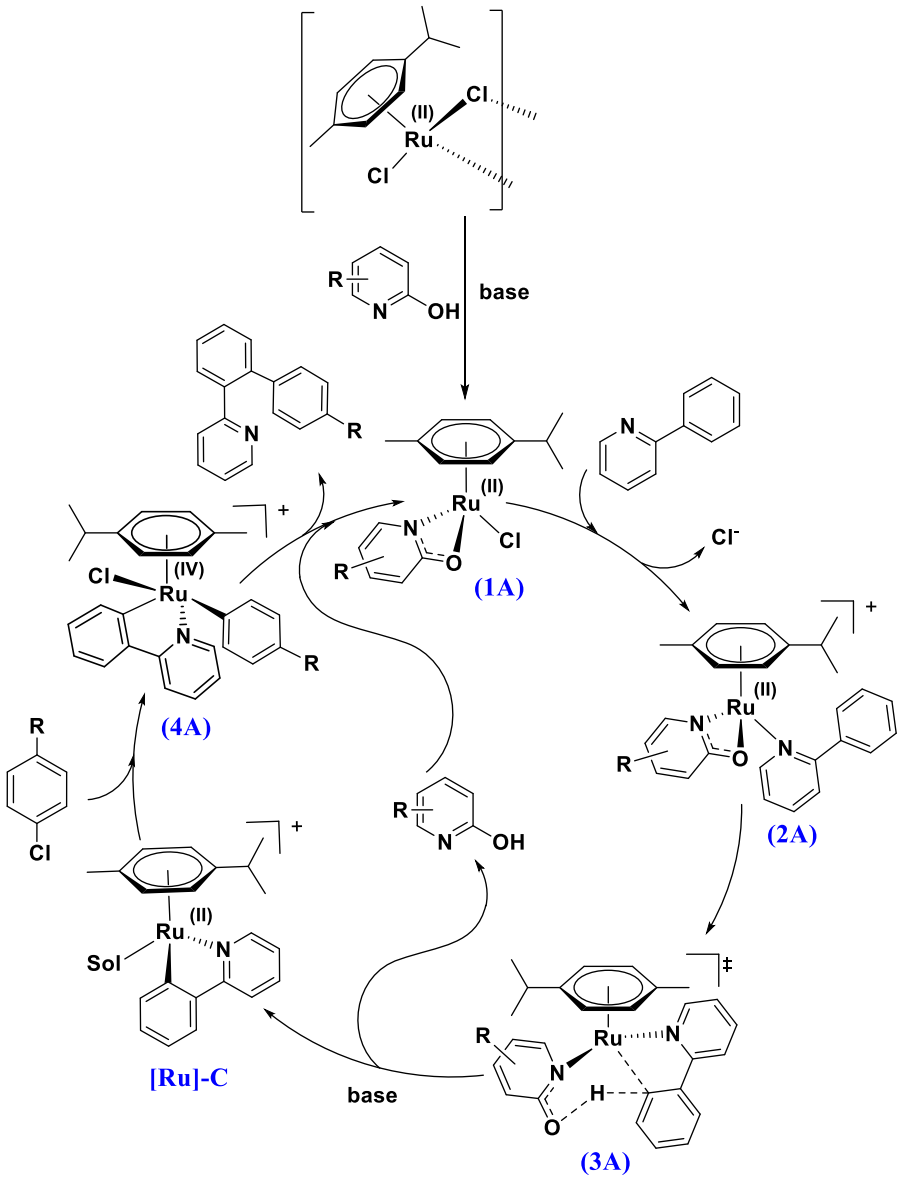


Figure 5.7. *Synthesis and identification of ligand coordinated species [(η^6-p-cymene)Ru(κ^2-**L28**)] (**[Ru]-H$_2$**) and cycloruthenated species [(η^6-p-cymene)Ru(κ^1-**L6**)(κ^2-C,N-2-phenylpyridine)]$^+$ (**[Ru]-I$_2$**) by ^{19}F NMR.*

On the basis of the above observation, plausible mechanism for the reaction has been proposed which includes the coordination of tautomeric 2-hydroxypyridine based ligands to the ruthenium metal center which further assist the deprotonation of 2-phenylpyridine. Formation of cyclometalated species followed by the oxidative addition step leads to the reductive elimination of monoarylated product and regeneration of active catalytic species for next cycle. Scheme shows the schematic representation of the predicted mechanism (Scheme 5.1).

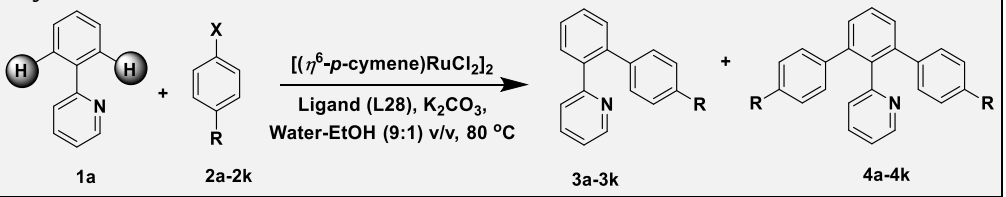


Scheme 5.1. *Plausible mechanism for ruthenium catalyzed ortho C-H bond activation/arylation of 2-phenylpyridine accelerated by N,O donor 2-hydroxypyridine based ligands.*

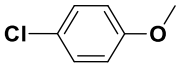
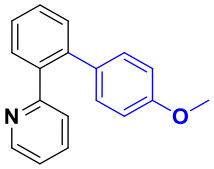
After optimizing the reaction condition with model substrates, 2-phenylpyridine (**1a**) and 4-chloroanisole (**2a**), a variety of aryl chlorides (**2b-2k**) were systematically explored and found to exhibit the moderate to high yield for corresponding monoarylated product, as major product during the reaction (Table 5.4). Unsubstituted aryl halide, chlorobenzene (**2b**) which is almost unreactive in nature, resulted in 89% yield for corresponding monoarylated product (**3b**) (Table 5.4, entry 2). Further, aryl halides such

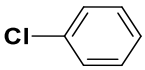
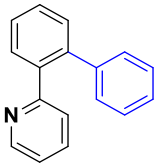
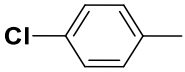
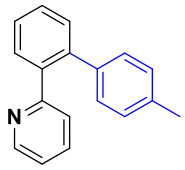
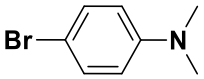
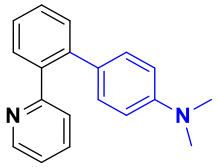
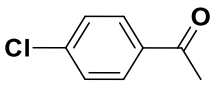
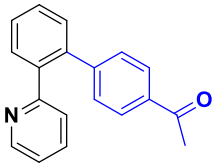
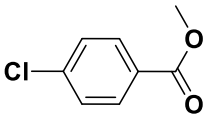
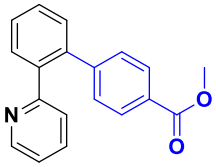
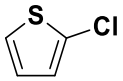
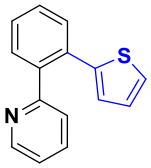
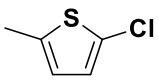
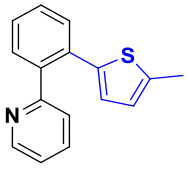
as, 4-chlorotoluene (**2c**) and 4-chlorostyrene (**2k**), having electron donating substitution, exhibited excellent activities towards C-H bond arylation of 2-phenylpyridine with 85% and 88% yield respectively to obtain monoarylated product **(3c** and **3k)** under analogous reaction condition (Table 5.4, entries 3, 10). Notably, very high selectivity (**3k:4k** = 99:1) was also observed when 4-chlorostyrene (**2k**) was used as a coupling partner. Another aryl halide, 4-bromo-*N*,*N*-dimethylaniline (**2d**), resulted into comparatively poor conversion (70%) with moderate yield (60%) for respective monoarylated product (Table 5.4, entry 4). Similarly, aryl chlorides having electron withdrawing groups, such as 4-chloroacetophenone (**2e**) and 4-chloromethylbenzoate (**2f**) also exhibited considerably high activities with 73% and 66% yield respectively to afford (**3e**) and (**3f**) with respectively (Table 5.4, entries 5, 6). When (hetero)aryl chlorides, 2-chlorothiophene (**2g**) and 5-methyl 2-chlorothiophene (**2h**) used for *ortho* C-H bond arylation of 2-phenylpyridine, it also resulted in complete conversion (>99%) to form respective C-H arylated products (**3g**) and (**3h**) in 87% and 83% yield, (Table 5.4, entries 7, 8). However, the reaction performed with 2-bromopyridine (**2i**) resulted in poor conversion probably due to strong coordination of pyridine nitrogen with ruthenium metal center during the oxidative addition step (Table 5.4, entry 9).

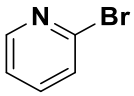
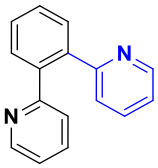
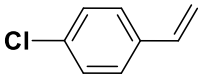
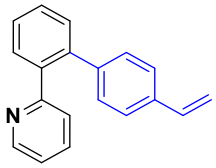
Table 5.4. Catalytic *ortho* C-H bond arylation of 2-phenylpyridine accelerated by 2-hydroxypyridine based ligands using various (hetero)aryl halides over **[Ru]-A** catalyst in water-ethanol[a]



1a 2a-2k 3a-3k 4a-4k

Entry	Substrate	Conv. [%]	Sel. [%]	Product [Yield%][b]
1.	 **2a**	90%	93/7 (**3a**:**4a**)	 **3a (75%)**

2.	 **2b**	>99%	95/5 (**3b**:**4b**)	 **3b (89%)**
3.	 **2c**	>99%	90/10 (**3c**:**4c**)	 **3c (85%)**
4.	 **2d**	70%	90/10 (**3d**:**4d**)	 **3d (60%)**
5.	 **2e**	87%	89/11 (**3e**:**4e**)	 **3e (73%)**
6.	 **2f**	94%	74/26 (**3f**:**4f**)	 **3f (66%)**
7.	 **2g**	>99%	92/8 (**3g**:**4g**)	 **3g (87%)**
8.	 **2h**	>99%	89/11 (**3h**:**4h**)	 **3h (83%)**

9.	 **2i**	-	79/21 (**3i**:**4i**)	 **3i (n.d.)**
10.	 **2k**	93%	>99 (**3k**:**4k**)	 **3k (88%)**

[a]**Reaction Condition:** [(η^6-*p*-cymene)$RuCl_2$]$_2$ **[Ru]-A** (1 mol%), ligand (**L28)** (2 mol%), K_2CO_3 (3 equiv.), 2-phenylpyridine (**1a**) (0.6 mmol), aryl halide (**2a-2k**) (0.5 mmol), water-ethanol (9:1 v/v, 2 mL), 80 ºC, 4 h, N_2 atmosphere, [b] isolated yield, conversion and selectivity were determined by ^{1}H NMR with TMS as internal standard, TON = Turn over number, TOF (h^{-1}) = Turn over frequency, n.d. = not determined.

5.3. Concusions

We systematically explored the role of a series of 2-hydroxypyridine based *N*,*O* donor ligands in the acceleration of reaction rate for Ru(II) catalyzed *ortho* C-H bond activation/arylation of 2-phenylpyridine. The catalytic system has been investigated with wide range of aryl halides ranging from aryl halides having electron donating to electron withdrawing substitution. Our studies demonstrated that 5-trifluoromethyl-2-hydroxypyridine **(L28),** with strong electron withdrawing substitution, outperformed among the studied ligands. Time dependent ^{1}H NMR studies inferred the higher rate constant with **L25** ($k = 2.94\times10^3$ sec^{-1}) and **L28** ($k = 12.1\times10^3$ sec^{-1}) as compared to that in the absence of any ligand ($k = 4.59\times10^{-4}$ sec^{-1}). It suggests crucial role of 2-hydroxypyridine ligand in the enhancement of the rate of reaction. Further, the extensive mass spectrometric and ^{19}F NMR studies identified the ligand coordinated cycloruthenated species [(η^6-*p*-cymene)RuCl(**L25/L28**)] **[Ru]-H$_{1/2}$** and [(η^6-*p*-cymene)Ru(**L25/L28**)(κ^2-*C*,*N*-2-phenylpyridine)]$^+$ **[Ru]-I$_{1/2}$** as a key intermediate during the reaction along with the well-established intermediate [(η^6-*p*-cymene)RuCl(κ^2-*C*,*N*-2-phenylpyridine)] **[Ru]-C**. We believe the findings of the present work will significantly

contribute towards the investigation and development of highly active ligand accelerated metal catalyzed catalytic systems for C-H bond activation and functionalization reactions.

5.4. Experimental section

5.4.1. Materials and instrumentation

All the catalytic reactions for C-H bond arylation of 2-phenylpyridine with aryl halides were performed under N_2 atmosphere using chemicals of high purity purchased from Sigma Aldrich and Alfa Aesar. Ruthenium-arene precursor $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ **[Ru]-A**, was synthesized according to the literature procedures.[22, 23] ^{1}H NMR (400 MHz), and ^{13}C NMR (100 MHz), ^{19}F NMR (376.5 MHz) spectra were recorded at 298 K using $CDCl_3$ as the solvent on a Bruker Advance 400 spectrometer. The chemical shifts in ppm are reported relative to the center of the singlet at 7.26 ppm for $CDCl_3$ in ^{1}H NMR and to the center of the triplet at 77.0 ppm for $CDCl_3$ in ^{13}C NMR. Coupling constants, *J* values are reported in Hertz (Hz), and the splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet.

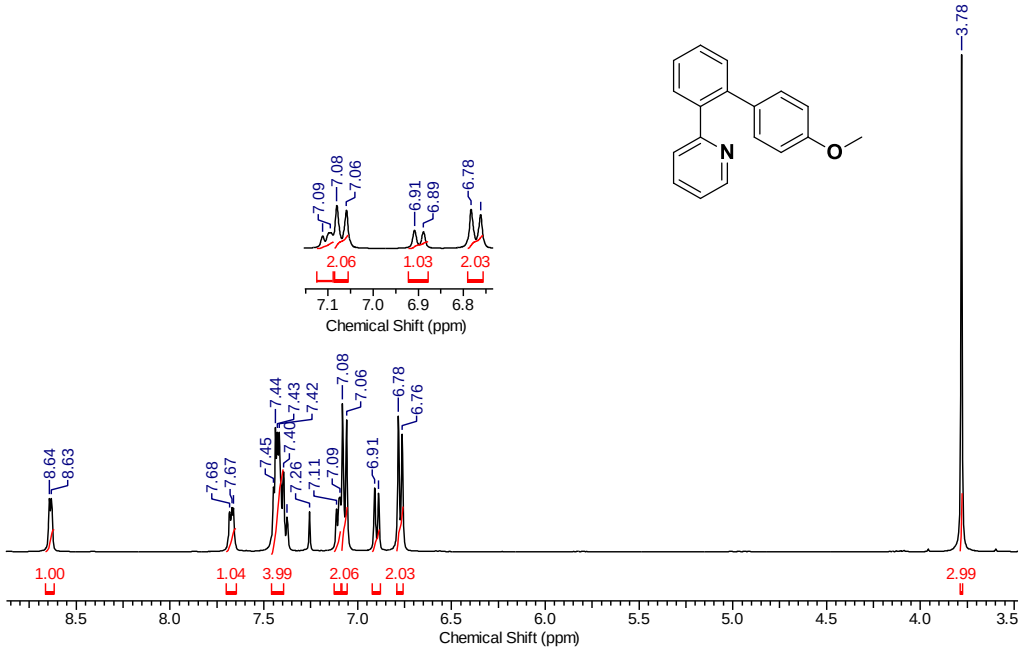
5.4.2. General procedure for catalytic ortho C−H bond arylation of 2-phenylpyridine with aryl halides

ortho C-H bond arylation reactions of 2-phenylpyridine were performed in a two necked round bottom flask under N_2 atmosphere. Flask was charged with ruthenium catalyst, $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ (**[Ru]-A**) (1 mol %, 0.005 mmol, 0.00306 g), ligand (2 equiv., 2 mol%) and K_2CO_3 (3 equiv., 1.5 mmol, 0.207 g) with water-ethanol (2 mL) in 9:1 v/v ratio. Solution was stirred for 15 minutes and then added 2-phenylpyridine (0.6 mmol, 86 µL) and aryl halide (0.5 mmol). The reaction was continued to stir at 80 ºC for 4 h and then cooled down to room temperature. Further, the reaction mixture was extracted with ethyl acetate (3×10 mL) and dried over anhydrous Na_2SO_4. All the volatiles were removed under vacuum to obtain the crude product. Conversion and selectivity of the mono and biarylated products were determined by ^{1}H NMR. Products were purified and isolated from the crude reaction mixture by using column chromatography on silica gel with ethyl acetate/*n*-hexane as eluents.

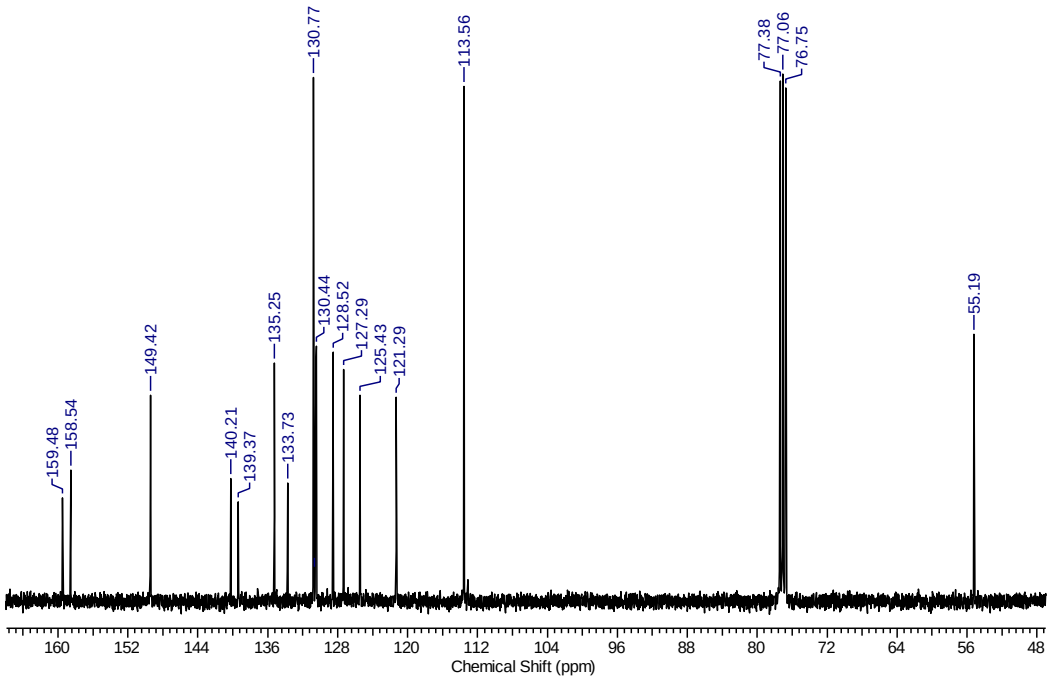
5.4.3. Typical procedure for mass spectrometric analysis for the identification of reactive intermediate species

Mass studies were also carried out in a two necked reaction flask containing [(η^6-*p*-cymene)$RuCl_2]_2$ (1 mol%, 0.005 mmol, 0.00306 g) in 2 mL water-ethanol [(9:1) v/v] with or without base. Then ligand (**L25** or **L28**, 2 mol%) and 2-phenylpyridine (0.025 mmol, 3.6 µL) was added for maintaining the catalyst: ligand: substrate ratio constant i.e. C:L:S = 1:2:5. Reaction mixture was heated at 80 ºC under nitrogen atmosphere for 1.5 h. 100 µL of aliquot from the reaction mixture was taken out at different intervals of reaction time (0, 30, 60, and 90 minutes), which was diluted with methanol. ESI-MS was recorded in positive mode. Mass spectra were analyzed, and active intermediates generated during the reaction have been identified.

5.4.4. NMR spectra of C-H activated monoarylated product 3a



^{1}H NMR spectra of compound **3a**



^{13}C NMR spectra of compound **3a**

Note: Spectral copies and NMR data for substrate has been given in the previous chapters (Chapter 2 and 3).

5.5. References

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Chapter 6

Conclusions and future scope

6.1 Conclusions

In summary, during my thesis work, I aimed to design and develop ruthenium based efficient catalytic systems to explore their activity for C-H bond activation/functionalization of aryl pyridines in water. Mechanistic investigations performed for C-H bond activation/arylation reaction with monodentate and bidentate nitrogen and *N,O/N,N* donor ligands provide the better understanding of the reaction pathway to further improve the designing of catalyst for better performance and efficiency.

In ***chapter 1***, background and importance of *ortho* C-H bond activation/arylation of heteroarenes in diverse fields like pharmaceuticals, material modifications and agricultural products were discussed and brief history of advancement in the field of C-H bond activation by developing efficient catalytic systems and smart strategies to overcome the difficulties in achieving the goal were also discussed.

In ***chapter 2***, a new class of water-soluble arene-ruthenium complexes with readily available aniline-based ligands for the *ortho* C-H bond activation/arylation of 2-phenylpyridine with a wide range of (hetero)aryl halides under mild reaction conditions were explored. Various studies including time scaled NMR and mass studies with structural analogues of aniline ligand to understand the structure activity relationship. Results revealed that aniline ligands, of varying electronic and steric behavior, exerts significant influence on the observed catalytic activity. Moreover, mass spectral identification of the cycloruthenated species, $[(\eta^6\text{-arene})Ru(\kappa^2\text{-}C,N\text{-phenylpyridine})]^+$, and several ligand coordinated cycloruthenated species, such as $[(\eta^6\text{-arene})Ru(4\text{-methylaniline})(\kappa^2\text{-}C,N\text{-phenylpyridine})]^+$, during the reaction of 2-phenylpyridine and arene-ruthenium-aniline complexes, further authenticating the crucial role of these species in the observed highly active and tuned catalytic activity. Further, structural identification of the representative active catalysts was also carried out by single crystal X-ray diffraction studies.

Chapter 3 further extends the scope of exploration and application of arene-ruthenium complexes for C-H bond activation reactions. This chapter includes the extensive study of arene-ruthenium complexes containing bidentate pyridine/iminopyridine based ligands. Synthesized complexes were successfully characterized by ^{1}H, ^{13}C NMR, mass and single crystal XRD and were furthur explored for the *ortho* C-H bond activation/arylation of heteroarene in water-based condition. A remarkable structure-activity relationship was observed with a series of *N,O*/*N,N* donor ligand based arene-ruthenium complexes. Results inferred that the complexes with bis-chelating *N,O* donor-based ligands (2-acteylpyridine and picolinate) outperform than those with *N,N* donor ligands (iminopyridine). Moreover, a unique behavior of *N,O* donor ligands was also observed towards *ortho* C-H bond activation/arylation of heteroarene, depending upon the coordinating nature of oxygen atom. In this context, ruthenium-arene complexes having *N,O* donor ligands (acetylpyridine) with neutral oxygen-donor atoms exhibit enhanced catalytic activity over those with anionic oxygen-donor atoms (picolinate). The observed trend in the ligand tuned catalytic activity of complexes can be attributed to the coordination-decoordination interconversion pathway. Further, mechanistic insights were provided by mass spectral identification of intermediate species.

Chapter 4 outlines the development of an efficient catalytic system for Ru(II) catalyzed *ortho* C-H bond activation/arylation of heteroarene. Here we explored, several biomass derived ligands such as levulinic acid (LA), 2-acetylfuran, 2-furanaldehyde (furfural), 5-(hydroxymethyl)furan-2-carbaldehyde (5-HMF), 5-methylfuran-2-carbaldehyde (5-MF), furfuryl alcohol and 2-furoic acid as effective additives with arene-Ru(II) dimer for *ortho* C-H bond arylation in a water-based condition. High compatibility of the studied Ru(II)-levulinate catalytic system was observed for C-H bond arylation of 2-phenylpyridine (**1a**) with a wide range of electron rich and electron deficient aryl halides and heteroaryl halides. Kinetic studies and mass spectral identification of ligand coordinated Ru(II) species (**[Ru]-F**) and the crucial cyclometalated species (**[Ru]-C**) under the catalytic and controlled reaction condition evidenced the possible crucial role of the ligand **L11** in the observed accelerated catalytic activity. In concurrence with the experimental

findings, DFT calculations also revealed that the C-H bond activation of 2-phenylpyridine (**1a**) is energetically more favorable (by 8.9 kcal/mol) in the presence of ligand **L11** as compared to the ligand-free reaction. Our experimental findings and DFT calculations evidenced the involvement of acetyl group of the ligand **L11** in the deprotonation step and suggesting that the anionic carboxylate group facilitated the strong anchoring of ligand to the metal center. Therefore, we believe that the present study utilizing biomass-derived ligands to achieve remarkably 7-fold enhanced catalytic activity for C-H bond activation/arylation over arene-Ru(II) catalyst is significant.

In ***chapter 5***, we systematically explored various *ortho*-substituted pyridine ligands to achieve accelerated *ortho* C-H bond arylation of 2-phenylpyridine over **[Ru]-A** catalyst. Our studies demonstrated that 5-trifluoromethyl-2-hydroxypyridine **(L28)**, outperformed over other 2-hydroxypyridine based ligands, where significant enhancement in the reaction rate was achieved with **L28** (k = 12.1×10^{3} sec^{-1}) as compared to that in the absence of any ligand (k = 4.59×10^{-4} sec^{-1}). The arene-Ru/**L28** catalytic system efficiently catalyzed *ortho* C-H bond arylation of 2-phenylpyridine using a wide range of electron donating and electron withdrawing aryl halides as coupling partners. Further, mass and NMR studies evidenced the presence of several ligand coordinated ruthenium species [(η^6-*p*-cymene)RuCl(**L25/L28**)] and [(η^6-*p*-cymene)Ru(**L25/L28**)(κ^2-*C*,*N*-2-phenylpyridine)]$^+$, which are considered as key intermediates for the C-H activation reaction. We believe these findings provide a way for further investigation and development of efficient ligand accelerated metal catalyzed systems for C-H bond activation and functionalization reactions.

Milestones of Ph.D.

Catalytic System	Rate constant (k)
Arene-ruthenium aniline complexes	3.22×10^{-4} sec^{-1}
Arene-ruthenium-2-acetylpyridine complexes	6.12×10^{-4} sec^{-1}
Ru(II) dimer + Levulinic acid ligand	1.02×10^{2} sec^{-1}
Ru(II) dimer + 2-hydroxypyridine based ligand	12.1×10^{3} sec^{-1}

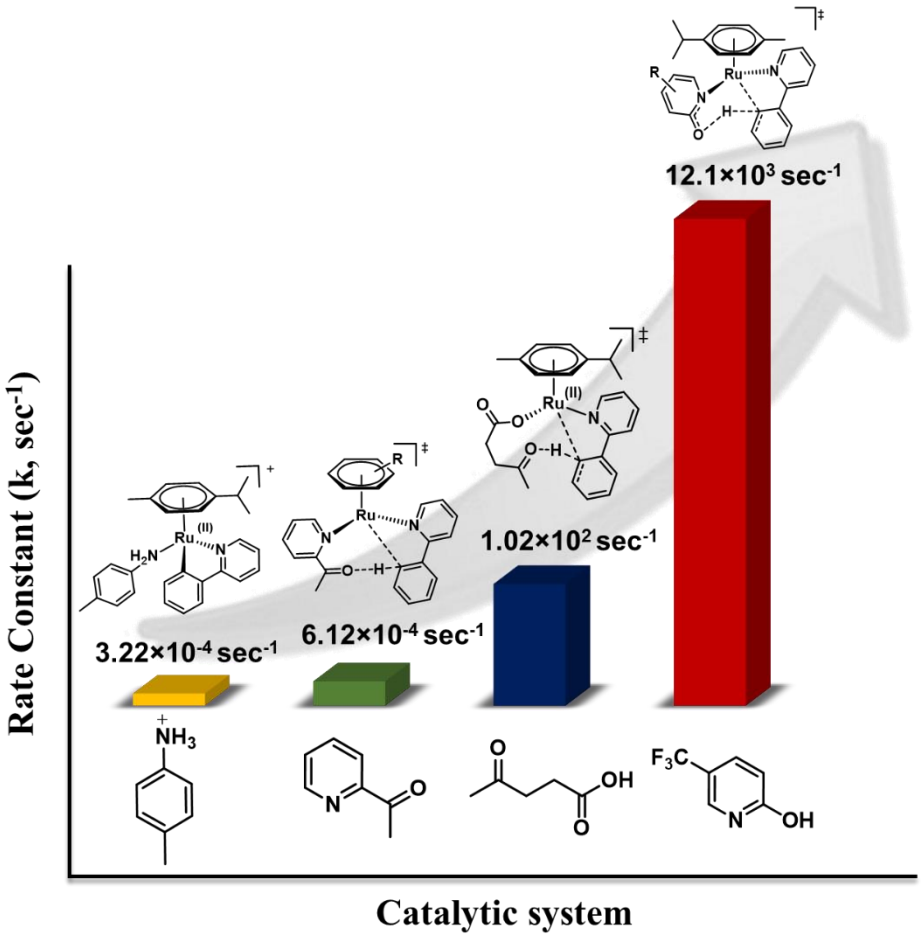

Figure 6.1. *Comparative study of rate constants (k) for various catalytic systems included in this thesis with Ru(II) metal.*

6.2. Future scope

C-H bond activation/functionalization is a very attractive field which has gathered the attention of various scientists from several fields. Development and designing of new, efficient catalysts for C-H bond functionalization for a wide range of substrate is highly desirable. In the recent past, extensive attention has been paid towards the use of homogeneous catalysts to achieve C-H bond functionalization with a variety of substrates, but efficient, easy to handle and recyclable heterogenous catalysts are still underexplored. Systematic studies in the area of heterogeneous catalysts for C-H functionalization reactions can revolutionize the field in various aspects. The heterogenization of the homogeneous catalysts will provide heterogeneous catalyst with high surface area for better efficiency. This will also

prevent the loss of metal catalyst due to decomposition of metal complex during the reaction and hence will increase the chances of recovery of active catalysts.

Despite rapid advancement in the field, development of robust catalytic system for enantioselective C-H bond activation is still the top-most requirement of the organic synthetic chemists. The generation of a tool-box of chiral catalysts for C-H bond activation/functionalization reactions will enable practitioners to control the site selectivity, not based on the properties of the substrate but rather determined by the catalyst choice. Trapping the active catalytic species is crucial to understand the pathway of catalytic reactions by performing control experiments. Several experimental techniques such as mass, NMR, UV-vis and IR spectroscopy, kinetic studies and single crystal XRD-studies may help in identification and isolation of crucial organic or organometallic intermediate species, which will boost up the mechanistic understanding of benchmark catalytic transformations.

APPENDIX – I

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Title:	C–H Bond Activation/Arylation Catalyzed by Arene–Ruthenium–Aniline Complexes in Water
Author:	Chinky Binnani, Deepika Tyagi, Rohit K. Rai, et al
Publication:	Chemistry - An Asian Journal
Publisher:	John Wiley and Sons
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