TRANSITION METAL CATALYZED REACTIONS OF ARYL, VINYL, BIFUNCTIONAL VINYL HALIDES AND NITRENES AND THEIR APPLICATION IN THE SYNTHESIS OF LACTONES, LACTAMS AND HETEROCYCLES

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

C. RAMESH

DIVISION OF ORGANIC CHEMISTRY (SYNTHESIS)

NATIONAL CHEMICAL LABORATORY

PUNE 411 008

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled " **Transition metal catalyzed reactions of Aryl, Vinyl, bifunctional Vinyl Halides and Nitrenes and their application in the synthesis of Lactones, Lactams and Heterocycles** " submitted by Mr. C. Ramesh was carried out by him under my supervision at the National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in the thesis.

Dr. Suresh Iyer

Date Research Guide

DECLARATION

I hereby declare that the thesis entitled " **Transition metal catalyzed reactions of Aryl, Vinyl, bifunctional Vinyl Halides and Nitrenes and their application in the synthesis of lactones, Lactams and Heterocycles** ", submitted for the degree of Doctor of Philosophy to the university of Poona, Pune, under the supervision of Dr. Suresh Iyer. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

Date : C. Ramesh

EN THANTHAIKKU ARPANIKKIREN

Acknowledgements

I would first like to thank my parents, brothers and sisters for their love, care and continuous encouragement throughout my education.

It is my great pleasure to thank my research advisor Dr. Suresh Iyer for his invaluable guidance, keen interest and constant encouragement throughout the period of the present investigation.

I am grateful to Dr. K. N. Ganesh for his support and encouragement and Dr. N. P. Argade for his kind and friendly suggestions.

My special thanks are due to my labmates, Dr.Bhosle, Dr. Toke, A. K. Sattar, Anil, Vinay, Sachin, Mangaleshwaran, Venkatesan, Santosh, Girish, Jayanthi and subramani for their kind cooperation and maintaining a friendly atmosphere.

I also thankful to NMR staffs for recording the spectra, especially Mr. A. G. Samuel, Mr. V. T. Sathe, Mrs. U. D. Phalgune, Dr. Rajmohanan and Dr. Sanjayan. I thank microanalysis group for elemental analysis and Mr. Mulla and Mrs. Santhakumari for mass spectra.

I would like to thank all my friends at NCL for their cheering company at all time.

Finally I thank CSIR and DST for financial assistance and the Director, NCL for providing necessary facilities to complete my work successfully.

C. Ramesh

CONTENTS

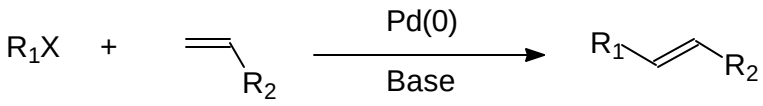
ABSTRACT

Chapter 1. Introduction

Section 1. Transition metal catalyzed reactions of aryl and vinyl halides with olefins.

The synthesis of arylated and vinylated olefins is of fundamental importance in organic chemistry. The palladium-catalyzed carbon-carbon coupling of haloalkenes and haloarenes with alkenes, generally known as the Heck reaction, provides an efficient gateway into such compounds. R. F. Heck discovered this reaction in 1968. As shown in scheme-1, styrenes and dienes can be prepared from the corresponding alkenes and aryl or vinyl compounds substituted with a group such as X= Cl, Br, I, N_2BF_4, OTf, and COCl.

Scheme -1



R_1 = aryl, alkenyl

R_2 = aryl, alkenyl, COOEt, etc

X = I, Br, OSO_2CF_3

This reaction is important owing to the possibility of preparing not only simple terminal or 1, 2-disubstituted olefins but also numerous complex molecular frameworks, e.g. tertiary and quaternary stereocenters. Synthetic usefulness of the Heck reaction i.e. explained by the following facts,

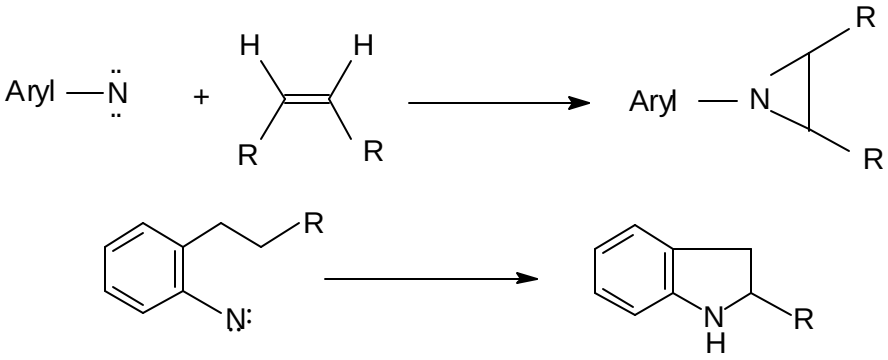
1 The methodology is amenable to a variety of easily available starting materials and this reaction can tolerate various functional groups.

2 The Heck reaction is remarkably chemoselective; hence educts containing most functional groups may be used.

Section 2. Nitrenes

Aryl nitrenes are uncharged, electron deficient reactive intermediates possessing a sextet of electrons in their outer shell. Nitrenes are versatile reactive intermediates to construct heterocyclic compounds. Nitrenes can undergo many reactions, e.g. inter and intramolecular reaction can be explained as follow (scheme-2).

Scheme-2



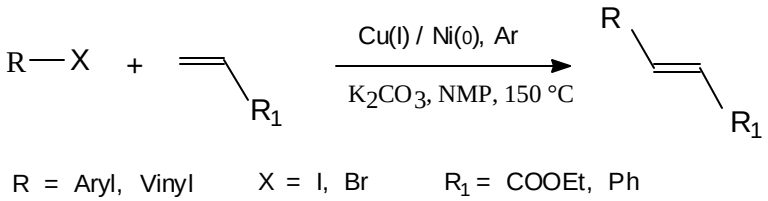
Chapter 2. New catalysts for Heck reaction

This chapter is divided into two sections

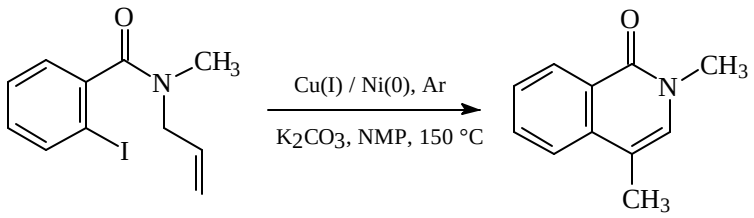
Section 1. Copper (I) and Ni (0) catalyzed reactions of aryl and vinyl halides

Copper iodide and $Ni[P(OPh)_3]_4$ complex are found to activate aryl iodides and vinyl bromides for the reaction with olefins and alkynes to get the corresponding coupled products. The inter and intramolecular reactions of aryl and vinyl halides with olefins and alkynes in the presence of CuI and Ni (0) were carried out to obtain the expected coupled product (scheme-3).

Scheme-3



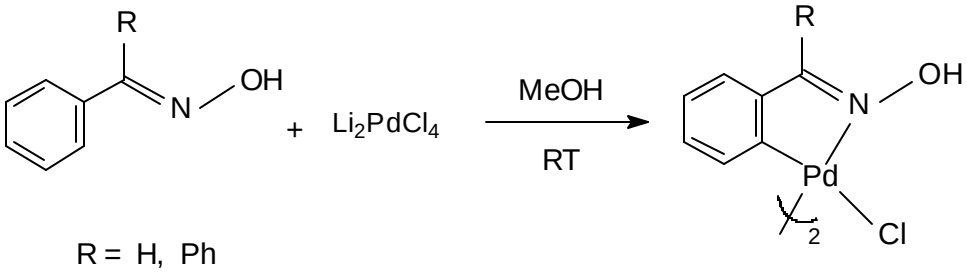
R = Aryl, Vinyl X = I, Br R_1 = COOEt, Ph



Section 2. Novel and Efficient catalyst for Heck reaction

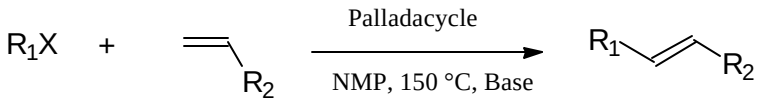
Oxime palladacycles were synthesized and applied for the activation of aryl halides, aryl iodides, bromides and activated aryl chlorides to react with olefins to achieve high turnover numbers and turnover frequencies. Oxime palladacycles were synthesized by the literature methods as shown in scheme-4.

Scheme -4



The reactions of various aryl halides including activated aryl chlorides with olefins in presence of oxime palladacycles were carried out to get the high turnover numbers and turnover frequencies as shown in scheme-5.

Scheme -5



R_1 = aryl

R_2 = Ph, COOEt, etc X = I, Br, Cl

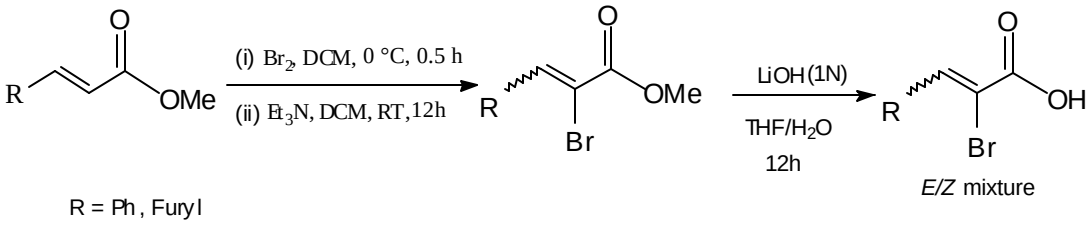
Chapter 3.

This chapter is divided into two sections

Section 1. Pd catalyzed reactions of ∝-Bromoacrylic acids with 1, 3-dienes.

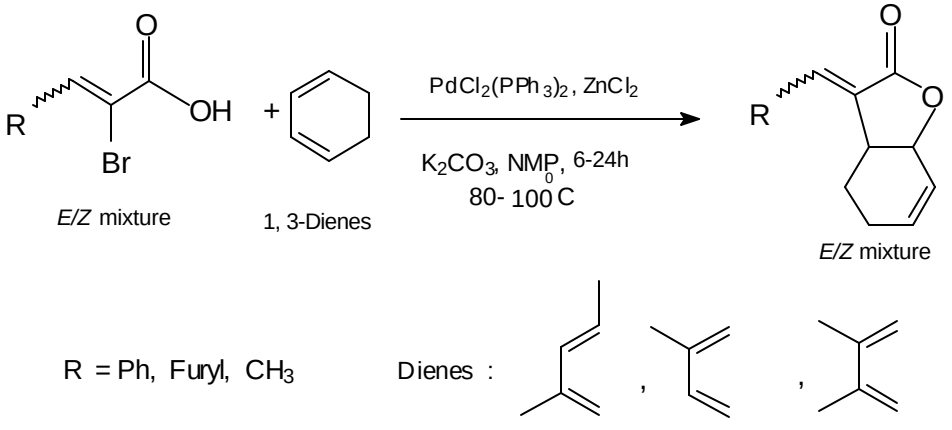
∝-Bromoacrylic acids were prepared from the corresponding esters by bromination and dehydrobromination followed by hydrolysis as shown in scheme-6.

Scheme -6



The reaction of ∝-bromoacrylic acids with 1, 3-dienes was carried out in the presence of $PdCl_2(PPh_3)_2$, $ZnCl_2$ as co-catalyst and K_2CO_3 in NMP at 80-100 ^{0}C under argon atmosphere to form γ-lactones in good yield (scheme-7).

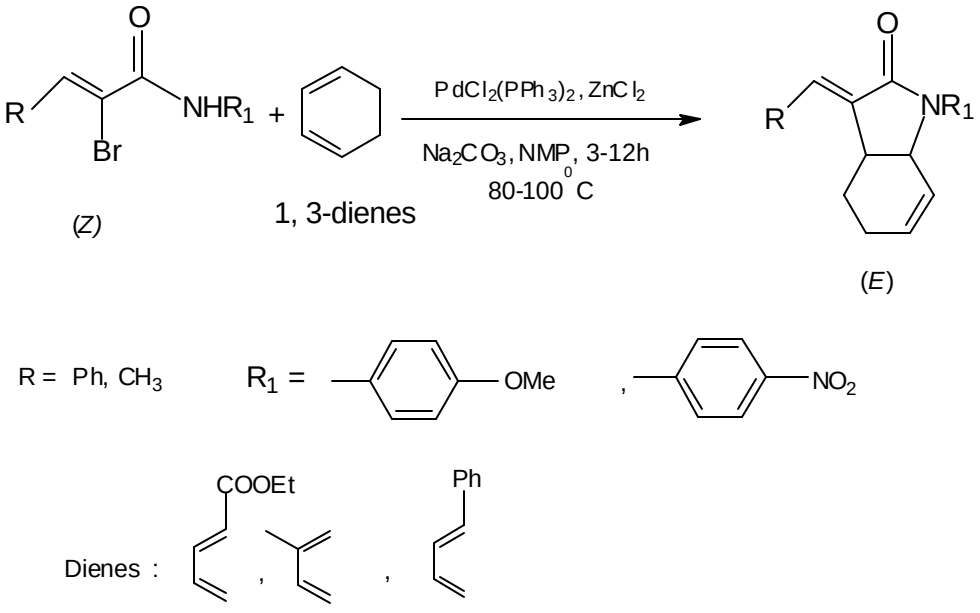
Scheme -7



Section 2. Reaction of ∝ Bromoacrylic amides with 1, 3-Dienes and Alkynes

∝-Bromoacrylic amides were prepared from the ∝-bromoacrylic acids by treating with $SOCl_2$ and Et_3N, R-NH_2. Palladium catalyzed reactions of ∝-bromoacrylic amides with 1, 3-dienes and alkynes in presence of zinc chloride as co-catalyst and sodium carbonate at 100 ^{0}C gave the expected γ-Lactams in good yield (scheme-8).

Scheme -8



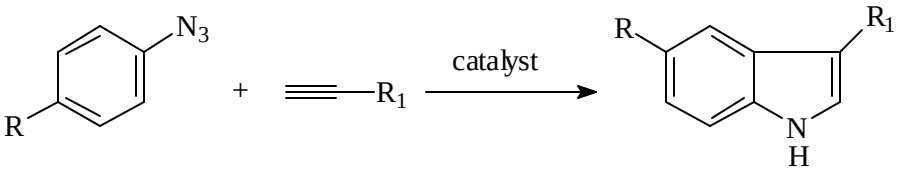
Chapter 4.

This chapter is divided in to two sections.

Section 1a. Transition metal catalyzed activation of aryl azides

The reaction of aryl azides with alkynes in the presence of various transition metal catalysts, $Ni(P(OPh)_3)_4$, $Mo(CO)_6$, $NiCl_2(PPh_3)_2$/Zn, $Fe(CO)_5$ and reduced copper has been attempted to form indoles (scheme-9).

Scheme -9



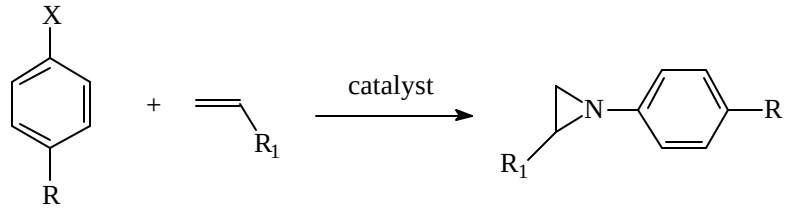
$R_1 = CH_3, OCH_3, Cl, NO_2$

$R = C_4H_9, Ph$

Section 1b. Reactions of aryl and tosyl azide with olefins

Copper chloride, Ni(0), Fe(0), Mo, W, Pd, Rh, Ru and Ir catalyzed reactions of aryl and tosyl azides with olefins were carried out to get aziridines (scheme-10).

Scheme -10

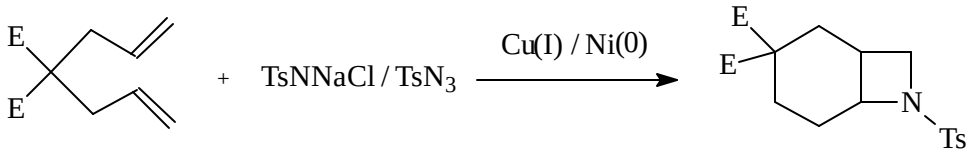


$X = SO_2N_3, N_3$ $R = OCH_3, CH_3$ $R_1 = Ph$

Section 2. Reactions of chloramine-T/ tosyl azide with 1, 6-dienes

Different 1, 6-dienes were prepared by the literature methods and the reactions of 1, 6 dienes with chloramine-T and tosyl azide in the presence of copper (I) and Ni (0) catalysts have been attempted to synthesize heterocyclic compounds (scheme-11).

Scheme -11



E = COOEt

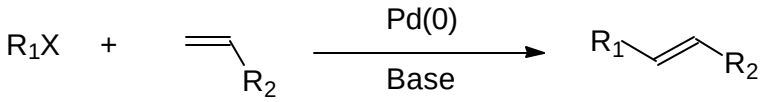
This chapter is divided into two sections

Section 1. Transition metal catalyzed reactions of aryl and vinyl halides with olefins.

The synthesis of arylated and vinylated olefins is of fundamental importance in organic chemistry. The palladium catalyzed coupling reactions of haloalkenes and haloarenes with alkenes, generally known as the Heck reaction, provides an efficient gateway into such compounds.[1] As shown in the scheme-1, styrenes and dienes can be prepared from the corresponding alkene and aryl or vinyl compounds substituted with a leaving group X = Cl, Br, I, N_2BF_4, OTf and COCl. This reaction is important owing to the possibility of preparing not only simple terminal or 1, 2-disubstituted olefins but also numerous complex molecular frameworks, e.g. tertiary and quaternary stereocenters. Dienes and alkynes can also be used as unsaturated compounds to get the corresponding coupled products. The reaction was discovered by R. F. Heck in late sixties. Initially, the reaction received much attention for forming new carbon-carbon bond in a single step and the reaction was not well developed in seventies and early eighties. Only few research groups continued to explore the reaction. In mid eighties many research groups focused on developing and exploring the scope and limitations of the reaction.

Scheme -1

HECK REACTION



R_1 = aryl, alkenyl

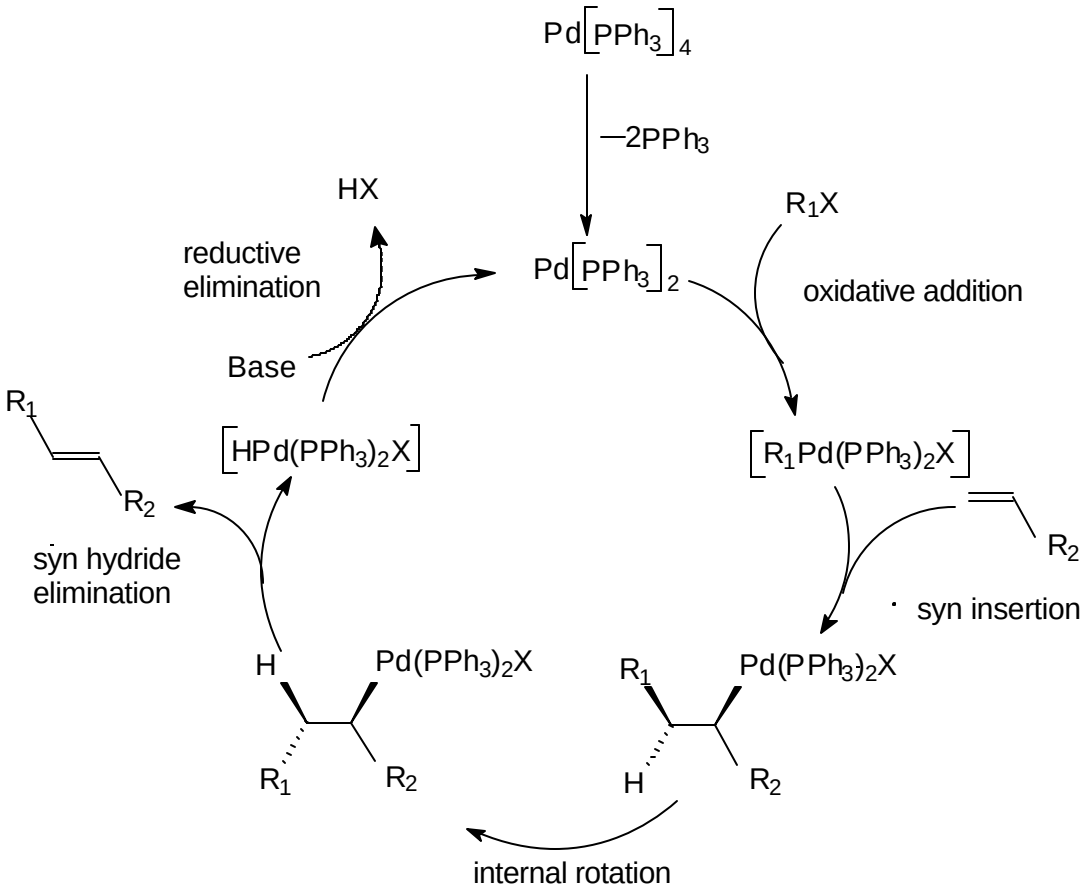
R_2 = aryl, alkenyl, COOEt, etc

X = I, Br, OSO_2CF_3

Mechanism of the Heck Reaction

The most accepted mechanism of this reaction goes through the following organometallic intermediates. There are two major steps involved in the reaction mechanism, oxidative addition and reductive elimination as shown in scheme-2.

Scheme -2 Mechanism



Synthetic usefulness of the Heck reaction is explained by the following facts

1. The methodology is amenable to a variety of easily availa ble starting materials.
2. The Heck reaction is remarkably chemoselective; hence educts containing most functional groups may be used.
3. The Palladium catalysts typically employed are water and air stable.

Much progress has been made over the past ten years and several reviews have appeared.[2] Since it's discovery in the late sixties, most particularly in the last few years, several exciting breakthroughs have been made in the reaction including

(i) Development of more active and thermally stable catalytic system

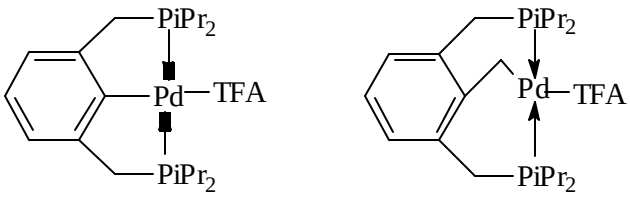
(ii) New more efficient enantioselective variants and

(iii) Expanded application in organic synthesis.

Catalysts

Palladium (0) phosphine complexes, such as $Pd(PPh_3)_4$ are generally used as Heck reaction catalysts. However Pd(II) salts in the presence of phosphine ligands are more often employed as *insitu* catalysts.

In recent years, new and efficient catalysts (palladacycle) have been synthesized and applied for the Heck reaction to achieve high turnover numbers and turnover frequencies and to activate less reactive chlorides.[3]

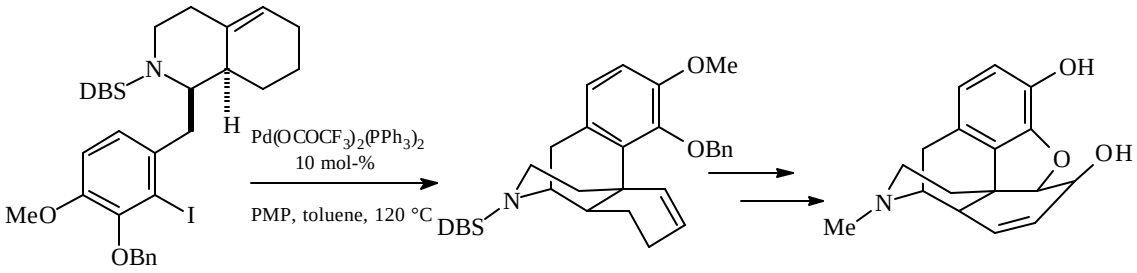


Recent applications of Heck reaction

The last decade has seen an extraordinary growth in the use of stereoselective palladium-catalyzed olefination of aryl and vinyl derivatives for complex total synthesis. In most cases intramolecular variants offer unprecedented ways to assemble structurally simple precursor molecule to congested polycyclic frameworks.

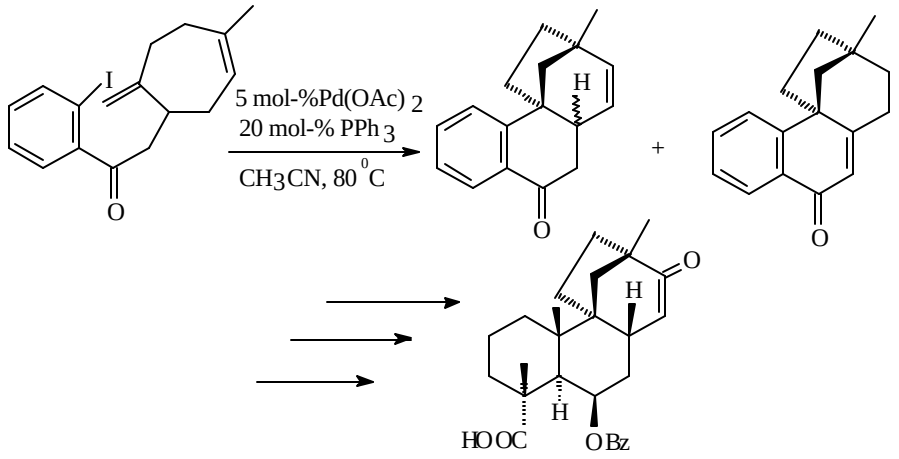
The synthetic potential of intramolecular Heck reaction is elegantly demonstrated by the work of Overman and his group towards the synthesis of morphine as shown in scheme-3.[4,5]

Scheme -3



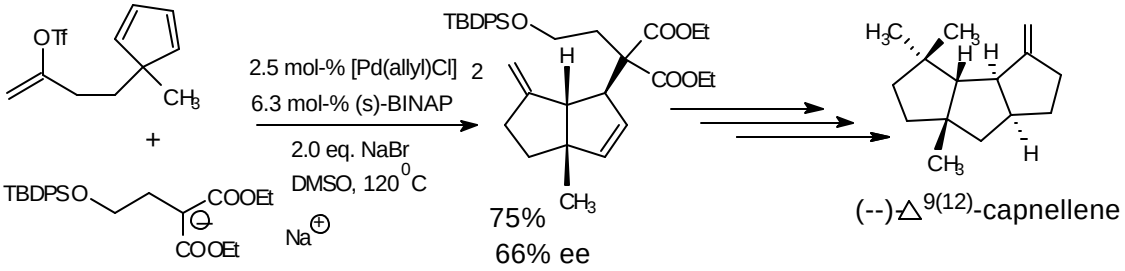
Other examples for the use of palladium-catalyzed cyclisations of aryl halides and vinyl halides with tethered alkenes to form quaternary carbon centers were developed by the Overman group include the total synthesis of scopadulcic acids A and B as shown below in scheme-4.[6]

Scheme -4



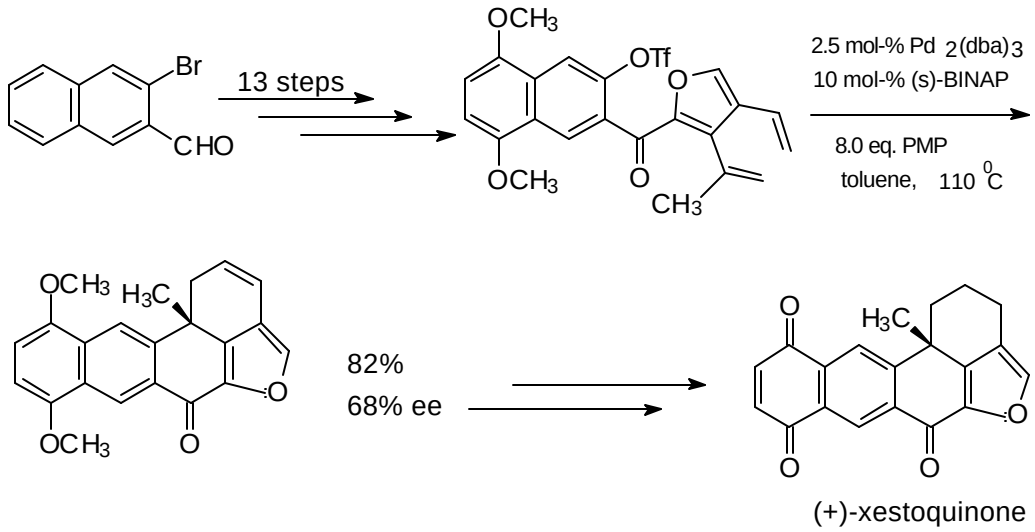
Shibasaki and co-workers reported the total synthesis of capnellene utilizing an asymmetric Heck reaction-carbanion capture process as a key step.[7] In this report, the vinyl triflate was cyclized in the presence of various carbanions to give key intermediate in the total synthesis of capnellene with 75% and an ee of 66% (scheme-5).

Scheme -5



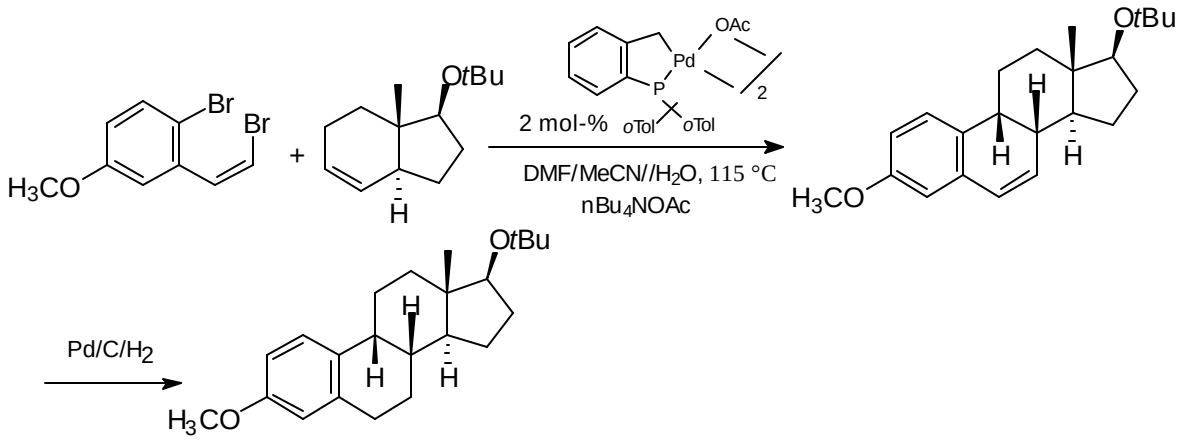
The asymmetric carbopalladation followed by further reactions of the alkylpalladium species was used by Keay and co-workers in the total synthesis of (+)-xestoquinone.[8] The key step in this total synthesis is an asymmetric palladium-catalyzed polyene cyclisation of the aryl triflate as shown in scheme-6.

Scheme -6



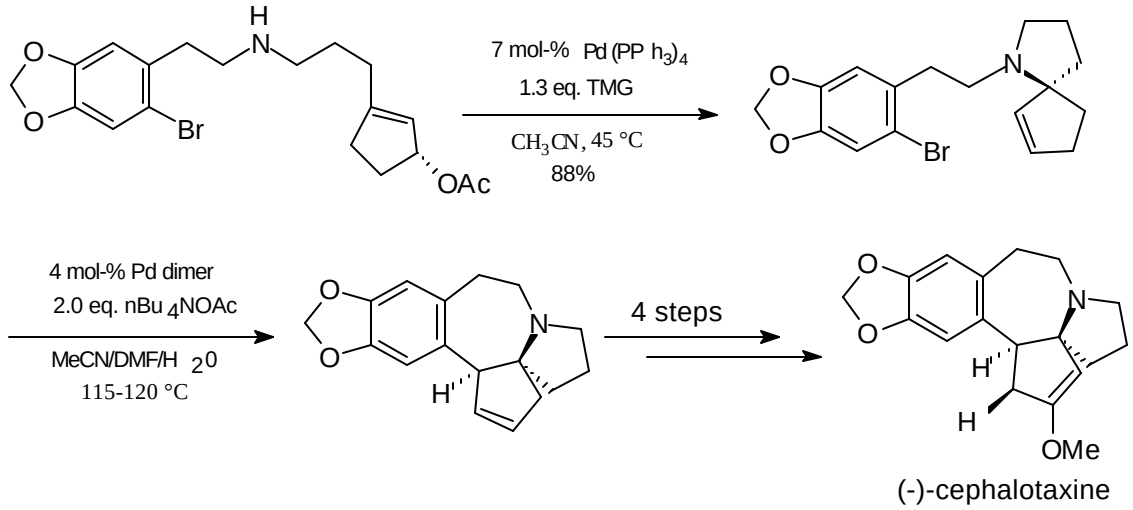
Significant contributions on the use of domino Heck processes for the synthesis of steroids and related molecules were disclosed by Tietze et al.[9] The synthesis of estrone derivatives was easily achieved by double Heck reaction of bromocompound with hexahydro-1H-indene as shown in scheme-7.

Scheme -7



Lutz et al. developed a novel highly efficient strategy for the enantioselective synthesis of (-)-Cephalotaxine with two palladium-catalyzed reactions as key steps starting from the secondary amine to give the pentacyclic product as shown in the scheme-8.[10]

Scheme 8



Section 2. Reactions of Nitrenes

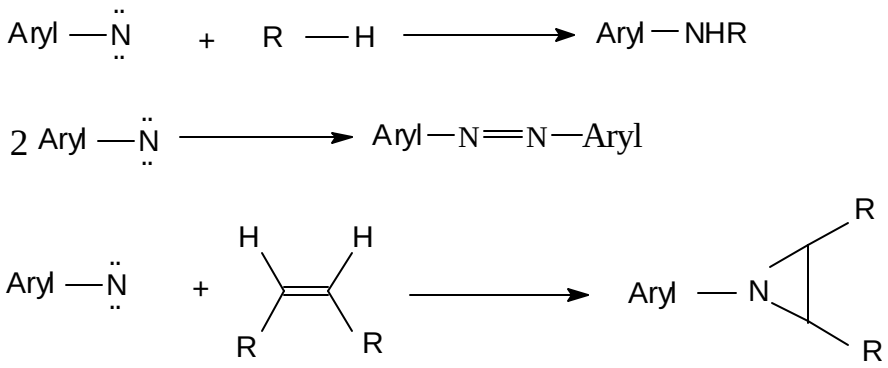
Aryl nitrenes are uncharged, electron deficient reactive intermediates possessing a sextet of electrons in their outer shell. Nitrenes are most useful reactive intermediates to construct

heterocyclic compounds.[11] Reactions of nitrenes can be discussed under various headings for example inter and intramolecular reactions.[12]

(a) **Intermolecular reactions**.

Aryl nitrenes can undergo many reactions as shown in scheme-9

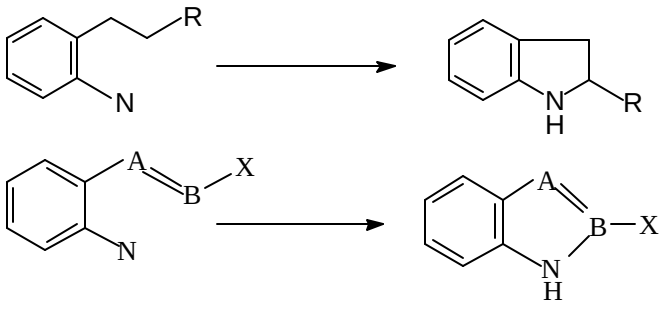
Scheme -9



(b) **Intramolecular reactions**

Intramolecular reactions involve cyclisation onto an *ortho*-substituted or a saturated side chain giving rise to five membered nitrogen heterocycles. This behavior constitutes one of the most important synthetic applications of aryl nitrenes because of its scope (scheme-10).

Scheme -10



Common methods of generating Nitrenes.

1. Thermolysis of arylazides at and above 120 ^{0}C
2. Photolysis of arylazides under milder conditions.

3. Reduction of nitro and nitrosoarenes.

4. Fragmentation of heterocycles.

Heterocyclic fragmentation which finally leads to arynitrenes is far less important Synthetically than the methods described above.

5. Photolysis of N-aryloxyaziridine in a quartz apparatus is thought to give nitrenes[13]

6. Oxidation of amines

By oxidation of o-aminodiphenylamine with litharge is a very old reaction to generate nitrenes.[14]

Modern Methods of Generating Nitrenes

1. Thermal deoxysilation of N, O-bis(trimethyl silyl) hydroxylamine.[15]

2. Copper initiated decomposition of N, N-Dichloromethanesulfonamide.[16]

CONCLUSION

This chapter described the importance of C-C bond formation between the aryl and vinyl halides with olefins catalyzed by palladium complexes (**Heck reaction**) and mechanism of the reaction which involves basic characteristic features of the transition metal complexes and their applications in synthesis of various natural products. This chapter also outlined the synthesis and application of nitrenes in synthetic organic chemistry.

References:

1. a) Heck, R. F. Palladium reagents in organic synthesis: Academic press : London, **1985**.

   b) Heck, R. F. In comprehensive organic synthesis; Trost, B. M., Flemming, I., Edn; pergamon press. Oxford and New York, **1991**; vol. 4, 833.

2. a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.

   b) de Maijere, A.; Meyer, F. E. *Angwe. Chem. Int. Ed. Engl*, **1994**, *33*, 2379.

   c) Carbri,W.; Candiani, I. *Acc. Chem. Res*. **1995**, *28*, 2.

3. Ohff, M.; Ohff, A.; Vander Boom , M. E.; Milstein, D. *J. Am. Chem. Soc*, **1997**, *119*, 11687.

4. a) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423.

   b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total synthesis*, VCH, Weinheim, **1996**, 566.

5. Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028.

6. a) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc*. **1993**, *115*, 2042.

   b) Kucera, D. J.; O' Connor, S. J.; Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Org. Chem.* **1993**, *58*, 5304.

   c) Overman, L. E .; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1997**, *119*, 12031.

7. Ohshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1996**, *118*, 7108.

8. Maddaford, S. P.; Andersen, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc*. **1996**, *118*, 10766.

9. Tietze, L. F.; Nobel, T. ; Spescha, M. *Angew. Chem.* **1996**, *108*, 2385 ; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2259.

10. Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264.

11. a) The chemistry of the azide group (Ed. S. Patai) wiley New-York(1971).

b) Reactive intermediates (Ed. R. A. Abramovitch)

vol. 2, 1982.

12. Iddon, B.; Meth-Cohn, O.; Scriven, E. F.; Suschitzky, H.; Gallagher, P. T. *Angew. Chem. Int. Edn. Engl.*, **1979**, *18*, 900.

13. a) Mayer, E.; Griffin, G. W. *Angew. Chem.*, **1967**, *79*, 649.

b) Splitter, J. S.; Cavin, M. *Tetrahedron Lett.*, **1968**, 1445.

14. a) Fischer, O.; Heiler, O. *Ber.*, **1893**, *26*, 378.

b) Schroppel, F.; Sauer, J. *Tetrahedron.Lett.*, **1974**, 2945.

15. Tuai, F. P.; Chang, Y. H.; Vogel, T. M.; Zon, G. *J. Org. Chem.*, **1976**, *41*, 3381.

16. a) Torimoto N.; Shingaki, T.; Nagai, T. *Bull. Chem. Soc. Jpn.*, **1977**, *51*, 2980.

b) Torimoto, N.; Shingaki, T.; Nagai, T. *Bull. Chem. Soc. Jpn.*, **1978**, *51*, 2983.

This chapter is divided into two sections

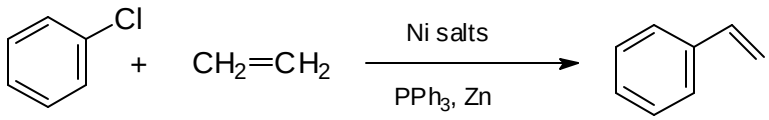
Section 1. Nickel (0) and Cu (I) catalyzed reactions of aryl and vinyl halides with olefins and alkynes.

Introduction and Background

The development of new catalysts for C-C bond formation reaction is a challenging area in organic synthesis. There are many reactions in which the C-C bond is formed by catalysis of various transition metal complexes. The most important reaction in which the facile and selective C-C bond formation is constructed is known as the Heck reaction, catalyzed by palladium complexes, described in the last chapter. Similar reaction catalyzed by the other transition metal complexes and transition metal salts will be described briefly below.

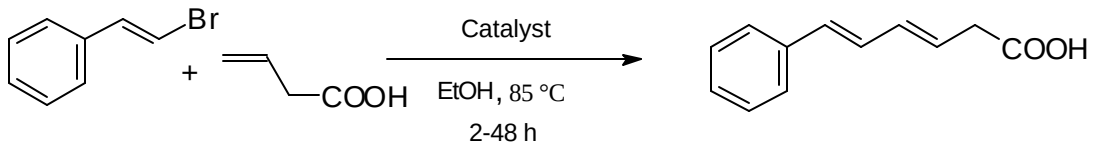
Styrene was prepared by the reaction of chlorobenzene with ethylene in the presence of nickel salts, triarylphosphine and zinc as shown in scheme-1.[1]

Scheme -1



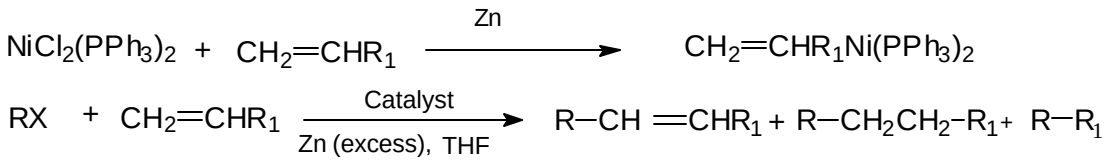
Boldrini *et al*. reported the use of $RhCl(PPh_3)_3$, $Ni(PPh_3)_4$, $[Rh(COD)(PPh_3)_2]$ PF_4 for the reaction of vinyl halides with alkali salts of 3-butenoic acids to furnish dienoic acids containing 3, 5 conjugated double bonds (scheme-2).[2]

Scheme -2



The reactions of aryl and vinyl halides with activated olefins in the presence of catalytic amount of $NiCl_2(PPh_3)_2$ and excess of zinc powder in tetrahydrofuran gave the coupled products (scheme-3).[3]

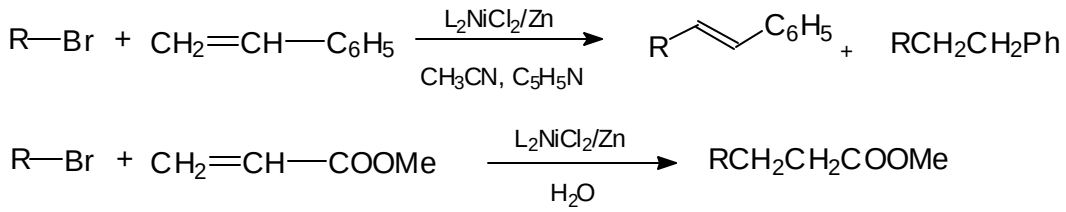
Scheme -3.



R= aryl, vinyl

S. A. Lebedev *et al.* studied the effective catalytic system for the activation of aryl and alkyl bromides with styrene and methyl acrylate to give stilbenes and cinnamates respectively (scheme-4).[4]

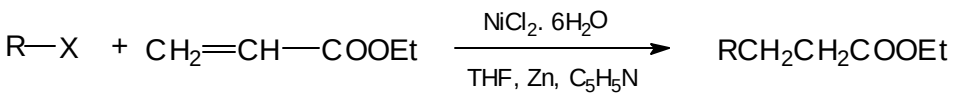
Scheme -4



R= aryl, alkyl L=PPh_3

Sustmann *et al.* reported the reaction of alkyl halides, aryl and vinyl halides with electron deficient olefins catalyzed by $NiCl_2.6H_2O$ in the presence of zinc and pyridine in tetrahydrofuran to give the conjugate addition product (scheme-5).[5]

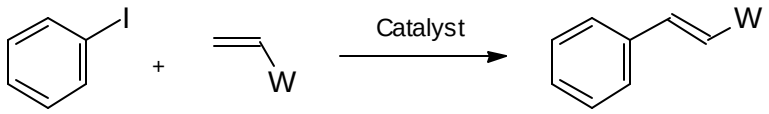
Scheme -5



R= alkyl, aryl and vinyl

S. Iyer reported the vinylation of aryl iodides catalyzed by $CoCl(PPh_3)_3$, $RhCl(PPh_3)_3$, and $IrClCO(PPh_3)_2$ to give the corresponding cinnamates and stilbenes in high yield using K_2CO_3 and N-methyl pyrrolidinone (scheme-6).[6]

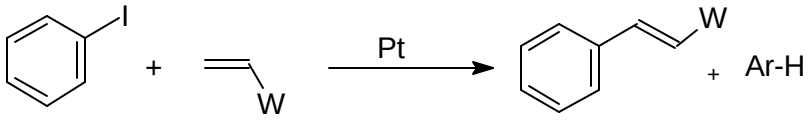
Scheme -6



W=C_6H_5, COOR

Vinylation of aryl iodides using $Pt(COD)Cl_2/PPh_3$ as a catalytic system was studied by Kelkar and it was found that dehalogenated products were formed in the reaction in presence of organic base (scheme-7).[7]

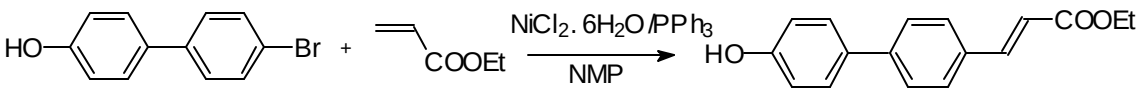
Scheme -7



W= COOR, Ph

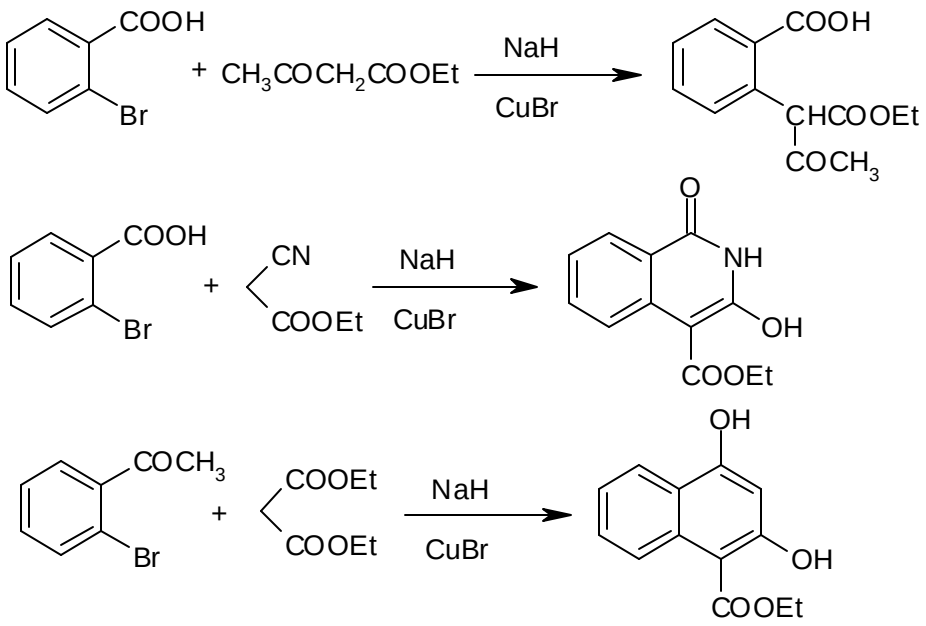
Kelkar *et al.* reported the vinylation of 4-bromo-4'-hydroxybiphenyl with ethyl acrylate in the presence of $NiCl_2.6H_2O$, PPh_3 and organic base to afford ethyl 4-(4'-hydroxyphenyl) cinnamate with high selectivity (98%) (Scheme-8).[8]

Scheme -8



A detailed study on the copper catalyzed condensation of 2-bromobenzoic acids with *b*-dicarbonyl anions to α-arylated-β-dicarbonyl compounds in high yield reported by A. Mckillop *et al.* is shown in scheme-9.[9]

Scheme -9



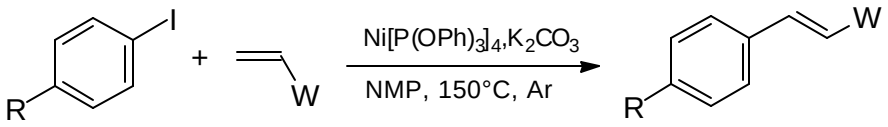
OBJECTIVE

The aim was to develop new catalysts for the coupling reactions of aryl and vinyl halides with olefins, alkynes, carbon and nitrogen nucleophiles based on the oxidative addition and reductive elimination properties of the transition metal complexes and salts.

PRESENT WORK

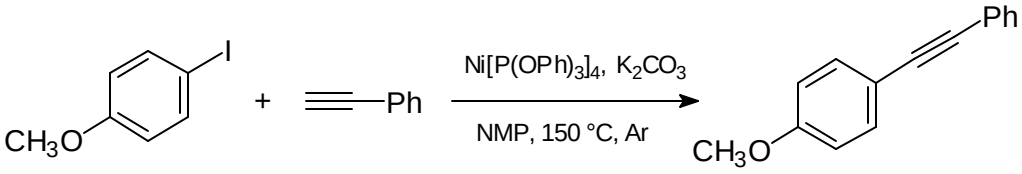
Our present study involves the investigation of new catalysts for the Heck reaction. Some of the transition metal complexes which are in lower oxidation state can easily undergo ligand dissociation, oxidative addition and reductive elimination reactions. Our initial study was on the reactions of aryl iodides with olefins, catalyzed by the low valent nickel complexes for example, $Ni[P(OPh)_3]_4$ and $Ni[P(OEt)_3]_4$ which affords the expected Heck type coupling products, stilbenes and cinnamates is shown in scheme-10. The reaction of aryl iodide with alkyne in the presence of $Ni[P(OPh)_3]_4$ was also carried out (Sonagashira coupling) (Scheme-11).

Scheme -10



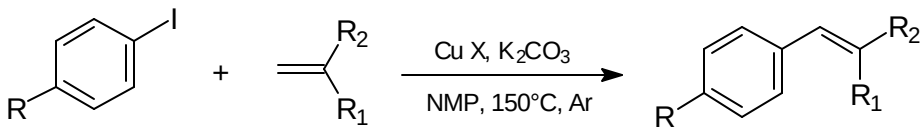
$R = OCH_3$, Cl W = Ph, COOEt etc.

Scheme -11



Some of the transition metal salts, say copper iodide and copper bromide are known to catalyze the reactions of aryl halides with various carbon and heteroatom nucleophile. The reactions of aryl iodides with olefins catalyzed by copper iodide and copper bromide in the presence of potassium carbonate were carried out to form the expected coupling products in good yield by using both stoichiometric and catalytic amount of copper salts (scheme-12).

Scheme -12

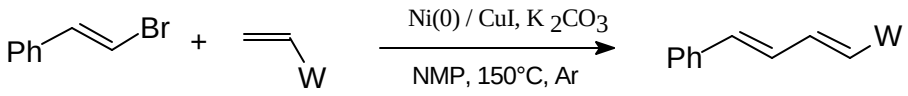


R = OCH_3, R_1 = CHO, COOEt , R_2 = H, CH_3

X = Br, I

The reaction of vinyl halide (β-bromostyrene) with olefins in the presence of nickel (0) complexes and copper salts have been carried out (scheme-13).

Scheme -13



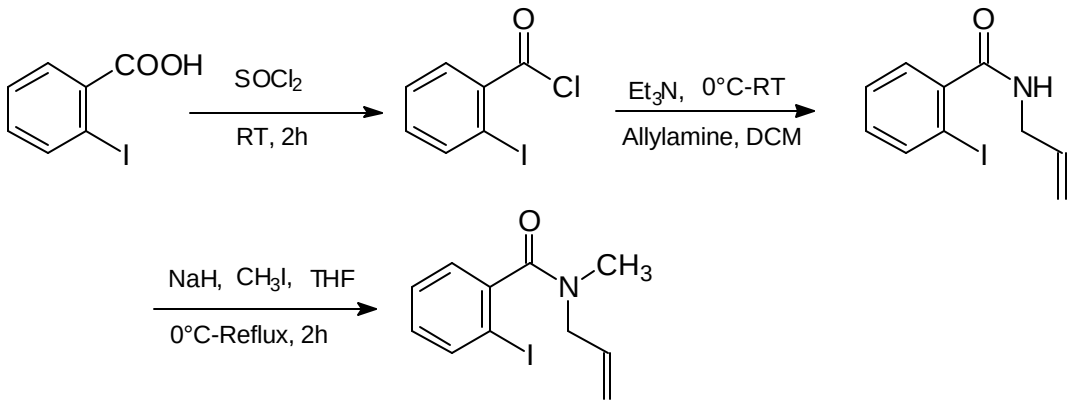
W = Ph, COOEt

Ni(0) = $Ni(P(OPh)_3)_4$, $Ni(P(OEt)_3)_4$

Cu(I) = CuI, CuBr

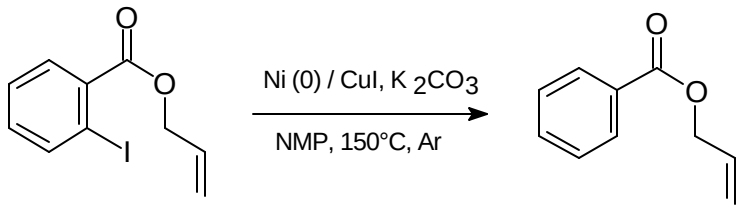
The precursors for intramolecular Heck reaction were synthesized from *o*-iodobenzoic acid by the following reaction sequences shown in scheme-14.[10]

Scheme -14



The intramolecular Heck reactions of allyl-2-iodobenzoate, 1*N*-allyl-2-iodobenzamide and 1*N*-allyl-1*N*-methyl-2-iodobenzamide catalyzed by $Ni[P(OPh)_3]_4$ and copper salts in the presence of potassium carbonate were performed to get the corresponding heterocyclic compounds (scheme-15 and 16).

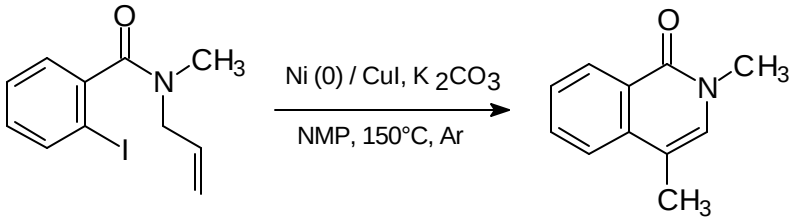
Scheme -15



Ni(0) = $Ni(P(OPh)_3)_4$, $Ni(P(OEt)_3)_4$

Cu(I) = CuI, CuBr

Scheme -16

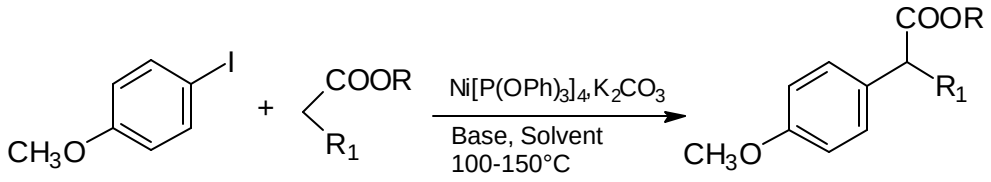


Ni(0) = $Ni(P(OPh)_3)_4$, $Ni(P(OEt)_3)_4$

Cu(I) = CuI, CuBr

The reactions of 4-iodoanisole with vinyl ketones, carbon and nitrogen nucleophiles catalyzed by $Ni[P(OPh)_3]_4$ and CuI have been carried out with various modifications of reaction conditions (scheme 17 and 18).

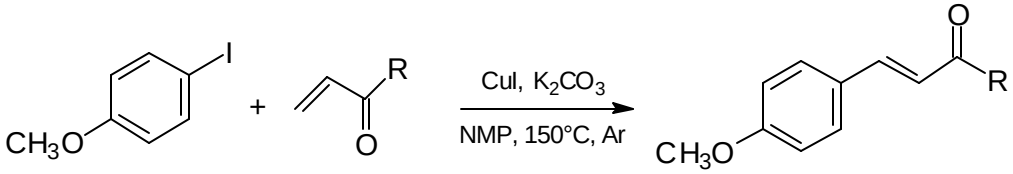
Scheme -17



R_1 = CN, COOEt Base = NaH, K_2CO_3

R = Et Solvent = Dioxane, NMP

Scheme -18



R = CH_3, CH_2CH_3, C_6H_5

The results of inter and intramolecular reactions of aryl and vinyl halides with olefins and alkynes catalyzed by $Ni[P(OPh)_3]_4$ and CuI are summarized in Table-1 and Table-2.

Table 1 : Ni(0) Catalyzed reactions of Aryl and Vinyl halides with Olefins/Alkynes

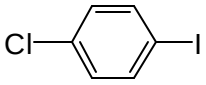
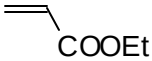
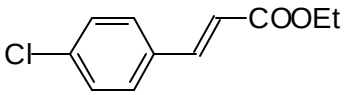
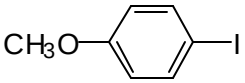
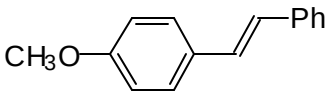
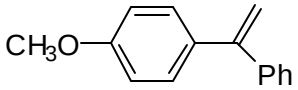
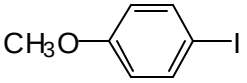
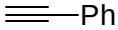
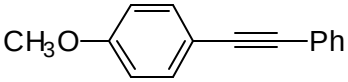
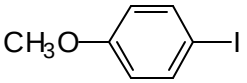
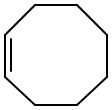
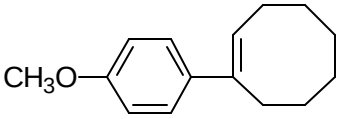
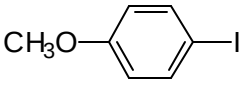
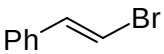
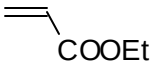
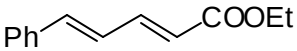
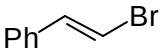
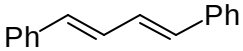
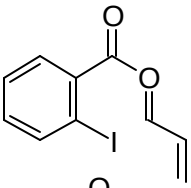
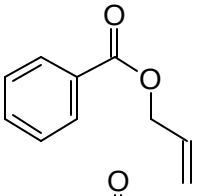
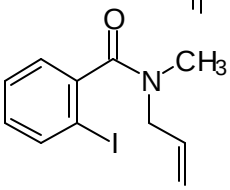
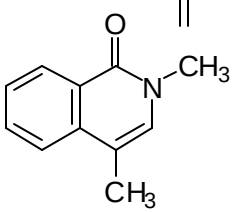
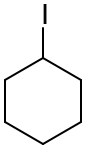
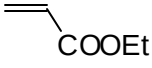
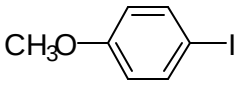
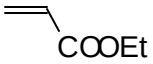
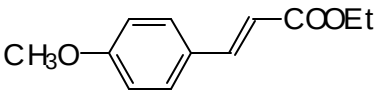
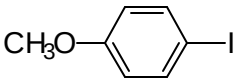
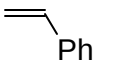
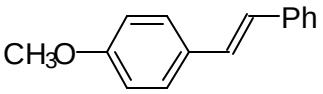
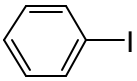
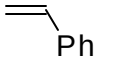
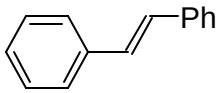
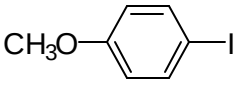
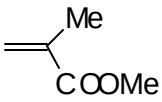
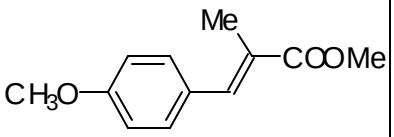
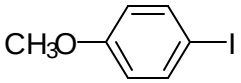
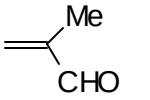
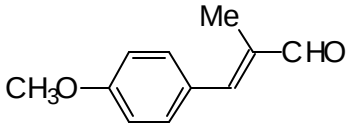
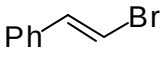
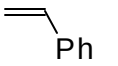
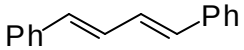
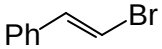
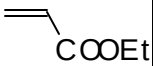
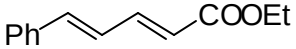
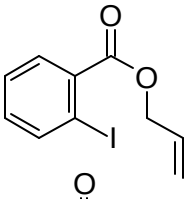
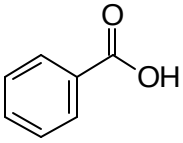
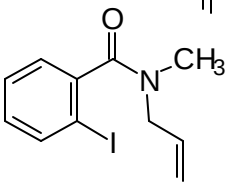
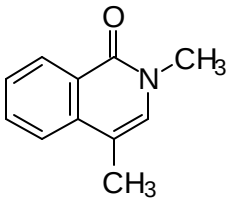
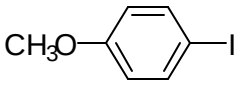
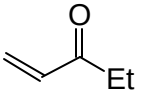
S.No	Aryl/Vinyl halide	Olefin/Alkyne	Time(h)	Product	Yield %
1			24		87
2			24	 (85%)  (15%)	95
3			24		67
4			24		55
5			24	—	—
6			24		64
7			24		44
8		—	23		16
9		—	48		79
10			24	—	—

Table2: CuI catalyzed reactions of aryl and vinyl halides with olefins

S.No	Aryl/Vinyl halide	Olefin/Alkyne	Time(h)	Product	Yield %
1			24		78
2			24		80
3			24		60
4			24		31
5			24		40
6			24		46
7			24		75
8		—	23		35
9		—	48		54
10			24	—	—

RESULTS AND DISCUSSION

The starting materials required for the Heck type coupling reactions were prepared by the literature methods[11] and characterized by the usual spectroscopic techniques. The inter and intramolecular reactions of aryl and vinyl halides with olefins and alkynes catalyzed by Ni(0) complex and Cu(I) salts afforded the Heck type coupling products in good yield. The $Ni[P(OPh)_3]_4$ complex was synthesized according to the literature method.[12] The precursors (**4** & **5**) for intramolecular Heck reaction were synthesized from *o*-iodobenzoic acid. The IR spectrum of the starting material, allyl 2-iodobenzoate (**4**) showed a sharp peak at 1732 cm^{-1} which indicating the presence of carbonyl group of ester. The ^1H NMR spectrum displayed a doublet at δ 8.0 with J = 8.8 Hz corresponding to one of the aromatic proton at 5th carbon and another doublet at δ 7.8 with J = 8.0 Hz confirmed the presence of proton at 3rd carbon. The other two aromatic protons appeared as multiplets at δ 7.4-7.25 and 7.15-7.0. A multiplet at δ 6.1-5.9 appeared indicating the presence of internal olefinic proton and the two terminal olefinic protons appeared as doublets, one at δ 5.5 with J = 17.6 Hz and another at δ 5.2 with J = 8.8 Hz. The ^{13}C NMR spectrum revealed the two methylenic carbons signals at δ 94.15 and 66.10 corresponding to olefinic and methylenic carbon adjacent to oxygen which was identified by DEPT experiments. The mass spectrum displayed a molecular ion peak at m/z 288. All the above data confirmed the structure of **4**. Similarly the structure of 1*N*-allyl-1*N*-methyl-2-iodobenzamide (**5**) was also confirmed. The inter and intramolecular reactions of aryl and vinyl halides with olefins and alkynes catalyzed by Ni(0) complex gave the Heck type coupling products in good yield. The reaction of 4-iodoanisole with styrene catalyzed by $Ni[P(OPh)_3]_4$ afforded two products (regioisomers) and characterized by IR, ^1H NMR and mass spectra. The IR spectrum of both the products showed a prominent peak at 1600 cm^{-1} indicating the presence of C=C of the olefinic systems. The ^1H NMR spectrum of one of the isomer showed a doublet at

δ 6.9 with coupling constant *J* = 12.1 Hz confirmed the presence of olefinic proton of *trans* product. The mass spectrum showed a molecular ion peak at m/z 210 supporting the formation of the expected product. These above data confirmed the structure of the product, 1-(4-methoxyphenyl)-2-phenyl-(*E*)-ethylene. The ^{1}H NMR spectrum of the other isomer showed two singlets, one at δ 4.95 and another singlet at δ 4.90 due to the presence of terminal olefinic protons. The IR spectrum of the product obtained from the reaction of 4-chloroiodobenzene with ethyl acrylate showed strong absorption bands at 1705 cm^{-1} and 1600 cm^{-1} which indicating the presence of carbonyl group and C=C of α, β-unsaturated systems. The ^{1}H NMR spectrum of the product displayed two doublets; one at δ 6.3 (*J* = 17.2 Hz) and another at δ 7.6 (*J* = 17.2Hz) which assigned to olefinic protons of the unsaturated esters and its trans stereochemistry. The mass spectrum of product showed a molecular ion peak at (m/z) 210, which supports the structure of the expected product.

The IR spectrum of the product obtained from the copper iodide catalyzed reaction of 4-iodoanisole with methacrolein gave a sharp peak at 1660 cm-1. The ^{1}H NMR spectrum displayed a singlet at δ 9.5 due to the presence of aldehyde proton and two doublets at δ 7.5 and 7.0 confirming the aromatic protons of A_2B_2 pattern. A singlet appeared at δ 7.2 corresponding to olefinic proton. Two sharp singlets at 3.85 and 2.1 could be assigned to methoxy and allylic methyl protons. The mass spectrum showed a molecular ion peak at m/z 176, which supporting the structure of the product (**12**). Similarly the structure of the product (**17**) obtained from the reaction of 4-iodoanisole with methylmethacrylate was also confirmed.

The ^{1}H NMR spectrum (shown in page 54) of the product formed from the reaction of 4-iodoanisole with cyclooctene displayed two doublets at δ 7.3 and 6.8 which assigned to aromatic protons of A_2B_2 type. A triplet appeared at δ 5.8 indicating the presence of olefinic proton and a singlet 3.85 due to the presence of methoxy protons. A triplet at δ 2.6 was assigned for allylic

methylene protons and a multiplet at δ 2.25-2.15 was attributed to the other methylenic protons. A multiplet appeared at δ 1.55-1.45 corresponding to eight methylenic protons. The mass spectrum showed a molecular ion peak at m/z 216. The above data confirmed the structure of the product (**14**).

The intramolecular reaction of *1N-allyl-1N-methyl-2-iodobenzamide* catalyzed by both $Ni[P(OPh)_3]_4$ and copper iodide gave the expected cyclised product, 2, 4-dimethylisoquinolinone in 79% and 54% yield respectively. IR spectrum of the product showed sharp peaks at 1699 cm^{-1} and 1626 cm^{-1} for C=O and C=C respectively which indicating the formation of the cyclised product. In the ^1H NMR spectrum, a singlet at δ 2.25 assigned to allylic methyl and a sinlget at δ 6.9 was assigned to the proton on heterocyclic ring of the product. A doublet at δ 8.5 corresponding to the proton of the aromatic ring, which is periplanar to the carbonyl. The ^{13}C NMR spectrum revealed all the carbon signals of the product and matching with literature.[13] The carbonyl carbon appeared at δ 162.02 and two signals at δ 36.39 and 15.00 confirmed the presence of *N*-methyl and allylic methyl respectively. Both ^1H NMR and ^{13}C NMR spectra shown in page 55. The mass spectrum displayed a molecular ion peak at (m/z) 173 supporting the formation of cyclised product, 2, 4-dimethylisoquinolinone.

The reaction of allyl-2-iodobenzoate catalyzed by the Ni(0) complex gave dehalogenated product and CuI afforded the dehalogenated and deallylated product which was evidenced by the ^1H NMR and Mass spectra. The reactions of *p*-iodoanisole with vinyl ketones, cyclohexenone, benzalacetone and cyclooctene catalyzed by copper salts were unsuccessful, the reason is that vinyl ketones are easily polymerized before it reacts with the metal complexes in the reaction medium. Similarly, $Ni[P(OPh)_3]_4$ catalyzed reaction of *p*-iodanisole with carbon and nitrogen nucleophiles were found to be unsuccessful under various modified reaction conditions.

CONCLUSION

In conclusion, we have found transition metal complex, $Ni[P(OPh)_3]_4$ and transition metal salt copper iodide as new alternative catalysts to catalyze the coupling reaction of aryl iodide and vinyl bromides with olefins (Heck reaction) and alkynes at high temperature.

EXPERIMENTAL

General

All commercial reagents were obtained from Aldrich Chemical Co., S. D. Fine Chemical Co. India and LOBA Chemical Co. India. Progress of the reaction was monitored by TLC and was visualized by UV absorption by fluorescence quenching or I_2 staining or by both. Silica gel 60-120 and 100-200 mesh obtained from S. D. Fine Chemical Co. India and Rico Industrial Chemicals Co. India for column chromatography.

All melting points were uncorrected in degree Celsius and were recorded on a Thermonik melting point apparatus. IR spectra were recorded on a perkin-Elmer infrared spectrometer model 599-B and model 1620 FT-IR. ^1H NMR spectra were recorded using TMS as internal reference on Bruker AC-200, Bruker MSL-300 and Bruker -500 intruements using $CDCl_3$ as solvent chemical shifts are reported in δ. ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker MSL-300 intruements operating at 50.32 MHz and 75.3 MHz, respectively. Mass spectra were recorded on Finnigan-Mat 1020C mass spectrometer and are obtained at an ionization potential of 70 eV.

Preparation of $Ni[P(OPh)_3]_4$

A mixture of nickel nitrate (0.76 g, 4.4 mmol) and triphenyl phosphite (3.9 g, 13 mmol) in ethanol (10 mL) was charged into a 50 mL conical flask. To this stirred solution, sodium boro

hydride (0.25 g, 6.94 mmol) in warm ethanol (10 mL) was added slowly for 10 minutes. The white precipitate obtained was filtered, washed with ethanol and dried.

M. P: 145 °C .

Recrystallisation of Copper iodide [14]

Copper iodide (1.9 g, 100 mmol) was charged into a 500 mL RB flask equipped with a magnetic stirring bar. To this stirred reaction mixture, potassium iodide solution (70 mL, 3.5 M) was added slowly in about 30 minutes with moderate heating (40-50 ^{0}C) followed by addition of charcoal (2.5 g). The mixture was allowed to stir at 45 °C for 1h. The resulting mixture was filtered through sintered funnel and the filtrate was diluted with water (250 mL). The solution was allowed to stand for 1h. The precipitated white solid was filtered through a sintered funnel, washed with water, ethanol and ether. The product was dried in a desiccator (calcium chloride).

Synthesis of Aryl and Vinyl halides

The starting materials, aryl iodides were prepared by the literature method from the corresponding aromatic amines by diazotisation followed by addition of potassium iodide and the vinyl bromide prepared from cinnamic acid *via* bromination, dehydrobromination and decarboxylation sequence.[15]

4-Iodoanisole (1)

Yield : 2.2 g (95%)

Mol. F : C_7H_7IO.

M. P : 51 °C.

IR (Nujol) : 2905 1600, 1410, 1305, 840, 760 cm^{-1}.

^{1}H NMR (200 MHz,$CDCl_3$) : δ 7.5 (d, *J* = 8.7 Hz, 2H), 7.0 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H).

Mass (*m/z*) : 234 (M^+, 61), 219 (16), 128 (12), 105 (19), 97 (44), 55 (100).

4-chloroiodobenzene (2)

Yield : 2.13 g (90%)

Mol. F : C_6H_4ClI

M. P : 52 °C

IR (Nujol) : 3005, 1600, 1480, 1220, 1100, 770 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.6 (d, *J* = 8.1 Hz, 2H), 7.1 (d, *J* = 8.1 Hz, 2H)

b-**Bromostyrene (3)**

Mol. F : C_8H_7Br

IR (neat) : 3015, 3000, 1605, 1470, 1280, 940 cm^{-1}

^{1}H NMR (200, $CDCl_3$) : δ 7.45 - 7.35 (m, 5H), 7.2 (d, *J* =17.0 Hz, 1H), 6.75 (d, *J* = 17.2 Hz, 1H)

Preparation of Allyl -2-iodobenzoate (4)

A 25 mL RB flask equipped with magnetic stirring bar was charged with *o*-Iodobenzoic acid (2.48 g, 10 mmol) and 1 mL of thionyl chloride and allowed to stir at room temperature for about 2h. The excess of thionyl chloride was removed by distillation under reduced pressure and the acid chloride stored under argon atmosphere. Another 25 mL two necked RB flask was equipped with magnetic stirring bar, charged with triethylamine (1.01g, 10mmol) and allyl alcohol (0.58g, 10 mmol) in dry dichloromethane (15 mL). To this, freshly prepared acid chloride was added slowly at 0°C. and the reaction mixture was allowed to stir for 1h. The reaction was quenched using dil. HCl (10% by volume) and the product extracted with

dichloromethane (3×10mL) and the combined organic layer dried over anhydrous sodium sulphate, concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel column chromatography using petroleum ether-ethyl acetate mixture (9: 1)

Yield : 2.72 g (95%)

Mol. F : $C_{10}H_9IO_2$

IR (Neat) : 1732, 1583, 1429, 1294, 1016, 740 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.0 (d, *J* = 8.8 Hz, 1H), 7.8 (d, *J* = 9.0 Hz, 1H), 7.4 (m, 1H), 7.15 - 7.0 (m, 1H), 6.1-5.95 (m, 1H), 5.5 (d, *J* = 17.6 Hz, 1H), 5.2 (d, *J* = 8.8 Hz, 1H)

^{13}C NMR (50.35 MHz, $CDCl_3$) : δ 165.85, 141.22, 134.97, 132.43, 130.89, 127.86, 118.76, 94.15, 66.10.

Mass (*m/z*) : 288 (19), 231 (100), 203 (35), 117 (7), 104 (11), 76 (44).

Preparation of 1*N*-allyl-2-iodobenzamide (5)

A 25 mL RB flask equipped with magnetic stirring bar was charged with o-iodobenzoic acid (2.48 g, 10 mmol) and thionyl chloride (1mL). The reaction mixture was allowed to stir at room temperature for 1h. The excess of thionyl chloride was removed by distillation under reduced pressure. The acid chloride was stored under argon atmosphere. A mixture of triethylamine (1.01g, 10 mmol) and allylamine in dry dichloromethane (15mL) was charged into another 50mL RB flask equipped with magnetic stirring bar. The acid chloride was added slowly at 0^0 C for 10 minutes and the reaction mixture allowed to stir for 1 h. The reaction was quenched with dil. HCl and the product extracted using dichloromethane (3×10 mL). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulphate

and concentrated under reduced pressure. The crude product purified by silica gel column chromatography using pet. ether-ethyl acetate mixture (8.5: 1.5).

Yield : 2.62 g (92%)

Mol. F : $C_{10}H_{10}INO$

M. P : 120 °C

IR ($CHCl_3$) : 3340, 1670, 1600, 1230, 770 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) : δ 7.8 (d, *J* = 7.3 Hz, 1H), 7.45 (m, 2H), 7.45 -7.25 (m, 2H), 7.1-7.05 (m, 1H), 6.05 - 5.85 (m, 1H), 5.4 -5.15 (m, 2H) Hz, 2H), 4.15 (t, *J* = 6.0 Hz, 2H)

Mass (*m/z*) : 287 (M^+, 19), 231 (100), 203 (24), 160 (11), 105 (8), 76 (16)

Preparation of 1*N*-allyl-1*N*-methyl-2-iodobenzamide (6)

A 25 ml two-necked RB flask equipped with magnetic stirring bar and a reflux condenser was charged with sodium hydride (0.58 g, 10 mmol) in dry tetrahydrofuran (10 mL). To this 1N-allyl-2-iodobenzamide in tetrahydrofuran (5 mL) was added slowly at 0°C for 5 minutes followed by addition of methyl iodide (1.072 g, 7.5 mmol). The reaction mixture was allowed to reflux for 3 hours and quenched with ice cold water, the product extracted with ethyl acetate (3x10 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using pet. ether and ethyl acetate mixture (8.5: 1.5).

Yield : 1.20 g (80%)

Mol. F : $C_{11}H_{12}INO$

IR (Neat) : 2986, 1730, 1600, 1040, 740 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) : δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.35 - 7.2 (m, 2H), 7.15 - 7.0 (m,

2H), 7.05 - 7.0 (m, 2H), 6.0 - 5.5 (m, 2H), 5.4 - 5.1 (m, 4H), 4.2 (bs, 1H), 3.6 (bs, 1H), 3.05 (s, 3H), 2.75 (s,3H).

^{13}C NMR (50.35 MHz, $CDCl_3$) : δ 170.32, 169.92, 142.35, 142.13, 138.75, 132.02, 129.81, 128.12, 127.70, 117.78, 92.37, 91.99, 53.11, 49.08, 35.44, 31.94.

Mass(*m/z*) : 301 (M^+, 16), 231 (100), 203 (43),174 (65), 146 (5), 127 (5), 105 (10), 76 (7).

General procedure for Ni(0) and Cu (I) catalyzed reactions of aryl halides with olefins

Ni(0) Catalyzed reactions of aryl and vinyl halides with olefins and alkynes

A 25 mL RB flask equipped with magnetic stirring bar, reflux condenser and argon balloon was charged with aryl iodide / vinyl bromide (1mmol), olefin (2.5 mmol) / alkyne (1 mmol), potassium carbonate (0.275 g, 2 mmol) and $Ni(P(OPh)_3)_4$ (0.12 g, 10 mol %) in N-methyl pyrrolidinone (4 mL). The reaction mixture was allowed to stir at 140-150 ^{0}C for 12-24 hrs and neutralized with dil. HCl (10% by volume). The product extracted with ethyl acetate (3 x 5 mL), the combined organic extracts was dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield the crude product. The crude product on silica gel column chromatographic purification using pet. ether and ethyl acetate mixture gave the pure products.

CuI Catalyzed re actions of aryl and vinyl halides with olefins

A 25 mL RB flask equipped with magnetic stirring bar, reflux condenser and argon balloon was charged with aryl iodide / vinyl bromide (1mmol), olefin (2.5 mmol), Potassium

carbonate (0.275 g, 2 mmol) and CuI (0.02 g, 10 mol %) in N-methyl pyrrolidinone (4 mL). The reaction mixture was allowed to stir at 140-150 °C and neutralized with dil. HCl (10% by volume). The product was extracted with ethyl acetate (3 x 5 mL), the combined organic extracts was dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield the crude product. The crude product on silica gel column chromatographic purification using pet. ether and ethyl acetate mixture gave the pure product.

Ethyl -3-(4-chlorophenyl)-(*E*)-2-propenoate (7)

Mol. F : $C_{11}H_{11}ClO_2$

IR (Neat) : 2980, 1716, 1638, 1592, 1490, 1269, 1173, 883 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.65 (d, *J* = 16.2 Hz, 1H),7.5 (d, *J* = 8.1Hz, 2H), 7.4 (d, *J* = 8.1 Hz, 2H), 6.4 (d, *J* = 16.2 Hz, 1H), 4.2 (q, *J* = 8.0 Hz, 2H),1.3 (t, *J* = 8.0 Hz, 3H).

Ethyl 3-(4-methoxyphenyl)-(*E*)-2-propenoate (8)

Mol. F : $C_{12}H_{14}O_2$

IR (Neat) : 2985, 1710, 1600, 1510, 1240, 1040, 830 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.6 (d, *J* = 17.0 Hz, 1H), 7.5 (d, *J* = 8.0 Hz, 2H), 6.9 (d, *J* = 8.0 Hz, 2H), 6.3 (d, *J* = 17.0 Hz, 1H), 4.2 (q, *J* = 8.0 Hz, 2H), 3.85 (s, 3H), 1.3 (t, *J* = 8.0 Hz, 3H)

^{13}C NMR (50.32 MHz, $CDCl_3$) : δ 166.9, 161.2, 143.7, 129.5, 127.0, 115.60, 114.11, 60.00, 55.00, 14.17.

Mass (*m/z*) : 206 (M^+, 100), 191 (1), 178 (6), 161 (19), 154 (30), 135 (9), 126 (20), 98 (63).

1-(4-Methoxyphenyl)-2-phenyl-(*E*)-ethylene (9)

Mol. F : $C_{15}H_{14}O$

M. P : 135 °C

IR ($CHCl_3$) : 2923, 1599, 1375, 1251, 814 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.6 - 7.25 (m, 8H), 7.1 (d, *J* = 17.7 Hz, 1H), 6.9 (d, *J* = 8.5 Hz, 2H), 3.85 (s, 3H).

Mass(*m/z*) : 210 (M^+, 100), 195 (25), 179 (17), 165 (66), 152 (59), 115 (26), 105 (25), 91(41), 77 (29).

1-(4-methoxyphenyl)-1-phe nylethylene (10)

Mol. F : $C_{15}H_{14}O$.

IR ($CHCl_3$) : 2923, 1600, 1453, 1245, 835 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.45 - 7.25 (m, 7H), 6.9 (d, *J* = 8.5 Hz, 2H), 4.95 (s,1H), 4.9 (s, 1H), 3.85 (s, 3H).

Ethyl 5-phenyl-(2*E*, 4*E*)-2,4-pentadienoate (11)

Mol. F : $C_{13}H_{14}O_2$.

IR ($CHCl_3$) : 2981, 1708, 1625, 1448, 1367, 1175, 841, 731 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.6 - 7.3 (m, 6H), 6.95 - 6.85 (m, 2H), 6.0 (d, *J* = 13.0 Hz, 1H), 4.2 (q, *J* = 8.0Hz, 2H), 1.3 (t, *J* = 8.0 Hz, 3H).

Mass(*m/z*) : 202 (M^+,14), 157 (17), 129 (100), 115 (7),77 (36), 63 (18)

3-(4-methoxyphenyl)-2-methyl-(*E*)-2-propenal (12)

Mol. F : $C_{11}H_{12}O_2$

IR (Neat) : 2920, 1660, 1600, 1320, 1240, 860 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 9.5 (s, 1H), 7.5 (d, *J* = 8.1Hz, 2H), 7.2 (s, 1H), 7.0 (d, *J* = 8.2 Hz, 2H), 3.85 (s, 3H), 2.1 (s, 3H).

Mass (*m/z*) : 176 (M^+, 43), 161 (5), 145 (27),76 (100).

1, 4-Diphenyl-(1*E*,3*E*)-1,3-butadiene (13)

Mol. F : $C_{16}H_{14}$

M.P : 151 °C

IR ($CHCl_3$) : 2985, 1600, 1460, 1230, 780 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.6 - 7.25 (m, 10H), 7.2 (d, *J* =14.2 Hz, 2H), 6.8 (d, *J* = 14.2Hz, 2H)

Mass (*m/z*) : 206 (M^+,13), 130 (49), 104 (100), 91 (89), 77 (54)

1-(4-Methoxyphenyl)-1-cyclooctene (14)

Mol. F : $C_{15}H_{20}O$

IR (Neat) : 2925, 1601, 1470, 1040, 940, 780 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.3 (d, *J* = 8.0 Hz, 2H), 6.8 (d, *J* = 8.0 Hz, 2H), 5.8 (t, *J* = 7.5 Hz, 1H), 3.85 (s, 3H), 2.6 (t, *J* = 8.5 Hz, 2H), 2.25 - 2.15 (m, 2H), 1.55 - 1.45 (m, 8H)

Mass (*m/z*) : 216 (53), 188 (98), 201 (11), 173 (40), 159 (40), 134 (36), 128 (31),121 (59), 115 (65), 91 (59), 77 (4), 65 (31).

1-(4-Methoxyphenyl)-2-phenylacetylene (15)

Mol. F : $C_{15}H_{12}O$

IR ($CHCl_3$) : 3057, 2108, 1597, 1487, 1443, 1242, 882 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.5 - 7.1 (m, 7H), 6.9 (d, *J* = 8.5 Hz, 2H), 3.85 (s, 3H).

2,4-Dimethyl-1,2-dihydro-1-isoquinolinone (16)

Mol. F : $C_{11}H_{11}NO$

M. P : 75 °C

IR ($CHCl_3$) : 2932, 1699, 1626, 1437, 1386, 768 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.5 (d, *J* = 8.1 Hz, 1H), 7.65 - 7.45 (m, 3H), 6.9 (s, 1H), 3.55 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 162.04, 137.12, 131.61, 130.00, 127.73, 126.32, 125.69, 122.08, 111.64, 36.39, 15.00.

Mass (*m/z*) : 173 (M^+, 100), 158 (14), 144 (38), 115 (7.5), 104 (11), 77 (4).

Methyl-2-formyl-3-(4-methoxyphenyl)-(*Z*)-2-propenoate (17)

Mol. F : $C_{12}H_{14}O_3$.

IR (Neat) : 2951, 2838, 1711, 1630, 1605, 1034, 836 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.7 (s, 1H), 7.4 (d, *J* = 8.0 Hz, 2H), 6.9 (d, *J* = 8.0 Hz, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 2.15 (s, 3H).

Mass (*m/z*) : 206 (100), 195 (41), 146 (97), 103 (41), 91(39), 77 (35).

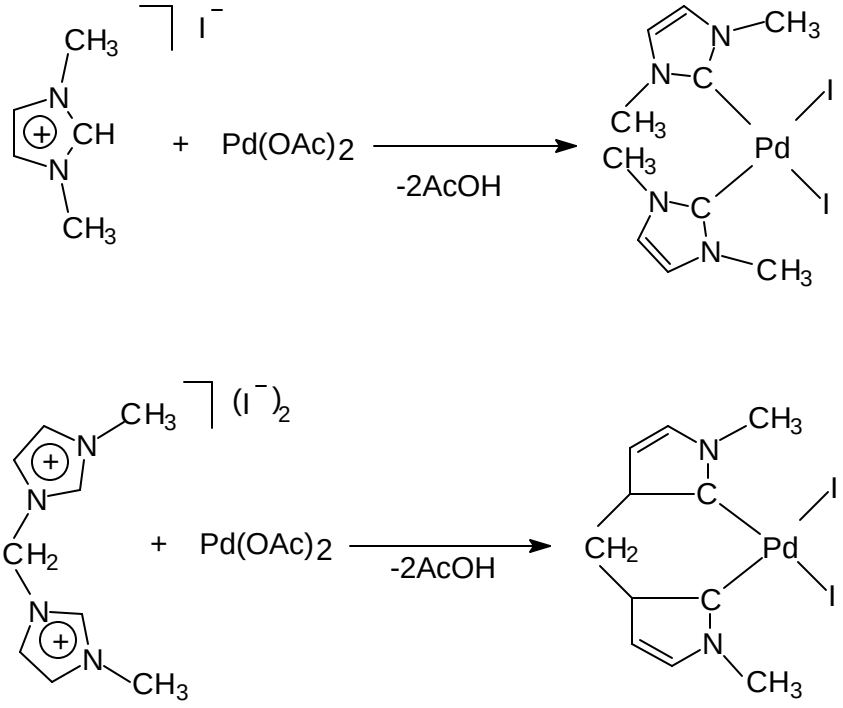
Section 2. Synthesis of oxime and amino palladacycles and their application in the catalysis of Heck reaction.

INTRODUCTION AND BACKGROUND

The transition metal catalyzed C-C bond formation in organic synthesis is very attractive in recent years. The design of structurally important, more selective and active catalysts are attractive prospects in C-C bond forming reactions, for example, synthesis of more active catalysts for Heck reaction. Some of the new, novel and active palladium catalysts for the Heck reaction is described below in detail.

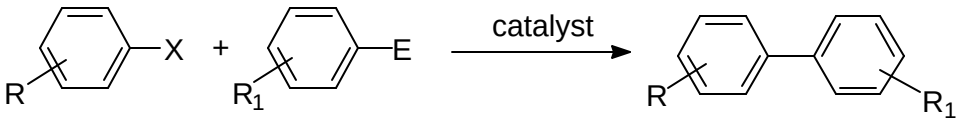
A structurally important N-heterocyclic carbene palladium catalysts were synthesized and applied for the coupling of aryl halides with olefins in homogeneous catalysis as reported by W. A. Herrmann *et al.* as shown in scheme-1.[16]

Scheme -1

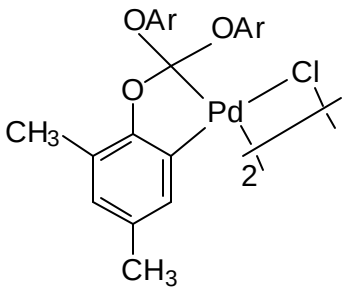


Robin *et al.* demonstrated the synthesis of extremely highly active orthopalladated triaryphosphite as catalysts in biaryl coupling reactions which gave unprecedented high turnover numbers upto 1000000 and turnover frequencies of nearly 900000 in Suzuki reaction and turnover numbers upto 830000 in the Stille reaction (scheme-2).[17]

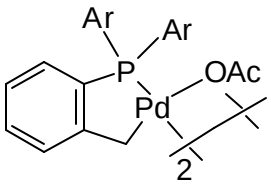
Scheme -2



E = $B(OH)_2$ (suzuki) and E = SnR_3 (stille)



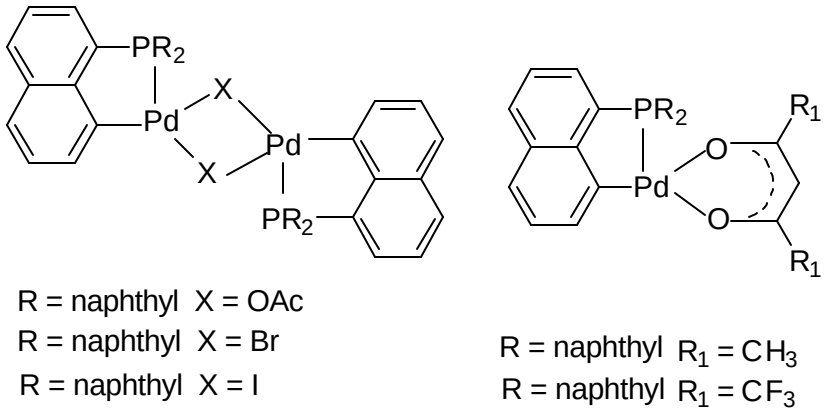
Ar = 2,4 - Bu^tC_6H_3



Ar = 2- MeC_6H_4

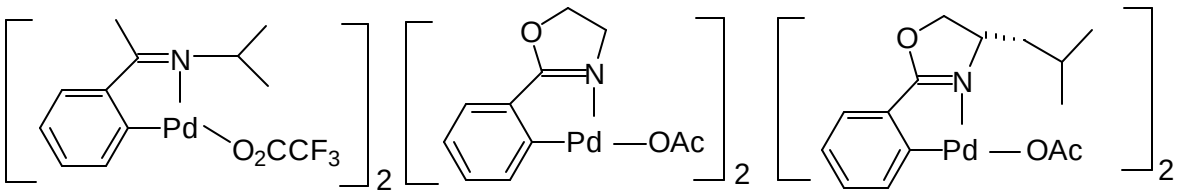
Shaw *et al.* reported new tri(1-naphthyl)phosphine palladacycles which are very active catalysts for Heck reaction as shown in scheme-3.[18]

Scheme -3



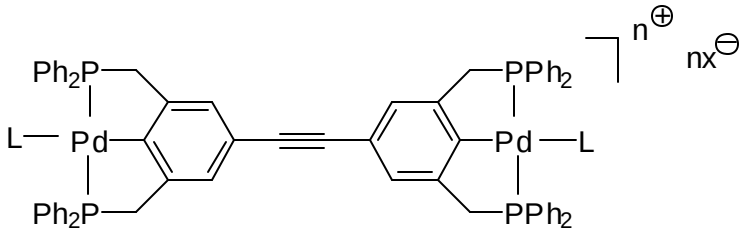
The new cyclopalladated, phosphine free thermally and air stable imine complexes are exceptionally highly active catalysts for the Heck reaction leading to more than million turnover numbers in some cases, reported by M. Ohff et al. as shown in scheme-4.[19]

Scheme -4



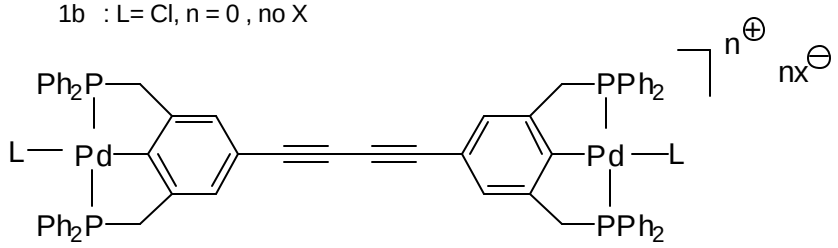
Bis-pincer-cyclopalladates containing an ethynediyl or butadiynediyl-bridge, have been used as catalysts for the Heck reaction (scheme-5).[20]

Scheme -5



1 a : L= MeCN, n = 2, X = BF_4

1b : L= Cl, n = 0 , no X



2 a : L= MeCN, n = 2, X = BF_4

2b : L= Cl, n = 0 , no X

OBJECTIVE

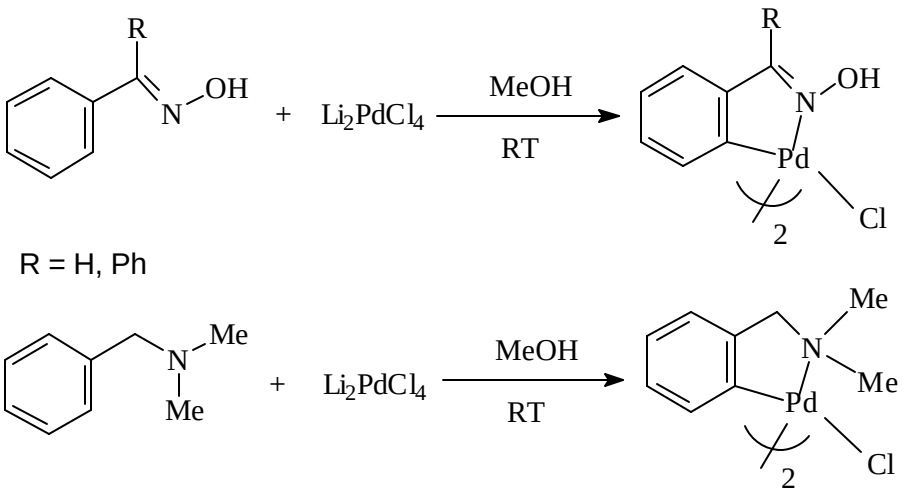
Our aim was to synthesis structurally important and more stable dimeric palladium complex as a catalyst for the coupling of aryl iodides, bromides and activated chlorides with olefins to achieve high turnover numbers and turnover frequencies. We were also interested in the synthesis of oximepalladacycle, which has a covalent palladium-carbon bond that could stabilize the complex at high temperature and activate aryl chlorides for Heck reaction.

PRESENT WORK

The present work involves designing and synthesizing very active dimeric oxime and amino palladacycles and their application in activating aryl halides including an activated aryl chloride for Heck type coupling reactions. Palladacycles were synthesized according to the

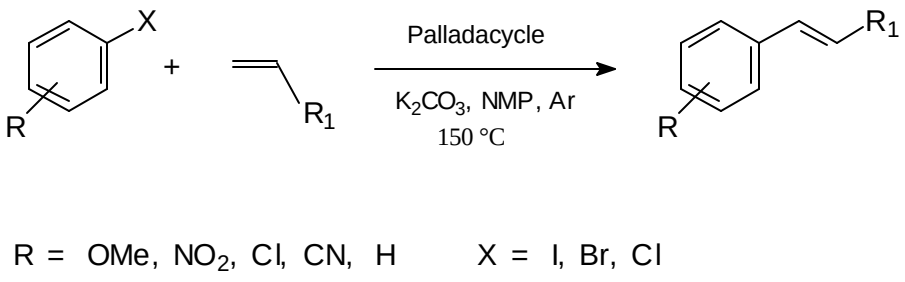
literature method from easily available starting materials like benzaldehydeoxime, benzophenoneoxime and *N*, *N*-dimethylbenzylamine with lithium tetrachloropalladate as shown in scheme-1.[21]

Scheme-1

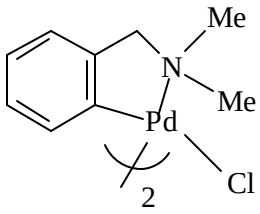


The reactions of various aryl halides, aryl iodide, bromide and an activated aryl chloride with olefins in presence of amino and oximepalladacycle using different co-catalysts $AlCl_3$, NBu_4Br and $ZnCl_2$ were studied in both small and large scale with 0.001 g of dimeric palladium catalyst to achieve high turn over numbers and turnover frequencies (scheme-2).

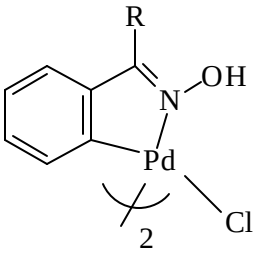
Scheme-2



Dimeric palladacycles :



1



2, R = H

3, R= Ph

The results of reactions of various aryl halides with olefins catalyzed by amino and oxime palladacycles are summarized in table-3

Table-3 : Heck vinylation of aryl halides catalyzed by amine and oxime palladacycle

S. No.	Reactant	Olefin	Catalyst	Product	Time (h)	Yield	TON	TOF
1.	4-Iodo-anisole (50 mmol)	Ethylacrylate (100 mol)	1	4-Methoxy Ethyl cinnamate	8	88	89, 540	11, 190
			3		2	90	453	226
2.	4-Iodoanisole (50 mmol)	Styrene (60 mol)	1	4-Methoxy stilbene	48	76	76, 000	1, 740
			2		48	92	1, 38, 666	2, 888
			3		6	97	485	80
3.	Iodobenzene (50 mmol)	Ethyl acrylate (100 mmol)	2	Ethyl cinnamate	7	96	1, 45, 454	20,778
4.	Bromo-benzene (50 mmol)	Ethylacrylate (100 mmol)	1	ethylcinnamate	34	90	90, 000	2, 647
			2		37	52	72, 000	1, 946
			3		1	89.8	437	437
5.	bromobenzene (50 mmol)	Styrene (60 mmol)	1	stilbene	29	86.6	86, 666	2, 988
			2		48	52	78, 000	240
			3		1	96	483	483
6.	4-Chloro nitro benzene (5 mmol)	Ethyl acrylate (10 mmol)	1	4-Nitroethyl cinnamate	31	51	287	
			2		30	60	300	
7.	4-Chloronitro benzene (50 mmol)	Styrene (60 mmol)	1	4-Nitro-stilbene	42	71	70, 000	1, 666
			2		40	69	350	
8.	4-Chlorobenzo nitrile (5 mmol)	Styrene (6 mmol)	2	4-Cyano stilbene	24	78.5	350	
9.	2-Bromo pyridine (5 mmol)	Ethyl-acrylate (10 mmol)	2	2-Pyridyl-ethyl acrylate	48	68	4, 090	
10.	4-Chloro toluene (2 mmol)	Styrene (4 mmol)	3[a]	4-Methyl-stilbene	12	18		
			3[b]		24	28		

Co-catalyst : $AlCl_3$; temperature 130 °C
Co-catalyst : Bu_4NI; Temperature 130 °C

RESULTS AND DISCUSSION

The amino and oxime palladacycles were synthesized and characterized by IR, ^{1}H NMR spectra and CHN analysis. The IR spectrum of benzaldehydeoxime palladacycle showed a broad peak at 3370 cm^{-1} and a sharp peak at 1625 cm^{-1} indicating the presence of O-H and C=N groups respectively. The ^{1}H NMR spectrum gave a sharp singlet at δ 8.1 confirming the presence of imine proton and a broad singlet at δ 9.5 due to the oxime O-H proton. The above IR and ^{1}H NMR spectra data were identical with the literature values.[28] The IR spectrum of benzophenoneoxime palladacycle showed a sharp peak at 1628 cm^{-1} and a broad peak at 3440 cm^{-1} for C=N and O-H groups correspondingly. The ^{1}H NMR spectrum displayed a broad singlet at δ 9.3 and multiplet at δ 7.5-7.0 that could be assigned to O-H and aromatic protons accordingly. Further the formation of benzophenoneoxime palladacycle was confirmed by the elemental analysis.

The product obtained from the reaction of *N*,*N*-dimethylbenzylamine and lithium tetrachloropalladate gave a sharp peak at 2990 cm^{-1} in IR spectrum. In the ^{1}H NMR spectrum a sharp singlet appeared at δ 3.4 is attributed to N-C$\underline{H}_3$ protons where as aromatic protons appeared as multiplet between δ 7.6-7.3. In addition to these, the elemental analysis also supported the structure of the complex.

The ^{1}H NMR spectrum of the product obtained from the reaction of 4-iodoanisole with styrene catalyzed by palladacycle showed a doublet at δ 6.9 with coupling constant J = 12.1 Hz which confirmed the presence of olefinic protons and *trans* geometry of the product. The mass spectrum showed a molecular ion peak at m/z 210 corresponding to the product. These above data confirmed the structure of one of the product, 1-(4-methoxyphenyl)-2-phenyl-(*E*)-ethylene.

The IR spectrum of the product obtained from the reaction of aryl iodide with ethyl acrylate showed a sharp peak at 1696-1705 cm^{-1} indicating the presence of ester carbonyl and another peak at 1600 cm^{-1} indicating the presence of C=C of α, β-unsaturated ester. The ^1H NMR spectrum of the product showed two doublets, one at δ 6.3 with coupling constant J = 17.2 Hz and another at δ 7.6 with coupling constant J = 17.0 Hz for olefinic protons of the unsaturated esters. The *trans* stereochemistry of the double bond was confirmed based on the coupling constant value (12-18 Hz for *trans* isomer). The mass spectrum of product showed molecular ion peaks supporting the expected products.

The IR spectrum of the product from the reaction of 4-chlorobenzonitrile with styrene showed sharp peak at 2225 cm^{-1} (C≡N) and 1600 cm^{-1} (C=C). ^1H NMR spectrum of the product displayed a doublet at δ 7.65 with coupling constant, J = 8.0 Hz assigned for the aromatic protons of A_2B_2 type and a multiplet at δ 7.55 - 7.50 indicating the presence of aromatic protons (4H) and another multiplet at δ 7.45-7.50 due to other aromatic protons (4H). The mass spectrum showed a molecular ion peak at (m/z) 204 for the expected product. The above data confirmed the structure of 1-(4-cyanophenyl)-2-phenyl-(*E*)-ethylene (**25**). Similarly, the other cinnamates and stilbenes were characterized by the usual spectroscopic methods.

The reaction of *p*-chloronitrobenzene with styrene gave the corresponding nitro substituted stilbene which was confirmed by IR and ^1H NMR spectral data. The IR spectrum showed a sharp peak at 1604 cm^{-1} due to the presence of C=C group. In the ^1H NMR spectrum, a multiplet at δ 7.6 - 7.2 is assigned to aromatic protons and a doublet at δ 8.3 with J = 16.2 Hz confirmed the presence of olefinic protons and their *trans* stereochemistry. Similarly, the product of *p*-chloronitrobenzene with ethyl acrylate was also characterized. Two sharp peaks at 1714 cm^{-1} and 1645 cm^{-1} are due to the presence of carbonyl and C=C groups respectively. The ^1H NMR spectrum showed two doublets, one at δ 7.7 (J = 14.8 Hz) and another at δ 6.6 (J = 14.0

Hz) which supporting the presence of olefinic protons. Two aromatic protons A_2B_2 type appeared as a doublet at δ 8.3 with coupling constant *J* = 7.5 Hz and other two protons appeared as a doublet at δ 7.2 Hz with coupling constant *J* = 7.5 Hz. The mass spectrum showed a molecular ion peak. The above data confirmed the product (**23**).

The product formed from the reaction of 2-bromopyridine with ethyl acrylate showed sharp peaks at 1705 cm^{-1} and 1620 cm^{-1} for C=O and C=C groups. The ^1H NMR spectrum showed two doublets at δ 7.55 (*J* = 17.0 Hz) and 6.8 (*J* = 17.0 Hz) confirming the presence of olefinic protons of α, β-unsaturated ester. The above data confirmed the structure of product (**26**)

CONCLUSION

Highly stable dimeric amino and oxime palladacycles were found to be efficient catalyst for Heck reaction. Both aryl bromides and an activated aryl chloride could be reacted with olefins to give high turnover numbers and turnover frequencies.

EXPERIMENTAL

Preparation of Benzaldehydeoxime and Benzophenoneoxime

The oximes required for the synthesis of palladacycle catalysts were prepared based on the literature methods (from the reaction of corresponding aldehyde and ketone with hydroxylamine hydrochloride). The aryl iodides were prepared according to the literature methods from the corresponding amino compounds.

Synthesis of [di-μ-chlorobis(benzophenoneoxime -6-C,N)dipalladium (II) (18)[22]

A 50 mL RB flask was equipped with magnetic stirring bar and argon balloon charged with a mixture of palladium chloride (0.885 g, 5mmol) and lithium chloride (0.43 g, 10 mmol) in dry methanol (10mL) and the reaction was allowed to stir for 1h at room temperature. After 1h, a solution of a mixture of benzophenoneoxime (0.98 g, 5 mmol) and sodium acetate (0.41 g, 5 mmol) in dry methanol (5 mL) was added slowly with stirring. The reaction was allowed to stand for a day and then diluted with distilled water (200 mol); the yellow solid formed was filtered and dried.

M.P : 180 ^{0}C.

IR (Nujol) : 3280, 3200, 1629, 13388, 1039, 1024 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.5 - 8.2 (bm, 2H), 7.6 - 6.4 (m, 18H).

Analysis **Calculated** : C (46.18), H (2.98), N (4.14)

Found : C (46.29, H (2.90), N (4.11).

Synthesis of [di-μ-chlorobis(benzaldehydeoxime -6-C,N)dipalladium (II) (19)[22]

A mixture of lithium chloride (0.43 g, 10 mmol) and palladium chloride (0.885 g, 5 mmol) was charged into a 25 mL RB flask equipped with magnetic stirring bar and it was allowed to heat at 100 °C for 45 minutes, the reaction mixture under distillation at reduced

pressure at 5 mm gave dry solid, to this dry methanol (15mL) was added, followed by addition of a mixture of benzaldehydeoxime (0.785 g, 5 mmol) and sodium acetate (0.41 g, 5 mmol) in dry methanol (5 mL). The reaction mixture was allowed to stand for 1 day and diluted with distilled water (200 mL), yellow crystals formed, filtered and dried.

Yield : 1.56 (60 %)

M. P : 200 °C

IR (Nujol) : 3410, 1622, 1595, 1189 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 9.65 (s, 2H), 8.05 (s, 2H) 7.9 - 7.8 (m, 2H), 7.5 - 7.3 (m, 4H)

Synthesis of [di-m-chlorobis(dimethylbenzylamine--6-C,N)dipalladium (II)[23]

A 50 mL RB flask was equipped with a magnetic stirring bar and argon balloon was charged with a mixture of $PdCl_2$ (.885 g, 5 mmol) and LiCl (0.43 g, 10 mmol) in dry methanol and the reaction is allowed to stir for 1 hour. After one hour a solution of a mixture of N,N-dimethylbenzylamine and sodium acetate (0.41 g, 5 mmol) in dry methanol (5 mL) was added slowly with stirring. The reaction was allowed to stir for a day and then diluted with distilled water (200 mL). A pale yellow colour precipitate was formed, filtered and dried.

IR (Nujol) : 2932, 1597, 1043, 940, 862 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$ + $DMSO_6$) : δ 7.21-7.02 (m, 4H), 6.9 - 6.85 (m, 4H), 3.92 (s, 4H), 2.72 (s, 6H)

General procedure for the Heck reaction catalyzed by Palladacycle.

Small scale reaction

A 25 mL RB flask equipped with magnetic stirring bar, reflux condenser and argon balloon was charged with aryl iodide / bromide/chloride (5 mmol), olefin (10 mmol), Potassium

carbonate (2.75 g, 10 mmol) and palladacycle catalyst (0.001 g, 0.005 mmol) in N-methyl pyrrolidinone (10 mL). The reaction mixture was allowed stir at 140-150 ^{0}C for 4-24 h and neutralized with dil HCl (10% by volume). The product was extracted with ethyl acetate (3 x 5 mL), the combined organic extracts dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield the crude product. The crude product on silica gel column chromatographic purification using pet. ether-ethyl acetate mixture gave the pure products.

Large scale reaction for TON and TOF

A 25 mL RB flask equipped with magnetic stirring bar, reflux condenser and argon balloon was charged with aryl iodide / bromide /chloride (75 mmol), olefin (150 mmol), potassium carbonate (20.7 g, 150 mmol) and palladacycle catalyst (0.001 g, 0.005 mmol) in N-methyl pyrrolidinone (100 mL). The reaction mixture was allowed stir at 140-150^0 C for 4-24 h and neutralised with dil HCl (10% by volume). The product extracted with ethyl acetate (4 x 50 mL), the combined organic extracts was dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield the crude product. The crude product on silica gel column chromatographic purification using pet.ether-ethyl acetate mixture gave the pure products.

Ethyl 3-(4-methoxyphenyl)-(*E*)-2-propenoate (20)

Mol. F : $C_{12}H_{14}O_3$.

IR (Neat) : 2985, 1710, 1600, 1510, 1240, 1040, 830 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.6 (d, *J* = 17.0 Hz, 1H), 7.5 (d, *J* = 8.5 Hz, 2H), 6.9 (d, *J* = 8.5 Hz, 2H), 6.3 (d, *J* = 17.0 Hz, 1H), 4.2 (q, *J* = 8.0 Hz, 2H), 3.8 (s, 3H), 1.3 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR (50.35 MHz, $CDCl_3$) : 166.9, 161.2, 143.7, 129.5, 127.0, 115.60, 114.11, 60.00,

55.00, 14.17.

Mass (*m/z*) : 206 (100), 191 (1), 178 (6), 161 (19), 154 (30), 135 (9), 126 (20), 98 (63).

4-Methoxy stilbene (21)

Mol. F : $C_{15}H_{14}O$.

M. P : 135 °C

IR ($CHCl_3$) : 2923, 1599, 1375, 1251, 814 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : 7.6 - 7.25 (m, 7H), 7.1 (d, *J* = 8.0 Hz, 2H), 6.9 (d, *J* = 12.1 Hz, 1H), 3.85 (s, 3H).

Mass *(m/z)* : 210 (M^+, 100), 195 (25), 179 (17), 165 (66), 152 (59), 115 (26), 105 (25), 91(41), 77 (29).

Ethyl - 3 -phenyl-(*E*)-2-propenoate (22)

Mol. F : $C_{11}H_{12}O_2$

IR (Neat) : 2980, 1716, 1638, 1592, 1490, 1269, 1173, 883 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.7 (d, *J* = 8.0 Hz, 1H), 7.6 - 7.5 (m, 2H), 7.4 - 7.25 (m, 3H), 1.45 (d, *J* = 16.0 Hz, 1H), 4.25 (q, *J* = 8.0 Hz, 2H), 1.35(t, *J* = 8 Hz, 3H).

1, 2 -Diphenyl-(*E*)-ethylene (22a)

Mol. F : $C_{14}H_{12}$

M. P : 120 °C

IR (Nujol) : 2855, 1602, 1506, 1375, 920, 765 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.6 (d, *J* = 14.0 Hz, 2H), 7.45 -7.25 (m, 10H)

Mass *(m/z)* : 180 (M^+, 100), 104 (42), 77 (100).

Ethyl- 3-(4-nitrophenyl)-(*E*)-2-propenoate (23)

Mol. F : $C_{12}H_{11}NO_4$.

M. P : 62 ℃

IR (Nujol) : 2925, 2854, 1714, 1645, 1109, 1029, 960 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.3 (d, *J* = 7.5 Hz, 2H), 7.7 (d, *J* =14.8 Hz, 1H), 7.2 (d, *J* = 7.5 Hz, 2H), 6.6 (d, *J* =14.8 Hz, 1H), 4.2 (q, *J* =7.0 Hz, 2H), 1.3 (t, *J* = 7.0 Hz, 3H).

Mass (m/z) : 233 (M^+, 5), 188 (43), 144 (61), 76 (100).

1-(4-nitrophenyl)-2-phenyl-(*E*)-ethylene (24)

Mol. F : $C_{14}H_{11}NO_2$.

M. P : 96 ℃

IR (Nujol) : 1604, 1034, 850, 765 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.3 (d, *J* = 16.2 Hz, 2H), 7.6 - 7.2 (m, 9H).

Mass (m/z) : 225 (M^+, 69), 178 (100), 151 (15), 165 (11), 77 (8).

1-(4-cyanophenyl)-2-phenyl-(*E*)-ethylene (25)

Mol. F : $C_{15}H_{11}N$

M. P : 103 ℃

IR (Nujol) : 2854, 2225, 1600, 1504, 1377, 922, 768 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.55 - 7.50 (m, 4H), 7.45 - 7.25 (m, 4H), 7.2 (d, *J* = 14.0 Hz, 1H).

Mass *(m/z)* : 204 (16), 190 (49), 177 (20), 165 (19), 151(11), 127 (8), 113 (6), 102 (41), 76 (59).

Ethyl- 3-(2-pyridyl)-(*E*)-2-propenoate (26)

Mol. F : $C_{10}H_{12}NO_2$.

IR (Neat) : 2983, 2854, 1705, 1620, 1043, 944, 776 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.55 - 850 (m, 1H), 7.6 (m, 1H), 7.55 (d, *J* =17.0 Hz, 1H), 7.3(d, *J* = 6.0 Hz, 1H), 7.2-7.1 (m, 1H), 6.8 (d, *J* =17.0 Hz 1H), 4.2 (q, *J* = 7.4Hz, 2H), 1.34 (t, *J* = 7.5 Hz, 3H)

^{13}C NMR (50.35 MHz, $CDCl_3$): δ 166.78, 153.20, 150.30, 143.47, 136.90, 124.34, 124.23, 122.66, 60.72, 14.42.

References

1. Colon, I. US patent, US 4, 334,081, *Chem. Abstr.* 97, 720524 (1982).
2. Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Ronchi, A.V. *J. Organomet.Chem.* **1981**, *C-16*, 21.
3. Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Ronchi. A. V. *J. Organomet. Chem.* **1986**, *C62*, 301.
4. Lebedev, . S. A.; Lopatina, A. V.; Patrov, E. S.; Beletskaya, I. P. *J. Organomet. Chem*, **1988,** *C-53*, 344.
5. Sustmann, R.; Hopp, P.; Hall, P. *Tetrahedron. Lett*., **1989**, *30*, 689.
6. Iyer, S. *J. Organomet. Chem*, **1995**, *C-27*, 490.
7. Kelkar, A. A. *Tetrahedron Lett*., **1996**, *37*, 8917.
8. Kelkar, A. A. ; Hanaoka, T.; Kubata, Y.; Sugi, Y. *Cat. Lett*., **1994,** *29*, 69.
9. Bruggink, A.; Mckillop. *Angew. Chem. Int. Edn Engl.* **1974**, 13, 340.
10. Marvel, C. S.; Moyer, W. W. Jr. *J. Org. Chem*., **1957**, *22*, 1065.
11. Vogel's Textbook of Practical organic chemistry, Vth Edn. 929.
12. Inorganic Synthesis XVII, 119.
13. Duddeck, H.; Mantred Kaiser, *Spectrochimica Acta*, **1985**, *41A*, 913.
14. Inorganic synthesis XXII, 101
15. Vogel's Textbook of Practical organic chemistry, Vth Edn., 511.
16. Hermann, W. A.; Elison, M.; Fischer, J.; Kocher, C.; Artus, G. R. J. *Angew. Chem. Int. Edn.Engl.*, **1995**, *34*, 2371.
17. Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095.
18. Shaw, B. L.; Perera, S. D.; Staley, E. A. *Chem. Commun.*, **1998**, 1361.
19. Ohff, M.; Ohff, A.; Milstein, D. *Chem. Commun.* **1999**, 357.

20. Zhang, Ch.; Trudell, M. L. *Tetrahedron Lett.,* **2000**, *41*, 595.

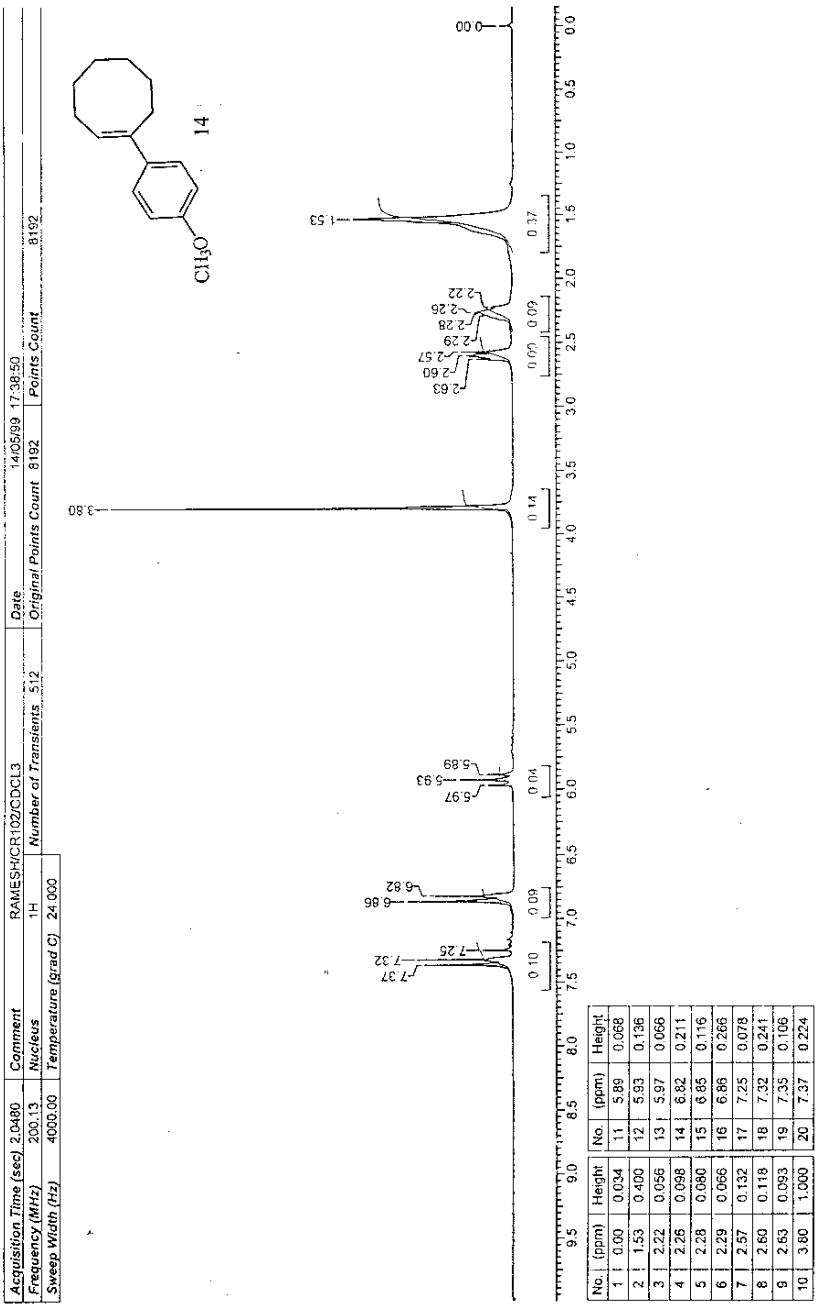
21. Vogel's Textbook of Practical organic chemistry, Vth Edn., 1048.

22. Onoue, H.; Minami, K.; Nakagawa, K. *Bull. Chem. Soc. Jpn*. **1970**, *43*, 3480.

23. Brisdon, B. J.; Nair, P.; Dyke, S. F. *Tetrahedron*, **1981**, 37, 173.

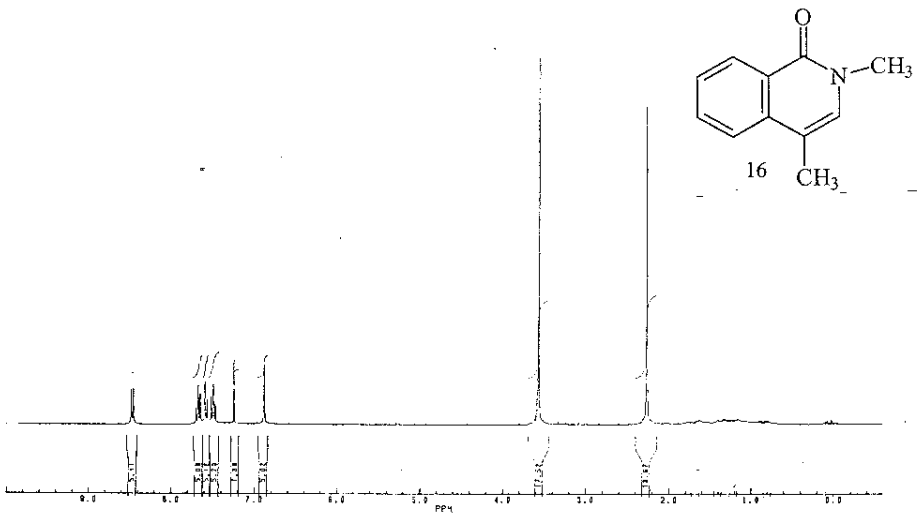
Spectra

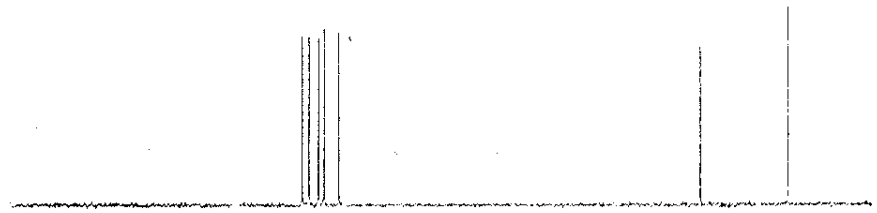
CR-102

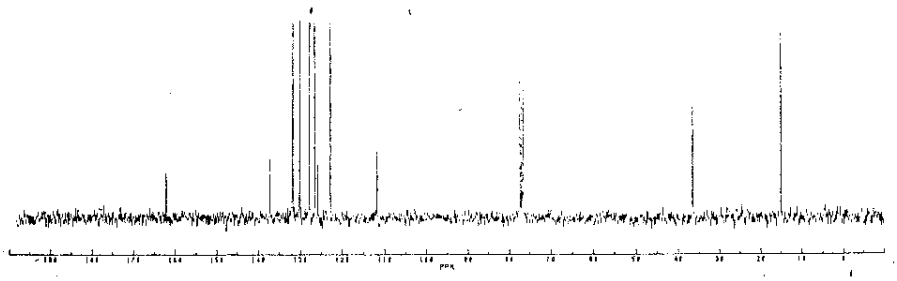


No.	(ppm)	Height
1	0.00	0.034
2	1.53	0.400
3	2.22	0.056
4	2.26	0.098
5	2.28	0.080
6	2.29	0.066
7	2.57	0.132
8	2.60	0.118
9	2.63	0.093
10	3.80	1.000

No.	(ppm)	Height
11	5.89	0.068
12	5.93	0.136
13	5.97	0.066
14	6.82	0.211
15	6.85	0.116
16	6.86	0.266
17	7.25	0.078
18	7.32	0.241
19	7.35	0.106
20	7.37	0.224


O
N
CH3
CH3
16





Chapter 3.

This chapter is divided into two sections.

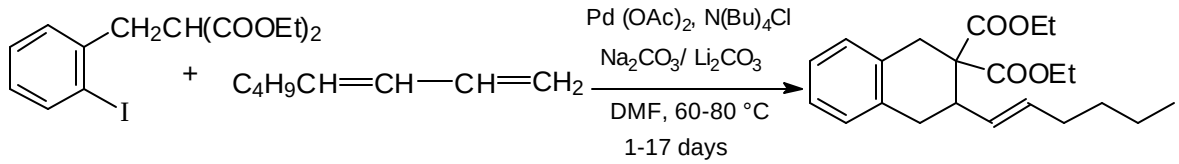
Section 1. Palladium catalyzed reaction of a -bromoacrylic acids with 1, 3-dienes.

INTRODUCTION AND BACKGROUND

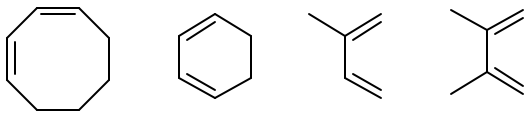
The palladium catalyzed C-C and C-X single bond formation is a challenging area in synthetic organic chemistry. The activation of bifunctional molecule for the reaction with alkynes and dienes in the presence of palladium catalyst to form complex organic molecules is a recent development in palladium chemistry. Such type of innovative reactions catalyzed by palladium complexes are described below in details.

The palladium-catalyzed arylannulation of 1, 3-dienes with functionally substituted aryl halides proceeds under mild conditions to yield a wide variety of functionally substituted carbocycles with good stereo and regio selectivity (scheme-1).[1]

Scheme -1

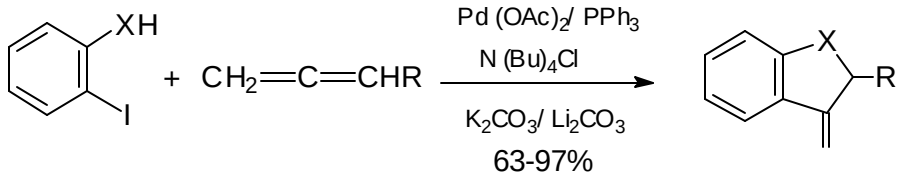


Dienes :



Aryl halides bearing heteroatom- or potential carbanion-containing functionality in *ortho* position, have been shown to react with 1, 2-dienes in the presence of a palladium catalyst and a carbonate base to afford five and six membered hetero- and carbo cycles in high yield (scheme-2).[2]

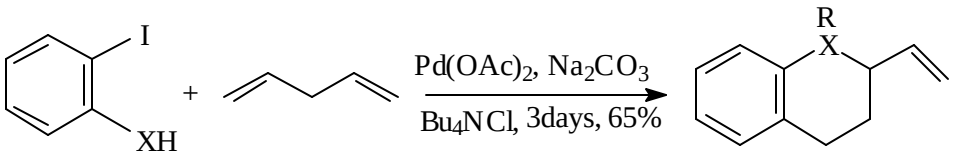
Scheme -2



X = NR, O

Monocyclic and bicyclic 6-membered ring heterocycles and carbocycles were synthesized by the palladium-catalyzed annulation of 1, 4-dienes with aryl halides bearing *ortho*-heteroatom and carbanion-stablizing groups (Scheme-3). The mechanism involves aryl palladium complex formation, addition to the diene, palladium migration and intramolecular *p*-allyl palladium displacement.[3]

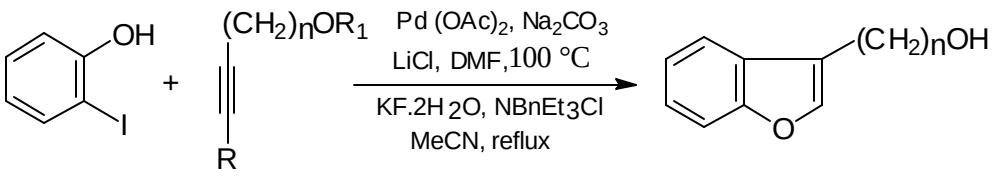
Scheme -3



X = NR, O

Synthesis of 3-Hydroxyalkylbenzo[b]furans *via* the palladium-catalyzed heteroannulation of silyl-protected alkynols with 2-iodophenol is shown in scheme-4.[4]

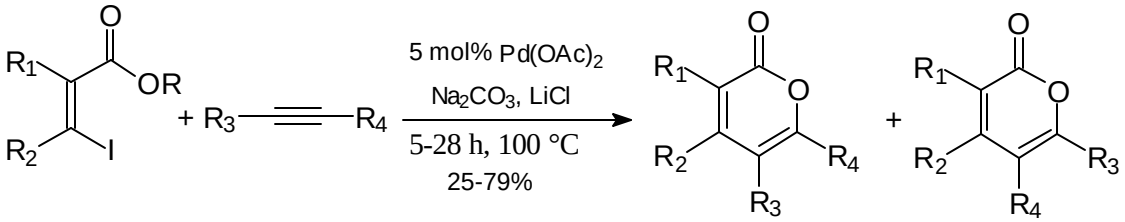
Scheme -4



R_1 = H, TES, TIPS, TBDMS R = TMS, TBDMS

A simple, convenient and regioselective route to synthesis of tri- and tetra- substituted pyrones by the palladium catalyzed reactions of vinylic iodides; bromides or triflates bearing ester functionality with internal alkynes is shown in scheme-5.[5]

Scheme -5

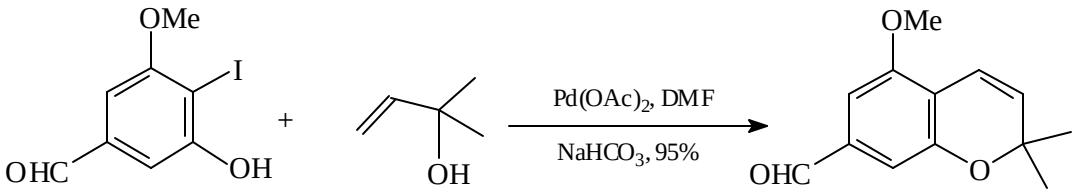


R_1 = Me, Ph, Et R_2 = H, Ph, Me

R_3 = Me, Ph R_4 = Ph, Me

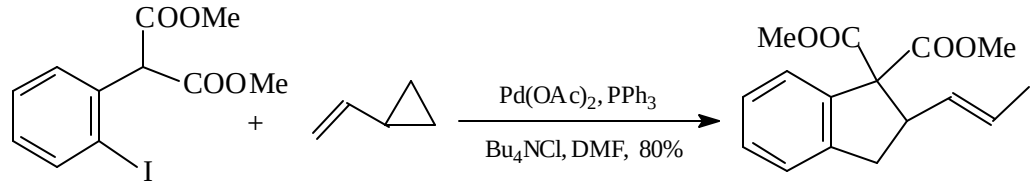
Ortho-substituted phenols have been reported to react with various allylic alcohols in the presence of palladium catalysts to give heterocyclic compounds in very good yield (scheme-6).[6]

Scheme -6



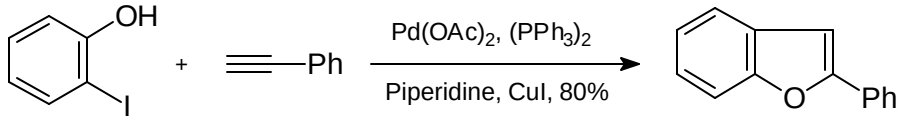
Larock *et al.* developed a methodology involving the palladium-catalyzed reaction of bifunctional molecule bearing halogen and a carbon nucleophile with vinyl cyclopropanes to form five membered carbocyclic rings as shown in scheme-7.[7]

Scheme -7



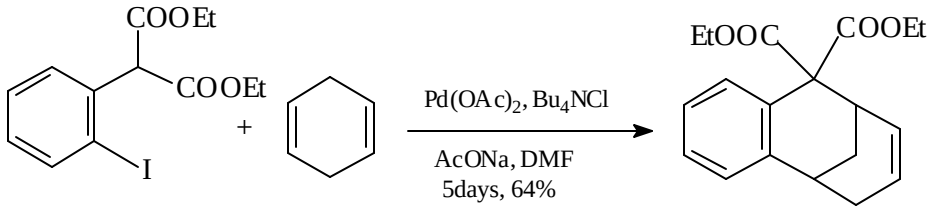
A highly convergent route to the synthesis of benzofurans by the palladium mediated reaction of *o*-iodophenol with terminal acetylenes and copper iodide as co-catalyst for this reaction (scheme-8).[8]

Scheme-8



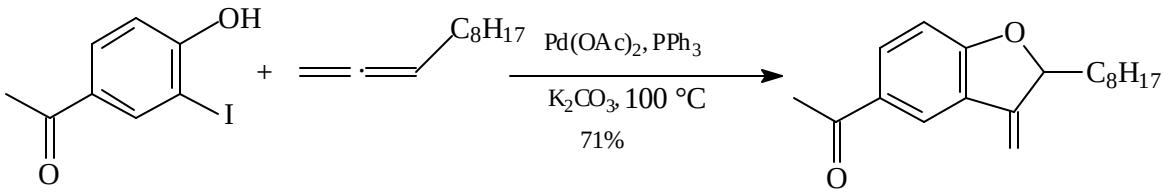
Larock *et al*. developed a methodology towards the synthesis of bicyclic compounds by activating bifunctional molecule bearing a halogen and carbon nucleophile for the reaction with 1, 4-cyclohexadiene (scheme-9).[9]

Scheme-9



The palladium catalyzed reaction of *o*-iodophenol with allenes gave the substituted benzofuran derivatives having exocyclic double bond (scheme-10).[10]

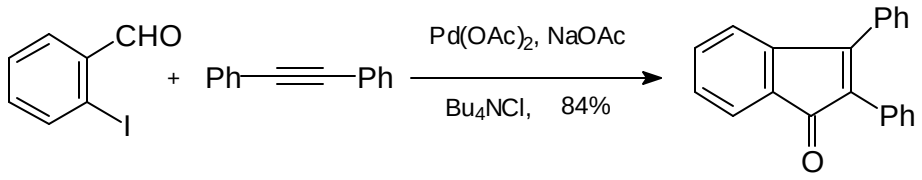
Scheme-10



Larock *et al.* exploited the palladium-mediated activation of bifunctional molecules with dienes and alkynes. The last example is the reaction of *o*-iodobenzaldehyde with internal alkyne

in presence of palladium acetate and tetrabutylammonium chloride to give the substituted indenones in very good yield (scheme-11).[11]

Scheme -11



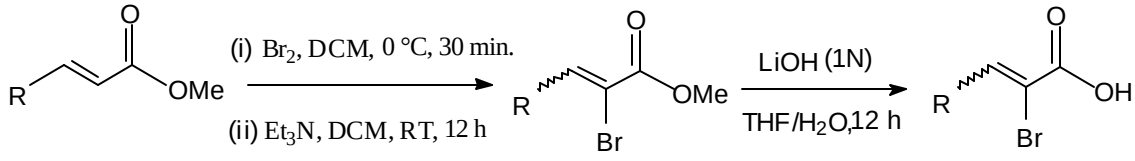
OBJECTIVE

The objective of the study was to develop an efficient synthetic methodology towards synthesis of biologically important butyrolactone by palladium catalyzed reaction of bifunctional molecule such as α-bromoacrylic acids with 1, 3 dienes. The reaction involves the formation of π-allylpalladium complex as intermediate and the subsequent nuleophilic attack of the carboxylic oxygen on π-allylpalladium to form the expected lactone.

PRESENT WORK

Our present study involves the activation of olefinic bifunctional molecule bearing halogen and an oxygen nucleophile to react with 1, 3-diene in the presence of palladium catalysts to form a new class of γ-butyrolactones. This reaction goes through π-allylpalladium intermediates followed by attack of the nucleophile on the π-allylpalladium complex to form cyclised product. To study the palladium catalyzed reactions of bifunctional molecules, different α-bromoacrylic acids were synthesized based on the literature methods. The α-bromocinnamic acid and 3-furyl-2-bromo-2-propenoic acid were synthesized from the corresponding acrylic esters, methylcinnamate and 3-furyl-2-propenoic acid-methyl ester by bromination, dehydrobromination and followed by hydrolysis as shown in scheme-12.[12]

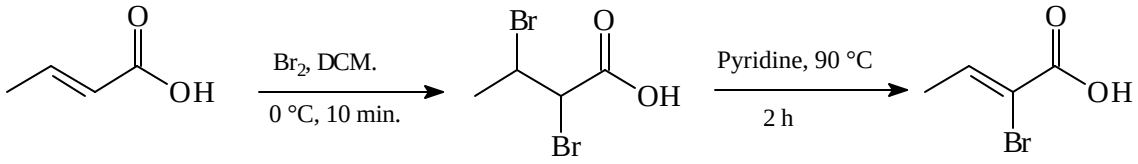
Scheme -12



R = Ph, Furyl

(*Z*) α-Bromocrotonic acid was synthesized from crotonic acid by bromination and dehydrobromination using excess of pyridine based on the literature method (scheme-13).[13]

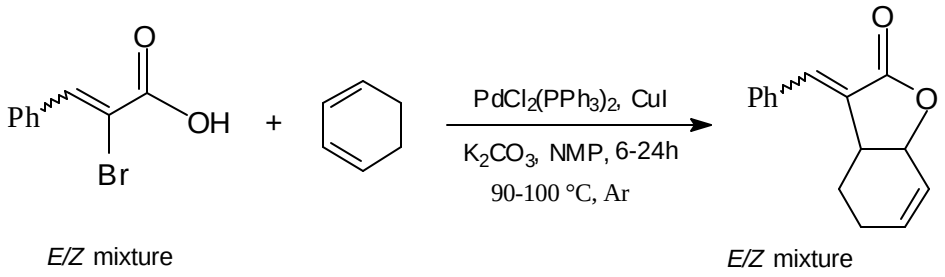
Scheme -13



Initially the reaction of α-bromocinnamic acid with 1, 3-cyclohexadiene was carried out in the presence of $PdCl_2(PPh_3)_2$ as catalyst. Copper iodide was used as co-catalyst in this reaction

and potassium carbonate as base and *N*-methylpyrrolidinone as solvent at 90-100 °C. The expected cyclised product was obtained in 30% yield (scheme-14).

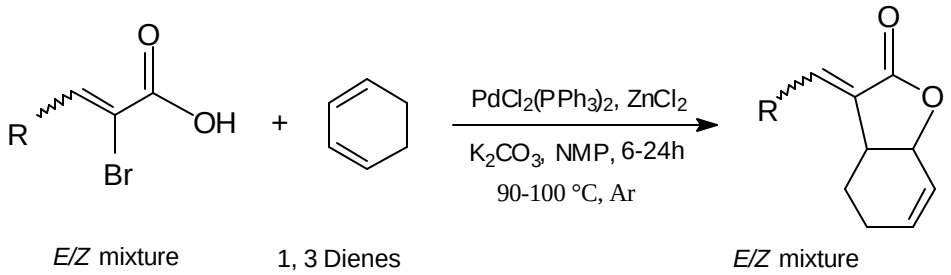
Scheme-14



E/Z mixture *E/Z* mixture

Later, a detailed study on the reactions of various α-bromoacrylic acids with 1,3 dienes was carried out with $PdCl_2(PPh_3)_2$ as catalyst(10 mol %) and $ZnCl_2$ was found to be the more effective co-catalyst than copper iodide for this reaction. Potassium carbonate was used as a base and the reaction was carried out at 90-100 °C. The butyrolactones were obtained in 22 to 74 % yield (scheme-15) and the results are tabulated in table-4.

Scheme-15



E/Z mixture 1, 3 Dienes *E/Z* mixture

R = Ph, Furyl, CH_3 Dienes :

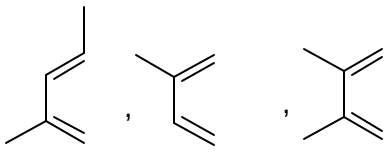
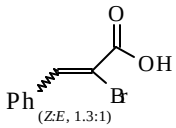
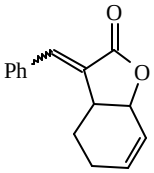
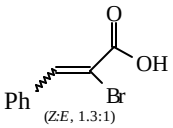
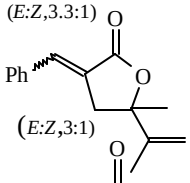
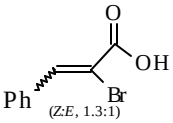
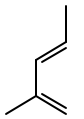
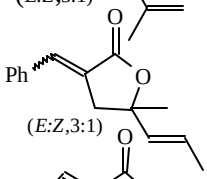
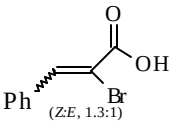
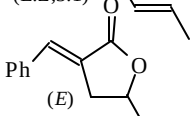
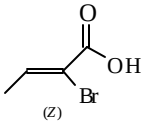
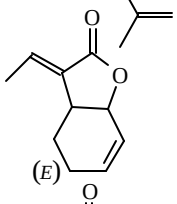
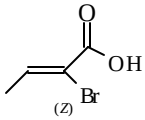
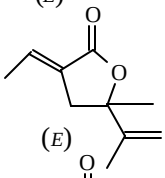
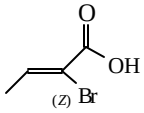
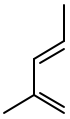
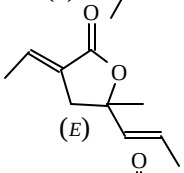
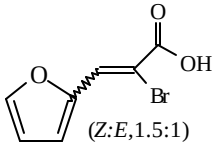
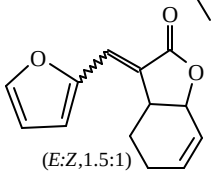
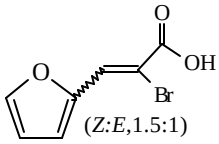
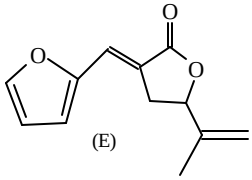
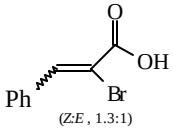


Table 4. Reactions of α-bromoacrylic acids with 1, 3-dienes

S.NO	α-Bromoacid	1,3-Diene	Time (h)	Product	Yield, %
1	 (Z:E, 1.3:1)		24	 (E:Z,3.3:1)	61
2	 (Z:E, 1.3:1)		23	 (E:Z,3:1)	51
3	 (Z:E, 1.3:1)		19	 (E:Z,3:1)	61
4	 (Z:E, 1.3:1)		2	 (E)	22
5	 (Z)		24	 (E)	48
6	 (Z)		25	 (E)	55
7	 (Z)		23	 (E)	52
8	 (Z:E,1.5:1)		6	 (E:Z,1.5:1)	74
9	 (Z:E,1.5:1)		10	 (E)	25
10	 (Z:E , 1.3:1)		24	—	–

RESULTS AND DISCUSSION

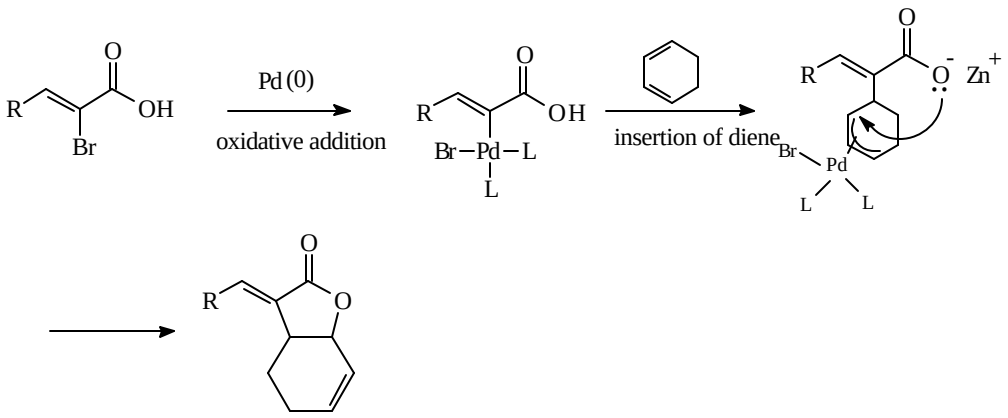
The α-bromoacrylic acids were prepared from the corresponding acrylic esters by bromination, dehydrobromination followed by hydrolysis. The IR, ^{1}H NMR,^{13}C NMR and Mass spectral data confirmed the structure of bromoacrylic acids . A mixture of E and Z α-bromocinnamic acids were synthesized from methylcinnamate. The IR spectrum of the mixture of products showed a broad peak at 3400 cm^{-1} and a sharp peak at 1680 cm^{-1} indicating the presence of O-H and C=O groups respectively. The ^{1}H NMR spectrum of the product gave a broad singlet at δ 9.5 corresponding to COO<u>H</u> group and two sharp singlets, at δ 8.45 (calculated chemical shift: δ 8.33) and 7.60 (calculated chemical shift: δ 7.40) confirmed the presence of olefinic protons of *Z* and *E* isomers respectively. The ratio of the isomer was determined based on the integration of olefinic protons. The stereochemistry of α-bromocinnamic acid was comfirmed by the literature evidence.[14] The mass spectrum of the product showed molecular ion peak at m/z 226 further evidence for confirming the structure of α-bromocinnamic acid.

In a similar manner the structure of α-bromocrotonic acid was also deduced. The IR spectrum gave a broad peak at 3300 cm^{-1} (O-H) and a sharp peak at 1678 cm^{-1} (C=O). The ^{1}H NMR spectrum displayed a broad singlet at δ 9.4 for O-H proton and a quartet at δ 7.5 corresponding to olefinic proton. The mass spectrum of the product showed a molecular ion peak at m/z 166. The above data confirmed the structure of α-bromocrotonic acid. The stereochemistry of the double bond was determined by comparing the chemical shifts with the calculated chemical shift value (δ 7.42) based on empirical rules.[15]

The structure of the product **(34)** obtained from the palladium catalyzed reaction of a mixture of (*E/Z*) α-bromocinnamic acid with 1, 3-cyclohexadiene was confirmed by IR, ^{1}H

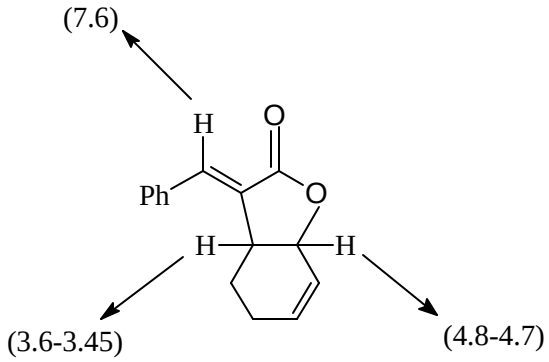
NMR, ^{13}C NMR and mass spectral data. The reaction goes through the formation of π-allylpalladium intermediate and the attack of oxygen nucleophile on the π-allylpalladium complexes to form α, β-unsaturated lactone (Figure-1).

Figure -1

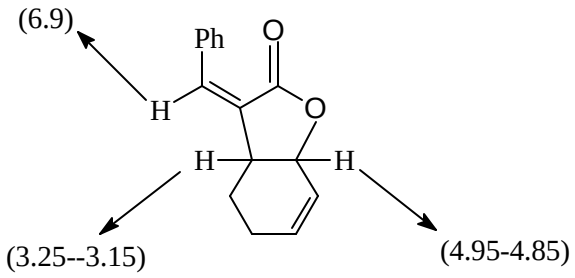


The IR spectrum of the product showed a sharp peak at 1745 cm^{-1} and 1640 cm^{-1} indicating the presence of C=O and C=C groups of lactone respectively. The ^1H NMR of the product showed two multiplets, one at δ 4.8 - 4.7 and another at δ 3.6 - 3.45 corresponding to the presence of ring junction protons of the product as shown below in figure-2. The olefinic proton of *E* **(34a)** and *Z* **(34b)** isomers was confirmed by comparing the observed chemical shift value with theoretical values. In the case of *E*-isomer, olefinic proton appeared at δ 7.6 (theoretical: δ 7.5) and the proton of *Z*-isomer showed a doublet at δ 6.9 (theoretical: δ 6.86) with allylic coupling.

Figure -2



E-isomer

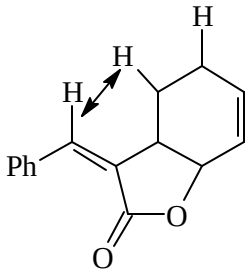


Z-isomer

The stereochemistry of the ring junction protons was determined by the coupling constants values obtained from the homonuclear proton decoupling experiments. The ^{1}H NMR , ^{13}C NMR spectra and spectra of decoupling experiments of the product are shown on page 112, 113 (34a) and 114, 115 (34b). The irradiation of the proton at δ 6.15 - 6.00 gave a clean doublet at δ 4.75 with coupling constant, J = 6.0 Hz, which determined the *cis* -stereochemistry of the ring junction. The stereochemistry of double bond was also determined by the calculation of chemical shifts for olefinic proton of both *E* and *Z* isomer based on the literature and by 2D NOESY experiments as shown on page 116.

The connectivity between the olefinic proton and methylenic protons of cyclohexyl ring was observed as shown in figure-3.

Figure -3

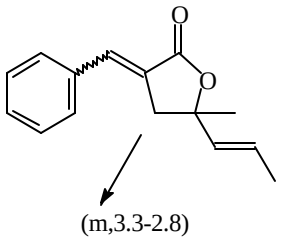


Z-isomer

The ^{13}C NMR spectrum revealed all required carbon signals of the product. The two signals appeared at δ 171.34 and 168.13 corresponding to carbonyl carbon of ***E*** **(34a)** and ***Z*** **(34b)** isomer of lactone. The mass spectrum of the product showed a molecular ion peak appeared at m/z 226. The structure of the product, 3- (1-phenyl-methylidene)-2,3,3a,4,5,7a-hexahydro(b)furan-2-one (**34**) was confirmed based on the above spectroscopic data.

The product **(35)** of the palladium catalyzed reaction between (*E/Z*) *a*-bromocinnamic and 2-methyl 1, 3-pentadiene showed a prominent peak at 1748 cm^{-1} and a sharp peak at 1646 cm^{-1} in infrared spectrum indicating the presence of C=O and C=C of butyrolactone respectively. The ^{1}H NMR spectrum displayed a multiplet at δ 3.3 - 2.8 corresponding to allylic methylene protons of the lactone ring of the product as shown below (figure-4). The comparison of ^{1}H NMR spectra of lactone (**35**) with (**34**), showed absence of one of the ring junction proton at δ 4.9 - 4.7 indicating the formation of quaternary center adjacent to oxygen atom of the product and the mode of insertion of 1, 3-diene between palladium and vinyl carbon in the reaction mechanism. The ratio of isomers was determined based on the integration of protons of ***E*** and ***Z*** .

Figure -4



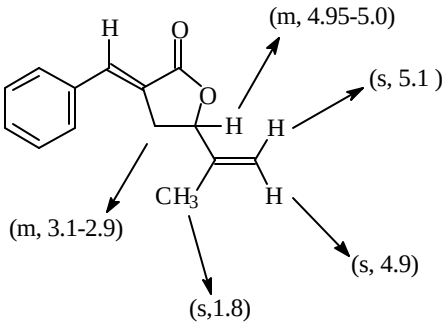
In addition, the mass spectrum of the product showed a molecular ion peak at m/z 228 corresponding to the expected 5-methyl-3-(1-phenylmethylidene)-5-((*E*)-1-propenyl)tetrahydro-2-furanone (**35**).

The IR spectrum of product formed from the palladium catalyzed reaction of a mixture of (*E/Z*) α-bromocinnamic with 2, 3 dimethyl-1, 3-butadiene displayed two strong absorption bands

at 1754 $cm^{-1}$and 1658 cm^{-1} for C=O and C=C groups of lactone. The ^{1}H NMR spectrum of the product showed two singlets, one at δ 1.8 and another one at δ 1.5 due to the presence of allylmethyl and quaternary methyl protons. Two singlets appeared at δ 5.1 and δ 4.9, which was assigned to terminal olefinic protons of the product **(36**). The ratio of the *E* and *Z* isomer calculated based on the integration of protons in ^{1}H NMR spectrum.

The product obtained from the reaction of (*E/Z*) α-bromocinnamic acid with isoprene showed a prominent peak at 1753 cm^{-1} and 1655 cm^{-1} in infrared spectrum indicating the stretching frequency of C=O and C=C groups of lactone **(37**). The ^{1}H NMR spectrum of the product **(37)** is shown in page 117 displayed a singlet at δ 1.8 confirming the presence of allylic methyl proton. The two multiplets,at δ 5.0 and 3.1 - 2.9 due to the presence of ring junction protons of butyrolactone **(37)**, as shown below (Figure-4).

Figure -4



The IR spectrum of butyrolactone obtained from the reaction of (*Z*)-*a*-bromocrotonic acid with 2, 3-dimethyl-1, 3-butadiene showed prominent peaks at 1755 cm^{-1} (C=O) and 1681 cm^{-1} (C=C). The ^{1}H NMR spectrum of the pr oduct (shown in page) displayed a multiplet at δ 2.65-2.50 indicating the presence of methylenic protons of cyclised product with coupling of allylic and geminal proton and there were two singlets at δ 5.1 and 4.9 corresponding to terminal olefinic protons. At δ 1.9-1.75 two doublets were overlapped with an integration of 6 protons showing the presence of two allylic methyl protons of the cyclised product. The ^{13}C NMR

(spectrum is shown in page 118) revealed all the carbon signals. The carbonyl carbon of lactone appeared at δ 170. The mass spectrum of the product showed a molecular ion peak at *m/z* 166. The above spectroscopic data proved the structure of expected butyrolactone (**38**).

The product formed from the reaction of (*Z*)-α-bromocrotonic acid and 2-methyl 1, 3-pentadiene showed a sharp peak at 1753 cm^{-1} in the infrared spectrum indicating the presence of C=O group of lactone. The ^{1}H NMR spectrum displayed a multiplet at δ 6.8 - 6.7 confirming the presence of olefinic proton of α, β- unsaturated system of lactone and a multiplet appeared at 5.85 - 5.60 could be assigned to other olefinic proton adjacent to methyl group. A doublet with *J* = 13.5 Hz at δ 5.5 showed the presence of other olefinic proton. The methylenic proton of lactone was identified by a multiplet at δ 2.85 - 2.60. One of the allylic methyl appeared as a doublet with coupling constant, *J* = 8.0 Hz at δ 1.9 and the other at δ 1.7. The ^{13}C NMR spectrum of the product revealed signals for all carbons of the product. The carbonyl carbon signal appeared at δ 170.92 and methylenic carbon at δ 32.36 in DEPT spectrum. The mass spectra showed a molecular ion peak at *m/z* 166. All the above spectroscopic data confirmed the structure of expected product 3-((*E*)-ethylidene)-5-methyl-5((*E*)-propenyl)tetrahydro-2-furanone (**39**).The ^{1}H NMR and ^{13}C NMR spectra shown on page 119.

The IR spectrum of the product obtained from the reaction of α-bromocrotonic acid with 1, 3-cyclohexadiene showed two strong absorption bands at 1750 cm^{-1} and 1701 cm^{-1} for C=O and C=C bonds respectively. The ^{1}H NMR spectrum (on page 120) displayed a quartet at δ 6.8 with *J* = 7.0 Hz which corresponding to olefinic proton on β-carbon. Two olefinic protons of the cyclohexene ring appeared as multiplets at δ 6.3 - 6.1 and δ 6.15 - 5.95. One of the ring junction proton which is adjacent to oxygen atom appeared as a multiplet at δ 4.75 -4.65. The other ring junction proton appeared at δ 3.22 - 3.0 as a multiplet with allylic and vicinal coupling. A multiplet at δ 2.15 - 2.05 is assigned for allylic methylenic protons (2H) and one methylenic

proton. A doublet appeared at δ 2.0 with coupling constant *J* = 9.0 Hz confirming the allylic methyl protons. The mass spectrum displayed a molecular ion peak at *m/z* 166. All the data mentioned above confirmed the structure of the expected product 3-((*E*)-ethylidene)-2,3,3a,4,5,7a-hexahydrobenzo (b)furan-2-one (**40**).

The reaction of 3furyl-2-bromo-2-propenoic acid (**33**) with isoprene gave the expected product in low yield and the product was characterized by the usual spectroscopic methods. The IR spectrum showed sharp peaks at 1747 cm^{-1} and 1643 cm^{-1} corresponding to the carbonyl and C=C of α, β-unsaturated system respectively. The ^1H NMR spectrum (shown on page 121) displayed a doublet at δ 7.85 indicating the presence of aromatic proton and a singlet at δ 7.5 assigned to the olefinic proton of the α, β-unsaturated system. The other two protons of furan ring appeared at δ 6.85 and 6.5. The terminal olefinic proton of the isoprene system appeared as two singlets, one at δ 5.1 and another at δ 4.9. A multiplet at δ 4.85 - 4.75 was due to the proton which is adjacent to the oxygen atom and two diastereotopic methylenic protons of the lactone ring gave two multiplets at δ 3.2- 3.1 and 2.95 - 2.85. A singlet at 1. 8 confirmed the presence of allylic methyl protons. The mass spectrum of the product showed a molecular ion peak at m/z 204. These data confirmed the structure of the expected product 3-(1-(2-furyl)- (*E*)-methylidene)-5-isopropenyl tetrahydro-2-furanone (**41**).

The product obtained from the reaction of 3-furyl-2-bromo-2-propenoic acid (**33**) with 1, 3-cyclohexadiene showed prominent peaks at 1740 cm^{-1} and 1652 cm^{-1}. The ratio of isomers (*E/Z*) was determined based on the ^1H NMR spectrum. The proton NMR spectra of both the isomers are shown on page 122 (**42a**) and 123 (**42b**). A molecular ion peak appeared at *m/z* 216 supported the formation of the expected lactone 3-(1-2-furyl)-methylidene-2, 3, 3a, 4, 5, 7a-hexahydrobenzo(b) furan-2-one (**42**). The palladium-catalyzed reaction of α-bromocinnamic acid (28) with phenyl propiolate was unsuccessful.

CONCLUSION

We have developed novel palladium catalyzed methodology towards the synthesis of a new class of α, β-unsaturated butyrolactone from simple precursors such as α-bromoacrylic acids and 1, 3-dienes in good yield.

EXPERIMENTAL

Preparation of a -Bromomethylcinnamate (27)

A 100 mL RB flask equipped with magnetic stirring bar was charged with methyl cinnamate (3.24 g, 20 mmol) and dichloromethane (30 mL). To the stirred solution, bromine (3.2 g, 20 mmol) was added slowly at 0 °C for 10 min. After addition of bromine, the reaction mixture was allowed to stir for 30 min. To this reaction mixture, triethylamine (2.02 g, 20 mmol) was added slowly at 0 °C and the reaction mixture was allowed to stir for 12 h. The reaction mixture was neutralised with dil HCl (10% by volume) and the product extracted with dichloromethane (3×10 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the crude product (Z:E, 0.6:0.4) which was purified by silica gel column chromatography using a mixture of petroleum ether-ethyl acetate (9:1).

Yield : 4.3 g (89%)

Mol. F : $C_{10}H_9BrO_2$

IR (Neat) : 2932, 1705, 1610, 1040, 860, 755 cm^{-1}

^{1}H NMR (200, MHz, $CDCl_3$) : δ 8.3 (s, 0.6H), 7.9 - 7.8 (m, 2H), 7.5 - 7.3 (m, 3.4H), 3.9 (s,1.8H), 3.8 (s, 1.2H)

Mass (*m/z*) : 241 (M^+, 35), 226 (14), 210 (40), 161 (100), 77 (60).

Preparation of a -bromocinnamic acid (28)

A 250 mL RB flask equipped with magnetic stirring bar was charged with α-bromomethycinnamate (2.4 g, 10 mmol) and 25 mL of THF. To the stirred solution, lithium hydroxide (1N, 1.15 g in 50mL of water) was added slowly at 0 °C and the reaction mixture was allowed to stir for 12 h. The reaction mixture was neutralised with dil HCl and the product

extracted with ethyl acetate (3× 15 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give α-bromocinnamic acid in 92% yield. (1.3:1, *Z*: *E*). The crude product was purified by column chromatography using 100-200 mesh silica gel and petroleum ether-ethyl acetate mixture (8:2).

Yield : 2.1g (92%)

Mol. F : $C_9H_7BrO_2$

M. P : 95 ^{0}C

IR (Nujol) : 2860, 1680, 1450, 1390, 1260, 930, 810, 780 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 9.0 (bs, 1H), 8.4 (s, 1H), 7.95 - 7.7 (m, 2H), 7.6 (s, 1H),7.50 -7.35 (m, 8H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 169.59, 169.34, 143.84, 143.53, 134.78, 133.60, 131.15, 130.94, 129.61, 128.81, 111.75, 110.94

Mass (*m/z*) : 226 (M^+, 31), 147 (100), 129 (38), 118 (7), 102 (42), 77 (26).

Synthesis of (Z)- a **-bromocrotonic acid (29)**

A 30 mL solution of crotonic acid (4.3 g, 50 mmol) in dichloromethane was charged into 100 mL RB flask equipped with magnetic stirring bar. To the stirred solution, bromine (8 g, 50 mmol) was added slowly at 0 °C for 15 min and the reaction mixture was continued to stir for 1h. Concentration of dichloromethane under reduced pressure gave white solid, dibromocrotonic acid in 100% yield. Dibromocrotonic acid (5 g, 20 mmol) and pyridine (10 mL) were charged into 100 mL RB flask equipped with magnetic stirring bar and the reaction was allowed to stir at 90 °C for 2h. The reaction mixture was neutralized with dil.HCl (10% by volume) and the product extracted with ethyl acetate (3× 10 mL). The combined ethyl acetate layer was dried

over anhydrous sodium sulphate, concentrated under reduced pressure to give α-bromocrotonic acid.

Yield : 1.0 g (30%)

Mol.F : $C_4H_5BrO_2$

M. P : 97 °C

IR ($CHCl_3$) : 3300, 2995, 1678, 1600, 1410, 1260, 1220, 770 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) : δ 9.4 (bs, 1H), 7.55 - 7.5 (q, *J* = 7.5 1H), 2.0 (d, *J* =7.5 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) : δ 167.49, 144.20, 117.12, 18.17.

Mass (*m/z*) : 166 (M^+, 82), 164 (100), 119 (14), 107 (1), 79 (3)

Synthesis of 3-furyl-2-propenoic acid (30)

A 100 mL RB flask equipped with magnetic stirring bar was charged with freshly distilled furfural (6.88 g, 70 mmol) and pyridine (7.5 g, 94 mmol). The reaction mixture was allowed to heat at 100 °C for 3 h. The reaction mixture was neutralized with dil.HCl (10% by volume) and the light brown color solid obtained was filtered , washed with water and dried over desicator for 12 h to give the pure product .

Yield : 4.3 g (56%)

Mol.F : $C_7H_6O_3$

M. P : 148 - 150 °C

IR (Nujol) : 3390, 1680, 1605, 1056, 960, 863 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 10.50 (bs, 1H), 7.55 - 7.45 (m, 2 H), 6.75 (d, *J* =7.0 Hz, 1H) 6.50 (d, *J* =7.0Hz, 1H), 6.25 (d, *J* =12.9 Hz,1H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 168.11, 151.01, 146.16, 131.42, 116.79, 115.91, 113.23.

Mass (m/z) : 138 (M^+, 100), 121 (31), 110 (23), 92 (27), 82 (16)

Synthesis of 3-furyl-2-propenoic acid-methyl ester (31)

A mixture of 3-furyl-2-propenoic acid (3.72 g, 30 mmol) and dry methanol (25 mL) was charged into 25 mL RB flask equipped with magnetic stirring bar. To the stirred solution, freshly distilled thionyl chloride (3 mL) was added slowly at 0 °C for 25 min. The excess of thionyl chloride was removed by distillation and the product obtained was purified by column chromotography using 60-120-mesh silica gel and petroleum ether -ethyl acetate mixture (9:1).

Yield : 3.13 g (76%)

Mol. F : $C_8H_8O_3$,

IR (Neat) : 2995, 2950, 1698, 1660, 1600, 1430, 840, 750 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.45 (d, *J* = 14.6 Hz, 1H), 6.6 (d, *J* = 7.0 Hz, 1H), 6.45 (s, 1H), 6.3 (d, *J* = 14.7 Hz, 1H), 3.8 (s, 3H)

^{13}CNMR (50 MHz, $CDCl_3$) : δ 164.08, 149.56, 144.45, 129.28, 115.38, 114.50, 112.51, 53.00.

Synthesis of 3-furyl-2-bromo-2-propenoic acid-methyl ester (*Z*:*E*, 1.5:1) (32)

A solution of 3-furyl-2-propenoic acid-methyl ester (2.72 g, 20 mmol) in dichloromethane (25 mL) was charged into 25 mL RB flask equipped with magnetic stirring bar. Bromine (3.2 g, 20 mmol) was added to the stirred solution at 0 °C and allowed to stir for 30 min. To this stirring solution, triethylamine (4.04 g, 40 mmol) was added dropwise at 0 °C and continued to stir at RT for 12 h. The reaction mixture was neutralised with dil.HCl and the product extracted with dichloromethane (3 × 10 mL). The combined organic layer was dried over anhydrous sodium sulphate, concentrated under reduced pressure to get the pure product.

Yield : 3.6 g (85%)

Mol. F : $C_8H_7BrO_3$

IR (Neat) : 2995, 1690, 1597, 1470, 1330, 1020, 790, 760 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.5 (s, 1H), 7.4 - 7.2 (m, 2H), 6.5 (d, *J* = 5.5 Hz, 1H), 3.90 (s, 3H)

Synthesis of 3-furyl-2-bromo-2-propenoic acid (33)

Yield : 2.0 g (90%)

Mol. F : $C_7H_7BrO_3$

M. P : 140 °C

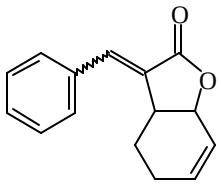
IR (Nujol) : 2920, 1670, 1595, 1460, 1420, 1340, 1030, 790 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.6 - 7.2 (m, 3H),7.1 (bs, 1H), 6.5 (d, *J* = 7.0 Hz, 1H)

General procedure for the Pd catalyzed reaction of α **-bromoacrylic acid with 1, 3-dienes**.

A 25 mL RB flask equipped with magnetic stirring bar, reflux condenser and argon balloon was charged with α-bromoacrylic acid (1 mmol), 1,3 diene (2 mmol), $PdCl_2(PPh_3)_2$ (0.07g, 0.1 mmol), potassium carbonate (0.275 g, 2 mmol), zinc chloride (0.067 g, 0.5 mmol) and degassed *N*-methylpyrrolidone (4 mL). The reaction mixture was flushed with argon thrice and allowed to stir at 90 °C for 2-48 h. The reaction mixture was neutralised with dil. HCl and the product extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product on silica gel column chromatographic purification using a mixture of petroleum ether and ethyl acetate (8:2) gave the corresponding lactones in moderate to good yields.

3- (1-Phenylmethylidene)-2,3,3a,4,5,7a-hexahydro(b)furan-2-one (34)



(*E* : *Z*, 3.3 : 1)

***E*-isomer (34a)**

Mol. F : $C_{15}H_{14}O_2$

IR (Neat) : 3000, 1745, 1640, 1440, 1230, 1180, 1000 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.6 - 7.3 (m, 6H), 6.45 - 6.35 (m, 1H), 6.15 - 6.0 (m, 1H), 4.8 - 4.7 (m, 1H), 3.6 - 3.45 (m, 1H), 2.3 - 2.0 (m, 3H), 1.55 - 1.35 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 171.34, 136.00, 134.37, 134.06, 130.89, 129.56, 129.51, 128.80, 122.79, 37.87, 23.43, 22.42.

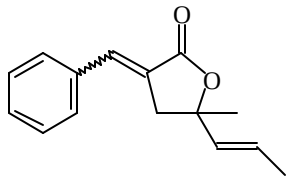
***Z* -isomer (34b)**

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.95 - 7.85 (m, 2H), 7.45 - 7.30 (m, 3H), 6.90 (d, J = 6.0 Hz,1H), 6.25 - 6.15 (m, 1H), 5.95 - 5.85 (m, 1H), 4.95 - 4.85 (m, 1H), 3.25 - 3.15 (m, 1H), 2.25 - 1.75 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 168.13, 138.44, 133.22, 130.20, 129.01, 128.70, 127.66, 123.48, 72.27, 40.96, 24.38, 21.64.

Mass (*m/z*) : 226 (M^+, 62), 208 (27), 181 (30), 165 (42), 141 (50), 115 (87), 104 (38), 91 (86), 77 (38).

5-Methyl-3-(1-phenylmethylidene)-5-((*E*)-1-propenyl)tetrahydro-2-furanone (*E*&*Z*, 2:1) (35)



Mol. F : $C_{15}H_{16}O_2$

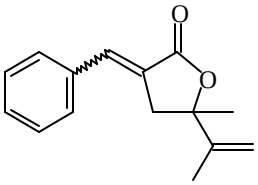
IR (Neat) : 2921, 1748, 1646, 1604, 1495, 1451, 1217, 1178, 1109 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.8 - 7.7 (m, 4H), 7.6 - 7.3 (m, 3H), 6.9 - 6.8 (m, 2H), 5.85 - 5.55 (m, 1H), 5.35 - 5.15 (m, 2H), 3.3 - 2.8 (m, 2H), 1.8 (d, *J* = 5.4 Hz, 3H), 1.6 (s, 3H), 1.5 (s,3H)

^{13}C NMR (50.35 MHz, $CDCl_3$) : δ 168.70, 168.19, 139.97, 139.46, 139.01, 136.77, 133.89, 133.84, 130.77, 130.05, 129.89, 129.49, 129.02,128.21, 125.96, 125.56, 125.41,123.42, 82.63, 81.86, 74.14, 44.50, 38.93, 27.47, 26.92, 25.88, 18.53, 17.76.

Mass (*m/z*) : 228 (M^+, 7), 213 (2), 200 (2), 187 (3), 173 (7), 144 (45), 121 (10), 116 (100), 105 (23), 91 (13), 77 (16).

5-Isopropenyl-5-methyl-3-(1-phenylmethylidene)tetrahydro-2-furanone (*E&Z*, 4 : 1) (36)



Mol. F : $C_{15}H_{16}O_2$

IR (Neat) : 2978, 1754, 1658, 1445, 1377, 1317 cm^{-1}

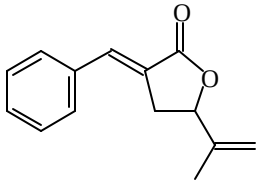
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.8 (d, *J* = 8.1Hz, 0.8H), 7.6 - 7.3 (m, 4H), 6.9 (s, 0.2H) 5.1 (s, 1H), 4.9 (s, 1H), 3.2 - 2.8 (m, 2H), 1.8 (s, 3H),1.5

(s, 3H).

^{13}C NMR (50.35 MHz, $CDCl_3$) : δ 171.47, 146.47, 139.60, 136.85,134.68, 130.71, 130.01, 129.90, 129.45, 128.98, 128.14, 125.64, 125.46, 111.00, 84.73, 83.71, 43.09, 39.67, 26.87, 26.33, 18.65.

Mass (*m/z*) : 228 (M^+, 1), 184 (36), 169 (10), 157 (8), 151 (23), 144 (100), 129 (23).

5-Isopropenyl-3-(1-phenyl-(*E*)-methylidene)tetrahydro-2-furanone (37)



Mol. F : $C_{14}H_{14}O_2$

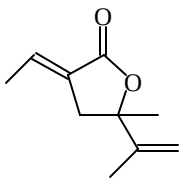
IR ($CHCl_3$) : 2923, 2853, 1753, 1655, 1449, 1043, 906 $cm^{-1.}$

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.6 - 7.3 (m, 6H), 5.1 (s, 1H), 5.0 (m, 1H), 4.9 (s, 1H), 3.45 -3.35 (m, 1H), 3.1 - 2.9 (m, 1H), 1.8 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 142.10, 136.12, 129.46, 129.34, 128.39, 124.58, 123.66, 113.26, 112.37, 79.11, 32.26, 16.33

Mass (*m/z*) : 214 (M^+, 12), 186 (5), 170 (7), 144 (44), 115 (100), 91 (7), 77 (7)

3-((*E*)-Ethylidene)-5-isoprpenyl-5-methyltetrahydro-2-furanone (38)



Mol. F : $C_{10}H_{14}O_2$

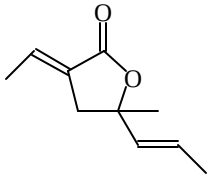
IR (Neat) : 2978, 2926, 1755, 1681, 1443, 1378, 1023, 987, 713 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.85 - 6.75 (m, 1H), 5.1 (s, 1H), 4.9 (s, 1H), 2.58 - 2.65 (m, 2H), 1.9 - 1.75 (m, 6H), 1.4 (s, 3H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 170, 147, 136, 128, 111, 84, 38, 25, 18, 15.

Mass (*m/z*) : 166 (M^+, 4), 151 (30), 125 (23), 105 (7), 91 (16), 82 (100).

3-((*E*)-Ethylidene)-5-methyl-5((*E*)-propenyl)tetrahydro-2-furanone (39)



Mol. F : $C_{10}H_{14}O_2$

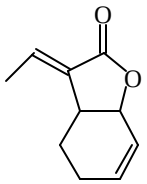
IR (Neat) : 2972, 2919, 2850, 1754, 1680, 1379, 1133, 973, 716 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.85 - 6.65 (m, 1H), 5.6 - 5.20 (m, 2H), 3.1- 2.95 (m, 1H), 2.65 - 2.45 (m, 1H), 1.8 - 1.6 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 170.92, 139.40, 135.19, 127.79, 123.87, 74.36, 32.36, 25.75, 18.42, 15.73.

Mass (*m/z*) : 166 (M^+, 4), 151 (20), 123 (13), 111(8) , 107 (13), 95 (25), 91 (30), 82 (100), 69 (18).

3-((*E*)-Ethylidene)-2,3,3a,4,5,7a-hexahydrobenzo(b)furan-2-one (40)



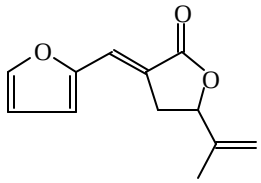
Mol. F : $C_{10}H_{12}O_2$

IR (Neat) : 3056, 2928, 1750, 1701, 1590, 1380, 996, 925 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.8 (q, *J* = 7.0 Hz, 1H), 6.3 - 6.1 (m, 1H), 6.15-5.95 (m, 1H), 4.75 - 4.65 (m, 1H), 3.2 - 3.0 (m, 1H), 2.15-2.05 (m, 3H), 2.0 (d, *J* = 7.0 Hz, 3H), 1.5 - 1.35 (m, 1H)

Mass (*m/z*) : 166 (M^+, 11), 136 (48), 122 (48), 105 (27), 91 (39), 79 (26).

3-(1-(2-Furyl)- (*E*)-methylidene)-5-isopropenyltetrahydro-2-furanone (41)



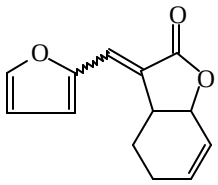
Mol. F : $C_{12}H_{12}O_3$

IR (Neat) : 2924, 2854, 1747, 1643, 1473, 1091, 904, 758 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.85 (d, *J* = 8.1 Hz), 7.5 (s, 1H), 6.85 (s, 1H), 6.5 (d, *J* = 8.0 Hz, 1H), 5.1 (s, 1H), 4.9 (s, 1H), 4.85 (s, 1H), 3.2 - 3.1 (m, 1H), 2.95 - 2.85 (m, 1H), 1.8 (s, 3H).

Mass (*m/z*) : 204 (M^+, 2), 160 (2), 149 (5), 134 (20), 106 (100), 91(8),78 (9), 57 (6).

3-(1-2-furyl)-methylidene -2, 3, 3a, 4, 5, 7a-hexahydrobenzo(b) furan -2 -one (42)



***E*:*Z*, 1.3:1**

Mol. F : $C_{13}H_{12}O_3$

IR ($CHCl_3$) : 3019, 2923, 1740, 1652, 1492, 1177, 1019 cm^{-1}

***E*-isomer**

^1H NMR (300 MHz, $CDCl_3$) : δ 7.55 (s, 1H), 7.25 (s, 1H), 6.75-6.65 (d, *J* = 4 Hz, 1H), 6.5 (d,

***E*-isomer** *J* = 4 Hz, 1H), 6.20-6.10 (m, 1H), 6.05 - 5.95 (m, 1H), 4.8 - 4.7 (m, 1H), 3.55 -3.45 (m, 1H), 2.15 - 1.95 (m, 3H), 1.45 - 1.25 (m, 1H).

***Z*-isomer** : δ 7.9-7.8 (d, *J* = 4 Hz, 1H), 7.5 (s, 1H), 6.8 (s, 1H), 6.5 (m, 1H), 6.15-6.05 (m, 1H), 5.95-5.85 (m, 1H), 4.9-4.8 (m, 1H) 3.25-3.25 (m, 1H), 2.15-1.75 (m, 4H).

Mass (*m*/*z*) : 216 (M^+, 52), 170 (24), 159 (37), 128 (49), 115 (57), 91 (100).

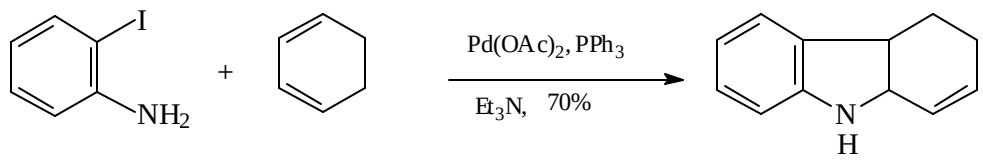
Section 2. Palladium catalyzed reaction of *a*-bromoacrylic amides with 1, 3-dienes.

INTRODUCTION AND BACKGROUND

Palladium mediated reactions of bifunctional molecule bearing halogen and soft nucleophile with alkynes and dienes to construct five and six membered carbocycles and heterocycles are very attractive reactions in synthetic organic chemistry. This kind of palladium-catalyzed reactions of bifunctional molecule bearing nitrogen nucleophile are discussed below.

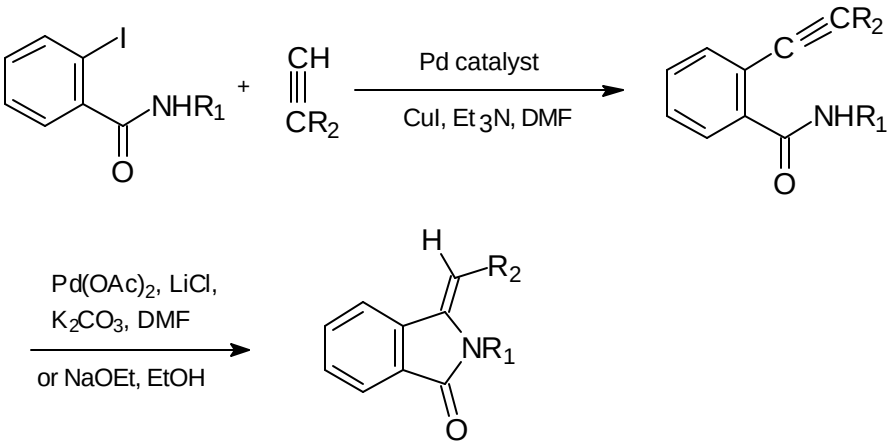
The palladium-catalyzed reaction of *o*-iodoaniline with 1, 3-diene using triethylamine as a base gave cyclised product reported by Connor *et al.* as shown in scheme-16. [16]

Scheme -16



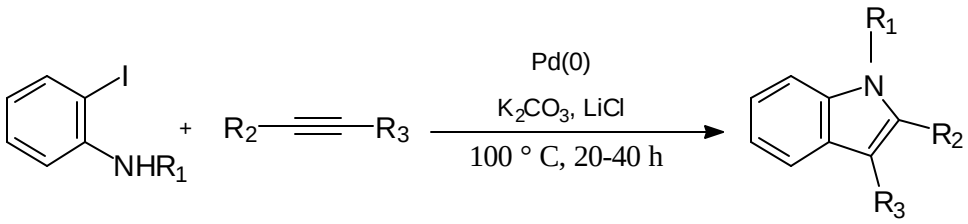
Kundu and co-workers reported the palladium catalyzed highly regio-and stereo-selective synthesis of (*Z*)-3-aryl(alkyl)ideneisoindolin-1-ones by annulation of alkynes with *ortho*- iodobenzamide (scheme-17). [17]

Scheme -17



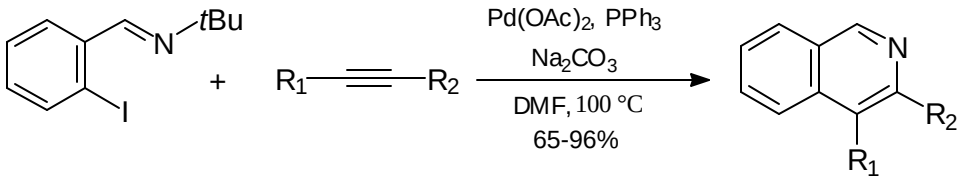
The palladium-catalyzed coupling of 2-iodoaniline and the corresponding *N*-methyl,*N*-acetyl and tosyl derivatives with a wide variety of internal alkynes provides 2, 3-disubstituted indoles in good yield as shown in scheme-18.[18]

Scheme -18



Larock *et al.* developed an efficient palladium catalyzed synthesis of isoquinolines, tetrahydroisoquinolines, pyridines from *ortho*-functionally substituted imines with internal alkynes in moderate to good yield (scheme-19).[19]

Scheme -19



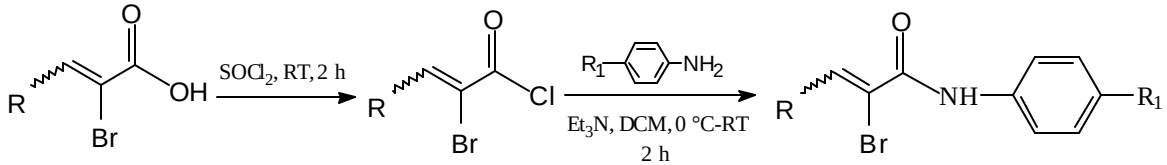
OBJECTIVE

Our aim was to study the palladium-catalyzed activation of bifunctional vinyl halides, α-bromoacrylic amides with 1, 3-dienes and alkynes to form α, β-unsaturated butyrolactams. The reaction involves the formation of oxidative addition complexes with vinyl halide and then the insertion of 1, 3 dienes between the carbon-palladium bond leading to π-allylpalladium complexes and the heteroatom nucleophile attack on the π-allylpalladium complexes, which leads the expected lactams.

PRESENT WORK

Our present study involves the synthesis of various α-bromoacrylic amides and palladium catalyzed reaction of α-bromoacrylic amides with 1, 3- dienes to form a new and novel class of butyrolactams. α-Bromoacrylic amides were synthesized from the corresponding α-bromoacrylic acids by treating with $SOCl_2$ and then the reaction of acid chloride with substituted anilines in the presence of triethylamine at room temperature (scheme-20).

Scheme -20

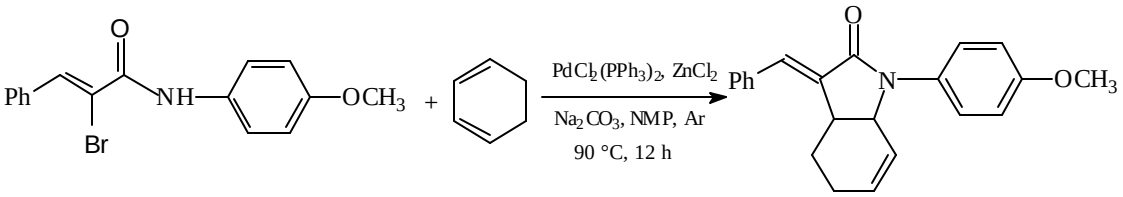


R = Ph, Me

R_1 = NO_2, OCH_3

Initial study was on the reaction of 1*N*-(4-methoxyphenyl)-2-bromo-3-phenyl-(*E*)-2-propenamide with 1, 3 cyclohexadiene catalyzed by $PdCl_2(PPh_3)_2$ and co-catalyst, zinc chloride to yield the expected butyrolactam, 1-(4-methoxyphenyl)-3-(1-phenyl-(*E*)-methylidene)-2,3,3a, 4,5,7a-hexahydro-1H-2-indolone as shown in scheme-21.

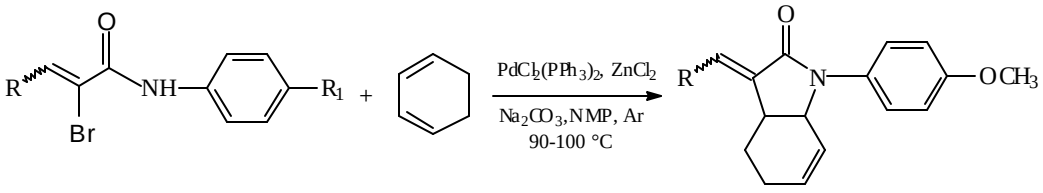
Scheme - 21



Z *E*

Similar reactions of various α-bromoacrylic amides with different 1, 3-dienes and alkynes were carried out in the presence of $PdCl_2(PPh_3)_2$ and zinc chloride at 90-100 °C under argon atmosphere to yield the corresponding substituted butyrolactams in good yield (scheme-22 & 23).The results of reactions of α-bromoacrylic amides with 1, 3 dienes are tabulated in table-5.

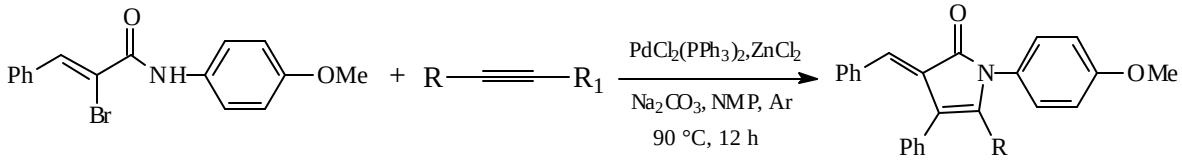
Scheme -22



R = Ph, Me R_1 = NO_2, OCH_3

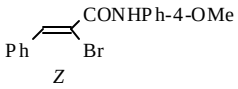
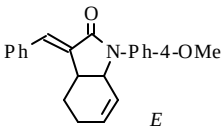
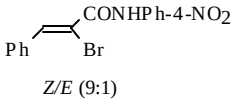
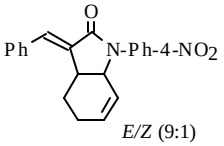
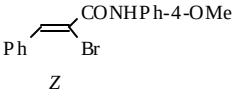
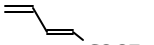
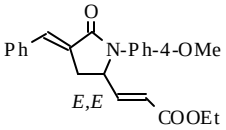
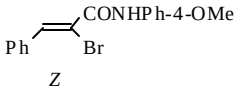
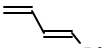
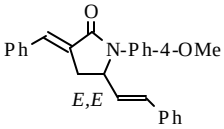
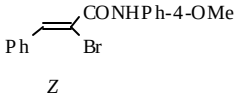
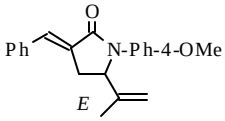
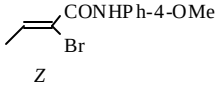
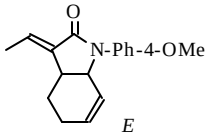
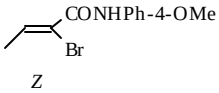
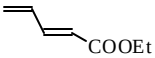
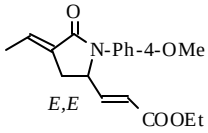
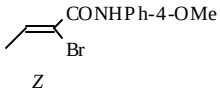
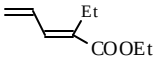
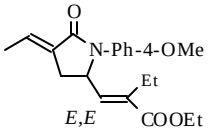
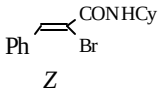
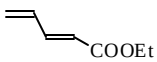
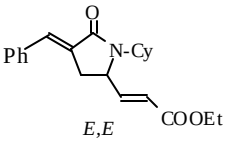
1, 3 dienes : , , , , Ph

Scheme -23



R_1 = COOMe, H R = Ph, C_6H_{13}

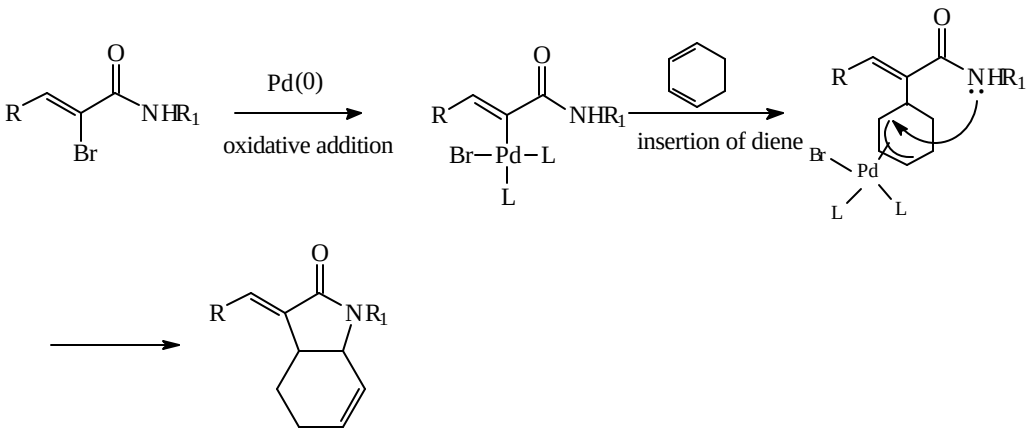
Table 5. Palladium catalyzed reaction of α-bromoacrylic amides with 1, 3-Dienes

S.No	α Bromoacrylicamide	1, 3-Diene	Product	Time(h)	Yield(%)
1.	 Z		 E	24	53
2.	 Z/E (9:1)		 E/Z (9:1)	6	51
3.	 Z		 E,E	10	70
4.	 Z		 E,E	4	45
5.	 Z		 E	6	26
6.	 Z		 E	6	20
7.	 Z		 E,E	4	60
8.	 Z		 E,E	6	55
9.	 Z		 E,E	24	30

RESULTS AND DISCUSSION

The reactions of α-bromoacrylic amides with 1, 3-dienes in the presence of palladium catalyst afforded the expected products which were characterized by IR, NMR and Mass spectroscopic studies. The reaction involves the oxidative addition of vinyl halide to palladium and the insertion of 1, 3-dienes in between the carbon-palladium bond, which led to the formation of π-allylpalladium intermediate and then attack by nitrogen nucleophile leads to expected α, β-unsaturated lactams (figure-1).

Figure -1



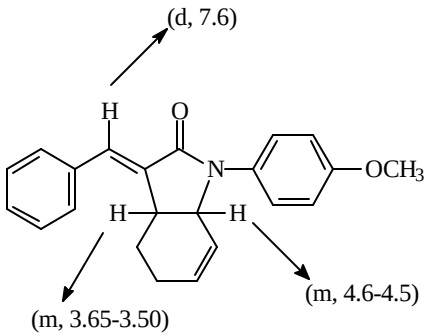
The precursors, α-bromoacrylic amides required for the palladium-catalyzed reaction with 1, 3-dienes were synthesized from corresponding α-bromoacrylic acids. Also, the 1, 3-dienes were prepared according to the literature methods.[15] Both isomers, 1*N*-(4-methoxyphenyl)-2-bromo-3-phenyl-(*Z*)-2-propenamide (**43**) and 1*N*-(4-methoxyphenyl)-2-bromo-3-phenyl-(*E*)-2-propenamide (**44**) were prepared and characterized by the usual spectroscopic methods. The IR spectrum showed a broad peak at 3300 cm^{-1} and a sharp peak at 1651 cm^{-1} indicating the presence of N-H and C=O groups of amide. The ^1H NMR spectrum displayed a broad singlet at δ 8.5 corresponding to proton on nitrogen and another singlet at δ 8.4

due to the presence of olefinic proton of *Z* isomer (compared with calculated chemical shift for olefinic proton of the *Z*-isomer, i.e. δ 8.2. The olefinic proton of *E*-isomer overlapping with aromatic protons (theoretical chemical shift δ 7.36) and a singlet at δ 3.79 confirmed the presence of methoxy proton. There was a multiplet at δ 7.5 - 7.3 corresponding to the aromatic protons. The mass spectrum showed a M+1 peak at *m/z* 333. These above data confirmed the structure of 1*N*-(4-methoxyphenyl)-2-bromo-3-phenyl-2-propenamide. In the literature, the NOE technique has been demonstrated to differentiate the olefinic protons of *Z* and *E* isomer of similar compounds.[20] Irradiation of the amide proton signal of *Z* isomer resulted in large negative enhancement of 34% for the olefinic proton of *Z* isomer but no enhancement was observed for the *E* isomer. The proton NMR and NOE irradiation spectra of both the isomers are shown on page 124, 125. The structure of the product obtained from α-bromocrotonic acid and *p*-anisidine was also characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis. The IR spectrum showed a broad peak corresponding to N-H stretching frequency at 3330 cm^{-1} and another sharp peak at 1650 cm^{-1} indicating the presence of C=O group of the product. The ^{1}H NMR spectrum displayed a broad singlet at δ 8.5 for amide proton. A quartet and doublet overlapping which corresponding to the olefinic and aromatic protons at δ 7.50 - 7.40 is also observed. The methoxy proton of the product appeared at δ 3.80 and allylic methyl protons appeared as a doublet at δ 1.9 with coupling constant of J = 4.0 Hz. The mass spectrum of the product showed a molecular ion peak at *m/z* 271. The above spectroscopic data confirmed the structure of 1*N*-(4-methoxyphenyl)-2-bromo-(*Z*)-2-butenamide (**45**). Similarly, the structure of 1*N*-(4-nitrophenyl)-2-bromo-3-phenyl-2-propenamide was confirmed based on spectroscopic data.

The palladium-catalyzed reaction of α-bromoacrylic amides with 1, 3-dienes and alkynes to form a new class of butyrolactams was carried out. All the products obtained from the reaction of α-bromoacrylic amide with 1, 3-diene and alkynes were characterized by IR, NMR and mass

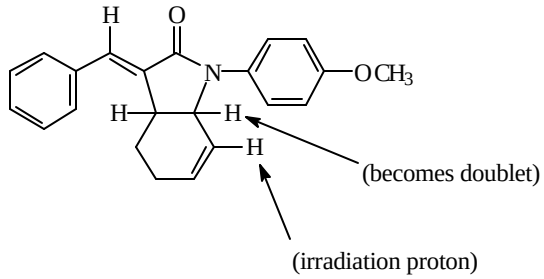
spectra. IR spectrum of the product obtained from 1*N*-(4-methoxyphenyl)-2-bromo-3-phenyl-(*Z*)-2-propenamide (**43**) with 1, 3-cyclohexadiene showed a sharp peak at 1681 cm^{-1} and another peak at 1645 cm^{-1} indicating the presence of C=O and C=C groups respectively. The ^{1}H NMR spectrum showed a doublet at δ 7.6 with the allylic coupling of J = 4.0 Hz which confirmed the presence of olefinic proton of the product and that was compared with the calculated chemical shift values based on empirical rule. A multiplet at δ 7.55 - 7.40 due to aromatic proton and the olefinic protons of cyclohexene ring appeared as multiplets, one at δ 6.15 - 6.05 and another at δ 5.85 - 5.70. One of the ring junction proton which is adjacent to nitrogen atom appeared as a multiplet at δ 4.60 - 4.50 and another multiplet appeared at δ 3.65 - 3.55 confirmed the other ring junction proton of the product. The chemical shift assignment product is shown in Figure-2. The ^{1}H NMR and ^{13} NMR spectra of the product **49** shown on page 126.

Figure -2.



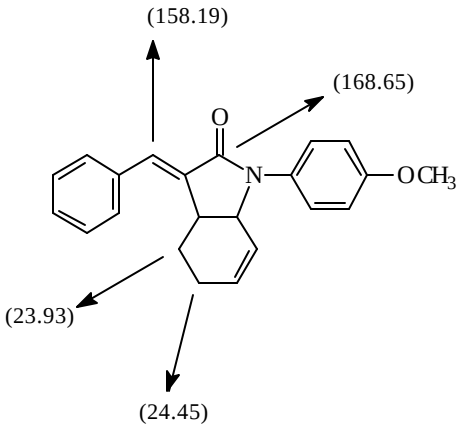
The stereochemistry of the ring junction protons was determined based on coupling constant value obtained from the homonuclear proton decoupling experiment. The irradiation of proton signal at δ 5.85 - 5.75 gave a clean doublet at δ 4.5 with coupling constant J = 6.0 Hz (Figure-3).

Figure -3



The proton decoupling NMR spectra and 2D COSY spectrum are shown on page 127 and 128. The stereochemistry of the double bond was confirmed by comparison with calculated chemical shift value for olefinic proton based on empirical rules and 2D NOE experiment. The 2D COSY spectrum is shown on page-. The ^{13} C NMR spectrum revealed all the carbon signals corresponding to the structure of the product. A carbonyl carbon signal appeared at δ 168.65 and a signal at δ 158.19 corresponding to the β-carbon of unsaturated lactam (figure-3). Two methylenic carbon signals appeared at δ 24.45 and 23.93 which was confirmed by DEPT spectrum.

Figure -4

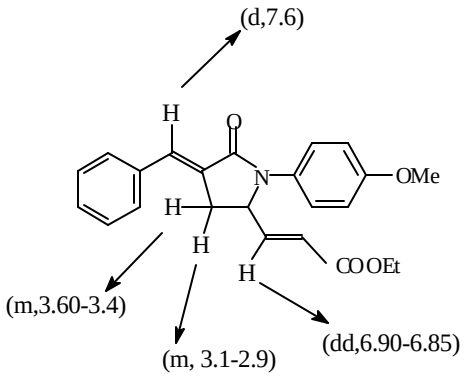


The mass spectrum gave a molecular ion peak at *m/z* 331 corresponding to the molecular weight of expected product. The above spectroscopic data confirmed the structure of product 1-(4-methoxyphenyl)-3-(1-phenyl-(*E*)-methylidene)-2,3,3a,4,5,7a hexahydro-1H-2-indolone (**49**).

The IR spectrum of product obtained from the palladium catalyzed reaction of 1*N*-(4-methoxyphenyl)-2-bromo-3-phenyl-(*Z*)-2-propenamide **(43)** with isoprene showed a sharp peak at 1681 cm^{-1} confirming the presence of carbonyl group of unsaturated system. The ^1H NMR spectrum displayed a doublet merged with a multiplet at δ 7.6 - 7.4 and indicating the presence of olefinic proton (with allylic coupling of J = 4.0 Hz) of α, β-unsaturated system and multiplet corresponding to aromatic protons. A doublet appeared at δ 6.9 with J = 8.0 Hz which assigned for aromatic protons of A_2B_2 pattern. The terminal olefinic protons appeared as two singlets, one at δ 5.05 and another at δ 4.90. One multiplet appeared at δ 4.85-4.75 indicating the presence one of the lactam ring protons adjacent to nitrogen atom of the product. The presence of two methylenic protons of the lactam was confirmed by the appearance of two separable multiplets, one at δ 3.55-3.25 and another at δ 2.95-2.65 with allylic, vicinal and geminal coupling. The allylic methyl proton appeared at δ 1.6 as a singlet. The mass spectrum showed a molecular ion peak at m/z 319. The above spectral data confirmed the structure of the expected product, 5-isopropenyl-1-(4-methoxyphenyl)-3-(1-phenyl-(*E*)-methylidene)tetrahydro-1H-2-pyrrolone (**50**). The ^1H NMR spectra is shown on page 129. Similarly, the structure of product obtained from the reaction of **43** with ethyl-(2*E*)-2,4-pentadienoate was also confirmed. The IR spectrum showed a sharp peak at 1687 cm^{-1} due to the presence of carbonyl group of the product. The ^1H NMR spectrum (page no. 130) showed a multiplet between δ 7.6 - 7.3 for aromatic and olefinic proton of α, β-unsaturated system and doublet at 6.9 with J = 8.0 Hz corresponding to A_2B_2 type aromatic protons. A multiplet appeared at 6.85 - 6.80 was assigned to olefinic proton on β carbon to the ester group (figure-4). A doublet at δ 5.8 with J = 13.0 Hz confirmed the presence of other olefinic proton of the unsaturated ester group. A multiplet appeared at δ 4.90 - 4.75 indicating the ring junction proton which is adjacent to nitrogen atom and a quartet at δ 4.2 with J = 8.0 Hz assigned to $OC\underline{H}_2$ of the ester group. A singlet at δ 3.81 was attributed to methoxy protons. Two

multiplets appeared, one at δ 3.65--3.40 and another at δ 3.10 - 2.90 confirming the presence of methylenic protons of lactam ring with geminal, vicinal and allylic coupling. A triplet at δ 1.25 confirmed the presence of methyl proton (figure-4).

Figure -4

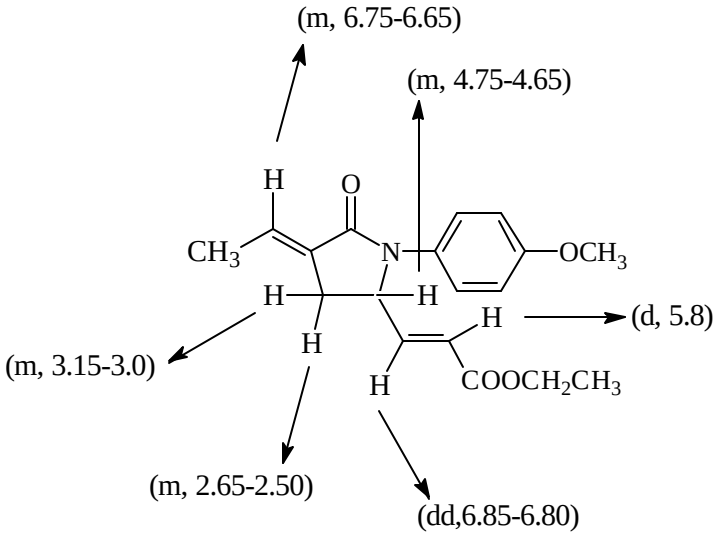


The ^{13}C NMR spectrum (page no. 130) showed two signals at δ 167.83 and 165.23 due to carbonyl carbons of lactam and ester respectively. Two methylenic carbon signals appeared at δ 60.43 and 31.43, which was reliably confirmed by DEPT experiment. The mass spectrum showed a molecular ion peak at *m/z* 377. The above spectroscopic data confirmed the structure of ethyl-3-(1-(4-methoxyphenyl)-5-oxo-4-(1-phenyl-(*E*)-methylidene)tetrahydro-1H-2-pyrrolyl)-(*E*)-2-propenoate(**51**). The stereochemistry also confirmed by 2D NOESY and COSY experiments (page no. 131 and 132).

The product obtained from the reaction of **45** with ethyl-(2*E*)-2,4-pentadienoate was characterized as follows. The IR spectrum showed two sharp peaks at 1704 cm^{-1} and 1674 cm^{-1} due to the presence of carbonyl groups of unsaturated ester and lactam respectively. The ^1H NMR spectrum showed two doublets at δ 7.4 and 6.9 indicating the aromatic protons of A_2B_2 type. The proton on β-carbon of α, β-unsaturated ester appeared as a doublet of doublet at δ 6.85-6.75 with the coupling constant, *J* = 4.0 Hz, 12.5 Hz. The olefinic proton of unsaturated lactam showed a multiplet at δ 6.7 - 6.6 due to the vicinal coupling with CH_3 and allylic coupling

with methylenic proton of lactam ring. The proton on α-carbon of unsaturated ester appeared as a doublet with J = 12.5 Hz indicating the *trans*-stereochemistry of olefinic protons. A multiplet at δ 4.85 - 4.75 due to proton of lactam ring, which is adjacent to nitrogen atom, which was strong evidence for the formation of lactam. A quartet at δ 4.2 and a singlet at δ 3.74 are due to the presence of OCH_2 and OCH_3 protons respectively. Two distinct multiplets appeared, one at δ 3.15 - 3.0 and another at δ 2.60 - 2.50 for CH_2 proton of lactam ring indicating that these protons have vicinal coupling, geminal coupling and allylic coupling. A doublet at δ 1.83 with J = 4.0 Hz and a triplet at δ 1.27 with J = 5.0 Hz is attributed to allylic CH_3 and CH_3 groups. The important chemical shift values and the corresponding protons are given in figure-5.

Figure -5



The ^{13}C NMR spectrum showed two signals at δ 165.45 and 165.72 due to the presence of carbonyl carbons of lactam and ester, respectively while the other two signals appeared at δ 159.77 and 159.69 were assigned to the β-carbons of unsaturated lactam and ester respectively. The ^{1}H NMR spectrum is shown on page 133. The mass spectrum showed a molecular ion peak at *m/z* 315 which confirming the expected product. The above spectroscopic data proved the structure of product (**52**). Similarly the structure of product, ethyl-2-ethyl-3-[4-[(*E*)-ethylidene]-

1-(4-methoxyphenyl)-5-oxoxotetrahydro-1H-2-pyrrolyl]-(*E*)-2-propenoate **(53)** obtained from the palladium catalyzed reaction of **45** with ethyl-2-ethyl-(2*E*)-2,4-pentadienoate was deduced from the spectroscopic data such as IR , ^{1}H NMR, ^{13}C NMR and Mass. The proton and ^{13}C NMR spectra are shown on page no. 134.

A mixture of (*E/Z*, 8:2) lactam (**54**) obtained from the reaction of mixture of **48** (*Z/E*, 9:1) was also characterized. The IR spectrum gave a sharp peak at 1693 cm^{-1} corresponding to carbonyl stretching frequency. The ^{1}H NMR spectrum showed two doublets between δ 8.80 - 8.70 for A_2B_2 type of aromatic proton and aromatic protons appeared as a multiplet between δ 7.8 - 7.3. The olefinic proton of the cyclohexene ring of lactam appeared as multiplets at δ 6.25 - 5.85. There were two multiplets at δ 4.85 - 4.70 and 4.75 - 4.65 could be assigned to ring junction proton which is adjacent to nitrogen atom with the integration of 0.2 H and 0.8 H respectively, which determined the ratio of the isomers. The ^{13}C NMR spectrum revealed all the required carbon signals of both the isomers. The mass spectrum gave a molecular ion peak at *m/z* 346. These above data helped us to prove the structure of the product **(54)**. One of the isomer separated from the mixture by column chromatography.

The IR spectrum of the product from the reaction of **47** with ethyl-1, 3-pentadienoic acid ester showed sharp peaks at 1682 and 1705 cm^{-1} indicating the carbonyl stretching frequency of both lactam and ester groups. The ^{1}H NMR spectrum (page no. 135) showed all important protons as multiplets at δ 4.55 - 4.45, 3.40 - 3.25 and 2.65 - 2.45 supporting the formation of expected lactam product. The presence of cyclohexyl ring protons was confirmed by the appearance of multiplet at δ 2.0 - 1.2. The ^{13}C NMR spectrum (page no. 135) was clearly indicating the presence of two carbonyl carbons by showing two signals at δ 168.74 and δ 165.51. The mass spectrum of the product gave a molecular ion peak at *m/z* 353, which is the

further evidence for the formation of expected lactam product. All these data confirmed the structure of required lactam **(56)**.

The IR spectrum of the product obtained from the reaction of amide (**43**) with 1-phenyl-1, 3-butadiene showed sharp peaks at 1683 cm^{-1} and 1605 cm^{-1} indicating the presence of C=O and C=C bonds respectively. In the ^1H NMR spectrum of the product, a multiplet appeared at δ 7.65 -7.25 confirming the presence of aromatic protons (13H). A doublet at δ 6.85 with coupling constant, J = 8.0 Hz was attributed to aromatic protons of A_2B_2 pattern. A doublet of doublet appeared at δ 6.65 (J = 4.0 Hz, J = 12.5 Hz) could be assigned to olefinic protons of the product. A doublet at 6.10 assigned for other olefinic proton. The most important proton which appeared as a multiplet at δ 4.90 - 4.80, 3.65 - 3.50 and 3.15 - 2.95 confirmed the formation of expected cyclised product 1-(4-methoxyphenyl)-5-[2-phenyl-(*E*)-1-ethenyl]-3-[1-phenyl-(*E*)-methylidene]-tetrahydro-1H-2-pyrrolone (**55**). The product obtained from the reaction of 1*N*-(4-methoxyphenyl)-2-bromo-3-phenyl-(*Z*)-2-propenamide **(43)** with phenyl propiolate in the presence of palladium catalyst was characterized by the usual spectroscopic method. The IR spectrum gave a strong absorption band at 1705 cm^{-1} and the ^{1} H NMR spectrum showed a multiplet at δ 7.75 - 7.25 was assigned to aromatic protons (13H) and two singlets at 3.84 and 3.72 with an integration of 3 protons of each indicating the presence of two methoxy groups. The mass spectrum displayed a molecular ion peak at m/z 411. The above data confirmed the structure of the expected product (**57**). Similarly the structure of the product (**58**) obtained from the reaction of amide (**45**) with 1, 3-cyclohexadiene was also confirmed.

CONCLUSION

A new and novel methodology was developed towards the synthesis of α, β-unsaturated butyrolactams by the palladium catalyzed reactions of α-bromoacrylic amides with 1, 3 dienes and alkynes.

EXPERIMENTAL

General procedure for synthesis of bromoacrylic amides

A 25 mL round-bottomed flask equipped with a calcium chloride guard tube was charged with α- bromoacrylic acid (10 mmol) and freshly dstilled thionyl chloride (1.62 g, 12 mmol). The reaction mixture was allowed to stand for 2 h at room temperature. The excess of thionyl chloride was removed by distillation and the pure acid chloride obtained was stored under argon atmosphere.

A mixture of dry triethylamine (10 mmol) and substituted anilines (10 mmol) in dry dichloromethane (25 mL) was charged into a two necked round bottomed flask equipped with a magnetic stirring bar and argon balloon. To the stirring solution, the freshly prepared acid chloride was added slowly at 0 °C for 10 min. and the reaction was allowed to stir for 1h at RT. The reaction mixture was neutralized with dil. HCl and the product extracted with dichloromethane (3 × 10 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the crude product. Silica gel column chromatographic purification of the crude product using a mixture of petroleum ether and ethyl acetate (9:1) gave the product in high yield.

α-bromoacrylic amides

1*N*-(4-methoxyphenyl)-2-bromo-3-phenyl-(*Z*)-2-propenamide (43)

Mol. F : $C_{16}H_{14}BrNO_2$

M. P : 107 - 108 °C

IR (Nujol) : 3294, 2925, 2854, 1651, 1608, 1596, 1460, 1446, 1309, 1033, 825, 690 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.5 (bs, 1H), 8.4 (s, 1H), 7.8 - 7.6 (m, 2H), 7.5 (d, *J* = 8.0 Hz, 2H), 7.5 - 7.3 (m, 2H), 6.9 (d, *J* = 8.0 Hz, 2H), 3.79 (s, 3H).

^{13}C NMR (50.32 MHz, $CDCl_3$) : δ 160.14, 156.87, 138.05, 133.97, 131.02, 130.15, 129.74,128.34, 122.17, 114.12, 55.34.

Mass (*m/z*) : 333 (M+1, 83), 271(11), 252 (100), 211(58), 181(28), 122 (33), 102 (45).

1*N*-(4-methoxyphenyl)-2-bromo-3-phenyl-(*E*)-2-propenamide (44)

Mol. F : $C_{16}H_{14}BrNO_2$

M. P : 137 - 138 ^{0}C

IR (Nujol) : 3263, 2923, 1650, 1616, 1184, 1024, 918, 825, 694 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.45 - 7.2 (m, 8H), 6.85 (d, *J* = 7.8 Hz, 2H), 3.78 (s, 3H).

^{13}C NMR (50.32 MHz, $CDCl_3$) : δ 162.60, 157.08, 136.65, 134.48, 130.29, 128.89, 128.41, 122.20, 116.50, 114.30, 55.60..

Mass (*m/z*) : 333 (M+1, 83), 271(11), 252 (100), 211(58), 181 (28), 122 (33), 102 (45).

1*N*-(4-methoxyphenyl)-2-bromo-(*Z*)-2-butenamide (45)

Yield : 1.25 g (92%)

Mol. F : $C_{11}H_{12}BrNO_2$

M. P : 59 - 60 °C

IR (Nujol) : 3330, 2954, 1650, 1596, 1413, 1029, 831, 732 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.5 (bs, 1H), 7.5 (m, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 6.8 (d, *J* = 8.0 Hz, 2H), 3.8 (s, 3H), 1.9 (d, *J* = 2.0 Hz, 3H).

^{13}C NMR (50.32 MHz, $CDCl_3$) : δ 159.58, 156.90, 137.93, 130.47, 122.16, 119.37, 114.19, 55.45, 17.77.

Mass (*m/z*) : 271(M^+, 43), 270 (6), 269 (47), 190 (25), 162 (12), 147 (65), 108 (49), 80 (16).

1-*N*-cyclohexyl-2-bromo-(*Z*)-2-butenamide (46)

Yield : 0.925 g (74%)

Mol. F : $C_{10}H_{16}BrNO$

IR (Nujol) : 3417, 2931, 1658, 1620, 760 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.4 (q, *J* = 6.0 Hz, 1H), 6.5 (bs, 1H), 3.8 - 3.6 (m,1H), 1.95 (d, *J* = 6.0 Hz, 3 H), 1.8 - 1.2 (m, 10 H).

^{13}C NMR (50.32 MHz, $CDCl_3$) : δ 160.34, 136.30, 119.54, 48.78, 32.42, 25.22, 24.34, 17.10

Mass (m/z) : 247 (M^+, 17), 245 (18), 204 (11), 166 (100), 147 (58), 121 (23), 98 (31).

1-*N*-cyclohexyl-2-bromo-3-phenyl-(*Z*)-2-propenamide (47)

Yield : 1.31 g (85%)

M. P : 109 - 111 °C

Mol. F : $C_{15}H_{18}BrNO$

IR (Nujol) : 3309, 2920, 2854, 1645, 1616, 1020, 757 $cm^{-1.}$

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.31 (s, 1H),7.8 - 7.7 (m, 2H), 7.5 - 7.35 (m, 3H), 6.74 (bs,1H), 4.0 - 3.8 (m, 1H), 2.1 - 1.9 (m, 2H), 1.8 - 1.5 (m,

3H), 1.5 - 1.10 (m, 5H).

^{13}C NMR (50.32 MHz, $CDCl_3$) : δ 161.62, 144.53, 130.11, 129.77, 128.61, 115.92, 49.72, 33.00, 25.79, 25.00.

Mass (*m/z*) : 308 (M^+, 4), 210 (12), 183 (12), 145 (13), 131(19), 116 (4), 91(5), 76 (10).

1*N*-(4-nitrophenyl)-2-bromo-3-phenyl-2-propenamide (48)

Yield : 1.25 g (82%)

Mol. F : $C_{15}H_{11}BrN_2O_3$

M. P : 127 - 128 °C

IR (Nujol) : 3330, 1683, 1598, 852 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.9 (bs, 1H), 8.5 (s, 0.9 H), 8.30 (d, *J* = 8.0 Hz, 2H), 7.8 - 7.70 (m, 4H), 7.55 - 7.35 (m, 3.1H)

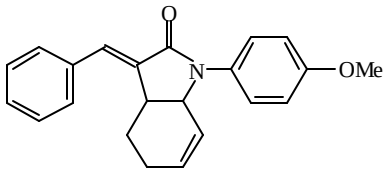
Mass (m/z) : 346 (M^+, 2), 267 (34), 221 (10), 183 (23), 102 (100), 91 (8).

General procedure for the palladium-catalyzed reactions of α-bromoacrylic amides with 1, 3-dienes.

A 25 mL RB flask equipped with a magnetic stirring bar, reflux condenser and argon balloon was charged with α-bromoacrylic amide (1 mmol), 1, 3-diene (2 mmol), $PdCl_2(PPh_3)_2$ (0.07g, 0.1 mmol), sodium carbonate (0.275 g, 2 mmol), zinc chloride (0.067 g, 0.5 mmol) and degassed *N*-methylpyrrolidone (4 mL). The reaction mixture was flushed with argon thrice and allowed to stir at 90 °C for 2-48 h. The reaction mixture was neutralized with dil. HCl and the product was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to give crude product. The

crude product on silica gel column chromatographic purification using a mixture of petroleum ether and ethyl acetate gave the corresponding butyrolactams in moderate to good yield.

1-(4-methoxyphenyl)-3-(1-phenyl-(*E*)-methylidene)-2,3,3a,4,5,7a-hexahydro-1H-2-indolone (49)



Mol. F : $C_{22}H_{21}O_2N$

M. P : 135 - 137 °C

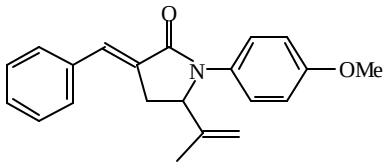
IR (Nujol) : 3018, 2935, 1681, 1645, 1608, 1290, 1247, 1033, 692 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.6 (d, *J* = 4.0 Hz, 1H), 7.55 - 7.4 (m, 5H), 7.3 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.15 - 6.05 (m, 1H), 5.85 - 5.7 (m, 1H), 4.6 - 4.5 (m, 1H), 3.8 (s, 3H), 3.65 - 3.50 (m, 1H), 2.25 - 2.0 (m, 3H), 1.6 - 1.45 (m, 1H).

^{13}C NMR (50.32 MHz, $CDCl_3$) : δ 168.65, 158.19, 136.52, 135.60, 133.25, 130.00, 129.77, 129.13, 126.63, 123.27, 114.64, 55.76, 54.77, 36.51, 24.45, 23.93.

Mass (m/z) : 331 (M^+, 100), 302 (15), 212 (18), 179 (12), 165 (22), 134 (19), 115 (37), 91 (24), 77 (54)

5-isopropenyl-1-(4-methoxyphenyl)-3-(1-phenyl-(*E*)-methylidene)tetrahydro-1H-2-pyrrolone (50)



Mol. F : $C_{21}H_{21}O_2N$

M. P : 183 - 184 °C

IR ($CHCl_3$) : 3016, 2839, 1704, 1674, 1512, 1180, 831, 761 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.65 - 7.4 (m, 8H), 6.9 (d, *J* = 8.0 Hz, 2H), 5.05 (s, 1H), 4.9 (s,1H), 4.85 - 4.75 (m, 1H), 3.82 (s, 3H), 3.55 - 3.25 (m, 1H), 2.95 - 2.65 (m, 1H), 1.65 (s, 3H).

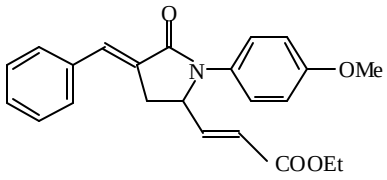
^{13}C NMR (75 MHz, $CDCl_3$) : δ 168.83, 157.56, 144.51, 136.09, 131.51, 130.07, 129.10, 124.15, 114.81, 114.36, 63.11, 55.76, 31.62, 16.75.

Mass (*m/z*) : 319 (79), 304 (23), 278 (66), 174 (12), 160 (24), 128 (48), 115 (100), 91 (21), 77 (14).

Analysis : **Calculated** : C (78.98), H (6.60), N (4.37)

Found : C (78.01), H (6.43), N (4.10)

Ethyl3-(1-(4-methoxyphenyl)-5-oxo-4-(1-phenyl-(*E*)-methylidene)tetrahydro-1H-2-pyrrolyl)-(*E*)-2-propenoate (51)



Mol. F : $C_{23}H_{23}NO_4$

M. P : 147 -148 °C

IR (Nujol) : 3018, 1716, 1687, 1652, 1512, 1215, 1035, 757 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.6 - 7.3 (m, 8H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.9 - 6.8 (m, 1H), 5.8 (d, *J* = 13.0 Hz, 1H), 4.9 - 4.75 (m, 1H), 4.2 (q, *J* = 7.5 Hz, 2H), 3.81(s, 3H), 3.65-3.40 (m,1H), 3.1 - 2.9 (m, 1H), 1.25 (t, *J* = 7.5 Hz, 3H).

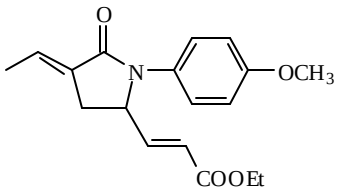
^{13}C NMR (50.32 MHz, $CDCl_3$) : δ 167.83, 165.23, 157.05, 146.25, 135.08, 131.84, 130.59, 129.43, 128.94, 128.52, 123.08, 113.99, 60.43, 57.59,55.12, 31.43, 13.86.

Mass (*m/z*) : 377 (M^+, 100), 348 (29), 304 (51), 204 (20), 160 (25), 116 (100).

Analysis **Calculated** : C (73.19), H (6.14), N (3.71)

Found : C (72.60), H (6.32), N (3.22)

Ethyl-3-[4-[(*E*)-ethylidene]-1-(4-methoxyphenyl)-5-oxotetrahydro -1H-2-pyrrolyl]-(*E*)-2-propenoate (52)



Mol. F : $C_{18}H_{21}O_4N$

IR (Nujol) : 3016, 2839, 1704, 1674, 1369, 1180, 975, 761 cm^{-1}

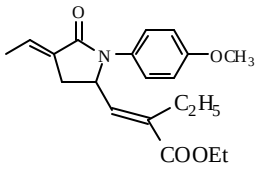
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.4 (d, *J* = 8.0 Hz, 2H), 6.9 (d, *J* = 8.0 Hz, 2H), 6.85 - 6.75 (dd, J_1 = 4.0 Hz, J_2 =12.5 Hz, 1H), 6.75 - 6.65 (m, 1H), 5.8 (d, *J* = 12.5 Hz,1H), 4.75 - 4.65 (m, 1H),4.1 (q, *J* = 7.5Hz,

2H), 3.78 (s, 3H),3.15 - 3.05 (m, 1H), 2.65 - 2.50 (m, 1H), 1.6 (d, J = 4.0 Hz,3H), 1.25 (t, J = 7.5 Hz, 3H).

^{13}C NMR (50.35 MHz, $CDCl_3$) : δ 167.45, 165.72, 159.77, 159.69, 150.32, 131.4 0, 130.10, 129.77, 123.89, 121.54, 114.11, 60.56, 55.38, 54.57, 29.28, 14.69, 14.17.

Mass (*m/z*) : 315 (M^+, 100), 286 (41), 270 (17), 242 (83), 134 (26), 106 (25), 91(12).

Ethyl-2-ethyl-3-[4-[(*E*)-ethylidene]-1-(4-methoxyphenyl)-5-oxoxtetrahydro-1H-2-pyrrolyl]-(*E*)-2-propenoate (53)



Mol. F : $C_{20}H_{25}NO_4$

M. P : 119 °C

IR (Nujol) : 2925, 1703, 1672, 1512, 1043, 831 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.3 (d, J = 8.0 Hz, 2H), 6.8 (d, J = 8.0 Hz, 2H), 6.7 - 6.6 (m, 1H), 6.5 (d, J = 4.0 Hz, 1H), 5.0 - 4.9 (m, 1H), 4.2 (q, J = 7.0 Hz, 2H) 3.77 (s, 3H), 2.3 (q, J = 7.5 Hz, 2H), 1.75 (d, J = 4.0 Hz), 1.3 (t, J = 7.0 Hz, 3H), 1.0 (t, J = 7.5 Hz, 3H).

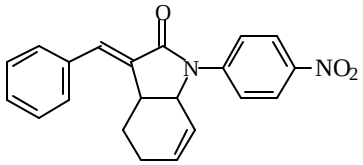
^{13}C NMR (50.35 MHz,$CDCl_3$) : δ 166.99, 166.48, 157.25, 140.42, 135.86, 130.90, 129.35, 124.50, 121.50, 113.88, 60.43, 55.03, 54.88, 29.34, 20.11, 14.30, 3.79, 13.64.

Mass (*m/z*) : 343 (M^+, 49), 328 (9), 314 (28), 254 (15), 173 (18), 134 (49), 108 (37).

Analysis : **Calculated** : C (69.96), H (7.33), N (4.07)

Found : C (69.90), H (7.06), N (4.14)

1-(4-nitrophenyl)-3-[1-phenyl-(*E*)-methylidene]-2,3,3a,4,5,7a-hexahydro-1H-2-indolone (54)



E/Z (8:2)

Mol. F : $C_{21}H_{18}N_2O_3$

M. P : 102 - 113 °C

IR (Nujol) : 3018, 2929, 1693, 852 cm^{-1}

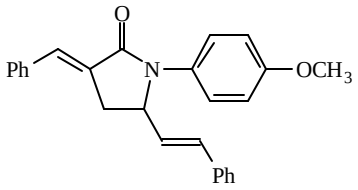
^{1}H NMR (200 MHz, $CDCl_3$) : δ 8.80 - 8.75 (m, 2H), 7.8 - 7.30 (m, 7.8H), 6.25 - 5.885 (m, 2H), 4.85 - 4.75 (m, .2H), 4.75 - 4.65 (m, 0.8H), 3.75 - 3.60 (m, 0.8H), 3.45 - 3.30 (m, 0.2H), 2.2 - 2.0 (m, 3H), 1.65 - 1.45 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 168.96. 168.26, 145.31, 143.78, 139.66, 135.05, 134.66, 134.14, 132.73, 130.92, 130.01, 129.01, 128.52, 127.97, 126.08, 124.43, 123.24, 121.62, 119.70, 119.20, 55.15, 53.26, 35.62, 23.41, 23.50.

Analysis : **Calculated** : C (72.62), H (5.21), N (8.06)

Found : C (72.32), H (5.22), N(8.01)

1-(4-methoxyphenyl)-5-[2-phenyl-(*E*)-1-ethenyl]-3-[1-phenyl-(*E*)-methylidene]-tetrahydro-1H-2-pyrrolone (55)



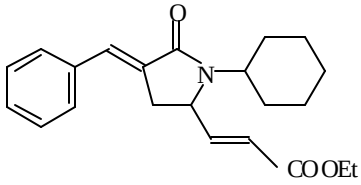
Mol. F : $C_{26}H_{23}NO_2$

IR (Nujol) : 2925, 1683, 1603, 1170, 970, 862 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.65 - 7.25 (m, 13 H), 6.85 (d, *J* = 8.0 Hz, 2H), 6.65 (dd, J_1 = 4.0 Hz, J_2 = 13 Hz, 1H), 6.10 (d, *J* = 4.0 Hz, 1H), 4.9 (m, 1H), 3.78 (s, 3H), 3.65 - 3.50 (m, 1H), 3.15 - 2.95 (m, 1H).

Mass (m/z) : 381 (M^+, 25), 350 (35), 304 (23), 277 (40), 105 (100), 77 (63)

Ethyl, 3-{1-cyclohexyl-5-oxo-4-[1-phenyl-(*E*)-methylidene]tetrahydro-1H-2-pyrrolyl-(*E*)-2-propenoate (56)



Mol. F : $C_{22}H_{27}NO_3$

M. P : 153 - 154 °C

IR (Nujol) : 3016, 2921, 1712, 18683, 1041, 763 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.60 - 7.30 (m, 5H), 6.90 - 6.80 (dd, J_1 = 4.0 Hz, J_2 = 12.5 Hz, 1H), 6.0 (d, *J* =12.5 Hz, 1H), 4.5 - 4.4 (m, 1H), 4.2 (q, *J* = 1.0 Hz, 2H), 4.0 -3.8 (m, 1H), 3.45 - 3.25 (m, 1H), 2.85 - 2.60 1.1 (m, 1H), 2.0 - 1.20 (m, 10H).

^{13}C NMR (50.35 MHz, $CDCl_3$) : δ 168.74, 165.51, 148.78, 135.54, 135.38, 130.53, 129.55,

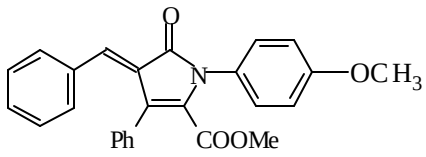
129.34, 128.52, 121.99, 60.61, 55.61, 52.35, 48.49, 32.87, 32.35, 31.71, 29.61, 25.67, 25.24, 24.72, 14.01.

Mass (m/z) : 353 (M^+, 75), 324 (15), 280 (61), 270 (37), 224 (46), 198 (64), 183 (100), 105 (84), 77 (14).

Analysis **Calculated** : C (74.77), H (7.69), N (3.96)

Found : C (74.14), H (7.40), N (4.01)

Methyl-1-(4-methoxyphenyl)-2-oxo-4-phenyl-3-[1-phenyl-(*E*)-methylidene-2, 3-dihydro-1H-5-pyrrolecarboxylate (57)



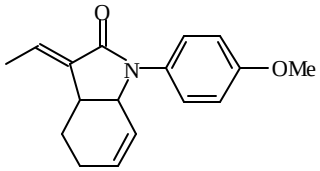
Mol. F : $C_{25}H_{21}NO_4$

IR ($CHCl_3$) : 1616, 1596, 1514, 1492, 1249, 1031, 932 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 8.14 (d, *J* = 8.0 Hz, 2H), 7.75 - 7.25 (m, 13H), 3.74 (s, 3H), 3.18 (s, 3H).

Mass (m/z) : 411 (M^+, 100), 352 (9), 325 (18), 210 (58), 105 (18), 77 (12).

3-[(*E*)-ethylidene]-1-(4-methoxyphenyl)-2, 3, 3a, 4, 5, 7a-hexahydro-1H-indolone (58)



Mol. F : $C_{17}H_{19}NO_4$

IR ($CHCl_3$) : 2923, 1683, 1603, 1430, 1047, 932 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.4 (d, *J* = 8.0 Hz, 2H), 6.9 (d, *J* = 8.0 Hz, 2H), 6.8 - 6.7 (m,

1H), 6.0 - 5.9 (m, 1H), 5.7 - 5.6 (m, 1H), 4.6 - 4.5 (m, 1H), 3.78 (s, 3H), 3.3 - 3.2 (m, 1H), 2.1 - 1.9 (m, 3H), 1.76 (d, *J* = 4.0 Hz, 3H), 1.6 - 1.5 (m, 1H).

Mass (m/z) : 271 (M^+, 23), 240 (50), 164 (43), 139 (27), 105 (100), 76 (60)

References

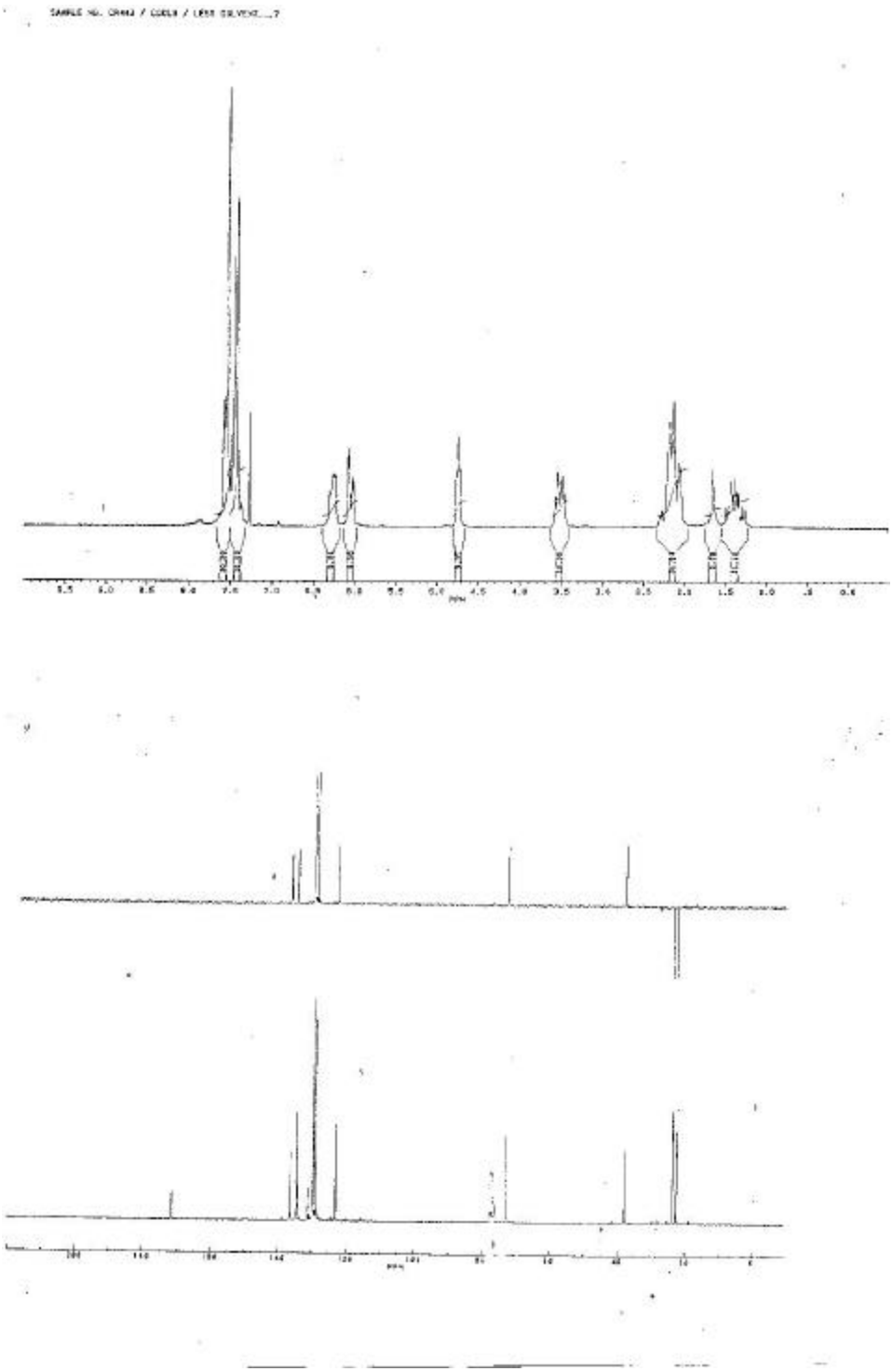
1. Larock, R.C.; Colleen, A. F. *J. Am. Chem. Soc*., **1990**, *112*, 5882.
2. Larock, R. C.; Berrios-Pena, N.G.; Colleen A. F. *J. Org. Chem.*, **1991**, *56*, 2615.
3. Larock, R. C.; Berrios-Pena, N. G.; Colleen A. F.; E. K. Yum.; C. Tu.; Leong., W. *J. Org. Chem.*, **1993**, *58*, 4509.
4. Bishop, B. C.; Cottrell, I. F.; David Hands., *Synthesis*, **1997**, 1315.
5. Larock, R. C.; Xiaojun Han and Doty, M. J. *Tetrahedron Lett.*, **1998**, *39*, 5713.
6. Garcias, X.; Ballester, P and Saa, J. M. *Tetrahedron Lett.*, **1989**, *30*, 6629.
7. Larock, R. C.; Yum, E. K. *Synlett.*, **1990**, 529.
8. Arcadi, A, Marinelli, F.; Cacchi, S. *Synthesis*, **1986**, 749.
9. Larock, R. C.; Berrios-Pena, N. G.; Colleen A. F.; Yum, E. K.; Tu, C.; Leong. W. *J. Org. Chem.*, **1993**, *58*, 4509.
10. Larock, R. C.; Berrios-Pena, N. G.; Colleen A. F. *J. Org. Chem.*, **1991**, *56*, 2615.
11. Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579.
12. Rossi, R.; Bellina, F.; Bechini, C.; Mnnina, L.; Vergamini, P. *Tetrahedron*., **1998**, *54*, 135.
13. Pfeiffer, P, *Ber.*,**1910**, *43*, 3039.
14. Stevens, C. L.; Glinski, R. P.; Gutowski, G. E.; Dickerson, J. P. *Tetrahedron Lett.* **1967**, 649.
15. Silvertein, R. M,; Bassler, C. G,; Morrill, C. T. Spectrometric identification of organic compounds, 3rd edition, 223.
16. O' Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, S. Y. L.; Spada, R. E.; Stevenson, T. M.; Dieck.,*J. Org. Chem,* **1983**, *48*, 807.

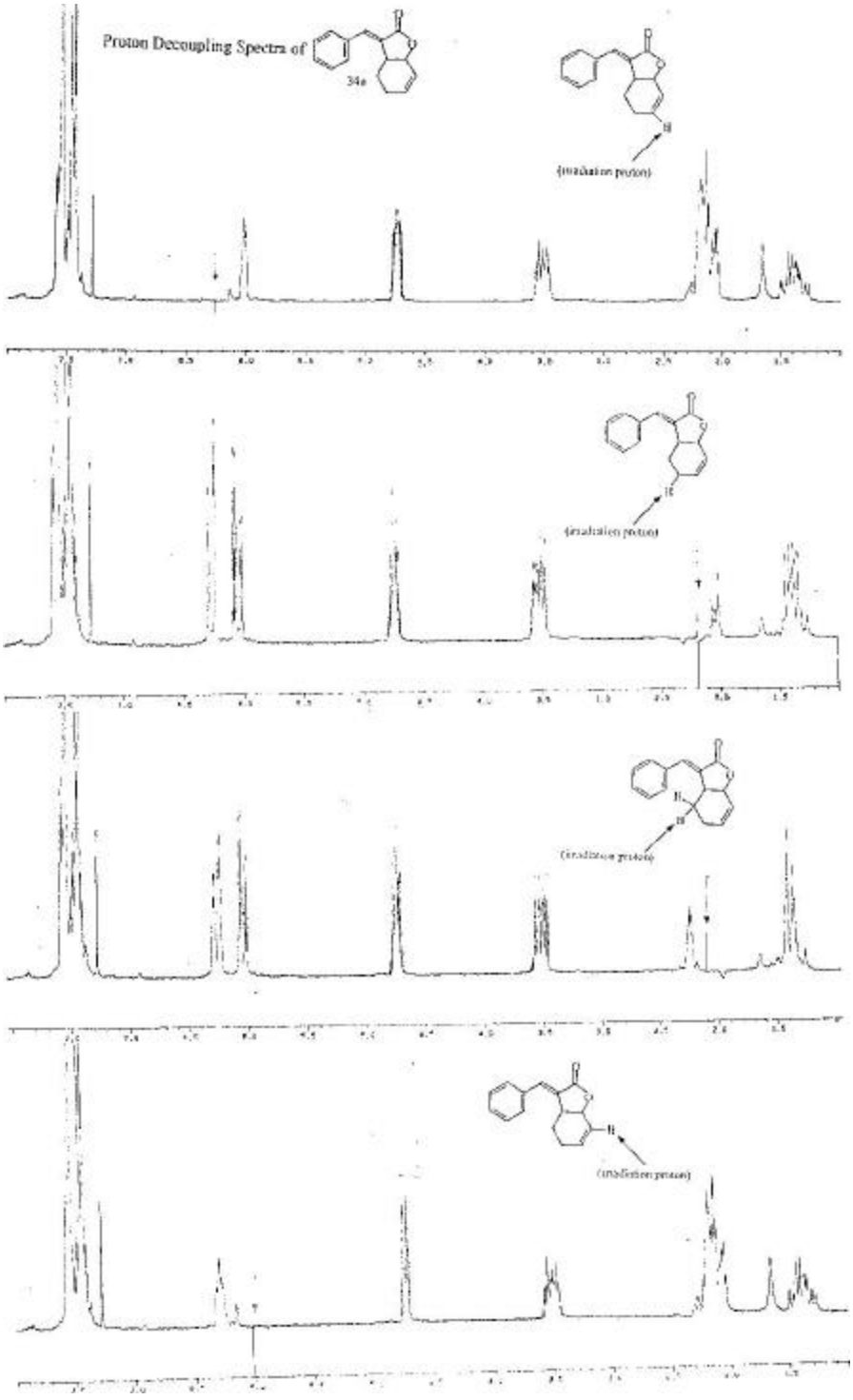
17. Wahab Khan, M.; Nitya Kundu., *Synlett*, **1997**, 1435.

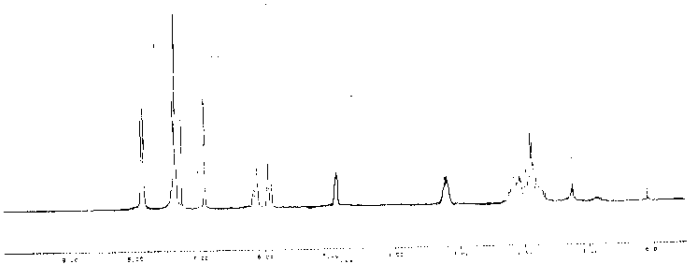
18. Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem*. **1998**, *63*, 7652.

19. Larock. R. C.; Roesch. K. R. *J. Org. Chem*., **1998**, *63*, 5306.

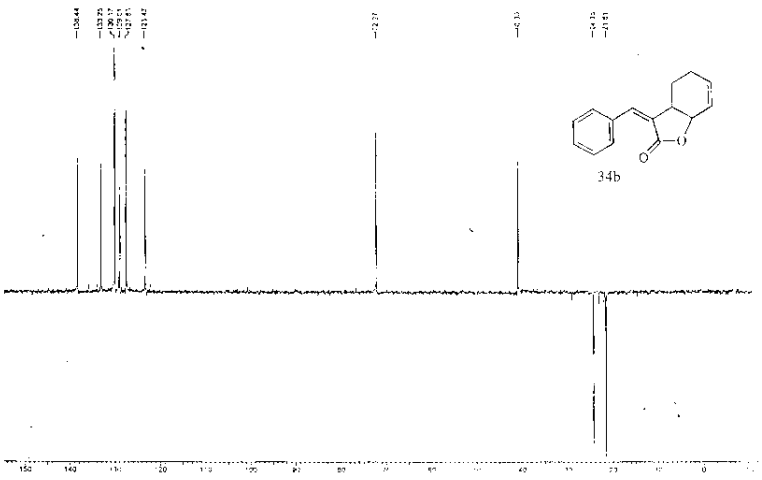
20. Anne-Sotie C.; Torbjorn F. *Synthesis*, **1989**, 414.




Proton Decoupling Spectra of
34a

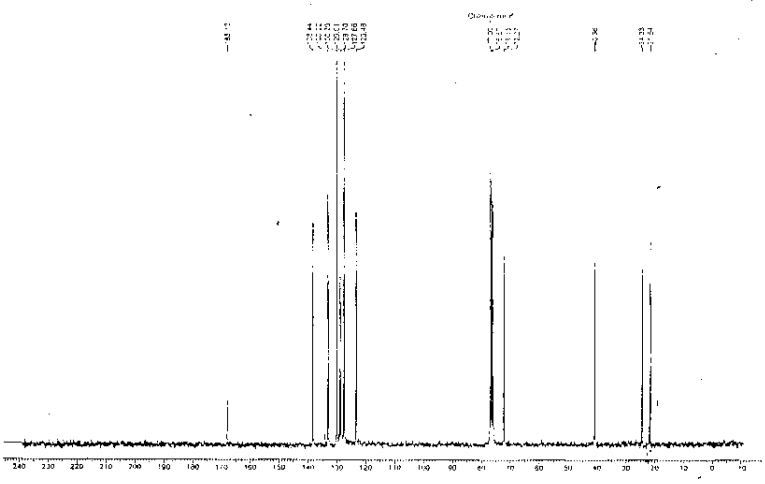


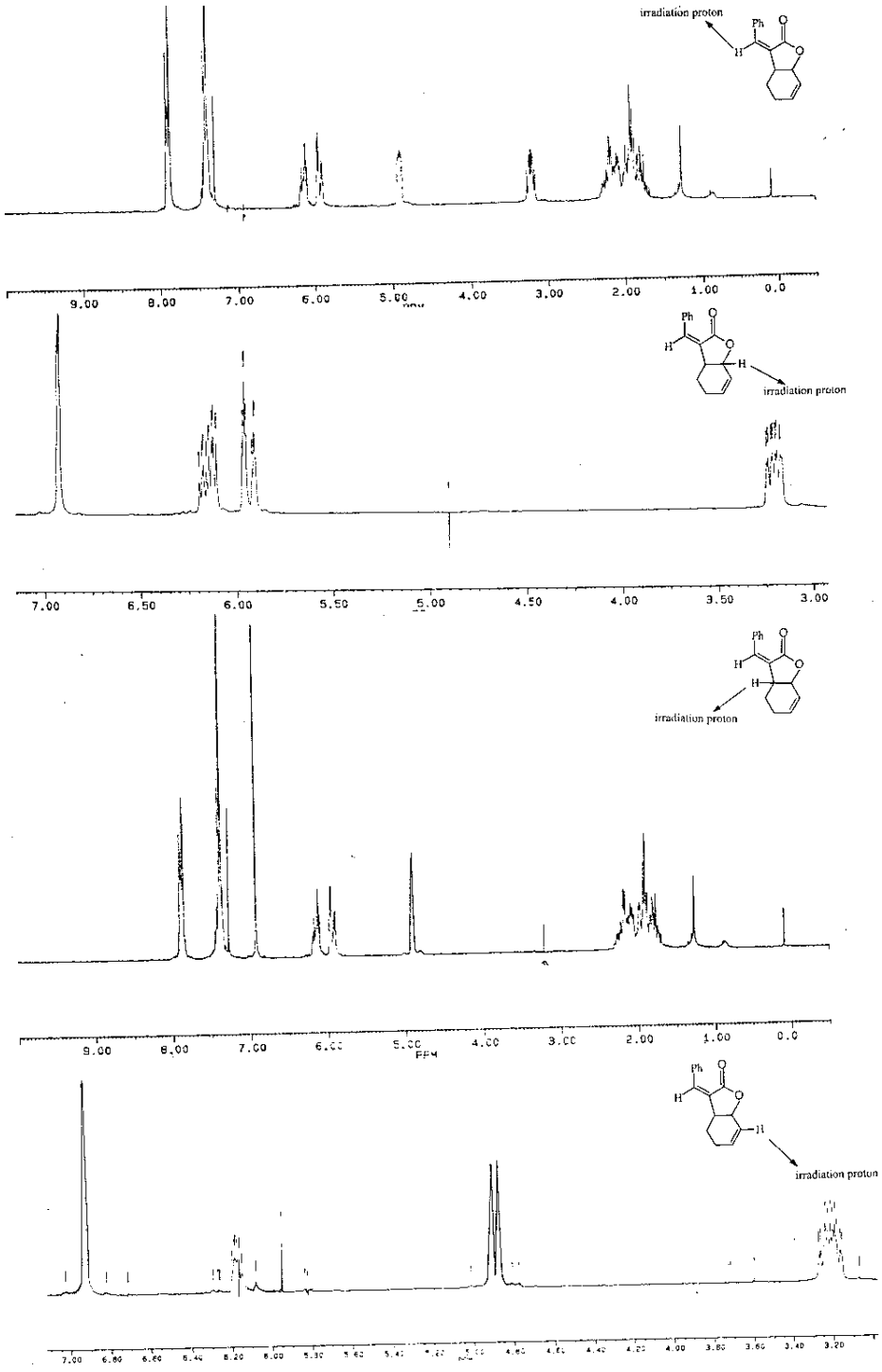
Z isomer dept

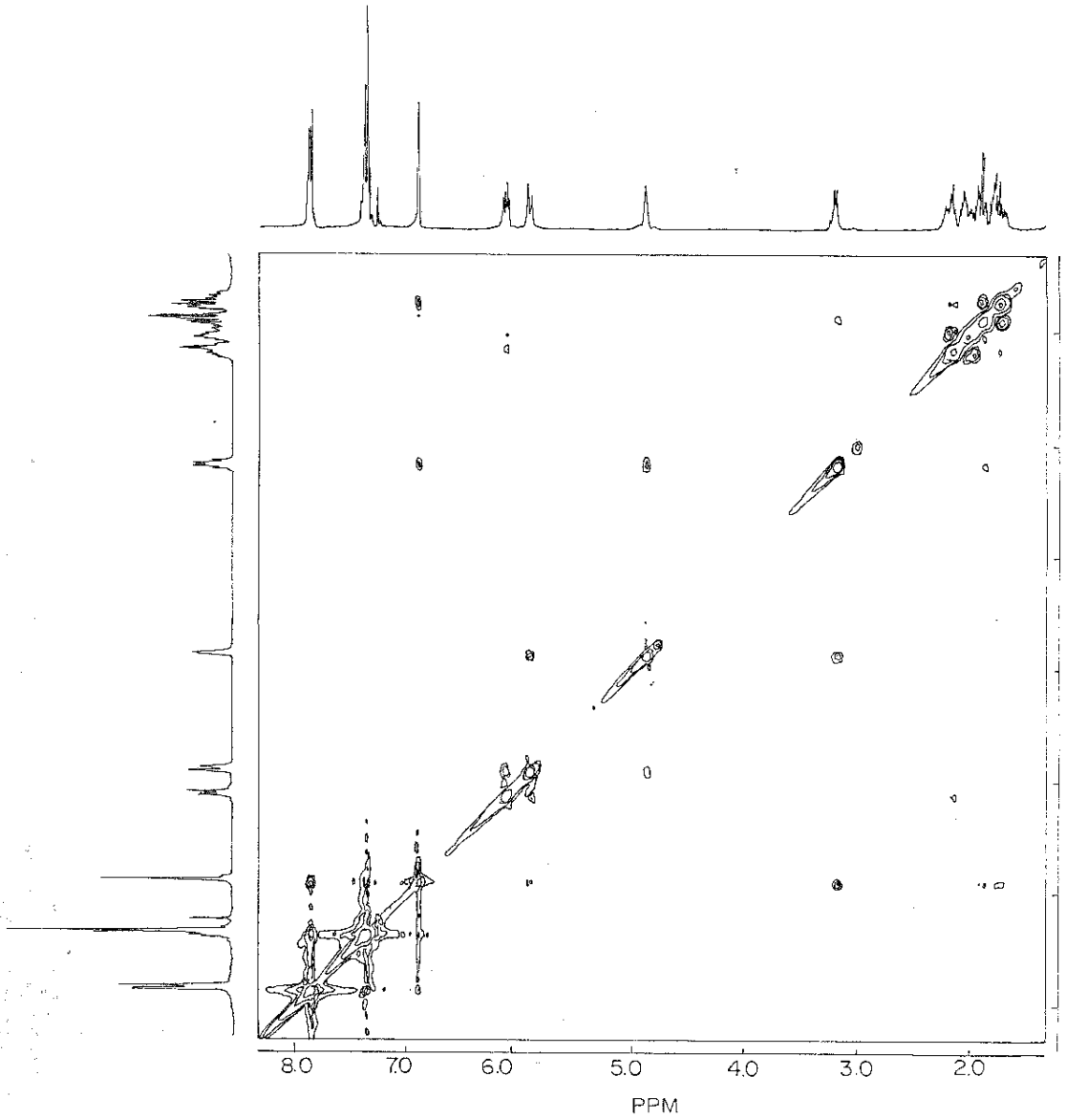


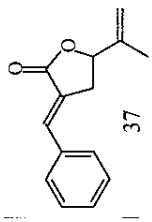
34b

chd + bromo acid, Z isomer

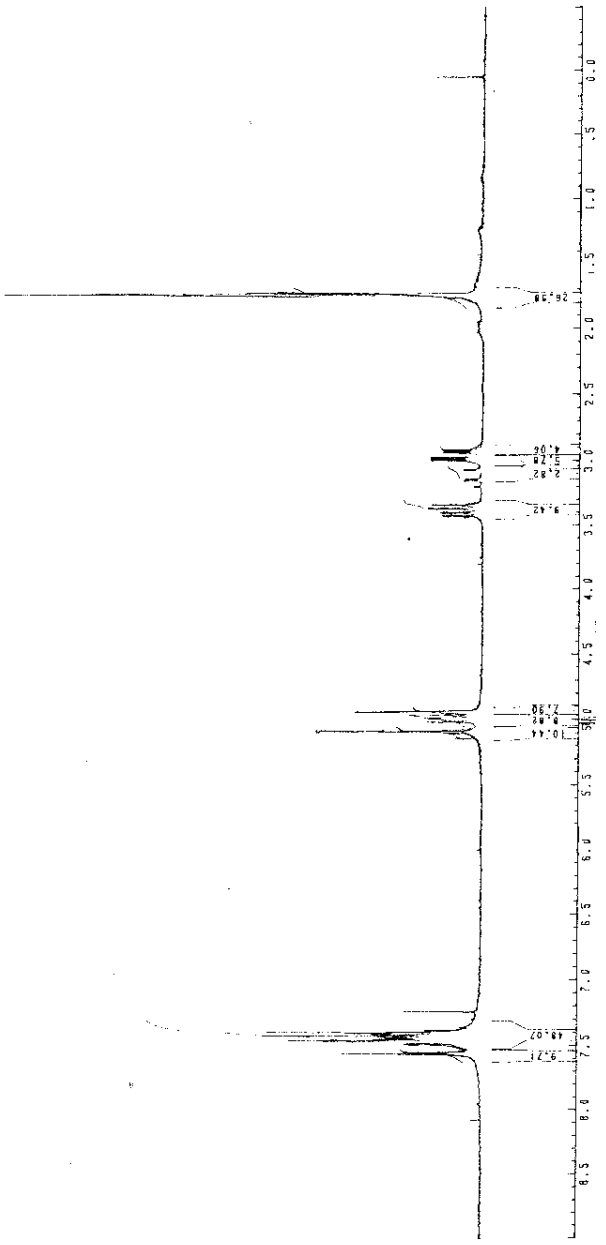


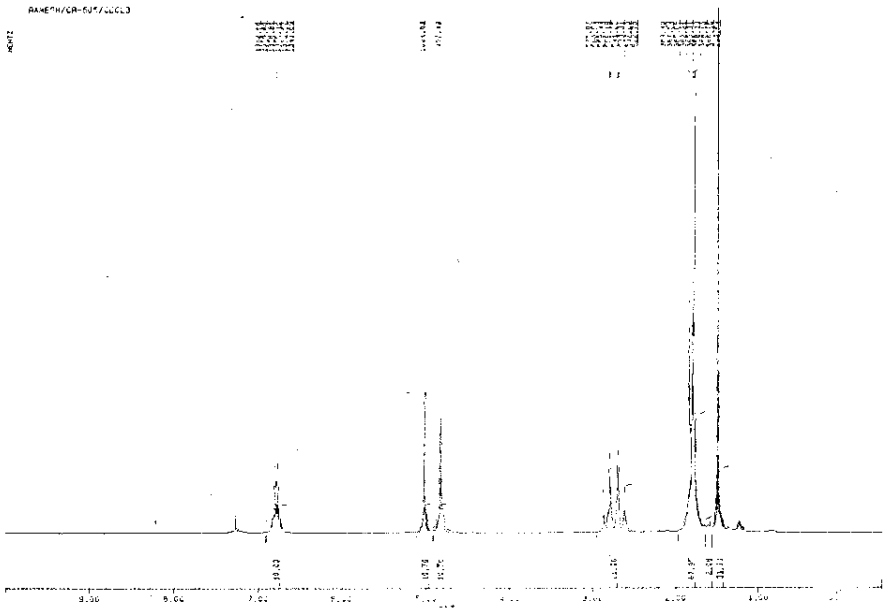

irradiation proton
Ph
O
H
O
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
irradiation proton
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
irradiation proton
PPM
irradiation proton

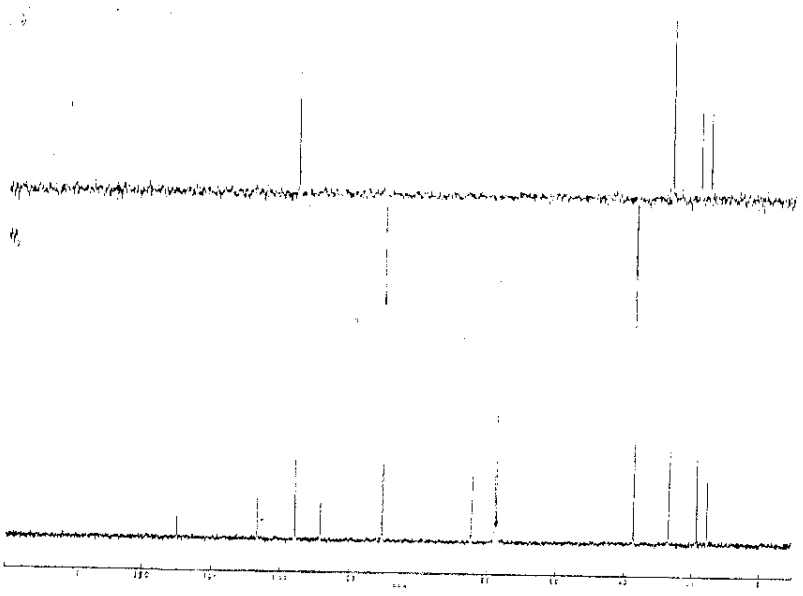

8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM

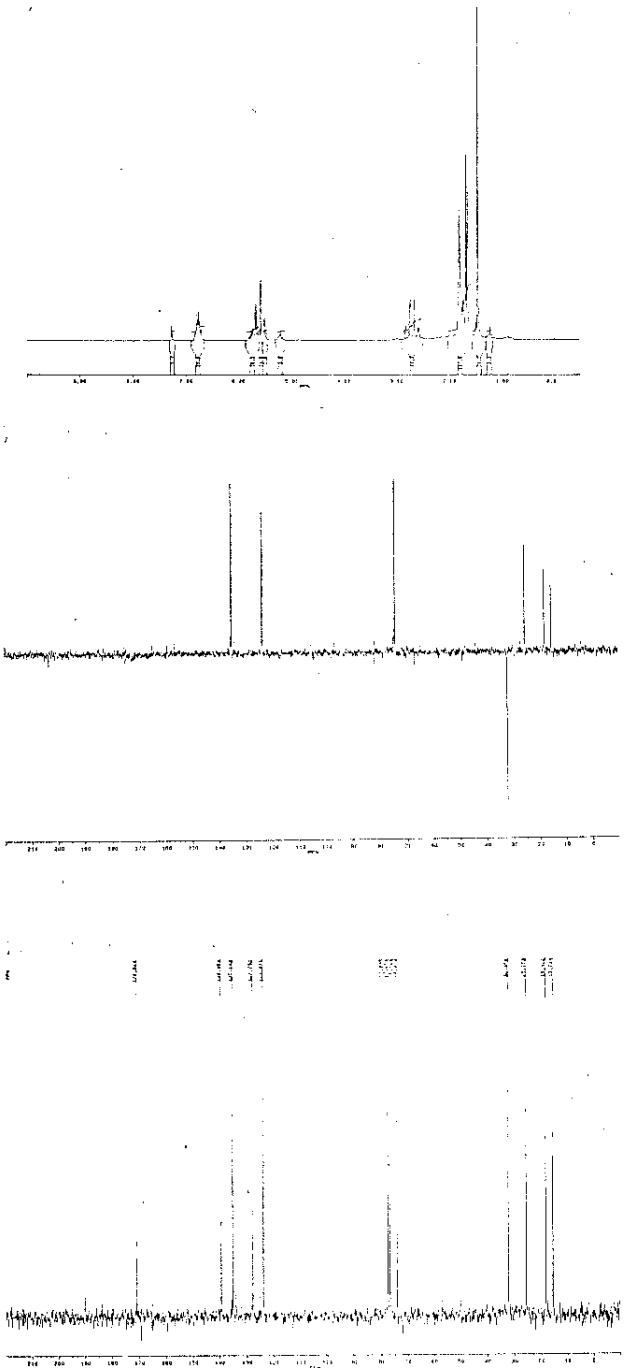


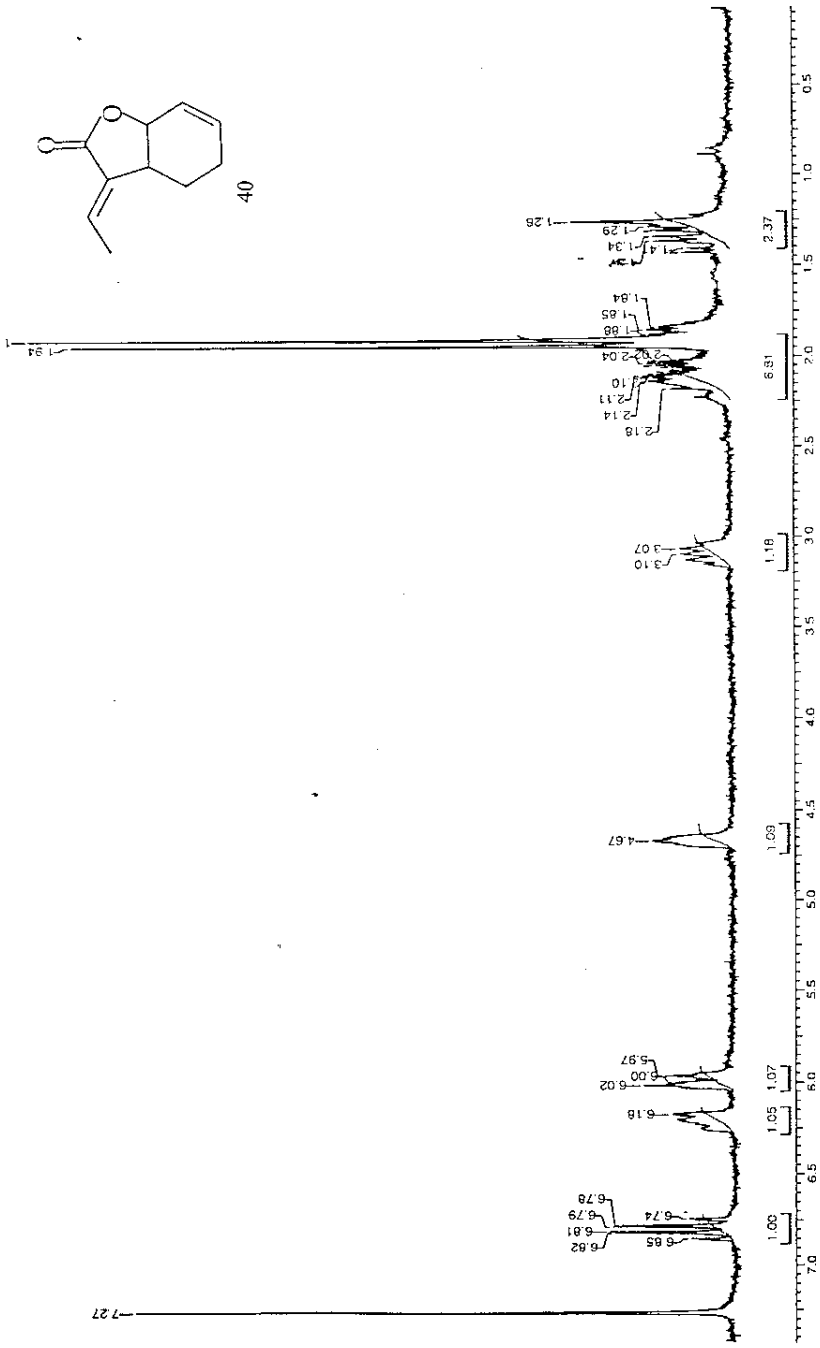
37

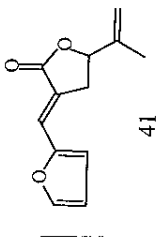




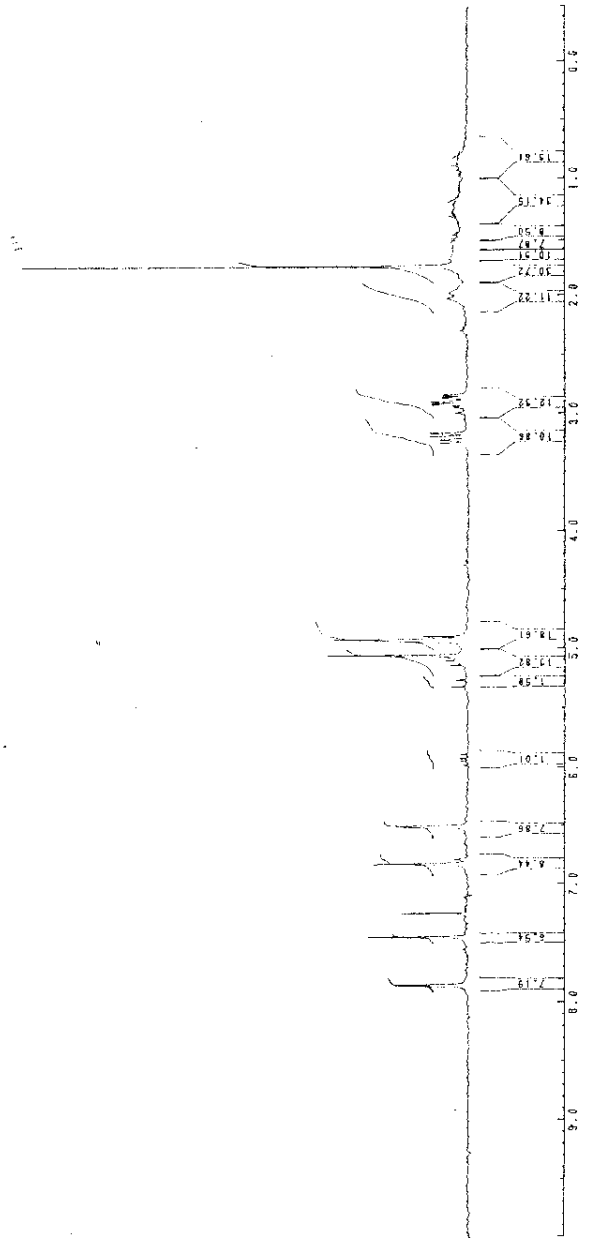


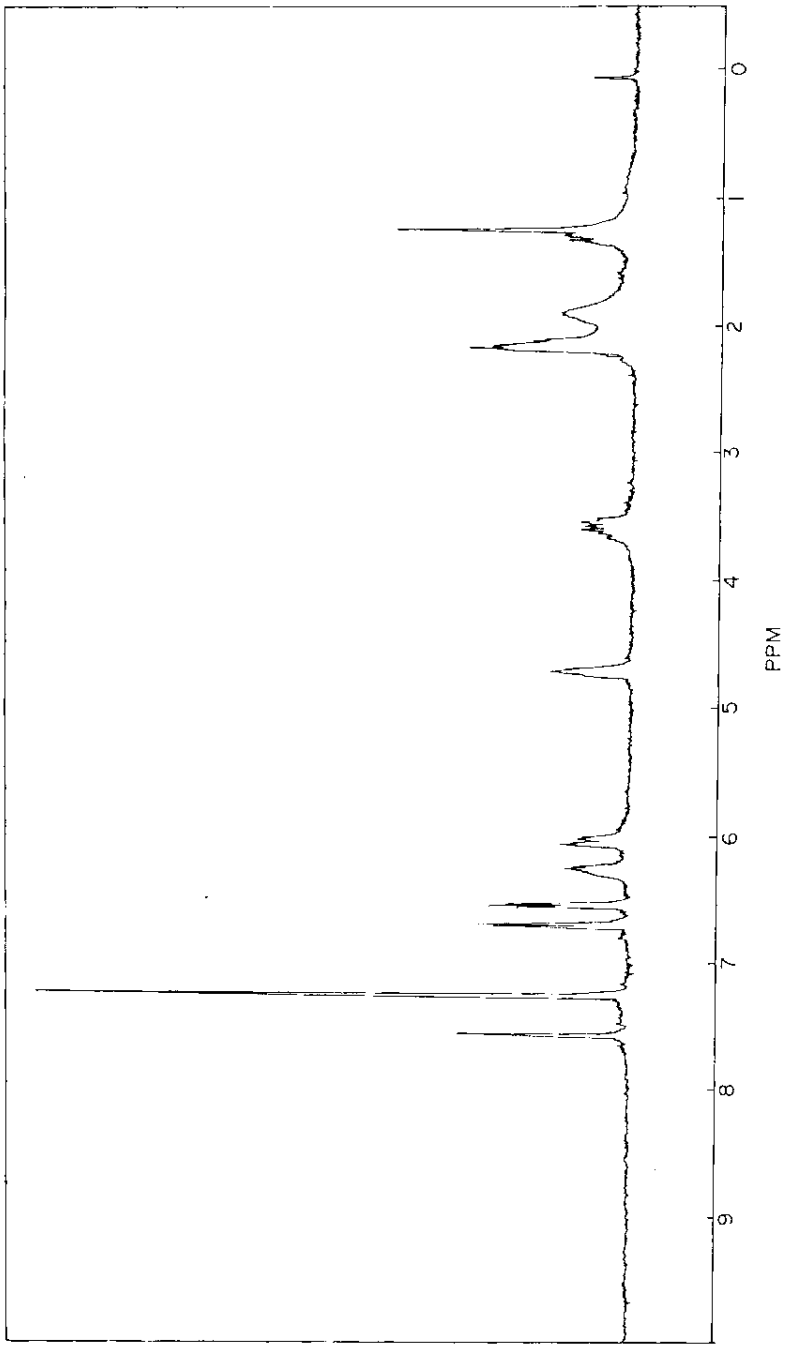


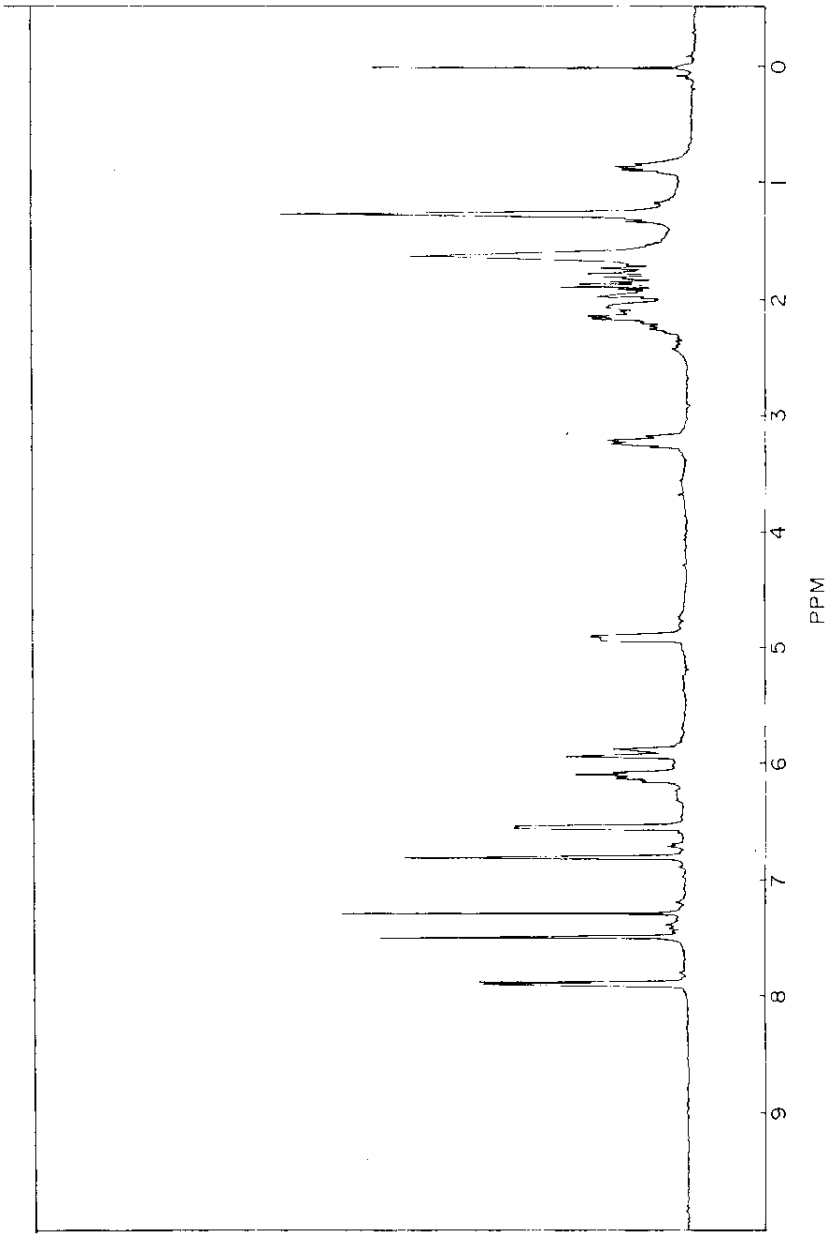

40
7.27
6.85
6.82
6.81
6.79
6.78
6.74
6.18
6.02
6.00
5.97
4.67
3.10
3.07
2.18
2.14
2.11
2.10
2.04
2.02
1.94
1.88
1.85
1.84
1.34
1.29
1.26
1.00
1.05
1.07
1.09
1.18
8.31
2.37



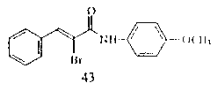
41



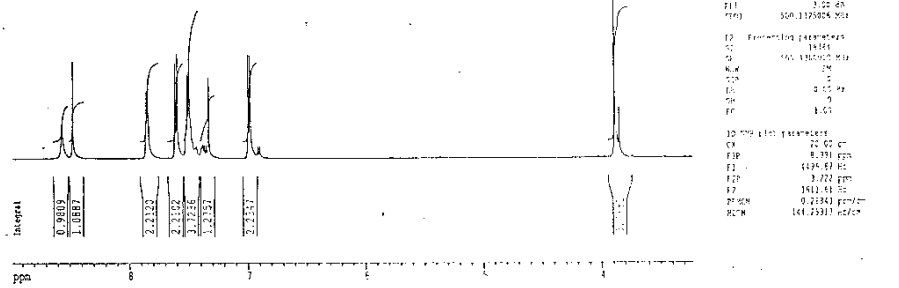

0
1
2
3
4
5
6
7
8
9
PPM

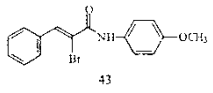

0
1
2
3
4
5
6
7
8
9
PPM

^{1}H NMR and NOE irradiation spectra of

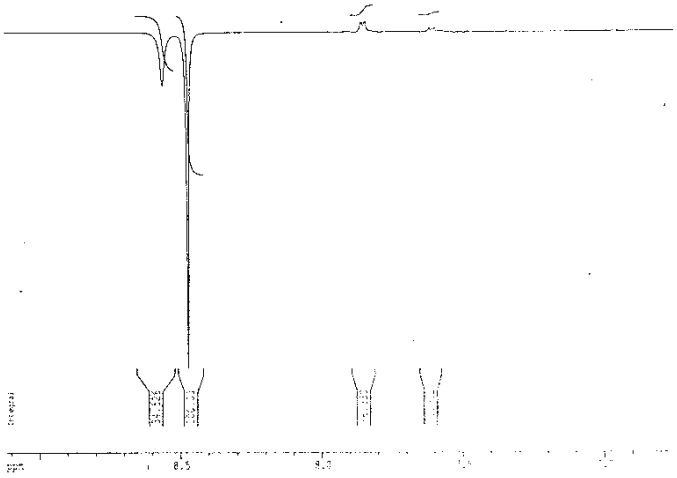


43

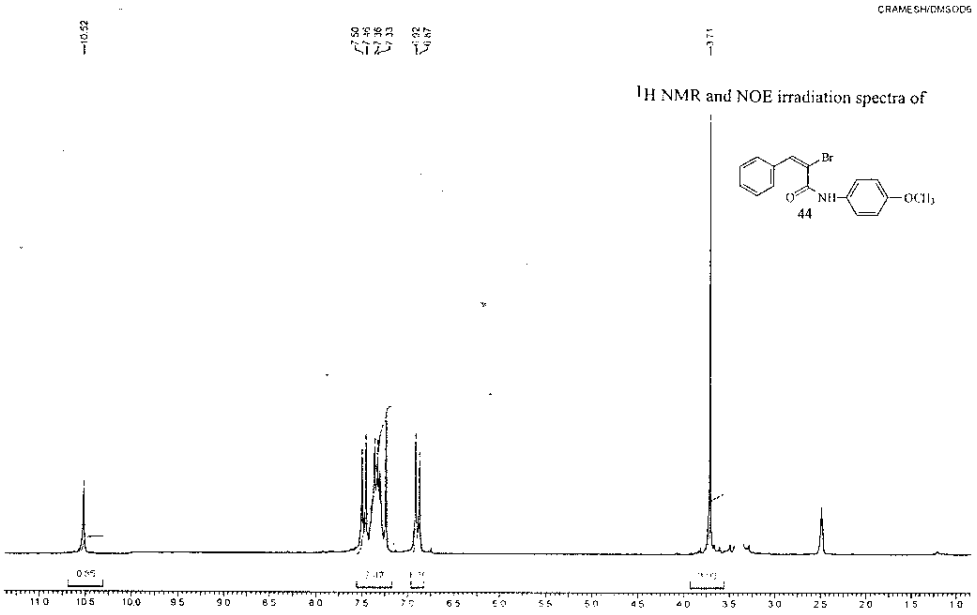


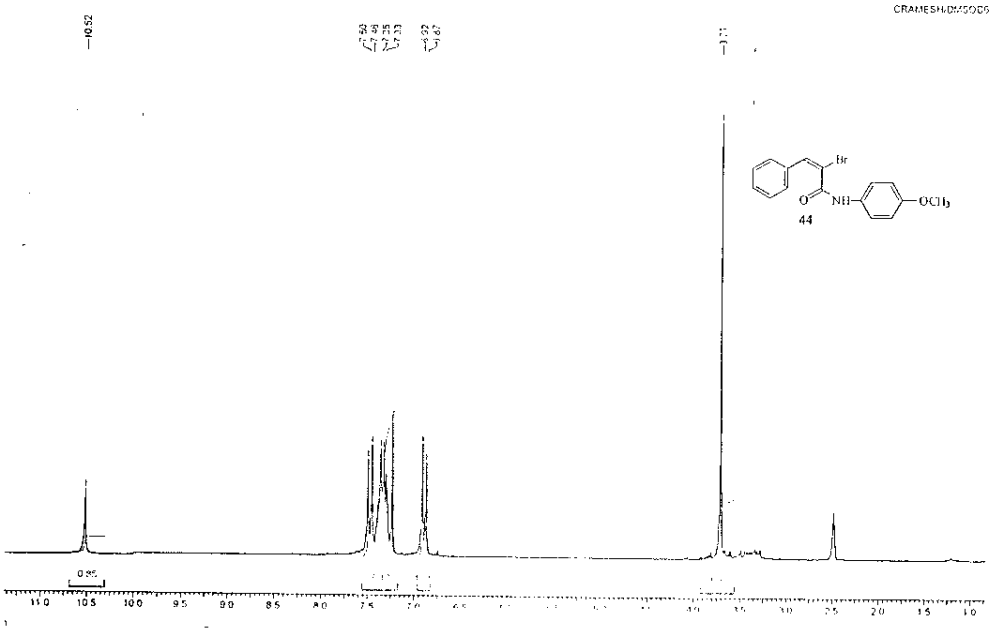


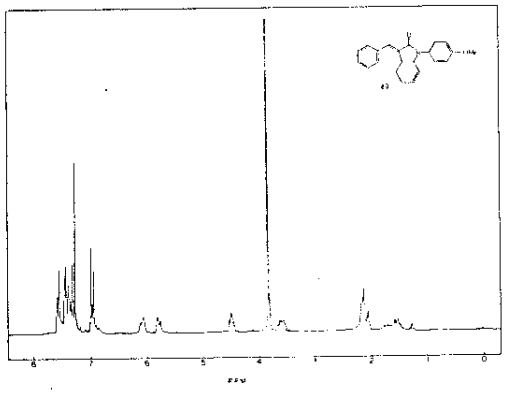
43



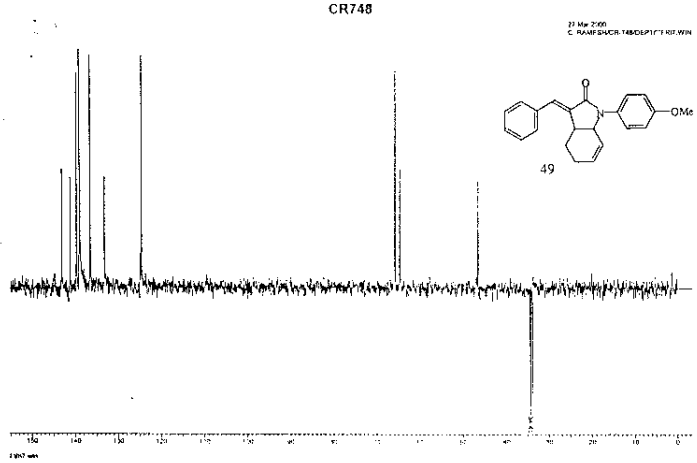
^{1}H NMR and NOE irradiation spectra of





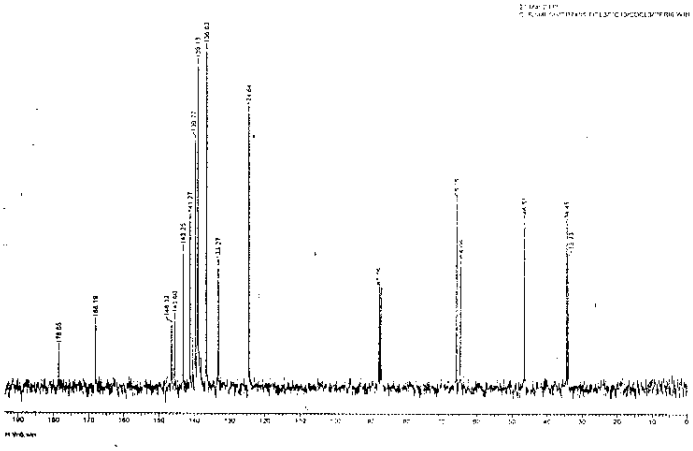


CR748

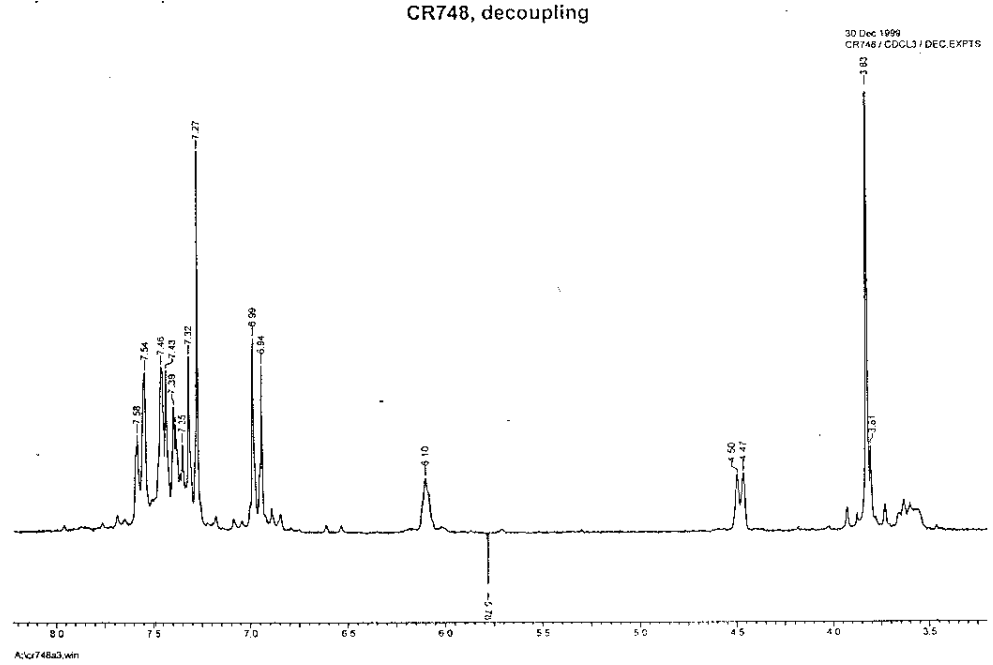


49

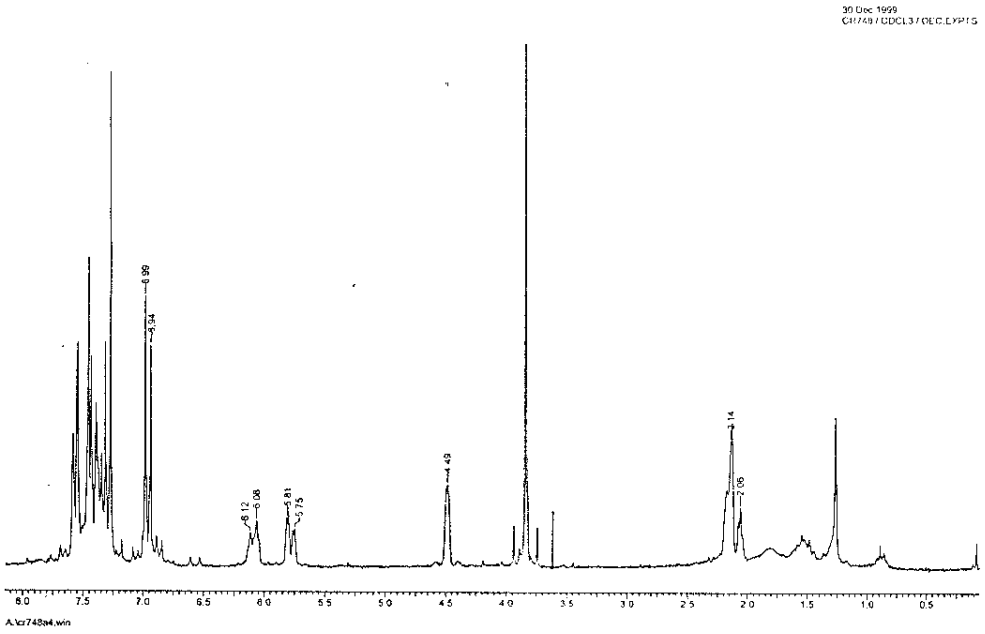
CR748

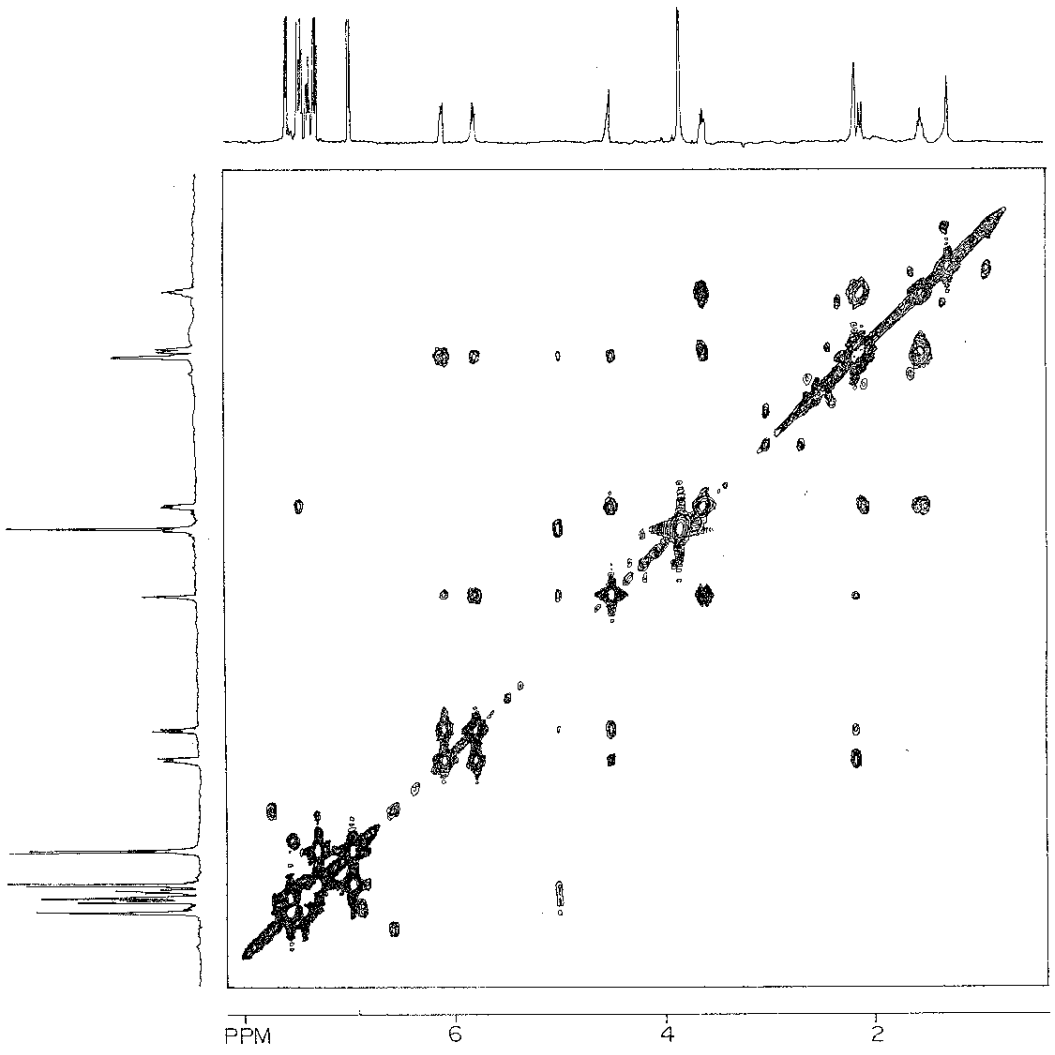


CR748, decoupling



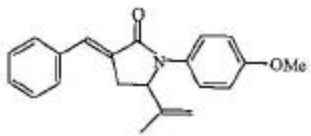
CR748, decoupling




PPM
6
4
2

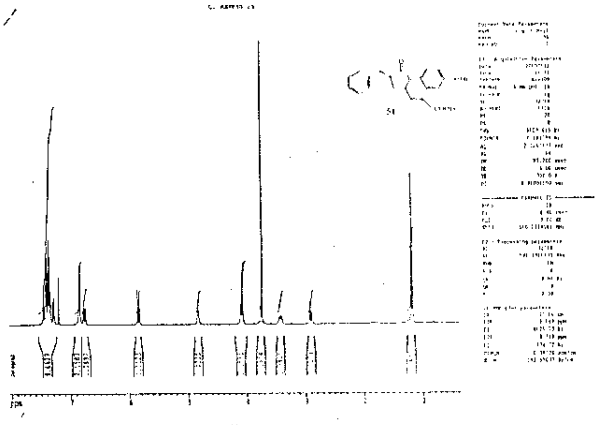
Acquisition Time (sec)	2.0480	Comment	CRAMESH/CDCL3/CR802		Date	25/01/00 15:00:07	
Frequency (MHz)	200.13	Nucleus	1H	Number of Transients 512	Original Points Count	8192	Points Count 8192
Sweep Width (Hz)	4000.00	Temperature (grad C)	24.000				

^{1}H NMR and ^{13}C NMR Spectra of

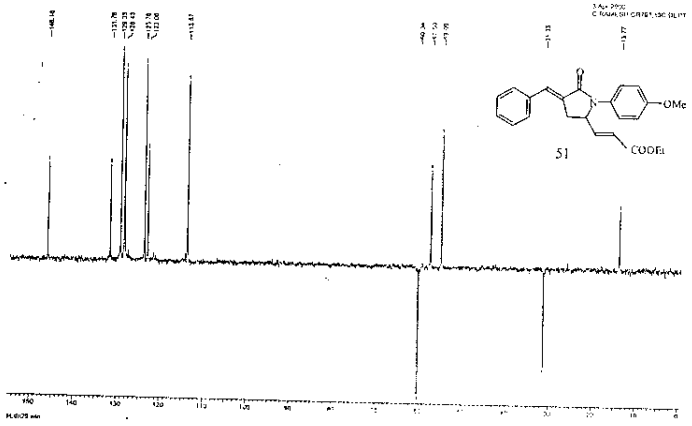


50

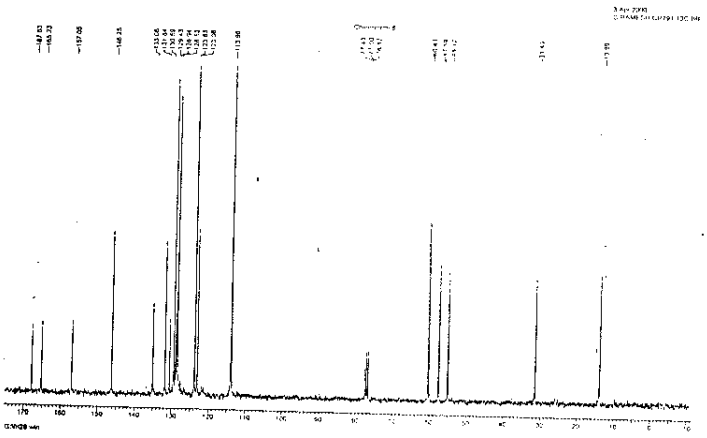
129

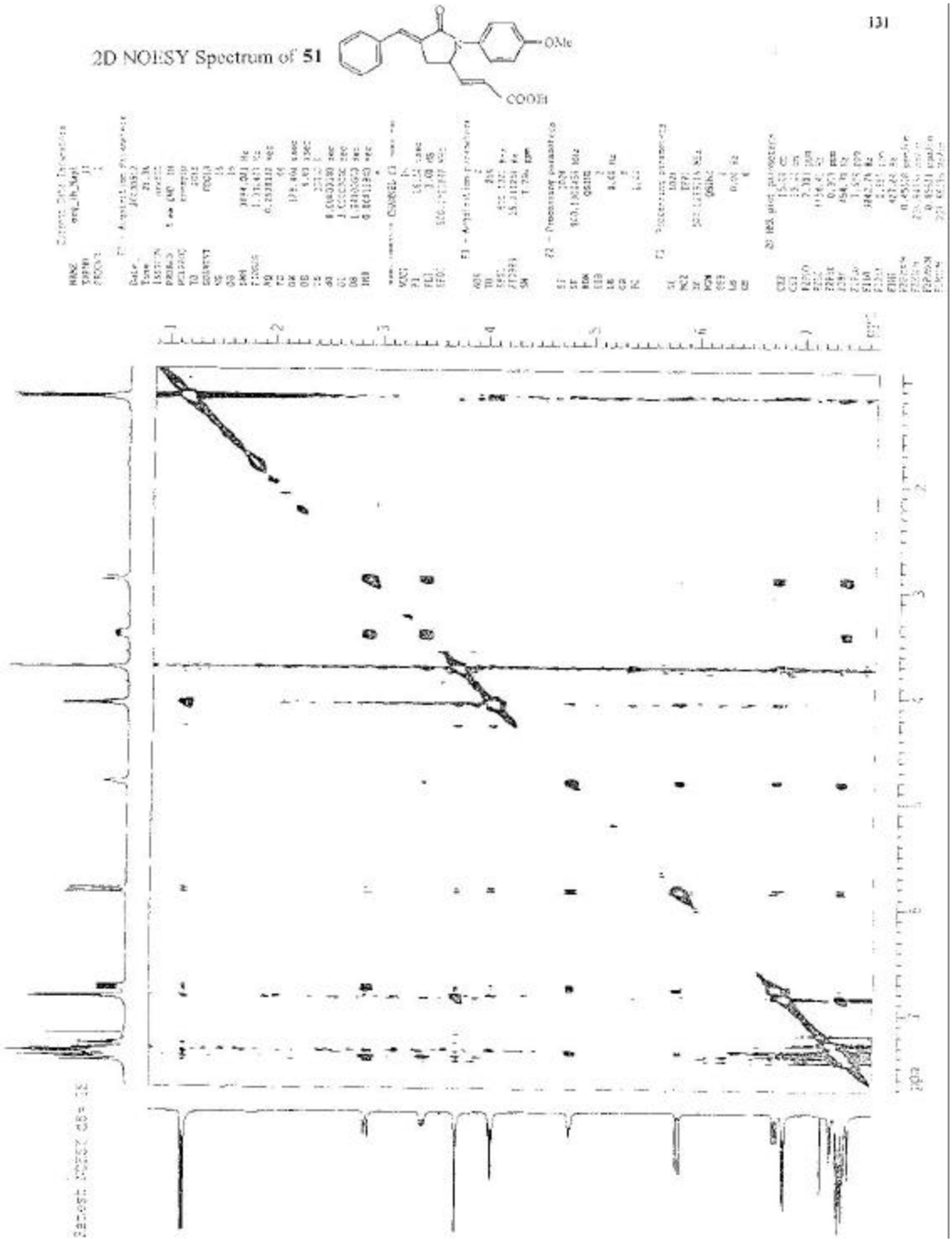


CR791 DEPT

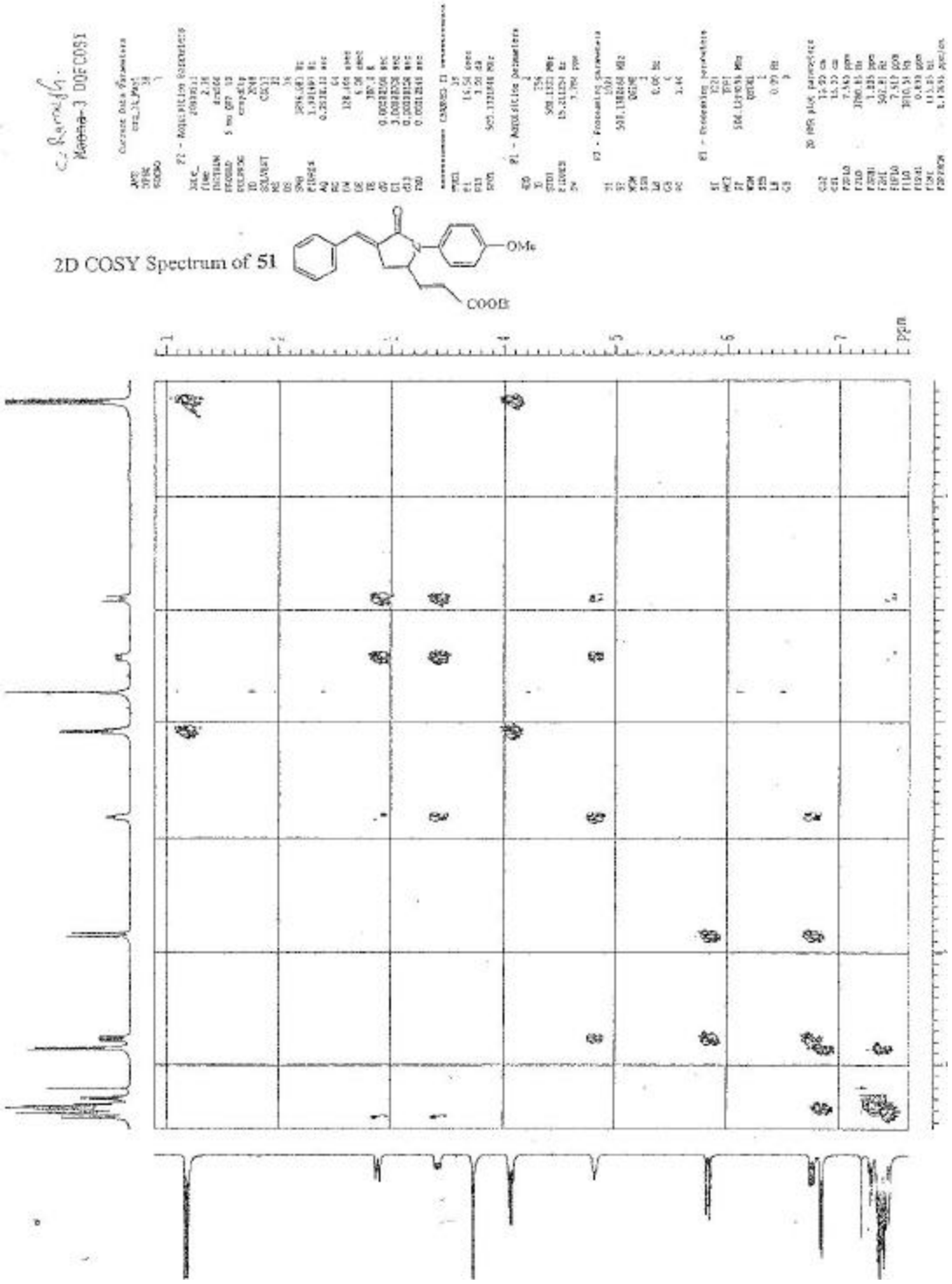


CR791




2D NOESY Spectrum of 51
OMe
COOH
131

132



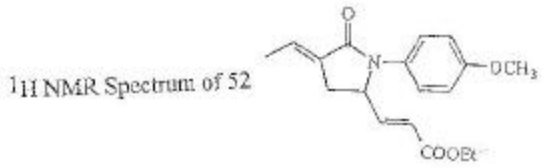
2D COSY Spectrum of **51**

CR797

24 Jan 2000
S. IYER/CR797F2/CDCL3/1 FR19.WIN

Acquisition Time (sec)	1.3648	Comment	S. IYER/CR797F2/CDCL3/1 FR19.WIN	Date	00/00/00 00:00:00		
Frequency (MHz)	300.13	Nucleus	1H	Number of Transients	40	Original Points Count	8192	Points Count	8192
Sweep Width (Hz)	5002.40	Temperature (grad C)	15.000				

^{1}H NMR Spectrum of 52



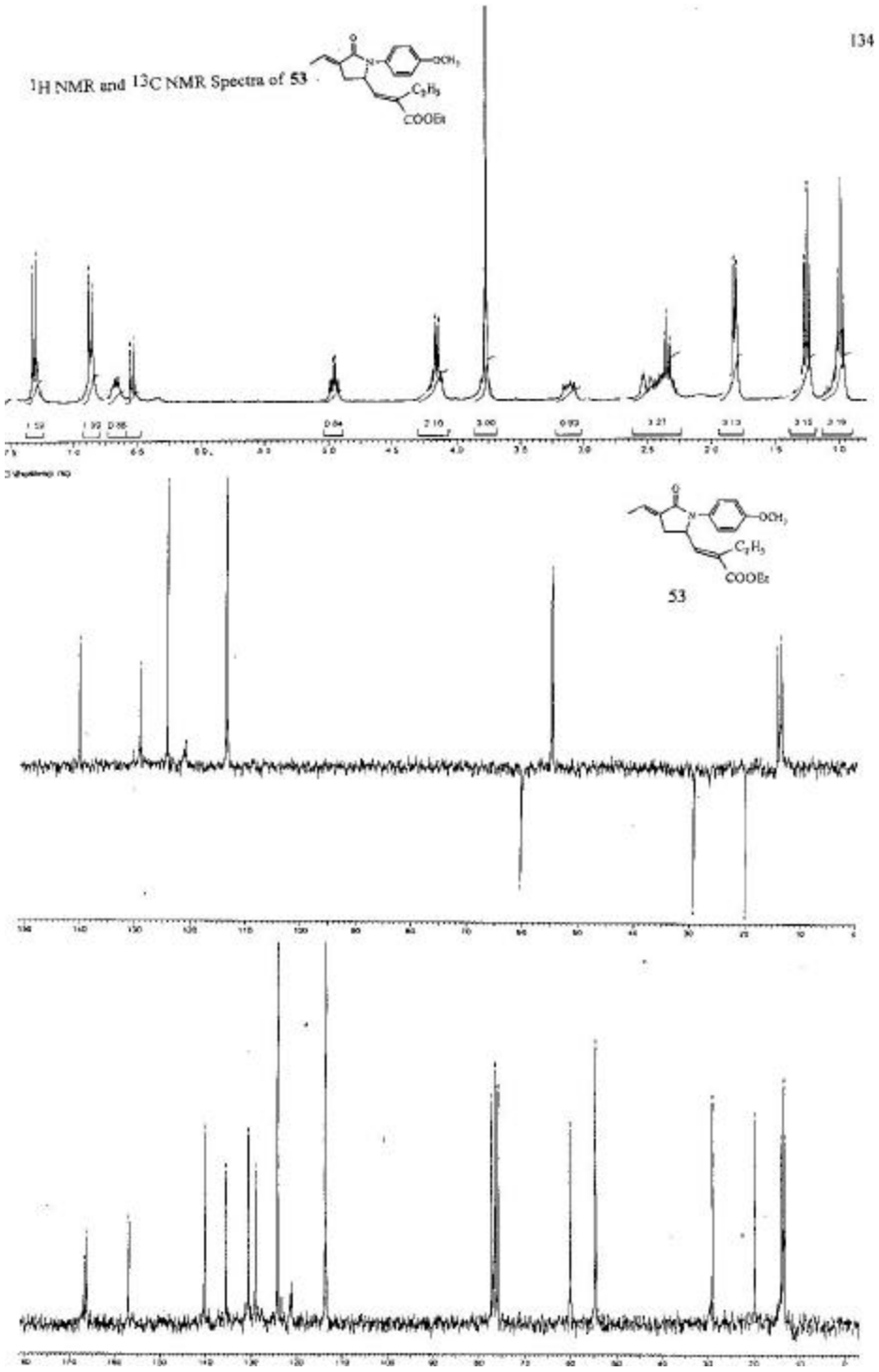
No.	(ppm)	Height	No.	(ppm)	Height
1	0.00	0.033	10	4.15	0.171
2	1.22	0.249	11	4.18	0.060
3	1.25	0.352	12	5.84	0.097
4	1.27	0.218	13	5.90	0.089
5	1.81	0.210	14	6.87	0.149
6	1.83	0.175	15	6.90	0.252
7	3.78	1.000	16	7.37	0.261
8	4.10	0.067	17	7.40	0.159
9	4.13	0.189			

133

A:\fr9.win

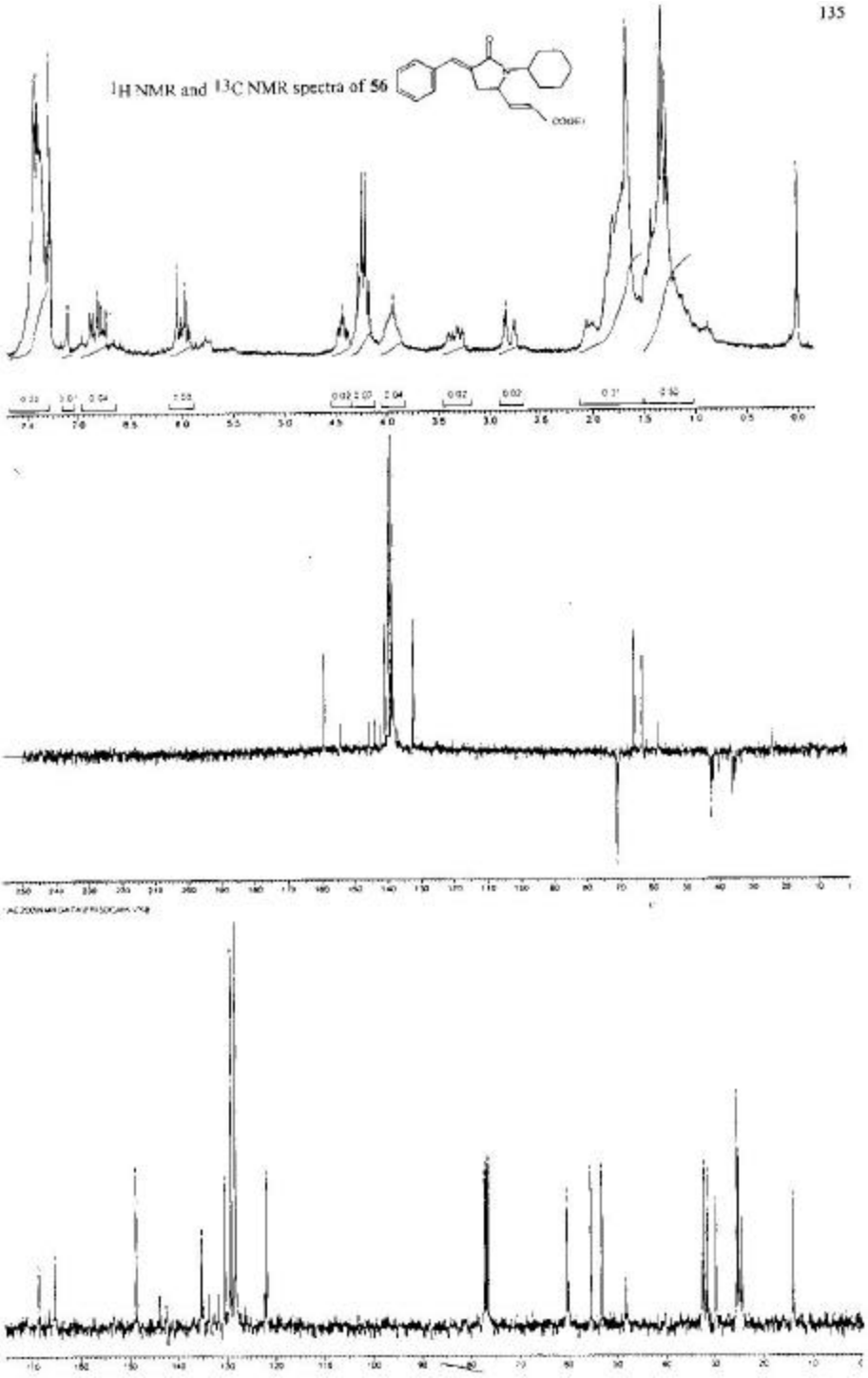
134

^{1}H NMR and ^{13}C NMR Spectra of **53**



53

^{1}H NMR and ^{13}C NMR spectra of **56**



Chapter 4

This chapter is divided into two sections.

Introduction and Background

The carbon-hetero bond formation reactions catalyzed by transition metal complexes has been a very attractive reaction to be studied in last two decades, especially, the formation of indoles, aziridines and other heterocycles which are important part of most of the biologically interesting natural products. The indole nucleus is prevalent in a wide variety of biologically active, naturally occurring compounds and numerous approaches to its synthesis have been reported including many employing transition metals[1] particularly palladium[2]. Transition metal catalyzed nitrogen atom transfer reactions are a fascinating way to construct novel hete rocyclic compounds. These reactions are not established much and there are a few reports on the nitrogen atom transfer reactions mediated by transition metal complexes described below in detail.

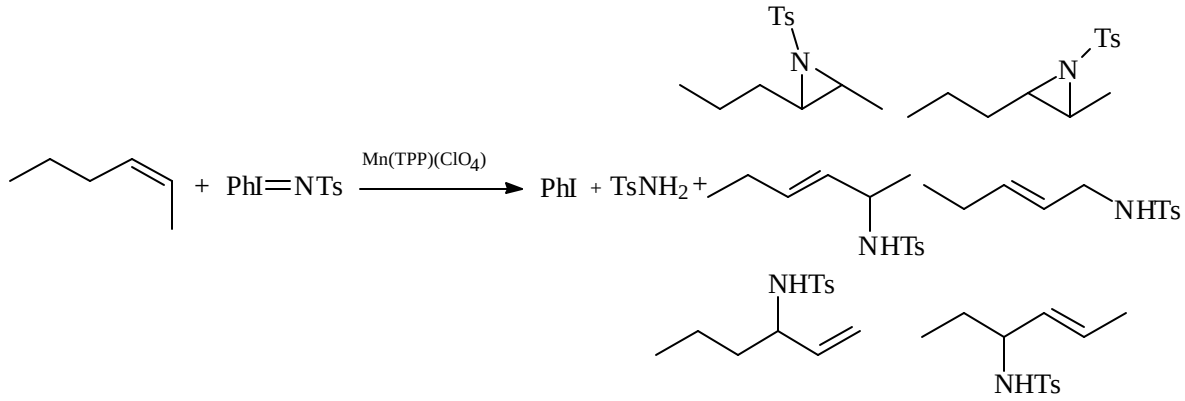
Kahn *et al.*[3] reported the copper catalyzed decomposition of benzenesulfonyl azide in hydroxylic medium to form aziridines. Subsequently Mansuy et al. studied the iron and manganese porphyrin catalyzed aziridination of alkenes by tosyl and acyl-iminoiodobenzene (scheme -1).[4]

Scheme -1

catalyst : Fe(TPP)Cl, Mn(TPP)Cl

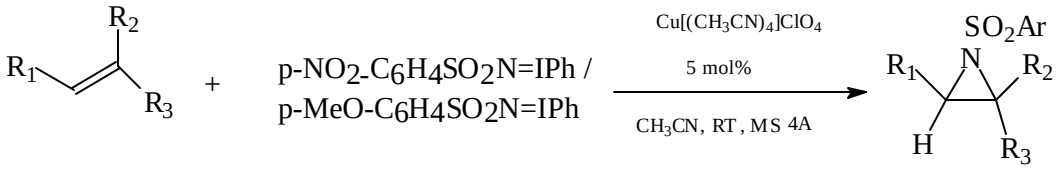
Manganese`porphyrin complexes were found to be much better catalyst than iron porphyrins for allylic *N*-tosylamination of alkenes by tosyliminoiodobenzene (scheme-2).[5]

Scheme -2



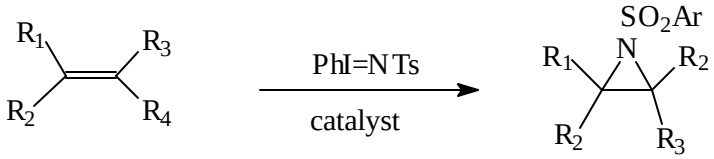
Andersson et al. studied the preparation of various nitrogen precursors and evaluation of their utility for the copper catalyzed aziridination of olefins. The best results were obtained with *p*-nitrotosyliminoiodobenzene and *p*-methoxytosyliminoiodobenzene (scheme-3).[6]

Scheme -3

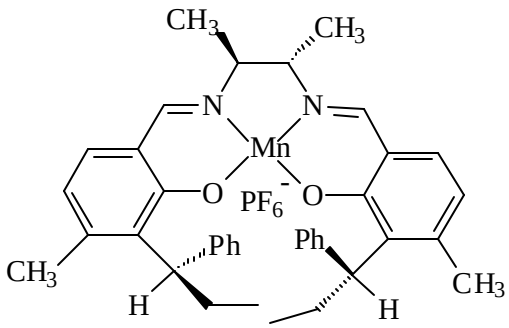


Highly enantioselective aziridination of styrene derivative catalyzed by newly designed manganese (III) salen complex was reported by Nishikori et al. (scheme-4)[7] and also various chiral metal salen complexes were utilized for asymmetric aziridination and epoxidation of alkenes. [8]

Scheme -4



catalyst :



Ph = 4-t-BuC$_6$H$_4$

Section 1. Transition metal catalyzed activation of aryl azides

OBJECTIVE

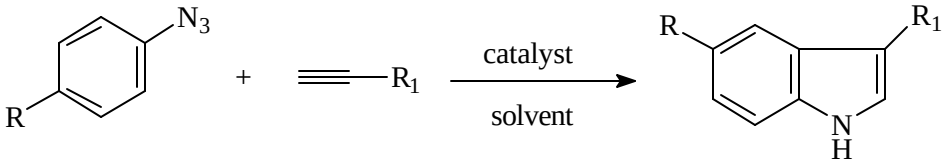
Our objective was generating metalnitrenes from simple starting materials such as aryl azides and their application in the aromatic C-H activation leading to develop a methodology towards the synthesis of indoles by reacting with alkynes. Our aim was also to apply this metalnitrene formation process in the synthesis of aziridines and other heterocyclic compounds by reaction with olefins.

PRESENT WORK

1 a. Reactions of aryl azides with alkynes.

The various substituted aryl and tosyl azides were prepared according to the literature methods. The reactions of aryl and tosyl azides with alkynes in the presence of various transition metal catalysts $Ni[P(OPh)_3]_4$, $MoCO_6$, $NiCl_2(PPh_3)_2$/Zn, $FeCO_5$ and reduced copper were studied (scheme-5).

Scheme-5



Catalyst : $Ni[P(OPh)_3]_4$, $Mo(CO)_6$, $NiCl_2(PPh_3)_2$, $Fe(CO)_5$, Cu(reduced)

Solvent : Dioxane, CH_3CN, Toluene.

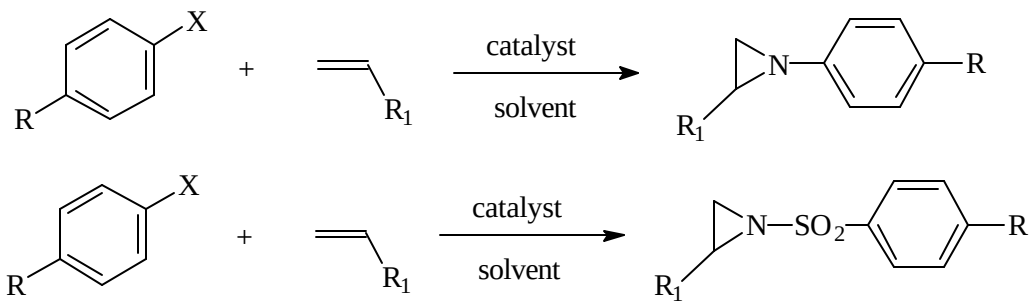
R = OCH_3, NO_2, Cl, CH_3.

R_1 = C_4H_9, Ph

1 b. Reactions of aryl azides and chloramines-T with alkenes.

The transition metal catalyzed reactions of various aryl, tosyl azides and chloramine-T with alkenes in the presence of $Ni[P(OPh)_3]_4$, $Fe(CO)_5$, $Mo(CO)_6$, $W(CO)_6$, $PdCl_2(PPh_3)_2$, $Rh(PPh_3)_3Cl$, $RuCl_2(PPh_3)_3$ and Vaska's complex were studied to form various substituted aziridines (scheme-6).

Scheme-6



Catalyst : CuCl, $Ni[P(OPh)_3]_4$, $Mo(CO)_6$, W(CO)6, $PdCl_2(PPh_3)_2$, $IrCl(CO)(PPh_3)$

Solvent : Dioxane, CH_3CN, Toluene.

R = OCH_3, NO_2, Cl, CH_3.

R_1 = COOEt, Ph.

X = N_3, SO_2N_3, SO_2NNaCl

RESULTS AND DISCUSSION

The aryl azides were prepared according to the literature methods and characterized by IR and ^{1}H NMR spectroscopic studies. The reactions of aryl azide with alkynes in the presence of various transition metal catalysts, CuCl, Ni(0), $Mo(CO)_6$, $W(CO)_6$, $PdCl_2(PPh_3)_2$, $IrCl(CO)(PPh_3)_2$ failed to give the expected product. Instead, the known 1, 3-dipolar cycloaddition product was formed under the various conditions. The 1, 3 dipolar cycloaddition products (two regioisomers) formed were characterized by spectroscopic data. The ^{1}H NMR spectrum (Figure-1) of the product (one isomer) obtained from the reaction of *p*-methoxyphenyl azide with 1-hexyne displayed a doublet and a singlet overlapping at δ 7.6 corresponding to two aromatic protons of A_2B_2 type and olefinic proton of triazole ring. A doublet at δ 6.95 indicated the presence of other two aromatic protons of A_2B_2 type. A singlet at δ 3.85 is due to the methoxy protons and a triplet at δ 2.75 corresponding to allylic methylene protons of alkyl side chain. Two multiplets appeared at δ 1.7 - 1.6 and δ 1.45 - 1.35 indicating the presence of homoallylic proton and methylenic protons ($-CH_2-C\underline{H}_2-C\underline{H}_2-CH_3$) respectively and a triplet at δ 0.95 assigned for $C\underline{H}_3$. The mass spectrum displayed a molecular ion peak at m/z 231. The above data confirmed the structure of 1, 3-dipolar cycloaddition product. Similarly the other isomer also was characterized by the respective ^{1}H NMR spectrum.

The reaction of chloramine-T, aryl and tosyl azide with olefins (styrene, ethylacrylate and methyl cinnamate) in the presence of various transition metal catalysts, $Ni[P(OPh)_3]_4$, $Mo(CO)_6$, $W(CO)_6$, $PdCl_2(PPh_3)_2$, $RhCl(PPh_3)_3$, $RuCl_2(PPh_3)_3$ failed to give the expected product under different reaction conditions, including solvent (CH_3CN, dioxane, toluene) and temperature (0 - 120 °C). The reaction of chloramine-T with styrene in the presence of $Fe(CO)_5$ afforded the expected product, which was confirmed by the IR, ^{1}H NMR and Mass spectra. The ^{1}H NMR and

^{13}C NMR spectra are shown on page 152. The mass spectrum displayed a molecular ion peak at *m/z* 273. The above data confirmed the structure of the expe cted product **61**.

CONCLUSION

In conclusion, the transition metal catalyzed reactions of aryl azides with alkynes failed to give the expected indole product. Instead the known 1, 3-dipolar cycloaddition product was formed under various modified reaction condition. The reaction of chloramine-T with olefin in presence of $Fe(CO)_5$ afforded the expected aziridine in good yield.

EXPERIMENTAL

Reactions of aryl azides with alkynes

A 25 mL RB flask equipped with magnetic stirring bar and condenser was charged with aryl azide (1 mmol), alkyne (1 mmol) and catalyst (10 mol%) in 5 mL of solvent (CH_3CN, dioxane, toluene). The reaction was allowed to stir at 80-100 °C and the solvent evaporated on rotavapor. The crude product was purified by silica gel column chromatography using pet-ether and ethyl acetate mixture (8:2).

4-(4-Butyl-1H-1,2,3-triazol-1-yl)phenylmethyl ether (59)

Mol. F : $C_{13}H_{17}N_3O$

IR (Nujol) : 3128, 2954, 1542, 1521, 1463, 1028, 831 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.6 (doublet and singlet overlapping , d, *J* = 8.0 Hz, 2H, s, 1H),7.0 (d, *J* = 8.0 Hz, 2H), 3.83 (s, 3H), 2.75 (t, *J* = 7.0 Hz, 2H), 1.7 - 1.65 (m, 2H), 1.45 - 1.35 (m, 2H), 0.95 (t, *J* = 7.0 Hz, 3H).

4-(5-Butyl-1H-1,2,3-triazol-1-yl)phenylmethyl ether (60)

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.58 (s, 1H), 7.3 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2 H), (s, 3H), 2.6 (t, *J* = 7.0 Hz, 2H), 1.6 - 1.45 (m, 2H), 1.4 - 1.25 (m, 2H), 0.85 (t, *J* = 7.0 Hz, 3H).

Mass (*m/z*) : 231 (M^+, 11), 160 (100), 107 (14), 92 (22), 77 (47).

1-(4-Methylphenylsulfonyl)-2-phenyl azirane (61)

M. P : 56 °C

IR (Nujol) : 2938, 2923, 1595, 1428 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.8 (d, *J* = 8.0 Hz, 2H), 7.4-7.2 (m, 7H), 3.75 - 3.70 (m, 1H), 3.0 (d, *J* = 5.0 Hz, 1H), 2.45-2.40 (s , 3H) 2.40 (d, *J* = 4.9 Hz, 1H).

^{13} C NMR (50.32 MHz, $CDCl_3$) : δ 144.49, 134.39, 129.60, 128.39, 128.13, 127.76, 126.40, 40.83, 35.72, 21.42.

Mass (m/z) : 273 (M^+, 1), 184 (79), 155 (91), 118 (20), 104 (14), 91 (100).

Section 2. Reactions of Chloramine -T and Tosyl azide with 1, 6-Dienes.

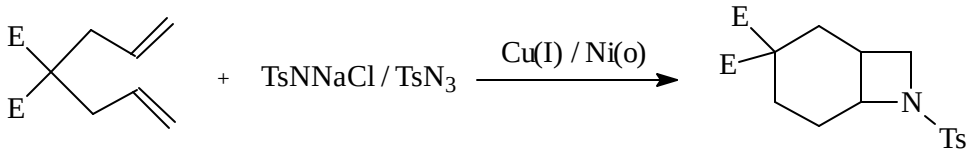
OBJECTIVE

Our aim was to study the transition metal catalyzed formation of metal nitrenes by activating tosyl azides and chloramine-T to develop a methodology towards the synthesis of nitrogen containing heterocyclic compounds. In literature there were some reports on the generation of nitrenes from chloramine-T and transfer of nitrogen atom to olefins to form aziridines. Our strategy was to generate metal nitrenes from easily available simple precursors, tosylazide and chloramine-T and study their application to the synthesis of new and novel heterocycles by reacting with 1, 6 dienes in the presence of various transition metal catalysts.

PRESENT WORK

The various 1, 6-dienes were synthesized according to the literature methods. The reactions of chloramine-T and tosyl azide with 1, 6-dienes have been carried out in the presence of copper (I) chloride and $Ni[P(OPh)_3]_4$ to form heterocyclic compounds (scheme-7).

Scheme -7



E = COOEt

RESULTS AND DISCUSSION

The precursors required for nitrogen atom transfer reactions were synthesized according to the literature. The IR spectrum of product obtained from the reaction of diethyl malonate with allyl bromide showed a sharp peak at 1735 cm^{-1}which indicating the presence of carbonyl group. The ^1H NMR of the product displayed a multiplet at δ 5.75 - 5.60 confirming the internal olefinic proton and a doublet at δ 5.2 assigned for terminal olefinic protons. A doublet appeared at δ 2.6 is due to the presence of allylic methylene protons. A quartet at δ 4.2 and a triplet at δ 1.3 are attributed to $OC\underline{H}_2$ and $C\underline{H}_3$ respectively. The mass spectrum showed a molecular ion peak at (*m/z*) 240. The above spectroscopic data confirmed the structure of the product, diethyl 2, 2-diallylmalonate. Similarly, the product of the reaction between the ethyl cyano acetate and allyl bromide was also characterized by IR, ^1H NMR and Mass spectra. The reaction of diethyl 2, 2-diallylmalonate with chloramine-T in the presence of copper (I) chloride afforded a cyclised product. The IR spectrum of the product showed a sharp prominent peak at 1727 cm^{-1} indicating the presence of carbonyl group. The ^1H NMR spectrum (page no. 153) gave a doublet at 7.65 for aromatic protons (2H) of A_2B_2 type and a doublet at 7.35 assigned for other two aromatic protons of A_2B_2 pattern. A quartet appeared at 4.2 corresponding to $OC\underline{H}_2$ protons. Methylenic protons adjacent to nitrogen atom of cyclobutane ring appeared as a doublet at δ 3.15. A multiplet at 2.85 - 2.5 confirmed the four methylenic protons and ring junction proton (two protons) and tolyl methyl appeared as a singlet at δ 2.4. A multiplet appeared at 2.0 - 1.85 indicating the presence of methylenic proton of the product. Two triplets overlapping at 1.25 could be assigned to $C\underline{H}_3$ protons. The mass spectrum showed a molecular ion peak at *m/z* 409. The above spectroscopic data confirmed the structure of expected product **68**.

The reaction of 1, 6-dienes with chloramine-T and tosyl azide catalyzed by different transition metal catalysts, CuCl, and $Ni[P(OPh)_3]_4$ was unsuccessful except the reaction of chloramine-T with diethyl 2, 2-diallylmalonate in the presence of copper chloride.

CONCLUSION

In conclusion, the reaction of bis-olefin, diethyl 2, 2-diallylmalonate with chloramine-T and tosyl azide catalyzed by copper (I) chloride afforded the expected product in good yield. The reactions of other bis-olefins failed under various modified reaction conditions, catalyst, solvent, temperature and co-catalyst.

EXPERIMENTAL

Preparation of diethyl 2, 2-diallylmalonate (62)

A 250 mL RB flask equipped with magnetic stirring bar was charged with diethylmalonate (4.0 g, 25 mmol), tetrabutylammonium bromide (1 g) and allyl bromide (6.6 g, 55 mmol) in 25 mL dichloromethane. To this, 10% sodium hydroxide (50 mL) was added slowly with stirring at room temperature. The reaction mixture was allowed to stir for overnight. The reaction mixture was neutralised with dil. HCl and extracted with dichloromethane (3 x 15 mL). The combined organic layer dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product obtained was purified by silica gel column chromatography using 60-120 mesh silica gel and a mixture of pet-ether and ethyl acetate (9:1).

Yield : 1.8 g (30%).

IR (Neat) : 2981, 1735, 1599, 1470, 960, 870 cm^{-1}

^{1}H NMR (200MHz, $CDCl_3$) : δ 5.75 - 5.6 (m, 2H), 5.1 (d, *J* = 11.0 Hz, 4H), 4.2 (q, *J* = 8 .0 Hz, 4H), 2.6 (d, *J* = 7.4 Hz, 4H), 1.3 (t, *J* = 8.0 Hz, 6H).

^{13}C NMR (75MHz, $CDCl_3$) : δ 170.68, 131.86, 118.92, 60.20, 58.08, 38.20, 16.82.

Mass (*m/z*) : 240 (5), 199 (10), 153 (64), 125 (37), 93 (100), 79 (70), 67 (25).

Preparation of ethyl-2-allyl-2-cyano-4-pentenoate (63)

A mixture of ethyl cyano acetate (2.8 g, 25 mmol), allyl bromide (6.6 g, 55 mmol) and tetrabutylammonium bromide (0.350 g, 1 mmol) charged into a 250 mL RB flask equipped with magnetic stirring bar. To this, dichloromethane (25 mL) was added followed by slow addition of 10 % aqueous sodium hydroxide (50 mL) with stirring at room temperature. The reaction mixture was allowed to stir for overnight. The reaction was quenched by addition of dil. HCl (10 % by volume) and the product was extracted with dichloromethane (3 x 15 ml). The combined organic layer washed with brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate- petroleum ether mixture (9:1).

Yield : 1.45 g (31 %)

IR (Neat) : 3014, 2301, 1735, 1605, 1470, 1280, 960 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.0 - 5.85 (m, 2H), 5.3 - 5.2 (2s, 4H), 4.2 (q, *J* = 6.0 Hz, 2H), 2.75 - 2.45 (m, 4H), 1.3 (t, *J* = 6.0 Hz, 3H)

Mass (*m/z*) : 192 (M^+, 1), 164(14), 154(13), 146(10), 124(100), 93(77).

1-[3-allyloxy-(*E*)-1-propenylbenzene (64)

A 25 mL two necked flask equipped with magnetic stirring bar was charged with sodium hydride (0.96 g, 40 mmol), in dry tetrahydrofuran (10 mL). To this, cinnamyl alcohol (1.34 g, 10 ml) was added slowly at ice-cold condition for 10 minutes. After that allyl bromide in 6 mL of tetrahydrofuran was added and allowed to stir at room temperature for overnight. The reaction

was quenched with ice-cold water, and the product was extracted with ethyl acetate (3x10 mL). The combined organic layer washed with brine solution (10 mL) dried over anhydrous sodium sulphate and concentrated. The silica gel column chromatographic purification of the crude product gave the pure compound.

Yield : 1.56 g (89 %).

IR (Neat) : 2923, 1597, 1470, 1045, 960 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.5 - 7.20 (m, 5H), 6.65 (d, *J* =14.0 Hz, 1H), 6.40 - 6.20 (m, 1H), 5.4 - 5.2 (dd, *J* = 15.0 Hz, 6.0 Hz, 2H), 4.2 (d, *J* = 6.0 Hz, 2H), 4.1 (d, *J* = 6.0 Hz, 2H)

Mass (*m/z*) : 174 (M^+, 2), 156 (2), 143 (3), 133 (25), 115 (50), 105 (100), 91(48), 77 (50).

Allyl cinnamate (65)

A mixture of cinnamic acid (2.96 g, 20 mmol) and allyl alcohol (1.45 g, 25 mmol) was charged into a 25 mL RB flask equipped with magnetic stirring bar. To this thionyl chloride (4 mL) was added slowly at 0 °C for about 10 minutes with stirring. The reaction mixture was allowed to stir at room temperature for 1 h. The excess of thionyl chloride was removed by distillation. The crude product was purified by silica gel column chromatography using a mixture of pet. ether and ethyl acetate (9.5:0.5).

Yield : 3.2 g (85%)

IR (Neat) : 3062, 3028, 1712, 1637, 980 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.8 (d, *J* =14.5 Hz, 1H), 7.50 - 7.25 (m, 5H), 6.4 (d, *J* = 14.0 Hz, 1H), 6.01 - 5.95 (m, 1H), 5.2 - 5.1(m, 2H), 4.35 (d, *J* = 6.0 Hz, 2H)

Mass (*m/z*) : 188 (M^+, 9), 143 (24), 131 (97), 103 (100), 77 (74).

***N*-allyl-4-methyl-1-benzene sulphonamide (66)**

A 50 mL RB flask equipped with magnetic stirring bar was charged with a mixture of allyl amine (1.4 g, 25 mmol) and triethylamine (5 g, 50 mmol) in dry dichloromethane (15 mL). Tosyl chloride (4.75 g, 25 mmol) in dry dichloromethane (5 mL) was added slowly at 0 °C for 10 minutes. The reaction mixture neutralised with dil. HCl (10% by volume) and the product extracted with dichloromethane (3x10 mL). The combined organic layer dried over anhydrous sodium sulphate, concentrated under reduced pressure. The crude product was purified by silica column chromatography using a mixture of pet-ether and ethyl acetate (9:1).

Yield : 4.6 g (87%)

M. P : 57 °C

IR (M.S.A) : 3249, 2923, 1595, 1460, 1321, 1163, 1064, 812, 707 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.8 (d, *J* = 8.0 Hz, 2H), 7.3 (d, *J* = 8.0 Hz, 2H), 5.9 - 5.75 (m, 1H), 5.2 (s, 1H), 5.1 (s, 1H), 3.6 (m, 2H), 2.4 (s, 3H).

1*N*, 1*N*-diallyl-4-methyl-1-benzene sulphonamide (67)

A 25 mL RB flask equipped with magnetic stirring bar was charged with a mixture of N-allyl-4-methyl-1-benzene sulphonamide (0.422 g, 2 mmol), allyl bromide (0.484 g, 4 mmol), and tetrabutylammonium bromide (0.05 g, 1.5 mmol) in dichloromethane (10 mL). To this 10 % sodium hydroxide added slowly at 0 °C and allowed to stir at room temperature for overnight. The reaction mixture was neutralised with dilute hydrochloric acid (10 % by volume) and the product extracted with dichloromethane (3x5 mL), the combined organic layer washed with brine solution (1x 5mL), dried and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using a mixture of pet.ether and ethyl acetate (9:1).

Yield : 0.376 g, (75 %)

IR (M.S.A) : 2981, 2922, 1596, 1442, 1043, 929, 763 cm^{-1}

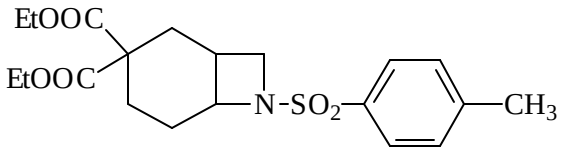
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.8 (d, *J* = 8.0 Hz, 2H), 7.3 (d, *J* = 8.0 Hz, 2H), 5.9 - 5.75 (m, 2H), 5.2 (s, 2H), 5.1 (s, 2H), 3.6 (m, 4H), 2.4 (s, 3H).

Mass (*m/z*) : 251 (M^+, 38), 236 (38), 224 (100), 210 (7), 186 (98), 172 (25).

Copper chloride catalyzed reaction of chloramine-T with bis-olefins

A 25 mL RB flask equipped with magnetic stirring bar, reflux condenser and argon balloon was charged with chloramine-T and bis-olefin and copper chloride was added slowly at 0 °C. The reaction mixture was allowed to reflux for 24 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography using 100-200 mesh silica gel and pet.ether-ethyl acetate mixture (9:1).

Diethyl -1-(4-methylphenylsulfonyl)perhydrobenzo[b]azete-4,4-dicarboxylate (68)



Mol .F : $C_{20}H_{27}NSO_6$

IR (Nujol) : 2978, 2930, 1727, 1446, 1190 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.2 (q, *J* = 6.0 Hz, 4H), 3.15 (d, *J* = 9.6 Hz, 2H), 2.83 - 2.5 (m, 6H), 2.4 (s, 3H), 2.0 - 1.85 (m, 2H), 1.25 (two triplets overlapping, 6H).

Mass (*m/z*) : 409 (M^+, 2), 363 (5), 254 (100), 110 (10), 91 (18), 79 (6).

References

1. a. Colquhoun, H.M.; Holton, J.; Thompson, D. J.; Twigg, M. V. New pathways for organic synthesis: Practical applications of Transition metals: plenum press: New York, 1984: 148.

b. Davidson, J. L.; Preston, P. N. *Adv. Heterocycl. chem.* **1982**, *30*. 319.

2. a . Hegedus, L. S. *Angew. Int. Ed. Engl.* **1988**, *27*, 1113.

b. Sakamoto, T.; Kondo, Y.; Hiroshi, Y. *Heterocycles*, **1988**, *27*, 2225.

3. Harold, K.; Kahn, A. A. *J. Am. Chem. Soc.* **1967**, *89*, 1950.

4. Mansuy, D.; Jean-Pierre, M.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc. Chem. Commun*., **1984**, 1161.

5. Mahy, J. P.; Bedi, G.; Battioni, P.; Mansuy, D. *Tetrahedron Lett.* **1988**, *29*, 1927.

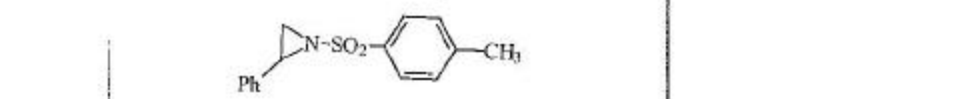
6. Sodergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1997**, *38*, 6897.

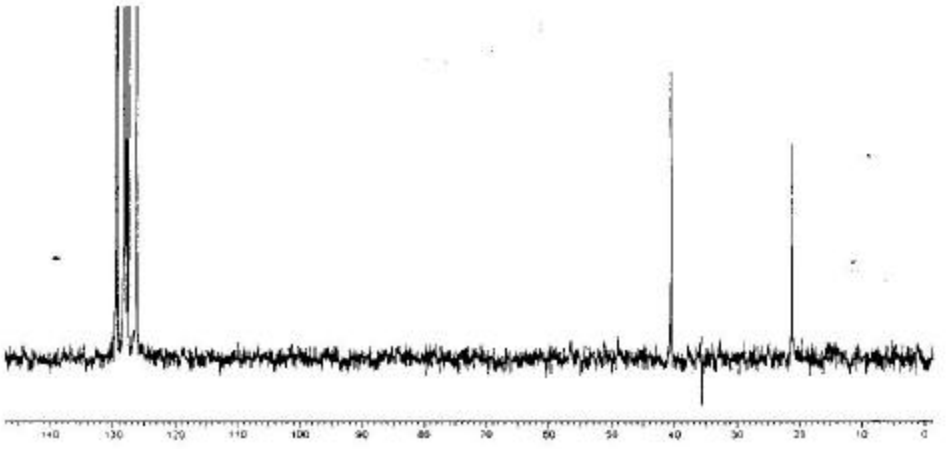
7. Nishikori, H.; Katsuki, T. *Tetrahedron Lett*. **1996**, *37*, 9245.

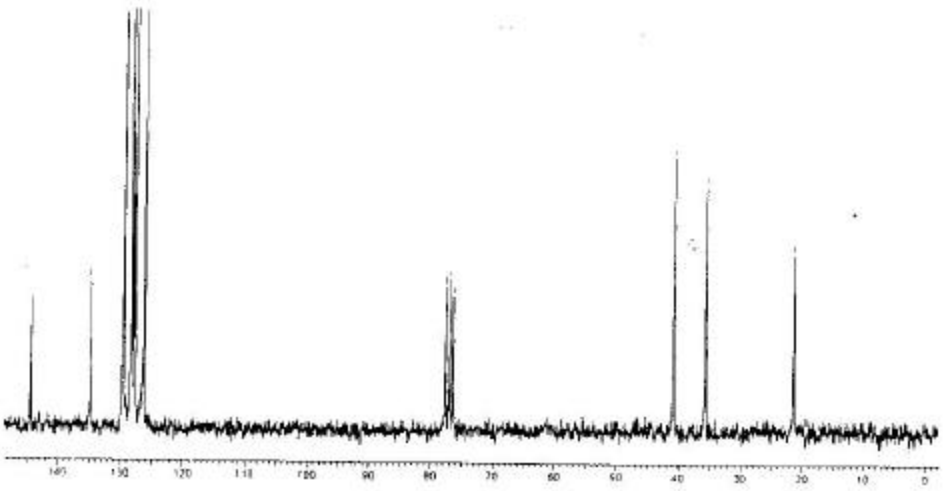
8. O' Connor, K. J.; Shiow -Jyi, W.; Burrows, C. J. *Tetrahedron Lett*. **1992**, *33*, 1001.

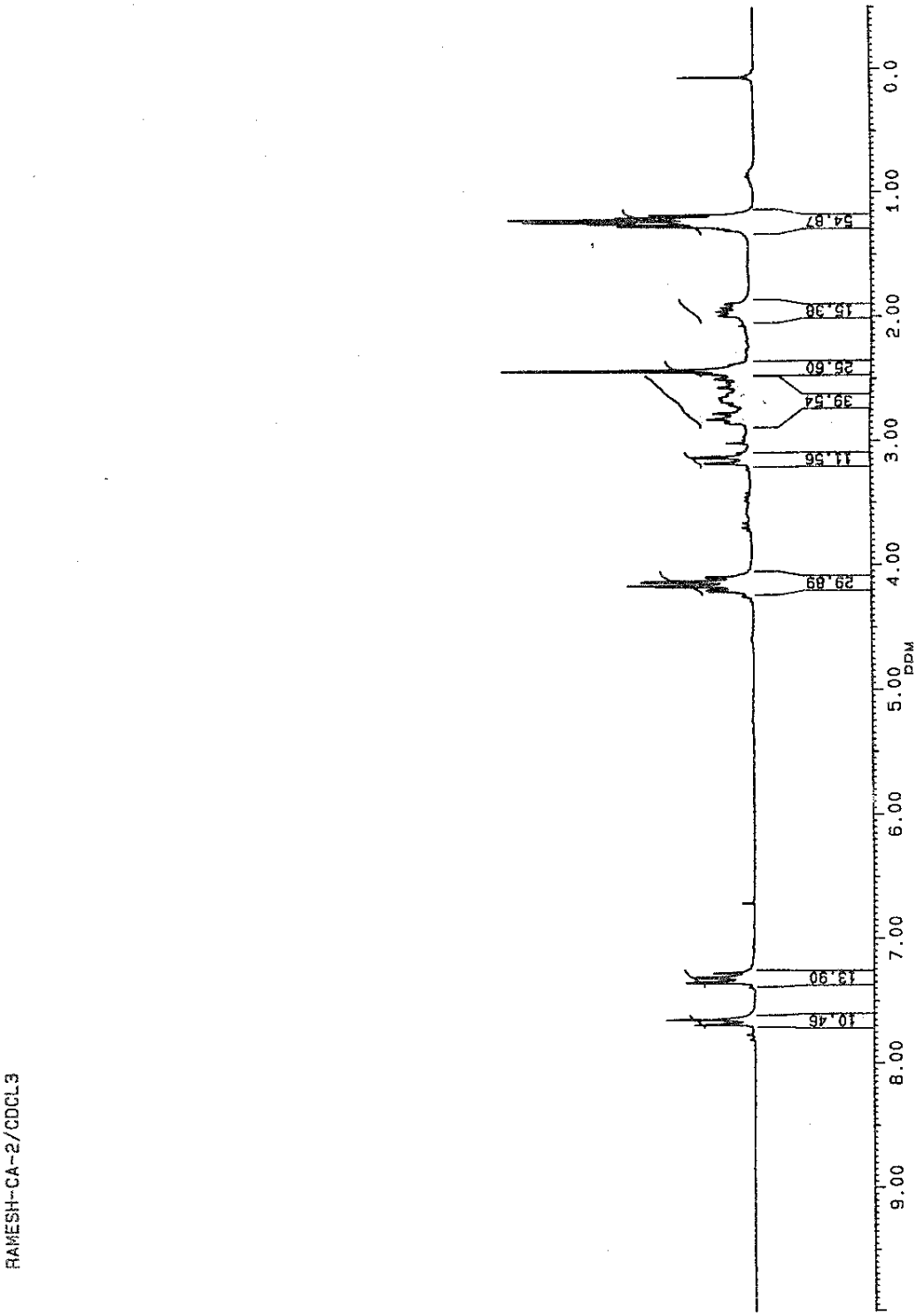
152

^{1}H NMR and ^{13}C NMR spectra of **61**








RAMESH-CA-2/CDCL3
54.87
15.38
25.60
39.54
11.56
29.09
13.90
10.46
0.0
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
PPM

List of Publications

1. The vinylation of Aryl and Vinyl halides Catalyzed by Copper salts
   Suresh Iyer, **Chinnasamy Ramesh**, Anjana Sarkar, Prakash P.Wadgaonkar.
   Tetrahedron Letters **1997**, *38*, 8113.

2. Ni (0) Catalyzed Reactions of Aryl and Vinyl halides with Alkenes and Alkynes.
   Suresh Iyer, **Chinnasamy Ramesh**, A. Ramani
   Tetrahedron Letters **1997**, *38*, 8533.

3. The Pd catalyzed reactions of α-Bromoacrylic acids with 1, 3-dienes to form γ-lactones
   Suresh Iyer, **C. Ramesh**
   Tetrahedron Letters **1999**, *40*, 4719.

4. Aryl-Pd covalently bonded palladacycles-novel amino and oxime catalysts [Di-mu-chlorobis benzaldehydeoxime-6-C,N)dipalladium(II), Di-mu-chlorobisbis (dimethylbenzylamine-6-C, N) dipalladium (II) for the Heck reaction.
   Suresh Iyer, **C. Ramesh**
   Accepted for Publication in Tetrahedron Letters.

5. The Pd catalyzed reactions of α-bromoacrylic amides with 1, 3-dienes to form γ-lactams.
   Suresh Iyer, **C. Ramesh**, Girish M. Kulkarni
   Communicated to Tetrahedron Letters

List of Abbreviations

Ac	Acetyl
aq	aqueous
Bn	benzyl
Bp	boiling point
Bu	butyl
DCM	dichloromethane
NMP	N-methyl pyrrolidone
DMF	N, N-dimethyl formamide
Et	ethyl
EtOAc	ethyl acetate
g	gram
h	hour
IR	infrared
m	molar
mL	milliliter
mmol	millimole
mp	melting point
rt	room temperature
TEA	triethylamine
THF	tetrahydrofuran
TLC	Thin Layer chromatography
TMS	trimethylsilane
TMSCl	chlorotrimethylsilane

"When two organic fragments are found on a metal framework, the possibility of coupling them becomes an attractive prospect."

R. Hoffmann

JACS, 1982, 104, 632