Visible light photocatalysis – A greener approach towards Mizoroki-Heck reaction & variables in Mizoroki-Heck reaction of mono & disubstituted olefins

Thesis Submitted to AcSIR

For the Award of the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMICAL SCIENCES

By

Pronnoy Govind Bangar
(Registration Number: 10CC11J26026)

Under the guidance of
Dr. Suresh Iyer

Division of Organic Chemistry,
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December 2018

Dedicated to

My Parents and beloved

Sisters

सीएसआयआर-राष्ट्रीय रासायनिक प्रयोगशाला
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CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Visible light photocatalysis – A greener approach towards Mizoroki-Heck reaction & variables in Mizoroki-Heck reaction of mono & disubstituted olefins"** submitted by **Mr. Pronnoy Govind Bangar** to Academy of Scientific and Innovative Research (**AcSIR**) in fulfillment of the requirements for the award of the Degree of Doctor of Philosophy, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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DECLARATION BY THE CANDIDATE

I hereby declare that the original research work embodied in this thesis entitled, **"Visible light photocatalysis – A greener approach towards Mizoroki-Heck reaction & variables in Mizoroki-Heck reaction of mono & disubstituted olefins"** submitted to Academy of Scientific and Innovative Research for the award of degree of Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of **Dr. Suresh Iyer**, Retired Principal Scientist, Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

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Acknowledgement

Ph.D. is like a long journey; an experience that takes you through the untraversed path, the green lush meadows and the island of Cyclopes to conquer the final goal fixed in mind. Once you achieve the target and turn back, you realize that all your efforts and the pain was worth going through. The small successes & the serendipitous discoveries, the frustrating failures & unexpected crystallizations, the imparted chemical wisdom & the laboratory camaraderie; they are all important parts of this beautiful voyage. But you can't succeed in this journey without the guidance and support of many.

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My family has always been a source of inspiration and a great moral support for me in pursuing my education. I take this opportunity to express my gratitude towards my father "Govind Bangar", mother "Mandakini Bangar" and beloved sisters for their love, support, encouragement and sacrifice.

I wish to thank the great scientific community whose achievements are a constant source of inspiration for me. Above all, I extend my gratitude to the Almighty God for blessing me with this wonderful life with its unique challenges and victories. Finally, it was the journey that has been more enjoyable than the destination itself.

Though many have not been mentioned, none is forgotten.

Pronnoy Govind Bangar

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Abbreviations

Units

°C	Degree centigrade
g	gram
mg	Milligram
h / hr	Hour
Hz	Hertz
mL	Millilitre
min	Minutes
MHz	Megahertz
mmol	Millimole
nm	nanometre
ppm	Parts per million
W	Watt

Chemical Notations

Ac	Acetyl
AcOH	Acetic Acid
Ar	Aryl
MeCN	Acetonitrile
BINAP	(2,2'-bis(Diphenylphosphino)-1,1'-binaphthyl)
$CDCl_3$	Deuterated Chloroform
DAB	Diazabutadiene
dba	Dibenzylideneacetone
DCM	Dichloromethane
DMF	*N, N'*-Dimethylformamide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EtOH	Ethanol
Et	Ethyl
EtOAc	Ethyl Acetate
MeOH	Methanol

Me	Methyl
NMP	N-methyl-2-pyrrolidone
PEG	Polyethylene glycol
Ph	Phenyl
THF	Tetrahydrofuran
TBAA	Tetra-*n*-Butylammonium Acetate
TBAB	Tetra-*n*-Butylammonium Bromide
TBACl	Tetra-*n*-Butylammonium Chloride
TMS	Tetramethylsilane

Other Notations

aq	Aqueous
calcd	Calculated
cat.	catalyst
δ	Chemical shift
J	Coupling constant in NMR
equiv.	Equivalents
ESI	Electrospray ionization Mass spectrometry
HRMS	High Resolution Mass Spectrometry
IR	Infra Red
L	Ligand
LED	Light emitting diode
m/*z*	Mass-to-charge ratio
M.S	Molecular sieves
mp	Melting Point
NMR	Nuclear Magnetic Resonance
R_f	Retardation factor
rt	Room temperature
TLC	Thin Layer Chromatography

General remarks

- Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR analysis were obtained using a Bruker or JEOL 200 MHz, 400 MHz, 500 or 700 MHz spectrometers. Coupling constants were measured in Hertz. All chemical shifts are quoted in ppm, relative to TMS, and referenced to internal TMS (δ 0.00 for ^{1}H NMR) or $CDCl_3$ (δ 77.0 for ^{13}C NMR). The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br =broad.
- HRMS spectra were recorded at UHPLC-MS (Q-exactive-Orbitrap Mass Spectrometer) using electron spray ionization [(ESI^{+}, +/– 5kV), solvent medium: water, acetonitrile, methanol and ammonium acetate] technique and mass values are expressed as *m*/*z*.
- Infrared spectra were recorded on Bruker ALPHA spectrometers with sodium chloride optics and are expressed in cm^{-1}.
- Melting points were recorded on Buchi M-535, M-560 melting point apparatus and are uncorrected and the temperatures are in centigrade scale.
- All reactions are monitored by Thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, Iodine adsorbed on silica gel or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *p*-anisaldehyde or $KMnO_4$ followed by heating with a heat gun for ~15 sec.
- All solvents and reagents were purified and dried according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- Chemical nomenclature (IUPAC) and structures were generated using ChemDraw Professional 15.1.
- Reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa.
- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.
- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification.

Synopsis

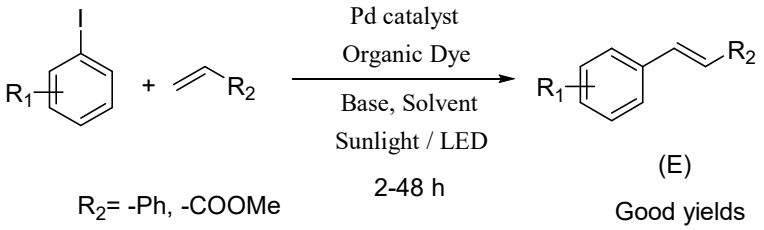
Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry	
Name of the Candidate	Pronnoy Govind Bangar
Degree Enrolment No. & Date	Ph. D in Chemical Sciences (10CC11J26026); January 2011
Title of the Thesis	Visible light photocatalysis – A greener approach towards Mizoroki-Heck reaction & variables in Mizoroki-Heck reaction of mono & disubstituted olefins.
Research Supervisor	Dr. Suresh Iyer

The proposed thesis is divided into three chapters. The first chapter deals with visible light mediated Mizoroki-Heck reaction of monosubstituted olefins using organic dyes or ruthenium complexes with diverse ligand structure as photoredox catalysts merged with palladium. The second chapter exhaustively deals with Mizoroki-Heck reaction on hitherto less explored 1,2-disubstituted olefins by studying variables of synthesis. The focal theme of last chapter is use of inexpensive, easily synthesized or commercially available N, O-ligands as phosphine alternatives for catalysis of Mizoroki-Heck reaction of monosubstituted olefins, Suzuki coupling & palladium mediated organic transformation.

Chapter 1: Organic dyes & ruthenium complexes as photoredox catalyst for Mizoroki-Heck reaction under sunlight & artificial LED.

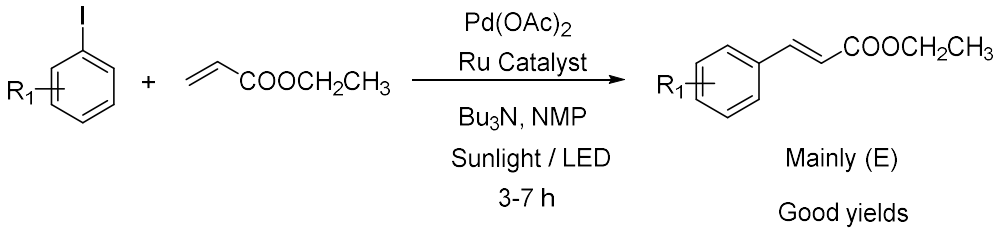
<u>Section A:</u> Organic dyes as photoredox catalyst for Mizoroki-Heck reaction under sunlight & artificial LED.

Visible light mediated photoredox catalysis has gained momentum over past decade for development of synthetic transformation[1]. It can be combined with transition metal catalyst namely palladium complexes to achieve unique C-C bond formation[2]. Our interest in this area is mainly due to ready availability of sunlight as a sustainable, environmentally clean & renewable natural source of energy as well as easy access to several artificial visible light sources making overall process highly economical & green. Traditionally such transformations are carried out using ruthenium or iridium bipyridyl (or its derivatives) photoredox complexes which are highly expensive. We have developed a new protocol using organic dyes as photoredox catalyst for Mizoroki-Heck reaction under sunlight & artificial LED merged with palladium to get exceptionally high yields within very short reaction times & milder conditions. By tuning palladium catalyst, we were also able to react aryl bromides at ambient conditions. Rose Bengal, Eosin Y & Fluorescein dyes were used for study.



<u>Section B:</u> Ruthenium complexes as photoredox catalyst for Mizoroki-Heck reaction under sunlight & artificial LED - Preliminary studies.

In continuation with previous approach, our quest to find alternatives for expensive ruthenium or iridium bipyridyl (or its derivatives) photoredox complexes led us to robust, inexpensive, bench stable & easily synthesized ruthenium complexes having diverse ligand structure. Ruthenium complexes explored were $RuCl_2(PPh_3)_3$, Ru(i-Pr-DAB)Cl_2 & $[Ru(p\text{-cymene})Cl_2]_2$. We were also able to get good yield under LED as opposed to same reaction using organic dye for Mizoroki-Heck reaction.

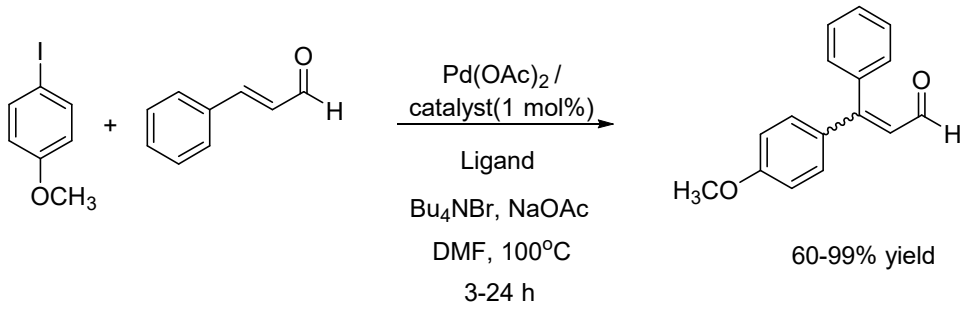


Chapter 2: Mizoroki-Heck reaction of 1,2-disubstituted olefins: variables of synthesis

1,2-disubstituted olefins are difficult substrates for Mizoroki-Heck reaction requiring long reaction times, special bases, reagents or ligands[3]. As such this presents a good opportunity to explore this area as resulting trisubstituted olefins are important bioactive molecules as well as this moiety is present in many OLED's. 1,2-disubstituted olefins are readily available or easily synthesized as well as structural diversity is very vast, thus Mizoroki-Heck reaction on these substrates leads to synthesis of huge library of compounds involving both functionally & structurally diverse trisubstituted olefins.

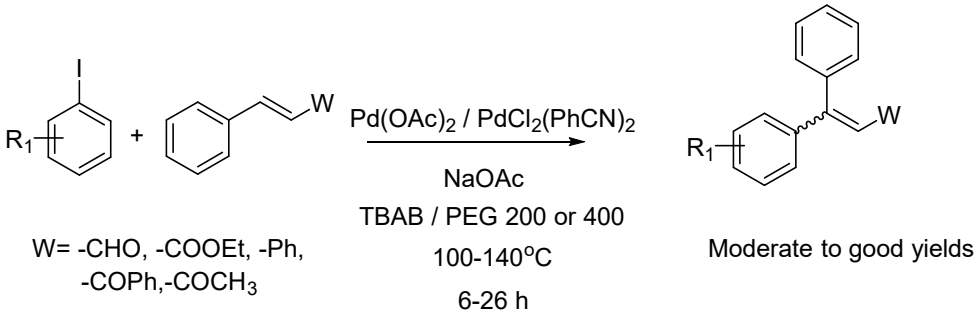
<u>Section A:</u> Ligand & catalyst as variables of synthesis for Mizoroki-Heck reaction.

Seventeen ligands/catalysts were studied for Mizoroki-Heck reaction of 4-Iodoanisole with trans-cinnamaldehyde as model 1,2-disubstituted olefin. Tri-tert-butylphosphonium tetrafluoroborate was the best choice in terms of yield & stereoselectivity.



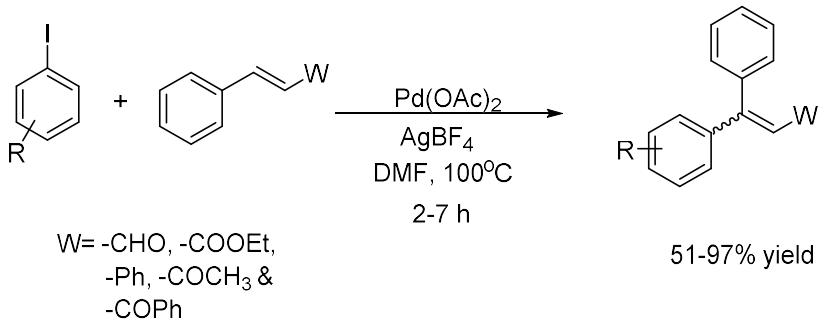
<u>Section B:</u> Exploring ligand less Mizoroki-Heck reaction in Tetrabutylammonium bromide or Polyethylene Glycol as solvent.

Organic synthesis involves use of various organic solvents which suffers from drawback of being pyrophoric, volatility & thereby hazardous for health & environment. Shifting to TBAB (an ionic liquid) or PEG 200/400 (liquid polymer) solves this problem & avoiding ligand makes the whole process cost effective & environmentally clean. We report here good to moderate yields for Mizoroki-Heck reaction in these solvents in absence of ligands. Stereoselectivity was moderate in this case.



<u>Section C:</u> Silver sequestration of halides for activation of $Pd(OAc)_2$ catalyzed Mizoroki-Heck reaction of 1,2-disubstituted olefins.

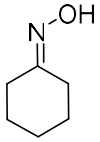
Silver salts have been used as additives in asymmetric Mizoroki-Heck reaction. They are known to suppress alkene isomerization, promote cyclization & accelerate reaction rate through cationic mechanism[4]. In the context of our interest in Mizoroki-Heck reaction of 1,2-disubstituted olefins we have developed a new protocol for mild, practical & ligand less Mizoroki-Heck reaction of aryl iodides with 1,2-disubstituted olefins using stronger sequestrating agent $AgBF_4$ to get trisubstituted olefins in good to excellent yields within very short reaction times & moderate to good stereoselectivity. It also tolerates broad substrate scope[5].



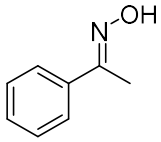
Chapter 3: N, O-ligands for catalysis of Mizoroki-Heck reaction, Suzuki coupling & organic transformations.

Mizoroki-Heck reaction & Suzuki coupling have revolutionized the way C-C bonds are formed. Phosphines ligands are commonly used & thus have dominated these reactions[6]. Phosphines suffer from serious drawbacks of being air oxidized, expensive & involving tedious synthesis. Nitrogen & oxygen ligands are excellent alternative to phosphines as they are readily synthesized, robust, inexpensive & provide vast structural diversity like phosphines. We have developed some simple N, O (Nitrogen & Oxygen) ligands & tested its applicability to Mizoroki-Heck reaction, Suzuki coupling & organic transformation.

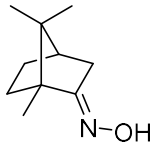
Ligands Screened



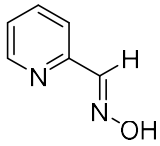
Cyclohexanone oxime



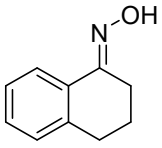
Acetophenone oxime



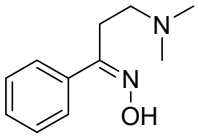
Camphor oxime



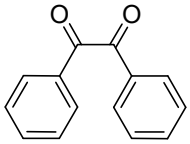
Pyridine-2- carbaldehyde oxime



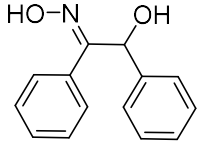
Tetralone oxime



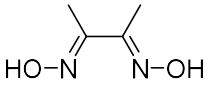
Acetophenone Mannich base



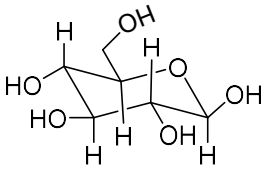
Benzil



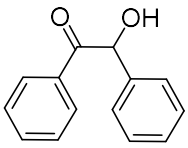
Benzoin alpha oxime



Dimethyl glyoxime



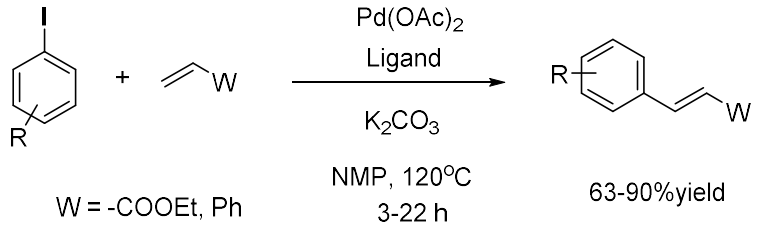
Glucose



Benzoin

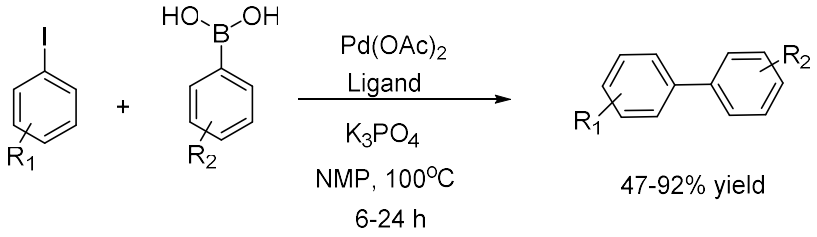
Section A: N, O-ligands for catalysis of Mizoroki-Heck reaction

Good to excellent yields were obtained for Mizoroki-Heck reaction of aryl iodides with monosubstituted olefins when these ligands were used.



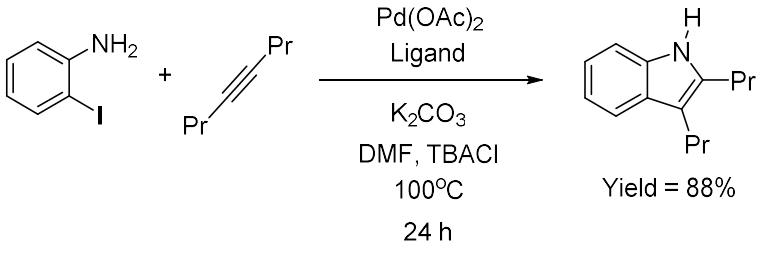
Section B: N, O-ligands for catalysis of Suzuki coupling-Preliminary studies

Preliminary studies revealed moderate to excellent yields for Suzuki reaction of substituted aryl iodides with aryl boronic acids using N, O-ligands.

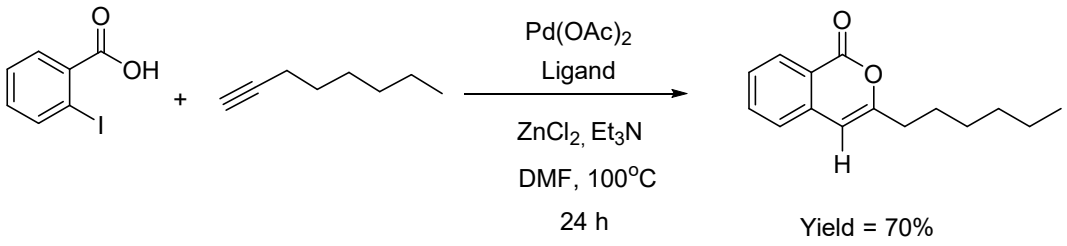


Section C: Application of N, O-ligands in organic transformations

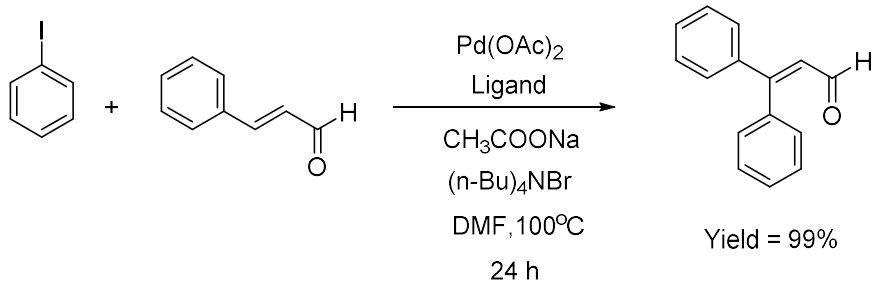
Acetophenone oxime was chosen as model ligand & used in palladium mediated organic transformations like Larock indole annulation, isocoumarin synthesis & Mizoroki-Heck reaction of iodobenzene with trans-cinnamaldehyde. Yields obtained were greater than when triphenylphosphine was used as ligand.



Ligand : Acetophenone oxime (Phosphine Alternative)



Ligand : Acetophenone oxime (Phosphine alternative)



Ligand : Acetophenone oxime (Phosphine Alternative)

References:

1) Ravelli, D,; Protti, S.; Fagnoni, M. *Chemical Reviews* **2016**, 116, 9850.
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Chapter I

Organic dyes & ruthenium complexes as photoredox catalyst for Mizoroki-Heck reaction under sunlight & artificial LED.

1.1 Introduction

Sunlight is unique, innocuous, environmentally friendly natural resource. It is renewable and superabundant source of never ending pure and clean energy. One of the core scientific quests of twenty-first century is development of novel methods for efficiently exploiting energy of solar radiation.[1] Solar energy is green and its use is in accordance with one of the twelve principles of 'Green chemistry' which was put forward by Warner and Anastas mentioning to the use of energy efficient synthetic processes.[2] The sixth principle is quoted as "The energy requirements of chemical processes should be recognized for their economic and environmental impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure".

Sunlight is a sustainable source and connection between environmental sustainability and solar energy is a very old idea indeed. Early twentieth century photo chemists realised that sun is an everlasting source of green, clean and pure chemical potential by simply observing the fact that light alone could execute distinctive chemical transformations in organic compounds.[3]

One of the earliest proclamations of this idea dates back to a lecture delivered in 1912 to the 8th International Congress of Applied Chemistry by Ciamician Giacomo, a pioneering figure in buildout of organic photochemistry. In this lecture, christened as 'The Photochemistry of the Future', Ciamician postulated that an environmentally friendly, new chemical industry could substitute synthetic high-energy process with cost-effective, clean photochemical changes, with noticeable ecological benefits.[4] Ciamician quotes as,

"On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plains and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry and mankind is. And if in a distant future the supply of coal becomes completely exhausted, civilization will not be checked by that, for life and civilization will continue as long as the sun shines!"

This ingenious idea though wonderful, looking good on paper for organic photochemistry is underdeveloped and challenging for several reasons. First, majority of organic molecules tend to absorb ultraviolet region (UV) that are not abundant in the sun's radiation penetrating

atmosphere. These hampers developmental rate in photochemical synthesis on a large industrial scale as specialized photoreactors are to be developed to safely produce high-energy UV radiation. A sizeable capital cost is linked with the fabrication of these huge photoreactors for industrial scale-up. Also, the size of photoreactor decides the scale of photochemical process. In addition, consumption of UV light for these reactions demands an input of energy for its production, increasing environmental footprint and cost of the processes when contrasted with straightforward utilization of incident solar radiation. Moreover, UV radiations are considerably higher in energy, on the order of a C-C bond causing unproductive side-reactions to occur, particularly when somewhat weak bonds exist or when the moiety possesses substantial structural complexity. Thus, global acquisition of clean photochemical methods in academia and industry requires development of photochemical reactions that are triggered by visible light which are copious in solar spectrum.

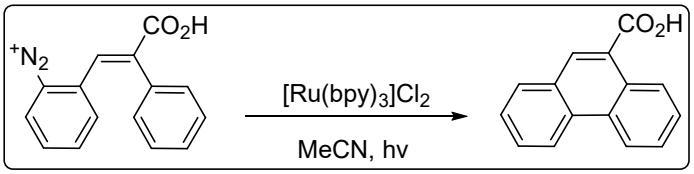
There are many organic dyes and specifically organometallic complexes that absorb heavily in visible spectrum and it is this visible light photochemistry of notably transition metal complexes like $Ru(bpy)_3^{2+}$ and associated ruthenium and iridium polypyridyl complexes that have been utilized in designing systems for converting solar energy into fuel by photoreduction of H_2O and CO_2 or into electrical current.[5]

Contrarily, the use of $Ru(bpy)_3^{2+}$ and related ruthenium and iridium polypyridyl complexes as a photocatalyst in core synthetic organic and organometallic chemistry has lately become an area of active research. This field is called photocatalysis and it solely depends on the mechanism that irradiation at wavelengths of visible light where usual organic molecules do not soak up, causes excitation of particular photoredox catalyst only which may be metal complex or an organic dye. The resultant excited species serves as both a strong reductant and a strong oxidant concurrently, thereby providing entrance to a reaction environment under exceptionally mild conditions that is special for organic chemistry. Thus, organic dyes and metal polypyridyl complexes ease the transformation of visible light into chemical energy. This leads to novel forms of reactivity with photoredox catalysis not observed with traditional reaction manifolds. Given the exceptional photophysical properties of these complexes as well as of organic dyes, transformations can be performed using any source of visible light, counting both ambient sunlight and store purchased fluorescent light bulbs.

A brief literature summary of utilization of photoredox catalysis in C-C bond formation is as presented below.

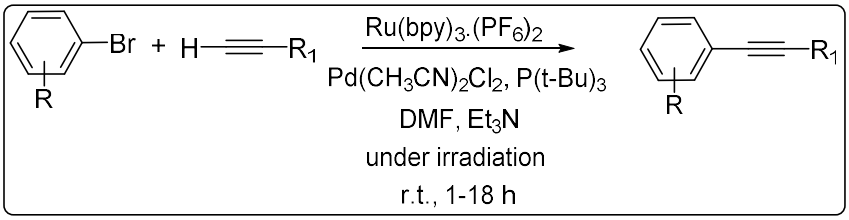
One of the earliest examples of visible light photoredox catalysis was demonstrated by Cano-Yelo and Deronzier. They were able to quantitatively synthesize phenanthrene product by Pschorr reaction employing [$Ru(bpy)_3$] Cl_2 (Scheme 1).[6]

Scheme 1



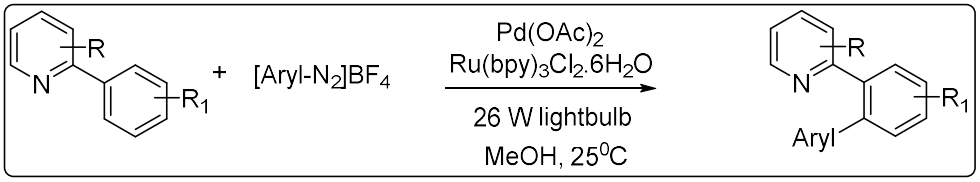
Osawa and co-workers successfully displayed Sonogashira reaction (copper free) at room temperature under visible light irradiation employing aryl bromides. A combined catalyst system of $Pd(CH_3CN)_2Cl_2$ / P(t-Bu)$_3$ / [Ru(2,2'-bipyridine)$_3$].2PF_6 was used (Scheme 2).[7]

Scheme 2



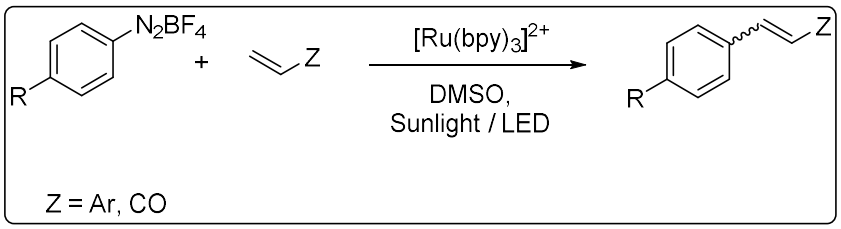
Aryl diazonium salts have attracted attention of synthetic organic chemists since a long time. They are classically applied in aromatic substitutions, acting substitutes to aryl halides and aryl triflates in transition metal catalyzed coupling reactions and are chief source of aryl radicals. Aryl diazonium salts absorb in UV spectrum, their inability to absorb visible light was put to advantage by Sanford and co-workers in room-temperature ligand-directed C-H arylation reaction using aryl diazonium salts by utilizing a dual photoredox Pd catalyst system in presence of household visible light source. Amides, oxime ethers, pyrazoles and pyrimidines pose as some suitable directing groups for this reaction (Scheme 3).[8]

Scheme 3



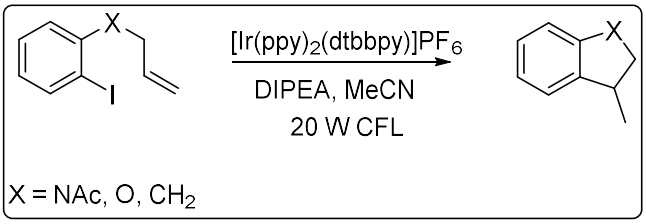
Konig *et. al.* reported efficient visible light mediated arylation of unsaturated compounds using sunlight at ambient temperature employing photoredox catalysis. Unsaturated compounds like alkynes, alkenes and enones were successfully coupled improving classical Meerwein arylation protocol significantly (Scheme 4).[9]

Scheme 4



Lee *et. al.* exploited visible light to their use in iridium catalyzed reductive cyclisation and hydrodehalogenation of organic halides. Alkyl, alkenyl and aryl halides participated in these free radical photocatalytic process (Scheme 5).[10]

Scheme 5



Ir catalyzed reductive cyclisation reaction mechanism is as delineated in figure 1. Through the use of photoredox catalytic cycle a free radical cyclization process is mediated by iridium complex. A SET i.e. single electron transfer from the Ir^{II} species (i.e. $[Ir^{III}(ppy)_2(dtbbpy^{\cdot-})]$) induces reductive splitting of C-I bond crucial to this mechanism. A discrete radical anion as intermediate is formed which then experiences electronic restructuring from π system to the orthogonal σ* (C-X) orbital for bond breaking leading to dissociation of

halide ion. Carbon centered radical then abstracts hydrogen atom from the α- amino position of the aminium radical cation completing finally the reductive process.

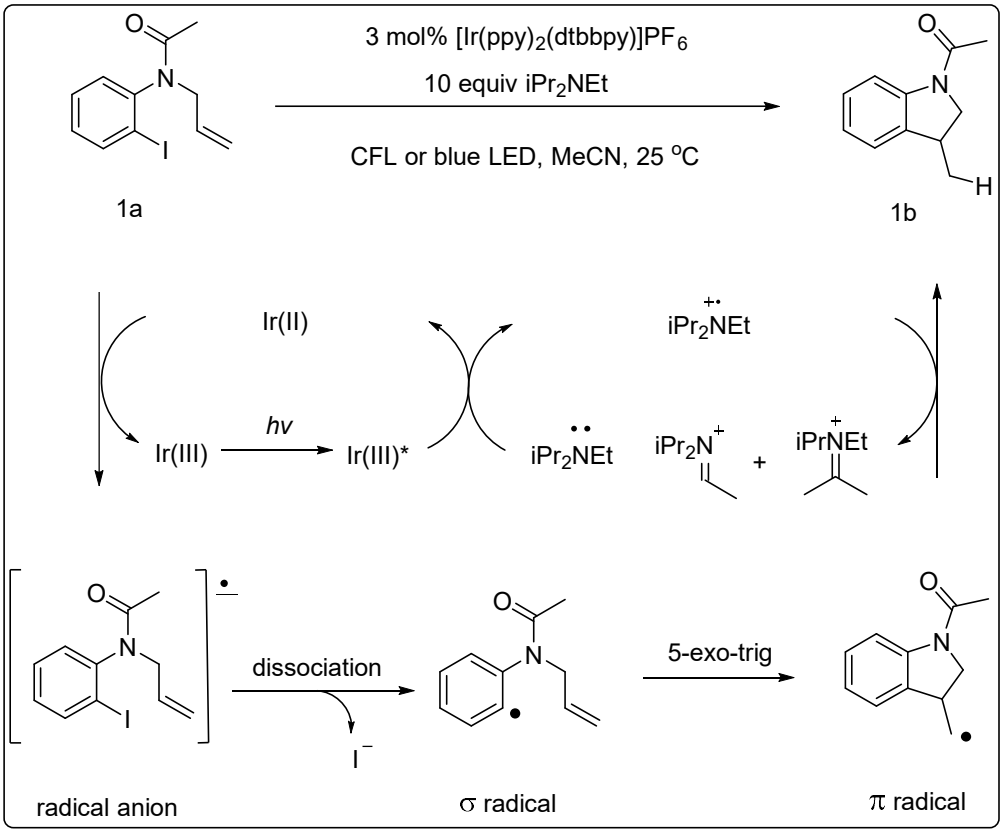
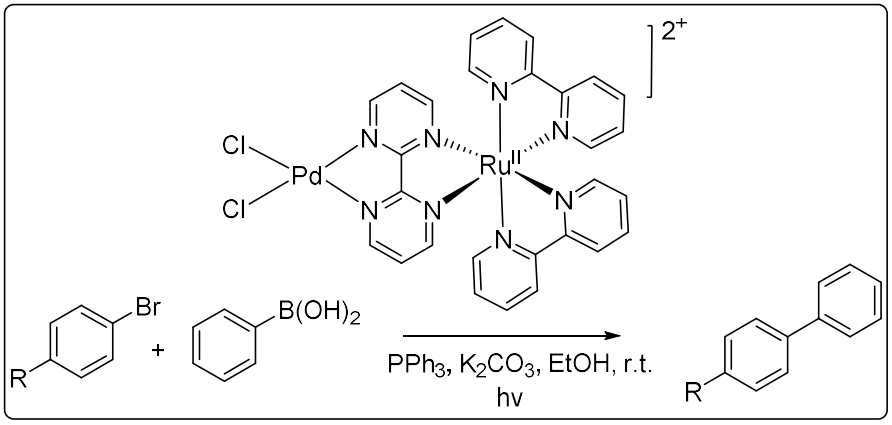


Figure 1. Proposed mechanism for the visible light promoted Ir catalyzed reductive cyclization.

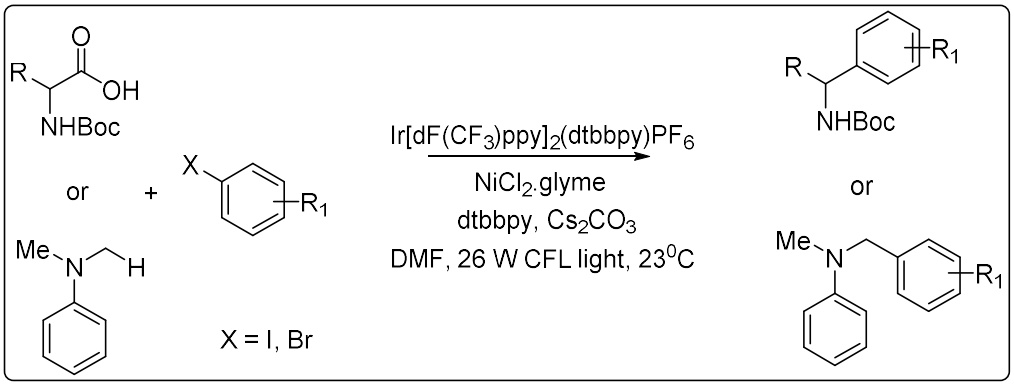
A bimetallic molecule complex of Pd(II) containing Ru(II) polypyridyl derivative by Yamashita and co-workers harvested light energy to demonstrate Suzuki-Miyaura coupling reactions between aryl bromides and phenyl boronic acid. Substantial increase in catalytic activity was observed under visible light irradiation when compared with thermal reaction conditions (Scheme 6).[11]

Scheme 6



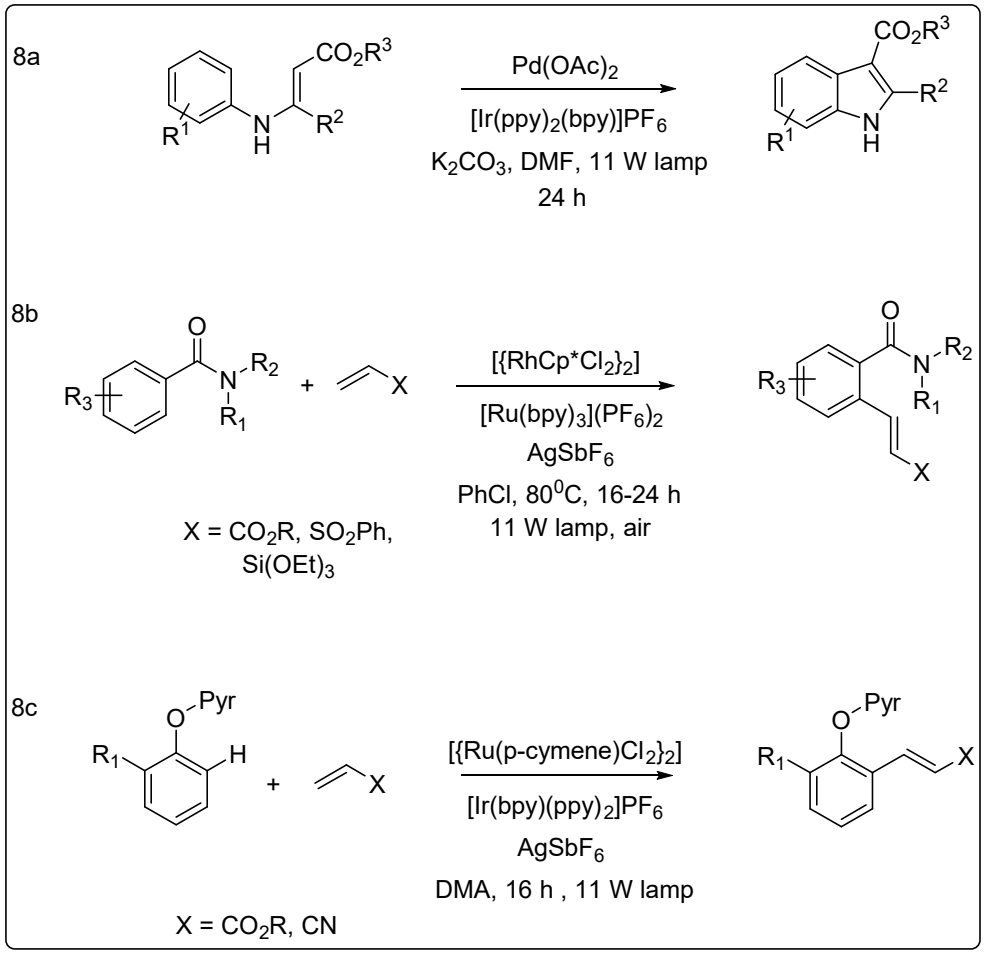
David Macmillan and co-workers exploited synergistic blend of nickel catalysis and photoredox catalysis to offer an alternative cross coupling pattern. They were able to achieve sp^2-sp^3 cross-coupling of aryl halides with amino acids by direct decarboxylative mode. This methodology was then extended to direct coupling of aryl halides with sp^3 C-H in dimethylaniline (Scheme 7).[12]

Scheme 7



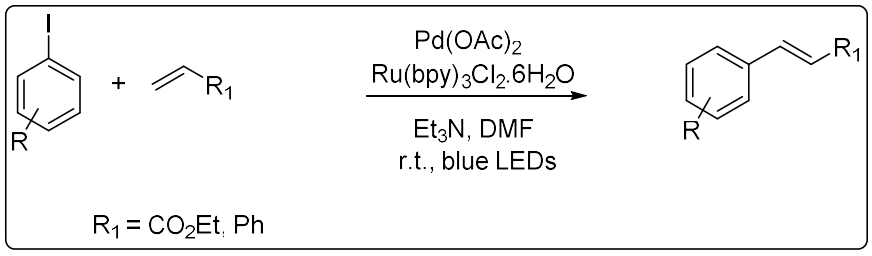
Rueping *et. al.* developed photoredox and palladium catalyzed intramolecular C-H olefinations to deliver indoles from aromatic enamines using visible light under mild reaction conditions (Scheme 8a).[13] Subsequently, Rueping demonstrated that dual catalysis concept can be extended for the *ortho* olefination of aryl amides (Scheme 8b)[14] and *ortho* olefination of o-(2-pyridyl) phenols (Scheme 8c).[15] Thus Rueping extensively used visible light and dual catalysis concept for oxidative Heck reactions.

Scheme 8



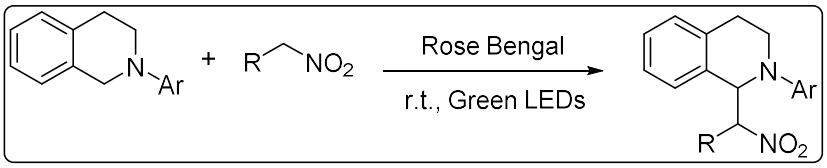
A mild Mizoroki-Heck reaction of aryl iodides with olefins by collaboration of photoredox catalyst and palladium under visible light irradiation was reported by Huang *et. al*. This protocol was used to synthesize stilbenes with high E/Z stereo selection and (E)-cinnamates at ambient temperature in absence of ligands (Scheme 9).[16]

Scheme 9



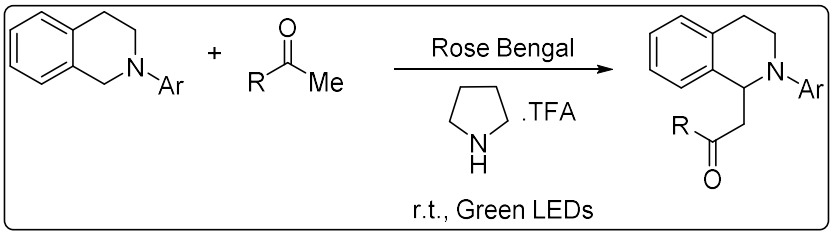
Ruthenium and iridium-based complexes gave access to visible light photocatalysis as they absorb efficiently in the visible region. Organic dyes are coloured and they too in analogy with these complexes absorb in the visible region. Simple aromatic ketones like benzophenone were the first known organic molecule as photoredox catalyst.[17] Dyes such as Rose Bengal or methylene blue are engaged in photochemical reactions chiefly to generate singlet oxygen by photosensitised process.[18] Very recently organic dyes have been applied as visible light photoredox catalysts because these are low-priced and easier to alter compared to metal photoredox catalyst. Choon-Hong Tan and co-workers exploited photoredox ability of Rose Bengal for dehydrogenative coupling reactions of tertiary amines using visible light to obtain α-functionalised tertiary amines. In one example dehydrogenative coupling between N-aryl-tetrahydroisoquinolines and nitroalkanes was reported as shown in scheme 10.

Scheme 10



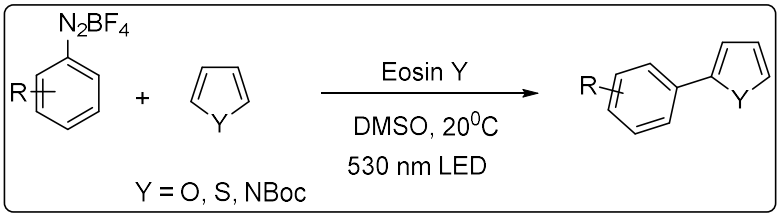
The other example detailed in the same paper was dehydrogenative Mannich reaction between tertiary amine N-aryl-tetrahydroisoquinoline and simple aliphatic ketones. Pyrrolidine with TFA was used to produce enamine nucleophiles from ketones (Scheme 11).[19]

Scheme 11



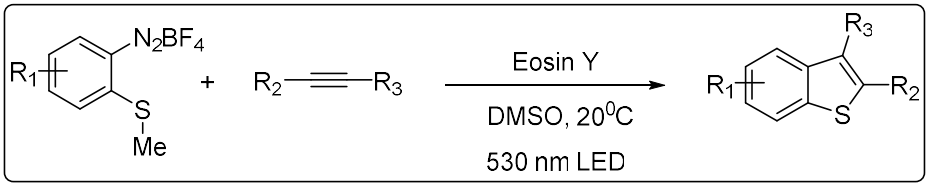
Visible light in conjunction with eosin Y as photoredox catalyst was responsible for catalysing direct arylation of C-H bond of heteroarenes with arene diazonium salts by a photoredox process (Scheme 12).[20]

Scheme 12



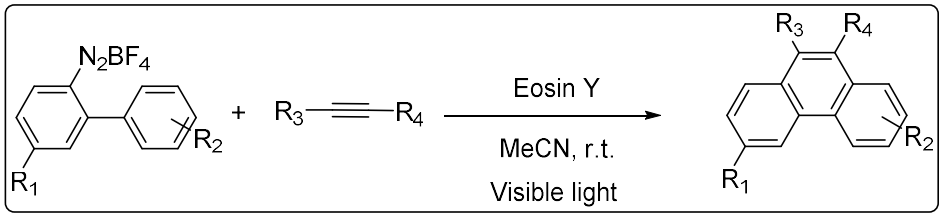
Konig *et. al.* reported photocatalytic reaction of alkynes with o-methylthio-arenediazonium salts under green light irradiation utilizing eosin Y to yield substituted benzothiophenes regioselectively (Scheme 13).[21]

Scheme 13



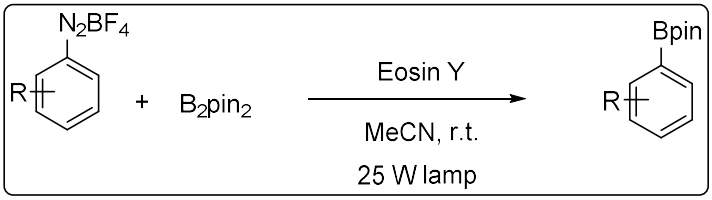
Lei Zhou and co-workers successfully displayed synthesis of diverse 9-substituted or 9,10-disubstituted phenanthrenes by [4+2] benzannulation of alkynes with biaryldiazonium salts employing eosin Y as photoredox catalyst in presence of visible light (Scheme 14).[22]

Scheme 14

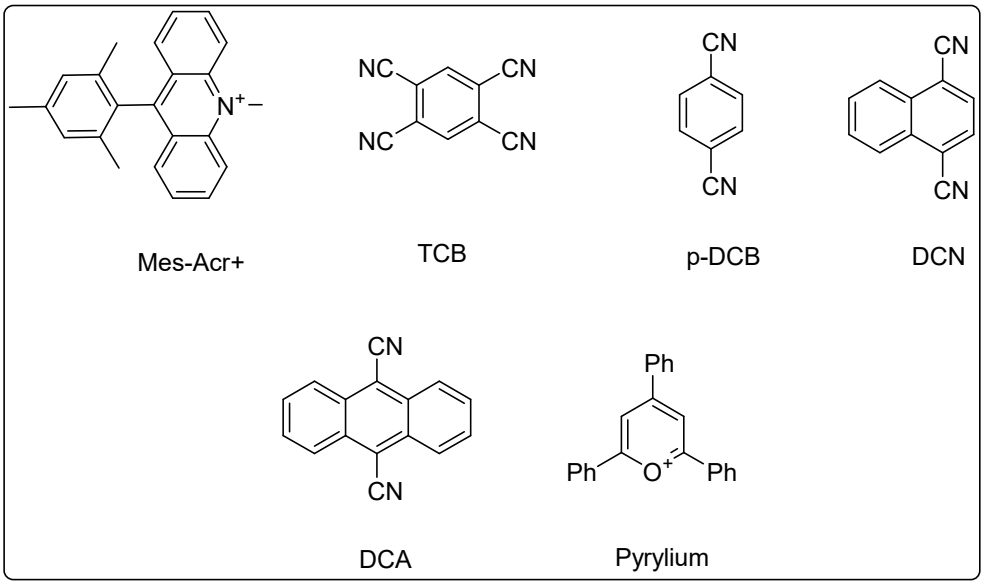


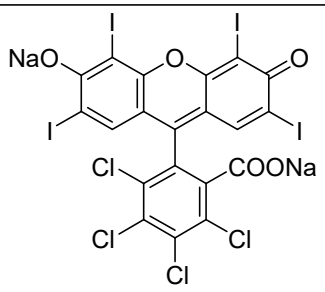
Aryl diazonium salts undergo borylation with bis(pinacolato)diboron under visible light irradiation catalyzed by eosin Y to yield aryl boronates. This was developed by Guobing Yan and co-workers. Thus, an alternative route for aryl boronates can be obtained using organic dye and visible light (Scheme 15).[23]

Scheme 15

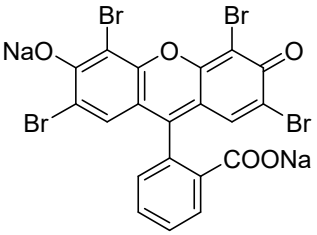


Figures below and on next page represents usual photoredox catalysts utilized for C-C bond formation in synthesis.

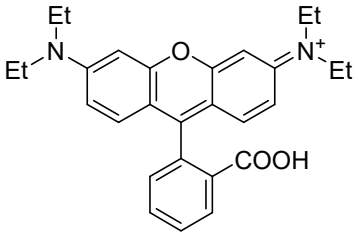




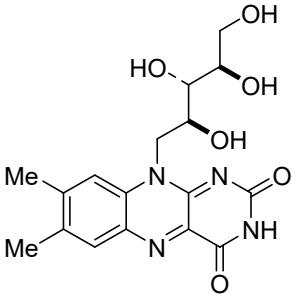
Rose Bengal



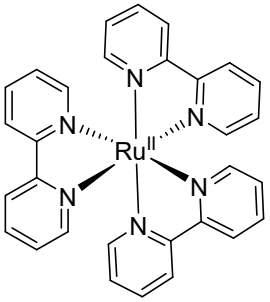
Eosin Y



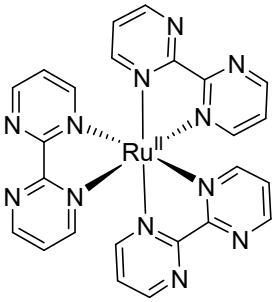
Rhodamine B



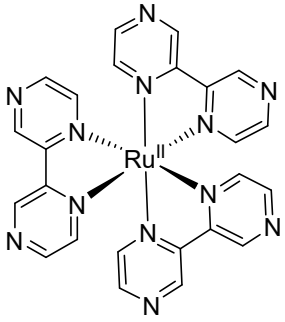
Riboflavin



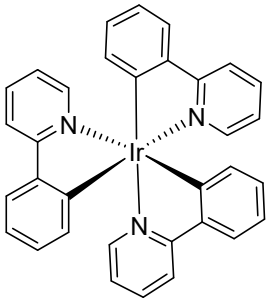
$Ru^{II}(bpy)_3^{2+}$



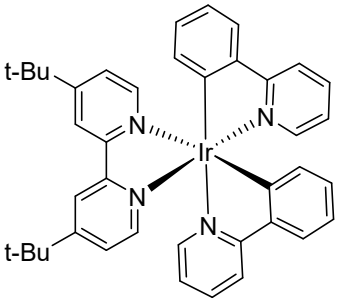
$Ru^{II}(bpm)_3^{2+}$



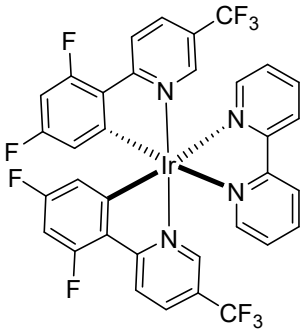
$Ru^{II}(bpz)_3^{2+}$



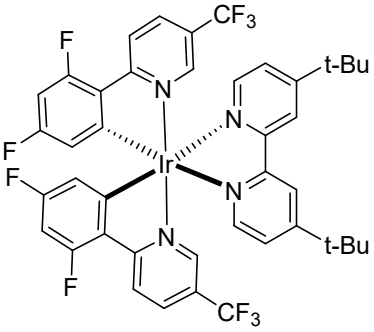
fac-$Ir^{III}(ppy)_3$



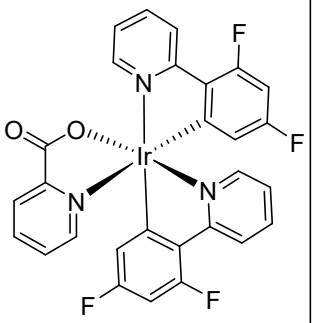
$Ir^{III}(ppy)_2(dtbbpy)^+$



$Ir^{III}(dF(CF_3)ppy)_2(bpy)^+$



$Ir^{III}(dF(CF_3)ppy)_2(dtbbpy)^+$



F Ir^{III}pic

1.2 Objective

Iridium and ruthenium polypyridyl complexes which have revolutionised visible light mediated transformations are very expensive and synthesis involved in their preparation is quite tedious. Our core objective of this chapter is utilization of organic dyes as a substitute for expensive metal polypyridyl complexes for Mizoroki-Heck reaction of monosubstituted alkenes with aryl iodides under sunlight or LED. Substituting organic dyes for metal polypyridyl complexes as a photoredox catalyst under sunlight or LED makes the overall process exceptionally mild, green and cost-effective which is the rationale behind this experimentation.

Another objective that we chose to study (Section B) is the application of traditional ruthenium complexes as a photoredox catalyst for Mizoroki-Heck reaction of aryl iodides with monosubstituted alkenes under sunlight or artificial visible light source (LED). These catalysts are inexpensive, robust, easy to synthesize as well as possess diverse ligand structure which differs from normal pyridyl ligands used to bind ruthenium or iridium. Figure 2 represents structure of organic dyes and ruthenium complexes used in this study.

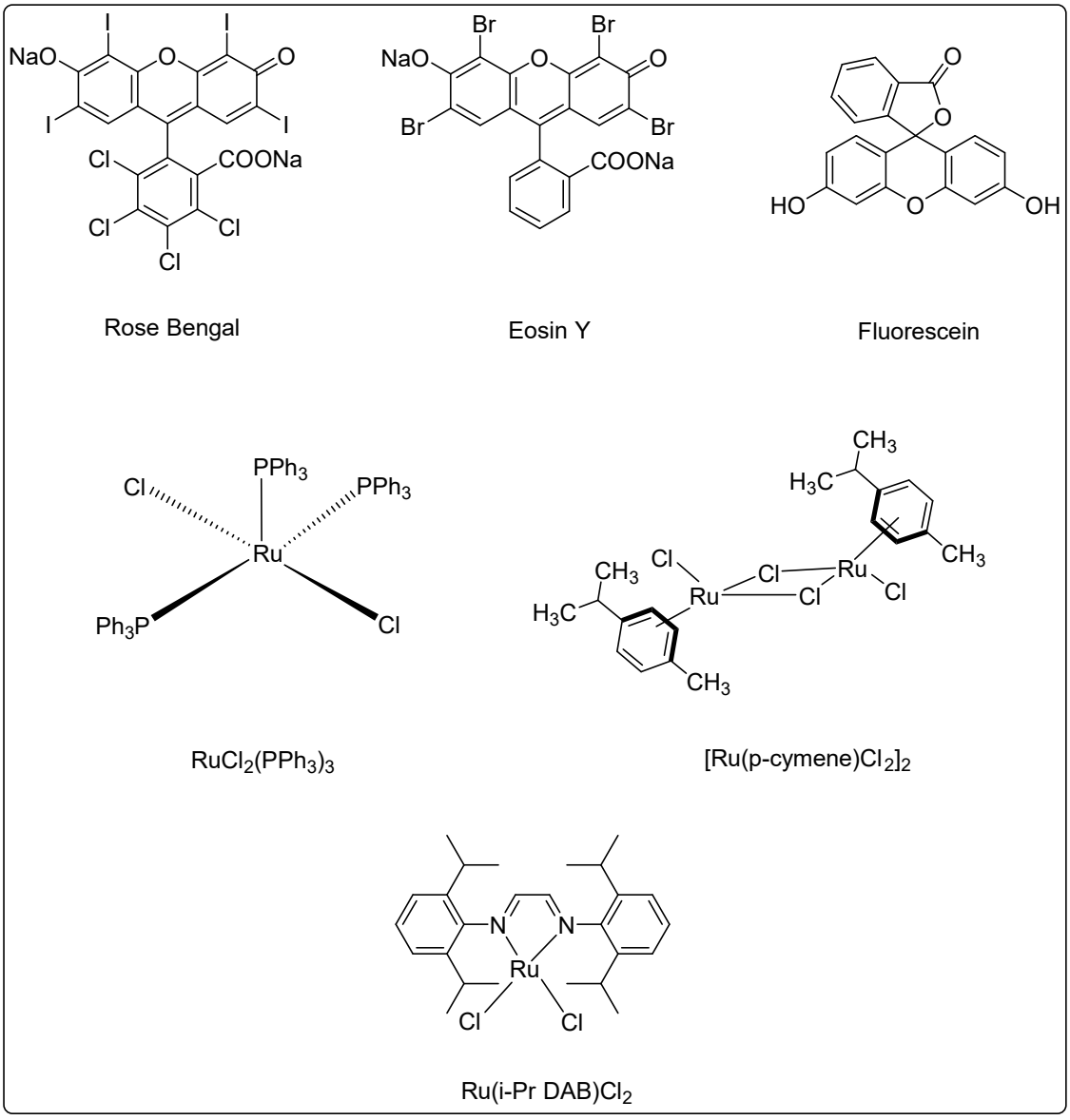


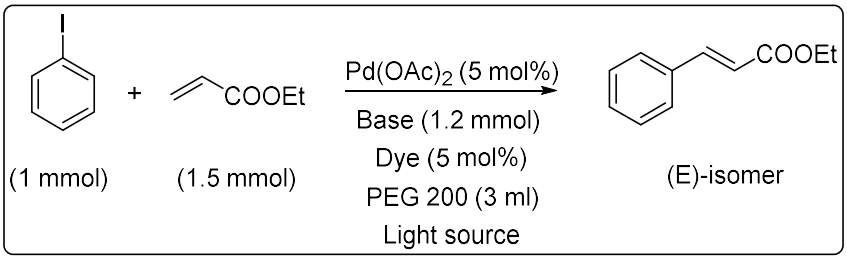
Figure 2. Structure of organic dyes and ruthenium complexes.

Section A: Organic dyes as photoredox catalyst for Mizoroki-Heck reaction under sunlight and artificial LED.

1A.1 Present work

To get an idea of reaction conditions for Mizoroki-Heck reaction i.e. to optimize reaction conditions we created a model system selecting Iodobenzene as ideal aryl iodide and ethyl acrylate as ideal olefin coupling partner. As we have merged visible light photoredox catalysis with transition metal catalysis (metallaphotoredox catalysis, a dual catalytic method) we chose palladium acetate as model transition metal. Base, dye, visible light source was varied. Thus, a short study of reaction parameters was conducted to get a general idea. The reaction is as shown in scheme 16.

Scheme 16



The results of scheme 16 are summarized in table 1.

Table 1: Study of reaction parameters.

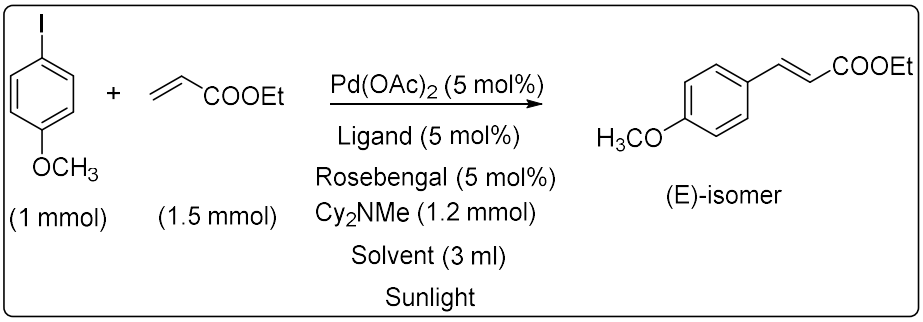
Sr.No.	Base	Dye	Source	Yield (%)	Time (hr)
1.	Bu_3N	Rose Bengal	LED	33	8
2.	Bu_3N	Fluorescein	LED	22	9
3.	Bu_3N	Eosin Y	LED	31	8
4.[a]	Bu_3N	Eosin Y	LED	7	23
5.[a, b]	K_2CO_3	Eosin Y	LED	_	48
6.[a]	Bu_3N	Rose Bengal	Sunlight	74	5
7.[a]	Bu_3N	Fluorescein	Sunlight	72	5

Sr.No.	Base	Dye	Source	Yield (%)	Time (hr)
8.[c]	Cy_2NMe	Rose Bengal	Sunlight	82	5

[a] 5 mol% tri-(o-tolyl) phosphine were used. [b] No reaction. [c] 2.5 mol% $Pd(OAc)_2$ were used and PEG 400 (3 ml) as solvent were used.

Palladium catalysts in conjunction with electron rich phosphines tend to increase their reactivity for cross-coupling reactions. We have applied our photoredox strategy to phosphine/Pd system to comprehensively study the effect of phosphine ligands in visible light mediated Mizoroki-Heck reaction. NMP and PEG 400 were also selected as solvent for our study. The reaction is as shown in scheme 17.

Scheme 17



The results of scheme 17 are summarized in table 2.

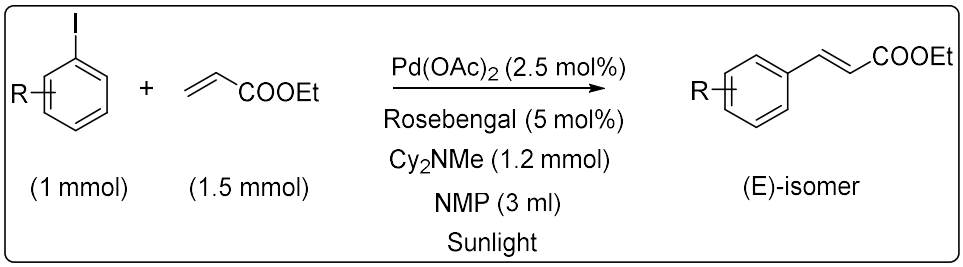
Table 2: Ligand studies in visible light mediated Mizoroki-Heck reaction.

Sr.No.	Ligand	Solvent	Yield (%)	Time (hr)
1.	dppe	NMP	75	4
2.	Xphos	PEG 400	69	2
3.	Xantphos	NMP	98	2
4.	Johnphos	PEG 400	73	2
5.	dppf	NMP	94	1
6.	Tri(o-tolyl)phosphine	PEG 400	95	3
7.	Triphenylphosphine	PEG 400	91	4:45
8.	Rac-BINAP	PEG 400	69	1:30

Sr.No.	Ligand	Solvent	Yield (%)	Time (hr)
9.	Sphos	NMP	91	2
10.	Tricyclohexylphosphine	NMP	93	3

We then examined the generality of this reaction by screening a small spectrum of aryl iodides with ethyl acrylate as olefin coupling partner under ligand less conditions. The reaction is as shown in scheme 18.

Scheme 18



The results of scheme 18 are summarized in table 3.

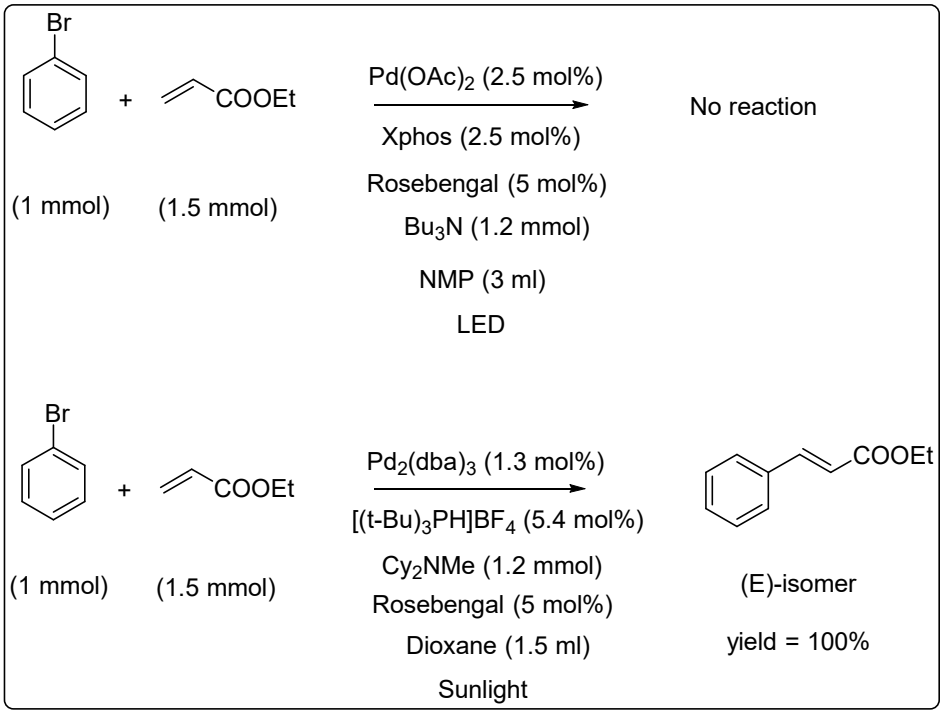
Table 3: Substrate scope of Mizoroki-Heck reaction.

Sr.No.	Aryl iodide	Yield (%)	Time (hr)
1.	4-$CF_3OC_6H_4I$	78	6:30
2.	4-ClC_6H_4I	84	3:30
3.	4-$CH_3C_6H_4I$	95	3
4.	4- FC_6H_4I	91	3:30
5.	2- $CH_3C_6H_4I$	83	3
6.[a]	4- $CH_3OC_6H_4I$	47	2

[a] PEG 200 (3 ml) solvent were used.

Aryl bromide activation plays an important role in coupling reactions as these are considerably cheaper than aryl iodides. Scheme 19 shows our progress in accomplishing our objective in reacting aryl bromides under sunlight or LED in Mizoroki-Heck reaction with ethyl acrylate as olefin coupling partner.

Scheme 19



A very short preliminary study of aryl bromides was then conducted to check its feasibility. Results are tabulated in table 4.

Table 4: Aryl bromides activation.

Sr.No. [a]	Aryl halide	Olefin	Source	Yield (%)	Time (hr)
1.	4-$CH_3OC_6H_4Br$	CH_2=$CHCOOC_2H_5$	Sunlight	65	6
2.	C_6H_5Br	CH_2=$CHCOOC_2H_5$	LED	17	8
3. [b]	C_6H_5Cl	CH_2=$CHCOOC_2H_5$	Sunlight	_	54

[a] Reaction conditions: 1 mmol aryl halide, 1.5 mmol olefin (ethyl acrylate), $Pd_2(dba)_3$ (1.3 mol%), $[(t\text{-}Bu)_3PH]BF_4$ (5.4 mol%), Base (Cy_2NMe, 1.2 mmol), Dye (Rose Bengal, 5 mol%) and Solvent (Dioxane, 1.5 ml). [b] No reaction.

1A.2 Results and Discussion

At first, Mizoroki-Heck reaction of Iodobenzene and ethyl acrylate was probed under the conditions illustrated in scheme 16. The reaction was conducted in a simple assembly of round bottom flask equipped with magnetic stirrer. Sunlight and LED as a light source were used interchangeably for this study. For sunlight mediated reactions the assembly was merely exposed to bright sunlight on terrace for utilizing maximum solar radiations for getting better results. For LED mediated reactions the flask was exposed to 45 W LED lamp. Product obtained was Ethyl (E)-3-phenylacrylate (1a) i.e. ethyl cinnamate with complete E selectivity of double bond. In ^{1}H NMR spectrum the signals at δ 7.70 (d, *J*=16.0 Hz, 1H) and δ 6.45 (d, *J*=16.0 Hz, 1H) confirmed presence of two *trans* olefinic protons of 1,2 disubstituted olefin ethyl cinnamate. The signals at δ 7.47 - 7.60 (m, 2H) and δ 7.31 - 7.46 (m, 3H) confirmed the presence of 5 aromatic protons. Finally, the signals at δ 4.28 (q, *J*=7.1 Hz, 2H) and δ 1.35 (t, *J*=7.1 Hz, 3H) confirmed ethyl group of ethyl cinnamate. Other spectroscopic techniques were also useful in deducing the structure of this product as mentioned in experimental section of this chapter.

LED mediated reactions using tributylamine as base furnished an encouraging quantity of the desired product (Table 1, entries 1-4, 7-33% yield) but these attempts were not sufficient enough to raise the yield to a reasonable amount. Using a concoction of potassium carbonate as a mild base with phosphine ligand, palladium metal & Eosin Y in LED frustratingly gave no yield of desired product even after 48 hr (Table 1, entry 5).

Switching to sunlight gave exciting yields of product (Table 1). Using tributylamine as base in combination with tri-(o-tolyl) phosphine as ligand furnished the expected product in good yields (Table 1, entries 6 and 7, 74% & 72% yield, respectively). In all these entries Rose Bengal emerged as a suitable dye for carrying out this Mizoroki-Heck transformation. The judicious selection of base can have vital effect on product distribution and rate of Mizoroki-Heck reactions.[24] Inspired by research from Buchwald laboratory that describes unusual efficaciousness of Cy_2NMe (a bulky tertiary amine), in Mizoroki-Heck reactions of disubstituted olefins at 85-100^{0}C, [25] we probed the replacement of tributylamine with Cy_2NMe and were glad to notice that its use increased the yield to 82% in presence of Rose Bengal dye (Table 1, entry 8).

Bedekar *et. al.* reported photothermal Mizoroki-Heck, Suzuki-Miyaura and Sonogashira reactions in sunlight using 1-(α-amino benzyl)-2-naphthols as ligands avoiding photoredox

catalyst.[26] This triggered us to investigate the role of phosphines ligands in non-conventional metallaphotoredox mediated Mizoroki-Heck reactions. A comprehensive phosphine ligand study was examined using 4-Iodoanisole and ethyl acrylate as coupling partners and the conditions are presented in scheme 17. NMP and PEG 400 (green solvent) were used interchangeably for this study. Rose Bengal dye and Cy_2NMe base were chosen based on results of reaction parameters study (Table 1). The obtained product in this study was Ethyl (E)-3-(4-methoxyphenyl) acrylate (2a) (Table 2). In ^1H NMR spectrum the signals at δ 7.65 (d, *J*=15.9 Hz, 1H) and δ 6.31 (d, *J*=16.0 Hz, 1H) confirmed presence of two *trans* olefinic protons of 1,2 disubstituted olefin. The signals at δ 7.48 (d, *J*=8.7 Hz, 2H) and δ 6.91 (d, *J*=8.8 Hz, 2H) confirmed the presence of 4 aromatic protons of A_2B_2 pattern of para substitution. A downfield signal at δ 3.84 (s, 3H) corresponds to methoxy group. Finally, the signals at δ 4.26 (q, *J*=7.2 Hz, 2H) and δ 1.34 (t, *J*=7.1 Hz, 3H) confirmed ethyl group (ester functionality) of the obtained product. The two signals at δ 144.24 and δ 115.80 in ^{13}C NMR spectrum were informative about two olefinic carbons of the product. Finally, *m/z* at 207.1016 $[M+H]^+$ fully confirms formation of product.

Traditional and simple phosphines like Triphenylphosphine, Tricyclohexylphosphine and Tri(o-tolyl) phosphine (sterically hindered) gave comparable and excellent yields of the product (Table 2, entries 7, 10 & 6, 91%, 93% & 95% yield, respectively). A family of sterically hindered dialkylbiaryl phosphanes like XPhos gave moderate yield of the product (69%) as well as unsubstituted congener of this family Johnphos also yielded moderate yield (73%) but SPhos, a more electron rich member of the same family gave excellent yield (91%) within same time frame albeit in different solvent (Table 2, entries 2, 4 & 9). Chelating phosphines like Rac-BINAP and dppe gave moderate to good yield whereas dppf gave excellent yield of the product (Table 2, entries 8, 1 & 5, 69%, 75% & 94% yield, respectively). Finally, the best yield of this study was obtained by use of Xantphos as 98% yield.

Having fairly established the optimized conditions of metallaphotoredox conversion, the generality and limitation of the present light mediated Mizoroki-Heck reaction were probed by conducting the reaction on 1 mmol scale (scheme 18, Table 3) with ethyl acrylate as the fixed olefin coupling partner. One change made in this study was avoiding phosphine ligand so as to make overall process inexpensive and to investigate the feasibility of reaction in absence of phosphines. As illustrated, a short spectrum of aryl iodides possessing electron-withdrawing or electron-donating groups can react with ethyl acrylate under our conditions, providing (E)-coupling products in good to excellent yields. Yields ranged from 78% to 95%. Of note, the

present phosphine ligand free Mizoroki-Heck reaction manifested negligible effect towards ortho substituent on aryl iodide which is considered to be sterically hindered (Table 3, entry 5, 83% yield). Unfortunately, reaction in PEG 200 as solvent led to lower yield of coupling product (Table 3, entry 6, 47% yield).

We were interested in activating C-Br bond as bromoarenes are readily available and comparatively cheaper than aryl iodides; however, they are generally inert under the conditions used to couple the related iodides. Activating C-Br bond using visible light can be quite economical from a synthetic standpoint. Our attempt using $Pd(OAc)_2$ and XPhos ligand in conjunction with Rose Bengal dye using LED as visible light source of energy proved futile as no reaction was observed (scheme 19). However, switching to $Pd_2(dba)_3$ as catalyst, $[(t\text{-}Bu)_3PH]BF_4$ as ligand, Cy_2NMe as base in sunlight as visible light source of energy plus Rose Bengal as chosen dye we were able to achieve 100% yield of coupling product (scheme 19). Using this condition unfortunately chlorobenzene coupling with ethyl acrylate was unsuccessful even after 54 hr (Table 4, entry 3). Bromobenzene coupling with ethyl acrylate under LED irradiation instead of sunlight led to very poor yield of desired product (Table 4, entry 2, 17% yield). Using standard conditions, 4-Bromoanisole coupled with ethyl acrylate to give a respectable yield of 65% (Table 4, entry 1) within very short reaction time. We also noticed extremely poor conversion and considerably longer reaction time (> 72 h) when Mizoroki-Heck coupling of aryl iodide with olefin was conducted without exposing to sunlight (dark) at room temperature or with only $Pd(OAc)_2$ in sunlight in the absence of dye.[27]

1A.3 Conclusion

The current findings demonstrate a simple way to employ sunlight as an innocuous, renewable energy source with aid from organic dyes for palladium catalyzed Mizoroki-Heck reactions to achieve coupled products as exclusive (E)- isomer with yields ranging from moderate to excellent under practical times of sunlight exposure. Thus, organic dyes can be a viable alternative for photoredox system reported in literature. This study also reveals that bromide activation under sunlight is operationally simple method which exhibits moderate to high yields and can compete with efficient known procedures. Finally, our findings demonstrate that these reactions can be conducted without using any special apparatus or reaction machinery.

Section B: Ruthenium complexes as photoredox catalyst for Mizoroki-Heck reaction under sunlight and artificial LED – Preliminary studies.

1B.1 Present work

Our previous approach dealt with cheaper organic dyes as photoredox catalyst for Mizoroki-Heck reaction of aryl halides (aryl iodides and bromides) with monosubstituted olefins. Our quest to find alternatives for highly expensive iridium or ruthenium polypyridyl complexes led us to try simple ruthenium complexes like $RuCl_2(PPh_3)_3$, $[Ru(p\text{-cymene})Cl_2]_2$ and $Ru(i\text{-Pr-DAB})Cl_2$ in coalition with $Pd(OAc)_2$. The rationale behind this was observance of excellent yields of Mizoroki-Heck adducts when several simple, easily prepared nickel photoredox complexes in conjunction with $Pd(OAc)_2$ were investigated under sunlight.[28] A very short preliminary study is presented in scheme 20 and results tabulated in table 5 are depicted below.

Scheme 20

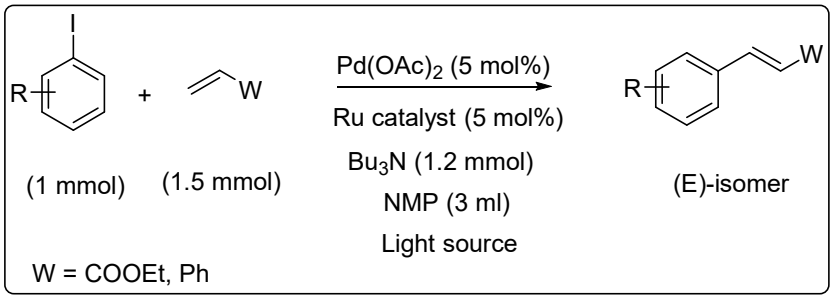
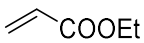
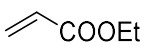
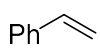
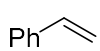


Table 5: Preliminary study of Mizoroki-Heck reaction using ruthenium complexes.

Sr.No.	Aryl iodide	Olefin	Catalyst [c]	Source	Yield (%)	Time (hr)
1.[a]	$4\text{-}CH_3OC_6H_4I$		$RuCl_2(PPh_3)_3$	Sunlight	86	7
2.	C_6H_5I		$[Ru(p\text{-cymene})Cl_2]_2$	LED	68	3
3.	C_6H_5I		$Ru(i\text{-Pr-DAB})\ Cl_2$	Sunlight	49	6
4.	$4\text{-}CH_3C_6H_4I$		$RuCl_2(PPh_3)_3$	Sunlight	62	5:30
5.[b]	$4\text{-}ClC_6H_4I$		$[Ru(p\text{-cymene})Cl_2]_2$	Sunlight	Trace	6

[a] E: Z = 1:0.19 ratio was obtained & determined by ^1H NMR. [b] PEG 200 (3 ml) as solvent were used. [c] $Pd(OAc)_2$ (5 mol%) was used in conjunction with Ruthenium photoredox catalyst.

1B.2 Results and Discussion

Ruthenium photoredox complexes used in this study were synthesized according to literature procedures and used directly for visible light mediated Mizoroki-Heck couplings.[29] A combination i.e. mix of $Pd(OAc)_2$ as active catalyst with several ruthenium complexes as photoredox catalysts were probed. The reaction of 4-Iodoanisole with ethyl acrylate employing $RuCl_2(PPh_3)_3$ under sunlight gave excellent yield of coupled product (86%) & using 4-Iodotoluene and styrene a respectable yield of 62% was observed (Table 5, entry 1 & 4). We were pleased to find out that LED irradiation of a cocktail of Iodobenzene, ethyl acrylate & $[Ru(p\text{-cymene})Cl_2]_2$ gave good yield of desired product (Table 5, entry 2, 68% yield). Employing, $Ru(i\text{-Pr-DAB})Cl_2$ as a photoredox catalyst however gave a moderate yield of 49% (Table 5, entry 3). Unfortunately using PEG 200 as solvent resulted in trace amount of product (entry 5). Obtained products were essentially (E)-isomers.

1B.3 Conclusion

We have tried to establish a robust strategy for direct formation of substituted olefins by Mizoroki-Heck reaction employing cheaper, first generation traditional ruthenium complexes as photoredox catalyst. Our study demonstrates first example of LED irradiation with moderate yields and good yields with sunlight exposure. Although these are preliminary results, a detailed study can give a clear-cut picture of this novel methodology, but as of now we can deduce that this bench stable, inexpensive ruthenium complexes can act as a photoredox viable alternative catalyst in place of highly costly transition metal polypyridyl complexes.

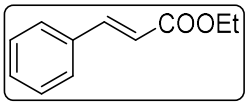
1.3 Experimental section

General procedure for the Mizoroki-Heck reaction under visible light irradiation catalyzed by photoredox catalyst (organic dye or ruthenium complex)

To an oven-dried 25 ml round bottom flask equipped with magnetic stirrer bar was charged aryl iodide (1 mmol), base (1.2 mmol), palladium acetate (5 mol%) in NMP (3 ml). To this reaction mixture olefin (1.5 mmol) and photoredox catalyst (5 mol%) was added. The reaction mixture was exposed to sunlight or irradiated with LED (45 W lamp). Upon completion of reaction, as monitored by TLC, the crude reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel to give the desired product.

Experimental data

Ethyl (E)-3-phenylacrylate (1a):



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as pale yellow oil (0.145g, 82%).

R_f = 0.4 (petroleum ether/EtOAc, 85:15).

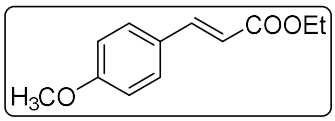
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.70 (d, *J*=16.0 Hz, 1H), 7.47 - 7.60 (m, 2H), 7.31 - 7.46 (m, 3H), 6.45 (d, *J*=16.0 Hz, 1H), 4.28 (q, *J*=7.1 Hz, 2H), 1.35 (t, *J*=7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 166.77, 144.39, 134.30, 130.04, 128.70, 127.87, 118.11, 60.29, 14.16.

IR ($CHCl_3$) ν_{max} = 3065, 2983, 1713, 1637, 1583, 1483, 1453, 1372, 1315, 1269, 1173, 1101, 1037, 983, 870, 768, 698.

HRMS: *m/z* = calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ 177.0915, found: 177.0907.

Ethyl (E)-3-(4-methoxyphenyl) acrylate (2a):



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as pale yellow oil (0.202g, 98%).

R_f = 0.36 (petroleum ether/EtOAc, 85:15).

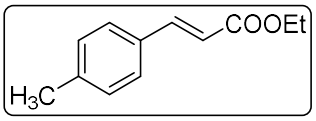
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.65 (d, *J*=15.9 Hz, 1H), 7.48 (d, *J*=8.7 Hz, 2H), 6.91 (d, *J*=8.8 Hz, 2H), 6.31 (d, *J*=16.0 Hz, 1H), 4.26 (q, *J*=7.2 Hz, 2H), 3.84 (s, 3H), 1.34 (t, *J*=7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 167.33, 161.35, 144.24, 129.69, 127.25, 115.80, 114.33, 60.33, 55.38, 14.37.

IR ($CHCl_3$) ν_{max} = 2970, 1708, 1603, 1511, 1456, 1374, 1301, 1254, 1167, 1111, 1032, 985, 830, 771, 665.

HRMS: *m/z* = calcd for $C_{12}H_{15}O_3$ $[M+H]^+$ 207.0978, found: 207.1016.

Ethyl (E)-3-(4-methylphenyl) acrylate (3a):



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as pale yellow oil (0.181g, 95%).

R_f = 0.39 (petroleum ether/EtOAc, 85:15).

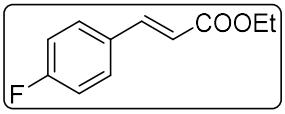
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.56 (d, *J*=16.0 Hz, 1H), 7.30 (d, *J*=8.0 Hz, 2H), 7.06 (d, *J*=7.8 Hz, 2H), 6.28 (d, *J*=15.9 Hz, 1H), 4.15 (q, *J*=7.1 Hz, 2H), 2.24 (s, 3H), 1.22 (t, *J*=7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 167.17, 144.56, 140.58, 131.72, 129.57, 128.01, 117.17, 60.37, 21.42, 14.31.

IR ($CHCl_3$) ν_{max} = 2920, 2856, 2347, 2286, 1711, 1610, 1383, 1314, 1267, 1169, 1118, 1038, 811, 767, 664.

HRMS: *m/z* = calcd for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1070, found: 191.1068.

Ethyl (E)-3-(4-fluorophenyl) acrylate (4a):



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as pale yellow oil (0.176g, 91%).

R_f = 0.28 (petroleum ether/EtOAc, 85:15).

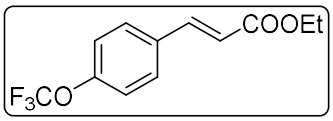
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.64 (d, *J*=16.0 Hz, 1H), 7.44 - 7.57 (m, 2H), 7.00 - 7.14 (m, 2H), 6.36 (d, *J*=16.0 Hz, 1H), 4.26 (q, *J*=7.1 Hz, 2H), 1.33 (t, *J*=7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 166.75, 166.26, 161.28, 143.16, 130.67, 130.60, 129.89, 129.73, 117.98, 117.93, 116.13, 115.71, 60.44, 14.22.

IR ($CHCl_3$) ν_{max} = 3064, 2982, 1712, 1639, 1599, 1510, 1461, 1409, 1372, 1314, 1271, 1231, 1169, 1099, 1038, 982, 880, 832, 782.

HRMS: *m/z* = calcd for $C_{11}H_{12}O_2F$ $[M+H]^+$ 195.0778, found :195.0816.

Ethyl (E)-3-(4-(trifluoromethoxy) phenyl) acrylate (5a):



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.204g, 78%).

R_f = 0.22 (petroleum ether/EtOAc, 85:15).

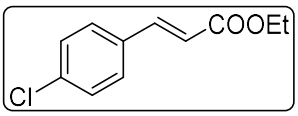
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.67 (d, *J*=16.0 Hz, 1H), 7.56 (d, *J*=8.7 Hz, 2H), 7.23 (d, J = 8.46 Hz, 2H), 6.41 (d, *J*=16.0 Hz, 1H), 4.27 (q, *J*=7.1 Hz, 2H), 1.34 (t, *J*=7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 166.63, 150.37, 142.77, 133.08, 129.43, 122.93, 121.12, 119.26, 117.80, 60.65, 14.27.

IR ($CHCl_3$) ν_{max} = 3065, 2984, 2936, 1715, 1640, 1600, 1509, 1461, 1412, 1373, 1311, 1267, 1168, 1106, 1035, 982, 928, 881, 840, 668.

HRMS: *m/z* = $[M^+ + H]^+$ calcd for $C_{12}H_{12}O_3F_3$ 261.0770, found: 261.0733.

Ethyl (E)-3-(4-chlorophenyl) acrylate (6a):



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.176g, 84%).

R_f = 0.28 (petroleum ether/EtOAc, 85:15).

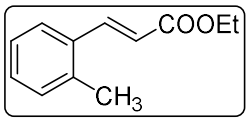
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.63 (d, J=16 Hz, 1H), 7.48-7.33 (m, 4H), 6.41 (d, J=16 Hz, 1H), 4.27 (q, J=7.07 Hz, 2H), 1.34 (t, J=7.07 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 166.69, 143.08, 136.07, 132.90, 129.15, 129.12, 118.82, 60.58, 14.26.

IR ($CHCl_3$) ν_{max} = 2980, 1716, 1638, 1592, 1490, 1363, 1269, 1227, 1173, 883, 786.

HRMS: *m/z* = calcd for $C_{11}H_{12}ClO_2$ $[M+H]^+$ 211.0526, found :211.0537.

Ethyl (E)-3-(2-methylphenyl) acrylate (7a):



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.157g, 83%).

R_f = 0.39 (petroleum ether/EtOAc, 85:15).

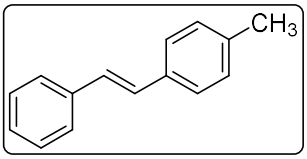
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.97 (d, J=15.92 Hz, 1H), 7.56-7.52 (m, 1H), 7.28-7.18 (m, 3H), 6.36 (d, J=15.92 Hz, 1H), 4.27 (q, J=7.07 Hz, 2H), 2.43 (s, 3H), 1.34 (t, J=7.07 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 166.98, 142.21, 137.55, 133.38, 130.71, 129.88, 126.33, 126.26, 119.25, 60.41, 19.72, 14.27.

IR ($CHCl_3$) ν_{max} = 2995, 2852, 2343, 2281, 1709, 1633, 1311, 1263, 1164, 1115,660.

HRMS: *m/z* = calcd for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1070, found: 191.1068.

(E)-1-methyl-4-styrylbenzene (8a):



Chromatography (97:3 petroleum ether: EtOAc) furnished the desired product as white solid (0.060g, 62%) on 0.5 mmol scale.

R_f = 0.4 (petroleum ether/EtOAc, 90:10).

^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.10 - 7.55 (m, 9H), 7.07 (s, 2H), 2.35 (s, 3H).

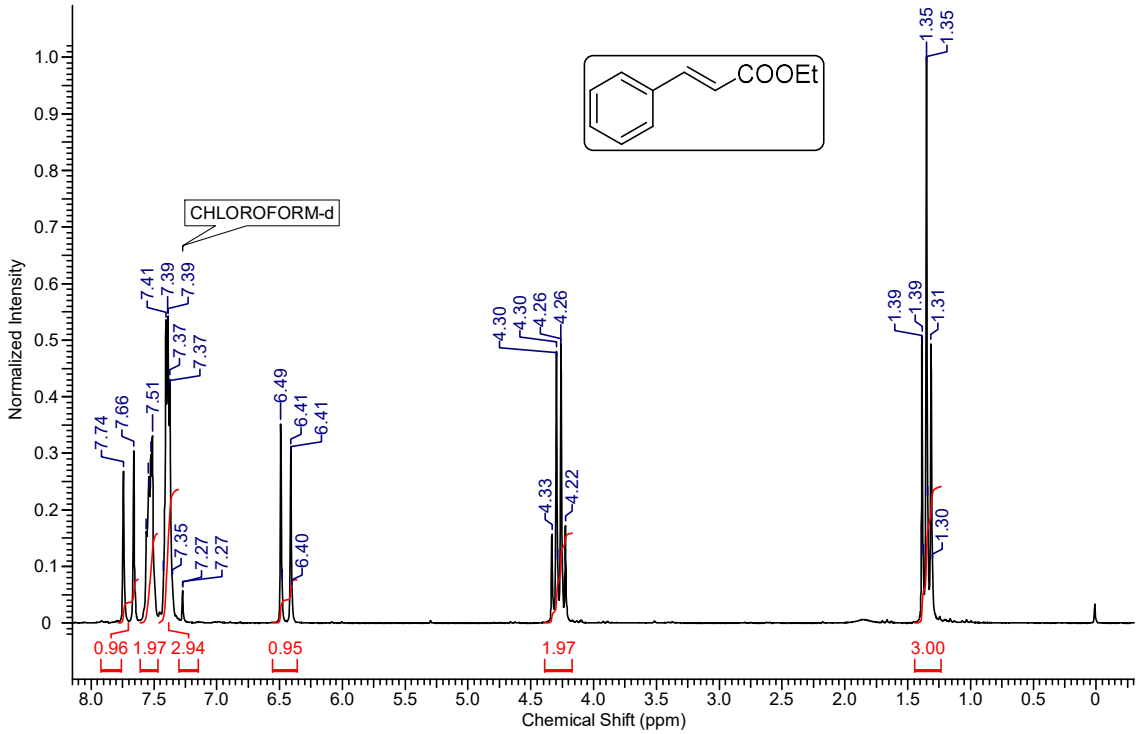
^{13}C NMR ($CDCl_3$, 50 MHz) δ = 137.5, 134.5, 129.4, 128.6, 127.7, 127.4, 126.4, 126.4, 21.2.

IR ($CHCl_3$) ν_{max} = 3019, 2926, 1595, 1515, 1450, 1216, 1117, 1035, 968, 911, 858, 809, 759, 696.

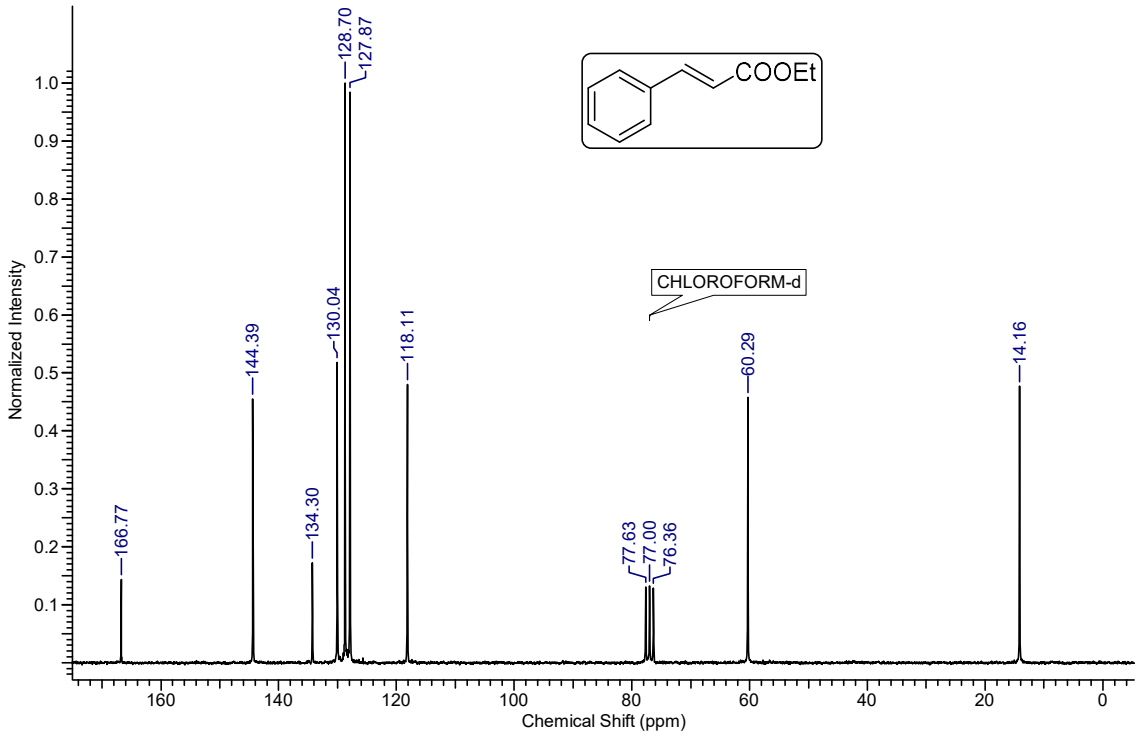
HRMS: *m/z* = calcd for $C_{15}H_{15}$ $[M^+ + H]^+$ 195.1166, found: 195.1168.

1.4 Spectral Data

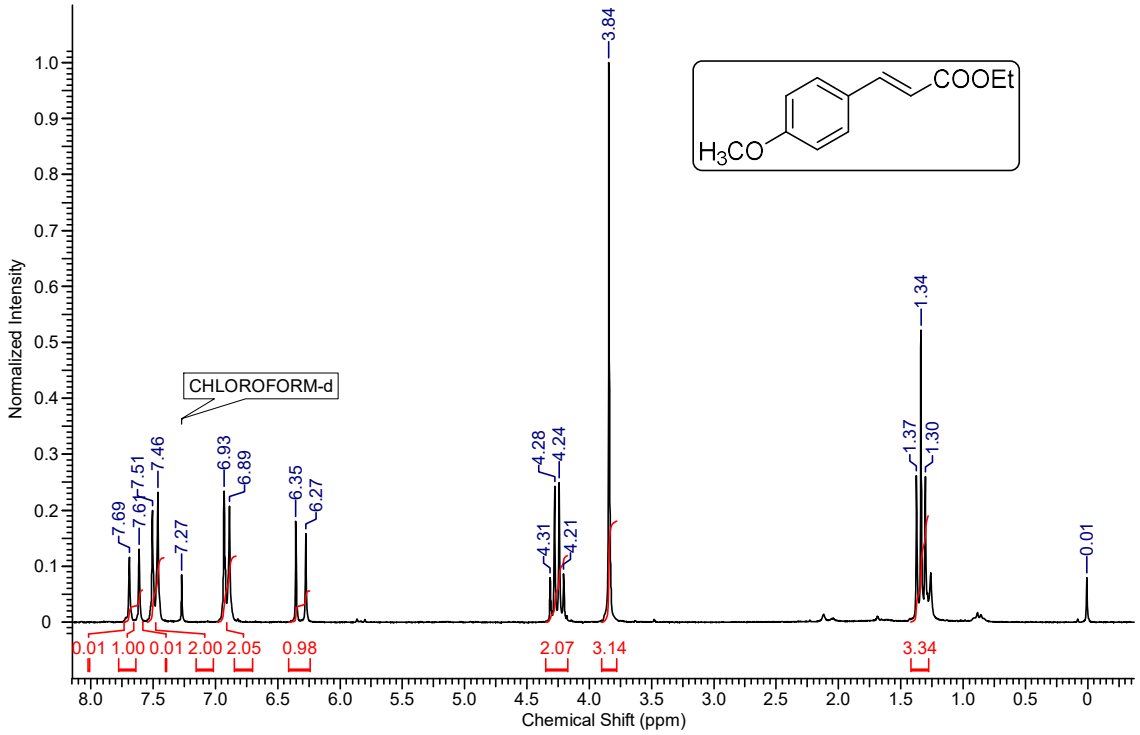
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of Ethyl (E)-3-phenylacrylate **(1a)**



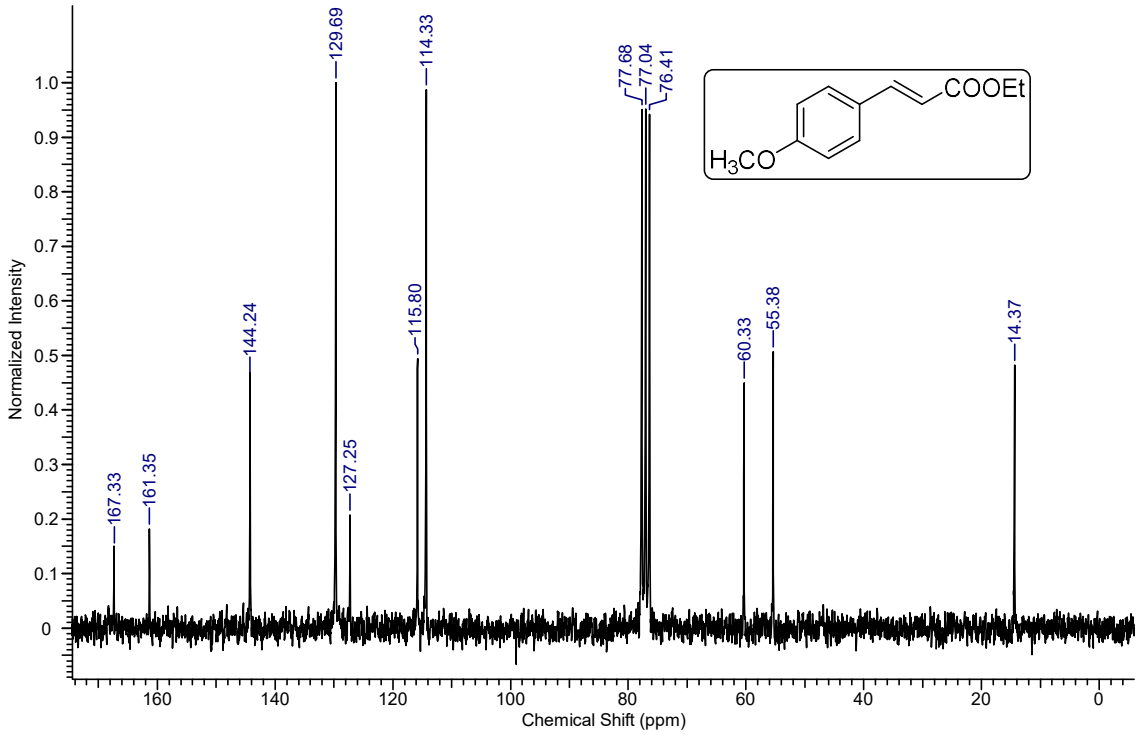
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of Ethyl (E)-3-phenylacrylate **(1a)**



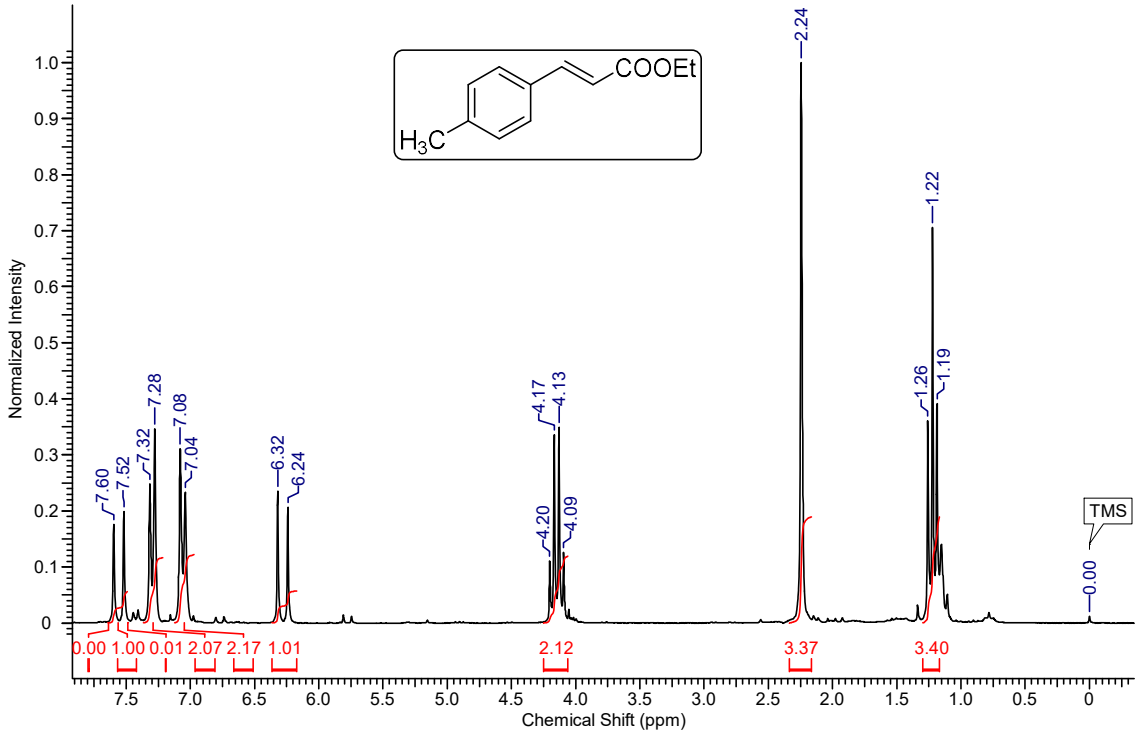
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of Ethyl (E)-3-(4-methoxyphenyl) acrylate **(2a)**



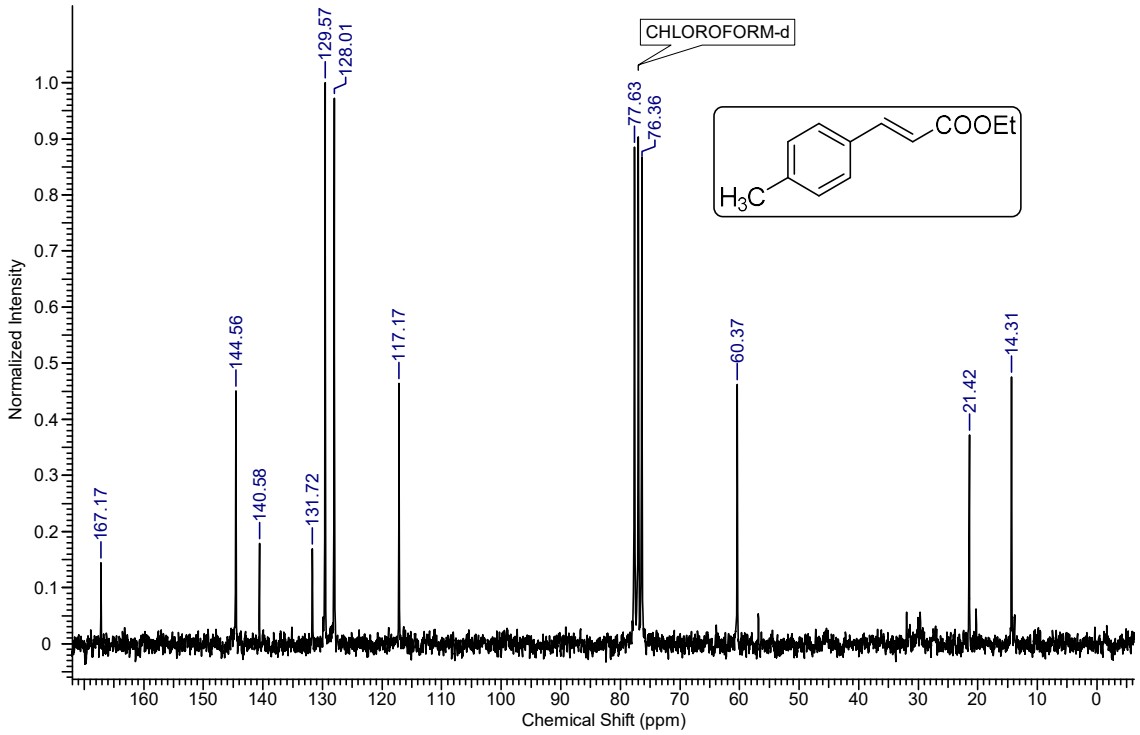
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of Ethyl (E)-3-(4-methoxyphenyl) acrylate **(2a)**



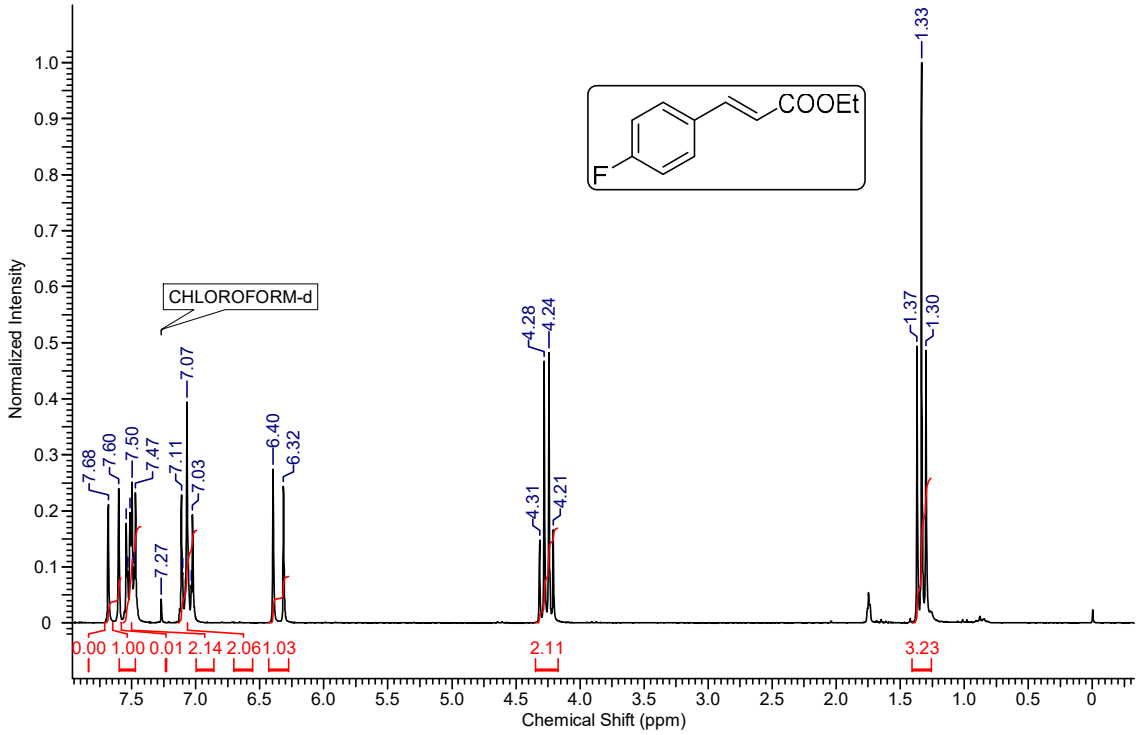
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of Ethyl (E)-3-(4-methylphenyl) acrylate **(3a)**



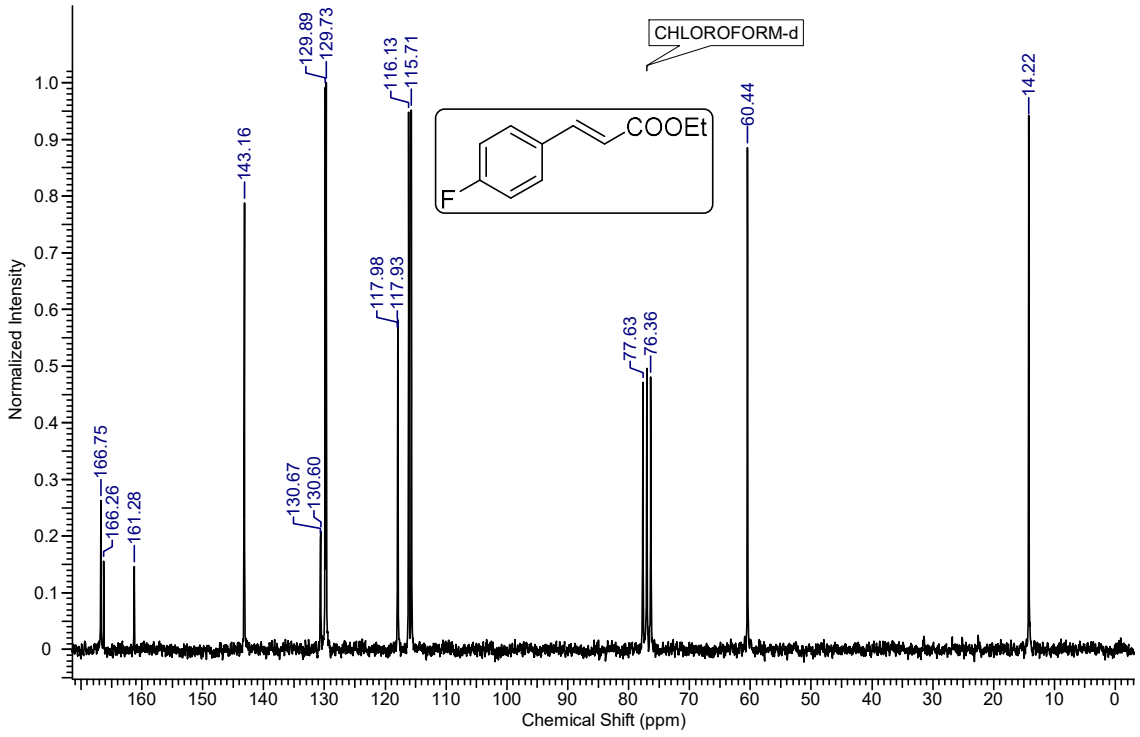
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of Ethyl (E)-3-(4-methylphenyl) acrylate **(3a)**



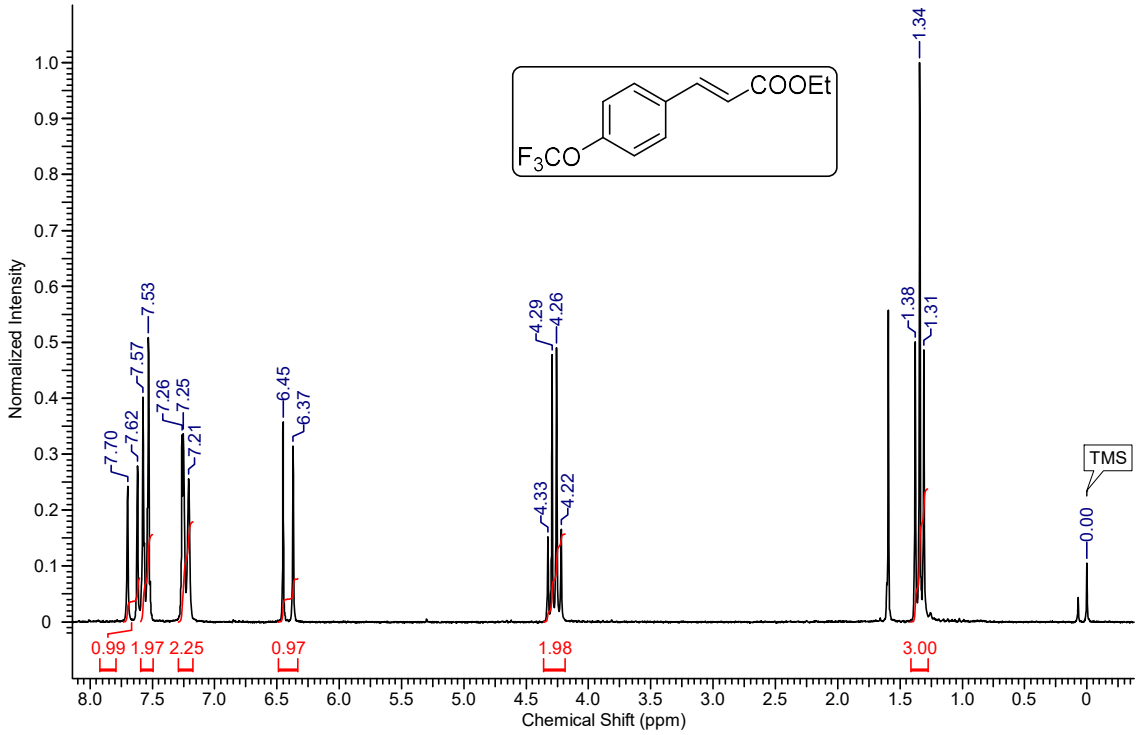
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of Ethyl (E)-3-(4-fluorophenyl) acrylate **(4a)**



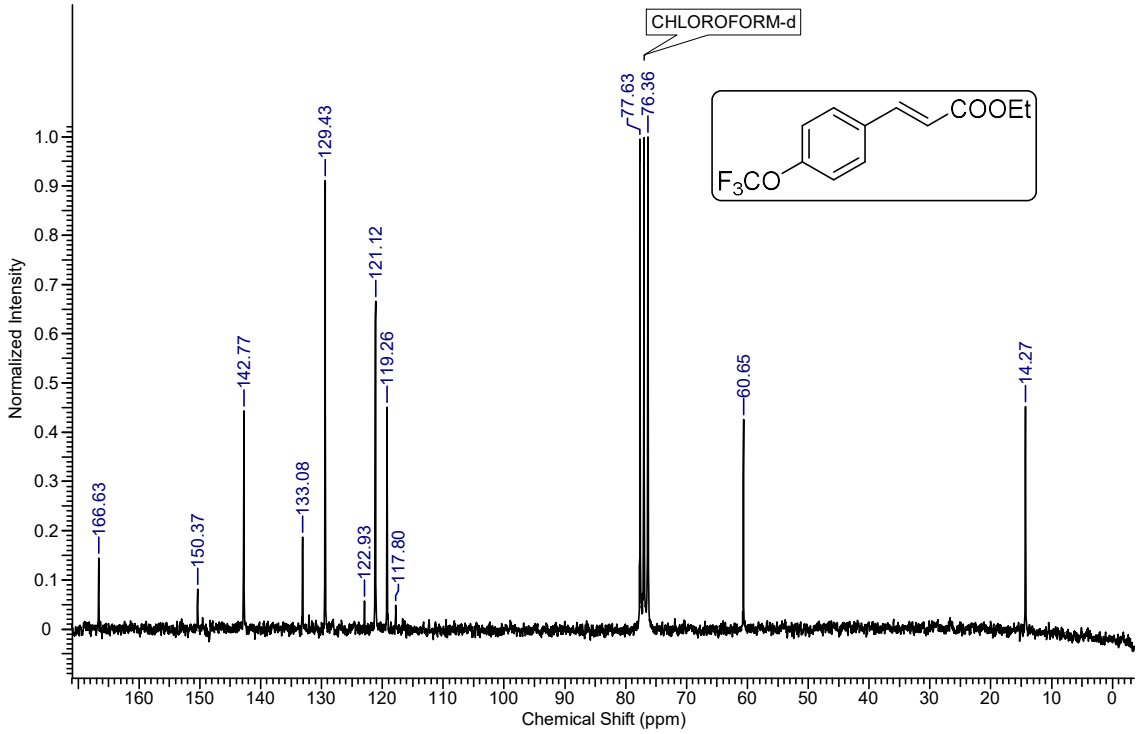
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of Ethyl (E)-3-(4-fluorophenyl) acrylate **(4a)**



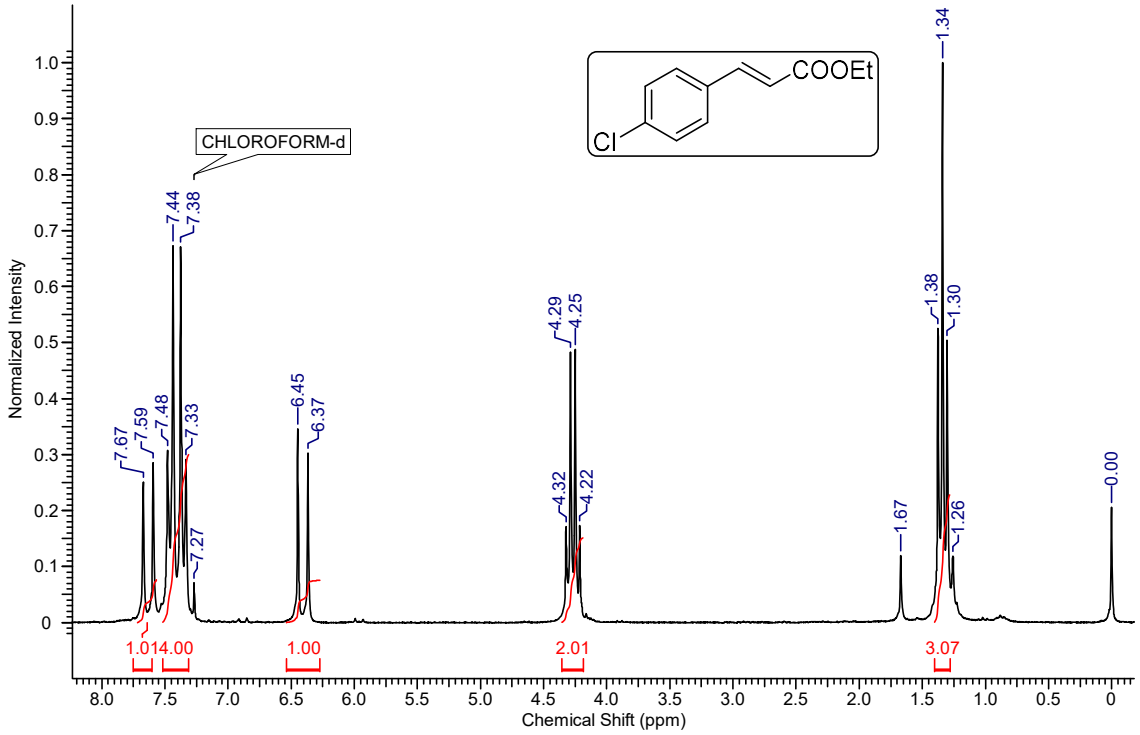
^{1}HNMR($CDCl_3$,200 MHz) spectrum of Ethyl (E)-3-(4-(trifluoromethoxy) phenyl)acrylate **(5a)**



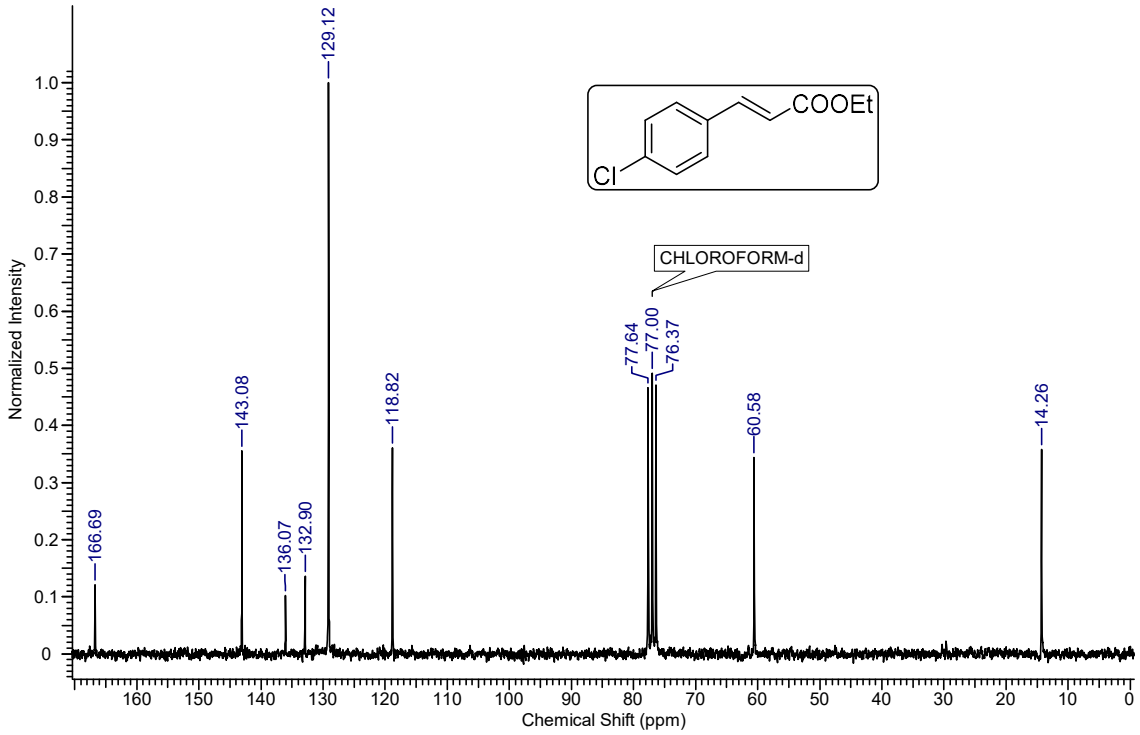
^{13}CNMR($CDCl_3$, 50 MHz) spectrum of Ethyl (E)-3-(4-(trifluoromethoxy) phenyl) acrylate **(5a)**



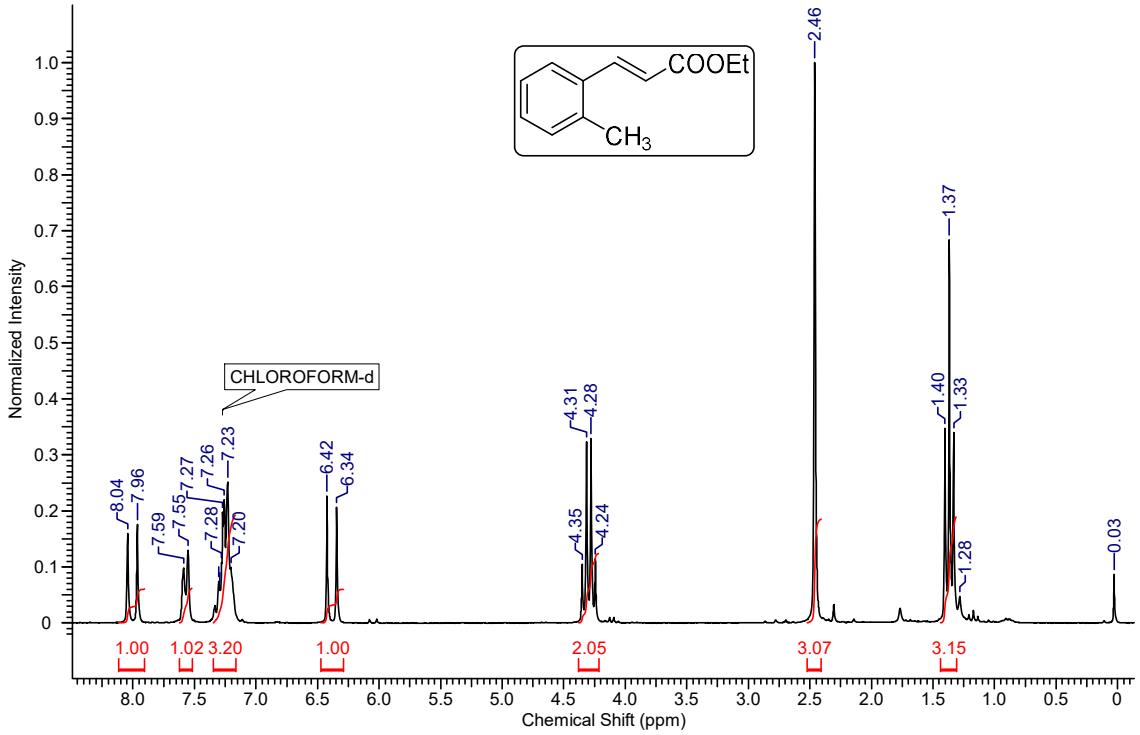
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of Ethyl (E)-3-(4-chlorophenyl) acrylate **(6a)**



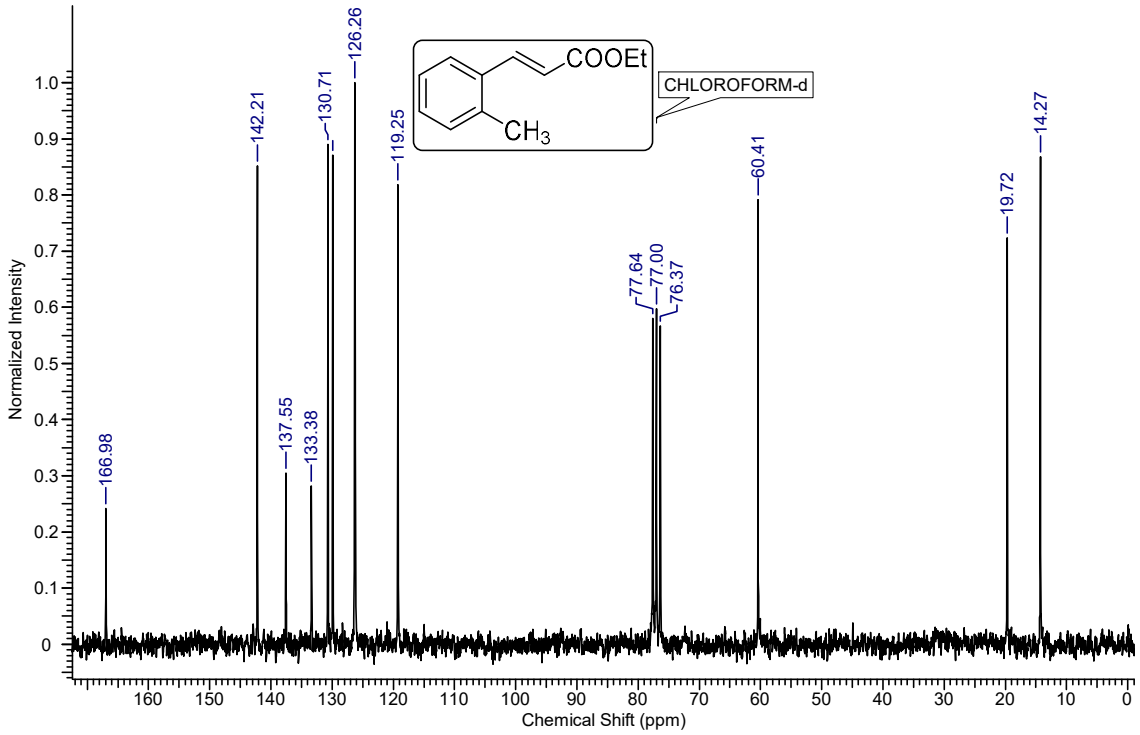
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of Ethyl (E)-3-(4-chlorophenyl) acrylate **(6a)**



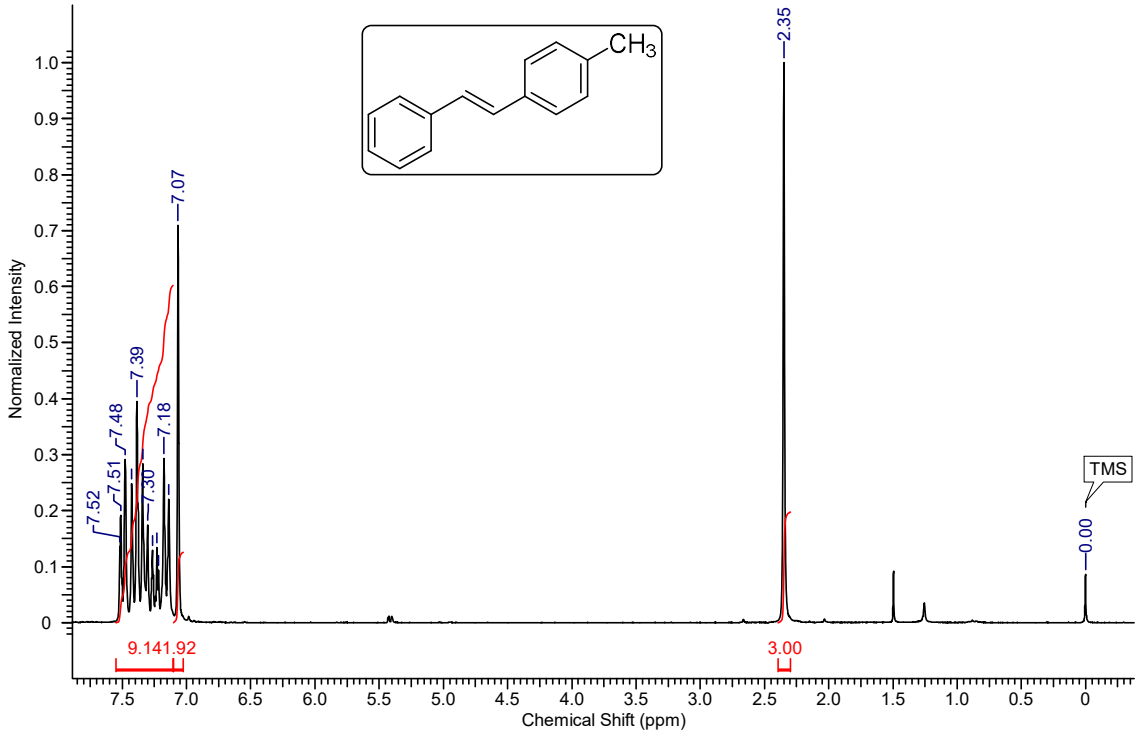
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of Ethyl (E)-3-(2-methylphenyl) acrylate **(7a)**



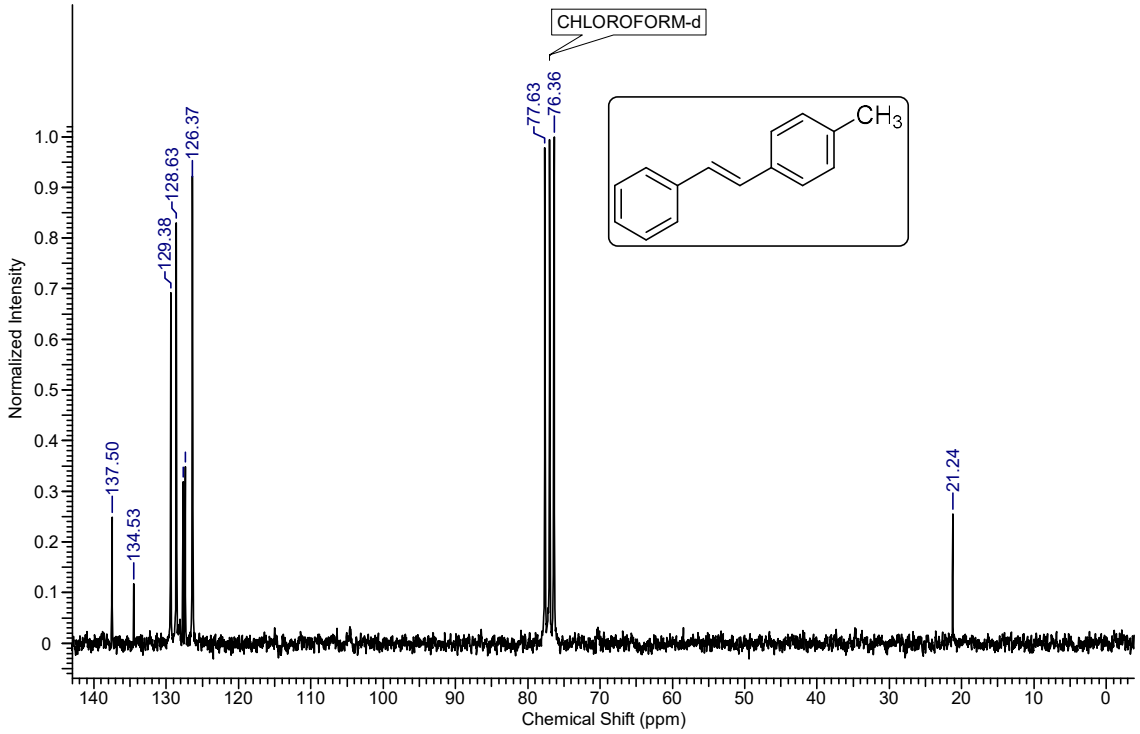
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of Ethyl (E)-3-(2-methylphenyl) acrylate **(7a)**



^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (E)-1-methyl-4-styrylbenzene **(8a)**



^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (E)-1-methyl-4-styrylbenzene **(8a)**



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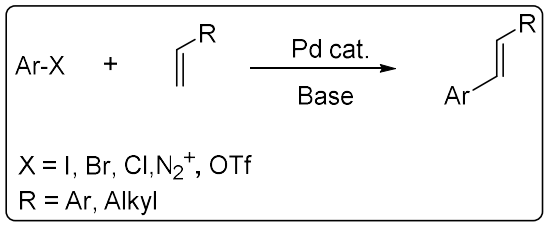
Chapter II

Mizoroki-Heck reaction of 1,2-disubstituted olefins: variables of synthesis.

2.1 Introduction

The palladium-catalyzed arylation and vinylation of alkenes is famously known as Mizoroki-Heck reaction (Scheme 1). It was discovered in the early 1970s.[1] It is well established synthetic method for carbon- carbon bond formation. This reaction has application to a varied array of fields which includes natural products synthesis [2], material science [3] and bioorganic chemistry[4].



Scheme 1. Mizoroki-Heck reaction

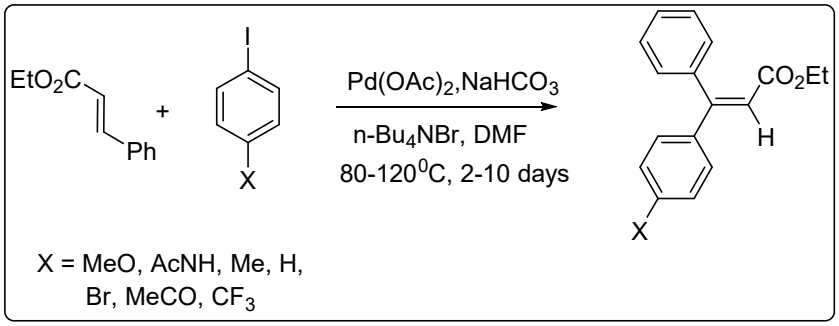
What contributes to the unprecedented and outstanding utility of Mizoroki-Heck reaction is the functional group tolerance, easy availability of simple, inexpensive olefins as contrast to vinyl metal compounds that are utilized in complementary Stille, Suzuki and other cross-coupling reactions.

A titanic number of reports have been published in scientific journals concerning synthetic applications, studies on regio- and stereoselectivity, recent advances and improvements in traditional Mizoroki-Heck reactions and new discoveries on mechanistic features.[5] The substitution pattern of alkenes is either monosubstituted or 1,1-disubstituted in most of these papers, little being known about Mizoroki-Heck reaction of 1,2-disubstituted olefins.

A brief summary on literature of Mizoroki-Heck reactions of disubstituted olefins is described below.

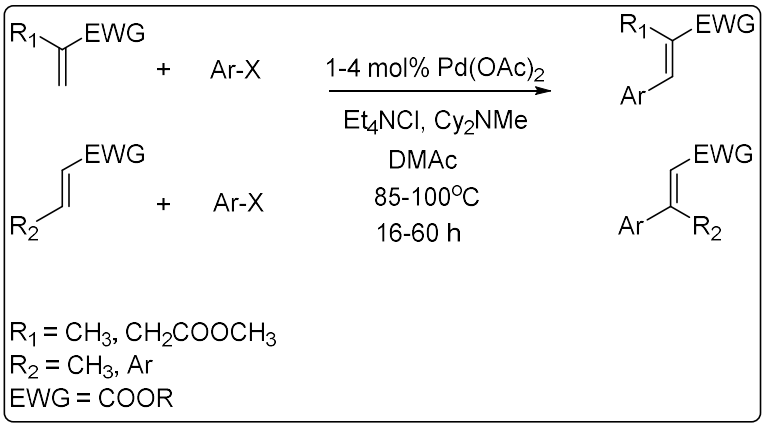
(E) and (Z) isomers of Ethyl-3-Aryl-3-phenylpropenoates were synthesized by reacting ethyl cinnamate with various *para*-substituted aryl iodides employing Jeffery-Larock conditions by Moreno *et al*. as shown in scheme 2.[6] Another approach adopted by this group was coupling of *para*-substituted ethyl cinnamates with Iodobenzene under related conditions to yield corresponding Z-isomers.

Scheme 2



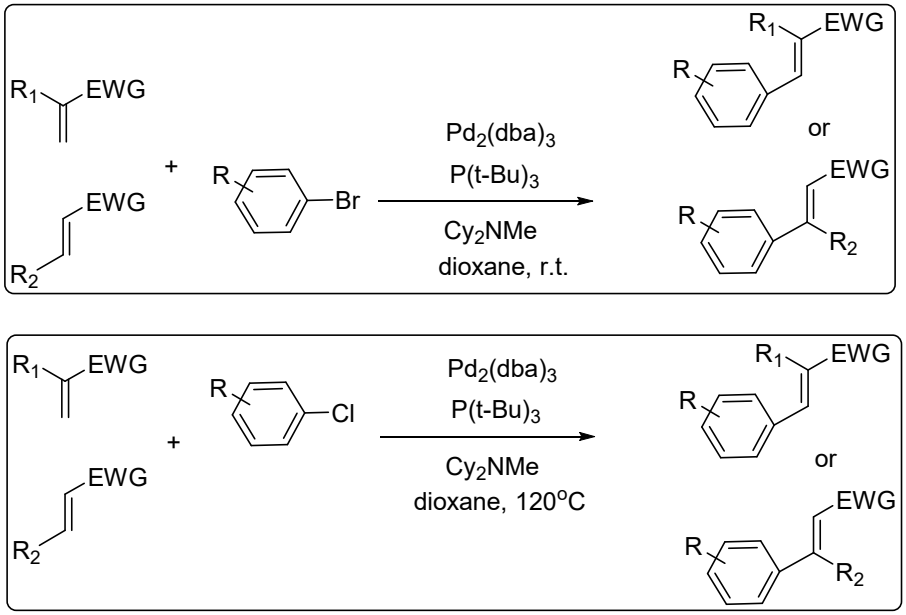
Buchwald *et al.* developed a new catalyst system comprising of methyl(dicyclohexyl) amine or dicyclohexylamine as base and one of two phase transfer catalysts to construct trisubstituted olefins. Electron-deficient and electron-rich aryl bromides in conjunction with $Cy_2(Me_2)NBr$ or Et_4NCl as phase transfer catalyst were effective in coupling activated olefins to yield desired trisubstituted olefins as shown in scheme 3.[7]

Scheme 3



Gregory Fu and co-workers exploited the use of Tri-tert-butyl phosphine ligand to generate unusually mild and multifaceted catalyst for Mizoroki-Heck arylation and vinylation of disubstituted olefins at room temperature to furnish trisubstituted olefins with high E/Z stereo selection. Aryl bromides reacted at room temperature. Aryl chlorides also coupled with disubstituted olefins at elevated temperatures as shown in scheme 4.[8]

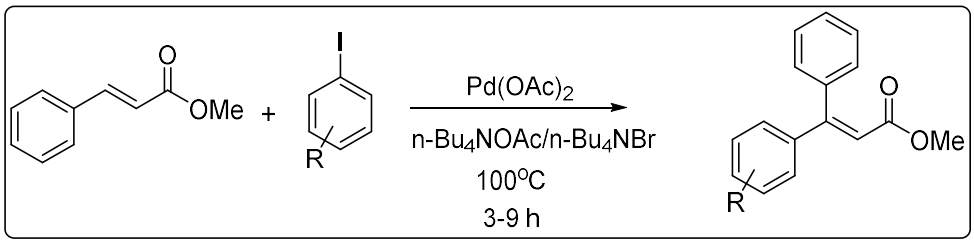
Scheme 4



Disubstituted olefins investigated by Fu *et al.* were methyl crotonate, methyl cinnamate and methyl methacrylate.

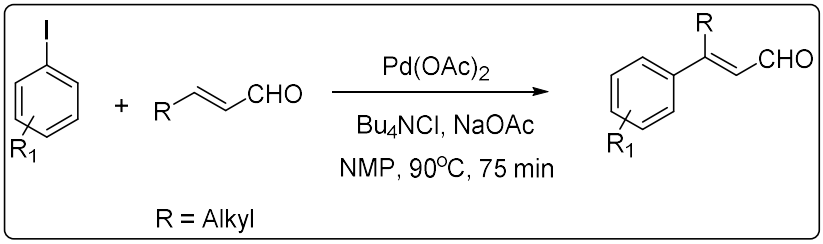
A highly effective and stereoselective method for the synthesis of both (E) and (Z)-isomers of 3,3-diarylacrylates using a recyclable 2:1.5 mixture of molten n-Bu_4NOAc/n-Bu_4NBr was developed by Cacchi *et al.* A phosphine free $Pd(OAc)_2$ was utilized to couple methyl cinnamate with aryl iodides as shown in scheme 5.[9]

Scheme 5



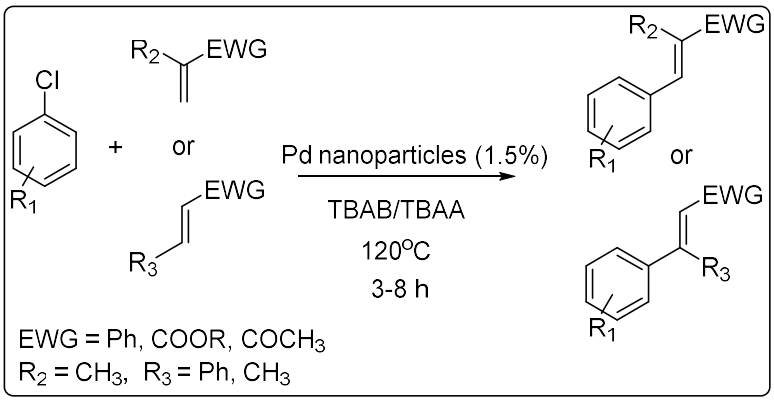
List *et al*. developed straightforward procedure for preparation of β,β-disubstituted α,β-unsaturated aldehydes via Mizoroki-Heck reaction of aryl halides with crotonaldehyde and corresponding substrates. This methodology was extended by List *et al*. for short asymmetric synthesis of (S)-Florhydral. The reaction adopted by List *et al*. is depicted in scheme 6.[10]

Scheme 6



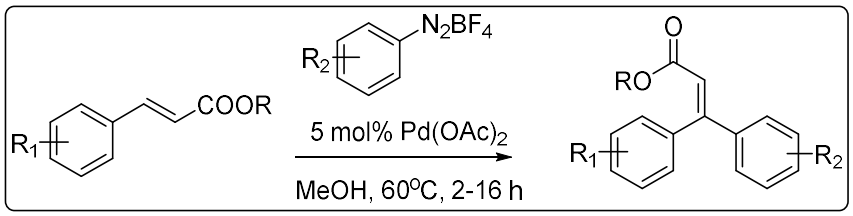
Nacci *et al.* displayed the use of ligand-free palladium nanoparticles in environmentally safer ionic liquids as a catalyst system (n-Bu_4NOAc/n-Bu_4NBr 1:2) for Mizoroki-Heck coupling of electron rich i.e. deactivated chloroarenes with substituted olefins of poor reactivity to generate trisubstituted olefins as depicted in scheme 7.[11]

Scheme 7



Correia *et al.* used ligand-free Heck-Matsuda coupling for stereoselective preparation of unsymmetrical β,β-diarylacrylates having varied steric and electronic properties. The reaction is as depicted in scheme 8.[12]

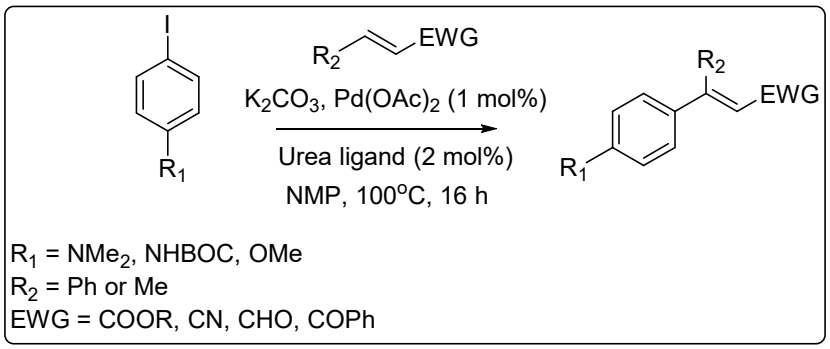
Scheme 8



Marco Ciufolini *et al.* described the use of 4-(methoxy) phenylurea and 4-(carbethoxy) phenylurea as ligands along with $Pd(OAc)_2$ as a catalyst system for Mizoroki-Heck arylation

of 2- or 3-substituted conjugated aldehydes, esters, ketones and nitriles with only electron rich aryl iodides as depicted in scheme 9.[13]

Scheme 9



Generation of trisubstituted olefins is of utmost importance because the unsaturated diaryl substituted carbon centres are related frameworks as they are present in Isocalophyllic acid and Kuhlmannene [14] as depicted in figure 1.

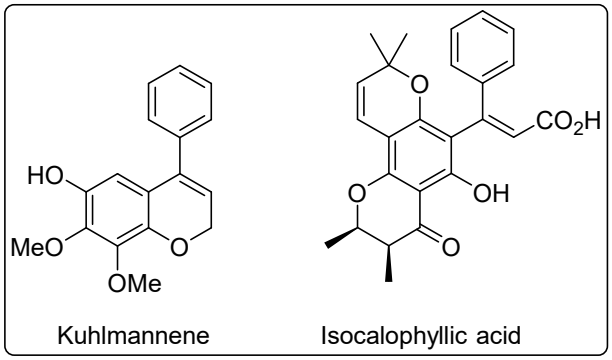


Figure 1. Structure of Kuhlmannene and Isocalophyllic acid.

Some trisubstituted olefins are precursors for the preparation of drugs that are marketed. This includes Sertraline, Tolterodine and some pharmacologically active secondary as well as tertiary 1-(3,3-Diarylpropyl) amines[15]. Structures are as depicted in figure 2.

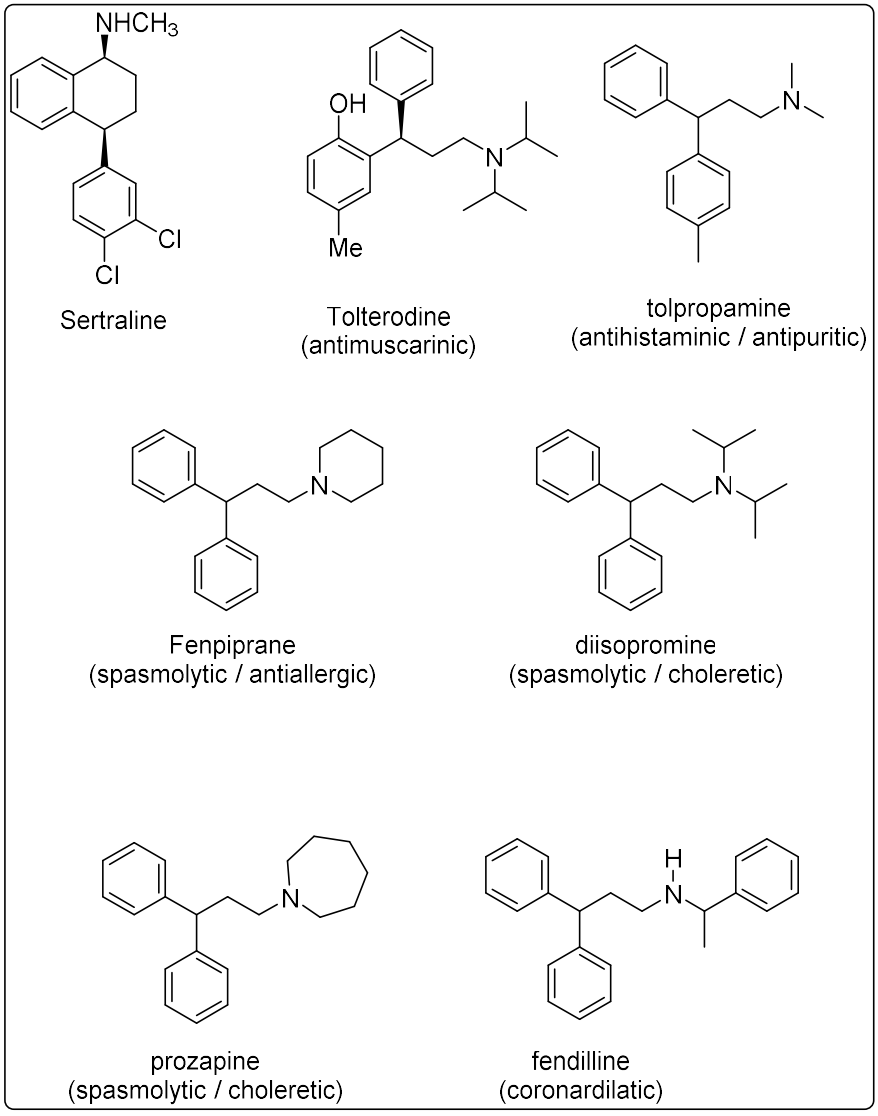


Figure 2. Structure of pharmacologically active compounds.

Trisubstituted olefins also find wide applications in material science. Many extended π systems like these are organic electroluminescence devices. A representative short library of trisubstituted olefins as fluorescent materials are depicted in figure 3.[16]

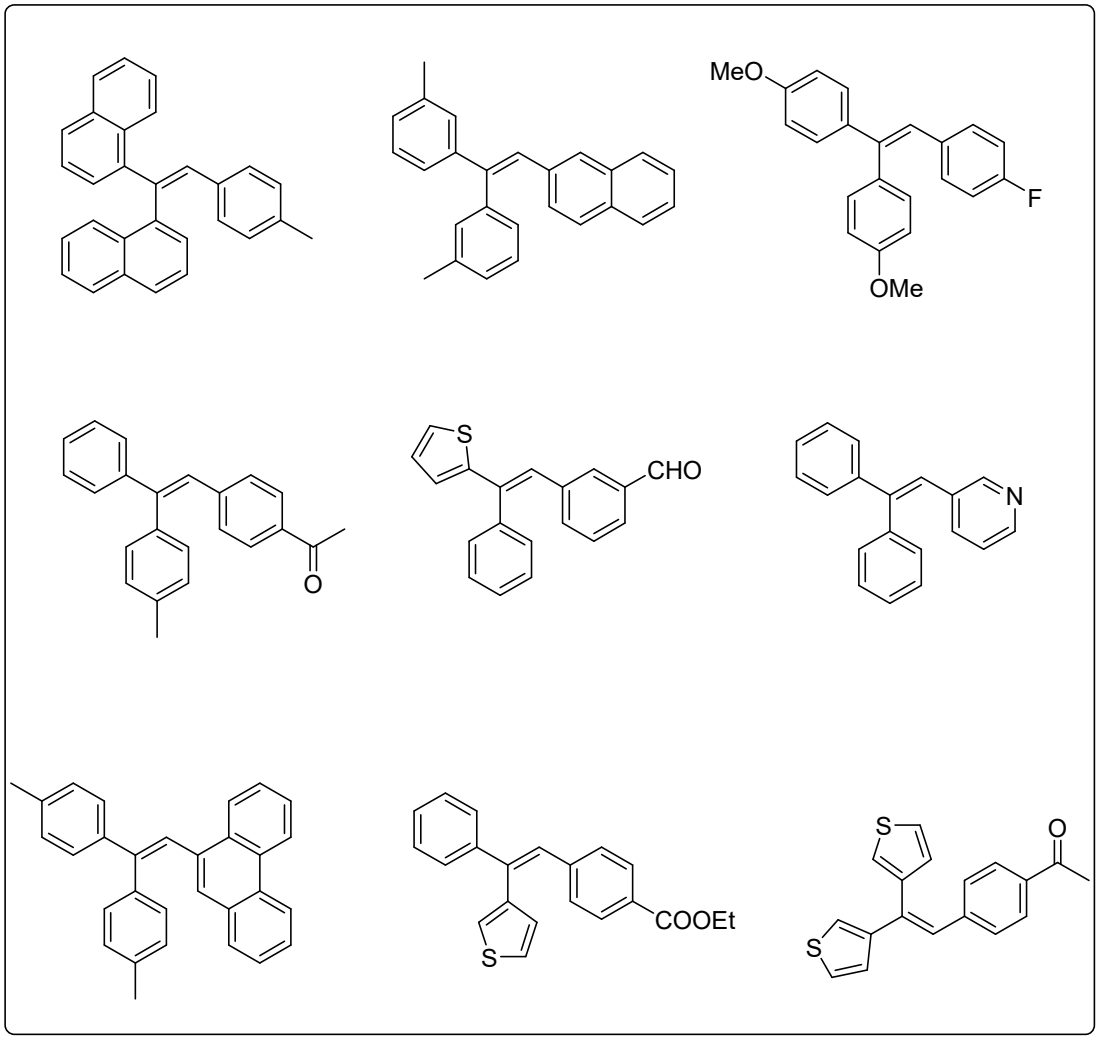


Figure 3. Trisubstituted olefins as organic electroluminescence devices.

Trisubstituted olefins obtained from trans-stilbene serve as starting point for synthesis of (Z)-tamoxifen, a tetra substituted olefin, which is used in the treatment of breast cancer[17] as shown in figure 4. This molecule belongs to category of selective estrogen receptor modulator (SERM).

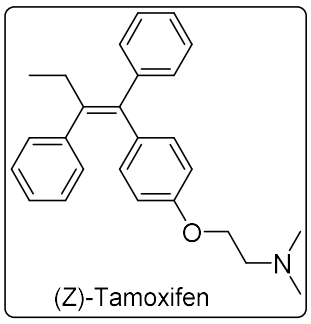


Figure 4. Structure of (Z)- Tamoxifen

A category of trisubstituted olefins is β,β-diaryl acrylates which are beneficial intermediates in the preparation of angiotensin II antagonists, SRS-A (slow-reacting substance of anaphylaxis) antagonists and platelet activating factor (PAF) antagonists.[18] To generate trisubstituted olefins Mizoroki-Heck reaction is preferred because of its E-stereoselective nature. Several β,β-diaryl acrylates can be constructed using Wadsworth-Emmons reaction but it leads to 1:1 mixture of *trans* and *cis* isomers.[18c] Aldol condensation related methodologies also yield mixtures of isomers.[18c]

2.2 Objective

Variables of synthesis as the chapter name suggests are nothing but reaction parameters of a reaction which in the case of Mizoroki-Heck reaction are ligand, catalyst, additive, coupling partner (aryl halides and olefins), temperature, base and solvent. Our aim is to vary either one or more or add / remove reaction parameter of a reaction so as to decrease bulk of experimentation and hit the optimum conditions. This is done to construct a simple, general protocol which accommodates sterically and electronically diverse array of 1,2-disubstituted olefins and aryl iodides and is also in combination with our approach to develop an efficient process for stereoselective Mizoroki-Heck arylation of 1,2-disubstituted olefins as geometrically pure isomer is necessary for bioactivity.

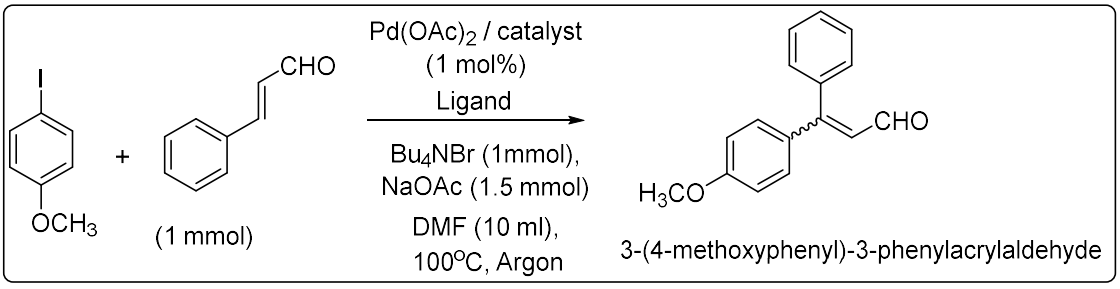
Mizoroki-Heck reaction of 1,2-disubstituted olefins presents a significant room for improvement as these olefins are difficult substrates, requiring long reaction times and special reagents as documented in literature. This study was chosen because 1,2-disubstituted olefins are readily available or easily synthesized and structural diversity is also vast. Thus Mizoroki-Heck reaction on these substrates will generate plethora of trisubstituted analogues that have wide applicability. In this chapter we report our progress towards fulfilling this intention.

Section A: Ligand and catalyst as variables of synthesis for Mizoroki-Heck reaction.

2A.1 Present work

Our present study involves thorough investigation of ligands and catalysts that will allow us to get an idea of what composition of catalyst / ligand cocktail will manifest best yield along with stereoselectivity. For this we chose trans-cinnamaldehyde as model 1,2-disubstituted olefin and 4-Iodoanisole as model aryl iodide. The reaction is as shown in scheme 10.

Scheme 10



The results of scheme 10 are summarized in Table 1.

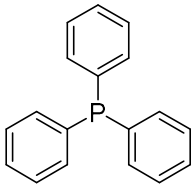
Table 1: Ligand and catalyst screening for Mizoroki-Heck reaction on trans-cinnamaldehyde.

Sr. No.	Ligand / catalyst	Yield (%)	E:Z ratio [d]	Time (hr)
1.[a]	Triphenylphosphine (2 mol%)	86	1:0.6	4
2.[a]	Tri(o-tolyl)phosphine (4 mol%)	99	1.7:1	24
3.[a]	1,2-bis(diphenylphosphino)ethane (2.1 mol%)	85	1.61:1	20
4.[a]	1,1'-bis(diphenylphosphino)ferrocene (2.1 mol%)	72	1.6:1	20
5.[b]	Johnphos (4 mol%)	65	1.37:1	21
6.[b]	Xphos (4 mol%)	71	1.6:1	20
7.[b]	Sphos (4 mol%)	81	1.5:1	20

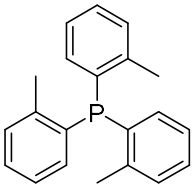
Sr. No.	Ligand / catalyst	Yield (%)	E:Z ratio [d]	Time (hr)
8.[b]	(R)-BINAP (4 mol%)	60	1.8:1	24
9.[b]	Xantphos (2.1 mol%)	91	1.5:1	19
10.[b]	Acetophenone oxime palladacycle [c]	66	1.6:1	23
11.[a]	Herrmann-Beller palladacycle [c]	79	1.6:1	22
12.[b]	Tris(2,4-di-tert-butylphenyl) phosphite palladacycle [c]	92	2:1	24
13.[a]	Acetophenone oxime (2.5 mol%)	93	1.5:1	24
14.[a]	L-Proline (2 mol%)	64	1:0.86	16
15.[a]	2-Thiophene carboxylic acid (2 mol%)	71	1:0.26	19
16.[a]	Tricyclohexylphosphine (2 mol%)	90	1:0.24	3
17.[a]	Tri-tert-butylphosphonium tetrafluoroborate (2 mol%)	96	1:0.08	5

[a] 1.2 mmol 4-Iodoanisole was used, [b] 1 mmol 4-Iodoanisole was used, [c] 1 mol% palladacycles were used, [d] E:Z ratio was determined by ^{1}H NMR

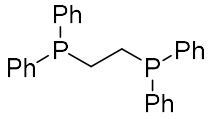
The structure of ligands and catalysts used in this study are depicted below in figure 5.



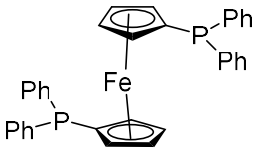
Triphenylphosphine



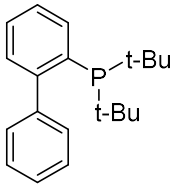
Tri(o-tolyl)phosphine



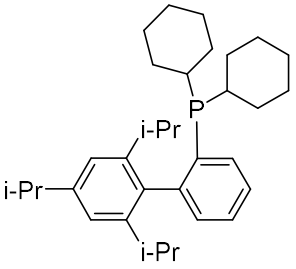
1,2-bis(diphenylphosphino)
ethane . dppe



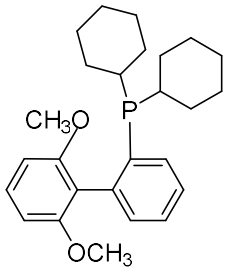
1,1'-bis(diphenylphosphino)
ferrocene . dppf



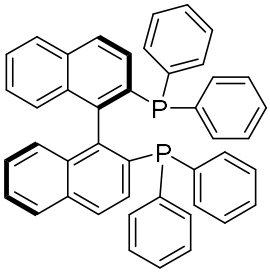
2-(Di-tert-butylphosphino)
biphenyl. Johnphos.



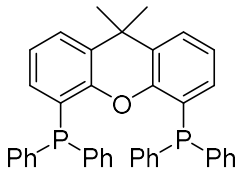
2-Dicyclohexylphosphino-2',4',6',-
triisopropylbiphenyl. XPhos



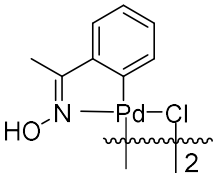
2-Dicyclohexylphosphino-2',6',
-dimethoxybiphenyl. SPhos



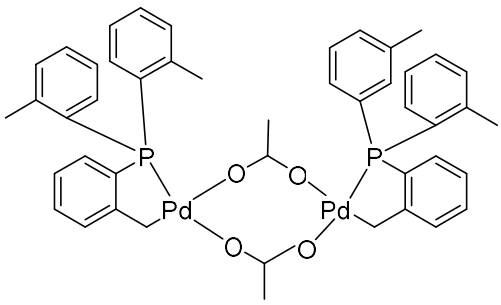
(R)-(+)-(1,1'-binaphthalene-2,2'-diyl)
bis (diphenylphosphine). (R)-BINAP



4,5-bis(diphenylphosphino)
-9,9-dimethylxanthene. Xantphos



Acetophenone oxime palladacycle



Herrmann Beller palladacycle

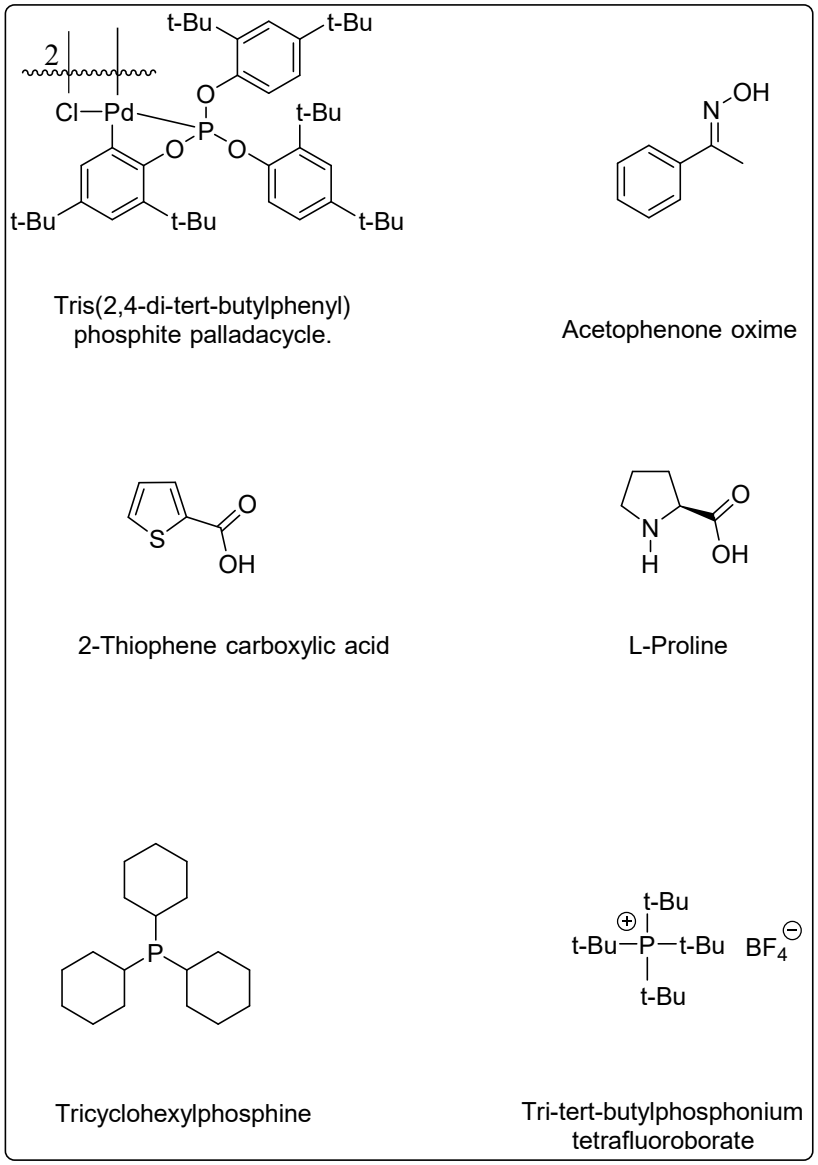
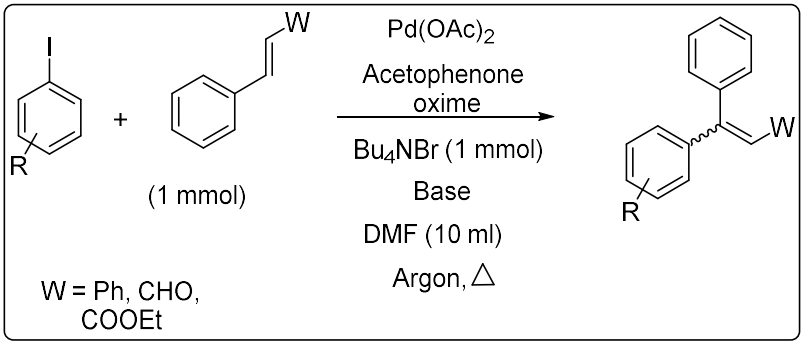


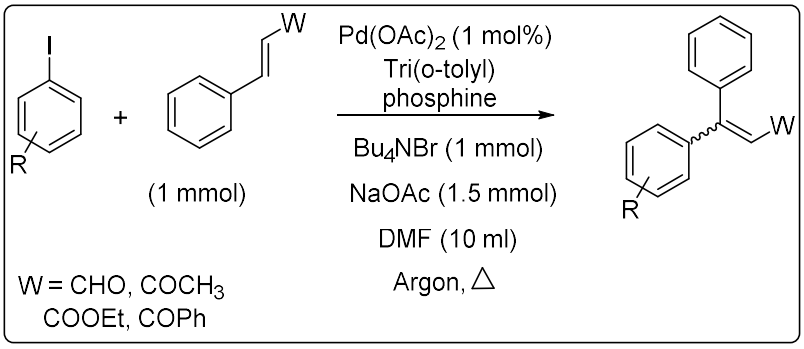
Figure 5: Structure of ligands and catalyst screened.

Next, we investigated Mizoroki-Heck reaction of 1,2-disubstituted olefins by varying aryl iodide and olefin but keeping ligand as a constant parameter. Three ligands were randomly selected for our study as acetophenone oxime (non-phosphine ligand), Tri(o-tolyl) phosphine (monodentate phosphine ligand) and racemic BINAP (chelating bidentate phosphine). Scheme 11, 12 and 13 depict Mizoroki-Heck reaction of disubstituted olefins by acetophenone oxime, Tri(o-tolyl) phosphine and racemic BINAP as ligands respectively.

Scheme 11



Scheme 12



Scheme 13

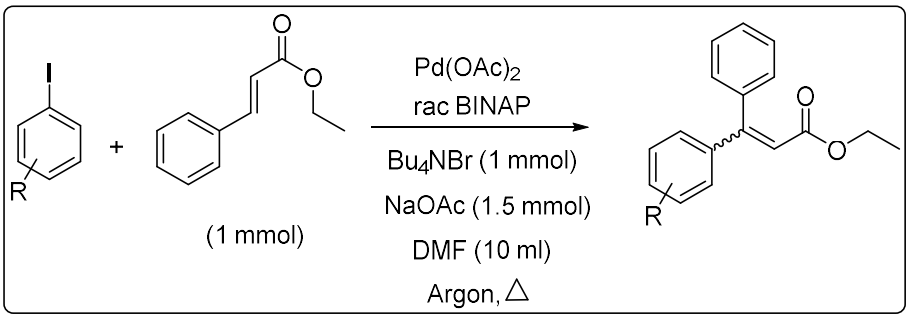
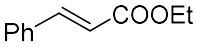
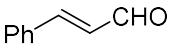
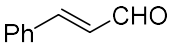
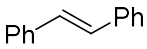
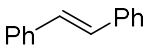


Table 2 depicts Mizoroki-Heck reaction of 1,2-disubstituted olefins using acetophenone oxime as ligand.

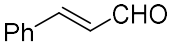
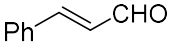
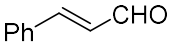
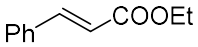
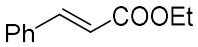
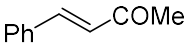
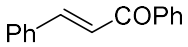
Table 2: Acetophenone oxime ligand mediated Mizoroki-Heck reaction.

Sr. No.	Aryl iodide	Olefin	Base	Yield (%) & E:Z ratio [f]	Time (hr)
1.[a]	4-$CH_3OC_6H_4I$		NaOAc (1.5 mmol)	64 (2.6:1)	40
2.[b]	4-ClC_6H_4I		NaOAc (1.5 mmol)	85 (1.4:1)	55
3.[c]	4-FC_6H_4I		NaOAc (1.5 mmol)	85 (1.2:1)	48
4.[d]	C_6H_5I		K_2CO_3 (2 mmol)	41	44
5.[e]	4-$CH_3OC_6H_4I$		K_2CO_3 (2 mmol)	49 (2:1)	48

[a] 2 mol% $Pd(OAc)_2$, 5 mol% ligand, 1.2 mmol aryl iodide, temp: 100°C then increased to 130°C after 7 hrs, [b] 1.5 mol% $Pd(OAc)_2$, 3 mol% ligand, 1.2 mmol aryl iodide, temp: 100°C, [c] 1 mol% $Pd(OAc)_2$, 4 mol% ligand, 1.2 mmol aryl iodide, temp: 100°C, [d] 2 mol% $Pd(OAc)_2$, 4 mol% ligand, 1 mmol aryl iodide, 1.5 mmol olefin, 4 ml DMF, temp: 130°C, [e] 2 mol% $Pd(OAc)_2$, 4 mol% ligand, 1 mmol aryl iodide, 1 mmol olefin, 4 ml DMF, temp: 120°C. [f] E:Z ratio was determined by ^1H NMR

Table 3 depicts Mizoroki-Heck reaction of 1,2-disubstituted olefins using Tri(o-tolyl) phosphine as ligand.

Table 3: Tri(o-tolyl) phosphine ligand mediated Mizoroki-Heck reaction.

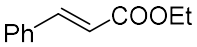
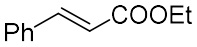
Sr.No.	Aryl iodide	Olefin	Yield & E:Z ratio [h]	Time (hr)	Temp (°C)
1.[a]	4-$CH_3C_6H_4I$		91 (1.3:1)	24	100
2.[b]	4-ClC_6H_4I		90 (1:1)	24	100
3.[c]	4-FC_6H_4I		99 (1.1:1)	24	100
4.[d]	4-$CH_3OC_6H_4I$		83 (2.4:1)	24	130
5.[e]	4-FC_6H_4I		86 (9:1)	24	145
6.[f]	4-$CH_3OC_6H_4I$		87 (1.1:1)	16	130
7.[g]	4-$CH_3OC_6H_4I$		94 (2.8:1)	21	130

[a, b, c, d] 1 mol% $Pd(OAc)_2$, 4 mol% ligand, 1 mmol aryl iodide. [e] 1 mol% $Pd(OAc)_2$, 4 mol% ligand, 1.4 mmol aryl iodide, [f, g] 1 mol% $Pd(OAc)_2$, 2 mol% ligand, 1.2 mmol aryl iodide

[h] E:Z ratio was determined by ^1H NMR

Table 4 depicts Mizoroki-Heck reaction of ethyl cinnamate using racemic BINAP as ligand.

Table 4: Racemic BINAP ligand mediated Mizoroki-Heck reaction.

Sr. No.	Aryl iodide	Olefin	Yield & E:Z ratio [c]	Time (hr)
1.[a]	4-$CH_3C_6H_4I$		70 (1.2:1)	24
2.[b]	4-ClC_6H_4I		99 (4.5:1)	24

[a] 1.5 mol% $Pd(OAc)_2$, 2.6 mol% ligand, 1 mmol aryl iodide, temp: 130°C

[b] 1 mol% $Pd(OAc)_2$, 2.1 mol% ligand, 1.4 mmol aryl iodide, temp: 145°C

[c] E:Z ratio was determined by ^1H NMR

2A.2 Results and Discussion

To the best of our knowledge, a comprehensive ligand survey for Mizoroki-Heck reaction of 1,2-disubstituted olefins with aryl iodides had not been described. Thus, we created a model system of 4-Iodoanisole as aryl iodide and trans-Cinnamaldehyde as 1,2-disubstituted olefin and Mizoroki-Heck reactions were investigated under the conditions presented in scheme 10. For scheme 10 described above we employed catalyst loading of 1 mol% and a moderate ligand loading of 2-4 mol%. As our aim was a quick survey of ligands affording best yields and high E/Z diastereoselection, we did not strive to independently optimize the catalyst and ligand loading for each i.e. individual coupling thus reducing bulk of experimentation. The olefin geometries (E or Z) were designated on the basis of analogy with known compounds as well as on the general notion that Mizoroki-Heck reactions generally yield E diastereomer as the major product.

The product of this study obtained when we were able to forge requisite C-C bond was 3-(4-methoxyphenyl)-3-phenylacrylaldehyde (1a) as E: Z mixture of varying ratios with E-isomer as the major diastereomer in the product. In ^{1}H NMR spectrum the signals at δ 9.6 (d, 1H, E isomer, J=8.01 Hz) and δ 9.49 (d, 1H, Z isomer, J=8.01 Hz) confirmed the presence of aldehydic proton of the E: Z mixture of obtained trisubstituted olefin. The signals at δ 7.51-7.26 (m, 7H) and δ 7.01-6.92 (m, 2H) were of the aromatic protons of the product. The signals at δ 6.60 (d, 1H, Z isomer, J=8.01 Hz) and δ 6.56 (d, 1H, E isomer, J=8.01 Hz) were of the lone olefinic proton of the obtained trisubstituted olefin product. Finally, the signals at δ 3.91 (s, 3H, E isomer) and δ 3.87 (s, 3H, Z isomer) affirmed the presence of methoxy group of the product. The ^{13}C NMR spectrum exhibited signal at δ 193.41 indicating carbonyl carbon of the aldehydic group. The signal at δ 55.34 manifested methoxy carbon. The IR spectrum unveiled an absorption at 1657 cm^{-1} indicating conjugated α,β-unsaturated enal system. The HRMS (ESI^{+}) peak at 239.106 corresponding to formula $C_{16}H_{15}O_2$ $[M + H]^{+}$ (calculated value 239.106) confirms the formation of product.

We started of with the simplest of known, mostly encountered trivial phosphine, Triphenylphosphine. Next, we tried slightly hindered, electron donating Tri(o-tolyl) phosphine, a derivative of triphenylphosphine. Yields obtained were excellent but stereoselectivity was modest (Table 1, entry 1 & 2).

We next turned our attention to chelating phosphine ligands in order to improve stereoselectivity of our system. Although dppe and dppf gave good yields of the product,

stereoselectivity once again in this case was low, but comparable with Tri(o-tolyl) phosphine (Table 1, entry 3 & 4, 85-72% yield respectively, E: Z: 1.61: 1). However, when (R)-BINAP was employed there was slight increase in E: Z diastereoselection with drop in yield of the product (Table 1, entry 8, 60% yield, E: Z: 1.8: 1).

Phosphines ligands have revolutionized transition metal promoted reactions as electronic and steric properties of this class of ligands can be modulated readily and independently, permitting modulation of coordinated species, enabling required properties of the complex to augment at separate steps of catalytic cycle. Thus, a new class of phosphine ligands based on dialkylbiaryl phosphane backbone that are air stable was developed which was widely employed in organometallic reactions. This caught our attention and we decided to check the utility of few structurally related variants of these class of ligands. Thus, when Johnphos, Xphos and Sphos were implemented in our study, good yields were obtained but our efforts to increase stereoselectivity was once again proved to be futile (Table 1, entry 5, 6 & 7, 65-81% yield respectively, E: Z: 1.37-1.6: 1).

As our efforts to increase E: Z diastereoselection were continuously thwarted, this did not dampen our spirits and we decided to investigate new class of diphosphine ligands, specially designed to promote large P-M-P angles due to rigid heterocyclic aromatic backbone of the xanthene type. Thus, when Xantphos was used, yield improved but there was no appreciable increase in E: Z ratio (Table 1, entry 9, 91% yield, 1.5:1: E: Z).

In order to get a combination of best yield and selectivity we decided next to investigate palladacycles which are nothing but palladium compound possessing single palladium-carbon bond stabilized intramolecularly either by one or two donor atoms (neutral), where the organic moiety functions as a C-anionic four or six electron donor ligands. Palladacycles required for this study were synthesized according to literature procedure and used directly for reaction[19]. When well-known acetophenone oxime palladacycle and Herrmann-Beller palladacycle were employed moderate to good yields were obtained with absolutely same modest E: Z ratio (Table 1, entry 10 and 11, 66-79% yield respectively, 1.6:1: E: Z). With Bedford palladacycle i.e. Tris(2,4-di-tert-butylphenyl) phosphite palladacycle, there was slight improvement in yield and E: Z ratio (Table 1, entry 12, 92% yield, E: Z: 2:1).

We were also curious to investigate non-phosphine ligands and check their utility in Mizoroki-Heck reaction of 1,2-disubstituted olefins with aryl iodides. From a plethora of non-

phosphine ligands, three ligands were randomly selected and investigated. These were acetophenone oxime, L-Proline and 2-Thiophene carboxylic acid.

Acetophenone oxime in cyclometallated form has been used as acetophenone oxime palladacycle in cross couplings and Mizoroki-Heck reactions[19b]. What reactivity does acetophenone oxime in naked form i.e. non-bonded to palladium displays on our system was the question we asked ourselves. Employing this ligand gave excellent yield with comparable E: Z diastereoselection shown by phosphine ligands (Table 1, entry 13, 93% yield, E: Z: 1.5:1). When compared with acetophenone oxime palladacycle yield was far much better although with a bit of drop in E: Z ratio (Table 1, entry 10).

L-Proline has been widely used in asymmetric catalysis and organocatalysis. L-Proline in the form of Pd(L-Proline)$_2$ complex has been used by Krishna Nand Singh and co-workers as phosphine free protocol for Mizoroki-Heck reactions of olefins (monosubstituted) with aryl iodides and bromides[20a]. Employing L-Proline ligand for our system resulted in moderate yield and stereoselectivity (Table 1, entry 14, 64% yield, E: Z: 1:0.86).

2-Thiophene carboxylic acid in the form of CuTC i.e. Copper (I) Thiophene-2-carboxylate has been used by Liebeskind *et al.* for Ullmann like reductive coupling of alkenyl, heteroaryl and aryl halides at ambient temperature [20b]. Utilizing this ligand on our model system exhibited good yield and E: Z diastereoselection (Table 1, entry 15, 71% yield, E: Z: 1:0.26).

There are primarily two classifications of phosphine ligands as triaryl phosphines and trialkyl phosphines. The change in structure leads to change in reactivity and there is growing evidence that trialkyl phosphines can provide reactivity that is generally not acquired with triaryl phosphines; this dichotomy undoubtedly arises from differences between these two families of phosphines in shape/sterics and electron richness (in general, trialkyl phosphines >> triaryl phosphines). Based on this rationale we decided to utilize two of the most common trialkyl phosphine ligands for our model system. Using tricyclohexyl phosphine resulted in good E:Z ratio and yield (Table 1, entry 16, 90% yield, E: Z: 1:0.24). But when Tri-tert-butylphosphonium tetrafluoroborate (a phosphonium salt acting as a precursor to phosphine ligand in order to prevent it from oxygen and moisture) ligand was employed we were able to achieve best combination of E: Z diastereoselection and yield (Table 1, entry 17, 96% yield, E: Z: 1:0.08).

Having reasonably established the ligand studies on trans-Cinnamaldehyde as model 1,2-disubstituted olefin we were curious to investigate the effect of ligands on broad array of

disubstituted olefins and aryl iodides and check its utility in organic synthesis as particular ligand behaves differently with a different disubstituted olefin and aryl iodide. Thus, randomly three ligands were chosen for our study as acetophenone oxime ligand (a non-phosphine ligand), Tri(o-tolyl) phosphine, (a hindered monophosphine ligand) and racemic BINAP, (a chelating diphosphine ligand).

Acetophenone oxime mediated reaction conditions are depicted in scheme 11 and results tabulated in table 2. Entries 1-5 of table 2 establish that this catalyst and ligand combination effects Mizoroki-Heck coupling of 1,2-disubstituted olefins with aryl iodides. Coupling of 4-Iodoanisole with ethyl cinnamate resulted in respectable yield and E: Z stereoselection (Table 2, entry 1). Electron deficient aryl iodides reacted with trans-Cinnamaldehyde to give identical good yields with approximately same E: Z ratio (Table 2, entry 2 & 3). With trans-Stilbene as olefin reasonable yields were obtained using electron neutral and electron rich aryl iodide employing K_2CO_3 as base (Table 2, entry 4 & 5).

Tri(o-tolyl) phosphine mediated coupling is delineated in scheme 12 and table 3. Excellent product yield is obtained when trans-Cinnamaldehyde is coupled with 4-Iodotoluene (Table 3, entry 1), the same yield and same, normal E: Z ratio was obtained when 1-Chloro-4-Iodobenzene was employed (Table 3, entry 2). However, with 4-Fluoroiodobenzene excellent yield with same, normal E: Z ratio was obtained (Table 3, entry 3). Ethyl cinnamate coupled with aryl iodides showed promising results. Although high yields were obtained with both 4-Iodoanisole and 4-Fluoroiodobenzene, it was with the latter aryl iodide that excellent E: Z diastereoselection was obtained (Table 3, entry 4 & 5). Benzalacetone and trans-Chalcone showed promising results with electron donating aryl iodide, 4-Iodoanisole (Table 3, entry 6 & 7).

As illustrated in scheme 13 and table 4 racemic BINAP exhibits quite high yields and good stereoselection when ethyl cinnamate is employed as olefin partner. 4-Iodotoluene, an electron donating aryl iodide results in good yield (Table 4, entry 1). A dramatic rise in yield and stereoselection is observed when para substituted mildly electron withdrawing aryl iodide is coupled with ethyl cinnamate (Table 4, entry 2).

2A.3 Conclusion

We have demonstrated that Mizoroki-Heck arylation of 1,2-disubstituted olefins can be mediated by ligands and allows construction of trisubstituted olefins in all instances. Tri-tert-butylphosphonium tetrafluoroborate exhibits best combination of E: Z diastereoselection and yield. Other ligands fare well in terms of yield and modestly in terms of stereoselectivity. This method is suitable for coupling of both electron rich and electron deficient substrates and exhibits a high level of functional group compatibility.

Section B: Exploring ligand less Mizoroki-Heck reaction in tetrabutyl ammonium bromide or polyethylene glycol as solvent.

2B.1 Introduction

''Agite, Auditores ornatissimi, transeamus alacres ad aliud negotii! quum enim sic satis excusserimus ea quatuor Instrumenta artis, et naturae, quae modo relinquimus, videamus quintum genus horum, quod ipsi Chemiae fere proprium censetur, cui certe Chemistae principem locum prae omnibus assignant, in quo se jactant, serioque triumphant, cui artis suae, prae aliis omnibus effectus mirificos adscribunt. Atque illud quidem Menstruum vocaverunt.'')[21]

Hermannus Boerhaave (1668-1738)

De menstruis dictis in chemia, in:

Elementa chemiae (1733)

Above quote translated in English means,

"Well then, my dear listeners, let us continue with fervor to another problem! Having sufficiently scrutinized in this manner the four resources of science and nature, which we are about to leave (i.e. fire, water, air and earth) we must examine a fifth element which can almost be considered the most vital part of chemistry itself, which chemists boastfully, no doubt with reason, favour above all others, and because of which they triumphantly celebrate, and to which they ascribe above all others the marvellous effects of their science. And this they call as the solvent (menstruum)."

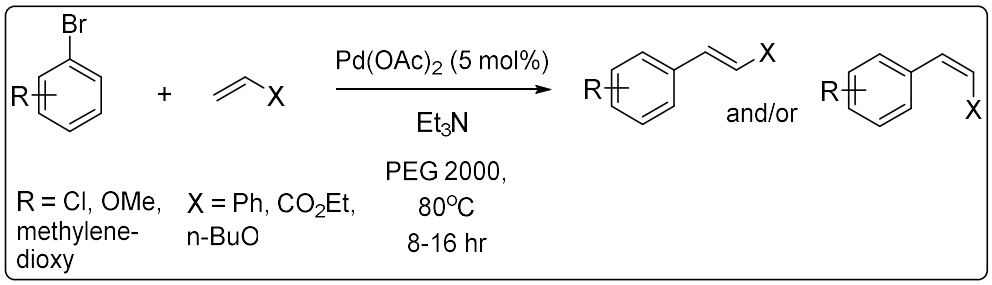
Above quote simply explains the importance of solvent. Solvents are extensively utilized in organic synthesis and plays pivotal role in making the overall reaction homogeneous and permitting molecular interactions to be extra effective but use of solvents in chemistry comes with a price, the major disadvantage being solvents as volatile organic compounds (VOCs), possessing pyrophoric nature and having poor recovery. Thus, from environmental point of view solvents are unsafe. Also, solvents rank highly on the list of damaging chemicals, as they are frequently used in vast amounts both in academia and industry and since they are volatile liquids that are difficult to hold. To address these issues, efforts have been made to design

solvent-free chemistry, which has been fruitful for some transformations.[22] Another approach adopted was the concept of "*organic reactions in water*".[23] This approach is least popular as most of the organic substrates are incompatible with aqueous media. Use of supercritical carbon dioxide as a reaction medium has been tried.[24] This system suffers from the drawback that it is an "under-pressure" system and it releases greenhouse CO_2 gas.

Another rapidly emerging class of compounds which can act as an alternative to solvents are polyethylene glycol and tetra alkyl ammonium salts. A very short literature summary of use of these compounds as solvents in Mizoroki-Heck reaction is presented below.

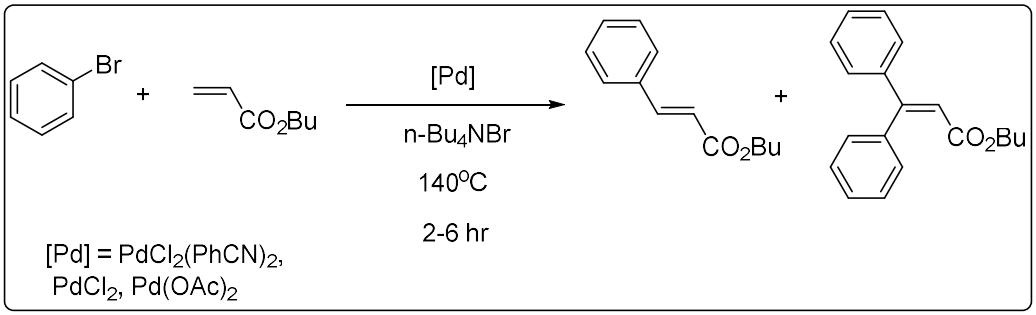
Chandrasekhar *et. al*. used PEG (polyethylene glycol) of molecular weight 2000 (or lower) as an effective reaction medium for Mizoroki-Heck reaction of monosubstituted olefins with aryl bromides.[25] It is as shown in scheme 14.

Scheme 14



Trzeciak *et. al.* demonstrated the use of molten tetrabutylammonium bromide as reaction medium for coupling of butyl acrylate with bromobenzene.[26] It is as depicted in scheme 15.

Scheme 15



Scheme 5 and scheme 7 of this chapter opening introductory part are the only examples of Mizoroki-Heck reaction of 1,2-disubstituted olefins in tetrabutylammonium bromide as reaction medium.

2B.2 Objective

Variables of synthesis in this part of our study is solvent. We chose to move away from traditional hazardous solvents used for Mizoroki-Heck reaction and adopt seemingly less hazardous and inexpensive polyethylene glycol (PEG) and tetrabutylammonium bromide (TBAB) as solvent for our study.

One parameter removed in our study is ligand. We also wanted to see the effect of ligand less catalyst system on yield and selectivity of Mizoroki-Heck reaction. Ligand free system is desirable, particularly for industrial applications. This system coupled with environmentally benign PEG and TBAB makes the overall process economically profitable and environmentally friendly.

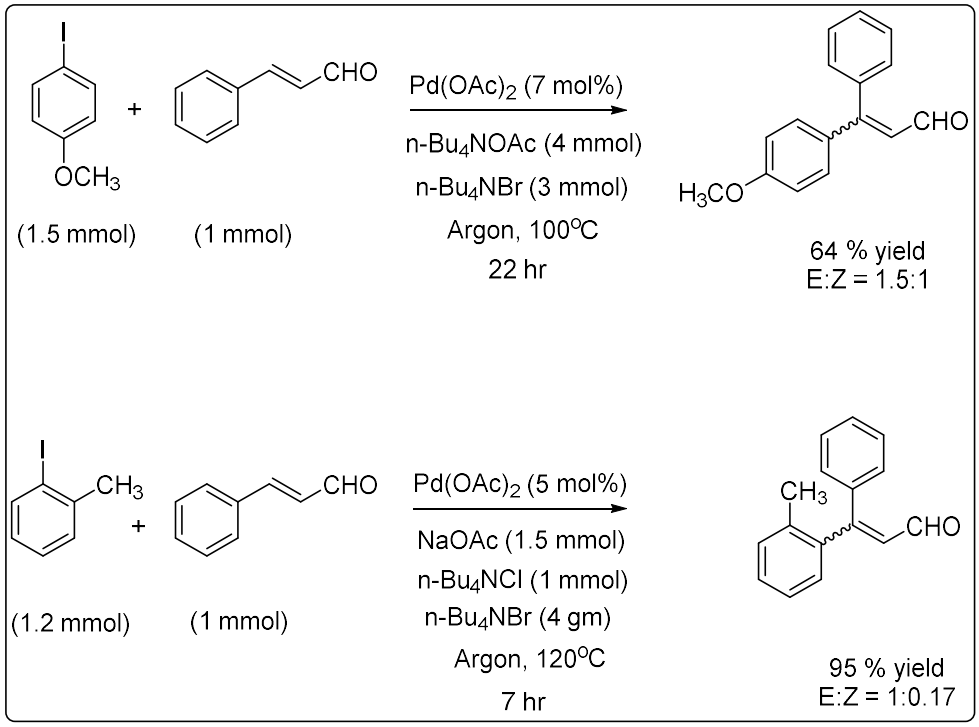
PEG was chosen for our study as it is inexpensive, significantly less hazardous, stable under ambient conditions (do not release VOCs as they have negligible vapour pressure) and have good stability in both acidic and basic media.

TBAB was chosen as it plays dual role of phase transfer agent and stabilising metal (Pd) colloids formed in situ, intercepting their accumulation to bigger size particles which are less active. Also, bromide ions provide ample electron density to the Pd^0 species instead of electron rich phosphines to smooth the oxidative addition step. Both PEG and TBAB if used on industrial scale can be reused simply by extracting the reaction mixture with ether.

2B.3 Present work

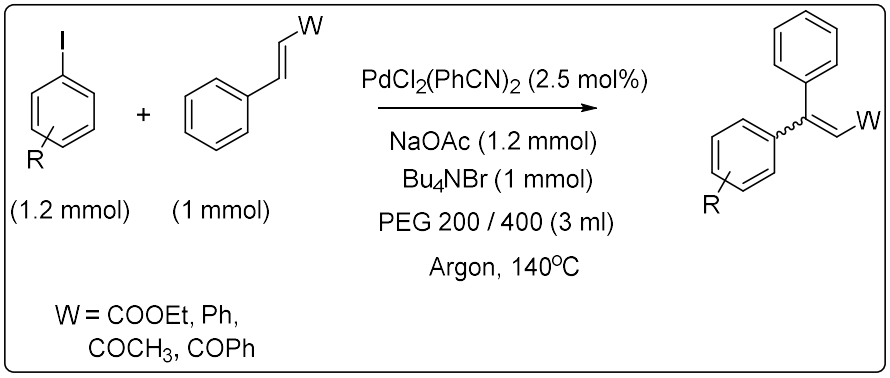
We investigated the use of TBAB in reaction of trans-cinnamaldehyde as model olefin with 4-Iodoanisole and 2-Iodotoluene as aryl iodides. In one case we used tetrabutylammonium acetate as base and in second case we used sodium acetate as base coupled with tetrabutylammonium chloride as additive. We were able to get good to excellent yields. This is presented in scheme 16.

Scheme 16



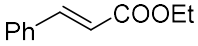
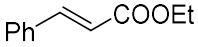
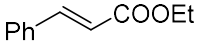
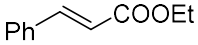
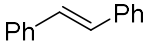
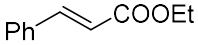
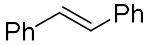
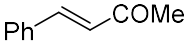
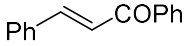
1,2-disubstituted olefins were reacted with aryl iodides in PEG 200 and its higher congener PEG 400 as solvent in presence of catalyst $PdCl_2(PhCN)_2$ to give Mizoroki-Heck products. It is represented in Scheme 17.

Scheme 17



The results of scheme 17 are summarized in Table 5.

Table 5: PEG as a solvent for Mizoroki-Heck reaction of 1,2-disubstituted olefins.

Sr. No.	Aryl iodide	Olefin	Solvent	Yield (%) & E:Z ratio [c]	Time (hr)
1.[a]	4-$CH_3OC_6H_4I$		PEG 200	66 (1:0.33)	18
2.	4-$CH_3OC_6H_4I$		PEG 200	75 (1:0.70)	22
3.	4-ClC_6H_4I		PEG 200	No reaction	27
4.	4-FC_6H_4I		PEG 200	No reaction	26
5.	4-$CH_3OC_6H_4I$		PEG 200	66 (1:1)	24
6.	4-FC_6H_4I		PEG 400	40 (1:0.60)	25
7.	2,4-FC_6H_3I		PEG 400	No reaction	25
8.[b]	4-$CH_3C_6H_4I$		PEG 400	Mixture	6
9.	4-$CH_3C_6H_4I$		PEG 400	43 (1:1)	20

[a] No TBAB (i.e. n-Bu_4NBr), [b] Mixture of Mizoroki-Heck & Michael adduct products, [c] E:Z ratio was determined by ^1H NMR

2B.4 Results and Discussion

Scheme 16 emphasizes the importance of n-Bu_4NBr as solvent in Mizoroki-Heck reaction. The coupling of 4-Iodoanisole with trans-Cinnamaldehyde using tetra n-butylammonium acetate as base with higher loading of palladium acetate (7 mol%) catalyst led to good yield and moderate selectivity (64% yield, E: Z: 1.5:1) after 22 hours of reaction.

The coupling of 2-Iodotoluene, a hindered ortho substituted aryl iodide, widely regarded as substrate known to undergo sluggish Mizoroki-Heck reaction coupled with trans-Cinnamaldehyde in presence of sodium acetate as base and tetra n-butylammonium chloride as additive under slightly elevated temperatures to give excellent yield and E: Z diastereoselection of coupled product (95% yield, E: Z: 1:0.17) within shorter reaction time (7 hr). Even slight decrease in molar ratio of aryl iodide to olefin (1.2:1) didn't affect the product yield.

Scheme 17 highlights the reaction conditions for use of polyethylene glycol as solvent and table 5 summarizes the substrate study. PEG 200 and PEG 400 were used interchangeably for this purpose.

Ethyl cinnamate reacted with 4-Iodoanisole to furnish good yield and E: Z ratio in PEG 200 as solvent. When additive n-Bu_4NBr was removed from reaction there was slight decrease in reaction yield (Table 5, entries 1 and 2) but increase in stereoselectivity.

Unfortunately, there was no product formation when ethyl cinnamate reacted with electron withdrawing aryl iodides even after considerable amount of reaction time (Table 5, entries 3 and 4) in PEG 200 as solvent but in PEG 400, we were able to achieve respectable yield and stereoselectivity (Table 5, entry 6, 40% yield, E: Z: 1:0.60) using 4-Fluoroiodobenzene, the same aryl iodide which failed to react in PEG 200 (entry 4).

trans-Stilbene coupled with 4-Iodoanisole in PEG 200 to furnish good yield but with poor stereoselectivity (Table 5, entry 5) but with 2,4-difluoroiodobenzene there was no product formation in PEG 400 (entry 7).

Whereas trans-Chalcone reacted with 4-Iodotoluene (entry 9) in PEG 400 to afford reasonable yield with equal E: Z diastereoselection, the same was not the case with Benzalacetone (entry 8). A mixture of Mizoroki-Heck and conjugate addition product was observed. Upon delving deeper into literature, we found that such systems are prone to both type of reactions and particular product yield depends upon reaction conditions and nature of

added base.[27] Switching from Bu_4NBr to Bu_4NCl and from NaOAc to $NaHCO_3$ excellent yields of Mizoroki-Heck products were observed.[28]

2B.5 Conclusion

The results illustrated above corroborate that Mizoroki-Heck reaction can be realized effectively with execution of simple catalytic system possessing phosphine free palladium precursor and molten tetrabutyl ammonium bromide as reaction medium.

Although small amount of conjugate addition product is formed in one case, and no reaction in some cases, detailed study is required to vanquish this problem to deploy low molecular weight PEG as an alternative reaction medium for Mizoroki-Heck reaction of 1,2-disubstituted olefins.

Section C: Silver sequestration of halides for activation of $Pd(OAc)_2$ catalyzed Mizoroki-Heck reaction of 1,2-disubstituted olefins.

2C.1 Introduction

Mizoroki-Heck reaction is an organic transformation that allows construction of C-C bonds between alkenyl motifs and aryl or alkenyl groups. This reaction has found widespread use in organic synthesis ranging from total synthesis of natural products to industrial processes. It has been found that some finer effects are caused by silver salt additives in this reaction i.e. addition of silver salts assists (facilitates) and boosts Mizoroki-Heck reactions. Silver salts have gained popularity as cocatalyst or catalyst in palladium mediated coupling reactions. They have been employed mainly for two reasons:

a) They are halogenophilic i.e. they can remove halides from organometallic intermediates making the metal (Pd) more electropositive and thus opening an empty site in the coordination sphere. The main role in such cases is formation of insoluble silver halides thereby activating the true catalytic species.

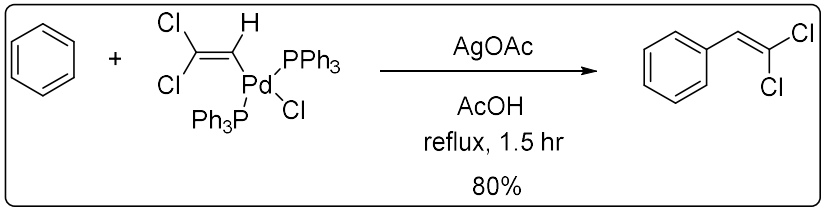
b) They can generate organosilver species which either reacts as such or transmetalates to various metals or organometallics, chiefly organopalladium intermediates.

Halide abstraction by silver ion alters the overall reaction pathway in Mizoroki-Heck reaction, which either suppresses alkene isomerization, promotes cyclisation or accelerates rate through cationic mechanism.

A short literature summary of use of silver additives in Mizoroki-Heck reaction is given below.

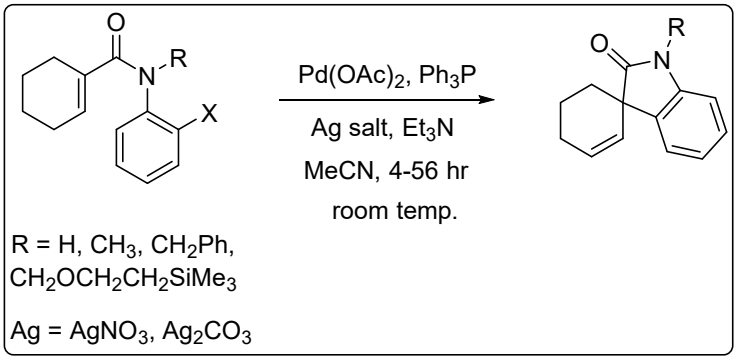
Moritani *et. al.* displayed vinylation of benzene with vinyl palladium (II) complexes promoted by silver acetate. This is the earliest example of silver abstracting halide from vinyl palladium species thus allowing the coordination of benzene feasible. The resulting intermediate complex, after reductive elimination generated vinylbenzene as shown in scheme 18.[29]

Scheme 18



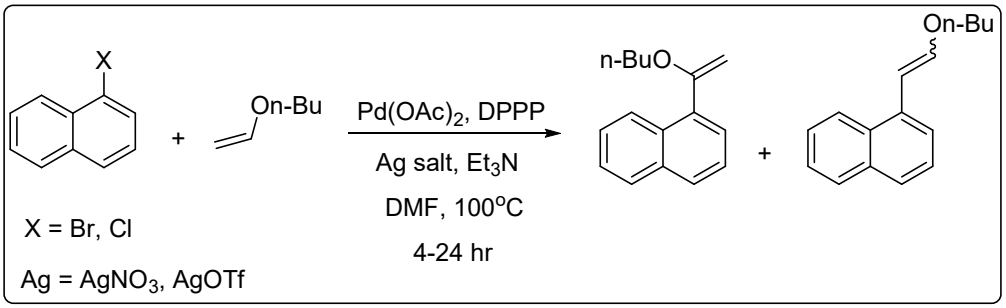
Overman *et. al.* outlined palladium catalyzed intramolecular Mizoroki-Heck cyclisation to construct tricyclic ring with quaternary centres. Their results showed that competing palladium catalyzed isomerization of cyclised alkene product can be greatly reduced by conducting cyclization in presence of silver salt at room temperature as shown in scheme 19.[30]

Scheme 19



Cabri *et. al.* exploited the use of silver (I) salts and thallium (I) salts in reaction between vinyl butyl ether and aryl halides to generate α– arylated product with high selectivity as shown in scheme 20.[31]

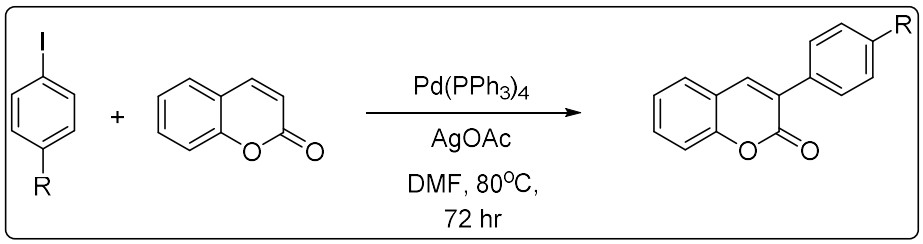
Scheme 20



Pereira *et. al*. used Mizoroki-Heck reaction to construct aryl coumarin derivatives regio selectively at 3rd position using silver acetate. Using AgOAc is beneficial in two ways as it

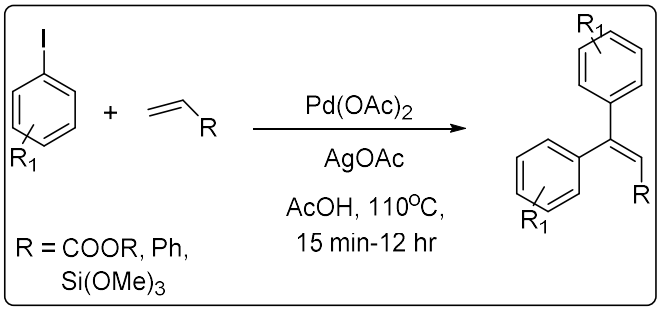
serves as a base and halide scavenger. This is useful if addition of stronger bases must be circumvented to control side reactions. This is represented in scheme 21.[32]

Scheme 21



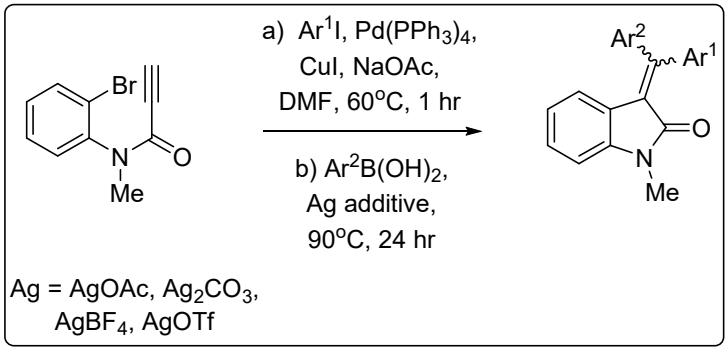
Chen *et. al.* reported Mizoroki-Heck diarylation of terminal olefins in acetic acid solvent under ligand free conditions using silver acetate as base. This procedure afforded trisubstituted olefins in good to excellent yield as shown in scheme 22.[33]

Scheme 22



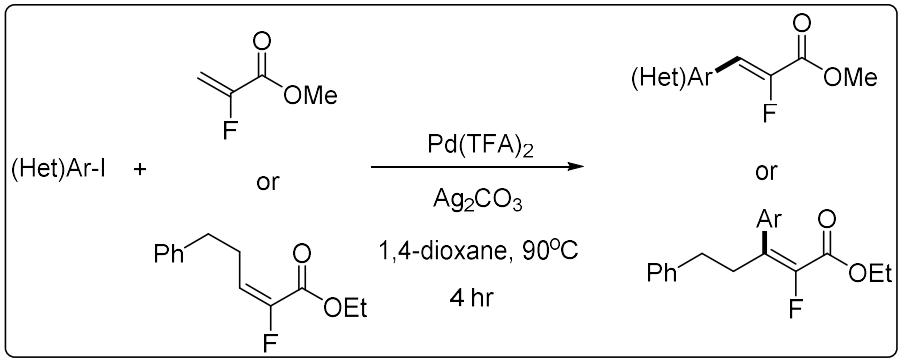
Construction of various 3- (diaryl methylene) oxindoles from simple propiolamides was shown by Jae Hong Seo and co-workers. Their methodology involved successive merger of three palladium promoted reactions (Sonogashira, Mizoroki-Heck and Suzuki-Miyaura). Dramatic enhancement in the E: Z stereoselectivity of the reaction was possible on addition of silver salts as shown in scheme 23.[34]

Scheme 23



Bonnaire *et.al.* displayed ligand free Mizoroki-Heck reaction between arene or hetero arene iodides and methyl α- fluoroacrylate to get trisubstituted fluoroalkenes. They also reported Mizoroki-Heck reaction on trisubstituted acrylate to get tetra substituted fluoroalkene as shown in scheme 24.[35]

Scheme 24



2C.2 Objective

Variables of synthesis in this part of our study is additive. We were curious to know the effect of silver salts as additive in Mizoroki-Heck reaction of 1,2 -disubstituted olefins with aryl iodides. As use of silver salts changes the overall pathway of reaction i.e. it leads the reaction by cationic pathway as opposed to neutral pathway in normal Mizoroki-Heck reaction, we were interested in seeing the outcome on yield and selectivity of Mizoroki-Heck products.

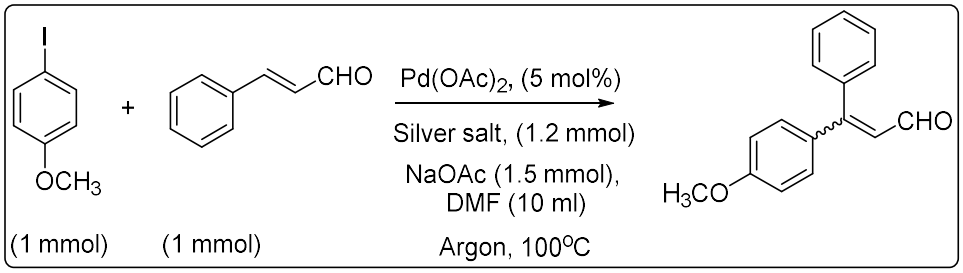
One parameter removed in our study is ligand. Ligand free systems (phosphines) are the need of hour as they are quite expensive and their use on an industrial scale increases the cost of product making overall process quite expensive.

Thus, avoiding highly expensive ligands and using moderately expensive silver salts our aim was to develop a ligand free, mild, efficient, general protocol encompassing broad spectrum of olefins and aryl iodides for β-arylation of 1,2-disubstituted olefins generating trisubstituted olefins in a least expensive way.

2C.3 Present work

For our investigation we created a model system which included 4-Iodoanisole as aryl iodide and trans-Cinnamaldehyde as 1,2 -disubstituted olefin. Two silver salts were selected for our study as silver acetate and silver tetrafluoroborate. From our previous study on Mizoroki-Heck reaction on 1,1-disubstituted olefins in acetic acid as solvent [36] where we achieved good to excellent yields our interest was more inclined to use normal solvent for our study as acetic acid was not a general-purpose solvent, so we decided to include N, N-Dimethylformamide as a mild, substrate tolerant general-purpose solvent for our study. Base (sodium acetate) was also chosen to see whether its inclusion enhances or diminishes reaction rate and yield. The reaction is as presented in scheme 25.

Scheme 25



The results of scheme 25 are summarized in table 6.

Table 6: Silver salt variation in Mizoroki-Heck.

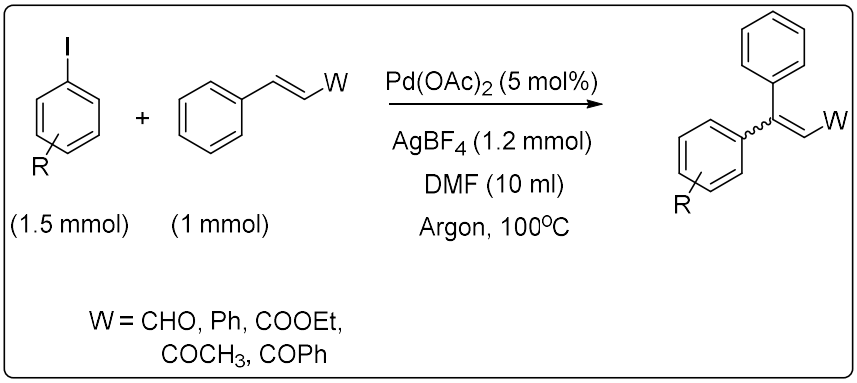
Sr. No.	Silver salt	Yield (%) & E:Z ratio [a]	Time (hr)
1.	AgOAc	68 (2:1)	10
2.	$AgBF_4$	99 (2.1:1)	3

[a] E:Z ratio was determined by ^1H NMR.

$AgBF_4$ gave best result confirming it as a stronger sequestering agent in comparison with silver acetate, selectivity being more or less the same. Here BF_4^- is a non-coordinating

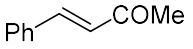
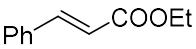
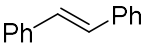
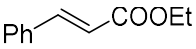
counterion. This prompted us to use silver tetrafluoroborate as silver additive to investigate its use in Mizoroki-Heck reaction of various 1,2-disubstituted olefins with different aryl iodides. We chose to remove base as a part of our study to see whether $AgBF_4$ alone is able to drive the reaction to completion or it needs an added base. The general reaction is as presented in scheme 26.

Scheme 26



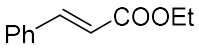
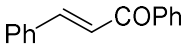
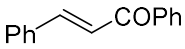
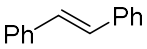
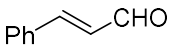
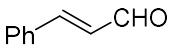
The results of scheme 26 are tabulated in table 7.

Table 7: $AgBF_4$ mediated Mizoroki-Heck reaction of 1,2-disubstituted olefins.

Sr. No.	Aryl iodide	Olefin	Yield (%) & E:Z ratio [c]	Time (hr)
1.	4-$CH_3C_6H_4I$		85 (1:1)	2
2.	4-$CH_3COC_6H_4I$		83 (2:1)	2
3.	4-$CH_3OC_6H_4I$		76 (2:1)	2
4.	4-$CF_3OC_6H_4I$		91 (14:1)	5

Continued on next page

Table 7: $AgBF_4$ mediated Mizoroki-Heck reaction of 1,2-disubstituted olefins.

Sr. No.	Aryl iodide	Olefin	Yield (%) & E:Z ratio [b]	Time (hr)
5.	4-$CH_3OC_6H_4I$		91 (3:1)	7
6.	4-$CH_3OC_6H_4I$		67 (2:1)	3
7.[a]	4-$CH_3COC_6H_4I$		83 (2:1)	3
8.[a]	4-$CH_3COC_6H_4I$		51 (1:0.07)	4
9.	4-$CH_3OC_6H_4I$		84 (2:1)	3
10.[a]	4-$CH_3COC_6H_4I$		97 (1:1)	3

[a] 1.2 mmol aryl iodide were used instead of 1.5 mmol. [b] E:Z ratio was determined by ^1H NMR.

2C.4 Results and Discussion

To gain an insight into the reactivity of silver salts in Mizoroki-Heck reaction of 1,2-disubstituted olefins with aryl iodides we zeroed in on two silver salts as they are easily available and very moderately expensive. At first, Mizoroki-Heck reaction of 4-Iodoanisole with trans-Cinnamaldehyde was probed under the conditions depicted in scheme 25 and results tabulated in table 6. With silver acetate (Table 6, entry 1) good yield with moderate stereoselectivity of the product was obtained. What was more astonishing was the use of silver tetrafluoroborate (Table 6, entry 2) yielding excellent yield with almost same stereoselectivity as that of silver acetate but with drastic reduction in reaction time (3 hr).

Having reasonably established the conditions of conversion, we proceeded with silver tetrafluoroborate as choice of additive with exclusion of base to screen a series of substrates which included arbitrary selection of aryl iodide and 1,2-disubstituted olefin. The general reaction is presented in scheme 26 and results compiled in table 7.

A high yield of product was obtained when Benzylideneacetone was coupled with 4-Iodotoluene to attain the product in 1:1 E: Z diastereoselection (Table 7, entry 1). trans-Stilbene threw up some bright results. With 4-Iodoanisole, good yield with moderate stereoselectivity of the product was noted (Table 7, entry 3), but with 4-Iodoacetophenone highest E: Z ratio

which was at par with Tri-tert-butylphosphonium tetrafluoroborate was noticed with slight drop in yield of product (Table 7, entry 8). trans-Chalcone reacted with 4-Iodoanisole and 4-Iodoacetophenone (Table 7, entries 6 & 7, 67-83% yield) to furnish product with same stereoselectivity. Ethyl cinnamate coupled with 4-Iodoacetophenone and 4-Iodoanisole to yield product in considerably high yield and moderate E: Z ratio (Table 7, entries 2 & 5) but with 4-(Trifluoromethoxy) Iodobenzene, drastic increase in E: Z diastereoselection was observed (Table 7, entry 4, E: Z: 14:1).

Finally, trans-Cinnamaldehyde reacted with 4-Iodoanisole (base exclusion) to exhibit high yield and moderate stereoselectivity (Table 7, entry 9). The product obtained when 4-Iodoacetophenone was coupled with trans-Cinnamaldehyde (entry 10) is (E)- 3-(4-acetylphenyl)-3-phenylacrylaldehyde (2a) obtained as E: Z mixture (1:1). In ^{1}H NMR spectrum the signals at δ 9.49 (d, 1H, J= 8Hz, E isomer) and δ 9.43 (d, 1H, J= 8Hz, Z isomer) confirmed the presence of aldehydic proton of the E: Z mixture of obtained trisubstituted olefin. The signals at δ 7.97(d, 1H, Z isomer) and δ 7.88 (d, 1H, E isomer) were of the lone olefinic proton of the obtained trisubstituted olefin product. The signals at δ 7.44-7.19 (m, 7H) and δ 6.55-6.54 (m, 2H) were of the aromatic protons of the product. Finally, the signals at δ 2.60 (s, 3H, Z isomer) and δ 2.55 (s, 3H, E isomer) affirmed the presence of methyl group of the product (-$COCH_3$ group). The HRMS (ESI^+) peak at 251.106 corresponding to formula $C_{17}H_{15}O_2$ $[M + H]^+$ (calculated value 251.106) confirms the formation of product.

Silver tetrafluoroborate mediated Mizoroki-Heck coupling gave good to excellent yields considering no ligands were employed. One feature worthy of note was drastic reduction in reaction time. Ligand studies (section A) and solvent studies (section B) took around 24 hours or longer to complete the reaction whereas by silver sequestration route within 2-7 hours reaction was accomplished.

Mechanistic aspects

A preferred mechanism is delineated in figure 6 based on the mechanism propounded by Heck. Aryl iodide oxidatively adds to palladium (0) to generate aryl palladium iodide species. Initial step is iodide extraction from the aryl palladium iodide which is mediated by silver. It results in generation of transition state aryl palladium tetrafluoroborate. It is hypothesized that transition state is then followed by an equilibrium embracing aryl palladium tetrafluoroborate, cationic aryl palladium species and tetrafluoroborate anion. Then insertion of the olefinic moiety and reductive elimination culminates in product formation. Typical Mizoroki-Heck coupling gives E-product, which is kinetically and thermodynamically favoured. The β-hydride

elimination requires that palladium and β-hydrogen atom are syn-coplanar. Also, free rotation of C-C single bond connected to palladium is not confined, consequently both E and Z products are created. Thus, silver salts are related with extraction of a halide anion, and therefore it drops behind a free coordination site for olefin binding.

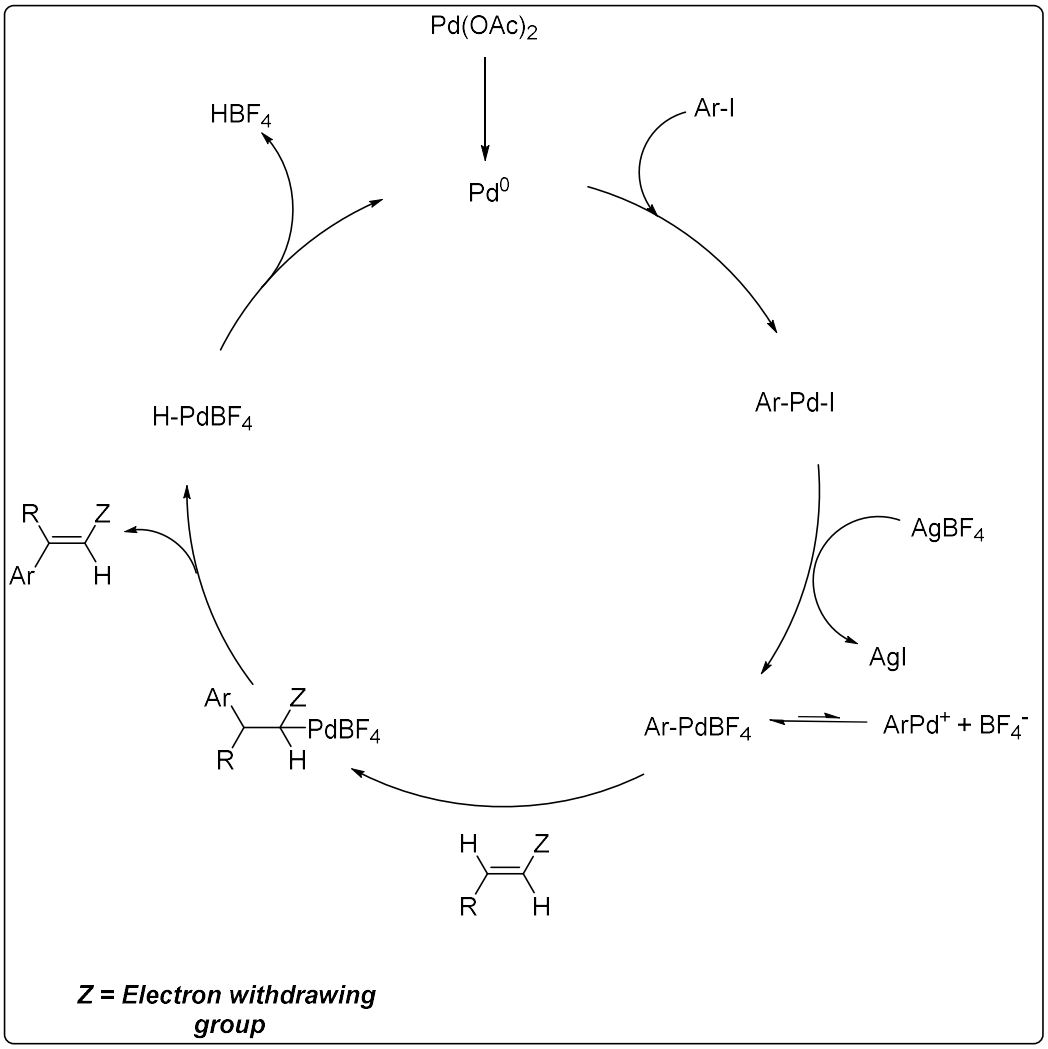


Figure 6: Plausible silver mediated mechanism.

2C.5 Conclusion

In summary, we have attempted to design a general method for the Mizoroki-Heck coupling of 1,2-disubstituted olefins with aryl iodides. The reaction conditions are outstanding:

1) It avoids toxic, air sensitive, highly expensive phosphine ligands making the whole process cost effective.

2) Avoids harsh experimental conditions (employs milder temperatures and shorter reaction times) making process simplified.

3) Accedes trisubstituted alkene formation using reluctant 1,2-disubstituted alkenes as partner in Mizoroki-Heck reaction.

4) Reaction tolerates diverse organic functionalities.

5) Employs DMF as more general-purpose solvent.

We anticipate that this study will provide a powerful stimulus to the development of application of silver salts in Mizoroki-Heck coupling and that this system will find wide applicability.

2.3 Experimental section

General procedure for ligand/catalyst mediated Mizoroki-Heck reaction of aryl iodides with 1,2-disubstituted olefins (Section A).

n-Bu_4NBr (1 mmol) and NaOAc (1.5 mmol) were added to an oven-dried two neck 25 ml round bottom flask equipped with stir bar and fitted with reflux condenser and rubber septum. The base of 25 ml round bottom flask was heated with hot air gun to melt the mixture under continuous gassing-degassing. Then the mixture was cooled under argon to solidify. Catalyst (1 mol%) or $Pd(OAc)_2$ (1 mol%) and ligand (2 or 4 mol%) were then introduced through second neck under argon flow. DMF (5 ml) was added via syringe through rubber septum and the mixture was stirred for five minutes to induce complex formation. Finally, aryl iodide (1.2 mmol) and 1,2-disubstituted olefin (1 mmol) dissolved in DMF (5 ml) were added via syringe. The septum was replaced with a Teflon stopcock, evacuated, refilled with argon and heated at 100°C (or indicated temperature) for the indicated amount of time. At the conclusion of the reaction, the mixture was diluted with EtOAc and washed three times with water. The organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel to afford pure product.

General procedure for ligand less Mizoroki-Heck reaction in tetra butyl ammonium bromide or polyethylene glycol as solvent (Section B).

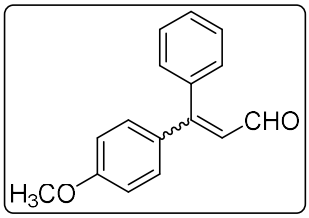
The aryl halide (1.2 mmol), the olefinic substrate (1 mmol), NaOAc (1.5 mmol), $Pd(OAc)_2$ (5 mol%) or $Pd(PhCN)_2Cl_2$ (2.5 mol%) and solvent (PEG 200/400, 3ml or n-Bu_4NBr, 4gm) were added to an oven-dried 25 ml single neck round bottom flask which was then sealed with reflux condenser and two way stopcock above it. The mixture was then purged with argon and heated at indicated temperature for the indicated amount of time. When the starting materials were consumed as determined by TLC, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc and washed three times with water. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to give the crude product. Purification by column chromatography afforded the analytically pure product.

General procedure for sequestration of halides by silver tetrafluoroborate in $Pd(OAc)_2$ catalyzed Mizoroki-Heck reaction of 1,2-disubstituted olefins (Section C).

To a solution of $AgBF_4$ (1.2 mmol) and palladium acetate (5 mol%) in DMF under argon, was added aryl iodide (1.5 mmol) and 1,2-disubstituted alkene (1 mmol). The resulting mixture was heated to 100°C under argon. After completion of reaction (monitored by TLC), water was added to quench the reaction. The aqueous solution was extracted three times with EtOAc and the combined extract was washed with brine and dried over Na_2SO_4. The organic layer was concentrated under vacuum and the crude product was purified by column chromatography on silica gel to give pure, desired product.

Experimental data

(E)-3-(4-methoxyphenyl)-3-phenylacrylaldehyde (1a)



Chromatography (92:8 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.214g, 90%), E: Z isomer ratio- 1:0.24.

R_f = 0.4 (petroleum ether/EtOAc, 80:20).

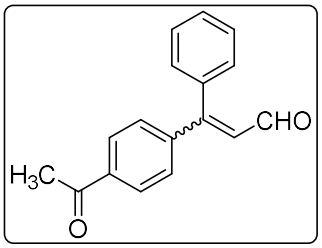
^{1}H NMR ($CDCl_3$, 500 MHz) δ = 9.6 (d, 1H, E isomer, J=8.01 Hz), 9.49 (d, 1H, Z isomer, J=8.01 Hz), 7.51-7.26 (m, 7H), 7.01-6.92 (m, 2H), 6.60 (d, 1H, Z isomer, J=8.01 Hz), 6.56 (d, 1H, E isomer, J=8.01 Hz), 3.91 (s, 3H, E isomer), 3.87 (s, 3H, Z isomer).

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 193.41, 162.18, 160.82, 140.25, 136.87, 132.47, 131.84, 130.60, 130.34, 130.24, 129.25, 128.96, 128.87, 128.50, 128.23, 127.00, 125.54, 114.02, 113.72, 55.34.

IR ($CHCl_3$) ν_{max} = 3019, 2961, 2930, 2844, 1657, 1603, 1511, 1463, 1443, 1421, 1388, 1344, 1295, 1217, 1180, 1158, 1129, 1032, 772, 669.

HRMS: *m/z* = calcd for $C_{16}H_{15}O_2$ $[M+H]^+$ 239.106, found: 239.106.

(E)- 3-(4-acetylphenyl)-3-phenylacrylaldehyde (2a)



Chromatography (92:8 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.256g, 97%), E: Z isomer ratio- 1:1.

R_f = 0.42 (petroleum ether/EtOAc, 80:20).

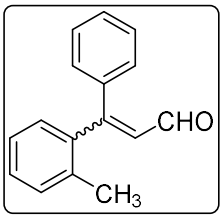
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 9.49(d, 1H, J=8Hz, E isomer), 9.43(d, 1H, J=8Hz, Z isomer), 7.97(d, 1H, Z isomer), 7.88 (d, 1H, E isomer), 7.44-7.19 (m, 7H), 6.55-6.54 (m, 2H), 2.60 (s, 3H, Z isomer), 2.55 (s, 3H, E isomer).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 197.34, 193.12, 192.69, 160.73, 160.62, 144.10, 138.91, 138.15, 135.99, 130.87, 130.63, 128.83, 128.49, 128.28, 127.67, 26.70.

IR ($CHCl_3$) ν_{max} = 3683, 3020, 2927, 2854, 2400, 1664, 1601, 1525, 1477, 1424, 1265, 1216, 1126, 1031, 928, 771, 669, 625.

HRMS: *m/z* = calcd for $C_{17}H_{15}O_2$ $[M+H]^+$ 251.106, found: 251.106.

(E)-3-phenyl-3-(o-tolyl) acrylaldehyde (3a)



Chromatography (94:6 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.210g, 95%), E: Z isomer ratio- 1:0.17.

R_f = 0.46 (petroleum ether/EtOAc, 80:20).

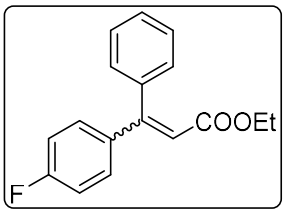
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 9.74(d, 1H, E isomer, J=8Hz), 9.38(d, 1H, Z isomer, J=8Hz), 7.45-7.20 (m, 9H), 6.71 (d, 1H, Z isomer, J= 8Hz), 6.26 (d, 1H, E isomer, J=8Hz), 2.07 (s, 3H, Z isomer), 2.05 (s, 3H, E isomer).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 193.40, 163.23, 140.72, 137.43, 136.14, 130.92, 130.39, 128.24, 127.50, 125.86, 20.48.

IR ($CHCl_3$) ν_{max} = 3019, 2400, 1662, 1594, 1445, 1217, 1124, 1046, 928, 771, 669.

HRMS: *m/z* = calcd for $C_{16}H_{15}O$ $[M+H]^+$ 223.111, found: 223.112.

(E)-Ethyl 3-(4-fluorophenyl)-3-phenylacrylate (4a)



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.109g, 40%), E: Z isomer ratio- 1:0.60.

R_f = 0.40 (petroleum ether/EtOAc, 90:10).

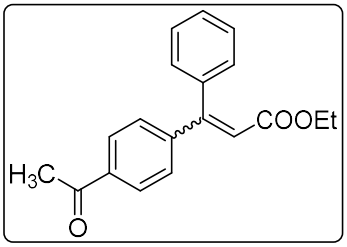
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.40-6.96 (m, 9H), 6.35 (s, 1H, Z isomer), 6.31 (s, 1H, E isomer), 4.13-3.99 (m, 2H), 1.19-1.07 (m, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 165.96, 165.14, 160.99, 155.52, 155.28, 140.73, 138.78, 136.94, 134.77, 131.14, 130.20, 129.04, 128.26, 127.93, 117.73, 117.29, 115.58, 115.15, 114.67, 60.06, 14.01, 13.93.

IR ($CHCl_3$) ν_{max} = 3012, 2975, 2930, 1723, 1600, 1565, 1515, 1227, 1161, 1265, 1144, 1025, 830, 705.

HRMS: *m/z* = calcd for $C_{17}H_{16}FO_2$ $[M+H]^+$ 271.112, found: 271.113.

(E)- Ethyl 3-(4-acetylphenyl)-3-phenylacrylate (5a)



Chromatography (95:5 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.243g, 83%), E: Z isomer ratio- 2:1.

R_f = 0.36 (petroleum ether/EtOAc, 90:10).

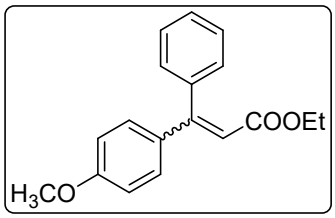
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 8.02-7.87 (m, 2H), 7.41-7.17 (m, 7H), 6.43 (s,1H, Z isomer), 6.42 (s,1H, E isomer), 4.34-4.24 (q, 2H, Z isomer), 4.12-4.01(q, 2H, E isomer), 2.64 (s, 3H, Z isomer), 2.60 (s, 3H, E isomer), 1.24-1.08 (m, 3H, E: Z isomer).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 197.45, 165.74, 154.89, 145.24, 138.26, 137.24, 129.69, 129.30, 129.03, 128.32, 128.02, 126.52, 119.30, 117.97, 60.26, 26.64, 13.99, 13.91.

IR ($CHCl_3$) ν_{max} = 3057, 3020, 2983, 1682, 1605, 1560, 1444, 1407, 1365, 1264, 1217, 1177, 1075, 1035, 958, 838, 751, 700, 683, 666.

HRMS: *m/z* = calcd for $C_{19}H_{19}O_3$ $[M+H]^+$ 295.132, found: 295.133.

(E)- Ethyl 3-(4-methoxyphenyl)-3-phenylacrylate (6a)



Chromatography (94:6 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.211g, 75%), E: Z isomer ratio- 1:0.70.

R_f = 0.30 (petroleum ether/EtOAc, 90:10).

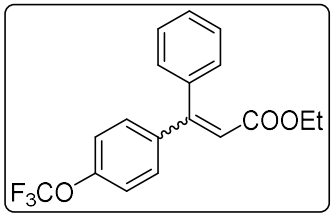
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.40-7.12 (m, 7H), 6.92-6.81 (m, 2H), 6.31 (s, 1H, E isomer), 6.27 (s, 1H, Z isomer), 4.14-3.98 (m, 2H) (E: Z isomer), 3.84 (s, 3H, Z isomer), 3.81 (s, 3H, E isomer), 1.20-1.06 (m, 3H) (E: Z isomer).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 166.26, 160.75, 159.71, 156.51, 156.21, 141.52, 139.25, 133.11, 131.03, 130.89, 129.71, 129.27, 129.05, 128.51, 128.26, 127.94, 127.80, 116.89, 115.39, 113.74, 113.20, 59.96, 59.85, 55.30, 55.19, 14.09, 13.97.

IR ($CHCl_3$) ν_{max} = 3018, 2981, 2935, 1717, 1601, 1573, 1511, 1465, 1444, 1419, 1369, 1353, 1251, 1218, 1151, 1116, 1035, 833, 755, 700.

HRMS: *m/z* = calcd for $C_{18}H_{19}O_3$, $[M+H]^+$ 283.132, found: 283.132.

(E)- Ethyl 3-phenyl-3-(4-(trifluoromethoxy) phenyl) acrylate (7a)



Chromatography (92:8 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.305g, 91%), E: Z isomer ratio- 14:1.

R_f = 0.26 (petroleum ether/EtOAc, 90:10).

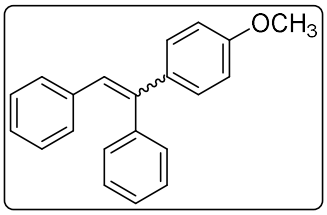
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40-7.15 (m, 9H), 6.38 (s, 1H, Z isomer), 6.34 (s, 1H, E isomer), 4.08-4.03 (m, 2H, E: Z isomer), 1.13-1.09 (t, 3H, E isomer), 0.97-0.94 (t, 3H, Z isomer).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 165.81, 154.77, 149.92, 139.36, 138.48, 132.24, 131.33, 129.72, 129.03, 128.34, 128.00, 124.21-116.56 (q, J_{C-F} 258.17 Hz), 120.58, 118.20, 60.16, 13.92.

IR ($CHCl_3$) ν_{max} = 2983, 1717, 1605, 1508, 1446, 1370, 1258, 1219, 1166, 1035, 922, 851, 771, 697, 670.

HRMS: *m/z* = calcd for $C_{18}H_{16}F_3O_3$, $[M^+ + H]^+$ 337.104, found: 337.105.

(E)- (1-(4-methoxyphenyl) ethene-1,2-diyl) dibenzene (8a)



Chromatography (98:2 petroleum ether: EtOAc) furnished the desired product as colourless oil (0.218g, 76%), E: Z isomer ratio- 2:1.

R_f = 0.26 (petroleum ether/EtOAc, 99:1).

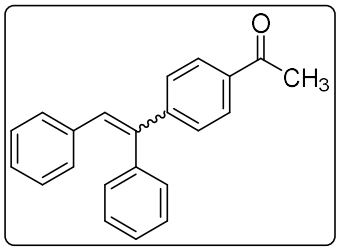
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.39-6.89 (m, 15H), 3.82 (s, 3H, Z isomer), 3.80 (s, 3H, E isomer).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 158.97, 158.68, 143.56, 141.98, 141.84, 140.28, 137.28, 135.78, 131.34, 130.10, 129.15, 128.49, 127.64, 126.25, 113.72, 113.32, 60.12, 55.03, 54.92.

IR ($CHCl_3$) ν_{max} = 3057, 3016, 2957, 2935, 2837, 1602, 1572, 1510, 1465, 1443, 1289, 1248, 1216, 1178, 1034, 825, 771, 715, 697, 668.

HRMS: *m/z* = calcd for $C_{21}H_{19}O$, $[M^+ + H]^+$ 287.142, found: 287.143.

(E)- 1-(4-(1,2-diphenylvinyl) phenyl) ethan-1-one (9a)



Chromatography (98:2 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.152g, 51%), E: Z isomer ratio- 1:0.07.

R_f = 0.29 (petroleum ether/EtOAc, 99:1).

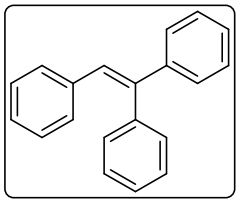
^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.89 (d, 2H), 7.40 (d, 2H), 7.35-7.02 (m, 11H), 2.61 (s, 3H, Z isomer), 2.58 (s, 3H, E isomer).

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 197.57, 147.98, 141.49, 139.64, 136.77, 135.86, 130.76, 130.23, 129.65, 129.50, 128.81, 128.31, 128.01, 127.59, 127.25, 127.09, 26.57.

IR ($CHCl_3$) ν_{max} = 3058, 3019, 1679, 1599, 1557, 1491, 1444, 1408, 1359, 1269, 1216, 1185, 958, 846, 822, 770, 708, 696, 668, 616.

HRMS: *m/z* = calcd for $C_{22}H_{19}O$, $[M^+ + H]^+$ 299.142, found: 299.143.

Ethene-1,1,2-triyltribenzene (10a)



Chromatography (100% petroleum ether) furnished the desired product as colourless oil (0.104g, 41%), E: Z isomer ratio- None.

R_f = 0.41 (petroleum ether/EtOAc, 99:1).

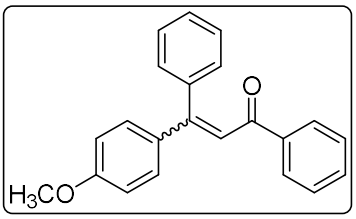
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.39-7.30 (m, 9H), 7.29-7.01 (m, 7H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 143.4, 142.6, 140.3, 137.4, 130.4, 129.5, 128.6, 128.2, 127.9, 127.6, 127.5, 127.4, 126.7, 116.5.

IR ($CHCl_3$) ν_{max} = 3023, 2402, 1597, 1522, 1428, 1216, 1028, 928, 768, 671.

HRMS: *m/z* = calcd for $C_{20}H_{17}$ $[M+H]^+$ 257.1325, found: 257.1324.

(E)- 3-(4-methoxyphenyl)-1,3-diphenylprop-2-en-1-one (11a)



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.210g, 67%), E: Z isomer ratio- 2:1.

R_f = 0.40 (petroleum ether/EtOAc, 90:10).

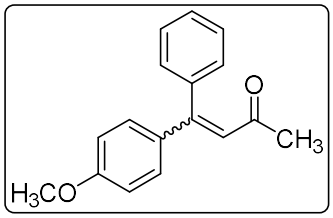
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.95-7.83 (m, 2H), 7.52-6.74 (m, 13H), 3.84 (s, 3H, Z isomer), 3.78 (s, 3H, E isomer).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 192.90, 192.28, 160.77, 159.83, 159.83, 154.97, 154.75, 141.88, 139.30, 138.35, 132.42, 131.46, 131.05, 129.67, 128.61, 128.28, 127.99, 123.36, 121.87, 113.81, 113.41, 55.35.

IR ($CHCl_3$) ν_{max} = 3018, 1656, 1601, 1582, 1510, 1493, 1462, 1446, 1419, 1355, 1251, 1216, 1178, 1154, 1035, 10.20, 834, 772, 698, 668.

HRMS: *m/z* = calcd for $C_{22}H_{19}O_2$, $[M^+{+}H]^+$ 315.137, found: 315.138.

(E)- 4-(4-methoxyphenyl)-4-phenylbut-3-en-2-one (12a)



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.218g, 87%), E: Z isomer ratio- 1.1:1.

R_f = 0.36 (petroleum ether/EtOAc, 90:10).

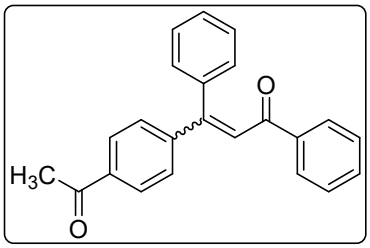
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.44-7.13 (m, 7H), 6.95-6.83 (m, 2H), 6.55 (s, 1H, E isomer) 6.50 (s, 1H, Z isomer), 3.86 (s, 3H, Z isomer), 3.82 (s, 3H, E isomer), 1.91 (s, 3H, Z isomer), 1.84 (s, 3H, E isomer).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 200.10, 131.36, 128.67, 128.42, 127.42, 126.00, 113.85, 55.32, 52.94, 30.30.

IR ($CHCl_3$) ν_{max} = 3065, 3000, 2934, 2838, 1683, 1650, 1601, 1585, 1509, 1461, 1433, 1352, 1292, 1245, 1177, 1028.

HRMS: *m/z* = calcd for $C_{17}H_{17}O_2$, $[M^+ + H]^+$ 253.122, found: 253.123.

(E)- 3-(4-acetylphenyl)-1,3-diphenylprop-2-en-1-one (13a)



Chromatography (93:7 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.270g, 83%), E: Z isomer ratio- 2:1.

R_f = 0.20 (petroleum ether/EtOAc, 90:10).

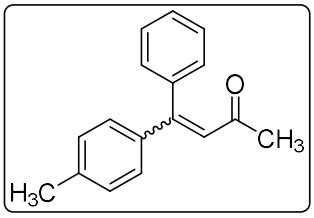
^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.00-7.88 (m, 4H), 7.59-7.17 (m, 11H), 2.65 (s, 3H, E isomer), 2.62 (s, 3H, Z isomer).

^{13}C NMR ($CDCl_3$, 125 MHz) δ = 197.49, 192.72, 191.66, 152.84, 145.80, 138.26, 137.78, 137.34, 132.92, 130.10, 129.66, 128.71, 128.43, 128.22, 125.82, 124.26, 26.69.

IR ($CHCl_3$) ν_{max} = 3058, 3024, 1683, 1601, 1492, 1446, 1405, 1358, 1310, 1265, 1214, 1178, 1035, 1016, 958, 836, 757, 716, 697, 644.

HRMS: *m/z* = calcd for $C_{23}H_{19}O_2$, $[M^+ + H]^+$ 327.137 found: 327.137.

(E)- 4-phenyl-4-(p-tolyl) but-3-en-2-one (14a)



Chromatography (94:6 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.200g, 85%), E: Z isomer ratio- 1:1.

R_f = 0.40 (petroleum ether/EtOAc, 90:10).

^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.44-7.13 (m, 9H), 6.57 (s, 1H, Z isomer), 6.54 (s, 1H, E isomer), 2.41 (s, 3H, Z isomer), 2.36 (s, 3H, E isomer), 1.89 (s, 3H, Z isomer), 1.86 (s, 3H, E isomer).

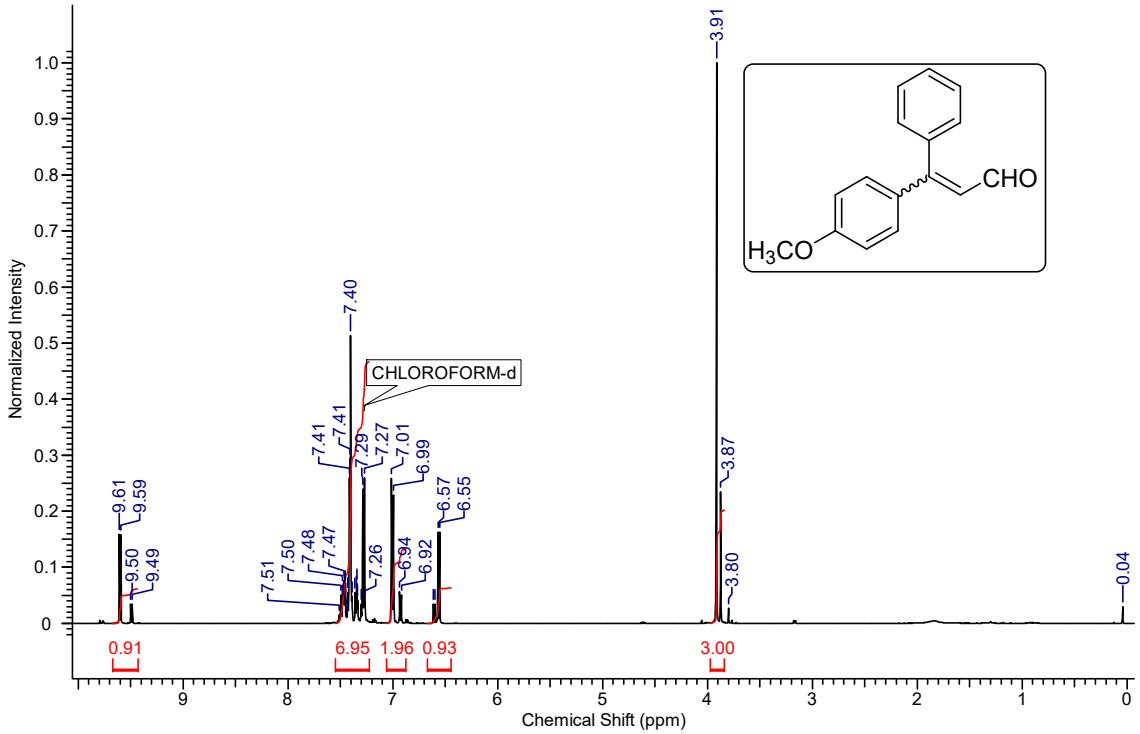
^{13}C NMR ($CDCl_3$, 50 MHz) δ = 200.45, 200.18, 154.19, 154.07, 141.04, 139.76, 139.12, 138.84, 137.88, 135.95, 129.57, 129.14, 128.33, 127.55, 126.88, 30.27, 21.21.

IR ($CHCl_3$) ν_{max} = 3681, 3374, 3019, 2400, 1644, 1590, 1513, 1422, 1357, 1216, 1117, 1043, 928, 851, 772, 669.

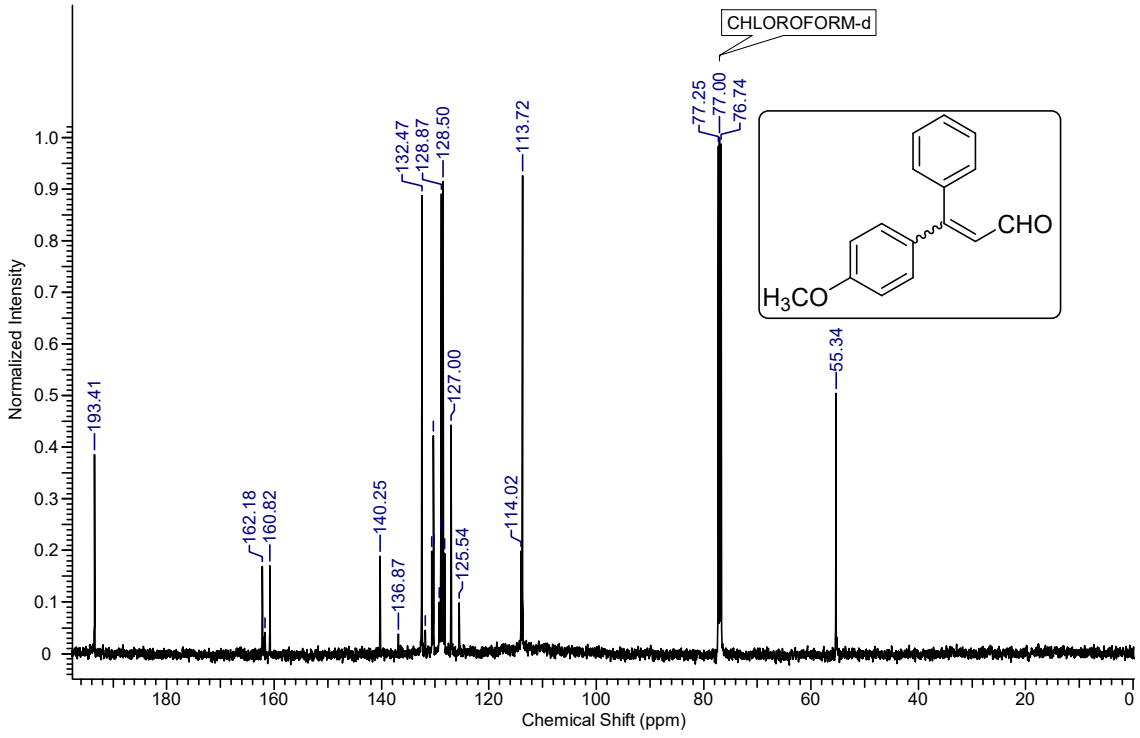
HRMS: *m/z* = calcd for $C_{17}H_{17}O$ $[M+H]^+$ 237.1271, found: 237.1270.

2.4 Spectral Data

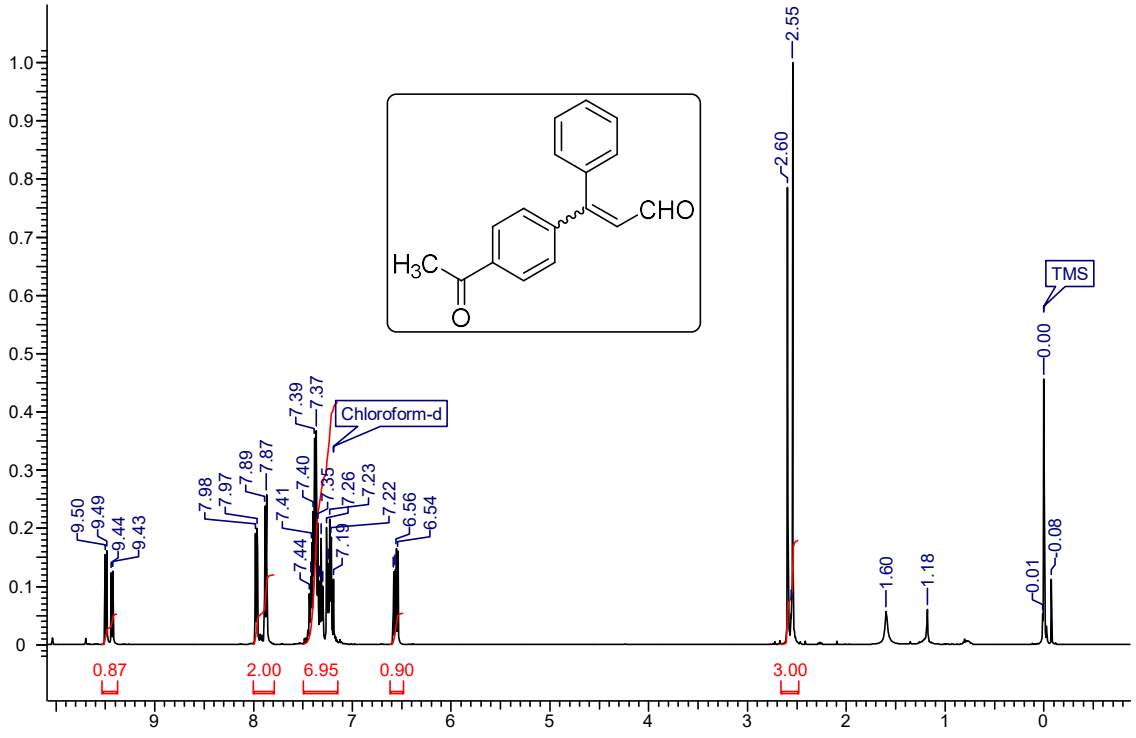
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of (E)-3-(4-methoxyphenyl)-3-phenylacrylaldehyde **(1a)**



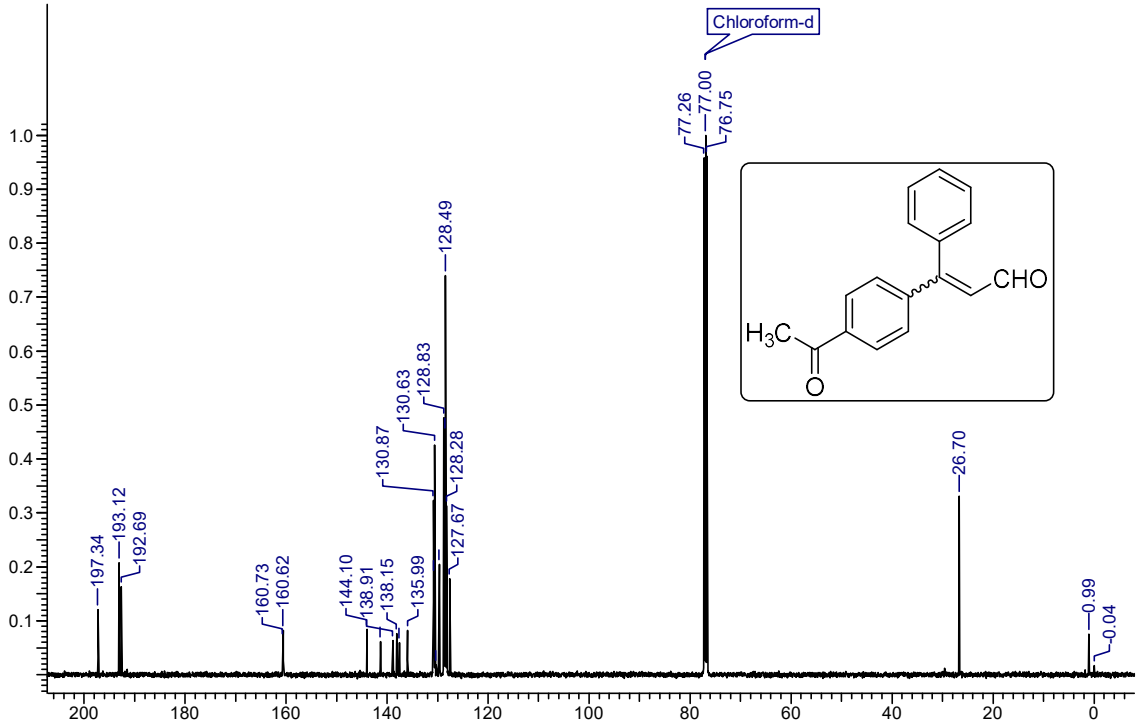
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of (E)-3-(4-methoxyphenyl)-3-phenylacrylaldehyde **(1a)**



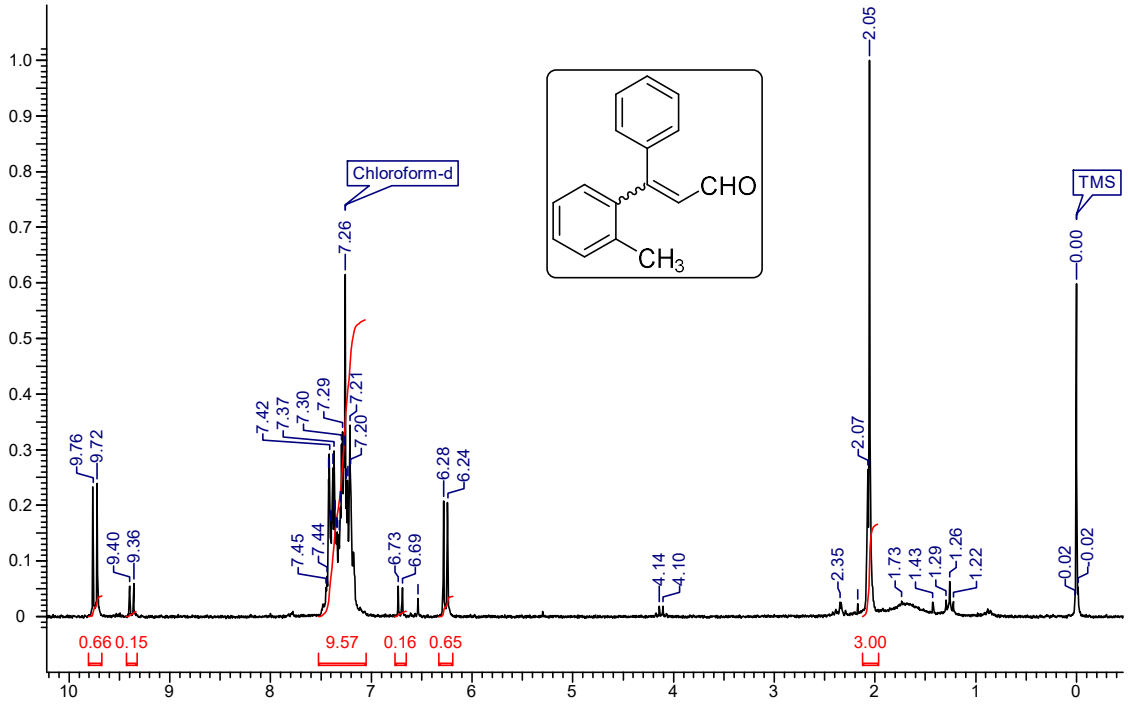
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (E)-3-(4-acetylphenyl)-3-phenylacrylaldehyde **(2a)**



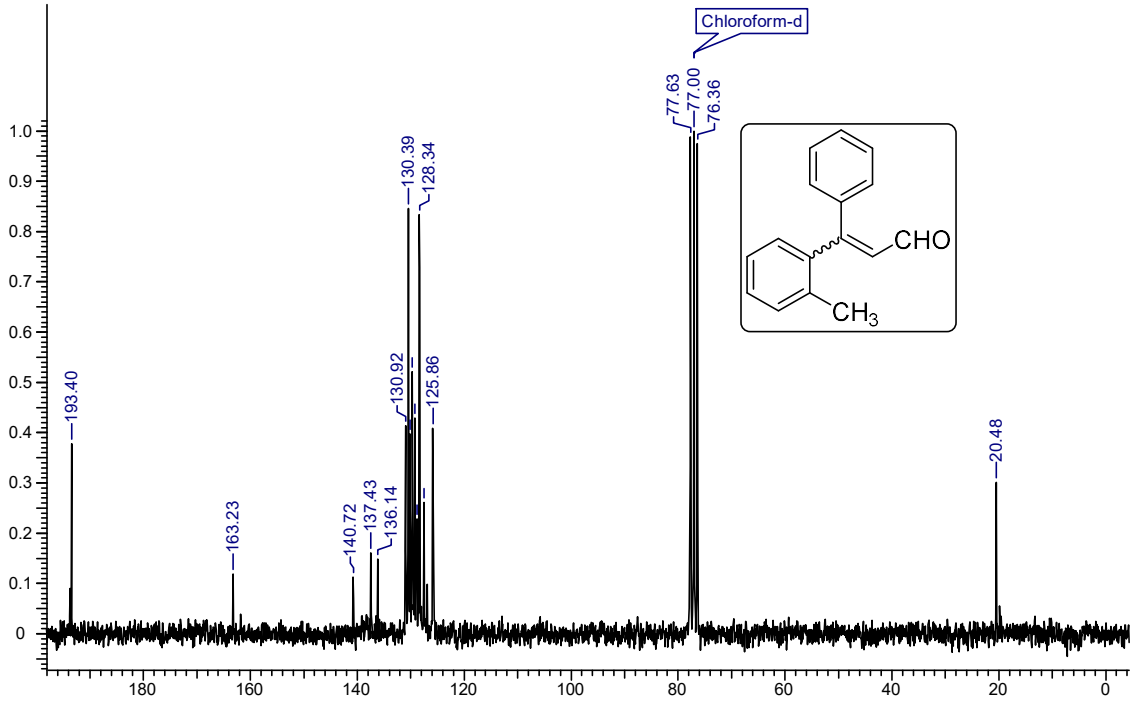
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (E)-3-(4-acetylphenyl)-3-phenylacrylaldehyde **(2a)**



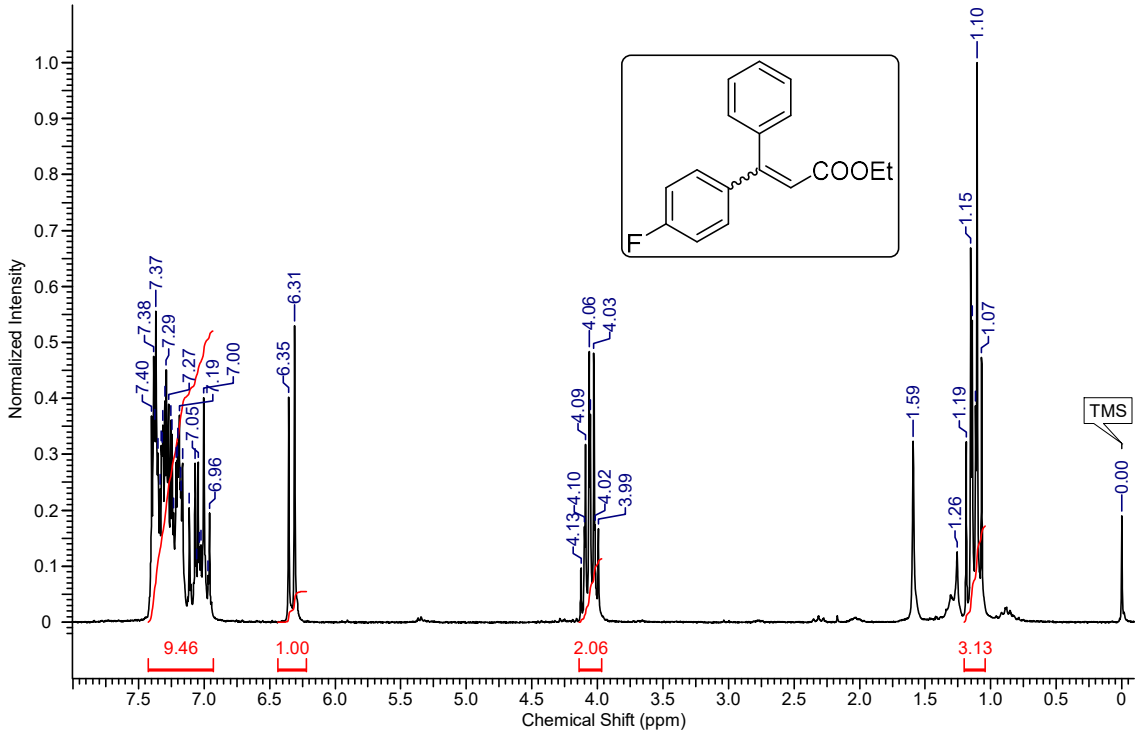
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (E)-3-phenyl-3-(o-tolyl) acrylaldehyde **(3a)**



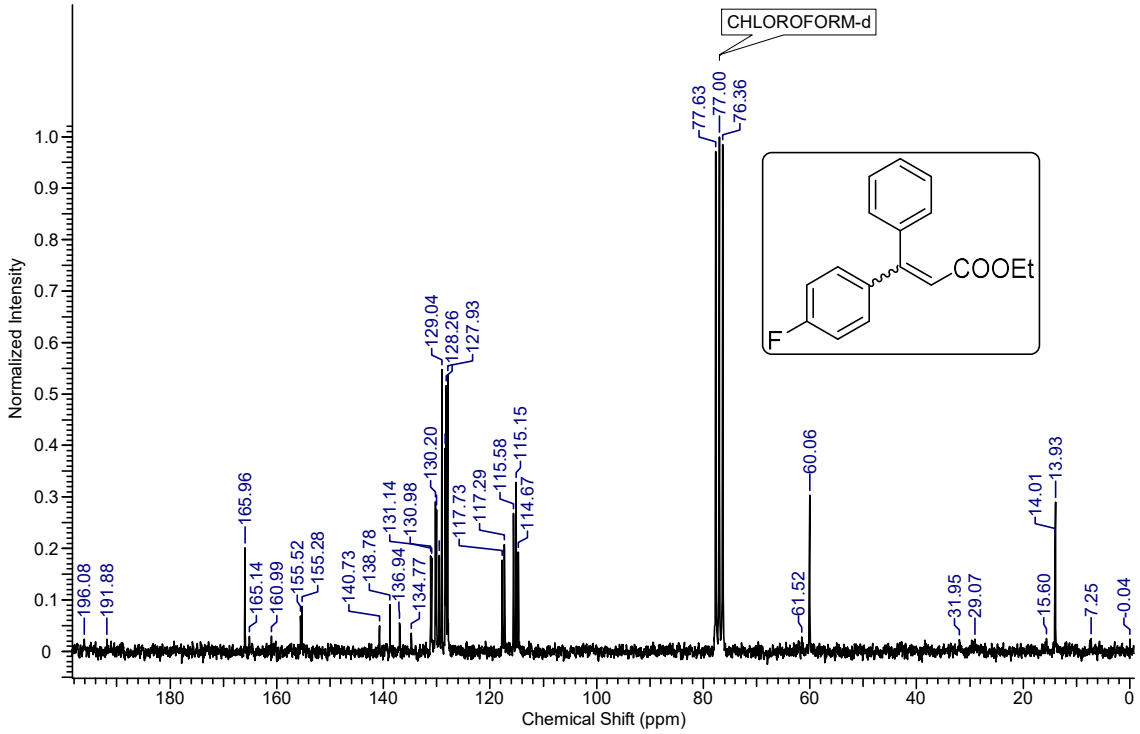
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (E)-3-phenyl-3-(o-tolyl) acrylaldehyde **(3a)**



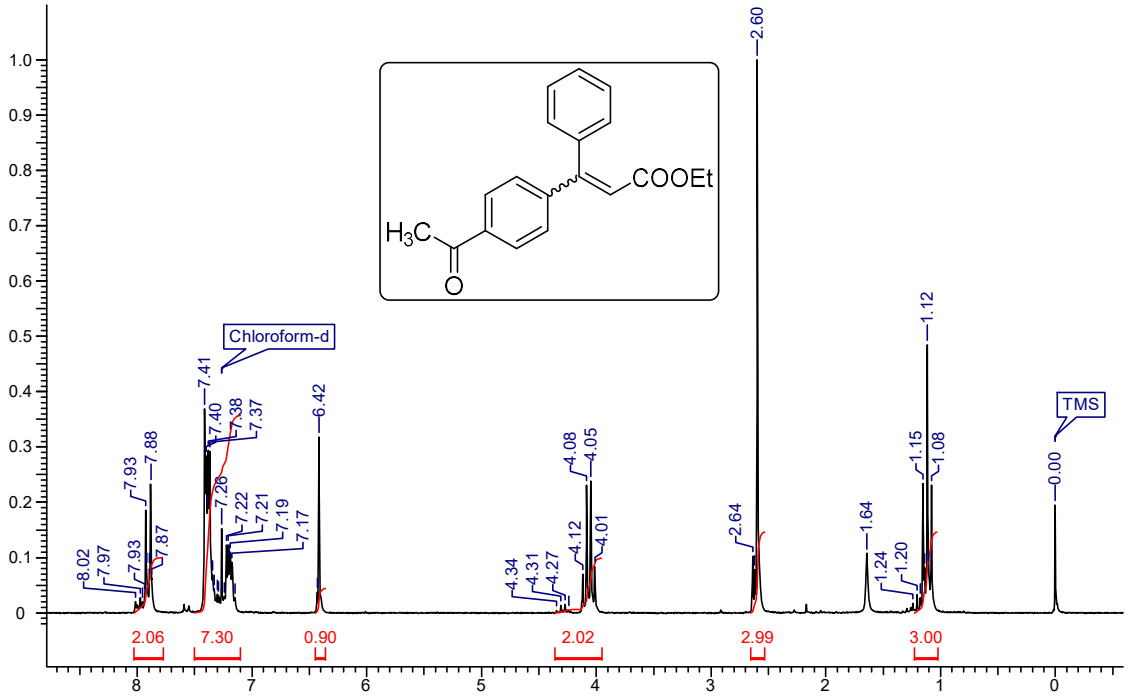
^{1}HNMR ($CDCl_3$, 200 MHz) spectrum of (E)-Ethyl 3-(4-fluorophenyl)-3-phenylacrylate **(4a)**



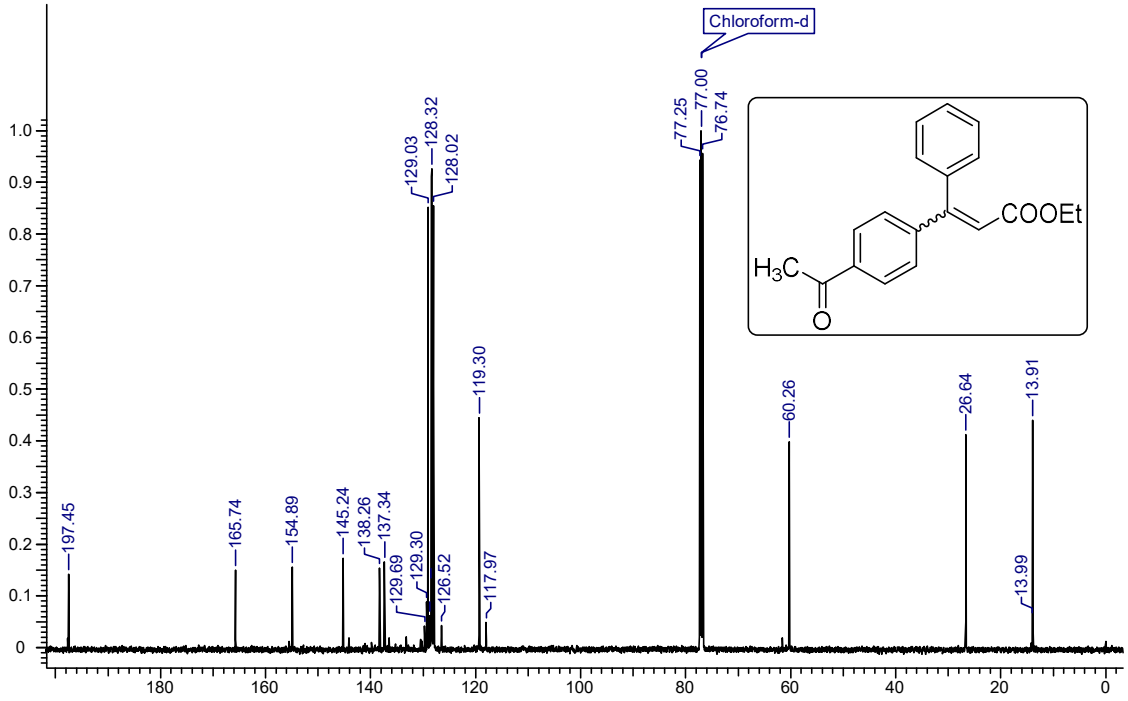
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (E)-Ethyl 3-(4-fluorophenyl)-3-phenylacrylate **(4a)**



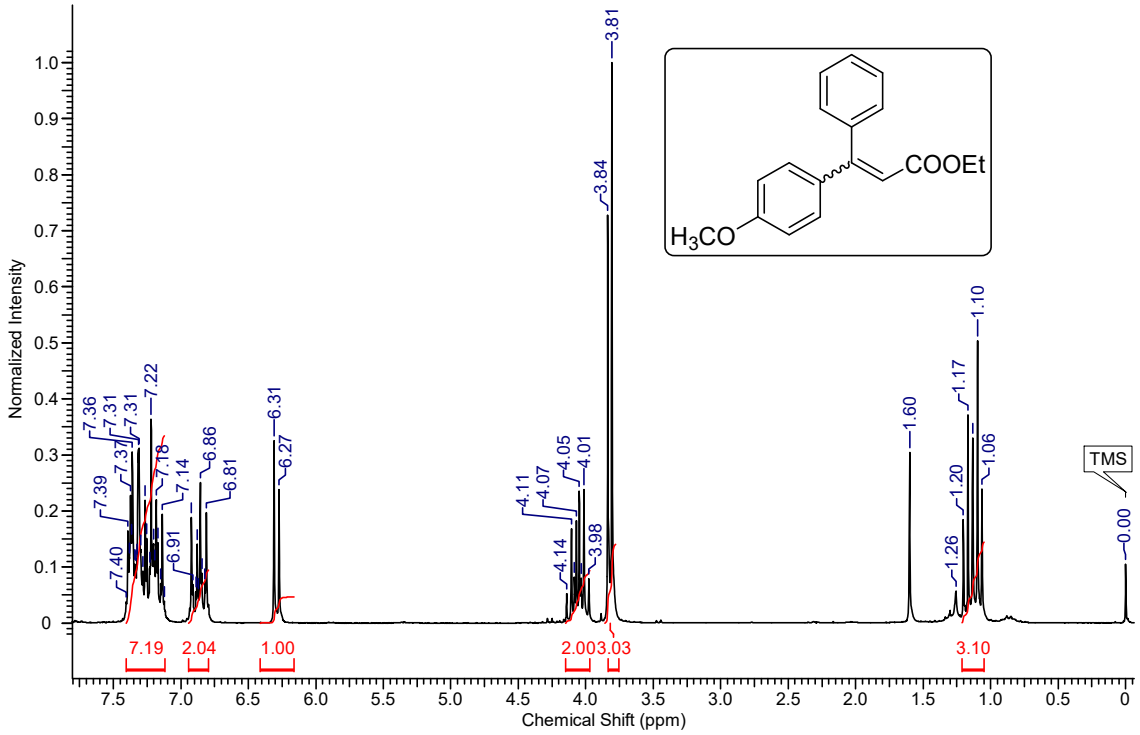
^{1}HNMR ($CDCl_3$, 200 MHz) spectrum of (E)- Ethyl 3-(4-acetylphenyl)-3-phenylacrylate **(5a)**



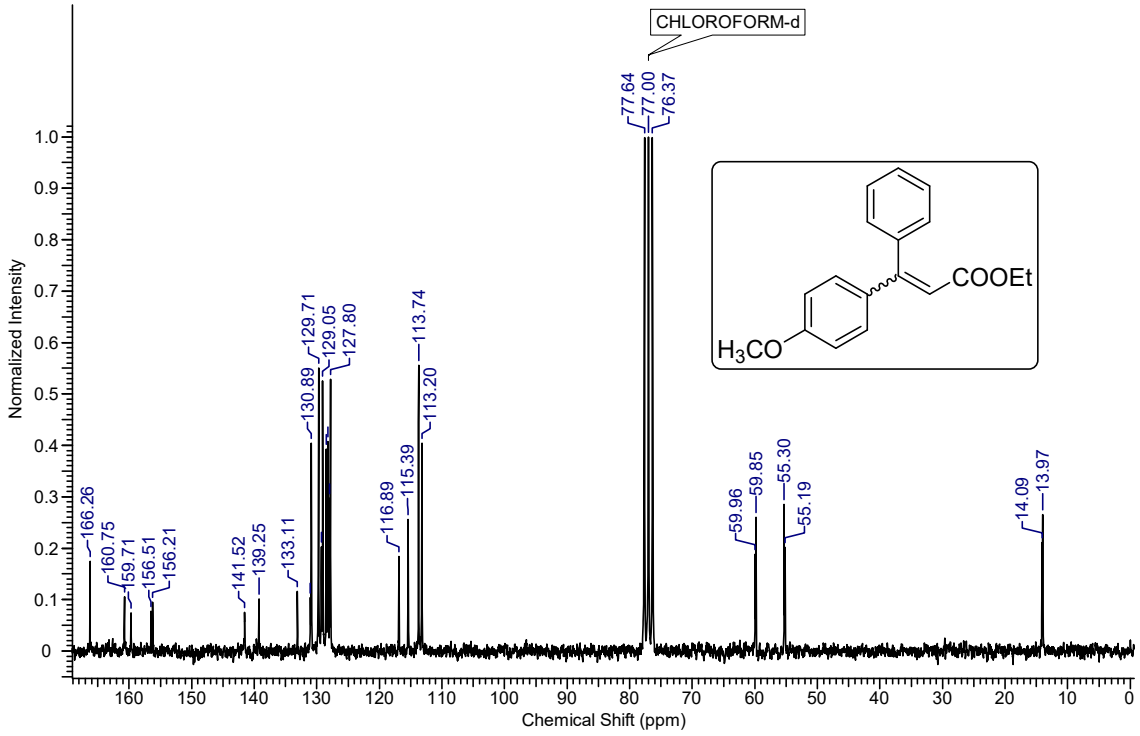
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (E)- Ethyl 3-(4-acetylphenyl)-3-phenylacrylate **(5a)**



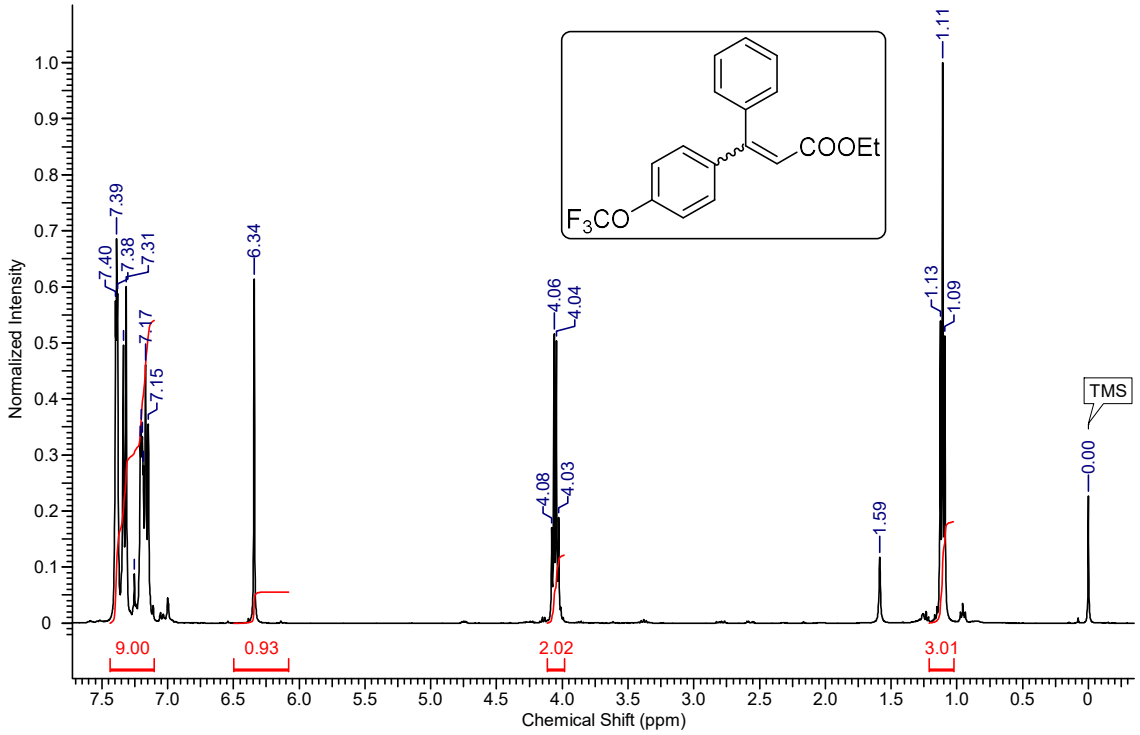
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (E)- Ethyl 3-(4-methoxyphenyl)-3-phenylacrylate **(6a)**



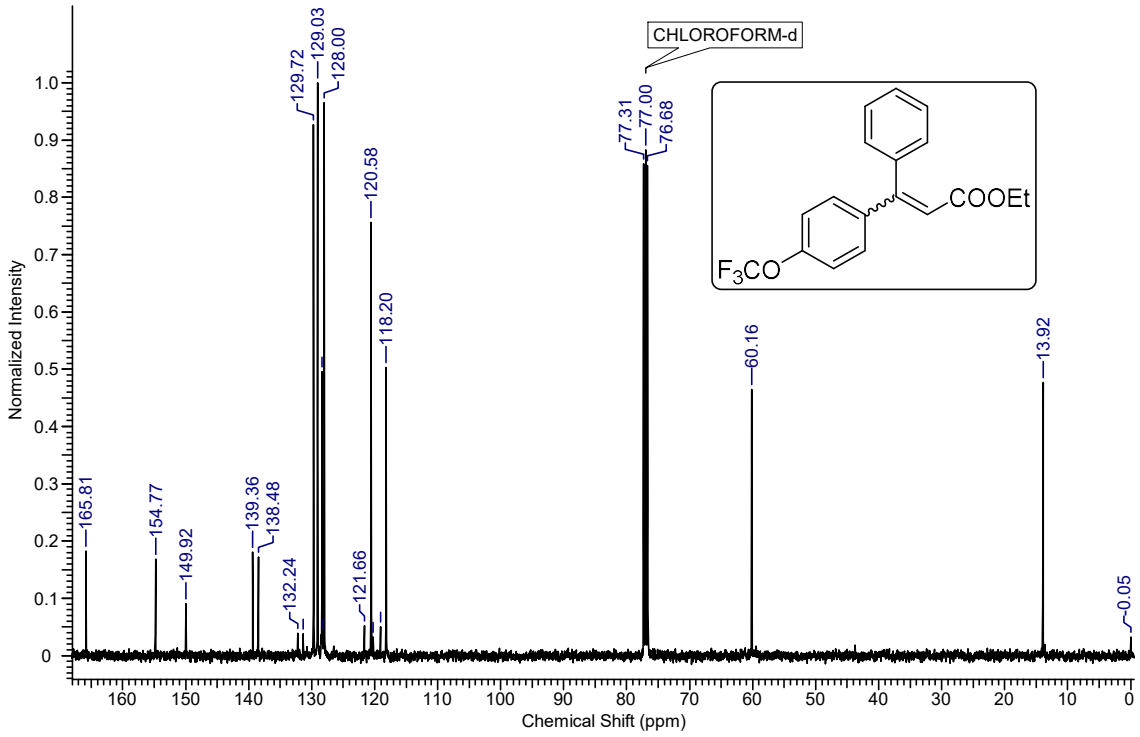
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (E)- Ethyl 3-(4-methoxyphenyl)-3-phenylacrylate **(6a)**



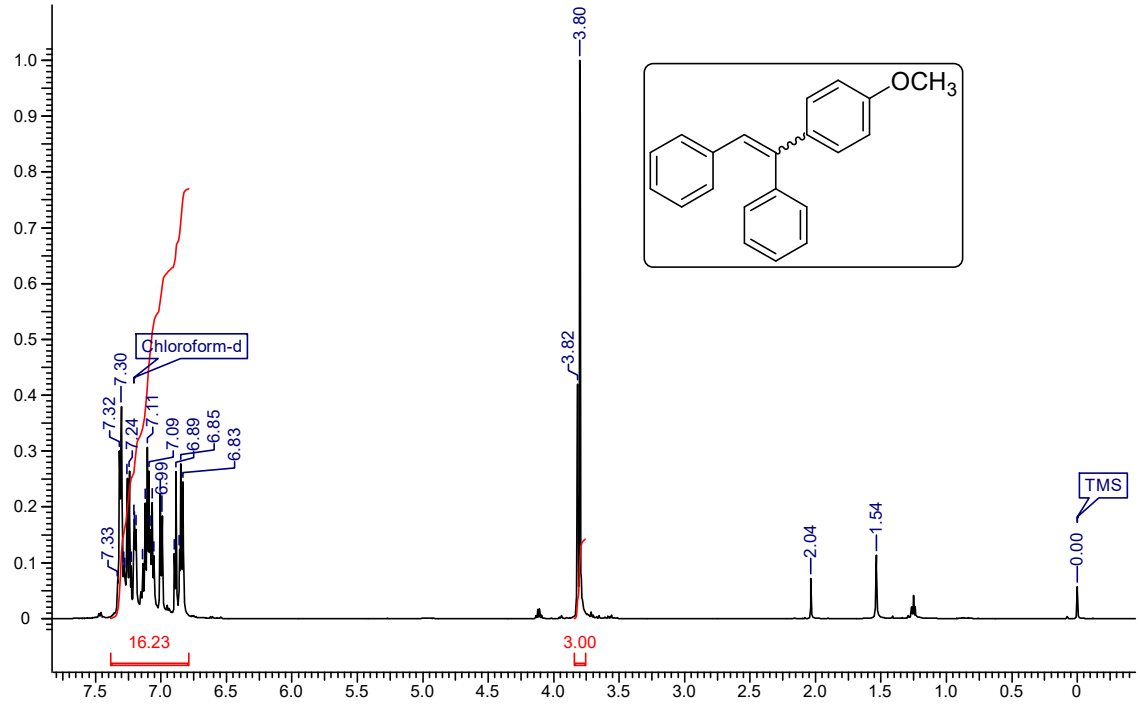
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of (E)- Ethyl 3-phenyl-3-(4-(trifluoromethoxy) phenyl) acrylate **(7a)**



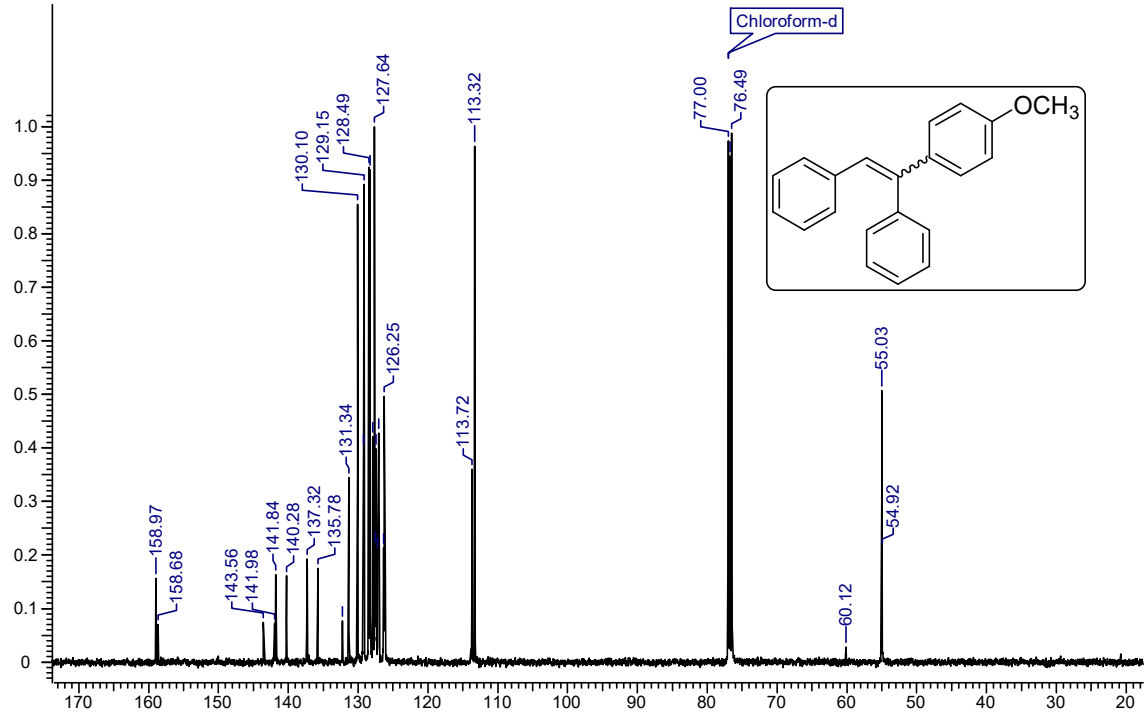
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of (E)- Ethyl 3-phenyl-3-(4-(trifluoromethoxy) phenyl) acrylate **(7a)**



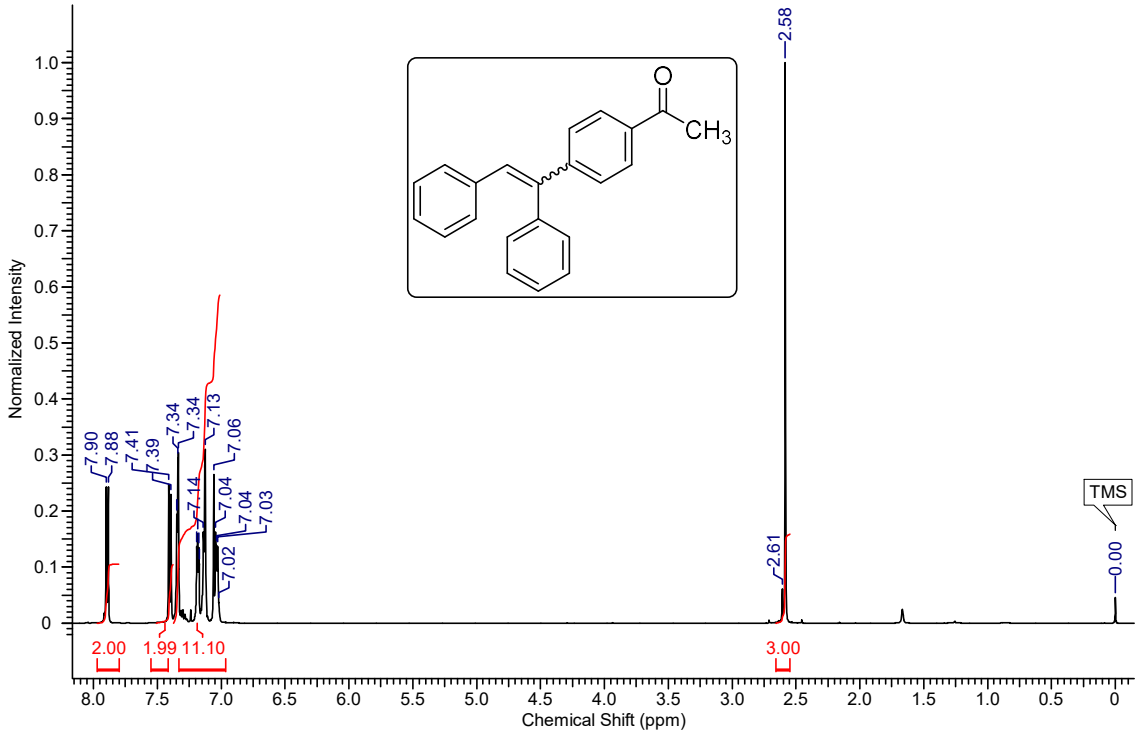
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (E)- (1-(4-methoxyphenyl) ethene-1,2-diyl) dibenzene **(8a)**



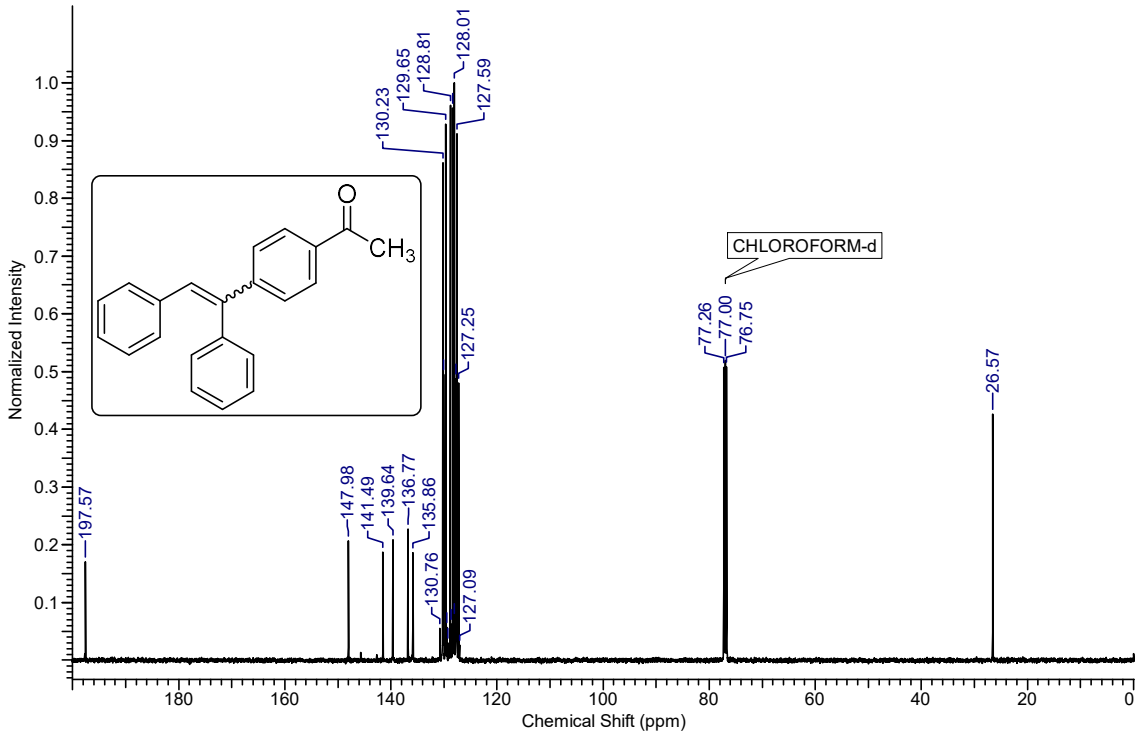
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (E)- (1-(4-methoxyphenyl) ethene-1,2-diyl) dibenzene **(8a)**



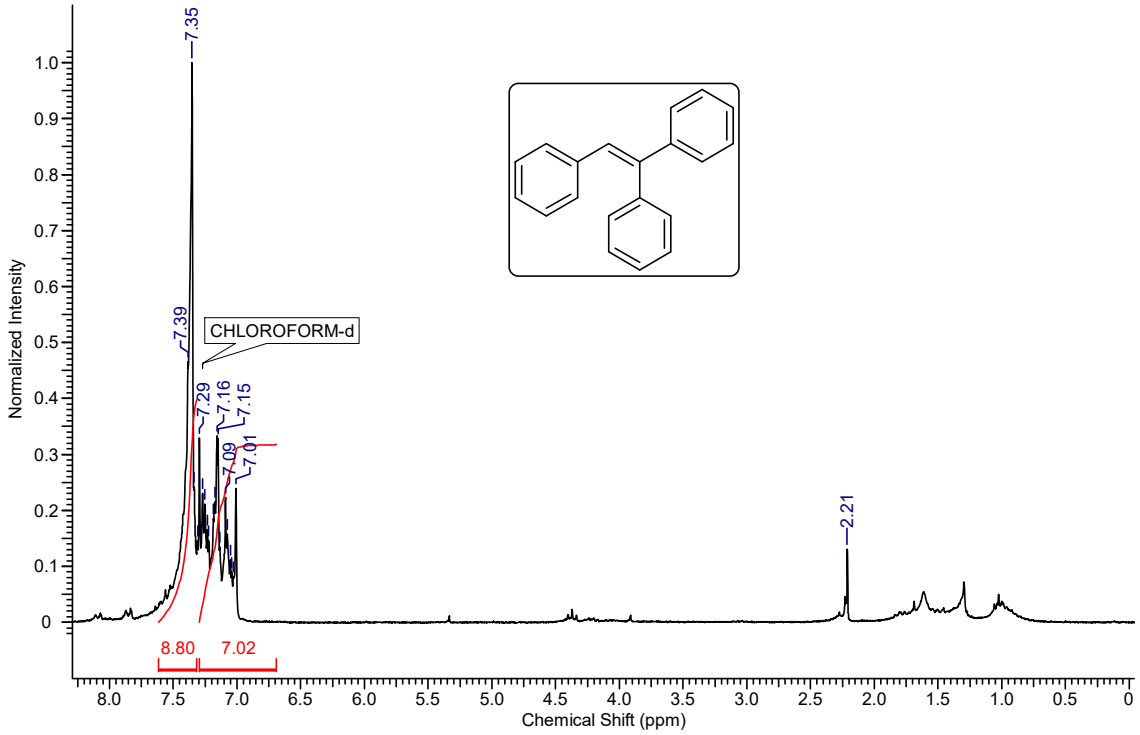
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of (E)- 1-(4-(1,2-diphenylvinyl) phenyl) ethan-1-one **(9a)**



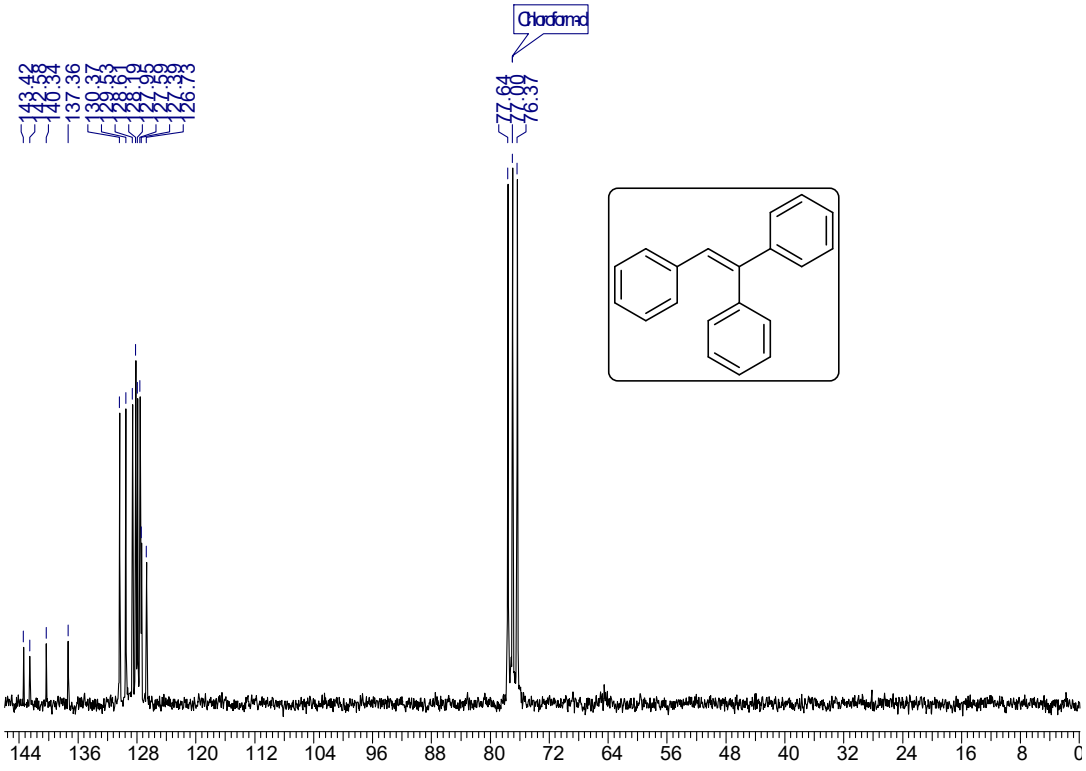
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of (E)- 1-(4-(1,2-diphenylvinyl) phenyl) ethan-1-one **(9a)**



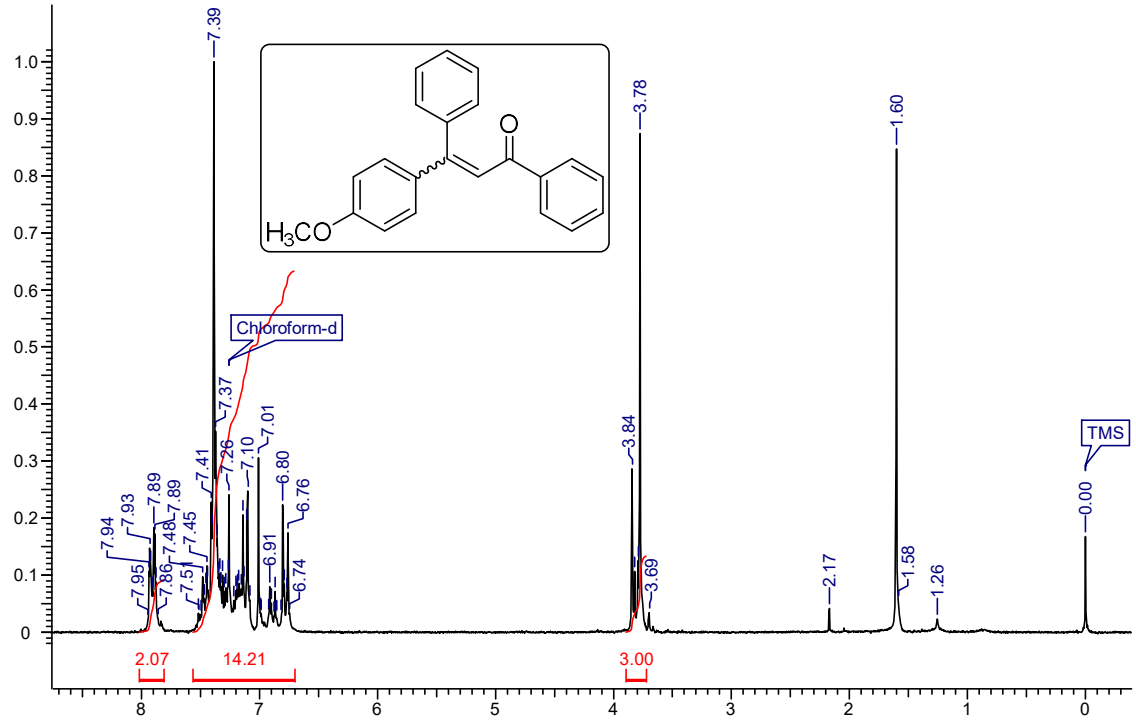
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of Ethene-1,1,2-triyltribenzene **(10a)**



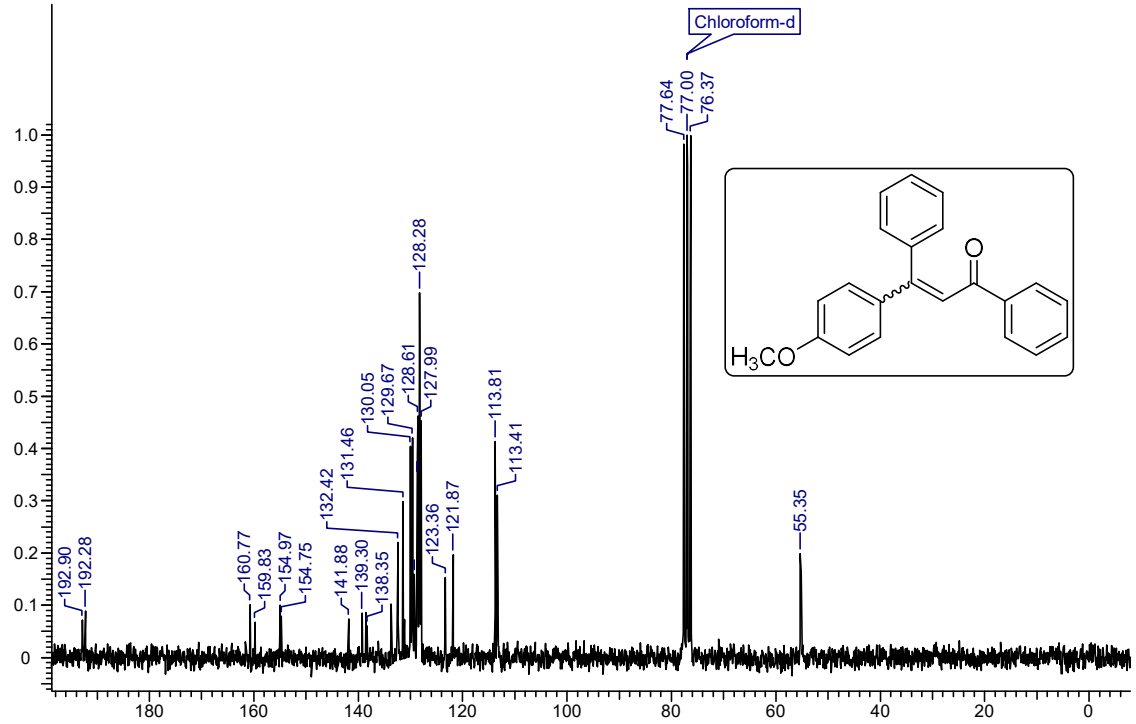
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of Ethene-1,1,2-triyltribenzene **(10a)**



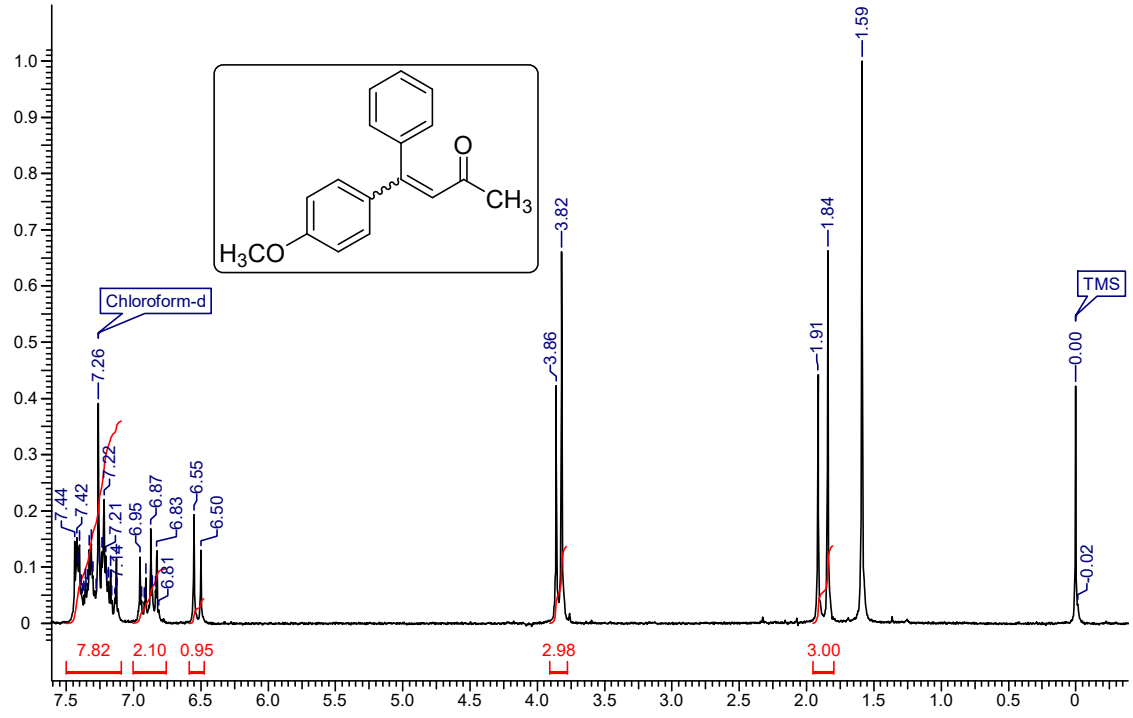
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (E)- 3-(4-methoxyphenyl)-1,3-diphenylprop-2-en-1-one **(11a)**



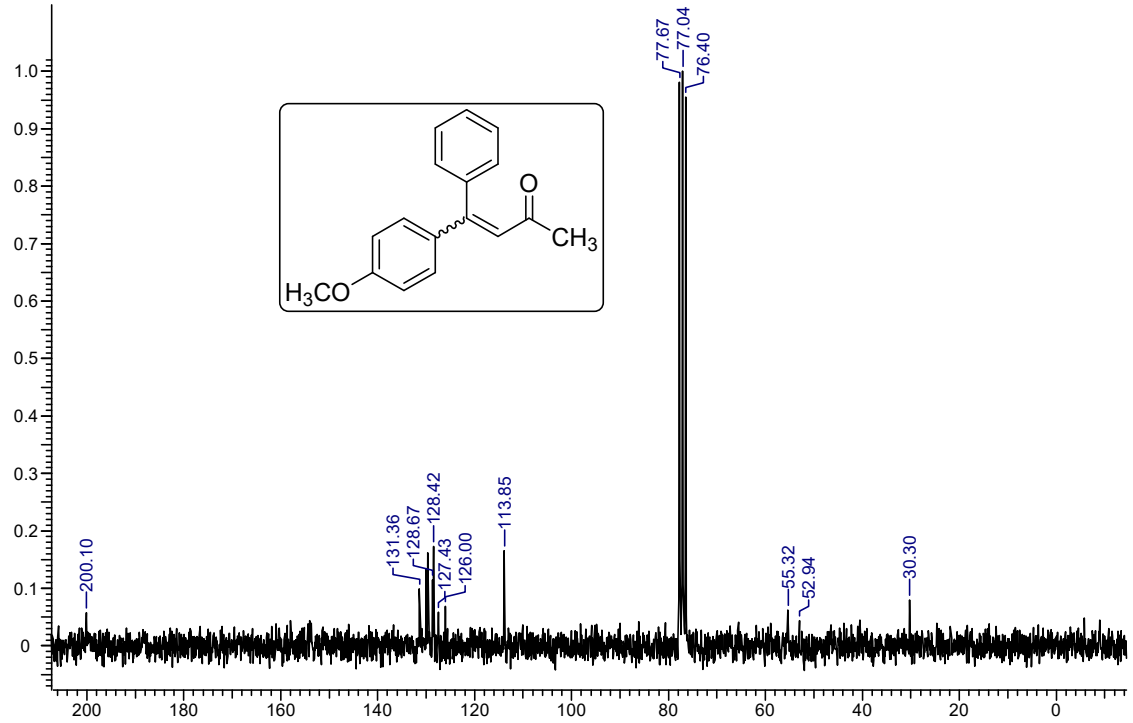
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (E)- 3-(4-methoxyphenyl)-1,3-diphenylprop-2-en-1-one **(11a)**



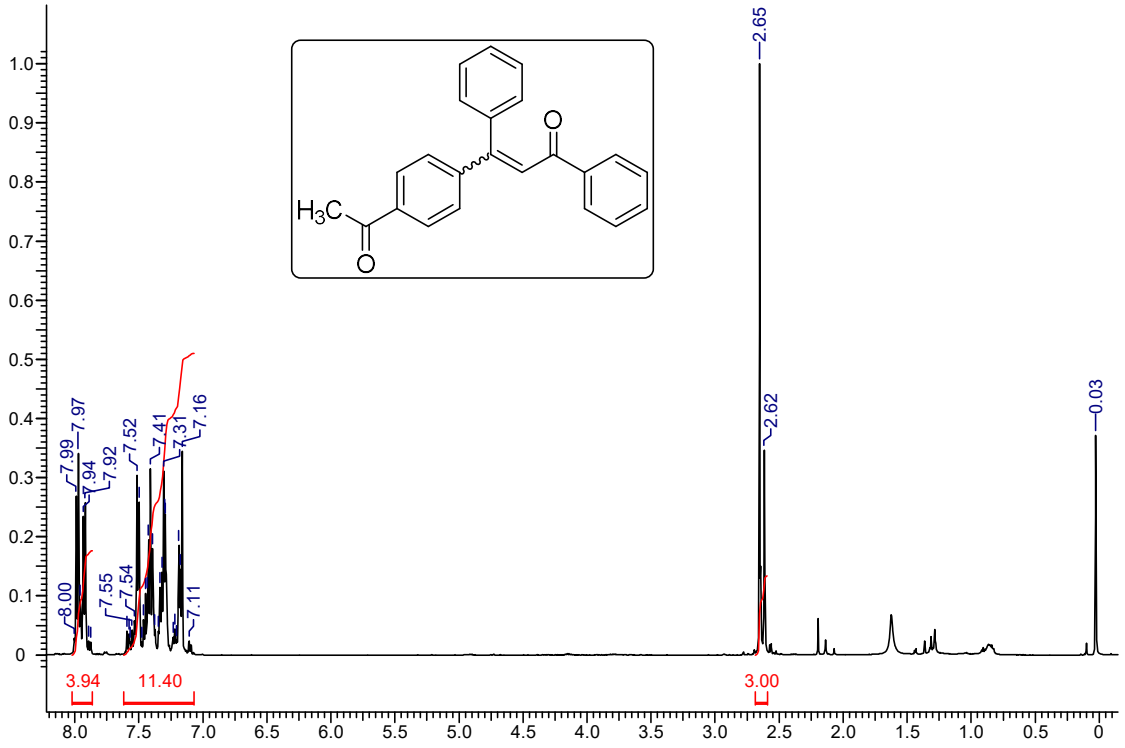
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (E)- 4-(4-methoxyphenyl)-4-phenylbut-3-en-2-one **(12a)**



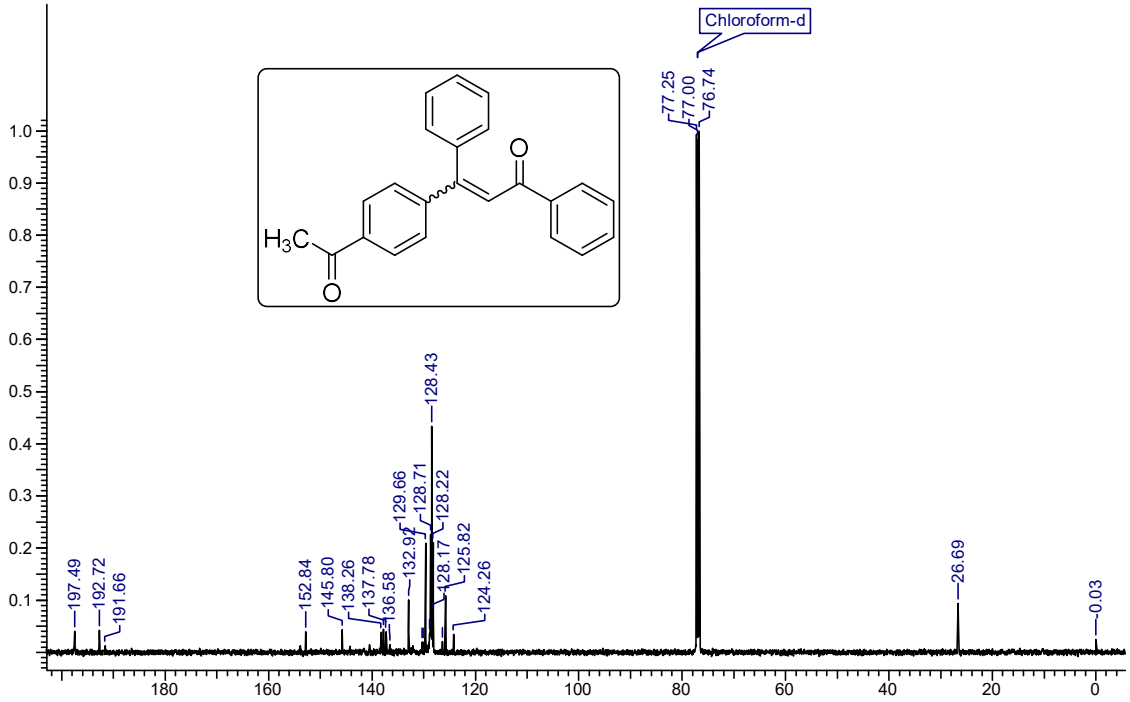
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (E)- 4-(4-methoxyphenyl)-4-phenylbut-3-en-2-one **(12a)**



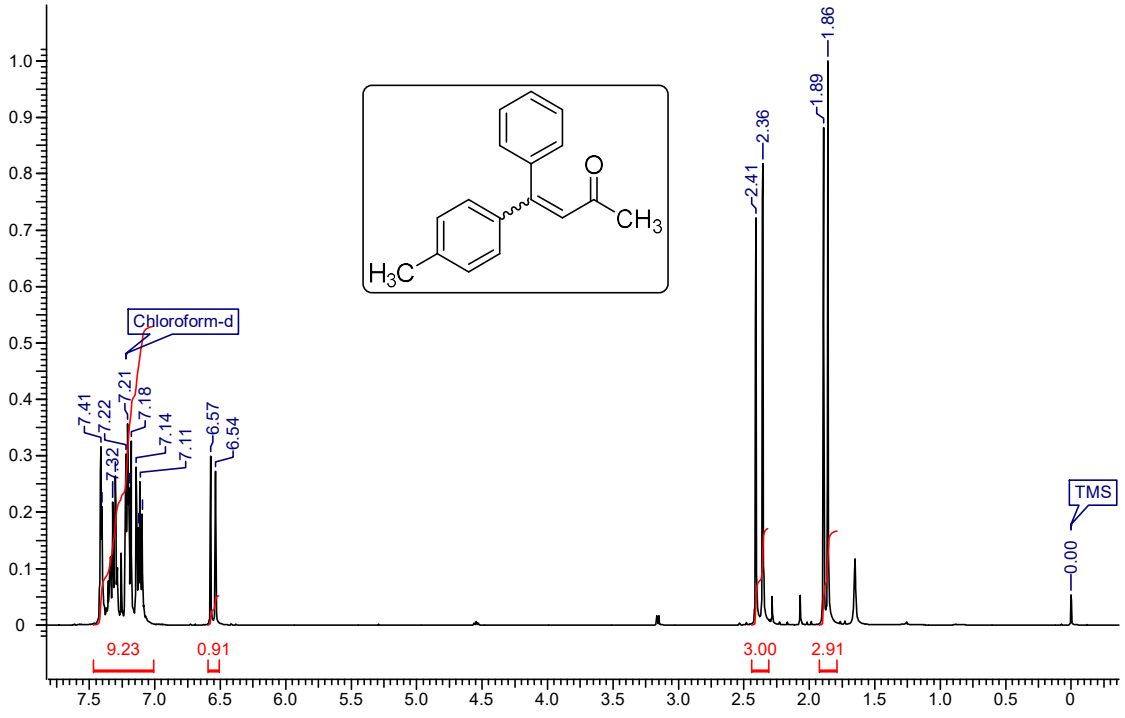
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of (E)- 3-(4-acetylphenyl)-1,3-diphenylprop-2-en-1-one **(13a)**



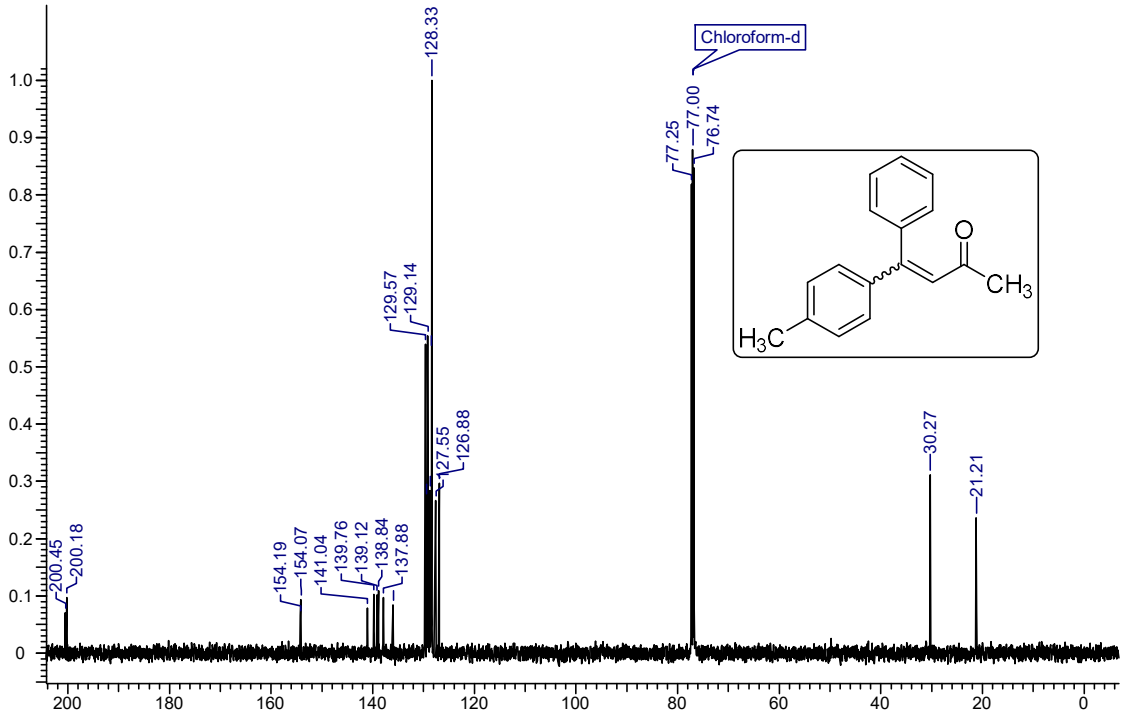
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of (E)- 3-(4-acetylphenyl)-1,3-diphenylprop-2-en-1-one **(13a)**



^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (E)- 4-phenyl-4-(p-tolyl) but-3-en-2-one **(14a)**



^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (E)- 4-phenyl-4-(p-tolyl) but-3-en-2-one **(14a)**



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Chapter III

N, O-ligands for catalysis of Mizoroki-Heck reaction, Suzuki coupling & organic transformations.

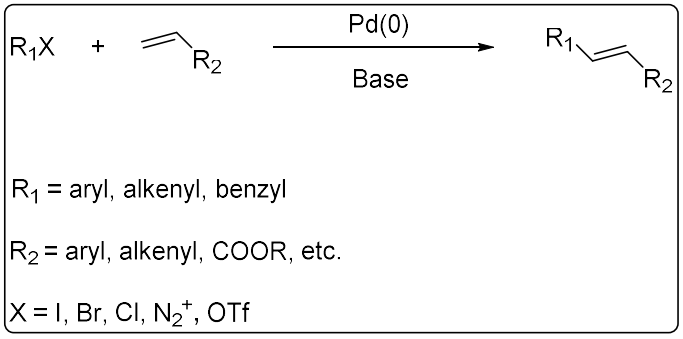
3.1 Introduction

One of the most indispensable reactions in organic chemistry is carbon-carbon bond creation. Reactions that involve forging of aryl-alkene and aryl-aryl bond by traditional noncatalytic methods generally involve numerous steps. Although aryl-aryl homocoupling mediated by copper was introduced by Ullmann in 1904 using aryl iodide, the major discoveries in coupling reactions, catalysed by notably one of the most famous transition metal palladium, began in 1972. Of the many carbon-carbon bond forming reactions catalysed by palladium, two reactions which are worthy of note and which have carved a niche for themselves in synthetic organometallic chemistry are 2010 Nobel prize winning reactions, Mizoroki-Heck reaction and Suzuki reaction along with Negishi coupling.

Mizoroki-Heck reaction

Mizoroki-Heck reaction was discovered solo by the efforts of T. Mizoroki and R. F. Heck [1]. Classical Mizoroki-Heck reaction includes palladium catalysed interchange of vinylic hydrogen with aryl, benzyl or vinyl group as shown in scheme 1.

Scheme 1



Thus, Mizoroki-Heck reaction can be thought of as alkene insertion into single carbon-palladium bond to furnish substituted olefins. The leaving group can be halide with reactivity order of I > Br >> Cl or it can be N_2BF_4, OTf and COCl. This reaction is a substitute for Wittig reaction in a couple of cases for synthetic planning purpose.

Mechanism

The most established mechanism of Mizoroki-Heck reaction is presented in figure 1.

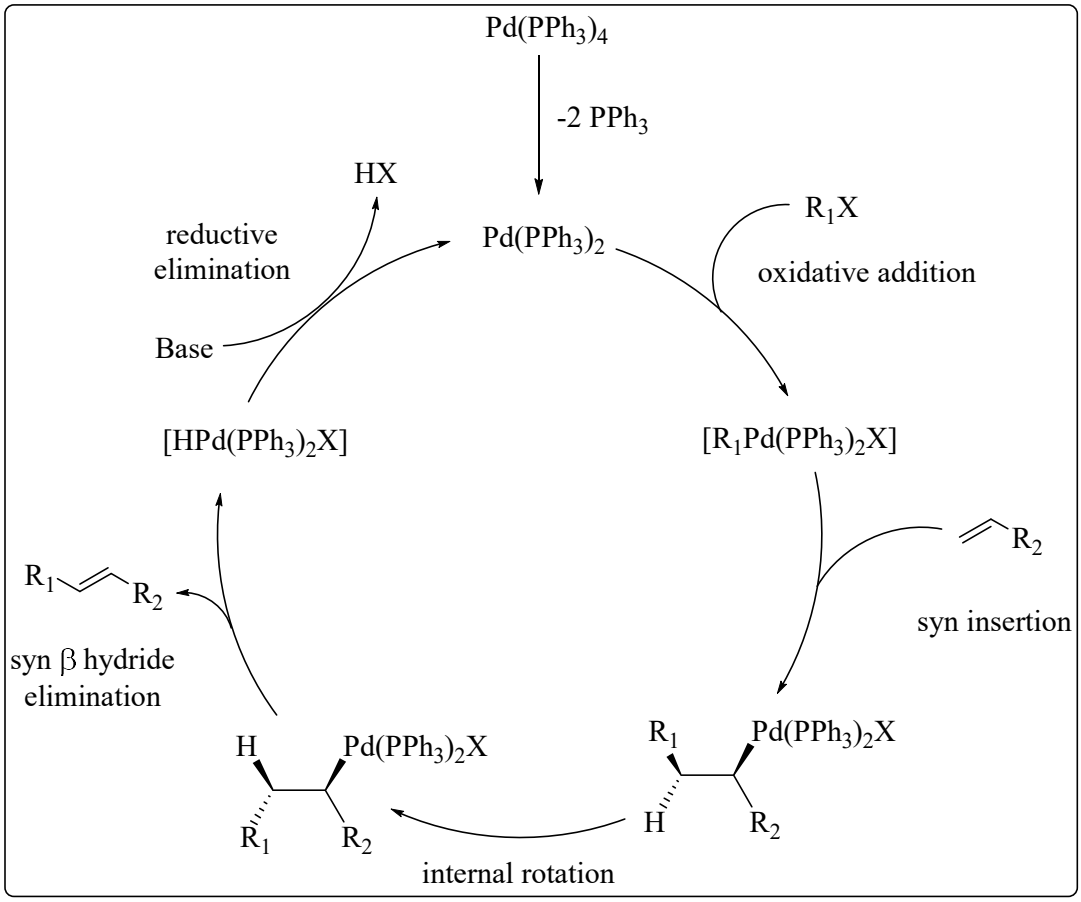


Figure 1. Outline of catalytic cycle for Mizoroki-Heck coupling.

The active form of the catalyst is a 14e Pd(0) complex with two triphenylphosphine ligands. The mechanism kick starts with oxidative addition of organic halide to the Pd(0) coordinatively unsaturated species to create an intermediate of organopalladium(II). Alkene then coordinates and inserts to create a new organopalladium(II) intermediate which experiences β-hydride elimination. The product detaches from the palladium, leaving behind a palladium(II) hydrohalide that restores the 14e palladium(0) catalytic species by reacting with base. Ligand associates and dissociates at several number of steps in the mechanism. There is a propensity for *trans* coupling as during reaction sequence bulky organic residue and palladium halide group move away from each other by bond rotation causing it to be a stereoselective reaction.

Mizoroki-Heck reaction's synthetic usefulness is evident by following facts:

1. The methodology is flexible as it accommodates readily available variety of starting materials.

2. Functional group tolerance has been the hallmark of this reaction, hence adducts containing most functional groups can be used.

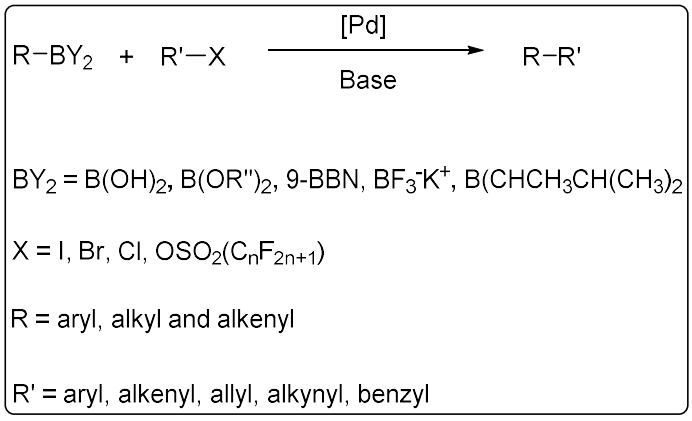
3. Air and water stability of employed palladium catalysts.

Mizoroki-Heck reaction finds its use in many industrial applications, as in synthesis of drugs like Naproxen and Ketoprofen by Albermale Corporation, herbicide Prosulfuron (Novartis), Singulair, an anti-asthma agent (Merck) and common sunscreen agent 2-ethylhexyl-*p*-methoxycinnamate.

Suzuki reaction

Suzuki reaction is one of the most powerful reactions for carbon-carbon bond formation in synthetic organic chemistry. It was formally developed by Suzuki group [2]. It involves cross-coupling between organoboron compounds and organic halides or triflates mediated by palladium. This is a highly versatile method for furnishing unsymmetrical biaryls. Classical Suzuki reaction is as shown in scheme 2.

Scheme 2



Neutral organoboron compounds possess low reactivity which is problematic as they do not participate in coupling reaction all by themselves. This calls for addition of Lewis base to the reaction which acts as a nucleophilic promoter by creating an “ate” -complex. During nascent developmental stages of Suzuki reaction relatively strong Lewis bases like ethoxide and hydroxide were used. Gradually, phosphate and carbonate were found to be as milder bases, allowing superior tolerance of functional group. Recent developments in this methodology have extensively broadened the possible applications of this reaction and the reaction partners are not confined to aryls only, but include alkyls, allyls, alkenyls, alkynyls

and benzyls. Trifluoroborates, cyclic boronate esters specially pinacol esters or organoboranes can be used in the place of boronic acids.

Mechanism

The most established mechanism of Suzuki reaction is delineated in figure 2.

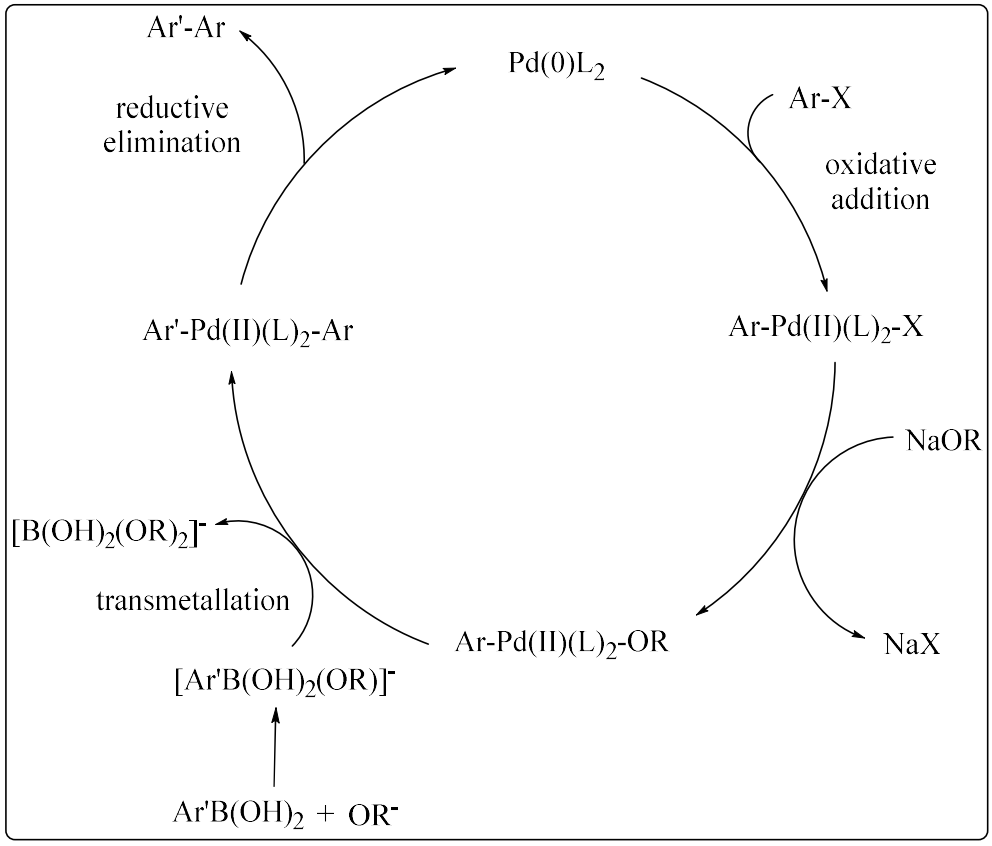


Figure 2. Outline of catalytic cycle for Suzuki coupling.

The reaction proceeds via general organometallic steps. The initial step is oxidative addition of coordinatively unsaturated palladium to organic halide to create organopalladium species. Reaction of this species with base leads to another new organopalladium intermediate which via transmetallation with the boron-ate complex generates another organopalladium species. Finally, reductive elimination restores the original palladium catalyst and furnishes the desired product, thus completing the catalytic cycle. One-point worth mentioning is the activation of boron atom by base which magnifies the polarisation of the organic ligand and thus eases i.e. smoothens transmetallation as it makes the boron atom more nucleophilic and more reactive towards palladium complex in transmetallation step. No reaction takes place

under neutral condition which is the trademark of boron chemistry compared to other organometallic reagents.

Suzuki reaction's synthetic usefulness is evident by following facts:

1. It employs milder reaction conditions.
2. High functional group tolerance i.e. Older traditional methods for merging of aryl groups typically required catalysts and reagents that are incompatible with substrates bearing polar functional groups.
3. Broad availability of starting materials.
4. The boronic acids are nontoxic as well as air and moisture stable. They are also commercially available.
5. The boron species that is formed as a side product after completion of reaction can be easily separated and is relatively nontoxic.

Suzuki reaction finds its use in industrial production of many bioactive and natural products. Valsartan an antihypertensive drug, is manufactured by Novartis. Boscalid, used on food crops, is manufactured by BASF. Suzuki reaction is also utilized in synthesis of light emitting polymers like polythiophenes and polyphenylene vinylenes. Organic LED manufactures employ Suzuki cross coupling in large measures.

Emergence of nonphosphine ligands in coupling reactions

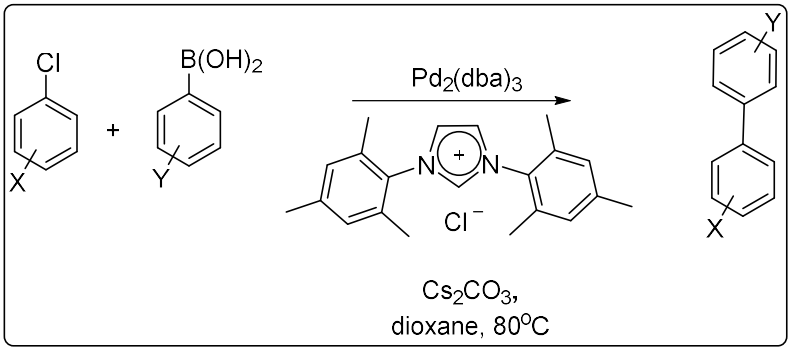
Phosphine ligands dominate Mizoroki-Heck, Suzuki as well as other coupling reactions. They have revolutionized the way modern organometallic reactions are conducted. In conjunction with palladium or other transition metal they impart excellent regio-, chemo- and enantioselectivity to product as well as furnish very high yields of desired products within short reaction times. However, application of phosphine ligands in synthetic organometallic chemistry on industrial and academia scale has its own share of drawbacks. A major pitfall in the use of phosphine ligands is the cleavage of P-C bond in catalytic reactions as well as phosphine oxidation to phosphine oxide, causing breakdown of the ligand, followed by metal reduction and finally cessation of catalytic cycle.[3] Another drawback is of the air sensitive nature of the active species and/or catalytic reaction intermediates of majority of Pd-phosphine derivatives, which are likely to be Pd(0) complexes. Also, most of these commercially available

phosphine ligands are expensive, while those that can be synthesized in laboratory, the process is quite cumbersome. Thus, ligands that are stable, inexpensive, easily accessible, easily synthesized from commercially available precursors having reactivity comparable to phosphine ligands are desired.

While tailored phosphine-based ligands are yet the subject of current research attempts, there are some optimistic developments for non-phosphine ligands, such as arylimines, amines, hydrazones, N,N-based diimines, C-based heterocyclic carbenes, C,N-based 2-aryl-2-oxazolines and palladacycles of amines and oximes. These nonphosphine ligands have the flair to vanquish the drawbacks of instable catalyst as well as environmental concerns. A short literature survey demonstrating promising developments in the utility of phosphine free ligands and complexes in Mizoroki-Heck and Suzuki reaction is as presented below.

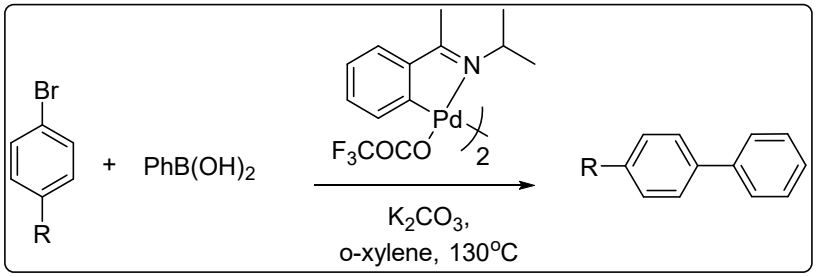
The imidazol-2-ylidenes belong to class of nucleophilic N-heterocyclic carbenes. They have been extensively used in coupling chemistry. The foremost advantage of these ligands is that they do not detach from metal centre. Thus, it avoids use of surplus ligand to impede accumulation of catalyst to yield the bulk metal. Salt of 1,3-bis-(2,4,6-trimethylphenyl)imidazole-2-ylidene (IMes) was checked as possible ancillary ligand by Nolan and co-workers in Suzuki reactions of aryl boronic acids with aryl chlorides (Scheme 3). [4]

Scheme 3



Phosphine free cyclopalladated imine complex was synthesized by Milstein *et. al*. It served as superb catalyst for Suzuki reaction of phenyl boronic acid with non-activated aryl bromides. The catalyst was reported to possess extraordinary air and thermal stability (Scheme 4). [5]

Scheme 4



Iyer and co-workers have explored phosphine free Pd complexes and palladacycles for Mizoroki-Heck reaction in-depth. Cyclopalladated aromatic rings possess high moisture, oxidative and thermal stability. This rationale was successfully exploited by them by synthesizing novel amino and oxime palladacycles for Mizoroki-Heck reaction. [6a, b] They also successfully displayed nitrogen ligands as worthy substitute for traditional phosphine ligands exclusively for Pd catalysed Mizoroki-Heck reaction. Pd complexes of DAB, dimethyl glyoxime, salen, 8-hydroxyquinoline, picolinic acid were prepared and reported to exhibit high yields of E-stilbenes and E-cinnamates. [6c] The N-ligands possessed advantage of easy modification of functional groups and suitable synthetic methods in contrast to P-ligands. In their overall study aryl iodides, aryl bromides and aryl chlorides (some cases) were activated (Scheme 5).

Scheme 5

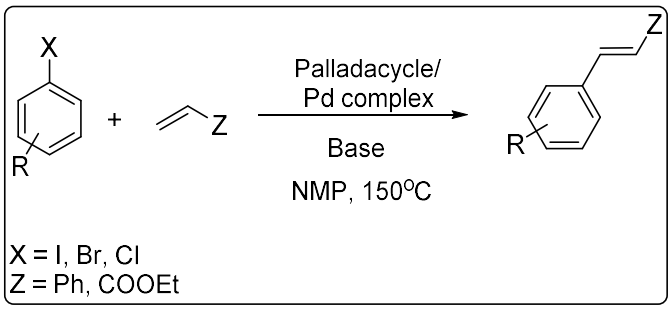


Figure 3 represents structure of Pd complexes and palladacycles used by this group.

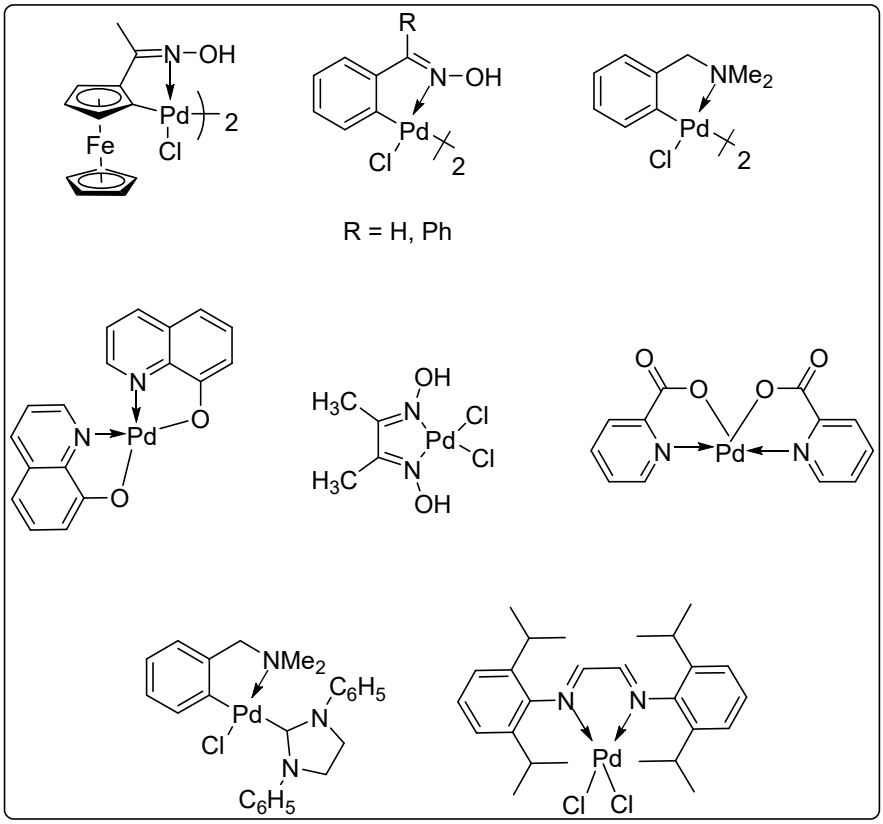
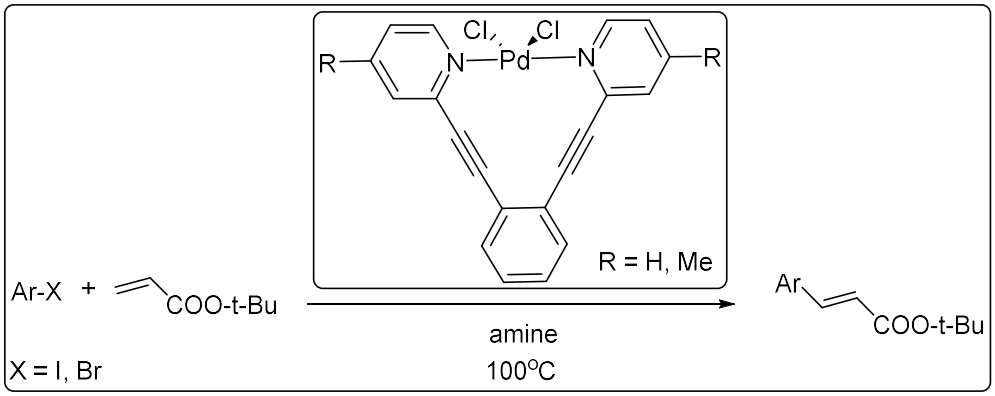


Figure 3. Structures of palladacycle and palladium complex.

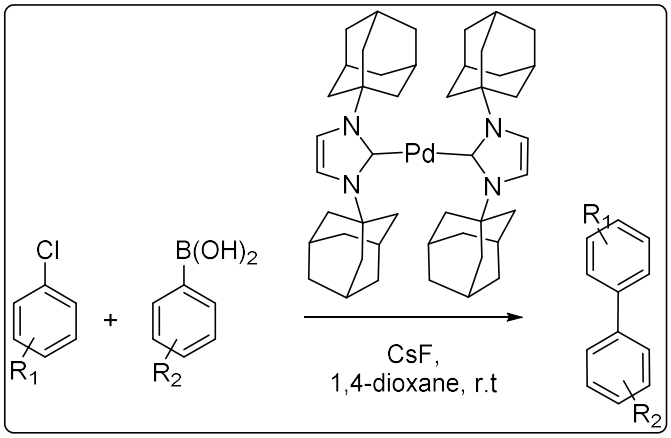
Novel palladium(II) complexes which were procured from 1,2-bis(2-pyridylethynyl)benzenes which serve as bidentate nitrogen ligands, were reported to have effective catalytic properties for Mizoroki-Heck reaction of aryl iodides under phosphine less conditions by Ikuo Ueda and co-workers (Scheme 6). [7]

Scheme 6



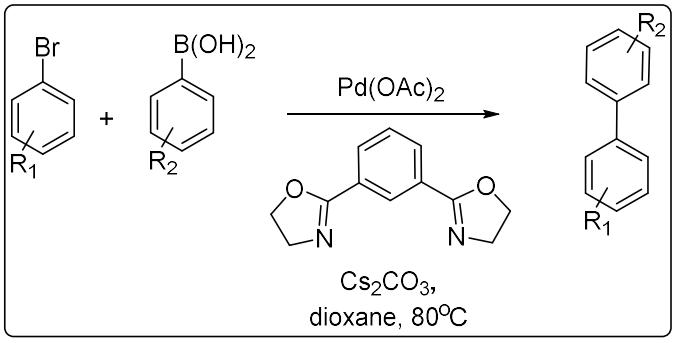
Herrmann and co-workers reported palladium(0) homoleptic complexes with (1,3-Bisadamantylimidazolin-2-ylidene), a class of N- heterocyclic carbene ligand for room temperature Suzuki reaction of aryl chlorides (Scheme 7). [8]

Scheme 7



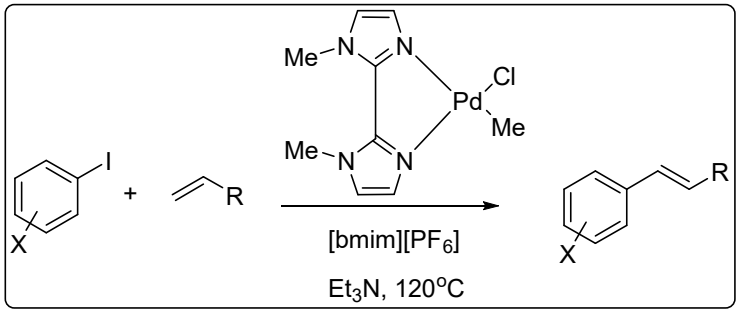
A range of 2-aryl-2-oxazolines were synthesized and scrutinized as ligands by Boykin *et. al.* for Suzuki cross-coupling reaction of aryl boronic acids with aryl bromides. A blend of 2,2'-(1,3-Phenylene)bisoxazoline and $Pd(OAc)_2$ were found to be the best combination for several substrates (Scheme 8). [9]

Scheme 8



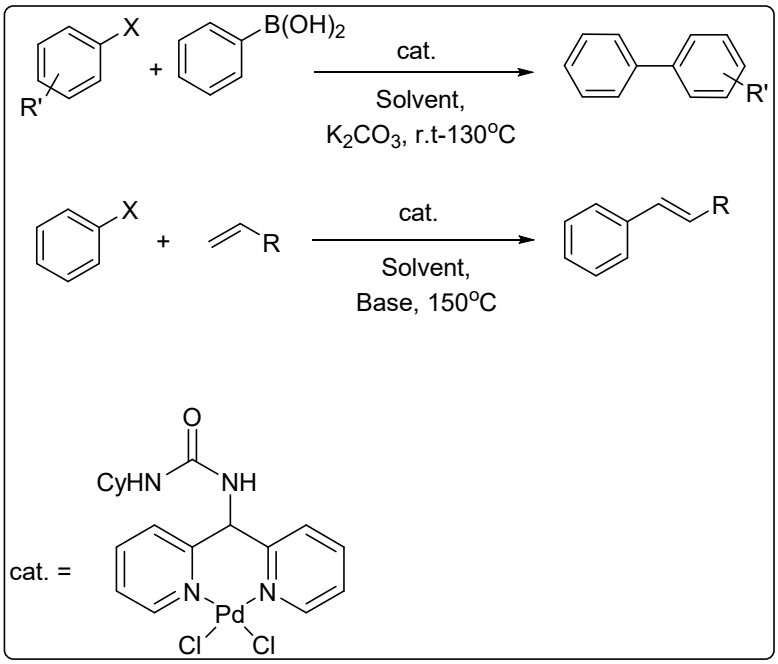
Howard Alper and co-workers successfully synthesized Pd(II) complexes using bisimidazole as ligand and demonstrated it to be an efficient catalyst for Mizoroki-Heck reaction under no phosphine conditions for aryl iodides using ionic liquid as solvent. This catalytic system can be successfully recycled for at least five times with no appreciable loss in activity (Scheme 9). [10]

Scheme 9



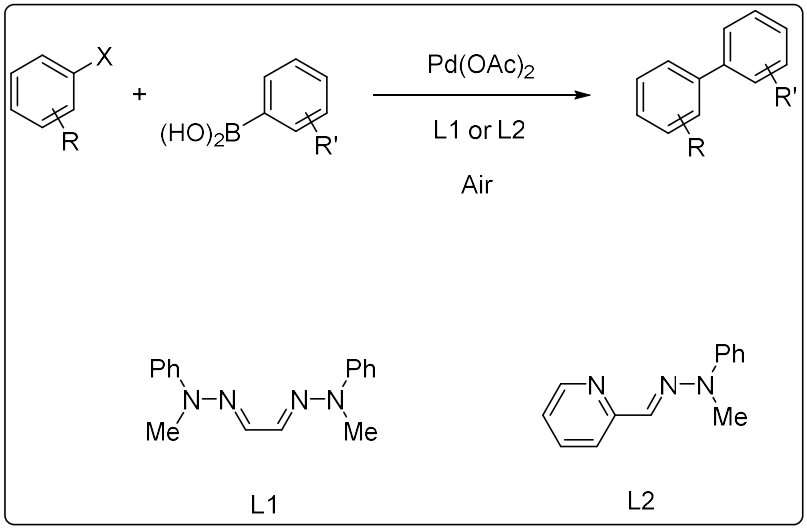
Carmen Najera and co-workers developed di-2-pyridylmethylamine based novel homogeneous palladium complexes as efficient catalysts for Mizoroki-Heck and Suzuki reactions in organic and aqueous solvents (Scheme 10). [11] She was also instrumental in developing thermally stable, air and moisture insensitive oxime palladacycles from inexpensive starting materials and deploying it for using Suzuki reactions. [12]

Scheme 10



Hydrazone ligands like Glyoxal bis(N-methyl-N-phenylhydrazone) and its structural derivative with 2-pyridine-carboxaldehyde were synthesized and probed for Suzuki reaction of arylboronic acids with aryl halides by Takashi Mino and co-workers (Scheme 11). [13]

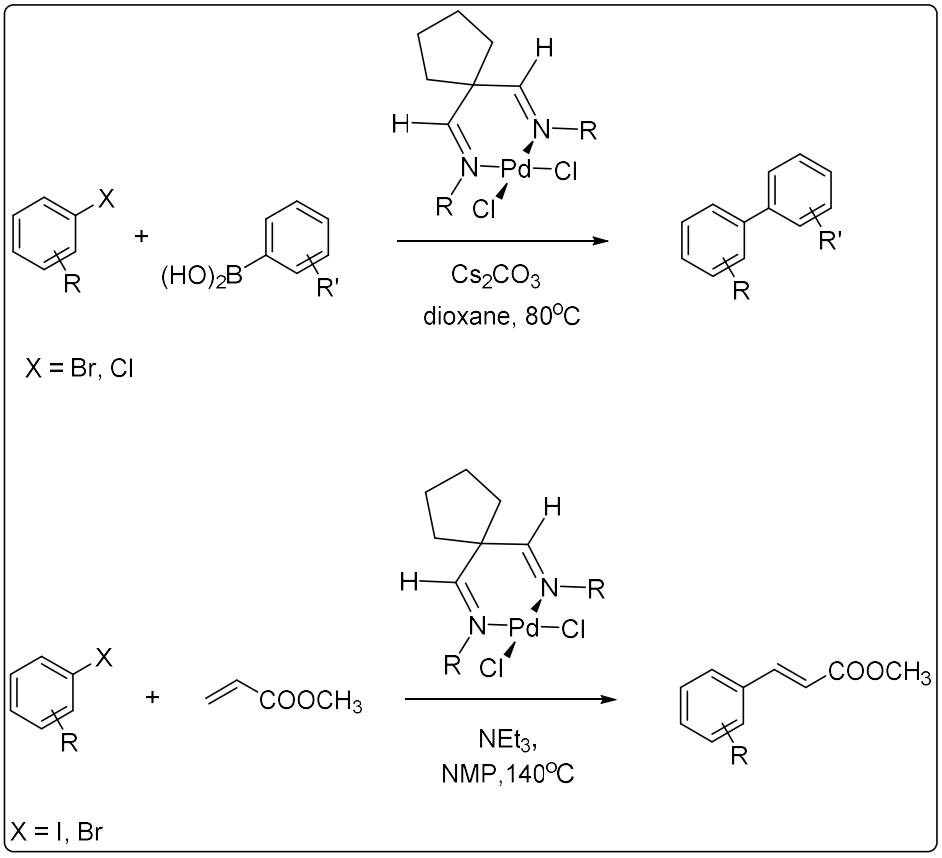
Scheme 11



This phosphine free blend of $Pd(OAc)_2$ with hydrazone ligand was found to be an effective coalition for diverse substrates and it furnished good yield of products.

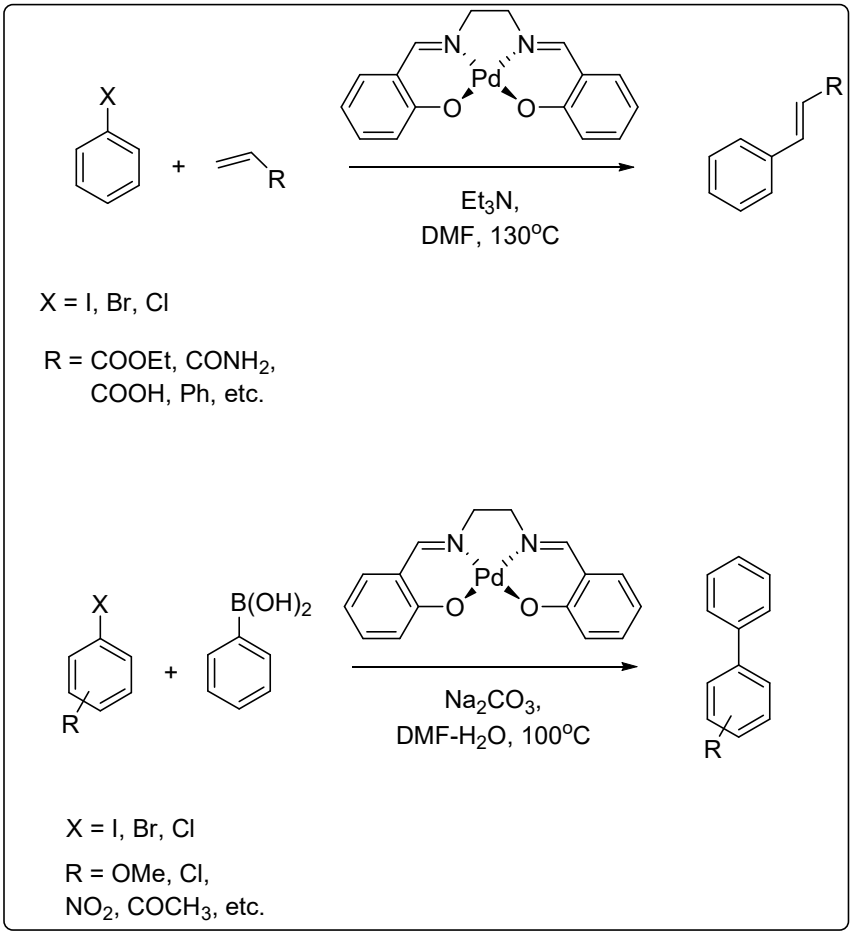
Kirchner and co-workers synthesized a series of β-diimine ligands (sterically hindered) and were able to create its complex with Pd(II). These complexes were then investigated for Suzuki coupling of aryl boronic acids with aryl halides as well as for Mizoroki-Heck reaction of methyl acrylate with aryl halides (Scheme 12). [14]

Scheme 12



Suresh Waghmode and co-workers synthesized phosphine free palladium-salen complexes and checked its utility for Mizoroki-Heck olefination employing aryl iodides and Suzuki reaction employing aryl iodides and aryl bromides. These were highly active catalysts furnishing excellent yield of products (70-90%) within short reaction times (10-60 min) under aerobic conditions. The complexes investigated were N,N'-bis(salicylidene)-ethylenediamino-palladium and its 1,2-phenylenediamino counterpart (Scheme 13). [15]

Scheme 13



The literature that is documented here just represents tip of an iceberg indicating the vastness of this area. Some other examples include use of Dabco (triethylenediamine) for Suzuki cross-coupling by Li *et. al.* [16], Use of Schiff bases acquired from substituted benzaldehydes as fruitful ligands for palladium(0) catalyzed Suzuki reaction by Sarkar *et. al.*[17] and application of N,N-Dimethyl-β-alanine as powerful phosphine free ligand for Mizoroki-Heck reaction of aryl halides by Qing-Xiang Guo and co-workers. [18]

3.2 Objective

Phosphine ligands which have revolutionized the way in which modern organometallic reactions (e.g. coupling reactions) are conducted are very expensive and synthetic methods involved in their preparation are quite cumbersome. Our core objective of this chapter is to search for effective non-phosphine ligands which can act as viable alternatives i.e. substitute for phosphine ligands. This has led us to nitrogen and oxygen compounds as phosphine free alternatives. Typically, we centred our attention mainly towards oximes as ligand for palladium catalyzed Mizoroki-Heck, Suzuki and some well-known organic transformations because oximes (acetophenone oxime) are very familiar ligands in organometallic chemistry as bonded to palladium in palladacycle form. Their naked form as ligand bonded to palladium (monomeric form) and its reactivity is hitherto unexplored. A plethora of commercially available, inexpensive aldehydes and ketones are available in market or readily synthesized. Thus, a vast library of aldoximes and ketoximes can be constructed and used as phosphine free ligands. These ligands also offer freedom i.e. scope for structural and electronic tuning by trouble-free simple functionalization to guide the reaction in an appropriate direction i.e. structural diversity is quite vast which is comparable to that in phosphines due to offering of wide variety of substituents by starting materials.

We have also tried Mannich base of ketone as ligand based upon the same rationale that wide variety of ketones are available that are not only good substrates for Mannich reaction but also open up the possibility of vast structural diversity observed in phosphines. This Mannich base with its bidentate ability to coordinate palladium forms a stable chelate making the complex long lasting for reaction and resistant to oxidation as observed in case of phosphines.

We have also tried some oxygen compounds as ligand so as to get a clear-cut picture of which element serves as better donor to palladium metal as well as to illuminate ourselves that which ligand among few selected oxygen compounds serves as best ligand in palladium catalyzed coupling reactions. Figure 4 represents structure of N, O-ligands used in this study.

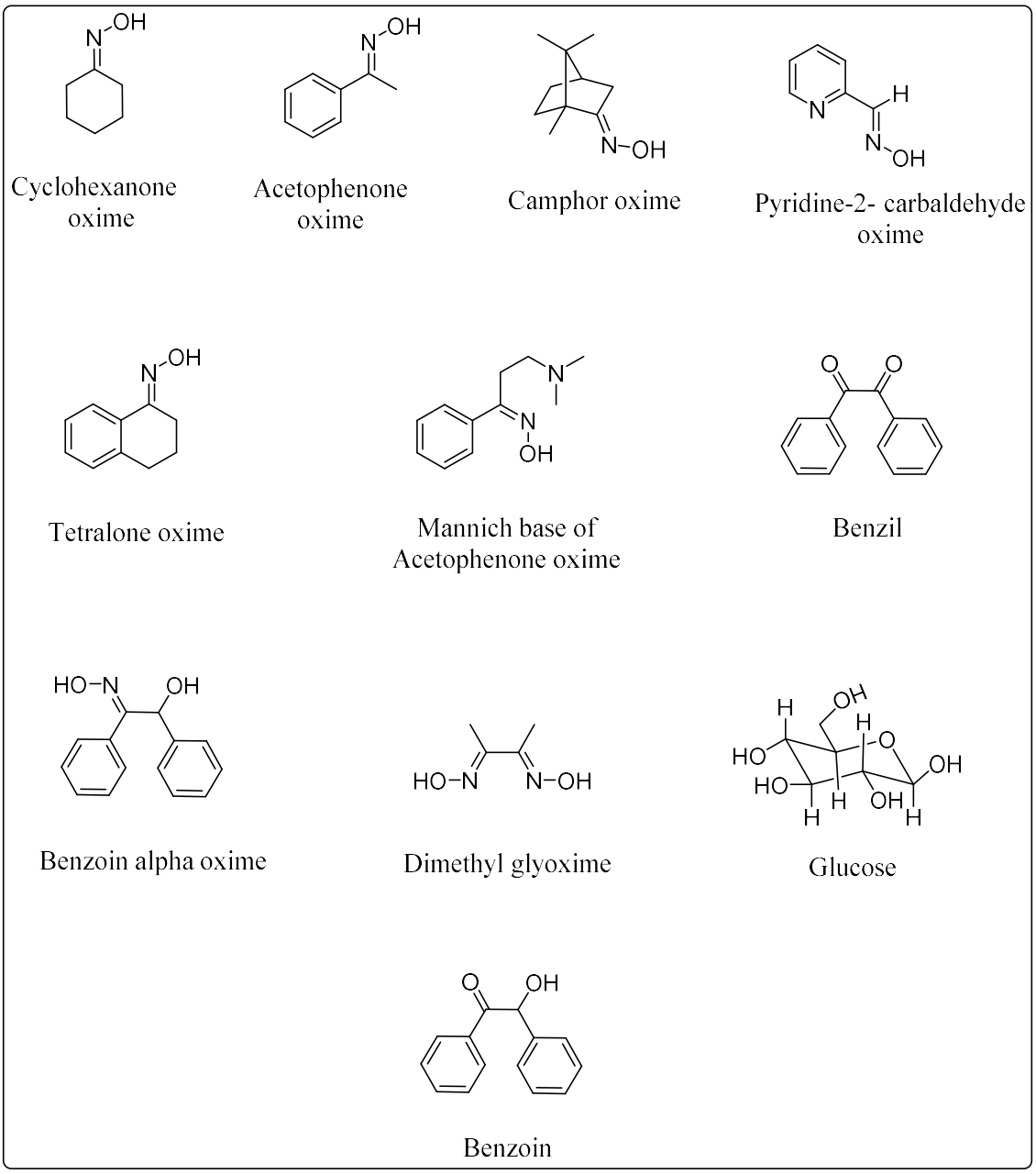


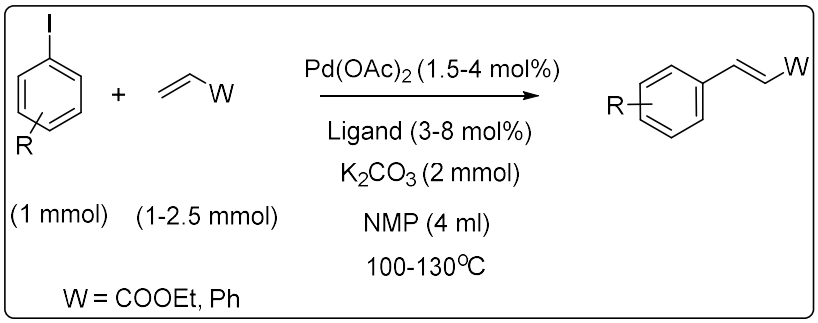
Figure 4. Structure of N, O-ligands.

Section A: N, O-ligands for catalysis of Mizoroki-Heck reaction.

3A.1 Present work

We were interested in investigating N, O- ligands for Mizoroki-Heck reaction of aryl iodides with simple monosubstituted olefins like ethyl acrylate and styrene. Scheme 14 shows the generalised reaction.

Scheme 14



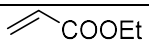
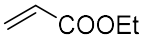
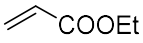
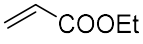
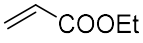
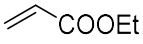
Results of scheme 14 are tabulated in table 1.

Table 1: N, O- ligands in Mizoroki-Heck reaction of aryl iodides with monosubstituted olefins.

Sr. No.	Aryl iodide	Olefin	Ligand	Time (hr)	Yield (%) [h]
1.[a]	C_6H_5I	COOEt	Cyclohexanone oxime	5	96
2.[a]	C_6H_5I	COOEt	D-Glucose	7	85
3.[b]	C_6H_5I	COOEt	Cyclohexanone oxime	4	100
4.[c]	C_6H_5I	COOEt	Benzil	4	94
5.[d]	C_6H_5I	COOEt	Acetophenone oxime	5	63
6.[e]	C_6H_5I	Ph	Acetophenone oxime	5	79

Continued…

Table 1: N, O- ligands in Mizoroki-Heck reaction of aryl iodides with monosubstituted olefins.

Sr. No.	Aryl iodide	Olefin	Ligand	Time (hr)	Yield (%) [h]
7.[d]	C_6H_5I		Camphor oxime	15	65
8.[e]	C_6H_5I		Tetralone oxime	19	82
9.[e]	C_6H_5I		Pyridine-2-carbaldehyde oxime	19	65
10.[d]	C_6H_5I		Mannich base of acetophenone oxime	22	90
11.[d]	C_6H_5I		Benzoin α-oxime	22	87
12.[d]	4-$CH_3OC_6H_4I$		Mannich base of acetophenone oxime	22	84
13.[f]	4-$CH_3C_6H_4I$		Dimethylglyoxime	2	97
14.[f]	4-FC_6H_4I		Dimethylglyoxime	3	92
15.[g]	4-$CH_3OC_6H_4I$		Dimethylglyoxime	3	80

[a] 2 mol% $Pd(OAc)_2$, 4 mol% ligand, 1 mmol n-Bu_4NBr, 2.5 mmol olefin. [b] 4 mol% $Pd(OAc)_2$, 8 mol% ligand, 2.5 mmol olefin. [c] 1.5 mol% $Pd(OAc)_2$, 3 mol% ligand, 2.5 mmol olefin. [d] 4 mol% $Pd(OAc)_2$, 8 mol% ligand, 1.5 mmol olefin. [e] 4 mol% $Pd(OAc)_2$, 8 mol% ligand, 1 mmol olefin. [f] 2 mol% $Pd(OAc)_2$, 4 mol% ligand, 1.3 mmol olefin. [g] 2 mol% $Pd(OAc)_2$, 4 mol% ligand, 1 mmol olefin. [h] Temperature: 130°C (entry 1-12), Temperature: 100°C (entry 13-15).

3A.2 Results and Discussion

Oxime ligands used in this study were easily synthesized from appropriate ketone and 2 equivalent of hydroxylamine hydrochloride in methanol as reported in literature.[19] Mannich base of acetophenone oxime was also synthesized according to well-established literature procedure.[20] Both class of synthesized ligands were used directly for investigation. All reactions required elevated temperatures along with longer reaction times (in some cases) to furnish fruitful yields of the product. A 1:2 Pd:Ligand ratio furnishes the most active catalyst for our Mizoroki-Heck couplings. For the Mizoroki-Heck reactions detailed above, we implemented moderate loadings of catalyst (1.5-4 mol% Pd). As our objective is to screen various ligands, we did not strive to independently optimize catalyst concentration for each coupling reaction. NMP and K_2CO_3 were selected as solvent and base for our study.

Cyclohexanone oxime provided the best yield of coupling product (Table 1, entries 1 and 3, 96% and 100% yield, respectively). The slight difference in yield is due to ionic liquid n-Bu_4NBr. D-Glucose, a polyhydroxylated polydentate ligand also served as good oxygen-based ligand furnishing 85% yield of the Mizoroki-Heck coupling product (entry 2). Benzil, a bidentate oxygen-based ligand too exhibited excellent yield of coupling product (entry 4, 94% yield). Acetophenone oxime ligand exhibited good yield of coupling product when olefin coupling partner were ethyl acrylate or styrene (entries 5 & 6, 63% & 79% yield, respectively). Camphor oxime, a more sterically hindered ligand than cyclohexanone oxime provided good yield (entry 7, 65% yield) of desired product albeit with longer reaction time. However, Tetralone oxime furnished 82% yield of *trans*-stilbene (entry 8) within more or less same time frame.

Pyridine-2-carbaldehyde oxime, a bidentate ligand with the ability to donate electrons to metal atom from two nitrogen atoms can form 5-member chelate. This ligand however exhibited only 65% yield of *trans*-stilbene as desired product (entry 9). Whereas Mannich base of acetophenone oxime, a bidentate ligand with the ability to donate via forming 6-member chelate employing two nitrogen atoms exhibited excellent yield of desired product (entries 10 & 12, 90% & 84% yield, respectively). Benzoin α- oxime also furnished excellent 87% yield of product (entry 11).

The coupling of 4-Iodotoluene with ethyl acrylate as olefin partner employing dimethylglyoxime as ligand furnishes product Ethyl (E)-3-(4-methylphenyl) acrylate **(1a)** in excellent 97% yield (entry 13) with complete E selectivity of double bond. In ^1H NMR

spectrum the signals at δ 7.66 (d, J= 16.04 Hz, 1H) and δ 6.39 (d, J= 16.04 Hz, 1H) confirmed two *trans* olefinic protons of 1,2 disubstituted olefin. The signals at δ 7.43 (d, J= 8.08 Hz, 2H) and δ 7.19 (d, J= 7.83 Hz, 2H) confirmed the presence of 4 aromatic protons of A_2B_2 pattern indicative of *para* substitution. The signal at δ 2.37 (s, 3H) was suggestive of methyl group (-CH_3 group) attached to benzene ring. Finally, the signals at δ 4.26 (q, 2H) and δ 1.34 (t, 3H) confirmed ethyl group of formed alkene (-COOEt group). The ^{13}C NMR spectrum exhibited signal at δ 167.10 indicating carbonyl carbon of the -COOEt group. The signal at δ 21.36 manifested -CH_3 group attached to benzene ring. The signals at δ 144.51 and 117.12 were indicative of two vinylic carbons of 1,2-disubstituted olefin. Finally, HRMS (ESI^+) peak at 191.1068 corresponding to formula $C_{12}H_{15}O_2$ $[M+H]^+$ (calculated value 191.1072) confirms the formation of product.

Dimethyl glyoxime displayed better activity as a ligand not only with electron withdrawing but also with electron donating aryl iodides (entries 14 & 15, 92% & 80% yield, respectively). Similar good to excellent yields were obtained with these ligands when different aryl iodides and olefins were investigated.[21]

3A.3 Conclusion

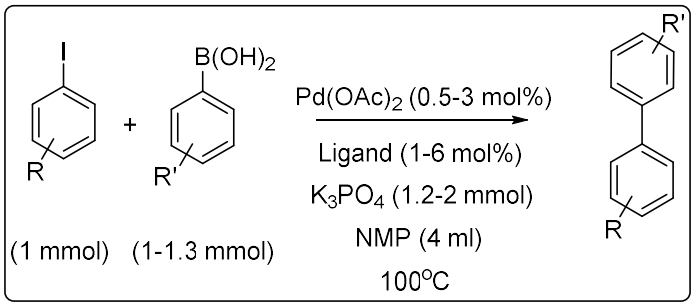
In conclusion, we have successfully screened N, O-ligands as phosphine alternatives for Mizoroki-Heck couplings of monosubstituted olefins with aryl iodides. These ligands are robust and bench stable. Some of these ligands are commercially available at low cost while others can be readily synthesized. Good to excellent yields of Mizoroki-Heck product can be obtained within practical reaction times. Obtained products are *trans* selective. The reaction is feasible even on low catalyst: ligand loading.

Section B: N, O-ligands for catalysis of Suzuki coupling-Preliminary studies.

3B.1 Present work

N, O-ligands utility was examined in Suzuki cross coupling of aryl iodides with aryl boronic acids. Scheme 15 represents the generalised Suzuki reaction for a very short preliminary study conducted by us. This was done to check whether inexpensive, easily synthesizable N, O-ligands (phosphine alternatives) have wide applicability in organometallic coupling reactions and whether they truly can become phosphine alternatives or not. Following scheme present our progress toward accomplishing this target.

Scheme 15



Results of scheme 15 are tabulated in table 2.

Table 2: N, O-ligands in Suzuki cross coupling.

Sr. No.	Aryl iodide	Boronic acid	Ligand	Time (hr)	Yield (%)
1.[a]	4-ClC_6H_4I	$C_6H_5B(OH)_2$	Cyclohexanone oxime	24	92
2.[b]	C_6H_5I	$C_6H_5B(OH)_2$	Benzil	10	69
3.[c]	C_6H_5I	$C_6H_5B(OH)_2$	Benzoin	10	47

Continued…

Table 2: N, O-ligands in Suzuki cross coupling.

Sr. No.	Aryl iodide	Boronic acid	Ligand	Time (hr)	Yield (%)
4.[d]	4-$CH_3OC_6H_4I$	$C_6H_5B(OH)_2$	Acetophenone oxime	6	29
5.[e]	4-ClC_6H_4I	4-$CH_3C_6H_4B(OH)_2$	Benzoin	14	60
6.[e]	4-FC_6H_4I	4-$CH_3OC_6H_4B(OH)_2$	Benzil	18	55

[a] 0.5 mol% $Pd(OAc)_2$, 1 mol% ligand, 1.3 mmol boronic acid, 2 mmol base. [b] 1.5 mol% $Pd(OAc)_2$, 3 mol% ligand, 1.3 mmol boronic acid, 2 mmol base. [c] 1.5 mol% $Pd(OAc)_2$, 3 mol% ligand, 1 mmol boronic acid, 2 mmol base. [d] 2 mol% $Pd(OAc)_2$, 4 mol% ligand, 1.2 mmol boronic acid, 1.2 mmol base. [e] 3 mol% $Pd(OAc)_2$, 6 mol% ligand, 1.2 mmol boronic acid, 1.2 mmol base.

3B.2 Results and Discussion

Many N- and O- based compounds efficiently work as ligands for Suzuki as well as other coupling reactions. It has been well documented in literature too. However, simple and readily prepared our N, O- ligands have not been reported for Suzuki and other C-C bond forming coupling reactions. So, we thought to implement i.e. screen our N, O-based compounds as potential ligands for Suzuki coupling employing various aryl iodides and aryl boronic acids in presence of 0.5-3 mol% $Pd(OAc)_2$ as catalyst, 1.2-2 mmol K_3PO_4 as base in N-methyl-2-pyrrolidone at 100°C. A very short quick survey of this reaction was done to check its feasibility. Cyclohexanone oxime ligand gave the best yield (entry 1, 92% yield) with electron withdrawing 1-Chloro-4-iodobenzene and phenyl boronic acid. Benzil and benzoin ligands gave good to moderate yield of desired Suzuki product (entries 2 & 3, 69% & 47% yield respectively). Electron donating 4-Iodoanisole when treated with phenyl boronic acid in presence of acetophenone oxime as ligand furnished low yield of the desired product (entry 4, 29% yield). Finally, electron withdrawing aryl iodides when reacted with electron donating aryl boronic acids led to good yields of coupled product (entries 5 & 6, 60% & 55% yield, respectively) using benzoin and benzil as ligand.

3B.3 Conclusion

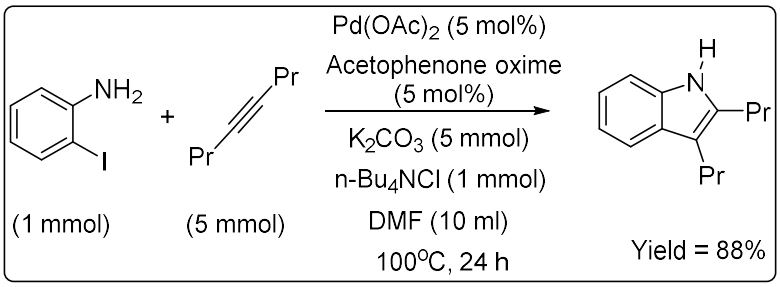
We have successfully tried to establish a robust strategy for direct formation of various biphenyls by Suzuki reaction using cheaper, robust and readily synthesizable N, O-ligands (phosphine alternatives). Reaction conditions are very mild with product yield ranging from moderate to good, and demonstrating adequate tolerance to range of substituents on aryl iodides and aryl boronic acids. Preliminary studies thus sheds light on the practicality of the reaction using N, O-ligands.

Section C: Application of N, O-ligands in organic transformations.

3C.1 Present work

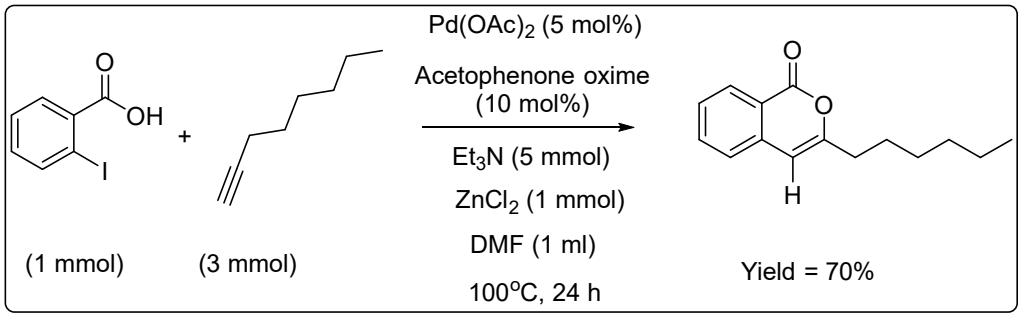
Annulation reactions catalyzed by palladium in conjunction with phosphine ligands is well known and well-established synthetic methodology. One such example is Larock indole synthesis. [22] We attempted Larock indole annulation using representative acetophenone oxime as phosphine alternative N, O-ligand. Good yield of the product was obtained. Scheme 16 shows substituted indole formation employing 2-Iodoaniline and 4-Octyne.

Scheme 16



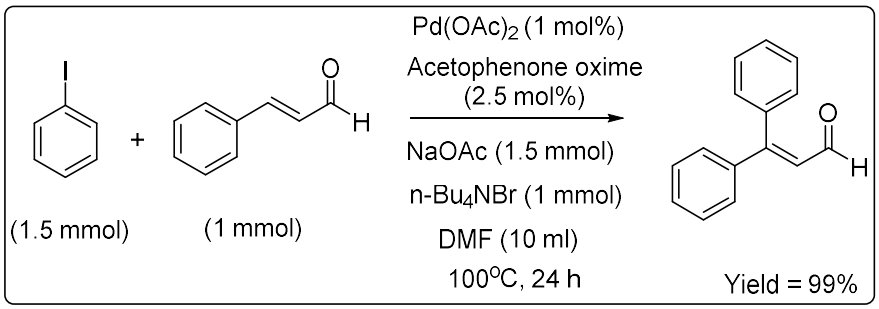
Isocoumarins are a category of lactones which exhibit extensive biological activity. Several syntheses of this class of naturally occurring lactones using organometallic reagents have been evolved. The same benzocoumarin synthesis using palladium-phosphine cocktail has also been reported. [23] We tried the same palladium catalyzed reaction using representative acetophenone oxime as phosphine alternative N, O-ligand. Good yield of the product was obtained. Scheme 17 shows benzocoumarin derivative obtained by reacting 2-Iodobenzoic acid with 1-Octyne.

Scheme 17



The application of N, O-ligand using representative acetophenone oxime was then extended to Mizoroki-Heck arylation of 1,2-disubstituted olefin employing (E)-cinnamaldehyde and Iodobenzene as model substrates to generate trisubstituted olefin. Scheme 18 summarizes the reaction.

Scheme 18



3C.2 Results and Discussion

In pursuance of our research under development of novel non-phosphine N, O-ligands for Mizoroki-Heck and Suzuki reactions, we became interested in implementation of these ligands in commonly encountered palladium catalyzed organic transformations. Two reactions selected for this purpose were Larock indole annulation and isocoumarin synthesis i.e. synthesis of nitrogen and oxygen containing heterocycles. We were curious to investigate the outcome on yield and selectivity of products upon application of these ligands. For this purpose, acetophenone oxime as ligand was chosen randomly from a group of our N, O-ligands. Promising results were obtained when we utilized these ligands. 2,3-Dipropyl-1H-Indole was formed in excellent yield (88%) when 2-Iodoaniline (1 mmol) was reacted with 4-Octyne (5 mmol) in presence of cocktail of $Pd(OAc)_2$ (5 mol%), acetophenone oxime (5 mol%), K_2CO_3 (5 mmol), n-Bu_4NCl (1 mmol) in DMF (10 ml) at 100°C for 24 hour as depicted in scheme 16.

For isocoumarin synthesis, 3-Hexyl-1H-Isochromen-1-one was obtained in good 70% yield (scheme 17) when 2-Iodobenzoic acid (1 mmol) was reacted with 1-Octyne (3 mmol) in presence of $Pd(OAc)_2$ (5 mol%), excess ligand acetophenone oxime (10 mol%), Et_3N (5 mmol), $ZnCl_2$ (1 mmol) in DMF (1 ml) at 100°C for 24 hour. Excellent selectivity for six-membered ring isocoumarin was observed with no formation of five-membered phthalide ring which was confirmed by proton NMR. In ^1H NMR spectra, the signal of olefinic proton on

lactone ring in an isocoumarin predominantly surfaces in range of 6.2-6.9 ppm (6.26, s, 1H in our case), whereas the corresponding olefinic proton signal for an alkylidene phthalide manifests at δ 5.2-5.8 ppm.

Having successfully explored N, O-ligand in heterocycle synthesis we then next explored use of acetophenone oxime as selected N, O-ligand in Mizoroki-Heck reaction of 1,2-disubstituted olefins as olefinic partner. This reaction generates trisubstituted olefin which has wide applicability. As depicted in scheme 18, Iodobenzene (1.5 mmol) was coupled with *trans*-Cinnamaldehyde (1 mmol) as chosen 1,2-disubstituted olefin in presence of $Pd(OAc)_2$ (1 mol%), acetophenone oxime (2.5 mol%), base NaOAc (1.5 mmol) and n-Bu_4NBr (1 mmol) in DMF (10 ml) at 100°C for 24 hour. A yield of 99% of desired product 3,3-Diphenylacrylaldehyde (8a) was obtained. In ^1H NMR spectrum the signal at δ 9.55 (d, J= 7.93 Hz, 1H) was informative of aldehydic proton. Signal at δ 7.52-7.28 (m, 10 H) were suggestive of aromatic protons. Finally, signal at δ 6.63 (d, J= 7.93 Hz, 1H) was of lone olefinic proton of obtained trisubstituted olefin. Ligand less Mizoroki-Heck reaction of Iodobenzene with *trans*-Cinnamaldehyde was reported by Varinder Aggarwal and co-workers where they mention 89% isolated yield of product. [24] Using simple blend of $Pd(OAc)_2$ and acetophenone oxime ligand we were able to increase yield up to 99%.

3C.3 Conclusion

In conclusion, we have successfully displayed acceptable activity of N, O-ligand in palladium catalyzed Larock indole annulation, isocoumarin synthesis and Mizoroki-Heck reaction of Iodobenzene with 1,2-disubstituted olefin *trans*-Cinnamaldehyde.

3.3 Experimental section

General procedure for N, O-ligands mediated Mizoroki-Heck reaction (Section A).

To an oven-dried 25 ml round bottom flask equipped with magnetic stirrer bar was charged palladium acetate (1.5-4 mol%) and ligand (3-8 mol%) in NMP (1 ml). The reaction mixture was stirred for 3 minutes. To this reaction mixture base K_2CO_3 (2 mmol), aryl iodide (1 mmol), olefin (1-2.5 mmol) and NMP (3 ml) was added and the reaction mixture was stirred at the indicated temperature for the indicated amount of time. At the conclusion of the reaction as monitored by TLC, the crude reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel to give the desired product.

General procedure for N, O-ligands mediated Suzuki reaction (Section B).

To an oven-dried 25 ml round bottom flask equipped with magnetic stirrer bar was charged palladium acetate (0.5-3 mol%) and ligand (1-6 mol%) in NMP (1 ml). The reaction mixture was stirred for 3 minutes. To this reaction mixture base K_3PO_4 (1.2-2 mmol), aryl iodide (1 mmol), aryl boronic acid (1-1.3 mmol) and NMP (3 ml) was added and the reaction mixture was stirred at the indicated temperature for the indicated amount of time. At the conclusion of the reaction as monitored by TLC, the crude reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel to give analytically pure product.

General procedure for Larock indole annulation using acetophenone oxime ligand (Section C).

Palladium acetate (11 mg, 5 mol%), acetophenone oxime (7 mg, 5 mol%), n-Bu_4NCl (277 mg, 1 mmol), K_2CO_3 (691 mg, 5 mmol), 2-Iodoaniline (219 mg, 1 mmol), 4-Octyne (551 mg, 5 mmol) and DMF (10 ml) were added to an oven-dried 25 ml round bottom flask equipped with magnetic stirrer bar. The system was degassed and heated at 100^oC for 24 h. At the conclusion of the reaction as monitored by TLC, the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride and water. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by column chromatography on silica gel to give analytically pure product.

General procedure for Benzocoumarin synthesis using acetophenone oxime ligand (Section C).

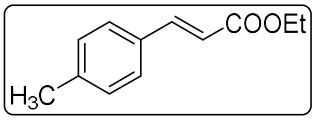
To a solution consisting of 2-Iodobenzoic acid (248 mg, 1 mmol), 1-Octyne (330 mg, 3 mmol) and Et_3N (0.69 ml, 5 mmol) in DMF (1 ml) under argon were added $Pd(OAc)_2$ (11 mg, 5 mol%), acetophenone oxime (14 mg, 10 mol%) and zinc chloride (136 mg, 1 mmol). The mixture was heated at 100°C for 24 h. At the conclusion of the reaction as monitored by TLC, the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride and water. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by column chromatography on silica gel to give analytically pure product.

General procedure for Mizoroki-Heck reaction of (E)-cinnamaldehyde with Iodobenzene (Section C).

A mixture of NaOAc (123 mg, 1.5 mmol) and n-Bu_4NBr (322 mg, 1 mmol) was heated in 25 ml round bottom flask equipped with magnetic stirrer bar until it melts. Then trans-Cinnamaldehyde (132 mg, 1 mmol), Iodobenzene (306 mg, 1.5 mmol), palladium acetate (2 mg, 1 mol%) and acetophenone oxime (4 mg, 2.5 mol%) dissolved in dry DMF (10 ml) was added. The reaction mixture was heated at 100°C for 24 h. Upon completion of the reaction as monitored by TLC, the reaction mixture was poured on saturated $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in the rotary evaporator. The obtained residue was purified by column chromatography on silica gel to give the desired product.

Experimental data

Ethyl (E)-3-(4-methylphenyl) acrylate (1a):



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as pale-yellow oil (0.184g, 97%).

R_f = 0.39 (petroleum ether/EtOAc, 85:15).

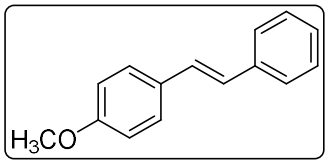
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.66 (d, J= 16.04 Hz, 1H), 7.43 (d, J= 8.08 Hz, 2H), 7.19 (d, J= 7.83 Hz, 2H), 6.39 (d, J= 16.04 Hz, 1H), 4.26 (q, 2H), 2.37 (s, 3H), 1.34 (t, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 167.10, 144.51, 140.52, 131.67, 129.53, 127.97, 117.12, 60.31, 21.36, 14.27.

IR ($CHCl_3$) ν_{max} = 2920, 2856, 2347, 2286, 1711, 1610, 1383, 1314, 1267, 1169, 1118, 1038, 811, 767, 664.

HRMS: *m/z* = calcd for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1072, found: 191.1068.

(E)-1-methoxy-4-styrylbenzene (2a):



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as white solid (0.168g, 80%).

R_f = 0.45 (petroleum ether/EtOAc, 90:10).

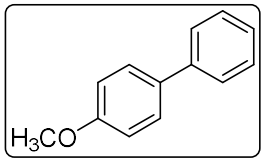
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.31 - 7.69 (m, 7H), 7.17 (d, *J*=7.5 Hz, 2H), 7.05 (d, *J*=8.7 Hz, 2H), 3.82 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 159.4, 137.7, 130.2, 129.5, 128.7, 128.3, 128.2, 127.8, 127.7, 127.3, 126.7, 126.3, 114.2, 113.6, 113.0, 55.3.

IR ($CHCl_3$) ν_{max} = 3017, 2925, 2850, 1602, 1510, 1452, 1298, 1253, 1218, 1177, 1113, 1030, 967, 906, 819, 761, 687.

HRMS: *m/z* = calcd for $C_{15}H_{15}O$ $[M^+ + H]^+$ 211.1115 found: 211.1114.

4-methoxy-1,1'-Biphenyl (3a):



Chromatography (96:4 petroleum ether: EtOAc) furnished the desired product as white solid (0.053g, 29%).

R_f = 0.4 (petroleum ether/EtOAc, 90:10).

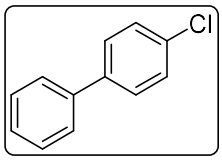
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.59-7.52 (m, 4 H), 7.47-7.31 (m, 3H), 7.03 – 6.96 (m, 2H), 3.87 (s, 3 H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 128.71, 128.14, 126.73, 126.64, 114.19, 55.34.

IR ($CHCl_3$) ν_{max} = 3383, 2923, 2858, 2725, 1947, 1883, 1713, 1651, 1603, 1520, 1455, 1374, 1282, 1252, 1187, 1120, 1035, 831, 758, 687.

HRMS: *m/z* = calcd for $C_{13}H_{12}O$ $[M]^+$ 184.0883, found: 184.0882.

4-chloro-1,1'-Biphenyl (4a):



Chromatography (97:3 petroleum ether: EtOAc) furnished the desired product as white solid (0.173g, 92%).

R_f = 0.45 (petroleum ether/EtOAc, 90:10).

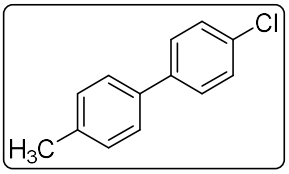
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.60 - 7.37 (m, 9 H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 139.98, 139.65, 133.35, 128.88, 128.37, 126.97.

IR ($CHCl_3$) ν_{max} = 3381, 2846, 2725, 1712, 1602, 1460, 1376, 1308, 1216, 1161, 1094, 1011, 970, 832, 761, 726, 666.

HRMS: *m/z* = calcd for $C_{12}H_9Cl$ $[M]^+$ 188.0387, found: 188.0386.

4-chloro-4'-methyl-1,1'-Biphenyl (5a):



Chromatography (97:3 petroleum ether: EtOAc) furnished the desired product as white solid (0.121g, 60%).

R_f = 0.50 (petroleum ether/EtOAc, 90:10).

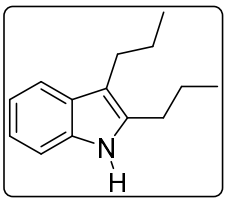
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.54-7.42 (m, 6 H), 7.24 – 7.23 (m, 2 H), 2.41 (s, 3 H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 139.54, 137.38, 137.05, 132.99, 129.57, 128.81, 128.13, 126.77, 21.07.

IR ($CHCl_3$) ν_{max} = 3387, 2923, 2858, 1571, 1455, 1372, 1030, 842, 777, 724, 658.

HRMS: *m/z* = calcd for $C_{13}H_{12}Cl$ $[M+H]^+$ 203.0622, found: 203.0527.

2,3-Dipropyl-1H-Indole (6a):



Chromatography (95:5 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.177g, 88%).

R_f = 0.25 (petroleum ether/EtOAc, 90:10).

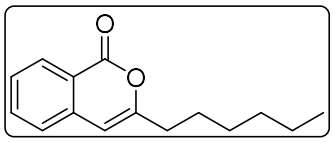
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.71 (s, 1H), 7.54-7.50 (m, 1H), 7.30-7.26 (m, 1H), 7.14-7.02 (m, 2H), 2.74-2.63 (m, 4H), 1.78-1.57 (m, 4H), 0.97 (q, J= 7.33 Hz, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 135.23, 135.14, 128.79, 120.73, 118.81, 118.35, 112.10, 110.14, 29.68, 28.12, 26.23, 24.09, 23.14, 14.23, 13.97.

IR ($CHCl_3$) ν_{max} = 3412, 2961, 2931, 1608, 1575, 1462, 1352, 903, 752, 735.

HRMS: *m/z* = calcd for $C_{14}H_{19}N$ $[M]^+$ 201.1517, found: 201.1513.

3-Hexyl-1H-Isochromen-1-one (7a):



Chromatography (95:5 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.161g, 70%).

R_f = 0.60 (petroleum ether/EtOAc, 90:10).

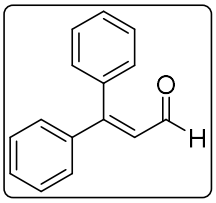
^{1}H NMR ($CDCl_3$, 200 MHz) δ = 8.25 (d, J= 7.96 Hz, 1H), 7.71-7.63 (m, 1H), 7.48-7.33 (m, 2H), 6.26 (s, 1H), 2.52 (t, J= 7.71 Hz, 2H), 1.78-1.63 (m, 2H), 1.44-1.26 (m, 6H), 0.92-0.86 (m, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 163.07, 158.29, 137.60, 134.64, 129.43, 127.46, 124.96, 120.06, 102.81, 33.48, 31.45, 28.63, 26.81, 22.46, 13.99.

IR ($CHCl_3$) ν_{max} = 3066, 2932, 2860, 1806, 1732, 1656, 1473, 1318, 1213, 1155, 1028, 826, 754, 688.

HRMS: *m/z* = calcd for $C_{15}H_{18}NaO_2$ $[M+Na]^+$ 253.1205; found: 253.1204.

3,3-Diphenylacrylaldehyde (8a):



Chromatography (95:5 petroleum ether: EtOAc) furnished the desired product as yellow oil (0.205g, 99%).

R_f = 0.30 (petroleum ether/EtOAc, 90:10).

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 9.55 (d, J= 7.93 Hz, 1H), 7.52-7.28 (m, 10 H), 6.63 (d, J= 7.93 Hz, 1H).

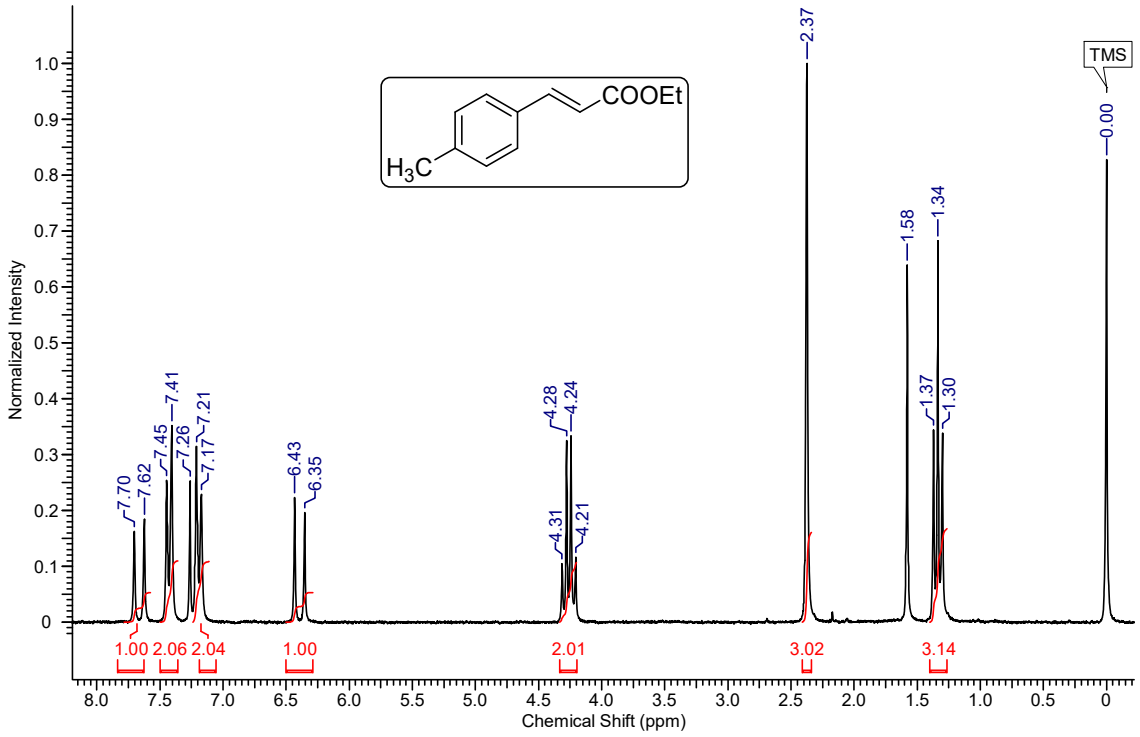
^{13}C NMR ($CDCl_3$, 125 MHz) δ = 193.49, 162.24, 139.65, 136.62, 130.69, 128.63, 128.57, 128.30, 127.22.

IR ($CHCl_3$) ν_{max} = 3305, 3019, 2852, 2400, 1660, 1593, 1572, 1492, 1445, 1422, 1389, 1343, 1215, 1156, 1127, 1075, 1046, 768, 701, 668.

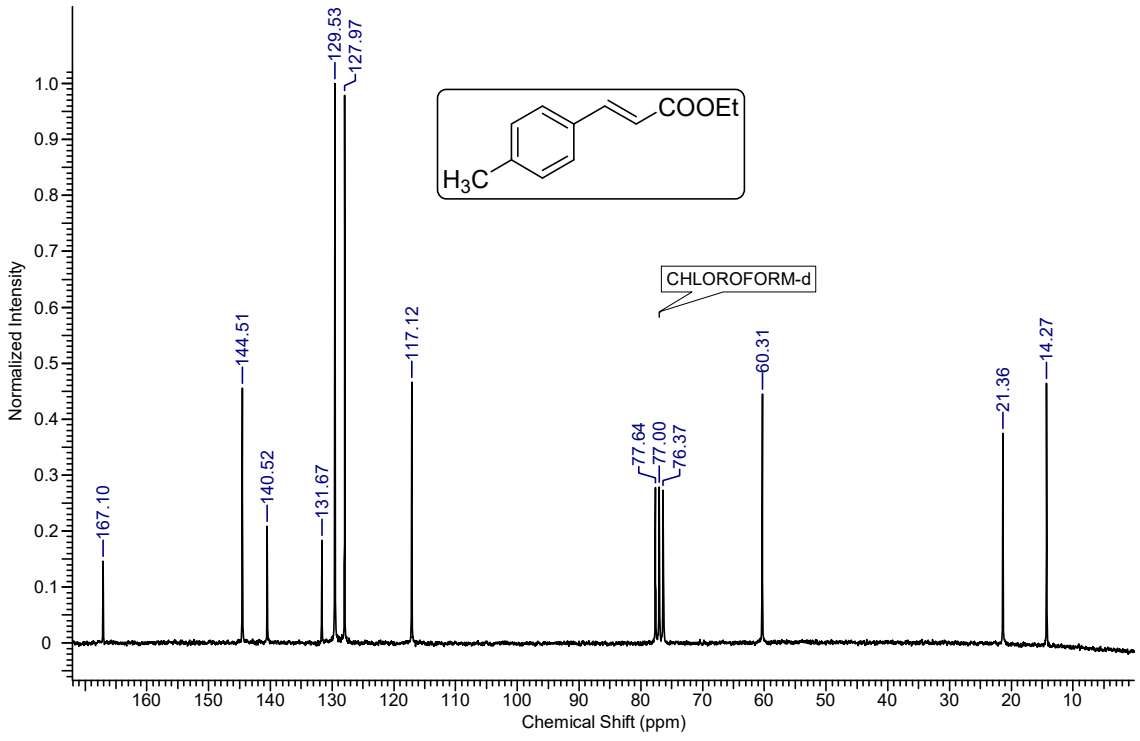
HRMS: *m/z* = calcd for $C_{15}H_{13}O$ $[M^+ + H]^+$ 209.0966; found: 209.0960.

3.4 Spectral Data

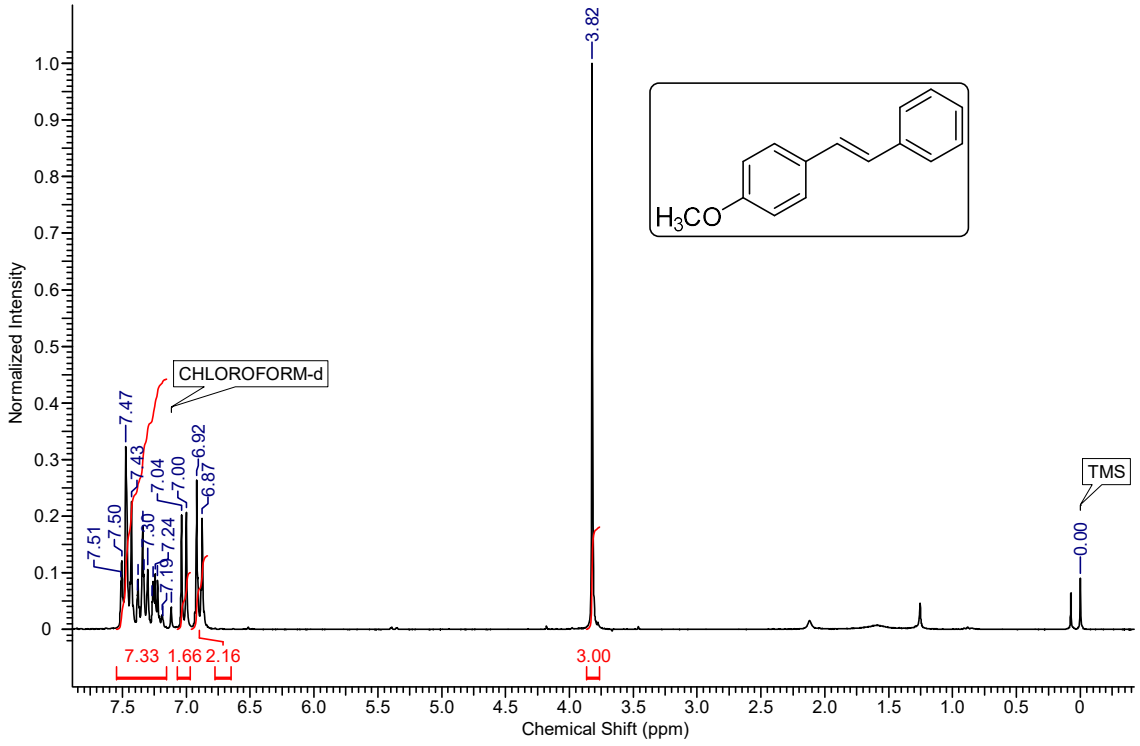
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of Ethyl (E)-3-(4-methylphenyl) acrylate **(1a)**



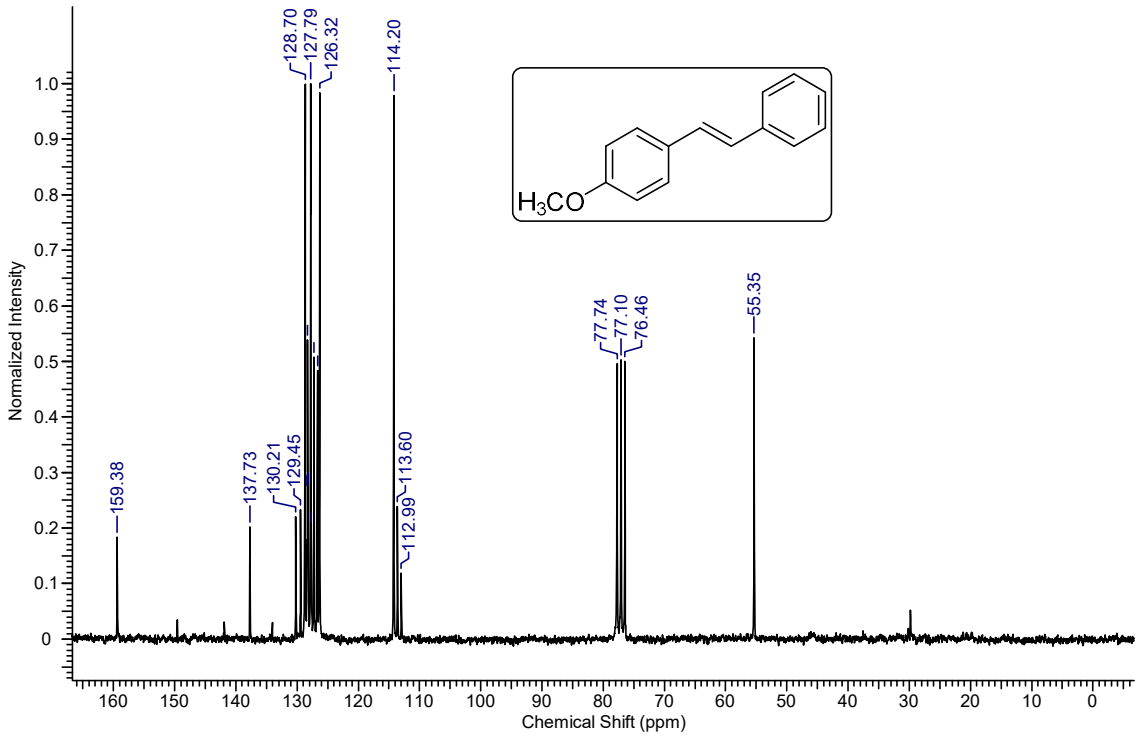
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of Ethyl (E)-3-(4-methylphenyl) acrylate **(1a)**



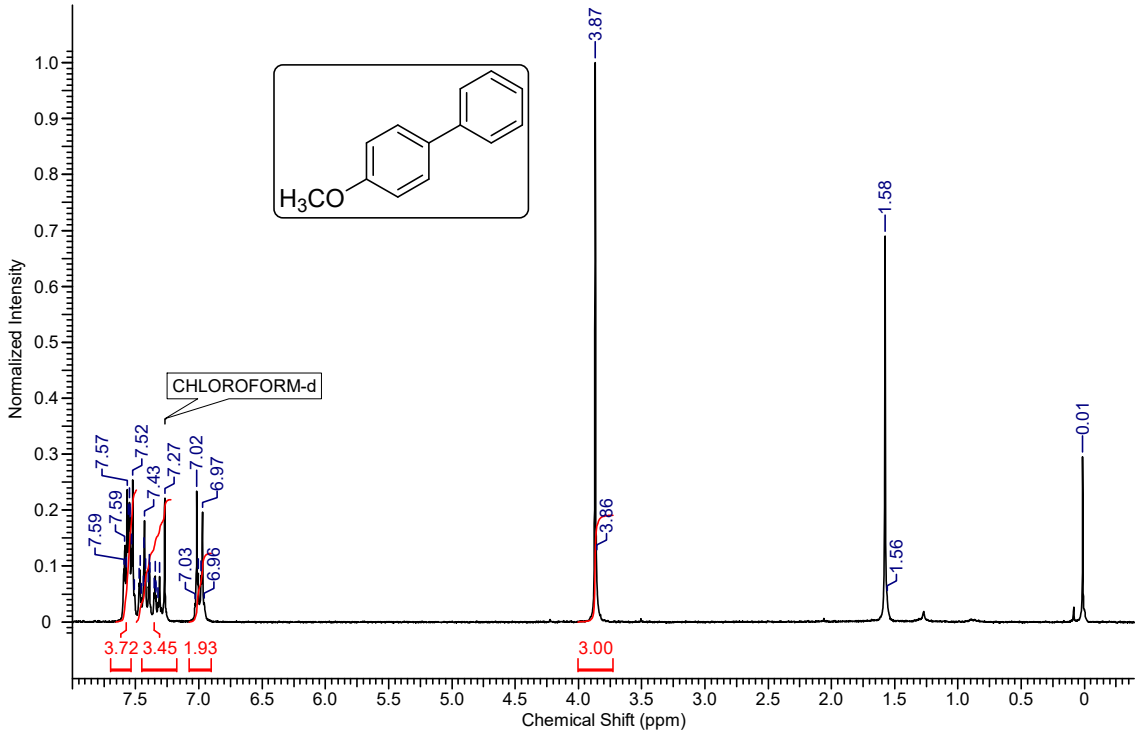
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (E)-1-methoxy-4-styrylbenzene **(2a)**



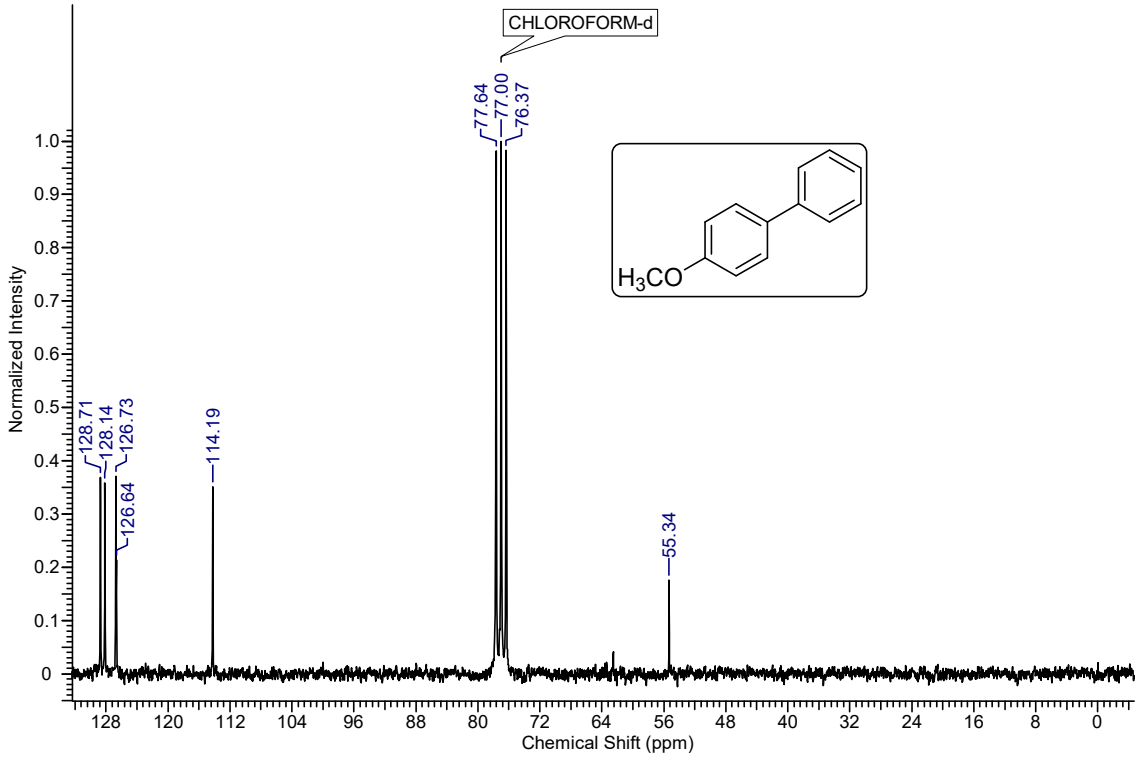
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (E)-1-methoxy-4-styrylbenzene **(2a)**



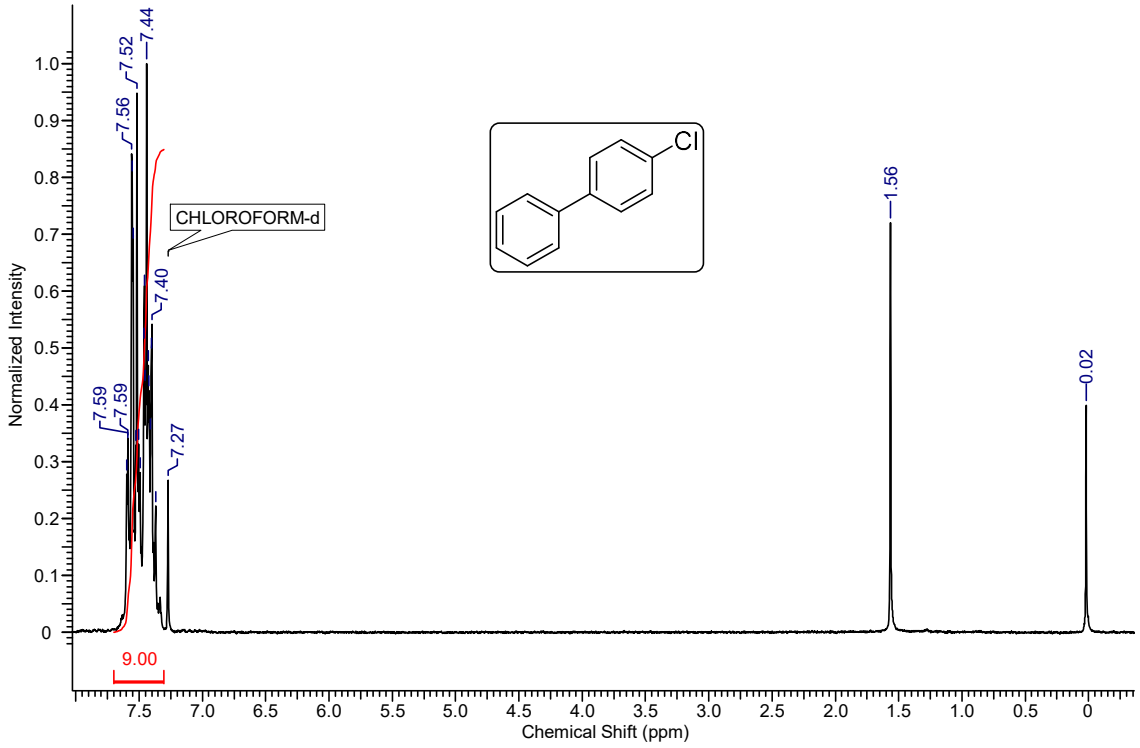
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of 4-methoxy-1,1'-Biphenyl **(3a)**



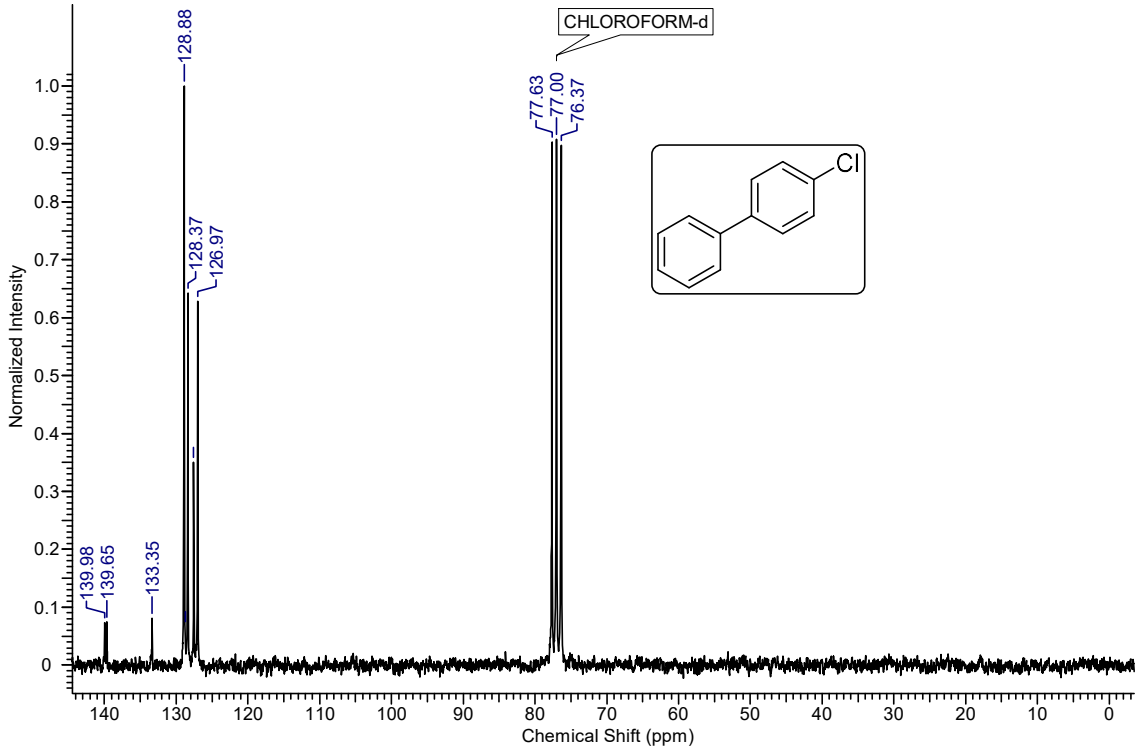
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of 4-methoxy-1,1'-Biphenyl **(3a)**



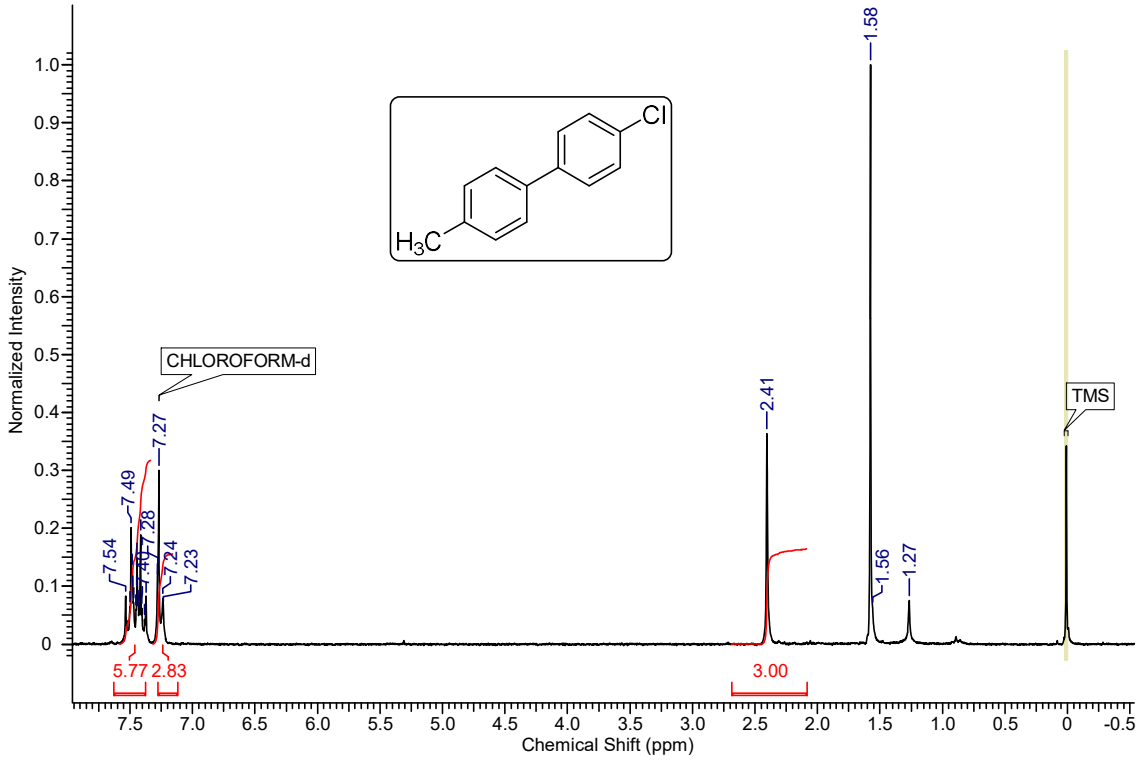
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of 4-chloro-1,1'-Biphenyl **(4a)**



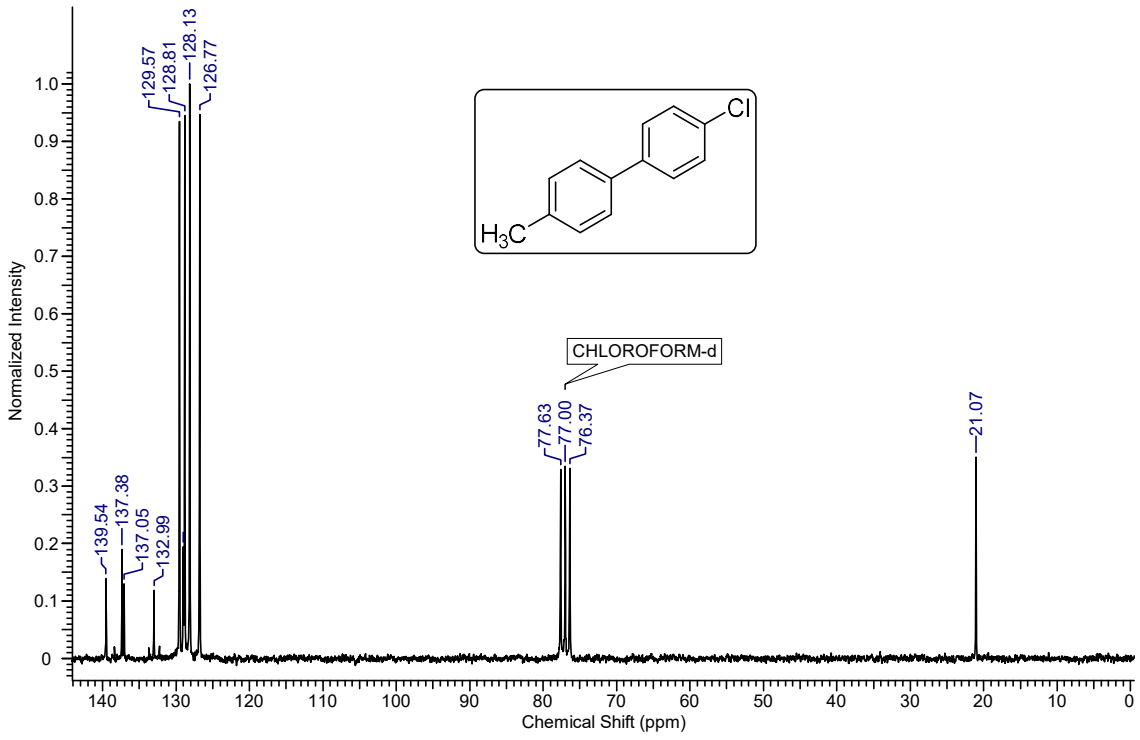
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of 4-chloro-1,1'-Biphenyl **(4a)**



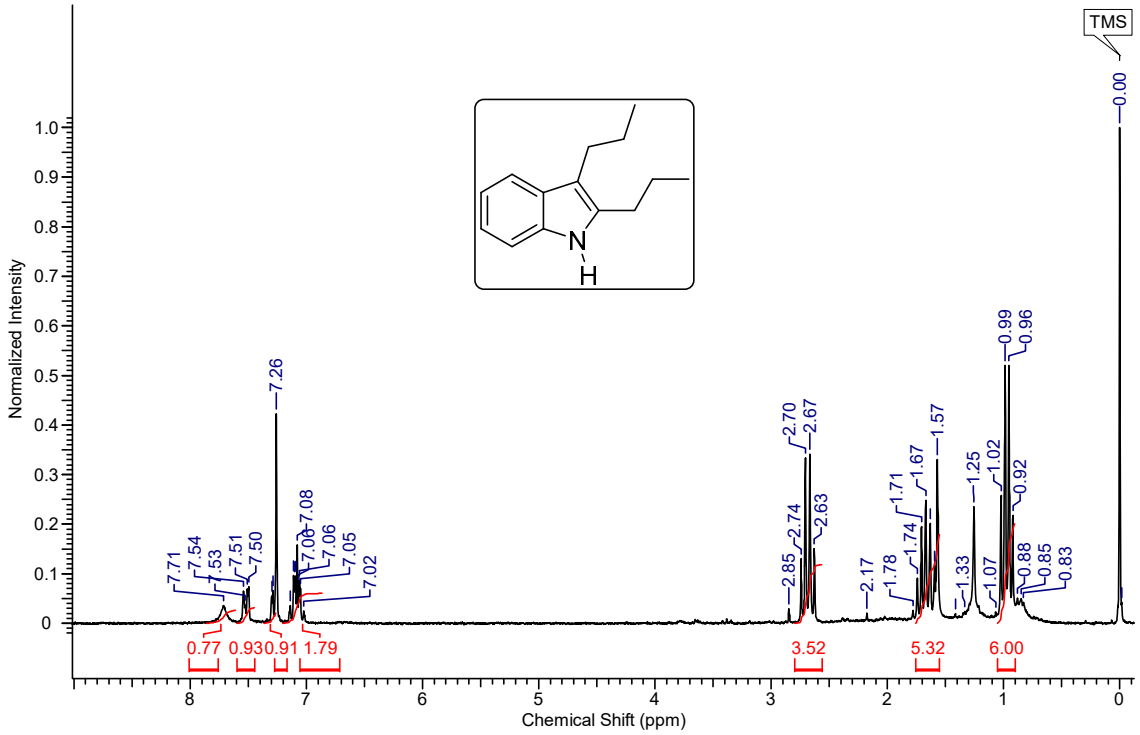
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of 4-chloro-4'-methyl-1,1'-Biphenyl **(5a)**



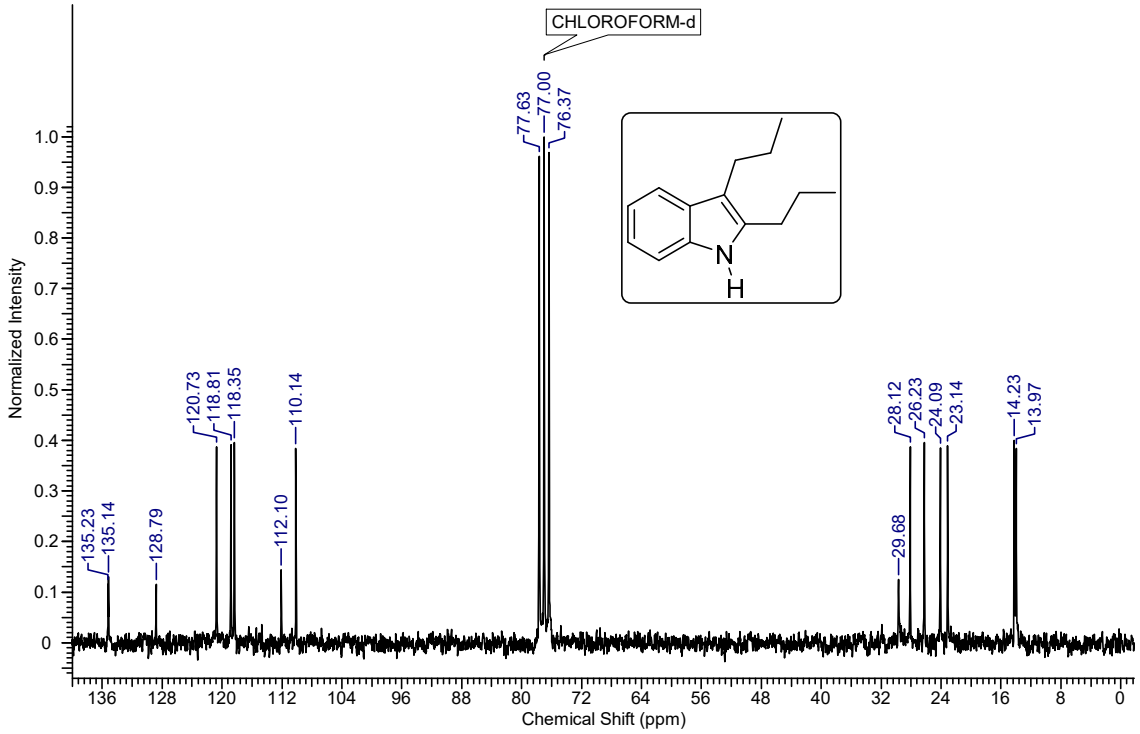
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of 4-chloro-4'-methyl-1,1'-Biphenyl **(5a)**



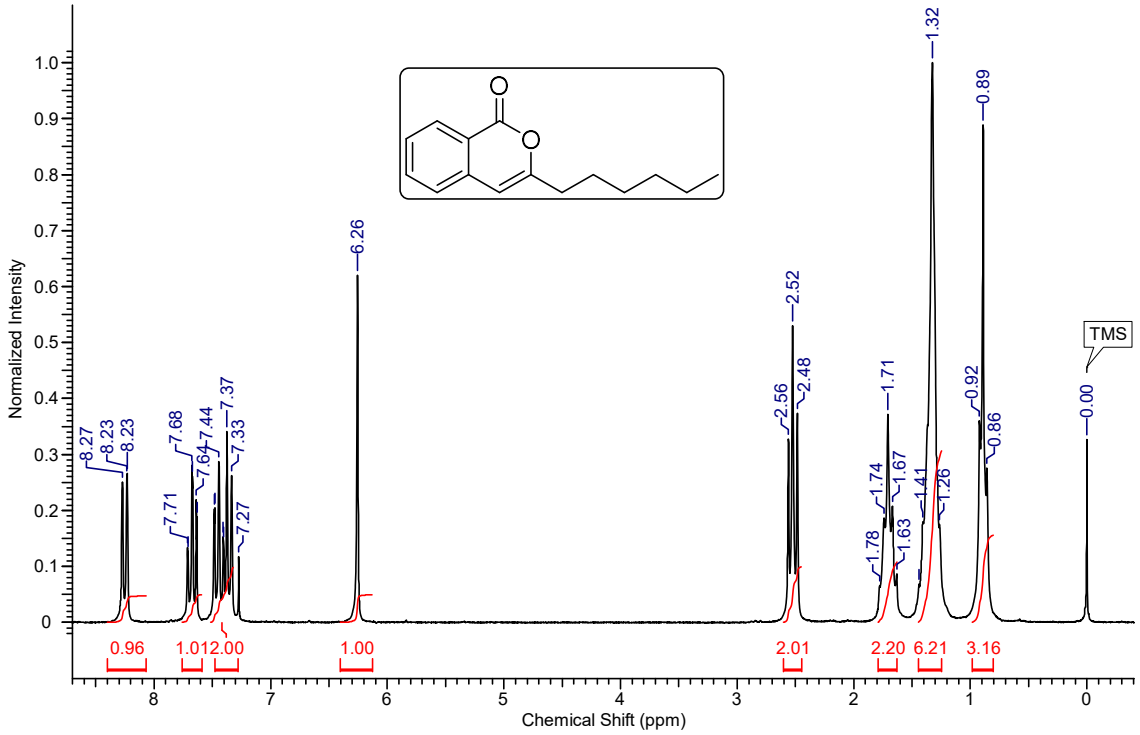
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of 2,3-Dipropyl-1H-Indole **(6a)**



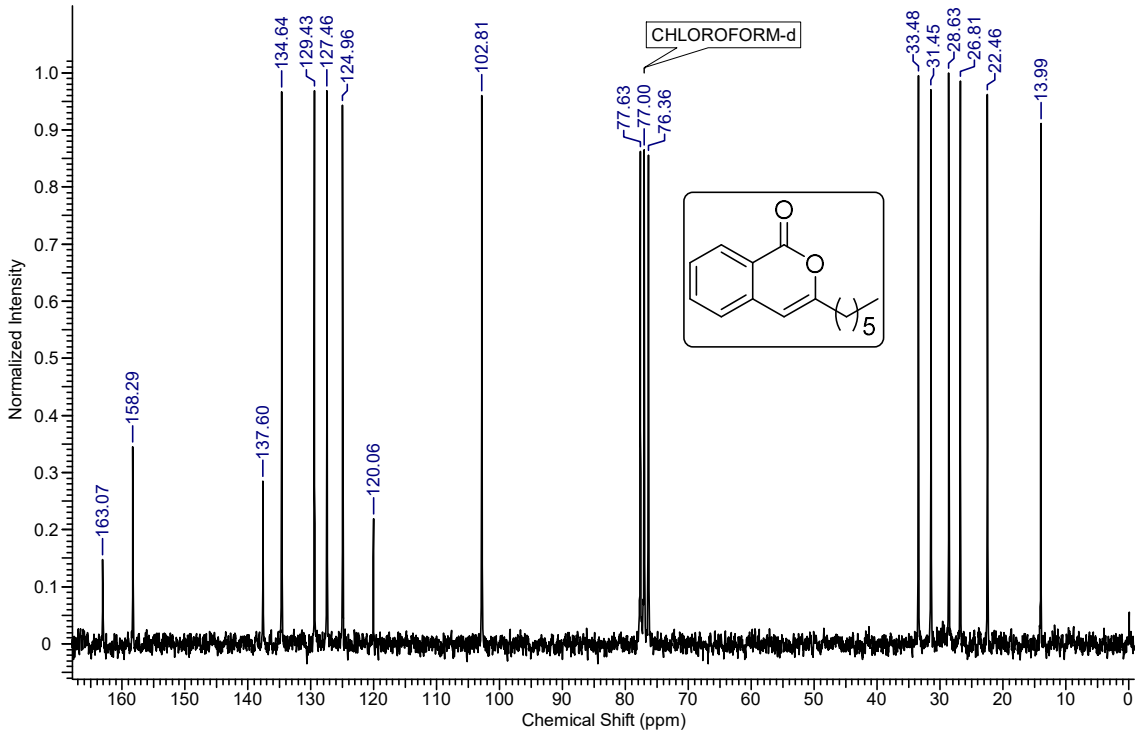
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of 2,3-Dipropyl-1H-Indole **(6a)**



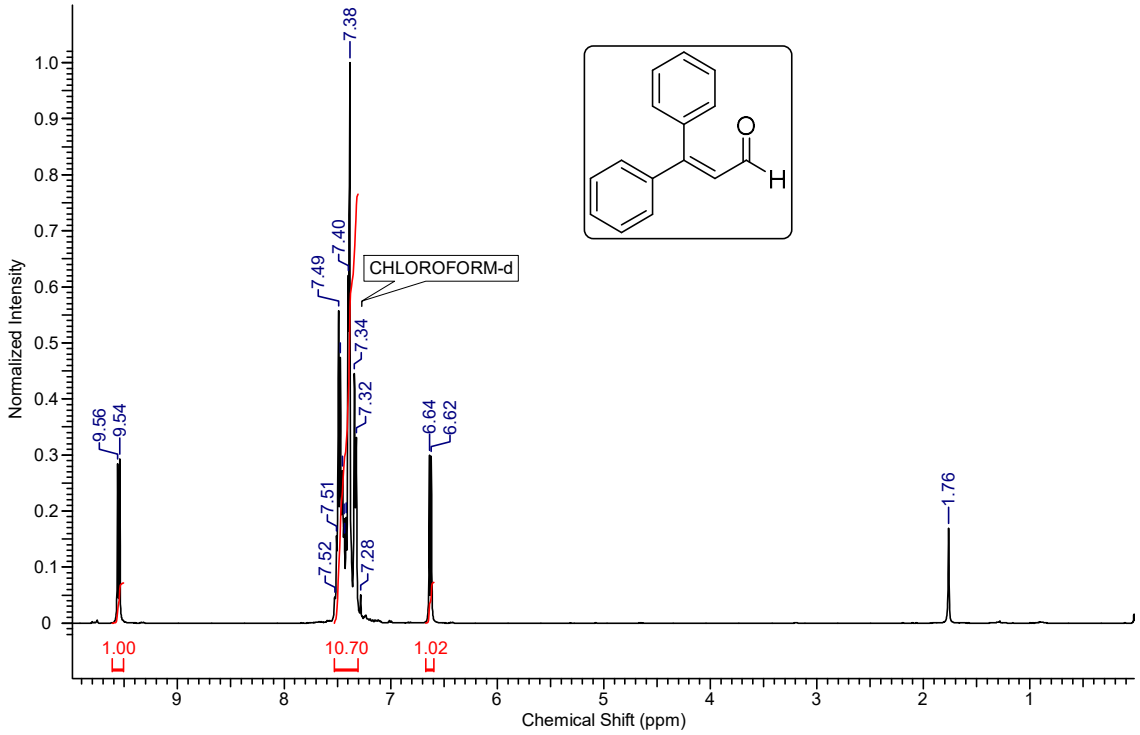
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of 3-Hexyl-1H-Isochromen-1-one **(7a)**



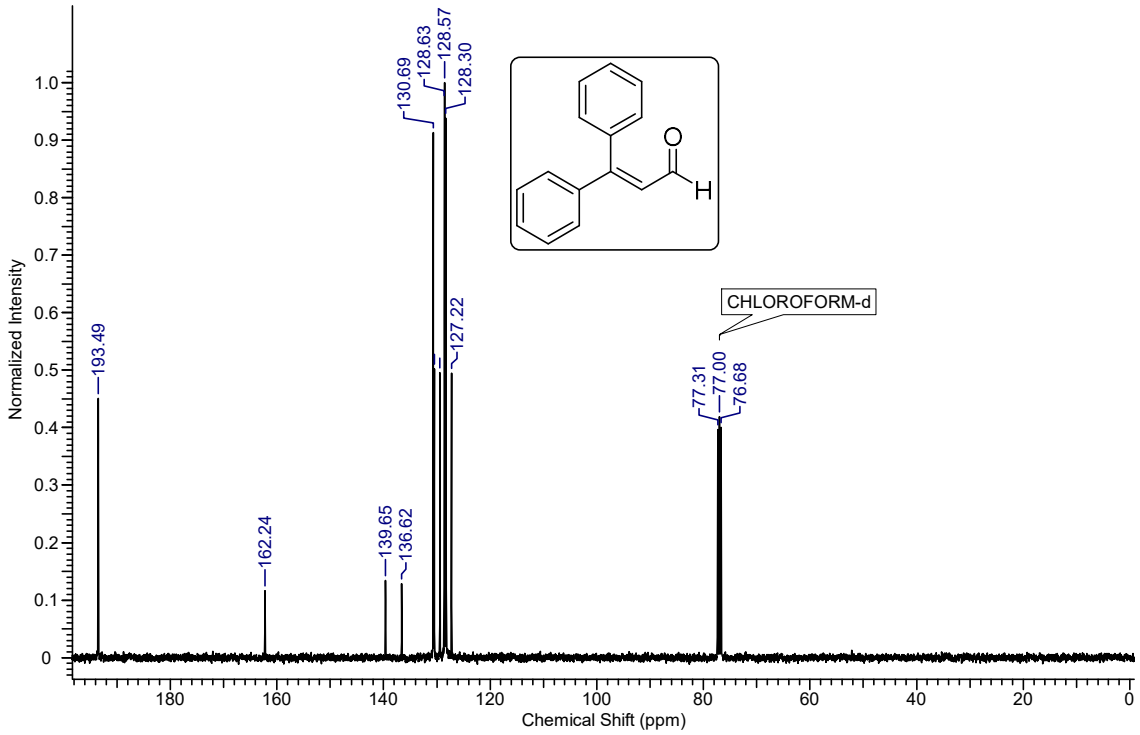
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of 3-Hexyl-1H-Isochromen-1-one **(7a)**



^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of 3,3-Diphenylacrylaldehyde **(8a)**



^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of 3,3-Diphenylacrylaldehyde **(8a)**



3.5 References

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Publications

1. "Silver sequestration of halides for the activation of $Pd(OAc)_2$ catalyzed Mizoroki-Heck reaction of 1,1 and 1,2-disubstituted alkenes" Pronnoy G. Bangar, Priyanka R. Jawalkar, Swapnil R. Dumbre, Dharmaraj J. Patil, Suresh Iyer* *Appl Organometal Chem*., **2018**, 32, 3, 1-6.
2. Mizoroki-Heck reaction of 1,1 and 1,2-disubstituted aryl alkenes – variables of synthesis – silver sequestration, solvent, ligand modulation of reactivity. Priyanka R. Jawalkar, Pronnoy G. Bangar, Swapnil R. Dumbre, Dharmaraj J. Patil, Suresh Iyer* *(Manuscript under preparation).*
3. An organic dye – Pd hybrid, dual metal (Ni-Pd, Ru-Pd) photoredox catalytic systems – Mizoroki-Heck reaction under sunlight and artificial visible light. Swapnil R. Dumbre, Pronnoy G. Bangar, Siddharth Arora, Dharmaraj J. Patil, Suresh Iyer* *(Manuscript under preparation).*