SYNTHETIC STUDIES TOWARDS BIOACTIVE MOLECULES USING ASYMMETRIC DIHYDROXYLATION AND ORGANIC TRANSFORMATION USING YTTRIA-ZIRCONIA AND OTHER HETEROGENEOUS CATALYST

A THESIS SUBMITTED TO THE

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FOR THE DEGREE OF
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IN
CHEMISTRY

BY
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C E R T I F I C A T E

This is to certify that the worked presented in the thesis entitled **"SYNTHETIC STUDIES TOWARDS BIOACTIVE MOLECULES USING ASYMMETRIC DIHYDROXYLATION AND ORGANIC TRANSFORMATION USING YTTRIA-ZIRCONIA AND OTHER HETEROGENEOUS CATALYST"** submitted by **S. Ramalingam** was carried out by the candidate at the National Chemical Laboratory, Pune 411 008 under my supervision. Such materials as obtained from other sources have been only acknowledged in the thesis.

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October 2005

C A N D I D A T E D E C L A R A T I O N

I hereby declare that thesis entitled "**SYNTHETIC STUDIES TOWARDS BIOACTIVE MOLECULES USING ASYMMETRIC DIHYDROXYLATION AND ORGANIC TRANSFORMATION USING YTTRIA-ZIRCONIA AND OTHER HETEROGENEOUS CATALYST"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune has not been submitted by me to any other University or Institution. This work was carried out at the National Chemical Laboratory, Pune 411 008, India.

S. Ramalingam

A C K N O W L E D G E M E N T S

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(*S. Ramalingam*)

Dedicated

In Memory Of My Father
Late Shri S. Sadyandy

CONTENTS

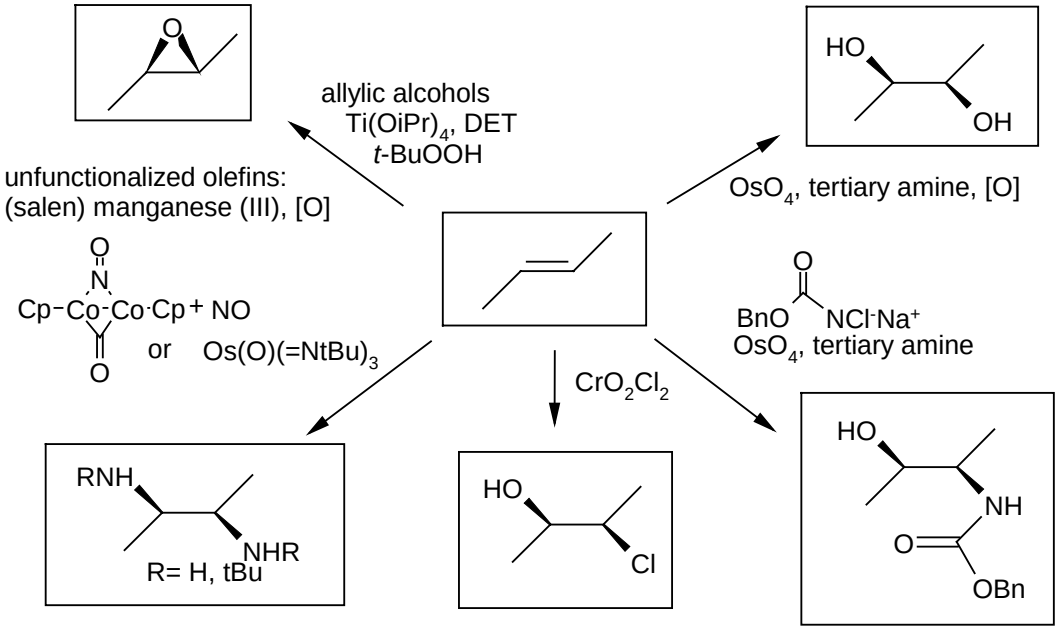
CHAPTER 1

Asymmetric Dihydroxylation(AD) and its Applications to Synthesis of Bioactive Molecules

1.1 Asymmetric Dihydroxylation (AD)

1.1.1 Introduction

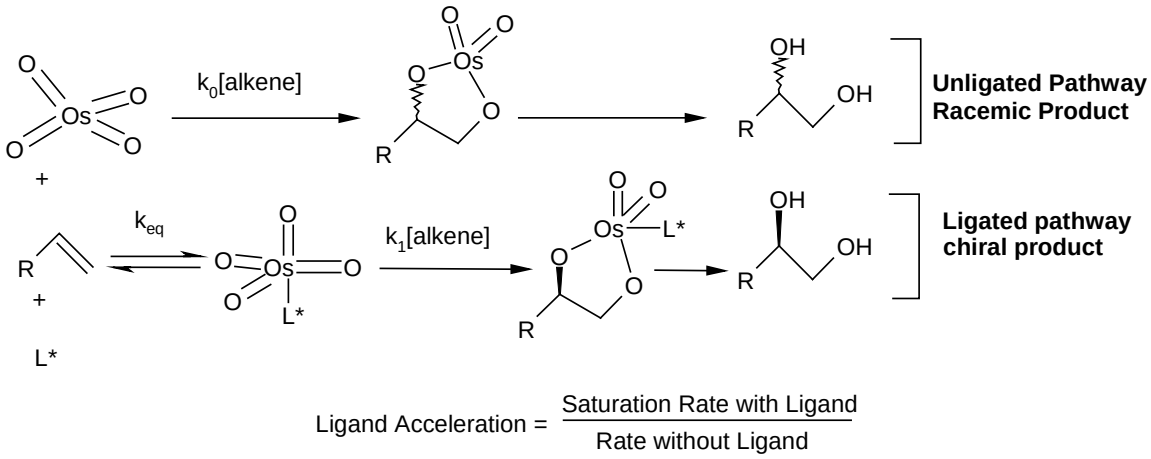
During the last decade, a number of powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetry inducing agents.[1] Especially useful are the carbon-hetero atom bond forming reactions, since the resulting functionality can be readily manipulated to produce many important classes of compounds. Therefore the oxidative addition of heteroatoms to olefins has been a fruitful area in recent years. Consequently a number of transition metal mediated methods for the epoxidation,[2] oxidative cyclization,[3] aminohydroxylation,[4] halohydrin formation,[5] and dihydroxylation[6] have been developed (Scheme 1).



Scheme 1. Transition metal mediated suprafacial 1,2 difunctionalization of olefins

The common feature of most of these processes is the phenomenon of ligand acceleration,[7] wherein a metal catalyzed process turns over faster in the presence of a co-ordinating ligand. Consequently reaction funneled through the ligated pathway with the additional consequence that the ligand may leave its imprint on the selectivity determining step. Hence, the ligand can influence the chemo-, regio-, and stereoselectivity of the reaction in a profound way, since

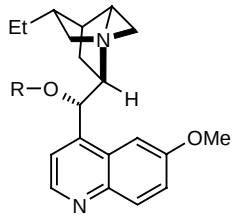
ligand acceleration ensures that the unligated pathway moves into the background. The principle of ligand acceleration is proving to be a powerful tool for discovering new reactivity and new asymmetric processes.



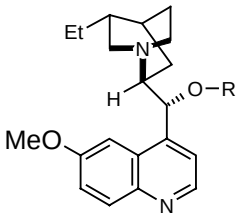
Scheme 2. Ligand accelerated catalysis-dihydroxylation of olefins

The Sharpless asymmetric dihydroxylation of olefin catalyzed by OsO_4 is extremely useful and realiable method to prepare chiral dihydroxy compounds. Initially, in stoichiometric reaction of OsO_4 with olefins, Criegee showed that pyridine accelerates the reaction considerably,[8] however cost consideration made this process uneconomical. Later, several developments were made but results were obtained with alkaline tert-butyl hydroperoxide, introduced by Sharpless and Akashi,[9] or *N*-methylmorpholine *N*-oxide,[10] (Upjohn Process). Minato *et al.* demonstrated that potassium ferricyanide in the presence of K_2CO_3 provides a powerful system for the osmium catalyzed dihydroxylation of olefins.[11] Initial efforts by Sharpless and Hentges to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4,[12] since the binding constant of a ligand is extremely sensitive to the steric hindrance near the reactivity center. Consequently, quinuclidine derivatives were used instead of pyridines for further investigations due to their intrinsically higher affinity for OsO_4.[13] Subsequently, moderate to good enantiomeric excess was obtained using acetate esters of cinchona alkaloids as chiral ligands.[14]

(a) Cinchona Alkaloid Ligands for AD under Catalytic Conditions[16,20,21]

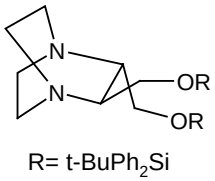


Dihydroquinidine (R= H)
DHQD



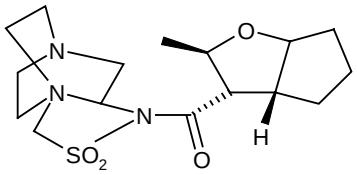
Dihydroquinine (R= H)
DHQ

(b) Recent Monodentate Ligands for AD under *Catalytic* Conditions



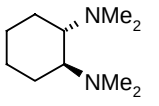
R= t-BuPh$_2$Si

Hirama *et al*.[14a]

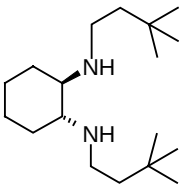


Murahashi *et al*.[14b]

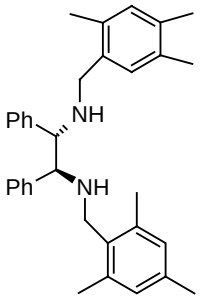
(c) Chiral Diamine Ligands for AD under *Stoichiometric* Conditions



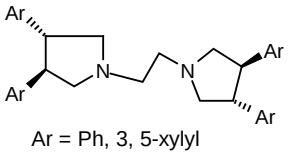
Snyder *et al*.[15b]



Hanessian *et al*.[15d]

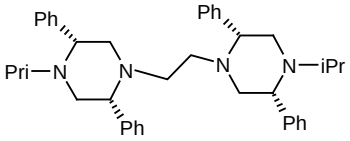


Corey *et al*.[15e]

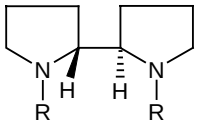


Ar = Ph, 3, 5-xylyl

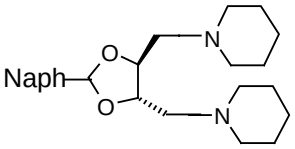
Tomioka *et al*.[15f,g,h]



Fuji *et al*.[15i]



R = neohexyl
Hirama *et al*.[15j, k]

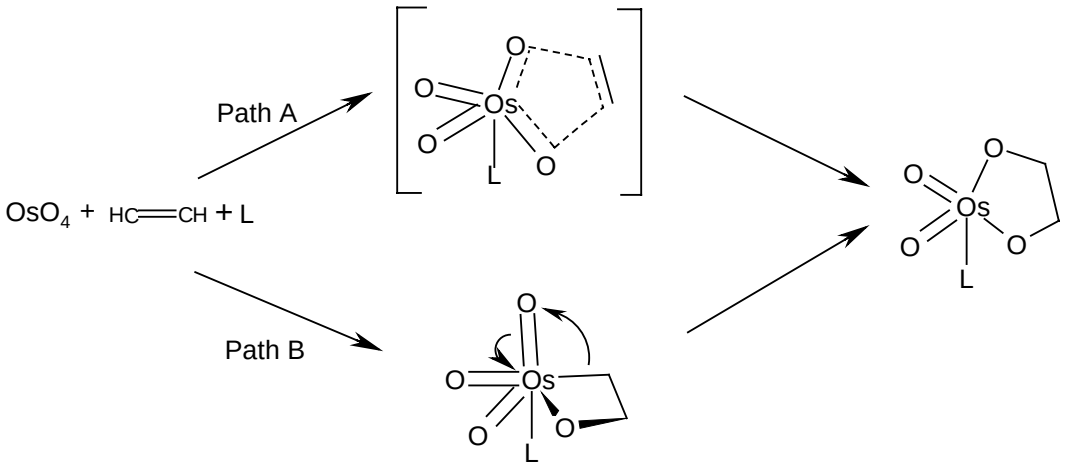


Naph = naphthyl
Narasaka *et al*.[15l]

Fig. 1 Some ligands for AD reaction

A number of recent methods employ chiral monodentate[14a] and bidentate diamine ligand[15] for the aymmetric osmylation of olefins. Good results have been achieved using chiral diamine ligands for the asymmetric osmylation of olefins,[15] but a serious drawback is the formation of stable chelate complexes due to their bidentate nature that they form very stable complex with Os(VI) glycolate products and as a consequence prevent in situ recycling of the osmium and the ligand. Hence, all the reactions involving bidentate ligands are stoichiometric in both OsO_4 and the chiral ligand.[16]

1.1.2 Mechanism of Osmylation



Scheme 3. Schematic presentation of [3+2] mechanism [17e] (Path A) and the stepwise osmaoxetane mechanism (Path B)[17f]

The osmium-catalyzed dihydroxylation reaction has been the center of extensive mechanistic investigations and two efficient mechanisms have been suggested. Boseken[17e] and Criegee[8] originally proposed a concerted [3+2] pathway while Sharpless *et al.*[17f] suggested a stepwise reaction which is initiated by [2+2]-like addition of the olefin across an Os=O bond followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product. The recent observation of a nonlinear Eyring relationship between ee and temperature[18] is inconsistent with Criegee's one-step [3+2] mechanism, but it can be explained by a reaction pathway with atleast two selectivity determining steps which are weighed differently according to temperature, owing to their different activation parameters, hence this observation suggests that the stepwise [2+2]–like mechanism is operative.

The mechanism of osmylation of olefin across double bond can be explained using two different catalytic cycles. The first catalytic version of the asymmetric dihydroxylation was based on the Upjohn process, using *N*-morpholine-*N*-oxide[10](NMO) as the stoichiometric reoxidant. However, it was found that the enantioselectivities in the catalytic version were inferior to those obtained under stoichiometric conditions. Mechanistic studies revealed that the culprit is a second catalytic dihydroxylation, which proceeds with poor to no face selectivity, since it does not involve the chiral ligand.

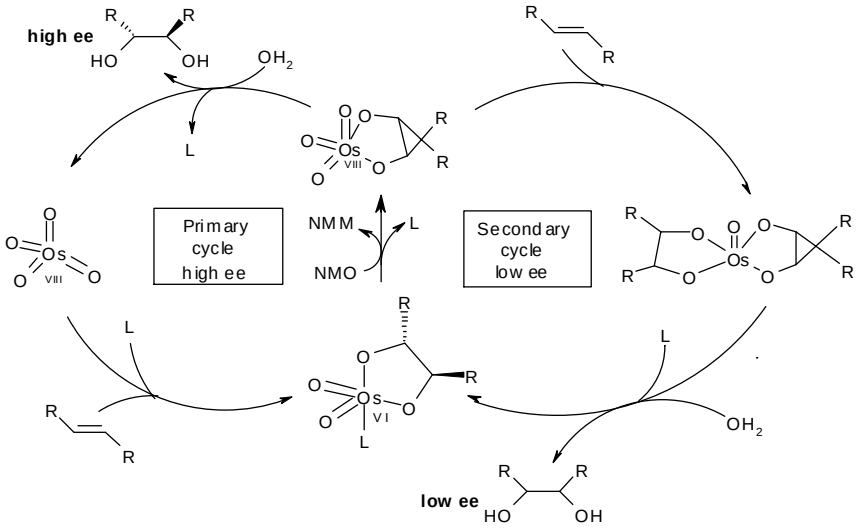


Figure 2. Two catalytic cycles for the AD reaction using NMO as the co-oxidant

The primary cycle proceeds with high face selectivity, since it involves the chiral ligand in its selectivity determining step, with the formation of the osmium (VI) glycolate which is oxidized to the Os (VIII) glycolate by the co-oxidant (NMO) resulting in loss of chiral ligand(Fig. 2). Intermediate plays a crucial role in determining the selectivity for it lies at the point of bifurcation of the good and bad catalytic cycles. The desired path involves hydrolysis of Os(VIII) glycolate to OsO_4 and the optically active diol, whereas the undesired, secondary molecule of olefin, yielding the osmium(VI)bisglycolate and hence diol of low enantiopurity. Wai and Sharpless developed a remedy for better selectivity by slow addition of olefin.[19] Another simpler protocol was developed [20] which was based on the use of potassium ferricyanide as the stoichiometric reoxidant [21] in heterogeneous solvent system, typically tert-

butanol/water (Fig.3). The actual osmylation takes place in the organic layer, giving rise to the Os(VI)glycolate which can not be oxidised to an Os(VIII)glycolate, because of the absence of the inorganic stoichiometric oxidant, $K_3Fe(CN)_6$, in the organic layer. Consequently, the second catalytic cycle can not occur. Further, reaction requires hydrolysis of the Os(VI)glycolate to the diol and a water soluble inorganic Os(VI) species which enters the basic aqueous layer ready to be oxidized by $K_3Fe(CN)_6$ to OsO_4. The latter returns to the organic phase, completing the catalytic cycle. The enantiomeric purities of diols obtained under these heterogeneous conditions are essentially identical to those obtained under stoichiometric conditions. Sharpless[22] discovered that alkyl sulfonamides (e.g. $CH_3SO_2NH_2$) accelerates the hydrolysis of the Os(VI) glycolate under heterogeneous conditions, and the reaction times can be up to 50 times shorter in the presence of this additive.

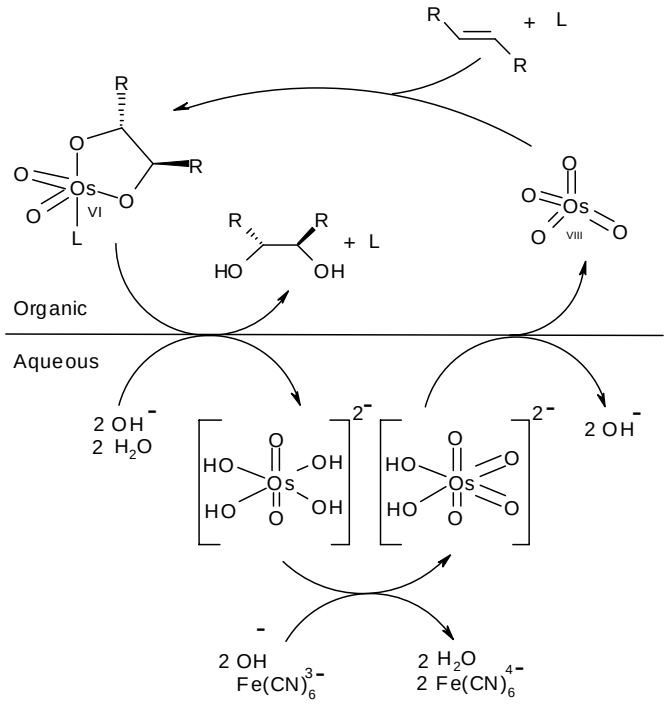
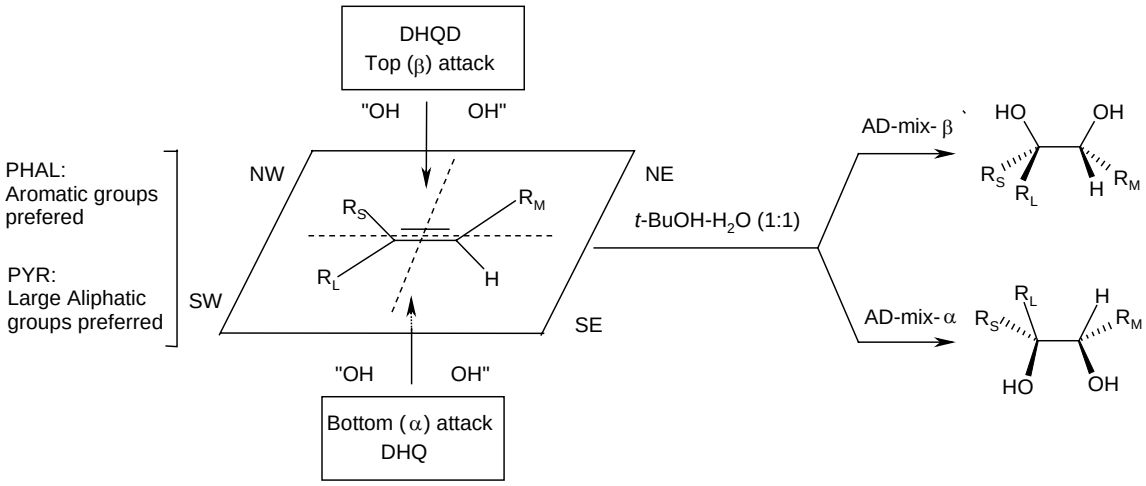


Figure 3. Catalytic cycle of AD reaction with $K_3Fe(CN)_6$ as co-oxdidant[21].

1.1.3 Empirical rules for predicting the face selctivity

Despite the mechanistic investigations, the face selectivity of the dihydroxylation can realiably be predicted using an empirical 'mnemonic device'.[23] The plane of the olefin is divided into the four quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few expections, no substituent other than hydrogen can be

placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is special in that its preferences are ligand dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in the case of PHAL ligands.[24] An olefin which is placed into this quadrant according to the above constraints receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i. e. from the α-face, in the case of DHQ derivatives (Scheme 4).



Scheme 4. The mnemonic device for predicting the face selactivity

1.1.4. Reaction Conditions

The catalytic asymmetric dihydroxylation is performed in a 1:1 mixture of water and *t*-BuOH and the olefin concentration is usually 0.1M.[22] The key reagents are 3 equivalents of $K_3Fe(CN)_6$ as the re-oxidant, 0.2-0.4 mol% osmium, 1 mol% of ligand, 3 equivalents of K_2CO_3 and 1 equivalent of $CH_3SO_2NH_2$. Additionally, the ligand can be recovered especially when large scale reactions are carried out. For PHAL ligand, the combined organic layers are extracted with 3% aq. H_2SO_4 satuarated with K_2SO_4 (ca. 40ml/1gm of ligand). The ligand enters the aqueous phase as the hydrogen sulphate salt and the solution can be reused directly for the subsequent AD reaction without further purification. However, the amount of K_2CO_3 in the subsequent reaction should be increased in order to neutralize excess H_2SO_4 and also to release the ligand salt as its free base, and the volume of aqueous ligand solution added to the reaction mixture.

1.1.5 The cinchona alkaloid ligand and their substrate preferences

Phthalazine (PHAL) ligands

Due to the ready availability of second generation ligands i.e. PHAL[22] (Phthalazine) ligands are widely used and this ligand class reacts especially when aromatic groups are present, and remarkably high enantioselectivities were observed when the aromatic substituents appear in certain optimal locations[25] like in trans-stilbene for which the enantioselectivity is as high as 99.8%.[25] However, PHAL ligands give inferior results with aliphatic olefins, especially if they are branched near the double bond or if they have very small substituents.

Anthraquinone (AQN) ligands

The anthraquinone ligands are well suited for almost all olefins having aliphatic substituents[26] and diols derived from allyl halides or allyl alcohols can be obtained with satisfactory enantiomeric purity, thereby giving access to valuable chiral building blocks. The AQN derivatives are the ligands of choice for the AD reaction, except for olefins with aromatic or sterically demanding substituents.

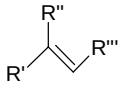
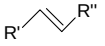
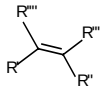
Pyrimidine (PYR) ligands

The pyrimidine ligands are the ligands of choice for olefins with sterically demanding substituents.[27]

Diphenyl pyrazinopyridazine (DPP) and diphenyl phthalazine (DP-PHAL) ligands

These ligands give improved enantioselectivities for almost all olefins except for terminal alkyl olefins which are better served by the AQN or PRY ligands.[28] The DPP ligand is normally slightly superior to the DP-PHAL ligand. The DPP derivatives are the optimal ligands for aromatic olefins and for certain cis-1, 2-disubstituted olefins.

Table1. Recommended ligands for each olefin class

Olefin Class						
Preferred Ligands	R = Aromatic DPP, PHAL R = Aliphatic AQN R= Branched PYR	R^1, R^2 = Aromatic DPP, PHAL R^1, R^2 = Aliphatic AQN R^1, R^2 = Branched PYR	Acyclic IND Cyclic PYR, DPP, AQN	R^1, R^2 = Aromatic DPP, PHAL R^1, R^2 = Aliphatic AQN	PHAL, DPP, AQN	PYR, PHAL

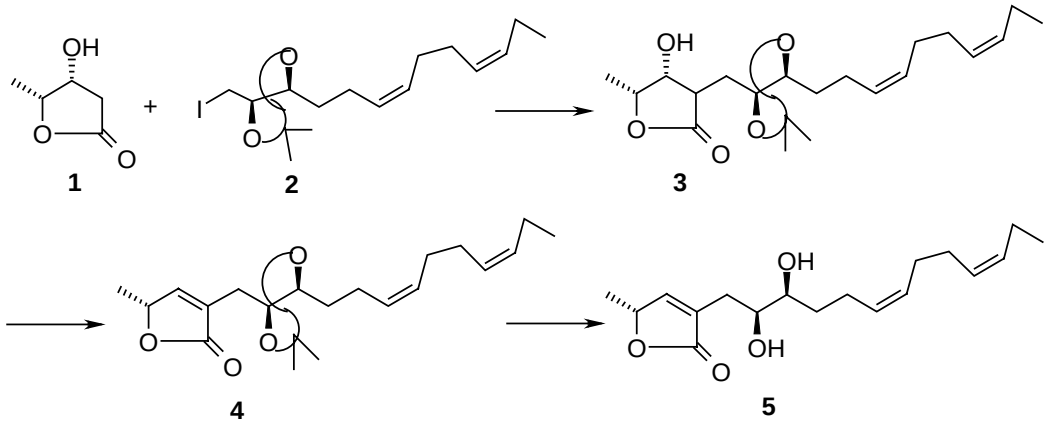
Indoline (IND) ligands

Cis-1, 2-disubstituted olefins generally are poor substrates for the AD reaction, and the IND derivatives are normally the ligands of choice.[29] However, in certain cases better results are obtained with the new second generation ligands.[30]

1.1.6 Application of asymmetric dihydroxylation to the synthesis of bioactive molecules

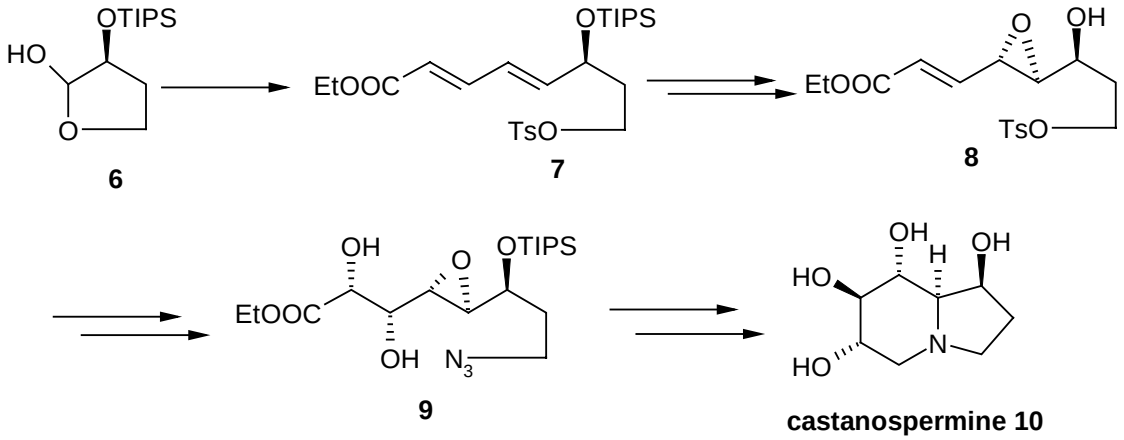
A few selected literature reports of the application of AD reaction are described below.

1. Bruckner *et al*.[32] synthesized (+)-montecristin which is a class of annonaceous acetogenins employing AD on trans-olefinic bond followed by standard organic transformation.



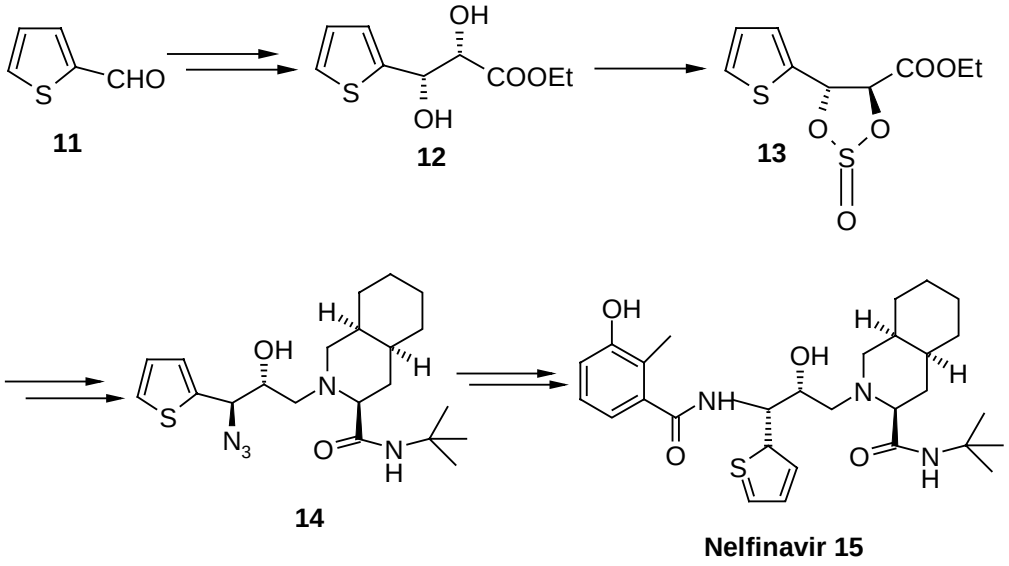
Scheme 5

2. A stereoselective synthesis of the polyhydroxy indolizidine alkaloids castanospermine[33] has been achieved using Sharpless asymmetric dihydroxylation where double sterodifferentiation was employed to synthesize the target molecule.



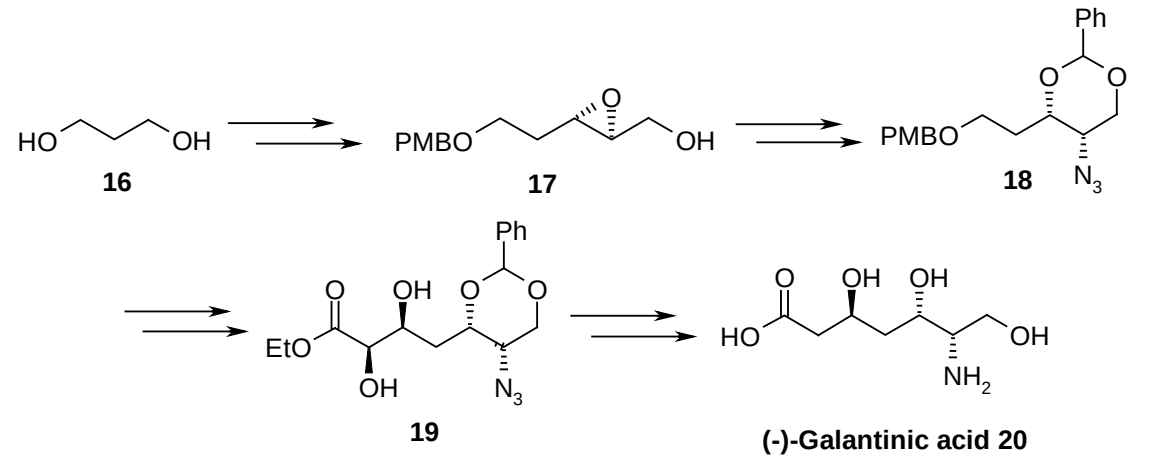
Scheme 6

3. Bonini and his co-workers[34] have achieved the thiophene containing analog of the HIV protease inhibitor nelfinavir utilizing Sharpless asymmetric dihydroxylation approach.



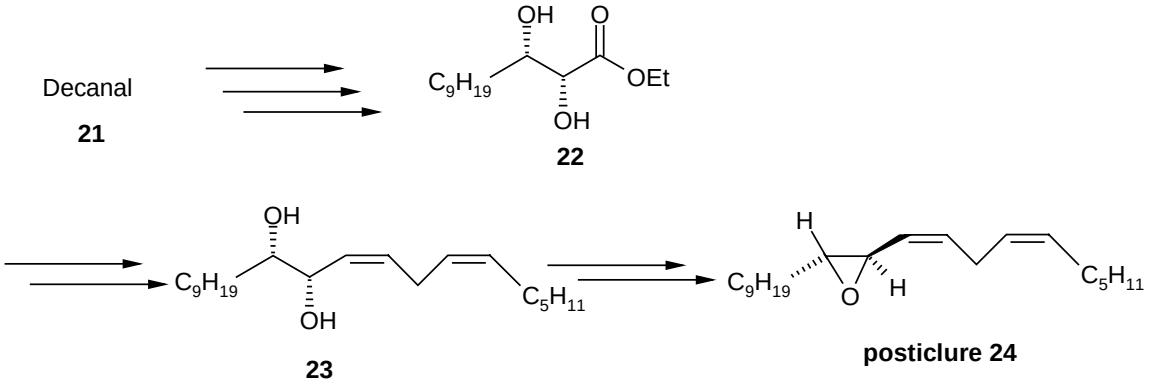
Scheme 7

4. P.Kumar and his co-workers,[35] successfully synthesized galantinic acid, a non-proteogenic aminoacid using AD and regioselective opening of a cyclic sulfite as key steps starting from commercially available 1,3-propanediol.



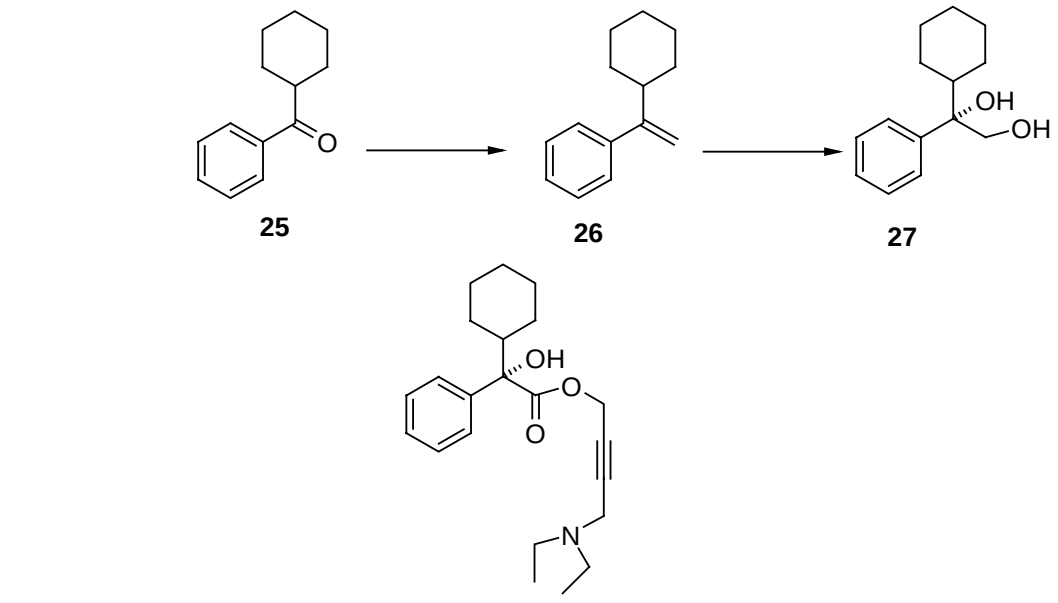
Scheme 7

5. A highly enantioselective synthesis of both enantiomers of a novel first *trans*-epoxide sex pheromone posticlure has been achieved by Kumar *et al*. using dihydroxylation approach.[36]



Scheme 8

6. An asymmetric synthesis of (*S*)-oxybutynin, a muscarnic receptor antagonist as been reported by Kumar *et al*. using Sharpless asymmetric dihydroxylation of α-cyclohexyl styrene as key step.[37]



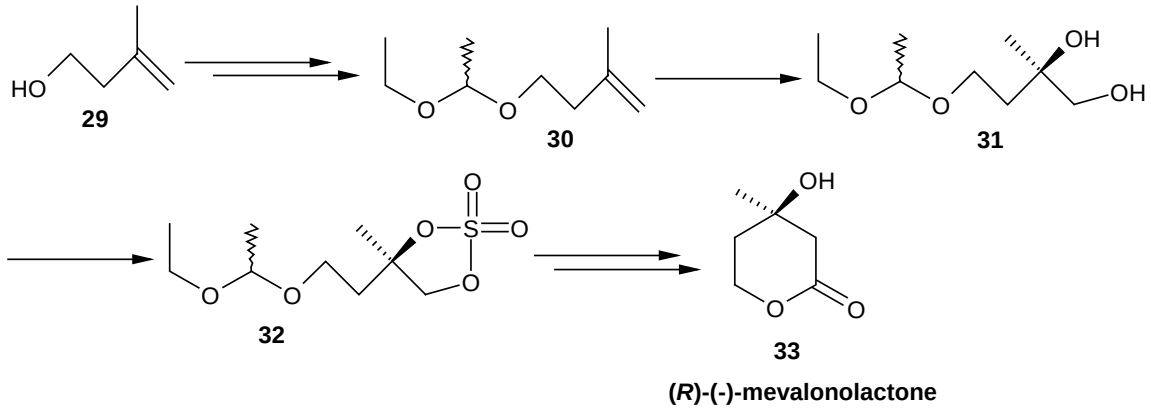
25 **26** **27**

(S)-oxybutynin

28

Scheme 9

7. Intersting synthesis of (*R*)-(-)-mevalonolactone has been achieved via cyclic sulfate methodology.[38]

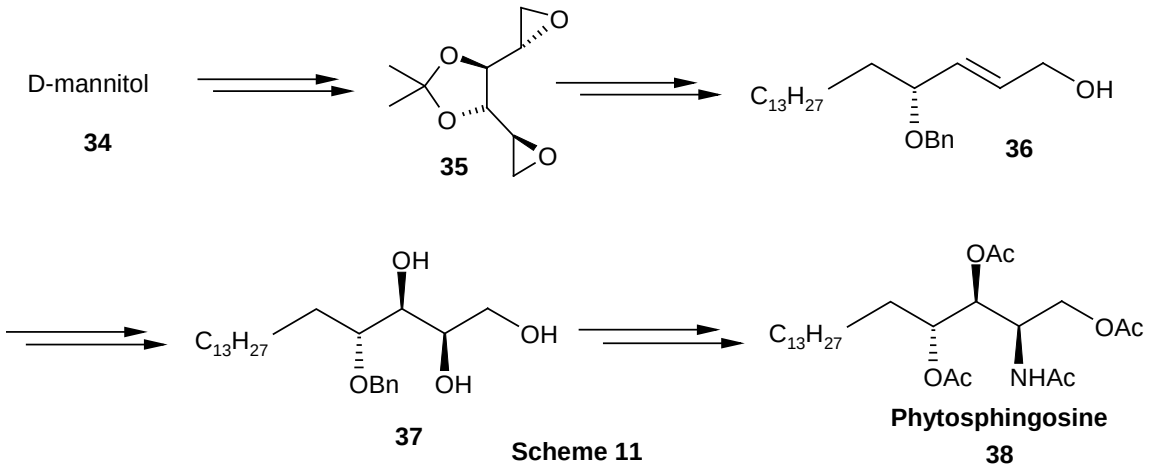


29 **30** **31** **32** **33**

(*R*)-(-)-mevalonolactone

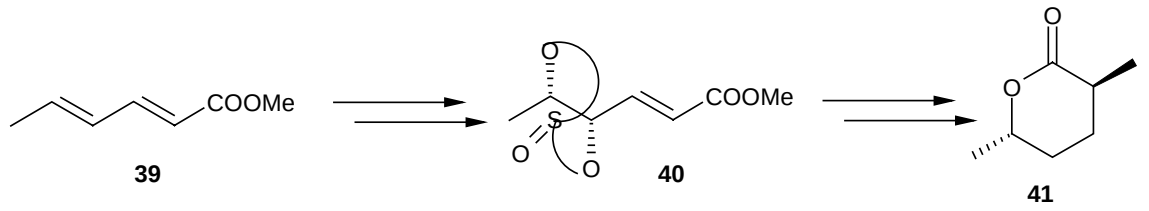
Scheme 10

8. AD is successfully employed in the synthesis of D-ribo-(2*S*, 3*S*, 4*R*)-C_{18}-phytosphingosine as its tetraacetate derivative, starting from D-mannitol.[39]



Scheme 11

9. Kang *et al.*[40] showed use of cyclic sulfate in the synthesis of Carpenter Bee pheromone (2*S*, 5*S*)-*trans*-2-methyl-5-hexanolide.[40]



Scheme 12

1.2. References :

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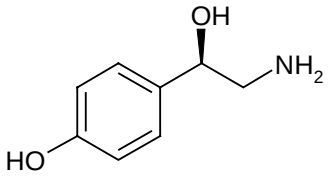
CHAPTER 2

Application of Sharpless Asymmetric Dihydroxylation to the Synthesis of the Enantiomerically Pure Octopamine, Tembamide, Ageline, Denopamine and Arbutamine

2.1 Section A Enantioselective synthesis of (*R*)-(-)-octopamine 1

2.1.1 Introduction

Many chiral β-amino alcohols[1] (β-aminoaryl ethanols) are found to be common structural component in a vast group of pharmaceutically important molecules. They are widely used as versatile chiral building blocks and chiral catalyst[2] in organic synthesis. Chiral 2-amino-1-arylethanols are important structural elements in pharmaceuticals such as α or β-adrenergic blockers and agonists in the treatment of cardiovascular disease.[3] Due to growing concern about chiral drugs being sold as racemates, many pharmaceutical industries are switching over to produce enantiomerically pure forms of chiral drugs. In most of the aryl ethanolamines drugs, the biological activity resides mainly in the (*R*)-enantiomer.[4] Recent studies revealed that the two enantiomers of chiral drugs display different biological activity. (*R*)-(-)-Octopamine **1** is a potent chiral drug possessing β-adrenergic activity.[5]



(*R*)-(-)-Octopamine 1

The other arylethanol amine which is having similar biological activity is (*R*)-(-)-phenylephrine hydrochloride.[6] Our group successfully applied the Sharpless asymmetric dihydroxylation approach to the synthesis of structurally related compounds phenylephrine hydrochloride, a sympathomimetic drug.[7] Although there is one or two reports of the enantioselective synthesis of octopamine,[8] there has been no report in the literature about the asymmetric synthesis of (*R*)-(-)-octopamine employing the Sharpless asymmetric dihydroxylation approach. As a part of our research programme aimed to develop enantioselective synthesis of naturally occurring lactones[9], and amino alcohols,[10] the Sharpless asymmetric dihydroxylation[11] was envisaged as powerful tool to the synthesis of chiral dihydroxy compound offering considerable opportunities for synthetic manipulations. In continuation, we have further exploited the AD reaction for the enantioselective synthesis of (*R*)-(-)-octopamine.

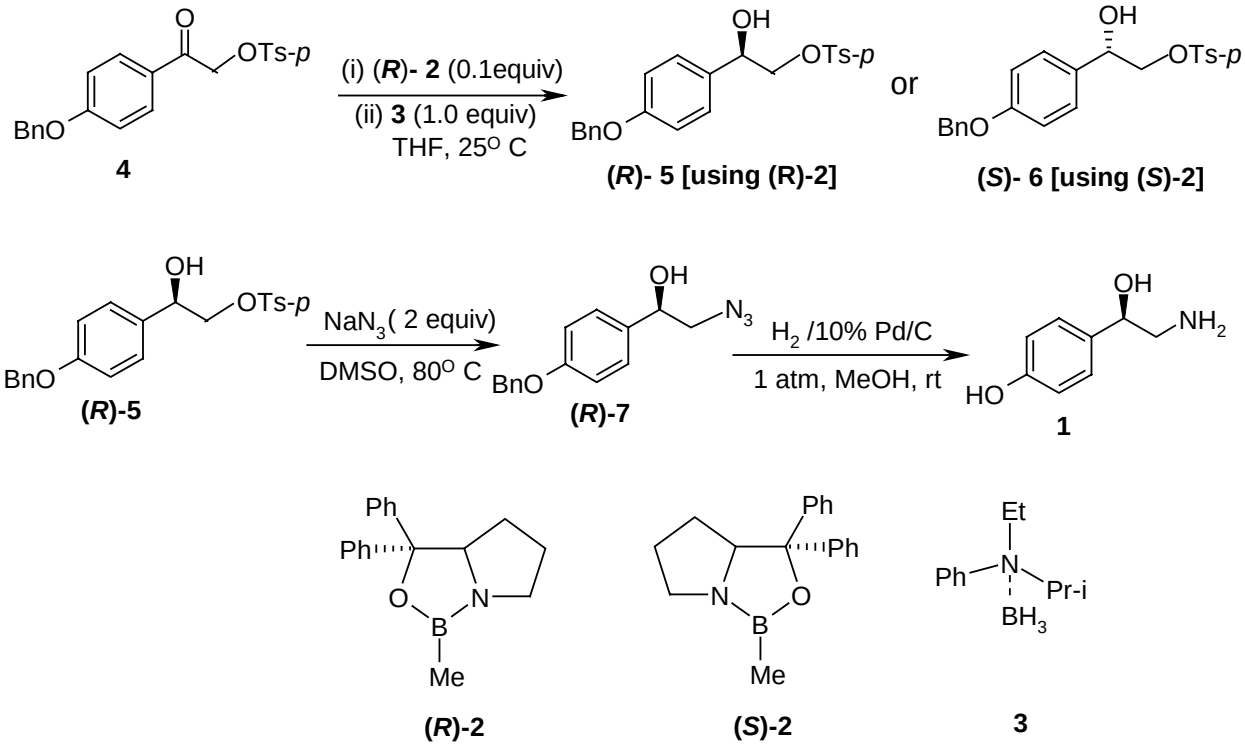
2.1.2 Review of literature

To date only few methods are available for the preparation of (*R*)-(-)-octopamine. The methods reported in the literature are described below.

Kappe *et al.* (1964)[5a]: Resolution of racemic octopamine by fractional crystallization of its salts has been accomplished with several optically active acids, these include mandelic, malic, quinic, D-tartaric and D-10-camphorsulfonic acid. Only D-10-camphorsulphonic acid gave significant enrichment in resolution of one of the optical isomers.

Cho *et al.* (2002)[8] Scheme 1: CBS-oxazaborolidine-catalyzed borane reduction of 1-substituted 2-(*p*-tosyloxyl)-ethanones was used as key step in this process.

Scheme 1



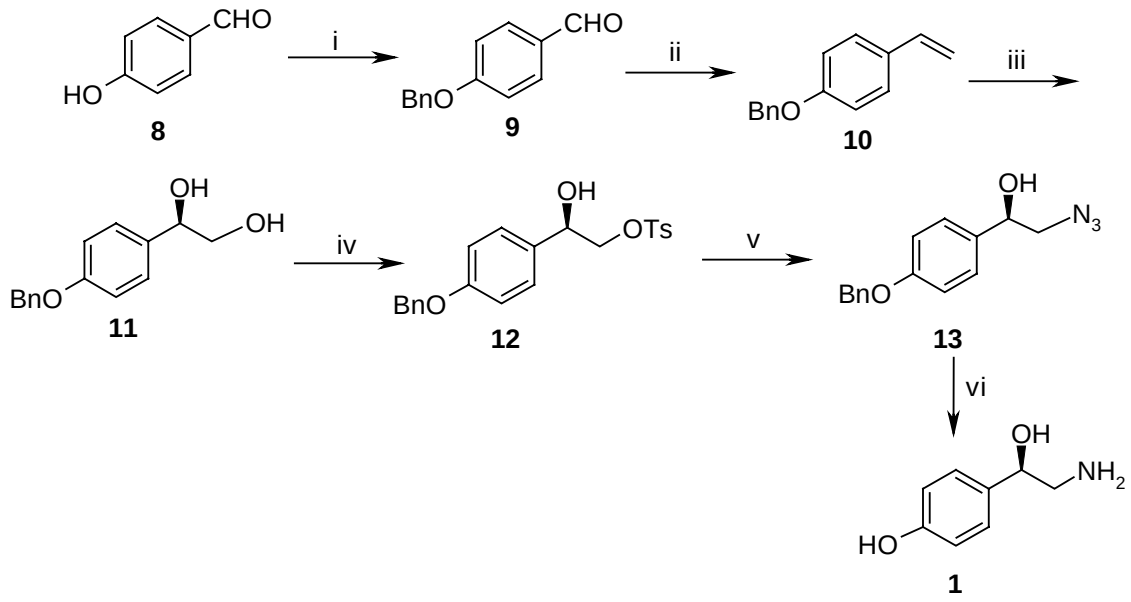
2.1.3 Present work

Objective

The natural occurrence of octopamine was first reported by Eraspamer[12] who identified it as a constituent of extracts of salivary glands of the octopus. He showed that natural octopamine has the same configuration as natural D-(-)-norepinephrine (l-noradrenaline). The pharmacological response given by purified octopamine was qualitatively same as those of

racemic octopamine, while quantitatively it appeared to be varied. Although both isomers produced adrenergic cardiovascular responses, (*R*)-(-)-octopamine **1** was found to be 3 times more potent than (*S*)-(-)-octopamine.[13] As described in introduction section, a few reports are available in the literature for the enantioselective synthesis of octopamine, we explored the chemistry of AD to develop an enantiomerically pure and high yielding new route for the synthesis of (*R*)-(-)-octopamine (**Scheme 2**).

Scheme-2



Scheme 2: ***Reagents and conditions***

(i) BnBr, K_2CO_3, DMF, TBAI (cat) 99%; (ii) $Ph_3P{=}CH_2$, THF, rt, 24 h, 78%; (iii) $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, OsO_4, *t*-BuOH/H_2O (1:1), 0°C, 18 h, 94%; (iv) *p*-TsCl; Pyridine, -15°C, 8 h, 76%; (v) NaN_3, DMF, 80°C, 4 h, 88%; (vi) $Pd(OH)_2/C$; H_2, 60 psi, EtOH, rt, 18 h, 86%.

2.1.4 Results and discussion

The present strategy for the synthesis of (*R*)-octopamine **1** is depicted in **Scheme-2**. 4-Hydroxybenzaldehyde **8** was reacted with benzyl bromide using K_2CO_3 as a base in DMF to give the corresponding ether **9** in 99% yield. The benzylic methylene proton of compound **9** appeared at δ 5.06 in the ^{1}H-NMR spectrum. The 4-benzyloxystyrene **10** was obtained by the one carbon Wittig reaction between the protected aldehyde **9** and ylide generated by the

reaction of triphenylphosphoniummethyl iodide salt and *n*-butyllithium in 78% yield. ^{1}H-NMR of the styrene compound **10** showed the characteristic signal of styrene at δ 5.13 as doublet and at δ 5.60 as doublet, and a quartet at δ 6.82. Compound **10** was subjected to Sharpless asymmetric dihydroxylation using $(DHQD)_2PHAL$ as chiral ligand to furnish the diol **11** in 94% yield. The IR spectrum of **11** showed a band at 3311cm^{-1} indicating the presence of hydroxyl functionality. The CH_2 protons attached to -OH group appeared as multiplet at δ 3.6-3.75 in ^{1}H NMR spectrum. The CH proton appeared at 4.76-4.80 as a multiplet. The ee of diol **11** was estimated to be 96.77% by HPLC. The optical rotation of the diol **11** was measured as $[\alpha]_D^{25}$ = -39.12 [*c* 0.5, $CHCl_3$].

The diol **11** was transformed into monotosyl compound **12** in 76% Yield. The ^{1}H NMR of spectrum of **12** showed the deshielding effect of tosyl group on CH_2 protons and CH protons. The CH_2 proton in monotosylate **12** appeared at 3.96- 4.11 δ as multiplet in comparison with CH_2 of diol which appeared δ 3.60-3.75. The optical rotation of **12** was measured as $[\alpha]_D^{25}$ = -34.7 [*c* 0.5, $CHCl_3$]. Also seen was the deshielding effect on CH proton which shifted from δ 4.76-4.8 to 4.89- 4.95. When **12** was treated with NaN_3 in DMF at 80°C for 4 h, the azido compound **13** was obtained in 88% yield. The IR spectrum of **13** showed a band at 2106 cm^{-1} characteristic of $-N_3$ group. In ^{1}H NMR spectrum, absence of one singlet at δ 2.44 and two doublet at δ 7.3 and at δ 7.75 in aromatic region indicated conversion of tosyl group into azido and appearance of multiplet for CH_2 group at δ 3.30-3.49 indicated the substitution of azido group (shielding effect). The optical rotation of **13** was measured as $[\alpha]_D^{25}$ - 68.4 [*c* 0.5, $CHCl_3$]. When compound **13** was stirred with 10% $Pd(OH)_2$ on charcoal in EtOH under H_2 atmosphere (60 psi) for 18 h, it furnished (*R*)-(-)-octopamine **1** in 86% yield. The physical and spectroscopic data were in full agreement with the literature data.[8]

2.1.5 Conclusion

A practical and highly enantioselective synthesis of (*R*)-(-)-octopamine **1** has been achieved for the first time using Sharpless asymmetric dihydroxylation as a source of chirality.

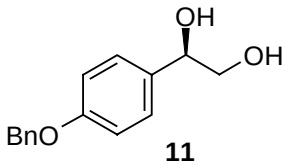
2.1.6 Expermental Section

General Information

Solvents were purified and dried by standard procedure before use; petroleum ether of boiling range 60-80°C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO P-1020 microprocessor based polarimeter. Infrared spectra were recorded on ATI Mattson RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer. Mass spectra were obtained with a TSQ 70, Finningen MAT mass spectrometer. Elemental analysis were carried out on a Carlo Erba CHNS-O analyzer. The same information is followed in the following sections of this chapter.

Benzyloxystyrene 10: This was prepared following the literature procedure[10d]

(*R*)-1-(4-Benzyloxyphenyl)-1, 2-ethanediol (11): To a solution of $K_3Fe(CN)_6$ (14.09 g, 42.80 mmol) K_2CO_3 (5.91 g, 42.80 mmol), $(DHQD)_2PHAL$ (111 mg, 0.143 mmol, 1 mol%) in *t*-BuOH:H_2O (1:1, 150 ml) was added OsO_4 (0.715 ml, 0.1 M soln in toluene, 0.5 mol%) at 0°C. After stirring for 5 min, 4-benzyloxystyrene **10** (3 g, 14.27 mmol) was added in one portion and the reaction mixture stirred for 18 h at 0°C. Solid Na_2SO_3 (3 g) was added and stirred for 1 h. The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 100 ml). The combined organic layer were washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether: EtOAc (7:3) as eluent to give **11** (3.3 g, 94%) as a colorless soild.



11

Yield: 94%

M.P.: 143-144°C

$[\alpha]_D^{20}$: -39.8 (*c*, 0.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3311, 2922, 1613, 1513, 1456, 1378, 1248, 501

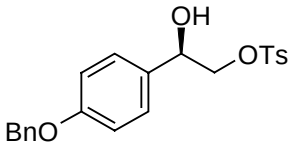
^{1}H NMR (200MHz, $CHCl_3$): δ 1.87(s, 2H), 3.66-3.75 (m, 2H), 4.76 (dd, 1H, *J* = 4.40 Hz, 7.82 Hz), 5.07 (s, 2H), 6.96 (d, 2H, *J* = 7.81 Hz), 7.32 (d, 2H, *J* = 8.31 Hz), 7.34-7.40(m, 5H)

^{13}C NMR (50MHz, $CDCl_3$): δ 67.6, 69.3, 73.5, 114.0 (2C), 126.8 (4C), 127.3, 127.9 (2C), 138.6, 136.1, 157.2

EIMS (m/z %): 243 (M^+-1] (13.2), 226 (12.5), 213 (9.3), 183 (40.3), 91 (100), 65 (13.8)

Analysis calcd. for $C_{15}H_{16}O_3$ (244.29): Found C, 73.82; H, 6.56{Required C, 73.75; H, 6.60}

(*R*)-2-(*O*-Tosyl)-1-(4-benzyloxyphenyl)-1, 2-ethanediol (12): To a solution of diol **11** (1.45 g, 5.94 mmol) in CH_2Cl_2 (50 ml) was added pyridine (0.72 ml, 8.91 mmol) and stirred for 15 min at room temperature. The reaction mixture was cooled to -15°C and *p*-TsCl (1.13 g, 5.94 mmol) was added in three portions at time interval of 30 min. The reaction mixture was stirred for 8 h at -15°C and allowed to warm to room temperature. An aqueous solution of $CuSO_4.5H_2O$ (10%, 20 ml) and EtOAc (100 ml) were added and stirred for 30 min. The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 50 ml). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petrol ether: EtOAc (17: 3) as eluent gave **12** (1.8 g, 76%) as colorless solid.



12

Yield: 76%

M.P.: 84-85°C

$[\alpha]_D^{20}$: - 34.7 (*c*, 0.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3550, 2925, 1613, 1514, 1463, 1378, 1173, 815, 555

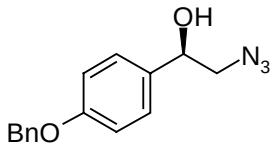
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.08 (s, 1H), 2.44 (s, 3H), 3.96-4.11 (m, 2H), 4.89-4.95 (dd, 1H, *J* = 3.41Hz, 8.31 Hz), 5.05 (s, 2H), 6.91 (d, 2H, *J* = 8.79 Hz), 7.20 (d, 2H, *J* = 8.30 Hz), 7.35-7.41 (m, 7H), 7.75 (d, 2H, *J* = 8.79 Hz)

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.3, 69.7, 70.9, 74.0, 114.6 (2C), 127.2 (2C), 127.6 (3C), 128.3 (2C), 129.6 (4C), 130.9, 132.4, 136.6, 144.7, 158.5

EIMS (m/z, %): 398 [M^+] (6.2), 380 (22.8), 340 (18.4), 229 (60.6), 197 (86), 91 (100), 77 (28.7), 65 (61.9)

Analysis Calcd. for $C_{22}H_{22}O_5S$ (398.48): Found: C, 66.12; H, 5.65; S 8.12;{Required: C, 66.31; H, 5.56; S, 8.05}

(*R*)-2-Azido-1-(4-benzyloxyphenyl)-ethanol (13): To a solution of **12** (618 mg, 1.55 mmol) in dry DMF (10 ml) was added NaN_3 (605 mg, 9.3 mmol) and stirred at 80°C for 4 h. The reaction mixture was cooled to room temperature and diluted with water and EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 20 ml). The combined organic layers were washed with water and then brine solution, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petrol ether: EtOAc (17:3) as eluent to give azido alcohol **13** (368 mg, 88%) as a colorless solid.



13

Yield: 88%

M.P.: 68-69°C [lit.[8] 69-70°C]

$[\alpha]_D^{20}$: - 68.4 (*c*, 0.5, $CHCl_3$) {lit.[8] $[\alpha]_D^{20}$ –72.2 (*c*, 1.1, $CHCl_3$)}

IR ($CHCl_3$, cm^{-1}): ν_{max} 3417, 2926, 2106, 1611, 1512, 1240, 1217, 1174, 769, 668, 475

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.59(brs, 1H), 3.34-3.54(m, 2H), 4.82 (dd, 1H, *J* = 4.39Hz, 7.82 Hz), 5.06 (s, 2H), 6.95 (d, 2H, *J* = 8.79 Hz), 7.27 (d, 2H, *J* = 8.30 Hz), 7.36-7.42 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 57.9, 69.9, 72.8, 114.9 (2C), 127.5 (2C), 127.9, 128.5 (2C), 133.1, 136.8, 158.7

EIMS (m/z %): 269 [M^+](11.16), 238 (9.3), 213 (100), 185 (15.8), 170 (40.8), 91 (67.7), 77 (13.8), 65 (20.2)

(*R*)-(-)-Octopamine 1: To a solution of azido alcohol **13** (302 mg, 1.12 mmol) in EtOH (10 ml) was added 10% $Pd(OH)_2$ (170 mg) on charcoal at room temperature and stirred under a

hydrogen atmosphere (60 psi) for 18 h. The catalyst was filtered on a pad of celite and the filtrate concentrated and purified by silica gel column chromatography using *n*-BuOH/AcOH/H_2O (3:1:1) as eluent to give (*R*)-(-)-octopamine **1** as colorless solid; mp 246-247°C]; $[\alpha]_D^{20}$ –35.7 (*c*, 0.54, H_2O) {lit.[8] $[\alpha]_D^{20}$ - 37.6 [*c* 0.56, H_2O]}. The spectroscopic data is in full agreement with the literature data.[8]

2.1.7 Spectra

1.^{1}HNMR spectrum of 11

2. ^{13}CNMR spectrum of 11

3. ^{1}HNMR spectrum of 12

4. ^{13}CNMR spectrum of 12

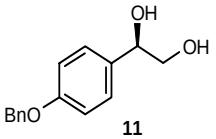
5. ^{1}HNMR spectrum of 13

6. ^{13}CNMR spectrum of 13

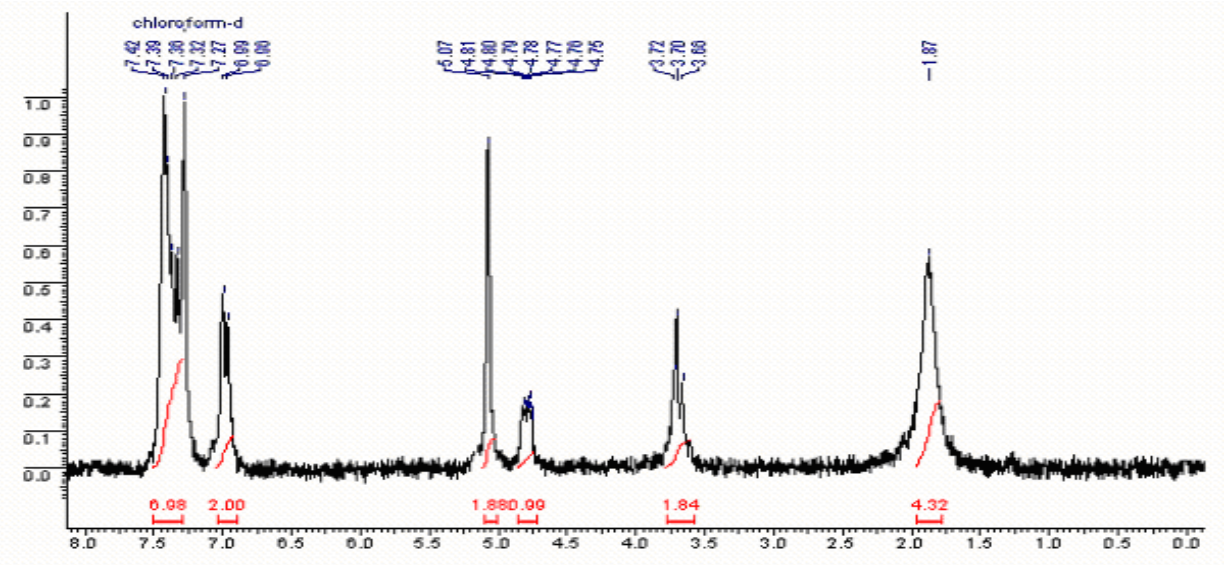
7. ^{1}HNMR spectrum of 1

8. ^{13}CNMR spectrum of 1

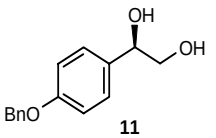
^{1}HNMR spectrum of **11**



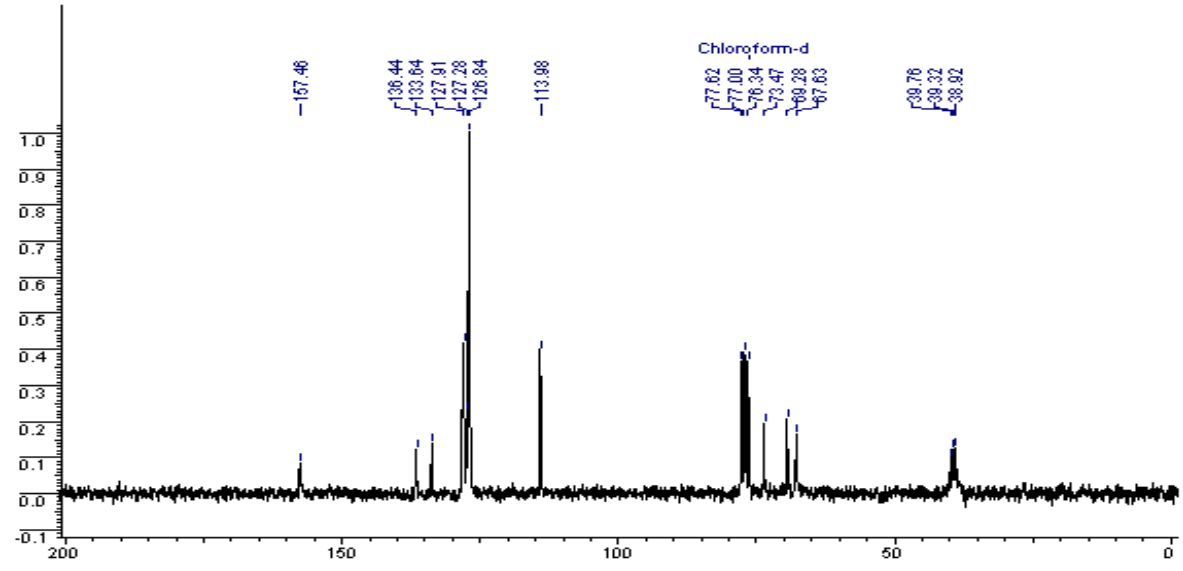
11



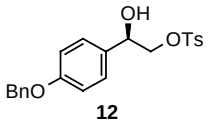
^{13}CNMR spectrum of **11**



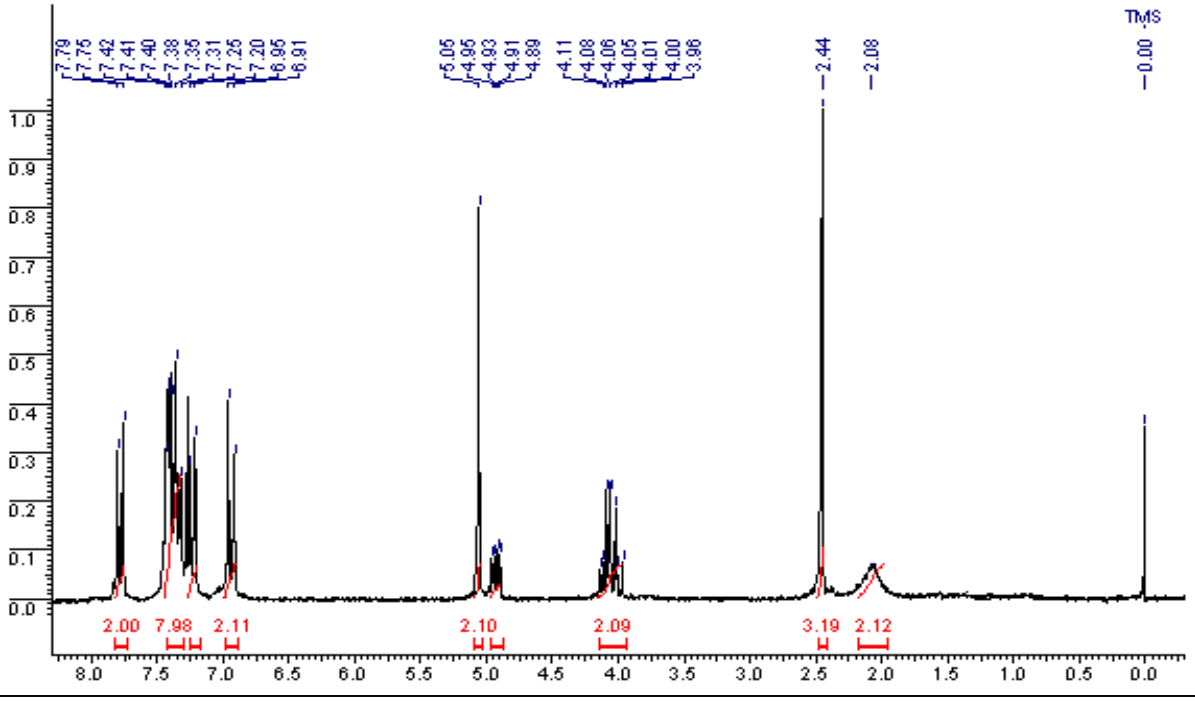
11



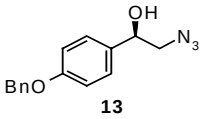
^{1}HNMR spectrum of **12**



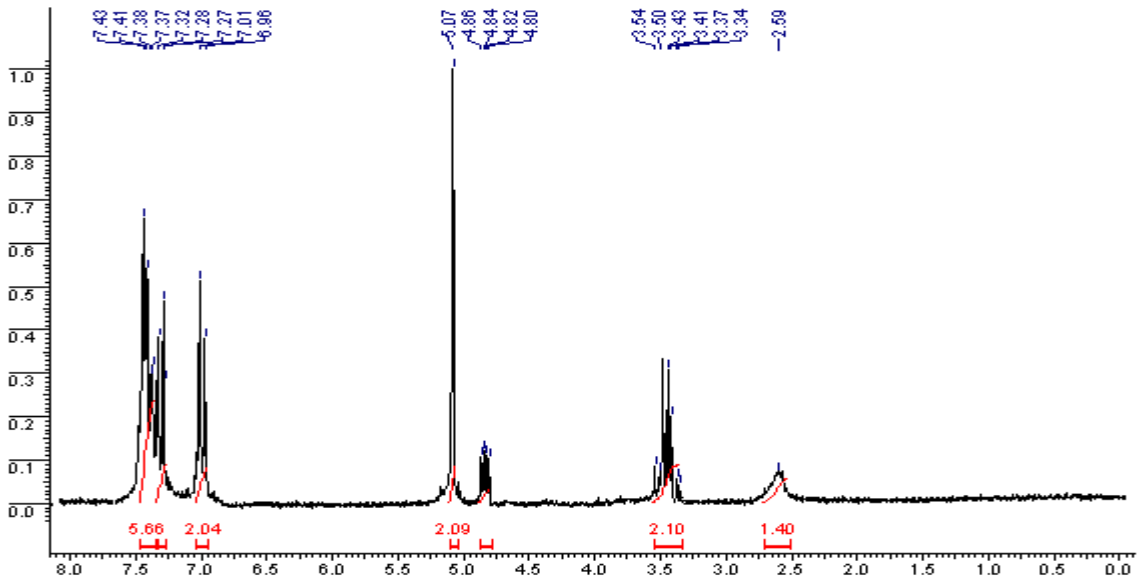
12

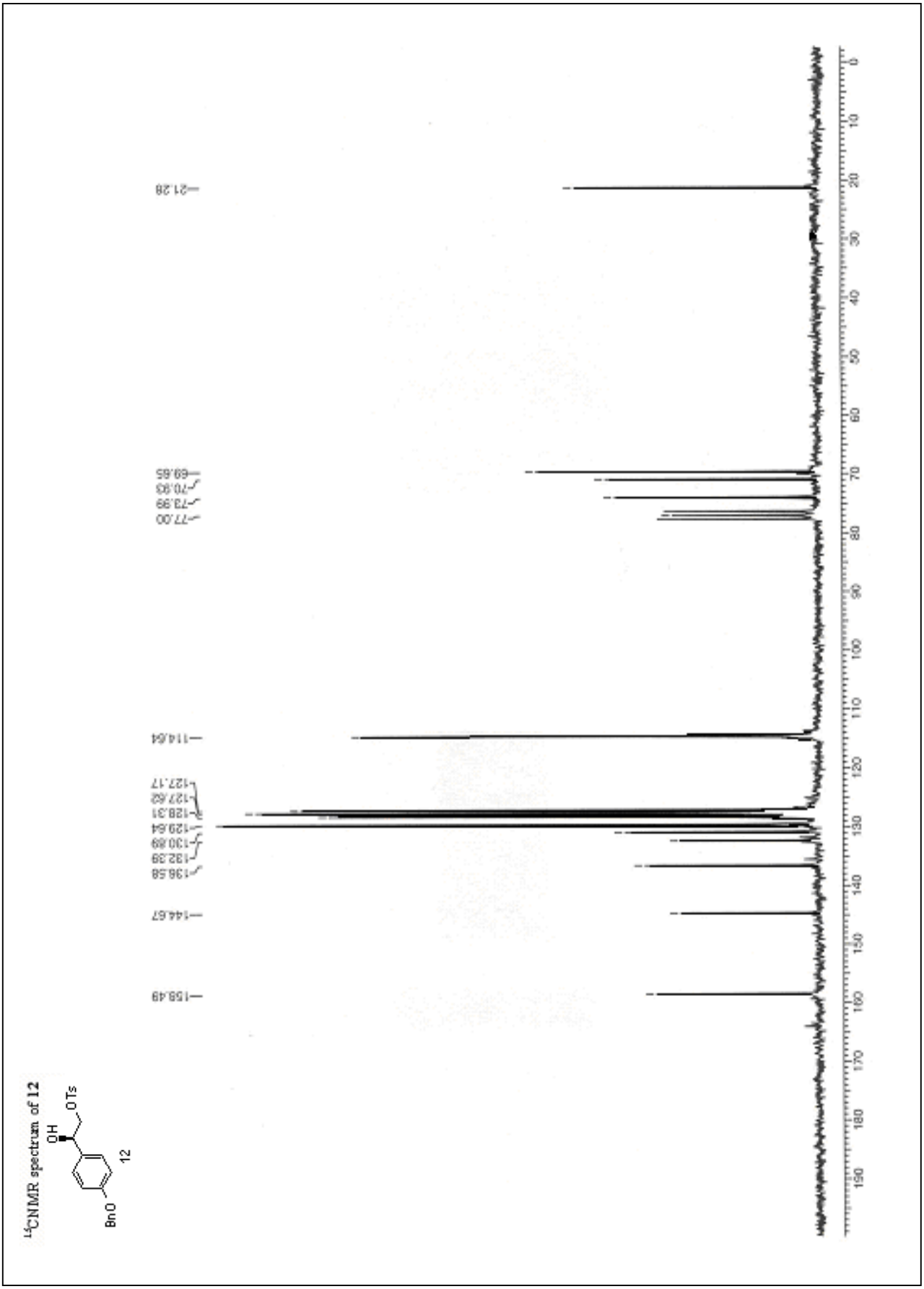


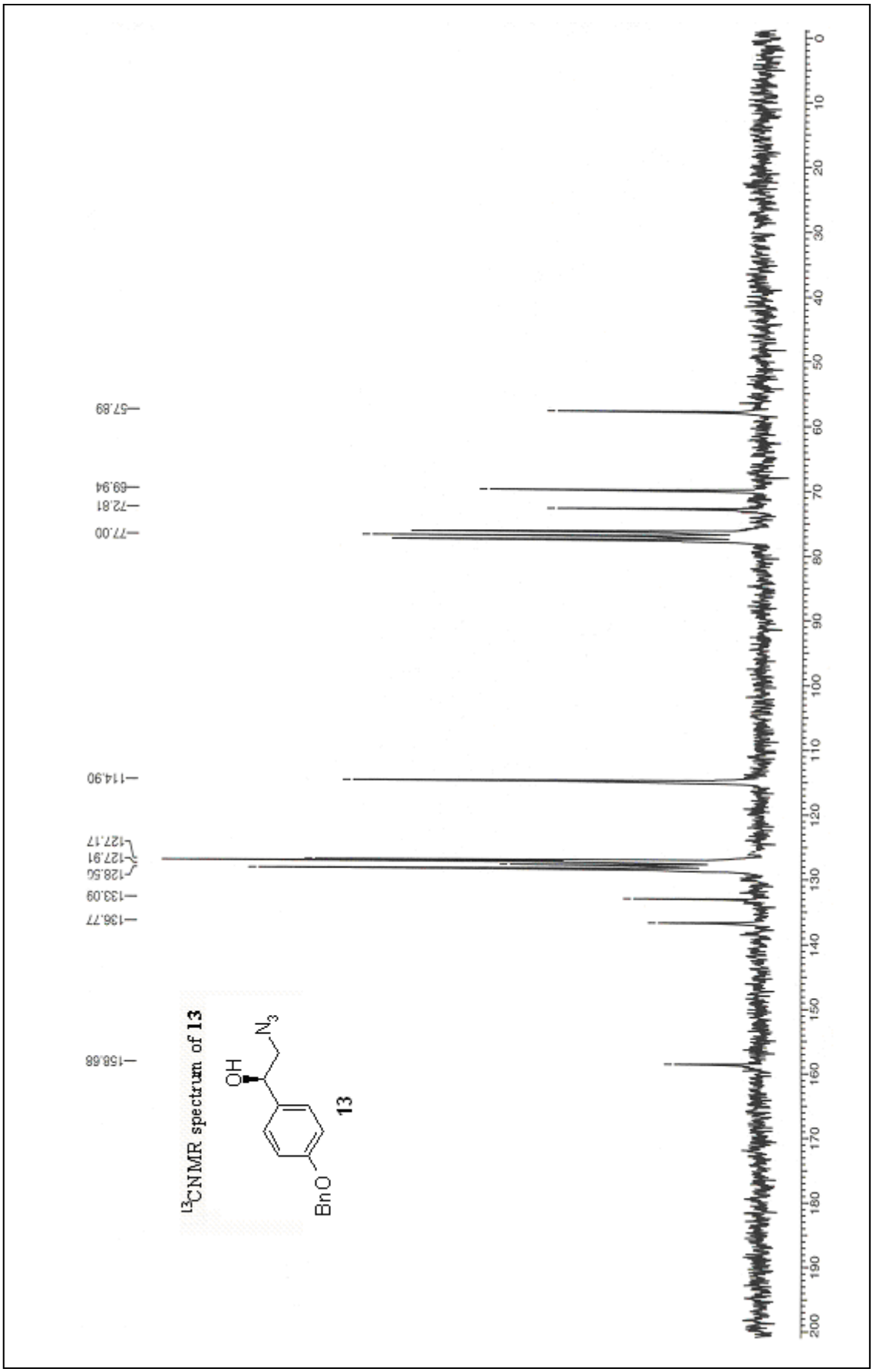
1HNMR spectrum of **13**



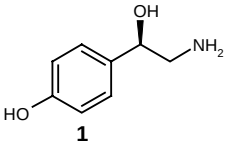
13



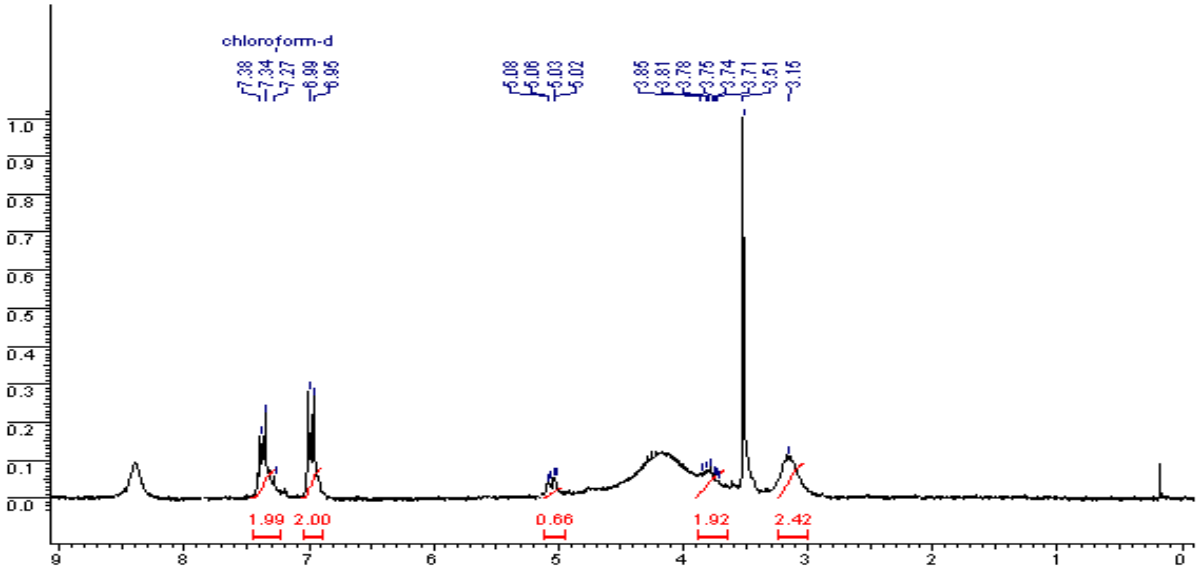

^{13}CNMR spectrum of 12
OH
OTs
BnO
12
21.28
69.85
70.85
73.99
77.00
114.64
127.17
127.62
128.31
129.64
130.89
132.39
136.58
144.67
158.49
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190


^{13}CNMR spectrum of **13**
OH
N_3
BnO
13
158.66
136.77
133.09
128.50
127.91
127.17
114.90
77.00
72.81
69.94
57.89

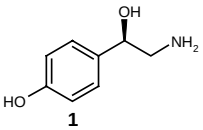
^{1}HNMR spectrum of **1**



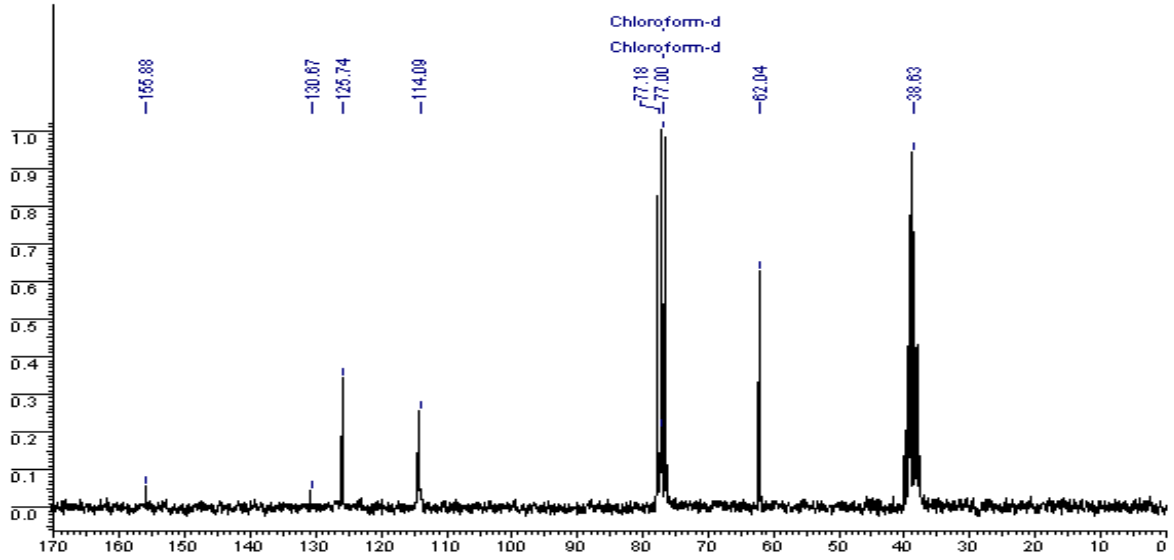
1



^{13}CNMR spectrum of **1**



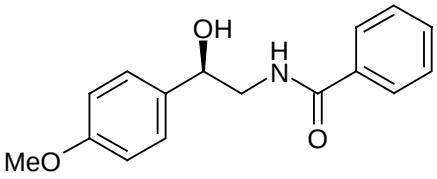
1



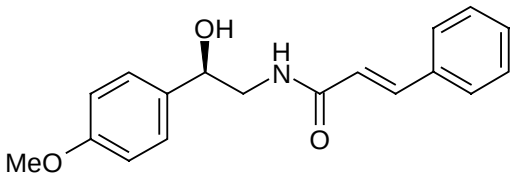
2.2 Section B
Enantioselective synthesis of (*R*)-tembamide (14a) and (*R*)-aegeline (14b)

2.2.1 Introduction

Tembamide **14a** and aegeline **14b** are naturally occurring hydroxyamides isolated from various members of the family Rutaceae[14] (Argentine species of *Fagara*). Tembamide was isolated from benzene extract of the bark of F. hyemalis (St. Hills) Engler. Tembamide and aegeline were also obtained from the extracts of *Aegle marmelos correa.* These hydroxyamides have been reported to have adrenaline-like and insecticidal activity.[15] They have been used in traditional indian medicine and have been shown to have good hypoglycemic activity.[16]



Tembamide **14a**



Aegeline **14b**

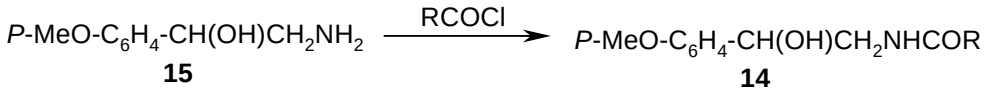
Tembamide **14a** and aegeline **14b** again the amide derivatives of β-amino aryl ethanols, possess a stereogenic center and have been isolated as total or partial racemates.[17] In view of its pharmacological importance along with its insecticidal properties, the enantioselective synthesis of these molecules has still attracted growing interest in recent years, because in most of the aryl ethanolamine drugs, in general the biological activity resides mainly in the (*R*)-enantiomer.[4] To date only a few methods for the preparation of these compounds have been reported, involving the resolution of a racemic mixture,[17] and a multi step synthesis using optically active cyanohydrins as starting materials.[18] Very recently, the asymmetric synthesis of (*R*)-tembamide and (*R*)-aegeline via enzymatic reduction of α-azido arylketones has been reported.[19] The latest one is CBS-oxazaborolide catalysed borane reduction of 1-substituted-2-(*p*-tosyloxy)ethanones.[8] Surprisingly there has been no report in the literature about the asymmetric synthesis of (*R*)-tembamide and (*R*)-aegeline employing the Sharpless asymmetric dihydroxylation procedure. As part of our research program aimed at developing enantioselective synthesis of naturally occurring lactones,[9] and aminoalcohols,[10] the Sharpless

asymmetric dihydroxylation[11] was envisaged as a powerful tool to chiral dihydroxy compounds offering considerable opportunities for synthetic manipulations. We have now developed a new and highly enantioselective synthesis of tembamide and aegeline through a common intermediate by employing the Sharpless asymmetric dihydroxylation as source of chirality.

2.2.2 Review of literature

Deulofeu *et al.* (1967)[17] Scheme 3: The enantiomers of amide could be prepared by resolving the 2-amino-1-*p*-methoxyphenylethanol **15** with tartaric acid and treating the optically pure salts with benzoyl chloride, when (+) and (-)-tembamide **14** with $[\alpha]_D^{20} \pm 55.8°$ ($CHCl_3$) were obtained. In ethanol, the rotation was of opposite sign.

Scheme 3



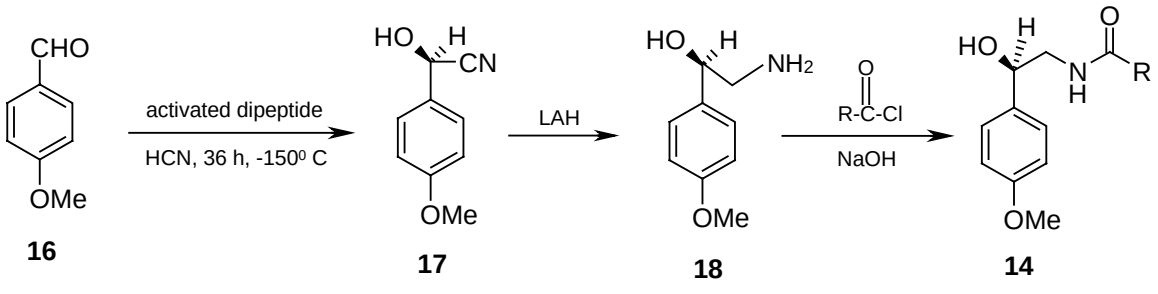
14a: R = Ph; Tembamide

14b: R = Ph-CH=CH-; Aegeline

By applying the method used for tembamide, both enantiomers of aegeline **14b** were synthesized.

Brown *et al.* (1994)[18a] Scheme 4: Involves optically active cyanohydrin as a key intermediate which in turn was prepared from its parent aldehyde using activated dipeptide [cyclo(phenyl alanylhistidyl, the Inoue catalyst].

Scheme 4

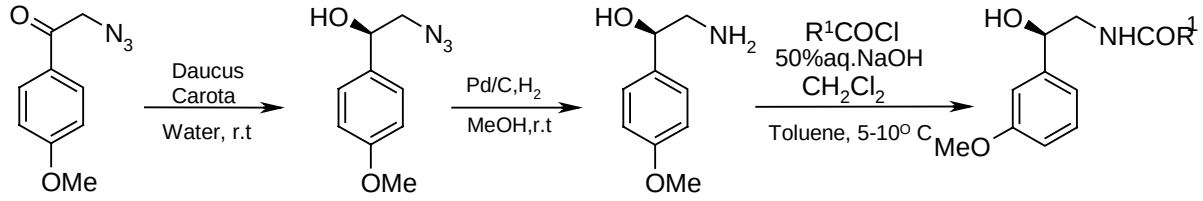


14a: R=Ph; $[\alpha]_D^{25}$ = -59.8

14b: R= Ph-CH=CH- ; $[\alpha]_D^{25}$ = -35.6

Yadav *et al.* (2001)[19] Scheme 5: This process used asymmetric bio-reduction of prochiral ketones (azidoketones) using plant cell culture Daucus carota in aqueous medium.

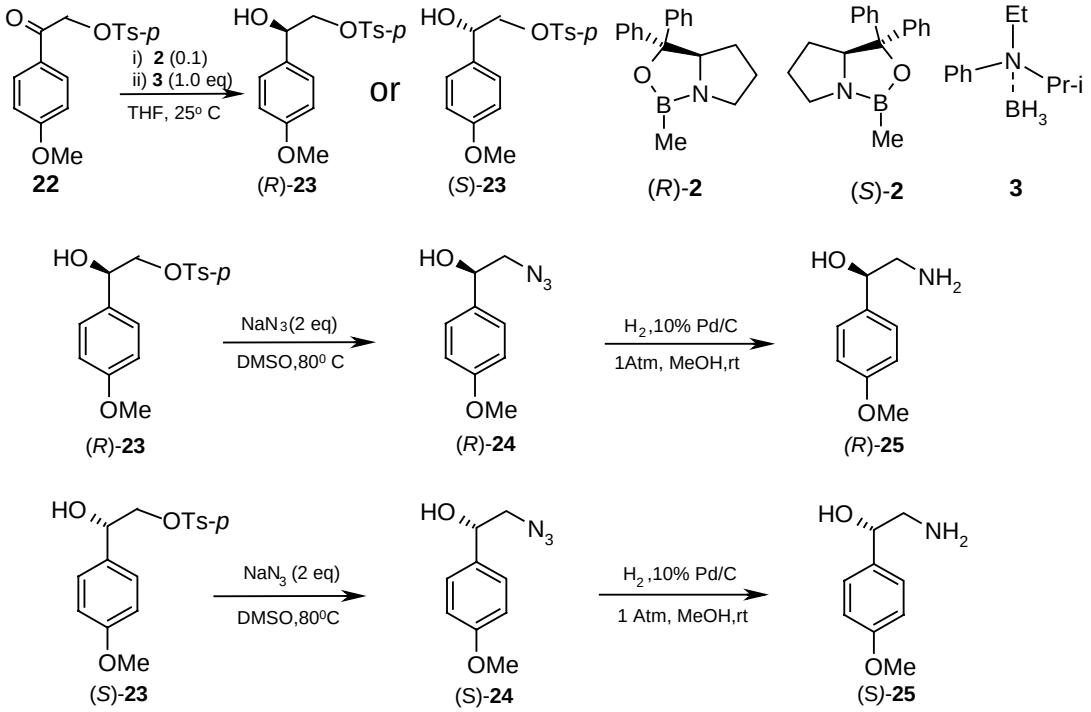
Scheme-5



14a; R = Ph, Tembamide
14b; R = trans- Ph-CH=CH-; Aegeline

Cho *et al.* (2002)[8] Scheme 6: CBS-oxazaborolidine-catalyzed borane reduction of 1-substituted-2-(*p*-tosyloxy)ethanones to 1,2-diol monotosylate is used as key step in this process (Scheme-6).

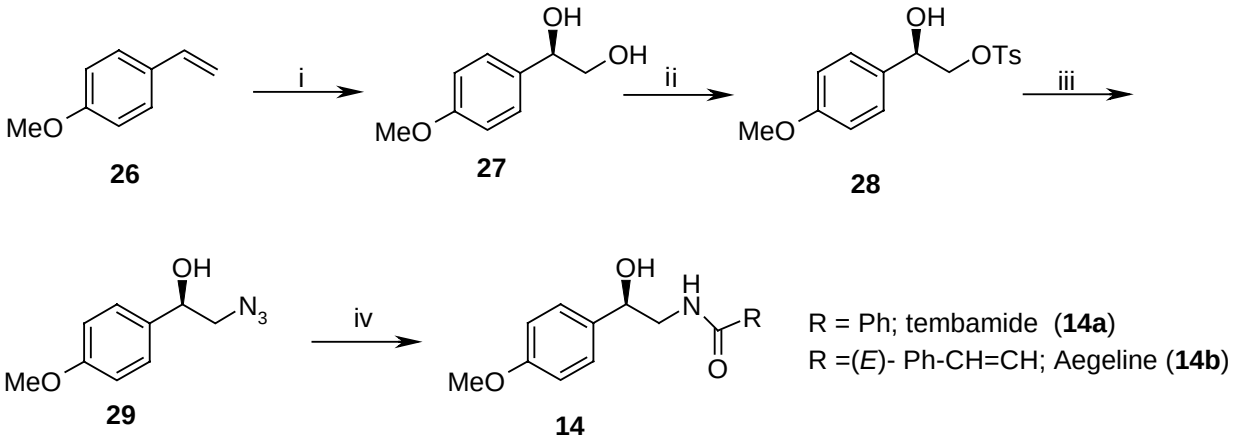
Scheme-6



2.2.3 Present work

Although the reported chemical and biological methods gave good enantio-selectivity, use of expensive reagents with multi-step synthesis, longer reaction time and low overall yield and the resolution methods suffer from the fact that the theoretical yields are limited to 50%. This prompted us to devise a practical method to synthesise (*R*)-(-) tembamide and (*R*)-(-)-aegeline, and to explore the chemistry of AD. We have now developed an enantiomerically pure and high yielding new route for the synthesis of (*R*)-(-)-tembamide and (*R*)-(-)-aegeline (**Scheme** 7).

Scheme-7



Scheme 7 ***Reagents and conditions*****:**

(i) $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, OsO_4, *t*-BuOH/H_2O (1:1), 0°C, 18 h, 93%; (ii) *p*-TsCl, pyridine, -15°C, 8 h, 76%; (iii) NaN_3/DMF, 80°C, 4 h, 93%; (iv) Pd/c, H_2, 8 h ; (b) 50% aq. NaOH, CH_2Cl_2, RCOCl, toluene, 0°C, 1h, 92%.

2.2.4 Results and discussion:

The present strategy for the synthesis of (*R*)-(-)-tembamide **14a** and (*R*)-(-)-aegeline **14b** is depicted in **Scheme 7**. 4-Methoxystyrene **26** was prepared by following the literature procedure from corresponding aldehyde. Compound **26** was subjected to asymmetric dihydroxylation using $(DHQD)_2PHAL$ as chiral ligand to furnish the diol **27** in 93% yield, and its optical rotation was measured as $[\alpha]_D^{20}$ -57.7 (*c* 1, $CHCl_3$). IR spectrum of **27** showed a band at 3279 cm^{-1} indicating the presence of hydroxyl functionality. The ^1H NMR spectrum showed the CH_2 proton attached to OH at δ 3.6-3.78 as multiplet. The CH proton appeared at δ 4.76 as doublet of doublet. The diol **27** was converted into the corresponding monotosylate compound **28** using pyridine as base in 80% yield. The IR spectrum of **28** showed a band at 3518 cm^{-1}, characteristic of -OH group. The mono tosylation of diol is marked by the presence of doublets at δ 7.25 and δ 7.75, in ^1H NMR spectrum, it is also confirmed by deshielding effect of tosyl group on CH_2 protons attached to it by shifting of δ values from 3.60-3.78 to 4.06-4.20. Also seen was the deshielding effect on -CH proton, the δ values shifted from 4.76 to 4.98. ^{13}C NMR spectrum of tosyl compound **28** showed a signal at 21.35 for CH_3 of the tosyl group. The optical rotation of **28** was measured as $[\alpha]_D^{20}$ = -53.0 (*c* 1,

$CHCl_3$). When **28** was treated with NaN_3 in dry DMF at 80°C, it gave the azido compound **29**. The formation of azido group was marked by appearance of a band at 2105 cm^{-1} in the IR spectrum. The band at 3441 cm^{-1} showed the presence of hydroxy functionality. The ^1H NMR spectrum of **29** showed the disappearance of doublets at δ 7.25 and δ 7.75 and appearance of new peak at δ 2.45 confirming the introduction of an azido group. The conversion of tosyl group into azido is again indicated by shielding effect of $–N_3$ group on $–CH_2$ protons. The chemical shift of $–CH_2$ groups is shifted to δ 3.35-3.50 from 4.06-4.20. The optical rotation is measured as $[\alpha]_D^{20}$ = -77.11 (*c* 1.02, $CHCl_3$). The mass spectrum showed a peak at 193 indicating M^+ ion. The elemental analysis of **29** was in good agreement with theoretical values. The azido compound **29** was treated with Pd/C under H_2 atmosphere at room temperature for 8h. After filtration of the catalyst, the amino alcohol was obtained as a pale yellow residue by concentration of the solvent. The residue was dissolved in CH_2Cl_2 and a solution of 50% aq. NaOH in water was added to it at 0°C and stirred for 15 min. Addition of benzoyl chloride in toluene to the above mixture and an additional stirring for 1h gave tembamide **14a** in 92% yield. The spectroscopic data, melting points and its optical rotation were in full agreement with the literature data.[19]Acylation of amino alcohol with (*E*)-cinnamoyl chloride under similar conditions gave aegeline **14b** in 90% yield. The physical and spectroscopic data, were in full agreement with the literature data.[19]

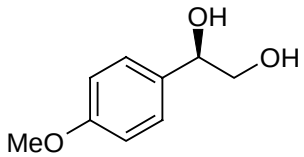
2.2.5 Conclusion:

In summary, a practical and highly enantioselective synthesis of (*R*)-(-)-tembamide and (*R*)-(-)-aegeline has been achieved for the first time using Sharpless asymmetric dihydroxylation as the source of chirality.

2.2.6 Experimental Section

Synthesis of 4-methoxystyrene (26): This was prepared by following the literature procedure.[10d]

(*R*)-1-(4-methoxyphenyl)-1, 2-ethanediol (27): To a solution of $K_3Fe(CN)_6$ (22.1 g, 67.07 mmol), K_2CO_3 (9.26 g, 67.07 mmol), $(DHQD)_2PHAL$ (174 mg, 0.224 mmol, 1 mol%) in *t*-BuOH : H_2O (1:1, 200 ml) was added OsO_4 (1.12 mL. 0.1 M soln in toluene, 0.5 mol%) at 0°C. After stirring for 5 min, 4-methoxystyrene **26** (3 g, 22.36 mmol) was added in one portion and the reaction mixture stirred for 18 h at 0°C. Solid Na_2SO_3 (3g) was added and stirred for 1 h. The organic layer was separated and the aqueous layer extracted with EtOAc (3×100 ml). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petrol ether: EtOAc (7:3) as eluent to give **27** (3.5 g, 93%) as a colorless solid.



27

Yield: 93%

M.P.: 103-105°C

$[\alpha]_D^{20}$: -57.7 (*c* 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3279, 2958, 1611, 1513, 1246

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.65 (s, 2H), 3.6-3.7 (m, 2H), 3.81 (s, 3H), 4.76 (dd, 1H, *J* = 4.40Hz, 7.81Hz), 6.92 (d, 2H, *J* = 8.79 Hz,), 7.26 (d, 2H, *J* = 8.79Hz)

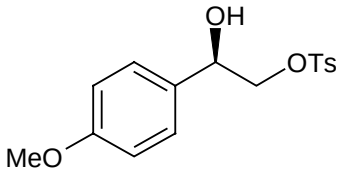
^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 54.0, 67.0, 72.9, 112.4 (2C), 126.3 (2C), 133.2, 157.7

EIMS (*m/z*, %): 168 [M^+] (3), 150 (1.5), 137 (69.3), 109 (42.3), 94 (71.53), 77 (100), 65 (38)

Analysis Calcd. for $C_9H_{12}O_3$ (168.19): Found: C, 64.15; H, 6.97{Required C, 64.27; H, 7.19}

(*R*)-2-(*O*-Tosyl)-1-(4-benzyloxyphenyl)-1, 2-ethanediol (28): To a solution of diol **27** (1.45 g, 5.94 mmol) in CH_2Cl_2 (50 mL) was added pyridine (0.72 mL, 8.91 mmol) and stirred for 15 min

at room temperature. The reaction mixture was cooled to −15°C and *p*-TsCl (1.13 g, 5.94 mmol) was added in three portions at time interval of 30 min. The reaction mixture was stirred for 8 h at −15°C and allowed to warm to room temperature. An aqueous solution of $CuSO_4.5H_2O$ (10%, 20 ml) and EtOAc (100 ml) were added and stirred for 30 min. The organic layer was separated and the aqueous layer extracted with EtOAc (2 × 50 ml). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petrol ether: EtOAc (17:3) as eluent gave **28** (1.89 g, 80%) as a colorless solid.



28

Yield: 80%

M.P.: 8-80°C

$[\alpha]_D^{20}$: -34.7 (*c* 0.5, $CHCl_3$);

IR ($CHCl_3$, cm^{-1}): ν_{max} 3518, 2938, 1612, 1514, 1359, 1250, 1176

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.20 (brs, 1H), 2.45 (s, 3H), 3.81 (s, 3H), 4.07 (dd, 1H, *J* = 3.41Hz, 8.30Hz), 4.89 (s, 1H), 6.88 (d, 2H, *J* = 8.79Hz), 7.21 (d, 2H, *J* = 8.79Hz), 7.25 (d, 7H, *J* = 7.81Hz), 7.75 (d, 2H, *J* = 7.81Hz)

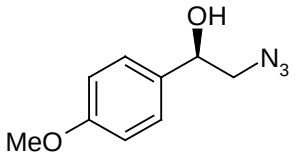
^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4, 55.0, 71.0, 74.1, 113.8 (2C), 127.3 (2C), 127.7 (2C), 129.7 (2C), 130.6, 132.4, 136.6, 144.8, 159.3

EIMS (*m/z*, %): 322 [M^+] (6.2), 304 (22.8), 392 (18.4), 264 (60.6), 252 (86), 227 (100), 196 (28.7), 172 (61.9), 149 (31.8)

Analysis Calcd for $C_{16}H_{18}SO_5$ (322.38): Found C, 61.41; H, 5.46; S, 9.86{Required C, 59.61; H, 5.62; S, 9.95}

(*R*)-2-Azido-1-(4-methoxyphenyl)-ethanol (29): To a solution of **28** (500 mg, 1.55 mmol) in dry DMF (10 ml) was added NaN_3 (605 mg, 9.3 mmol) and stirred at 80°C for 4 h. The reaction mixture was cooled to room temperature and diluted with water and EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc (3×20 ml). The combined organic layers were washed with water and then brine, and dried (Na_2SO_4) and

concentrated. The residue was purified by silica gel column chromatograpy using petrol ether: EtOAc (17:3) as eluent to give azido alcohol **29** (278 mg, 93%) as a colorless oil.



29

Yield: 93%

$[\alpha]_D^{20}$: −77.11 (*c* 1, $CHCl_3$) {lit.[19] $[\alpha]_D^{20}$ −117.4 (*c* 1.30, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3441, 2934, 2105, 1612, 1513, 1250, 832, 493

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.18 (s, 1H), 3.35-3.50 (m, 2H), 3.82 (s, 3H), 4.83 (dd, 1H, *J* = 4.40, 7.81Hz), 6.93 (d, 2H, *J* = 8.79Hz), 7.33 (d, 2H, *J* = 8.79Hz)

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.2, 57.9, 72.8, 113.9 (2C), 127.1 (2C), 132.8, 159.5

EIMS (*m/z*, %): 193 [M^+] (7.16), 162 (1.3), 137 (100), 109 (45.8), 94 (43.8), 77 (47.7), 66 (23.8)

Analysis Calcd. for $C_9H_{11}O_2N_3$ (193.2):. Found: C, 56.1; H, 5.79; N, 21.59. {Required C, 55.95; H, 5.74; N, 21.74}

(***R*)-(-)-Tembamide (14a):** To a solution of azido alcohol **14a** (500 mg, 2.58 mmol) in MeOH (5 ml) was added 10% Pd/C (20 mg) and the reaction mixture stirred at room temperature under hydrogen atmosphere (filled in a balloon) for 8 h. The catalyst was removed by filtration and the filtrate concentrated to give the amino alcohol. The residue was dissolved in CH_2Cl_2 (4 ml) and a solution of 50% aq NaOH (713 mg) in water (5 ml) was added at 0°C and stirred for 15 min. To the reaction mixture was added a solution of benzoyl chloride (0.37 mL, 3.23 mmol) in dry toluene (2 ml) dropwise and stirred for further 1 h. The solvent was removed in vacuo and the residue was diluted with cold water and extracted with EtOAc (3 × 50 ml). The combined organic layers were washed with water, brine and dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petrol ether: EtOAc (1:1) to give **14a** (645 mg, 92%) as a colorless solid. It was further recrystallized from petrol ether: EtOAc. Mp 154–156°C [lit.[19] 154-155°C]; $[\alpha]_D^{20}$ −60.45 (*c* 0.52, $CHCl_3$) {lit.[19] $[\alpha]_D^{25}$ -59.6[*c* 0.52, $CHCl_3$]. The spectroscopic data were in full agreement with literature data.[8, 19]

(*R*)-(-)-Aegeline (14b): Acylation of the intermediate amino alcohol with (*E*)-cinnamoyl chloride under similar condition as described above gave **14b** as white solid in 90% yield. Mp 196−198°C [lit.[19] 195−196°C]; $[\alpha]_D^{25}$ −35.21 (*c* 0.4, $CHCl_3$) {lit.[19] $[\alpha]_D^{20}$ −36.1 (*c* 0.45, $CHCl_3$)}. The spectroscopic data were in full agreement with the literature data.

2.2.7 Spectra

1. ^{1}HNMR spectrum of 27

2. ^{13}CNMR spectrum of 27

3. ^{1}HNMR spectrum of 28

4. ^{13}CNMR spectrum of 28

5. ^{1}HNMR spectrum of 29

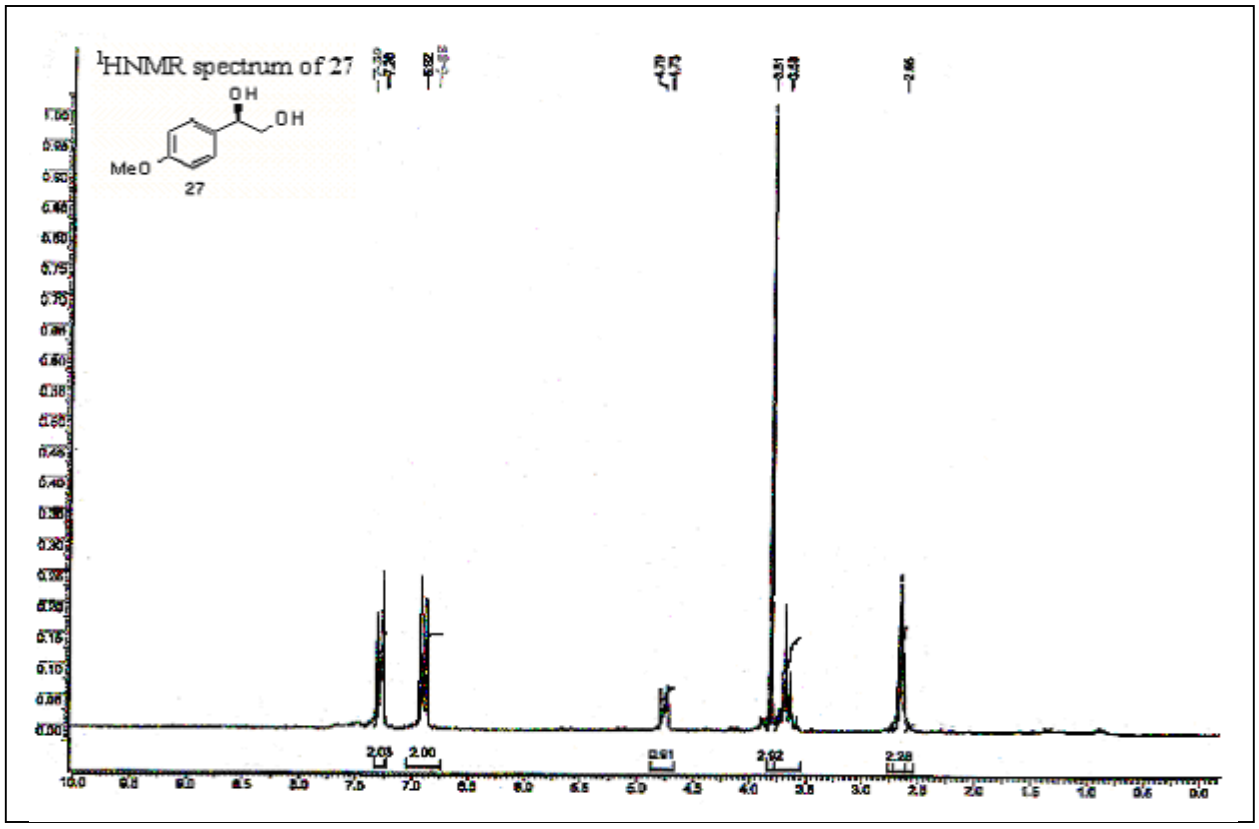
6. ^{13}HNMR spectrum of 29

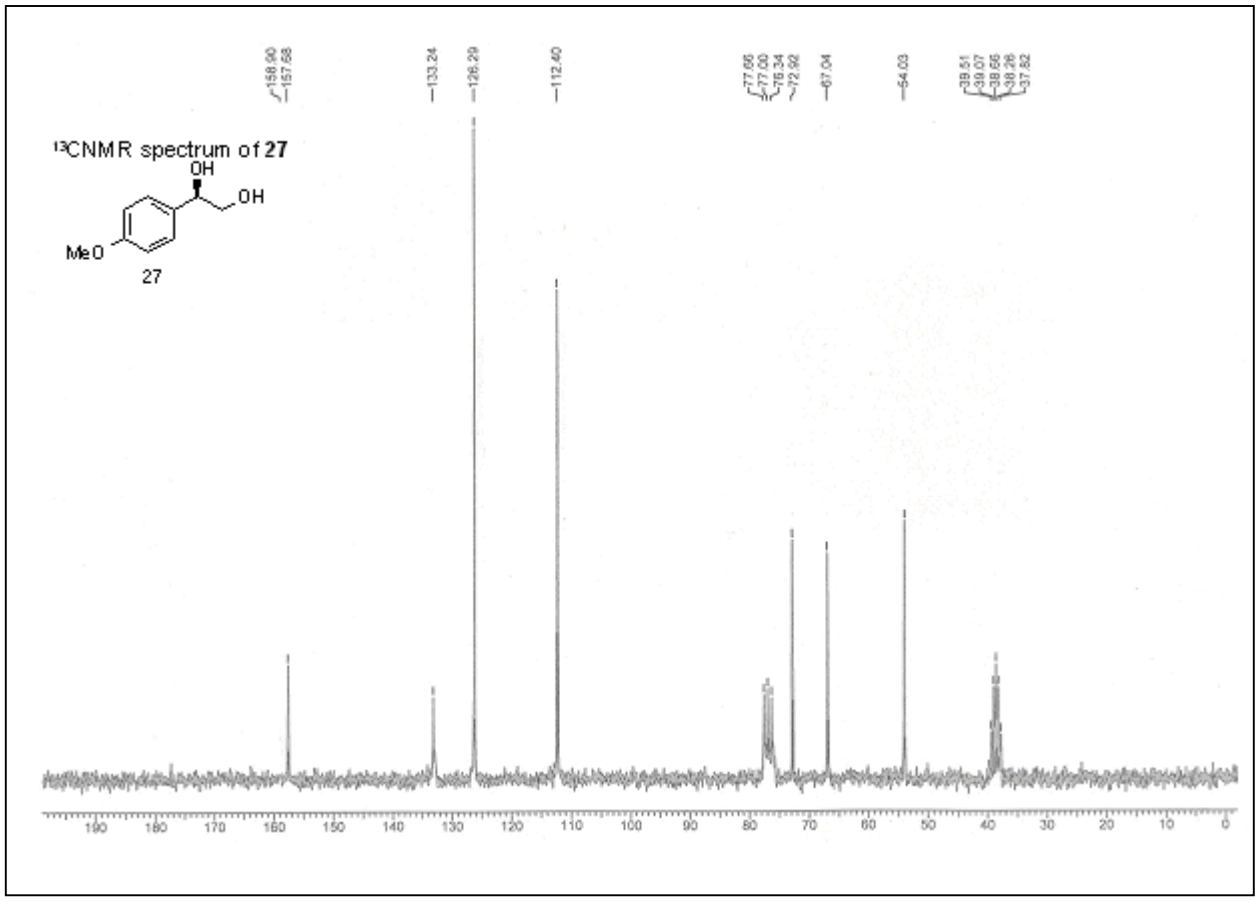
7. ^{1}HNMR spectrum of 14a

8. ^{13}CNMR spectrum of 14a

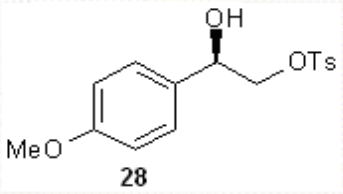
9. ^{1}HNMR spectrum of 14b

10. ^{13}CNMR spectrum of 14b


^{1}HNMR spectrum of 27
OH
OH
MeO
27

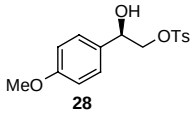

^{13}CNMR spectrum of 27
OH
OH
MeO
27

^{1}HNMR spectrum of **28**

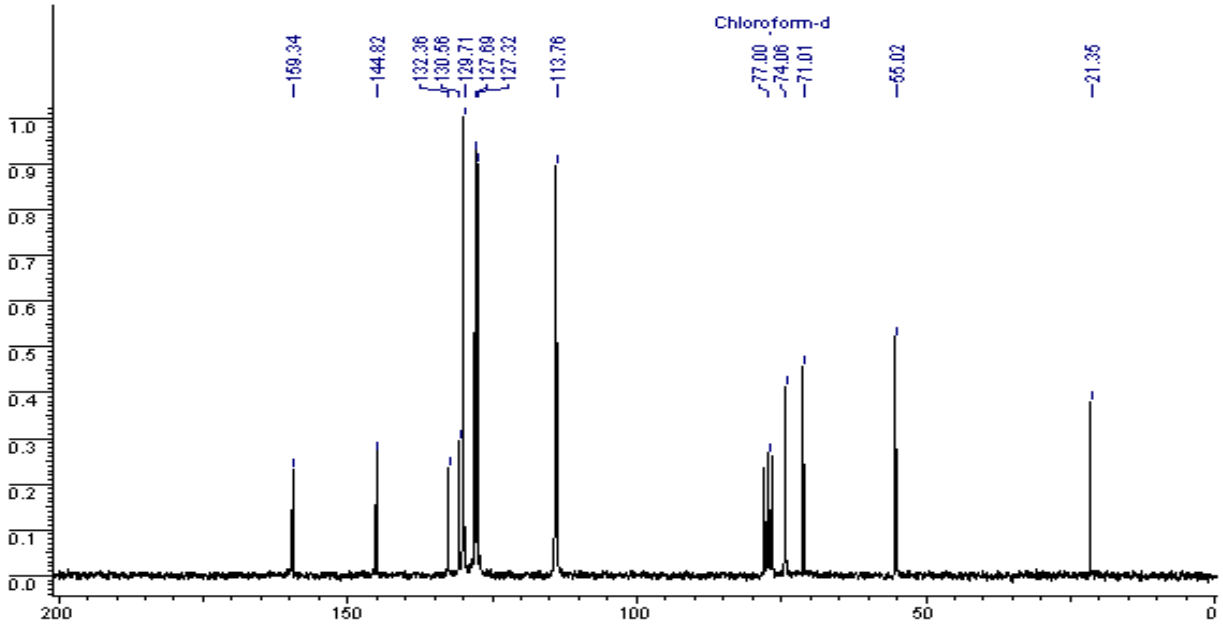


28

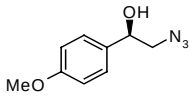
^{13}CNMR spectrum of **28**



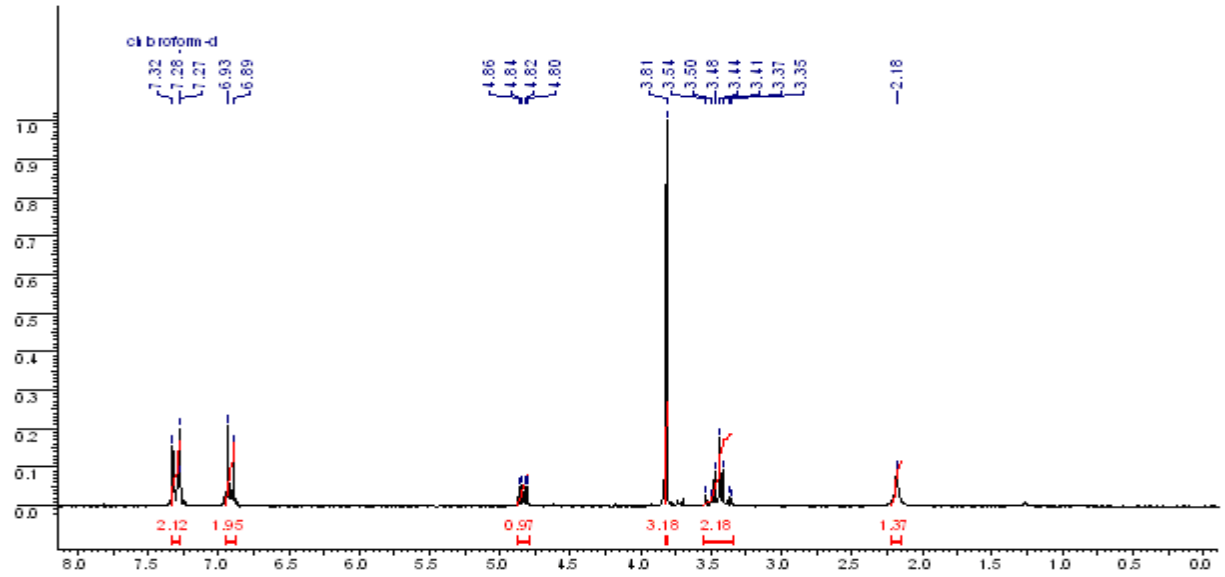
28



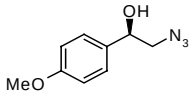
^{1}HNMR spectrum of **29**



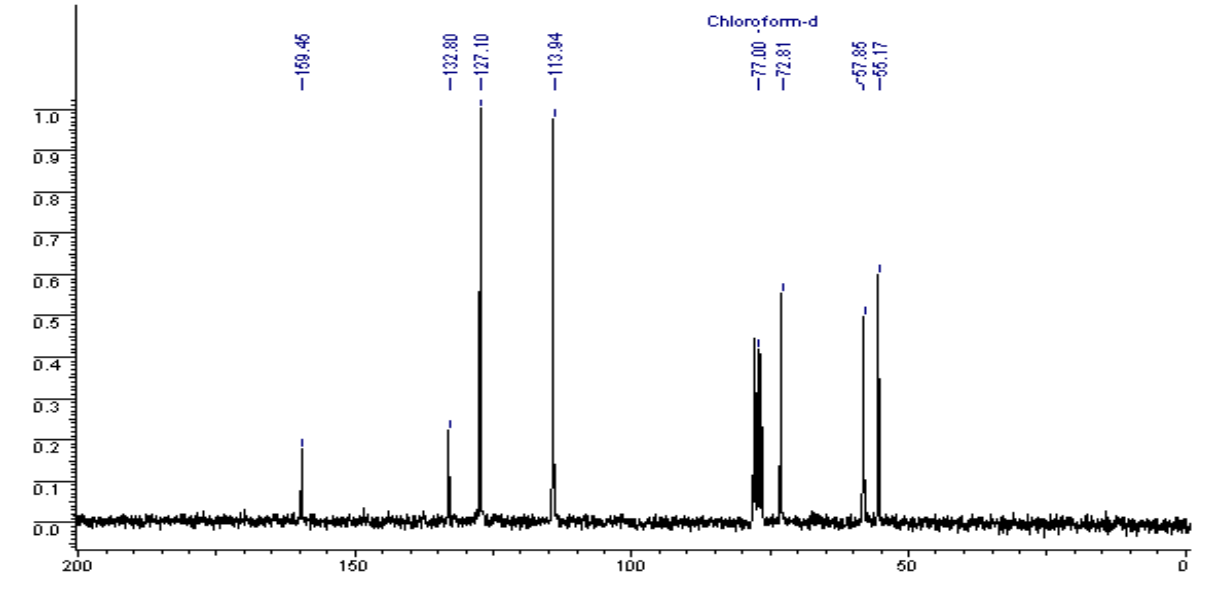
29



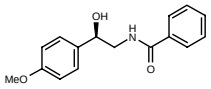
13CNMR spectrum of **29**



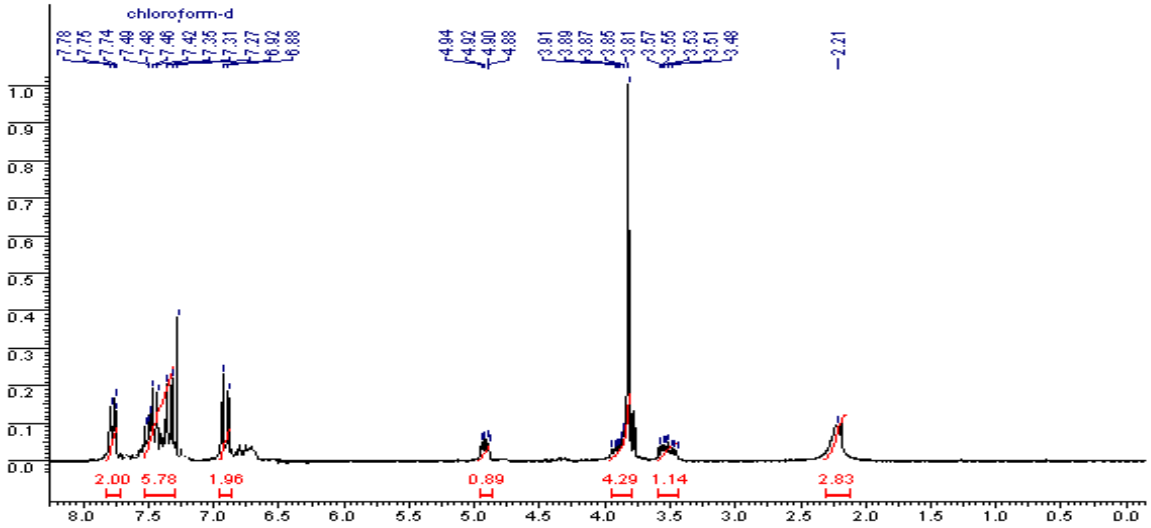
29



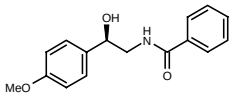
^{1}HNMR spectrum of **14a**



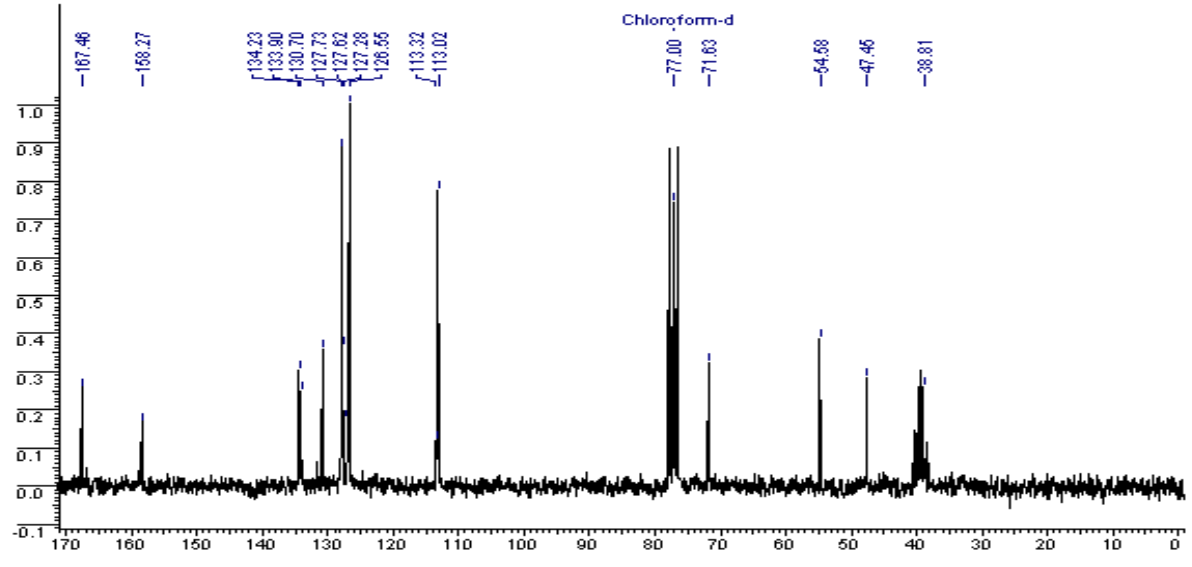
Tembamide **14a**



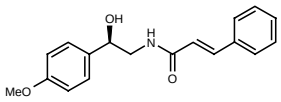
^{13}CNMR spectrum of **14a**

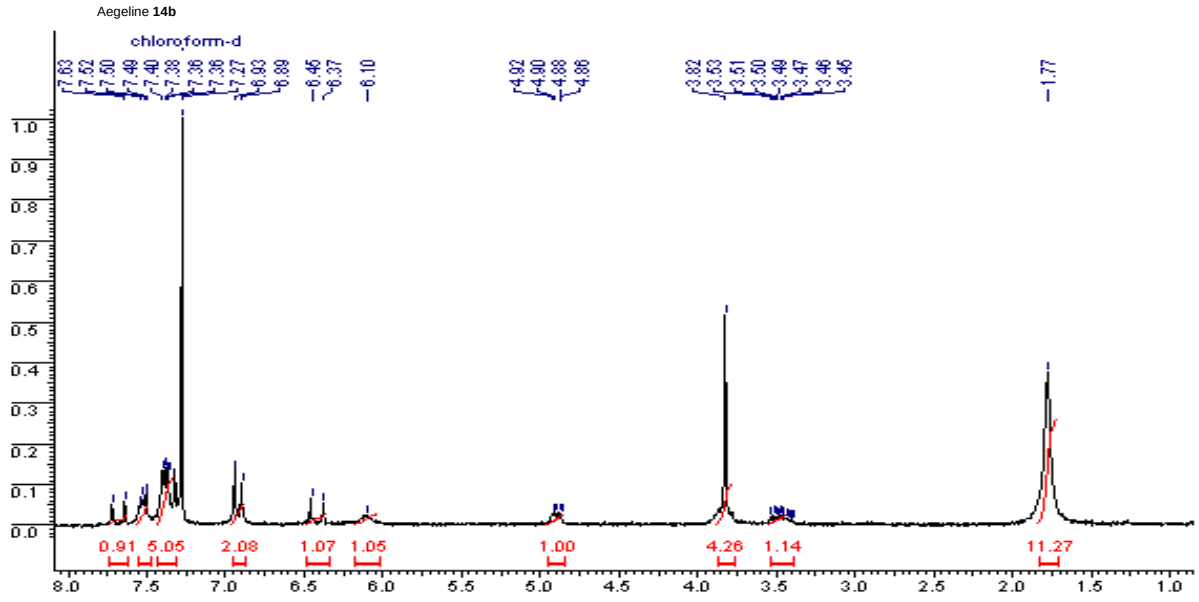


Tembamide **14a**

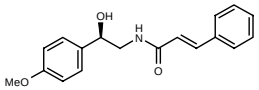


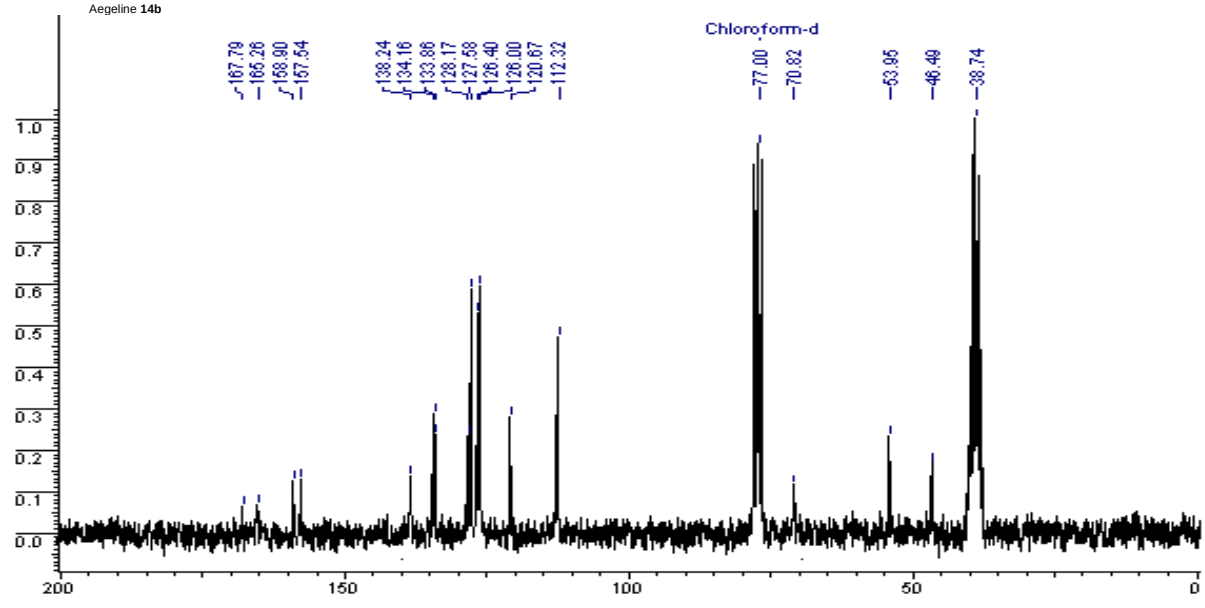
^{1}HNMR spectrum of **14b**





^{13}CNMR spectrum of **14b**



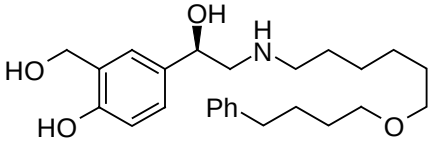


2.3 Section C Enantioselective synthesis of (*R*)-(-)-Denopamine (30)

2.3.1 Introduction

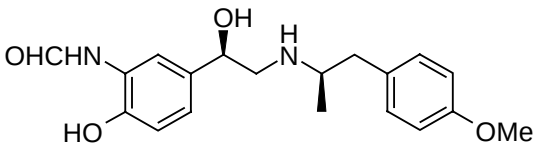
In drug formulation, along with the clear preference of using enantiomerically pure compounds, since the biological activity generally resides in a single enantiomer, the other important aspect to be considered is drug specificity and duration of action.[20] Inspite of these, recent advances have produced β-blockers and agonists that are highly effective in the treatment of cardiovascular disease, asthma and glaucoma, many β-adrenoreceptor active drugs are sold as racemates.[4] Amongst various β-adrenoreceptor agonist currently available, some of them are not selective and produce important side effects, such as "isoproterenol"[21] or display a short effect, such as salbutamol and terbutaline.[22] Though there are many selective β-adrenoreceptors available in the market, denopamine **30** is a relatively new[23a] β-receptor agonist.[23b,c] Denopamine, the [(±)-α-α-(3,4-dimethoxyphenylethylamino-methyl)-4-hydroxy benzyl alcohol] is an important β-adrenoreceptor agonists marketed as racemates of which the (*R*)-enantiomer is the active component, and (*S*)-(+)-isomer being much less active (approximately 1%) as potent as denopamine.[23a, 24]

The advantages of denopamine **30** over other drugs possessing positive inotropic activity is that it can be administered orally and has reduced toxicity. (*R*)-(-)-Denopamine is the first orally active and long-acting positive inotropic agent with a selective β-adrenoceptor agonistic activity to be brought into clinical use. It is effective in the treatment of congestive heart failure by increasing cardiac pumping function (Positive inotropic activity) without a significant increase in heart rate.[2]



(*R*)-Salmeterol

31



(*R*,*R*)-Formoterol

32

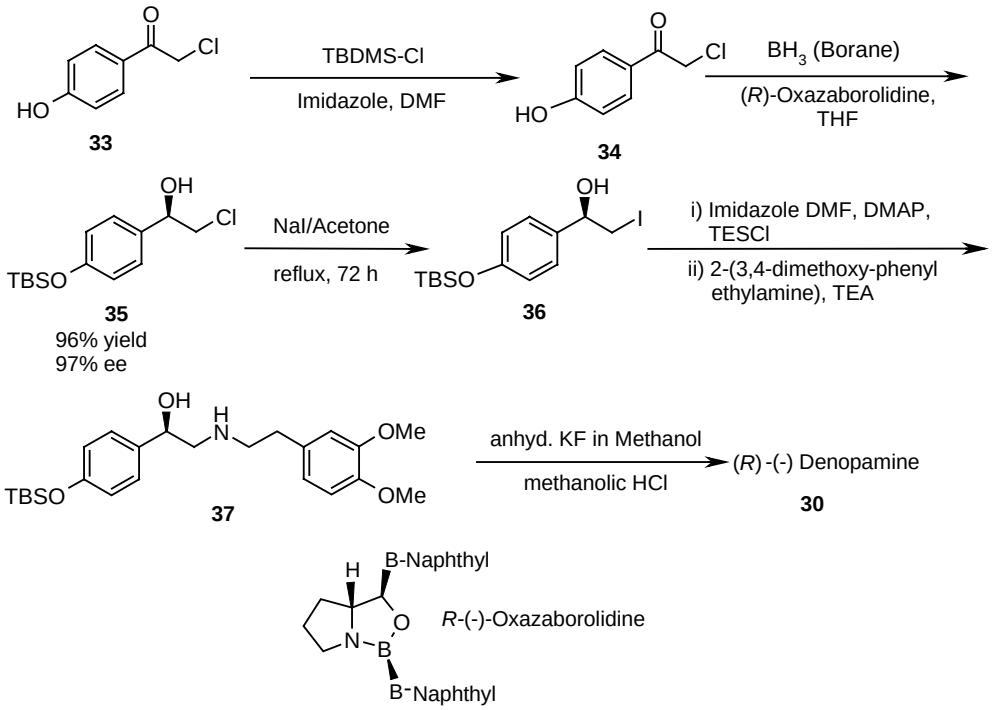
Other selective β-adrenoceptor drugs[26a,b]

2.3.2 Review of literature:

Earlier approaches to (*R*)-(-)-denopamine involve optical resolution or the use of chiral precursors with low overall yields.[27]

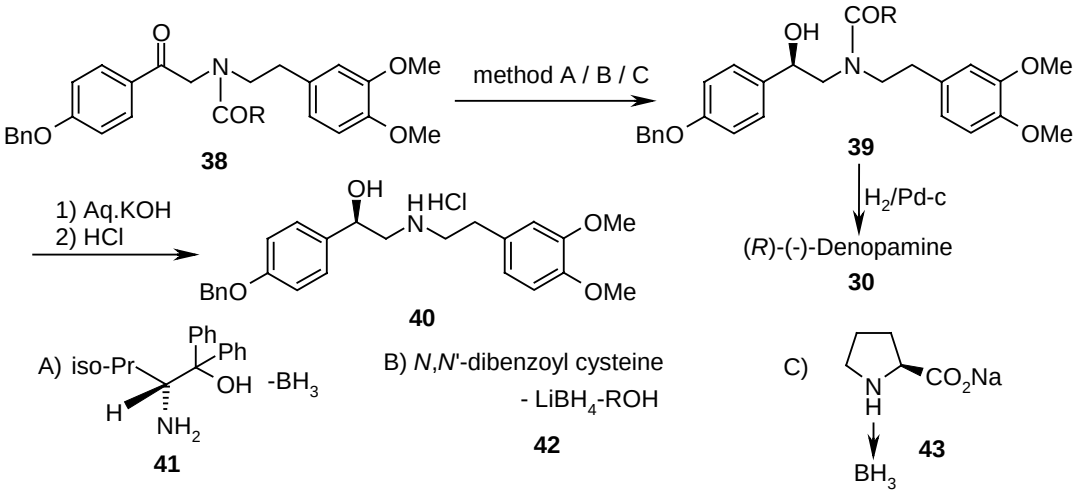
Corey *et al.* (1991)[28a] Scheme 8: A practical route to enantiomerically pure (*R*)-(-)-denopamine or its enantiomer is described in >60% overall yield that does not involve chromatography. This method demonstrates the applicability of the recently described CBS[4b] enantioselective catalysed reduction process to the synthesis of enantiomerically pure members of the therapeutically significant aryl ethanolamine drug class.

Scheme-8



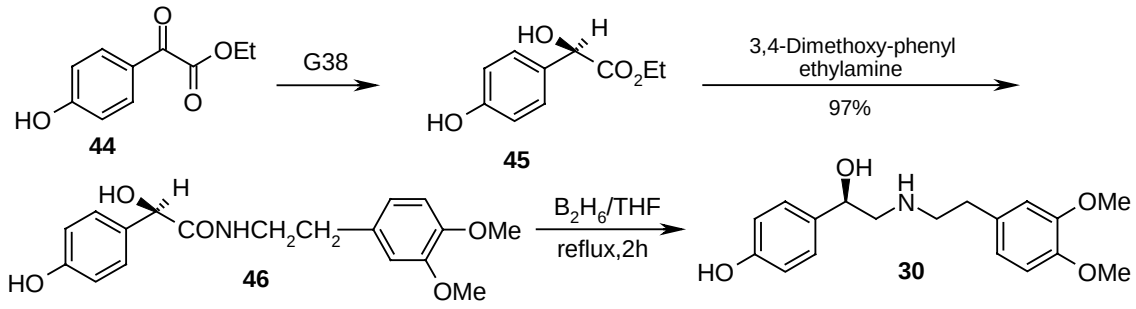
Matsuki *et al.* (1993)[29] Scheme 9: Asymmetric reduction of the *N*-protected amino ketone **38** with several chiral reducing agents i.e, (*R*)-(+)-2-amino-3-methyl-1,1-diphenylbutanol borane complex **41** (method A) (*S*,*S*')-*N*,*N*' dibenzoylcysteine $LiBH_4$-ROH complex **42** (method B) and sodium (*S*)-prolinate-borane complex **43** (method C), was investigated in an attempt to synthesize denopamine **30** enantioselectively. Reduction of **38** by method B in THF at 2-3°C gave the best result (88% ee) with 95% chemical yield.

Scheme-9



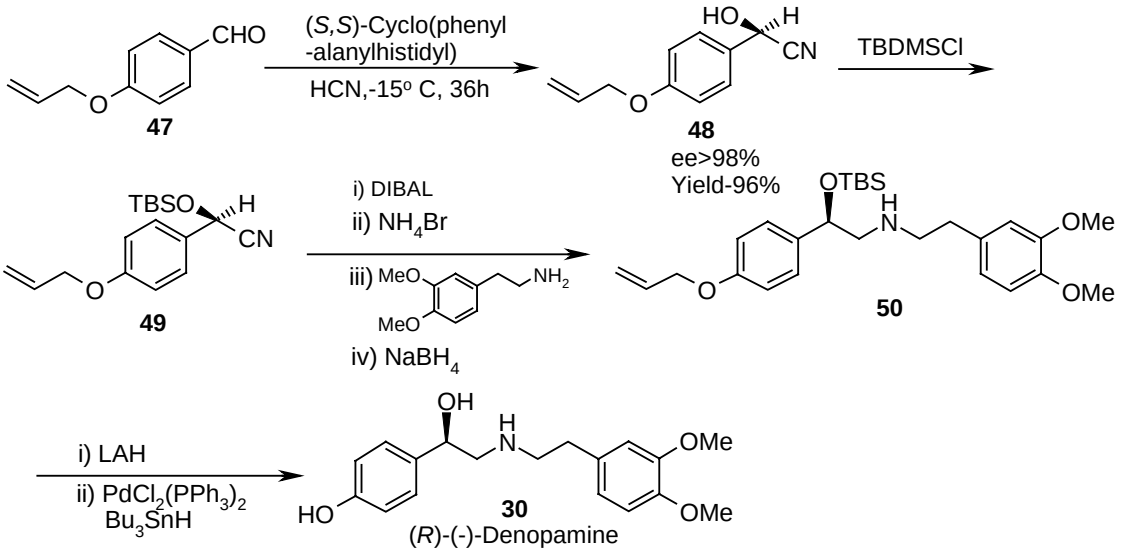
***Lin et al.* (1993)[30] Scheme 10**: Reductive bio-transformation of carbonyl compounds using fungus, Geotrichum sp. G38 is the key step in this synthesis.

Scheme-10



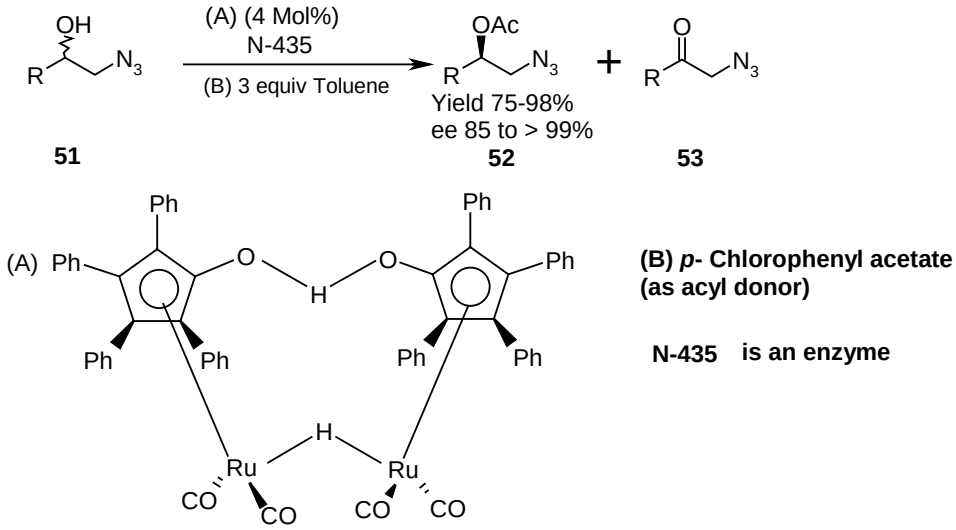
Brown *et al.* (1993)[31] Scheme 11: Brown *et al.* used the chiral cyanohydrin **48** as a key intermediate which in turn was prepared by addition of HCN to *p*-allyloxybenzaldehyde in presence (*S*,*S*)-cyclo(phenylalanylhistidyl) as catalyst at -15°C.

Scheme-11



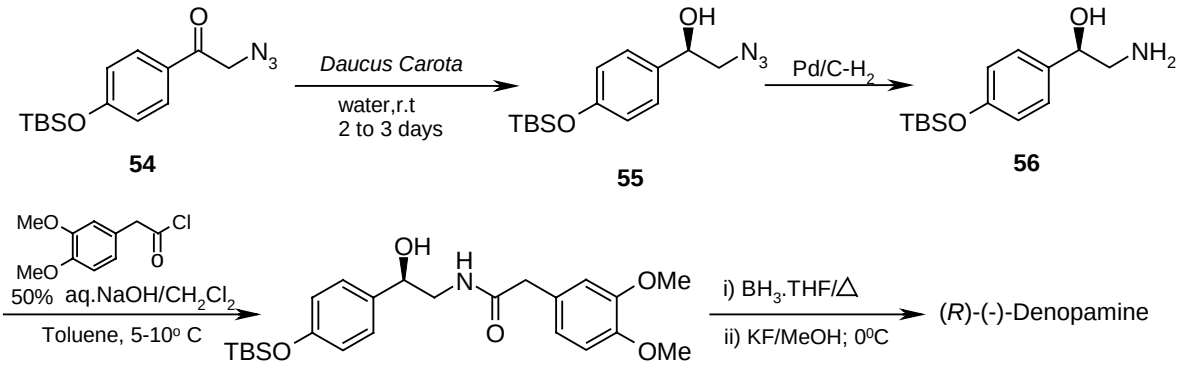
Backvall *et al.* (2001)[32] Scheme 12: Enzymatic resolution of β-azido alcohols in combination with ruthenium catalysed alcohol isomerisation led to a successful dynamic kinetic resolution. This method was used to synthesise (*S*)-propanalol and (*R*)-denopamine.

Scheme-12



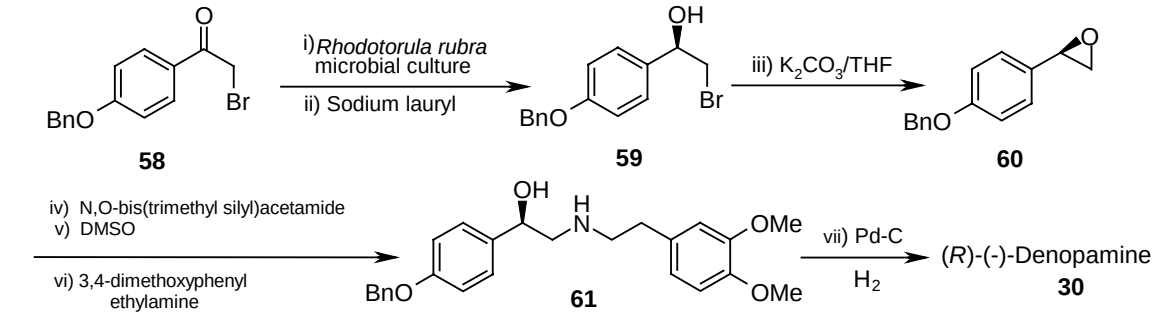
Yadav *et al.* (2001)[33] Scheme 13: This process involves stereoselective bio-reduction of prochiral α-azidoarylketones, using the plant cell cultures of <u>*Daucus Carota*</u> root in aqueous medium.

Scheme-13



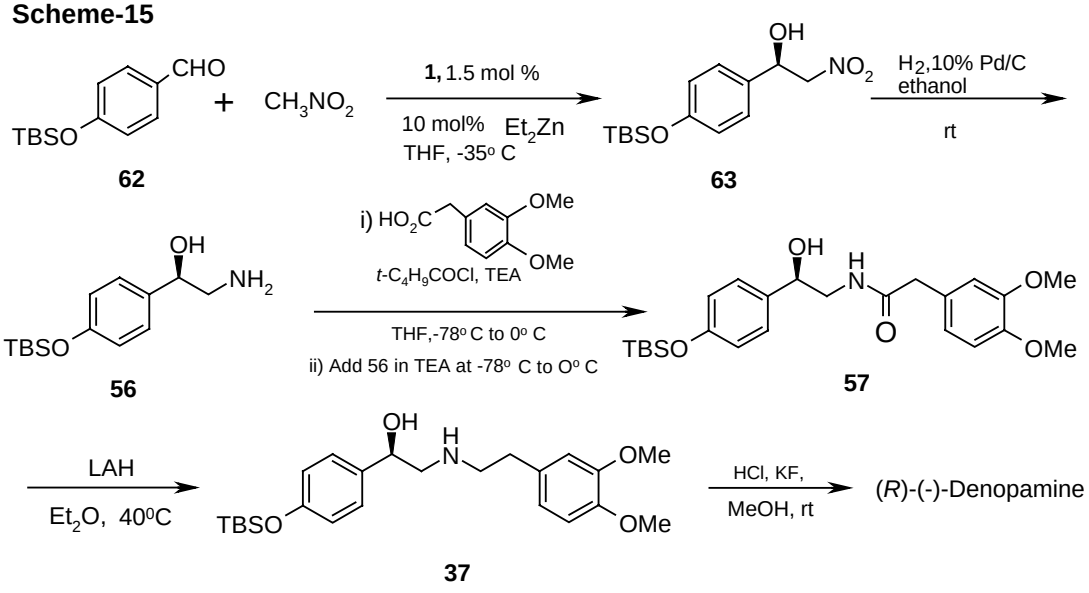
Goswami *et al.* (2001)[34] Scheme 14: Goswami *et al.* utilized the reductive bio-transformation of ω-bromoacetophenone to the corresponding chiral alcohol using <u>*Rhodotorula rubra*</u> microbial culture with very encouraging yield and enantio-selectivity.

Scheme-14

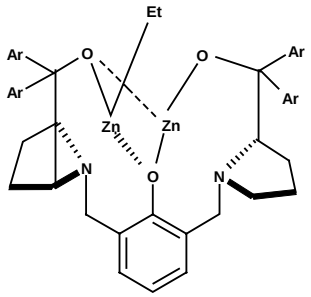


Trost *et al.* (2002)[35a] Scheme 15: Catalytic enantioselective nitroaldol (Henry reaction) reactions promoted by variously modified ligand with dinuclear zinc catalyst led to efficient synthesis of the β-receptor agonist (-)-denopamine.

Scheme-15


CHO
TBSO
+ CH_3NO_2
1, 1.5 mol %
10 mol% Et_2Zn
THF, -35° C
OH
NO_2
TBSO
H_2,10% Pd/C
ethanol
rt
62
63
OH
NH_2
TBSO
56
i) HO_2C
OMe
OMe
t-C_4H_9COCl, TEA
THF,-78° C to 0° C
ii) Add 56 in TEA at -78° C to O° C
OH
H
N
O
TBSO
OMe
OMe
57
LAH
Et_2O, 40°C
OH
H
N
TBSO
OMe
OMe
37
HCl, KF,
MeOH, rt
(*R*)-(-)-Denopamine

1

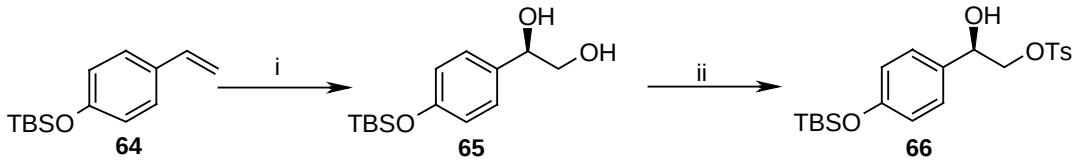

Et
Ar
Ar
O
O
Ar
Ar
Zn
Zn
N
O
N

2.3.3 Present work:

Objective:

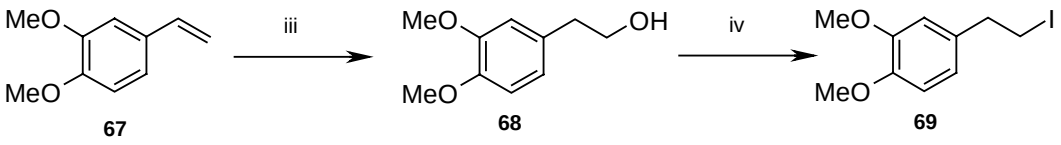
Despite the methods described above showing overall good yields, these methods involve either tedious chemical and biological methods or require use of expensive reagent with multi-step synthesis. The biochemical process involves longer reaction time. The resolution methods suffer from the fact that the theoretical yields are limited to 50%. Though there are many methods reported for the target molecule, surprisingly there has been no report in the literature using Sharpless asymmetric dihydroxylation. As part of our research programme aimed at developing enantioselective synthesis of naturally occurring lactones,[9] and amino alcohols,[10] the Sharpless asymmetric dihydroxylation[11] was envisaged as powerful tool to synthesize chiral dihydroxy compound offering considerable opportunities for synthetic manipulations. In continuation of our research interst we then further proceeded with our objective to explore the chemistry of AD and to develop an enantiomerically pure and high yielding new route for the synthesis of (*R*)-(-)-denopamine (**Scheme 16**)

Scheme-16

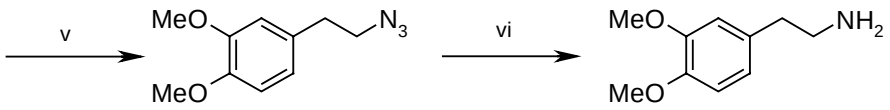


64 **65** **66**

Scheme-17

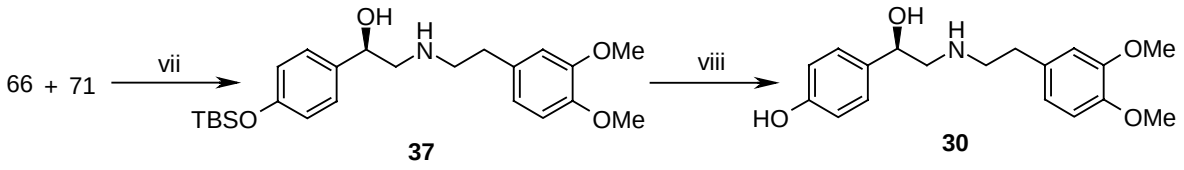


67 **68** **69**



70 **71**

Scheme-18



Scheme 16-18

Reagents and conditions: (i) $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, OsO_4, *t*-BuOH: H_2O(1:1), 0°C, 18h, 97%; (ii) Bu_2SnO, TsCl, TEA, CH_2Cl_2, rt, 91%; (iii) $BH_3.SMe_2$, THF, 10 min, 0°C, 4 h, rt, 83%; (iv) I_2, imidazole/PPh_3, CH_2Cl_2 rt, 5 h, 80%; (v) NaN_3/DMF, 85-90°C, 3h, 80%; (vi) H_2, Pd/C, MeOH, 60psi, 4h, 94%; (vii) THF, 70°C, 4h, 89%; (viii) Saturated soln of anhy. methanolic HCl, rt.

2.3.4 Results and discussion:

In our synthetic strategy we planned to synthesize the target compound **30** by coupling of monotosylate **66** with 3, 4-dimethoxyethylamine **71** (**Scheme 18**). The monotosylate **66** in turn was prepared from its corresponding diol **65** which could be obtained from styrene **64** (**Scheme 16**). The styrene was prepared from its aldehyde by the reported literature procedure.[10d] The chiral diol compound **65** was prepared from its corresponding styrene **64** by Sharpless asymmetric dihydroxylation using $(DHQD)_2PHAL$ as chiral ligand. The IR spectrum of **65** showed a broad band at 3364 cm^{-1} indicating the presence of hydroxy functionalities. The ^1H NMR spectrum showed CH_2 protons attached to OH as multiplet at δ 3.65-3.74. The –CH proton appeared as doublet of doublet at δ 4.75. The mass spectrum showed the M^+ ion peak at 268 confirming the formation of compound **65**. The optical rotation of **65** was measured as $[\alpha]_D^{20}$ – 39.7[*c* l, $CHCl_3$]. The diol **65** was converted into corresponding monotosylate **66** using dibutyltin oxide[35b] and TsCl in the presence of triethylamine in 91% yield. The IR spectrum showed a band at 3545 cm^{-1} indicating the presence of OH groups. The ^1H NMR spectrum of **66** showed the deshielding effect of tosyl group on CH_2 protons as indicated by shifting of δ values from 3.65-3.74 to 3.98-4.15. Also seen was the deshielding effect on –CH proton. The presence of additional aromatic protons at δ 7.32 and δ 7.76 in aromatic region, and a singlet at δ 2.46 corresponding to three protons

of CH_3 group confirmed the formation of monotosylated compound **66.** 3, 4-dimethoxyphenylethanol **68** was prepared from its corresponding styrene **67** by borane dimethyl sulphide reduction (**Scheme 17**). The IR spectrum **68** showed a band at 3345 cm^{-1} indicating the presence of hydroxyl group. The ^1H NMR spectrum showed a triplets at δ 2.82 and at δ 3.79 corresponding to 2 protons each of the two $–CH_2$ groups attached to the nitrogen. The peak at δ 3.87 corresponding to six protons and the multiplet at δ 6.75-6.81 corresponding to three protons confirmed the formation of compound **68**. Compound **68** was converted into corresponding iodo compound using I_2/PPh_3 in CH_2Cl_2 at room temperature. The ^1H NMR spectrum of **69** showed triplets at δ 3.12 and δ 3.30 and the singlets at δ 3.82 and 3.88 and the multiplet at δ 6.63-6.85. The iodo compound **69** was converted into azide compound **70** by treating with NaN_3 in DMF at 80°C. The peak at 2099cm^{-1} in IR spectrum confirmed the formation of azido compound **70**. The structure was further confirmed by ^1H NMR. The azido compound **70** was converted into the amine **71** by hydrogenation using Pd-C in EtOH. The IR spectrum of **71** showed a band at 3550 cm^{-1}, characteristic of amine. The ^1H NMR spectrum showed broad peaks at δ 2.62, triplet at δ 2.73 and δ 2.97. The coupling of **66** and **71** (**Scheme 18**) was carried out by stirring both together in absolute EtOH for 4 h to give **37**. The ^1H NMR spectrum of **37** showed a singlet at δ 0.18 corresponding to six protons, singlet at δ 0.97 corresponding to nine protons of TBS group, a broad singlet peak at δ 2.41 corresponding to three proton, triplet at δ 2.70 corresponding to two proton, a quartet at δ 3.16 corresponding to two proton, singlet at δ 3.80 corresponding to three proton of methoxy group, singlet at δ 3.84 corresponding to three proton of methoxy group, a triplet at δ 4.68–4.74 corresponding to one proton of –CH group attached to OH. Remaining protons corresponding to aromatic region resonated as usual confirming the formation of compound **71**. The IR spectrum of **71** showed a band at 3360 cm^{-1} and a broad band at 3017 cm^{-1} indicating the presence of OH and NH functionalities. Treatment of the compound **37** with anhy.methanolic HCl and KF, at room temperature gave (*R*)-(-)-denopamine **30** in 81% yield. The physical and spectroscopic data were in accordance with the reported literature.[27, 30]

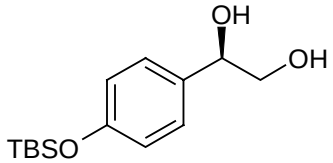
2.3.5 Conclusion

In summry, a practical and high yielding and highly enantioselective synthesis of (*R*)-(-)-denopamine was achieved using Sharpless asymmetric dihydroxylation as source of chirality.

2.3.6 Experimental Section

***tert*-Butyldimethylsilyloxy styrene 64**: Prepared by following the literature procedure.[10d]

(*R*)-1-(4-*tert*-butyldimethylsilyloxyphenyl)-1,2-ethane diol (65): To a solution of $K_3Fe(CN)_6$ (16.79 g, 51.2 mmol), K_2CO_3 (7.07 g, 51.2 mmol), $(DHQD)_2PHAL$ (133 mg, 0.17 mmol) in *t*-BuOH:H_2O (1:1, 170 ml) was added OsO_4 (0.86 mL, 0.1M soln. in toluene, 0.1 mol%) at 0°C. After stirring for 10 min. 4-*t*-butyldimethylsilyloxy styrene **64** (4 g, 17.06 mmol) was added in one portion and the reaction mixture was stirred for 18 h at 0°C. Solid Na_2CO_3 (3.5 g) was added and stirred for 1 h. The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 100 ml). The combined organic layer extracted were washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether: EtOAc (7:3) as eluent to give **65** (4.44 g, 95 %) as colorless oily compound.



65

Yield: 95%

$[\alpha]_D^{20}$: -39.7 [*c* 1, $CHCl_3$]

IR (Neat, cm^{-1}): ν_{max} 3364, 2954, 2857, 1607, 1509, 1466, 1408, 1256

^{1}H NMR: (200 MHz, $CDCl_3$): δ 0.19 (s, 6H), 0.98 (s, 9H), 2.25 (s, 2H), 3.67 (m, 2H), 4.74 (dd, 1H, *J* = 3.91Hz, 7.81Hz), 6.82 (d, 2H, *J* = 8.79Hz), 7.25 (d, 2H, *J* = 8.20Hz)

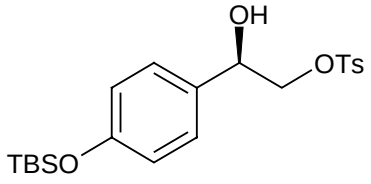
^{13}C NMR (200 MHz, $CDCl_3$): δ 4.5(2C) 18.1, 25.6(3c), 67.9, 74.3, 120.0(2C), 127.3(2C), 133.2, 155.3

Mass: 268 (M^+), 250, 237, 211, 193, 179, 165, 151, 123

Analysis Calcd for $C_{14}H_{24}O_3Si$ (268.33): Found C, 62.84; H, 8.89 (Required C, 62.66; H, 9.02)

***(R)*-1-Tosyloxy-2-(4-*tert*-butyldimethylsilyloxy)-2-ethanol (66)**: To a solution of diol **65** (3 g, 11.18 mmol) in CH_2Cl_2 (100 mL) was added dibutyltin oxide (6 g, 0.2 mol% of diol) and

triethylamine (1.56 mL, 11.18 mmol) and stirred at room temperature for 15 min. To the stirred above reaction mixture, *p*-TsCl (2.12 g, 11.18 mmol) was added in three portions at a time interval of 30 min. The reaction mixture was stirred at room temperature under nitrogen atmosphere. The progress of reaction was monitored by TLC and after completion of reaction (90 min), the mixture was quenched by adding water (100 mL). The reaction mixture was extracted with dichloromethane (3 x 30 mL) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (7:3) as eluent afforded monotosyl compound **66** (3.97 g, 91%) as a colorless viscous liquid.



66

Yield: 91%

$[\alpha]_D^{20}$: -34.07 (*c* 1, $CHCl_3$)

IR (Neat, cm^{-1}): ν_{max} 3315, 2865, 1601, 1495, 1425, 1401, 1245

^{1}H NMR (200 MHz $CDCl_3$): δ 0.18 (s, 6H), 0.97 (s, 9H), 2.45 (s, 3H), 2.50 (s, 1H), 3.98-4.15 (m, 2H), 4.89 (dd, 1H, *J* = 3.42Hz, 8.30Hz), 6.77 (d, 2H, *J* = 8.79Hz), 7.15 (d, 2H, *J* = 8.79Hz), 7.32 (d, 2H, *J* = 8.79Hz), 7.76 (d, 2H, *J* = 8.30Hz)

^{13}C NMR (200 MHz, $CDCl_3$): δ 4.5(2C), 18.1, 21.6, 25.6(3C), 71.4, 74.3, 120.2(2C), 127.4(2C), 127.9(2C), 129.9(2C), 131.0, 132.7, 145.0, 155.8

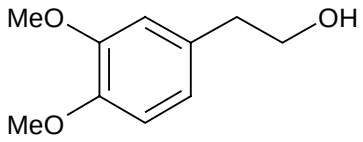
Mass: 307(-TBS), 268, 237, 211, 189, 193, 179, 165, 151, 123, 107, 91, 75

Analysis Calcd for $C_{21}H_{30}O_5SiS$ (422.62): Found C, 59.89; H, 7.35; S, 7.87 {Required C, 59.68; H, 7.15; S, 7.59}

3, 4-Dimethoxystyrene (67): Prepared by following literature procedure[10d]

2-(3, 4-dimethoxyphenyl)-1-ethanol (68): To the ice cold solution of **67** (2.9 g, 17.68 mmol) in dry THF was added 1.68 ml of $BH_3.SMe_2$ (1.34 g, 17.68 mmol) and the reaction mixture was stirred for 10 min. at 0°C and then brought to room temperature. After stirring for 4 h, 35

ml of 10% NaOH solution (1.41g of NaOH; 35.36 mmol dissolved in 18 ml of EtOH and 18 ml of water) and 5 mL of H_2O_2 (44.2 mmol, 30% solution) were added and stirring continued for another 30 min. The reaction mixture was poured into 50 g ice and extracted with EtOAc (3 x 50 ml), washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography with petroleum ether: EtOAc (75:25) gave colorless viscous oily compound **68** (2.66 g, 82%).



68

Yield: 82 %

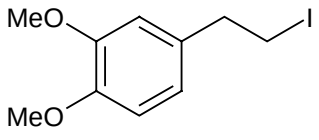
Colorless viscous oil

IR (Neat, cm^{-1}): ν_{max} 3365, 3069, 3010, 1597, 1496, 1401, 1255

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79 (s, 1H), 2.82(t, 2H, *J* = 6.31Hz), 3.81 (t, 2H, *J* = 6.50Hz), 3.87(s, 3H), 3.88(s, 3H), 6.75-6.81 (m, 3H)

Analysis cacld $C_{10}H_{14}0_3$ (182.17): Found C, 65.86; H, 7.73 {Required C, 65.93; H, 7.69}

2-(3, 4-Dimethoxyphenyl)-1-iodo ethane (69): To a stirred solution of imidazole (0.86 g, 12.57 mmol), PPh_3 (3.30 g, 12.60 mmol), iodine (3.29 g, 12.97 mmol) in dry CH_2Cl_2 (30 ml) was added compound **68** (2.29 g, 12.58 mmol) at room temperature and the mixture stirred for 5 h. The progress of reaction was monitored by TLC. After completion of reaction, it was quenched with water, and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic layer was washed (brine), dried (Na_2SO_4) and concentrated. After column chromatography, it gave compound **69** (4.23 g, 80%) as a colorless oil.



69

Yield: 80%

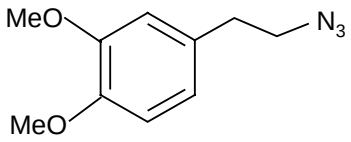
Colorless Oil

IR (Neat, cm^{-1}): ν_{max} 3020, 1606, 1590, 1516, 1466, 1461, 1454, 1441, 1265

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.08 (t, 2H, *J* = 7.33 Hz), 3.30 (t, 2H, *J* = 6.84 Hz), 3.88 (s, 3H), 3.89 (s, 3H), 6.63-6.85 (m, 3H)

Analysis calcd for $C_{10}H_{13}IO_2$ (292.198): Found C, 41.21; H, 4.37{Required C, 41.10; H, 4.48}

2-(3, 4-Dimethoxyphenyl)-1-azido ethane (70): To a solution of **69** (2.80 g, 9.59 mmol) in dry DMF (10 mL), was added NaN_3 (3.117 g, 47.95 mmol) and the mixture was stirred for 3 h at 85-90°C. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and quenched with water and extracted with EtOAc (3 x 50 ml). The combined organic layer was washed with brine; dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether: EtOAc (85:15) as eluent furnished compound **70 (**1.58 g, 80%**)** as colourless oil.



Yield: 80%

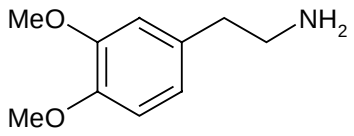
Colorless Oil

IR (Neat, cm^{-1}): ν_{max} 3351, 3000, 2936, 2835, 2099, 1607, 1591, 1516, 1464

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.84 (t, 2H, *J* = 6.84 Hz), 3.49 (t, 2H, *J* = 7.32 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 6.74-6.85 (m, 3H)

Analysis calcd for $C_{10}H_{13}N_3O_2$ (207.233): Found C, 58.09; H, 6.19{Required C, 57.97; H, 6.28}

1-(3, 4-Dimethoxyphenyl)-2-amino-ethane (71): Compound **70** (1.00 g, 4.83 mmol) dissolved in dry MeOH (50 ml) was stirred with Pd/C (10 mg) under H_2 atmosphere (60 psi) for 4 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered and concentrated to give **71** (0.82 g, 94 %) as a pale yellowish oil.



71

Yield: 94%

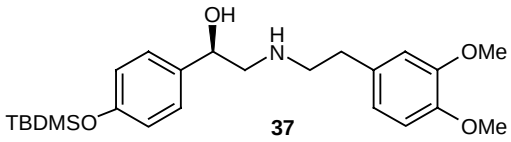
Pale yellow oil

IR (Neat, cm^{-1}): ν_{max} 3550, 3010, 2950, 3550, 30101605, 1550, 1423, 1350

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62 (brs, 2H), 2.73 (t, 2H, *J* = 6.83Hz), 2.97 (t, 2H, *J* = 6.33 Hz), 3.84 (s, 3H), 3.85 (s, 3H), 6.72-6.78 (m, 3H)

Analysis calcd for $C_{10}H_{15}NO_2$ (181.23): Found C, 66.12; H, 8.16 {Required C, 66.27; H, 8.34}

(*R*)-(-)-2-[(3,4-dimethoxyphenyl)-amino]-4-tosyloxybenzyl alcohol (37): To a stirred solution of **71** (1.0 g, 0.0055 mole) and Et_3N in 10 ml THF at room temperature, was added compound **66** (2.33 g, 0.0055mole) in 5 ml of THF at the interval of 20 min. Then the reaction mixture warmed to 70°C and stirred for 4 hr under nitrogen atmosphere. The reaction mixture was cooled to room temperature and passed through silica gel column chromatography to give compound **37** (2.20 g, 89%) as a colorless oil**.**



37

Yield: 9%

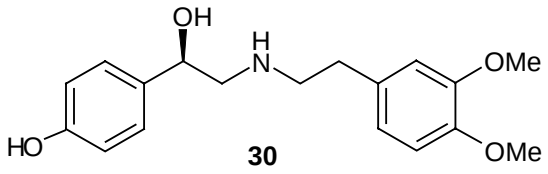
$[\alpha]_D^{20}$: -24.98 (*c* 1, $CHCl_3$) {Lit.[35] $[\alpha]_D^{25}$ – 25.3 (*c* 1.03, CH_2Cl_2)}

^{1}H NMR(200 MHz, $CDCl_3$): δ 0.18 (s, 6H), 0.98 (s, 9H), 2.41 (brs, 3H), 2.71(t, 2H, *J* = 6.84 Hz), 3.19(q, 2H, *J* = 6.84 Hz), 3.80 (s, 3H), 3.84 (s, 3H), 4.71 (t, 1H, *J* = 6.35 Hz), 6.57 (s, 1H), 6.59(d, 1H, *J* = 6.31 Hz), 6.75(d, 1H, *J* = 7.81 Hz), 7.26(d, 2H, *J* = 7.81 Hz), 7.67(d, 2H, *J* = 8.30 Hz).

Mass: 433(M^++2), 358(317+CH_3CN), 353(317+2H_2O), 336(317+H_2O), 319,279, 251, 165, 150

Analysis cacld for $C_{24}H_{37}NO_4Si$ (431.645): Found C, 66.69; H, 8.58; N, 3.33{Required C, 66.78; H, 8.64; N, 3.25}

(*R*)-(-)-Denopamine 30 : To a stirred solution of **37**(1.00g, 0.0023mole) in dry methanol a saturated solution of methanolic hydrochloride was added and stirred at 0^0C and stirred for 10h at room temperature. The reaction mixture was concentrated and diluted with water and extracted with CH_2Cl_2 (3x25ml). The combined organic layer was washed with brine, and dried over Na_2SO_4, and concentrated. Silica gel column chromatography with petroleum ether: EtOAc (40:60) gave denopamine **30**(0.52g, 81%) as a colourless solid.The physical and spectroscopic data are in agreement with literature data



30

Yield: 81%

M.P.: 161-163^{o}C (lit[37] M.P.: 163-164)

$[\alpha]_D^{20}$: -26.9 (*c* 1, MeOH), {lit[37] $[\alpha]_D^{20}$ -27.5}

IR (CHCl3, cm^{-1}): ν_{max} 3670, 3360, 3060, 3017, 2984, 1437, 1215, 1177, 1119.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.70(s, 1H), 2.43(s, 3H), 2.71(t, 2H, *J* = 6.84 Hz), 3.15(q, 2H, *J* = 6.83 Hz), 3.82 (s, 3H), 3.86(s, 3H), 4.38(t, 1H, *J* = 6.35 Hz), 6.57(s, 1H), 6.60(d, 1H, *J* = 7.81 Hz), 6.75(d, 1H, *J* = 7.81Hz), 7.27(d, 2H, *J* = 7.81Hz), 7.66(d, 2H, *J* = 8.30 Hz).

^{13}C NMR (200 MHz, CDCl3): δ 21.4, 25.6, 35.3, 44.3, 55.8, 111.7, 112.0, 120.8, 127.0, 129.6, 130.3, 137,1, 143.3, 148.9, 149.0, 159.8

Mass: 279(277.54)(M^++2), 251, 251, 217, 165, 150.

2.3.7. Spectra

1. ^{1}HNMR spectrum of 65

2. ^{13}CNMR spectrum of 65

3. ^{1}HNMR soectrum of 66

4. ^{13}CNMR spectrum of 66

5. ^{1}HNMR spectrum of 68

6. ^{1}HNMR spectrum of 69

7. ^{1}HNMR spectrum of 70

8. ^{1}HNMR spectrum of 71

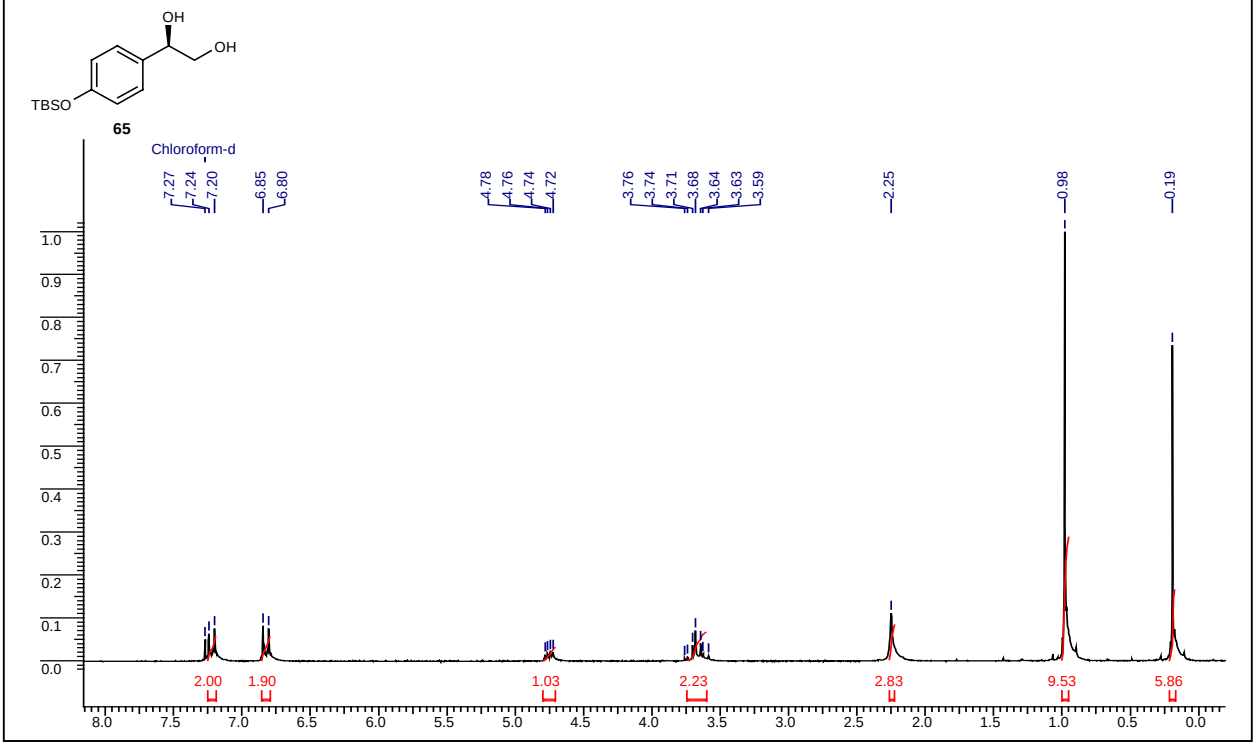
9. ^{1}HNMR spectrum of 37

10. Masss spectrum of 37

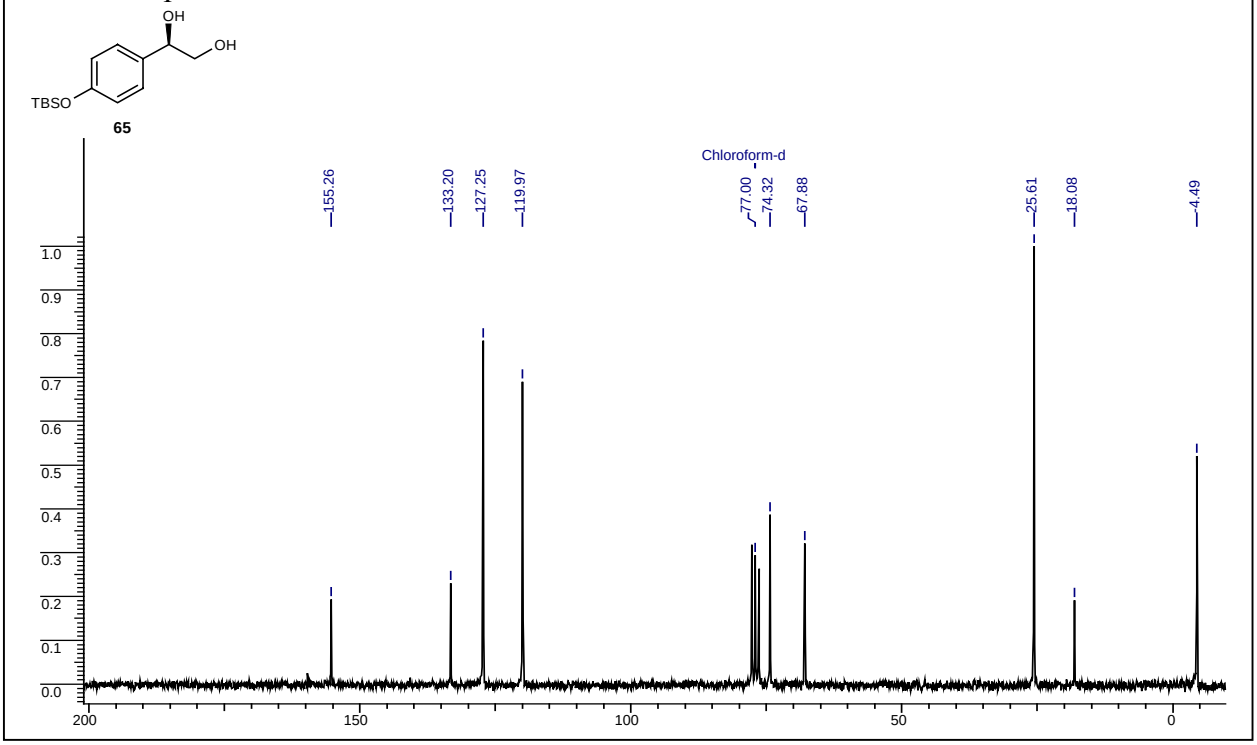
11. ^{1}HNMR spectrum of 30

12. ^{13}CNMR spectrum of 30

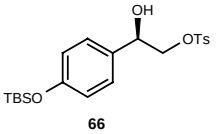
^{1}HNMR spectrum of **65**



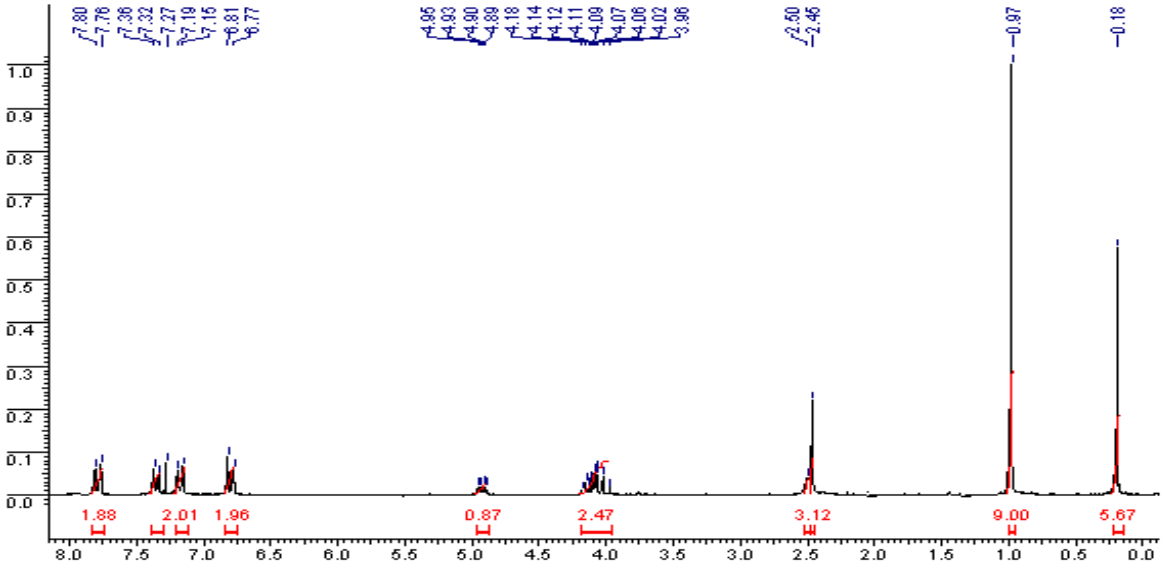
^{13}CNMR spectrum of **65**

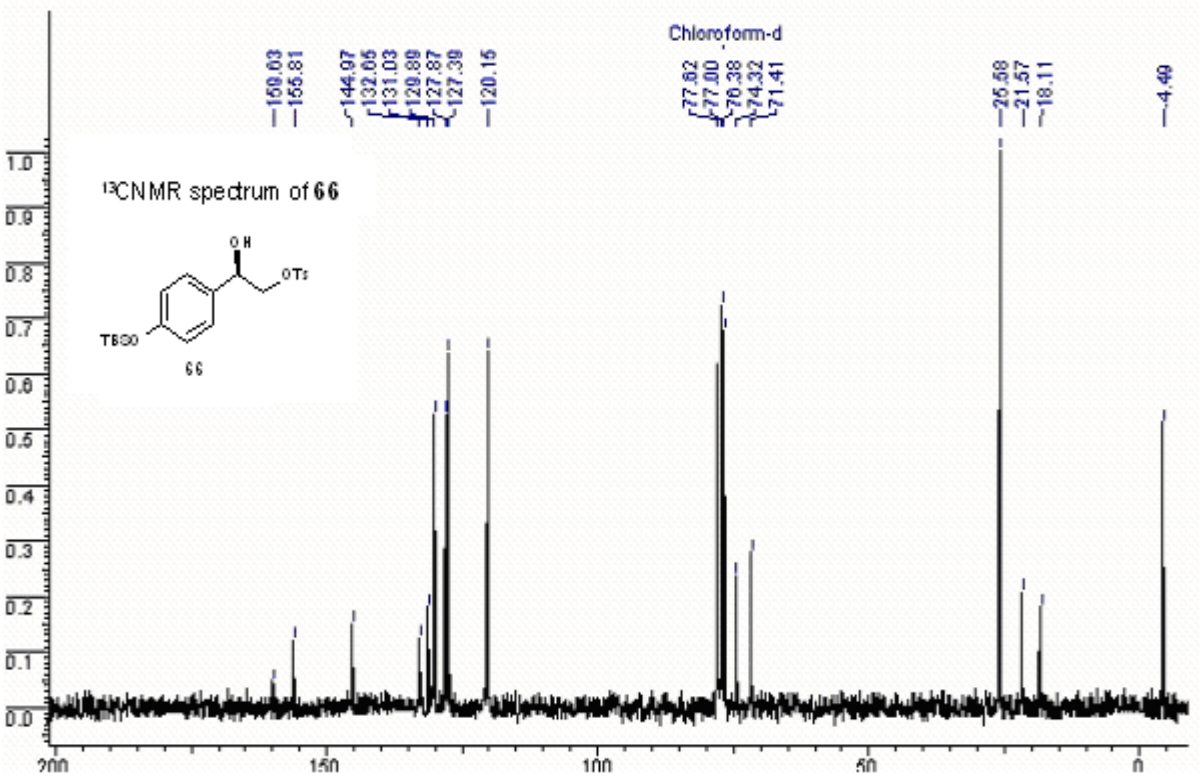


[1]HNMR soectrum of **66**

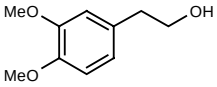


66

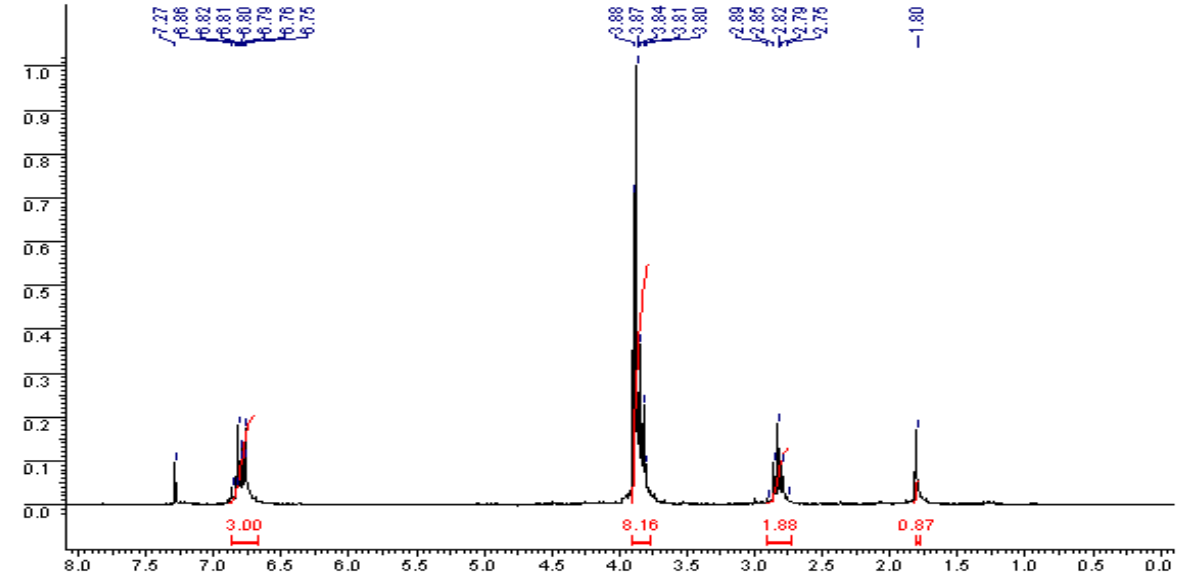




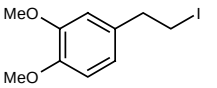
^{1}HNMR spectrum of **68**



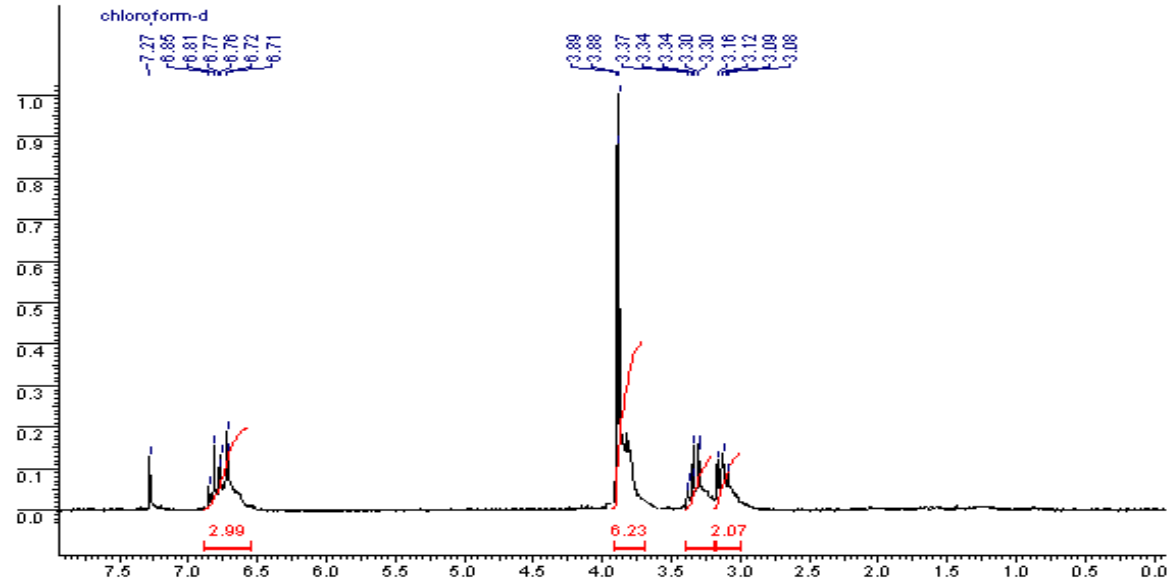
68



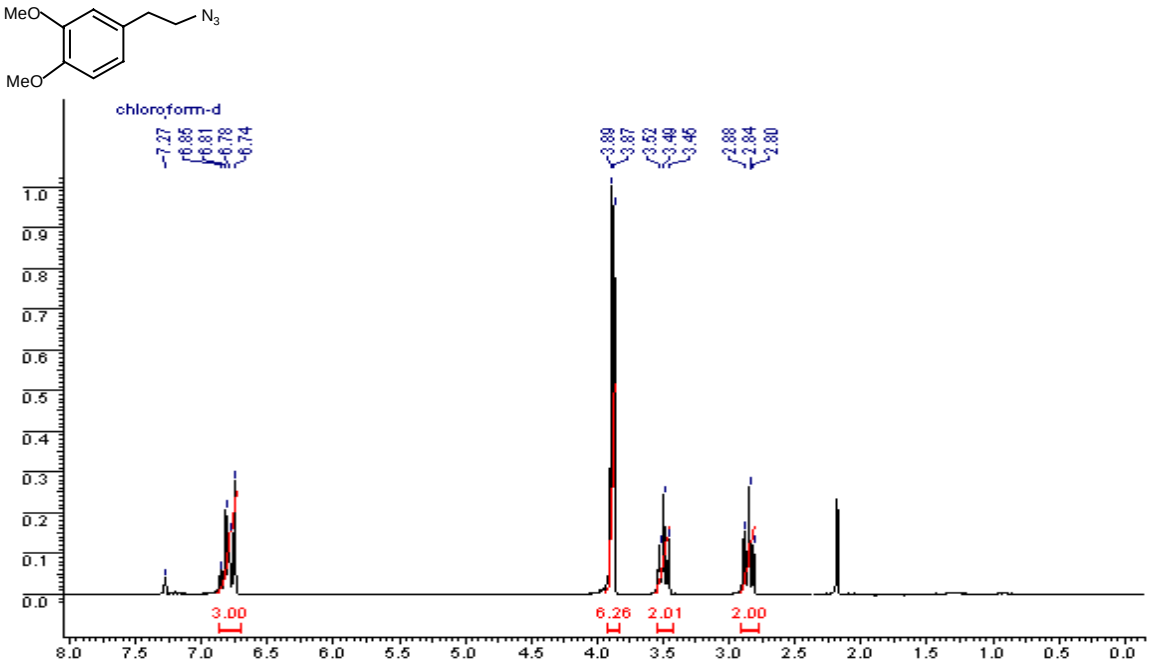
^{1}HNMR spectrum of **69**



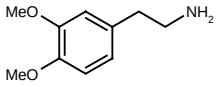
69



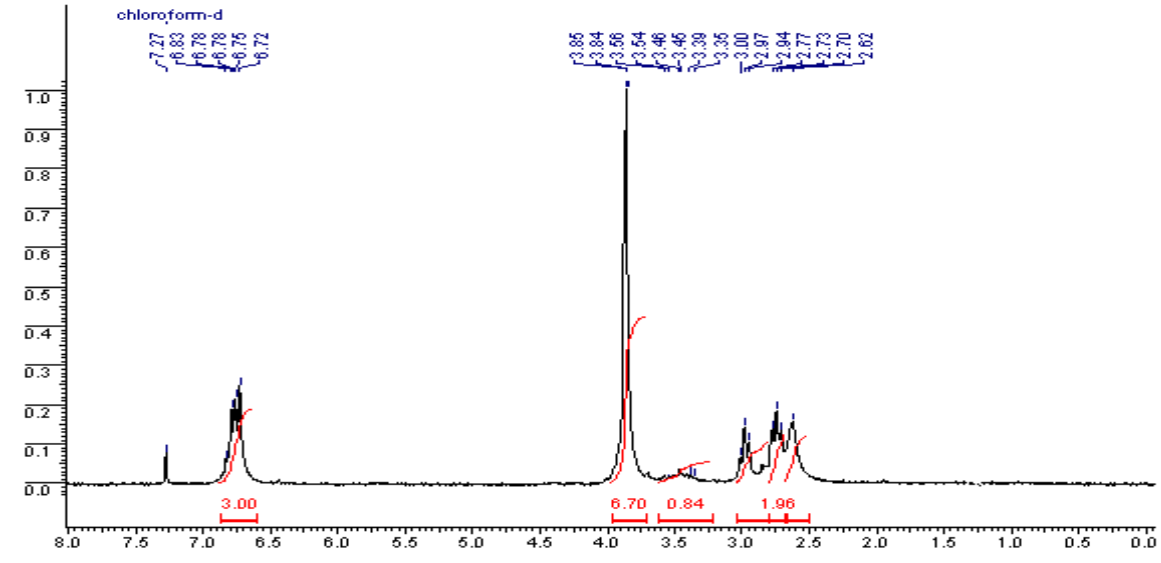
^{1}HNMR spectrum of **70**



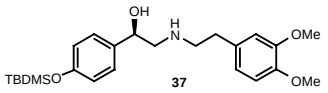
^{1}HNMR spectrum of **71**



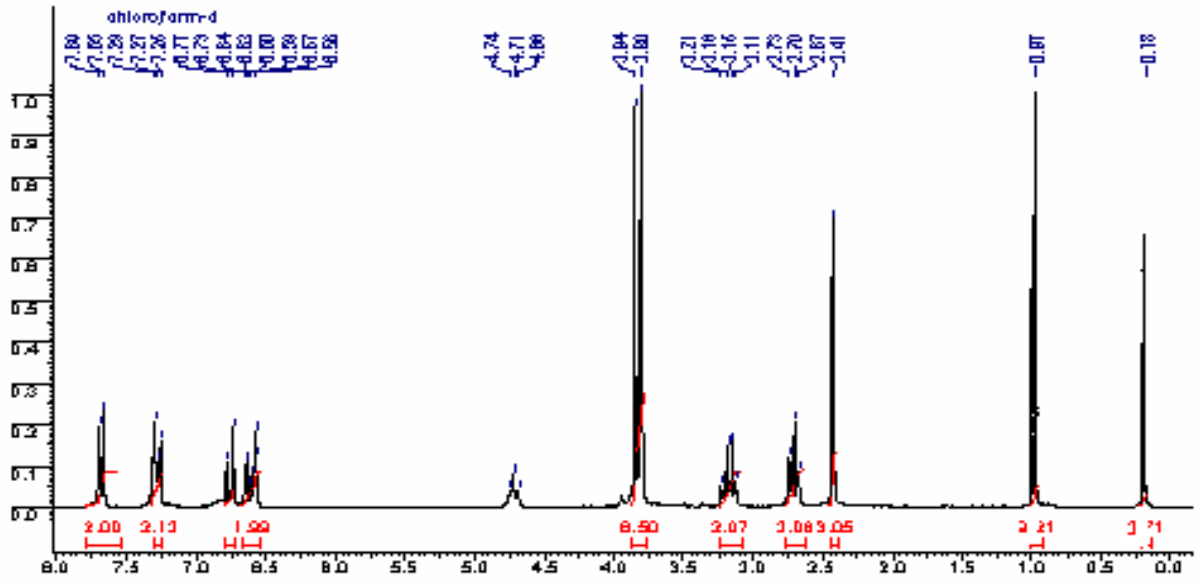
71

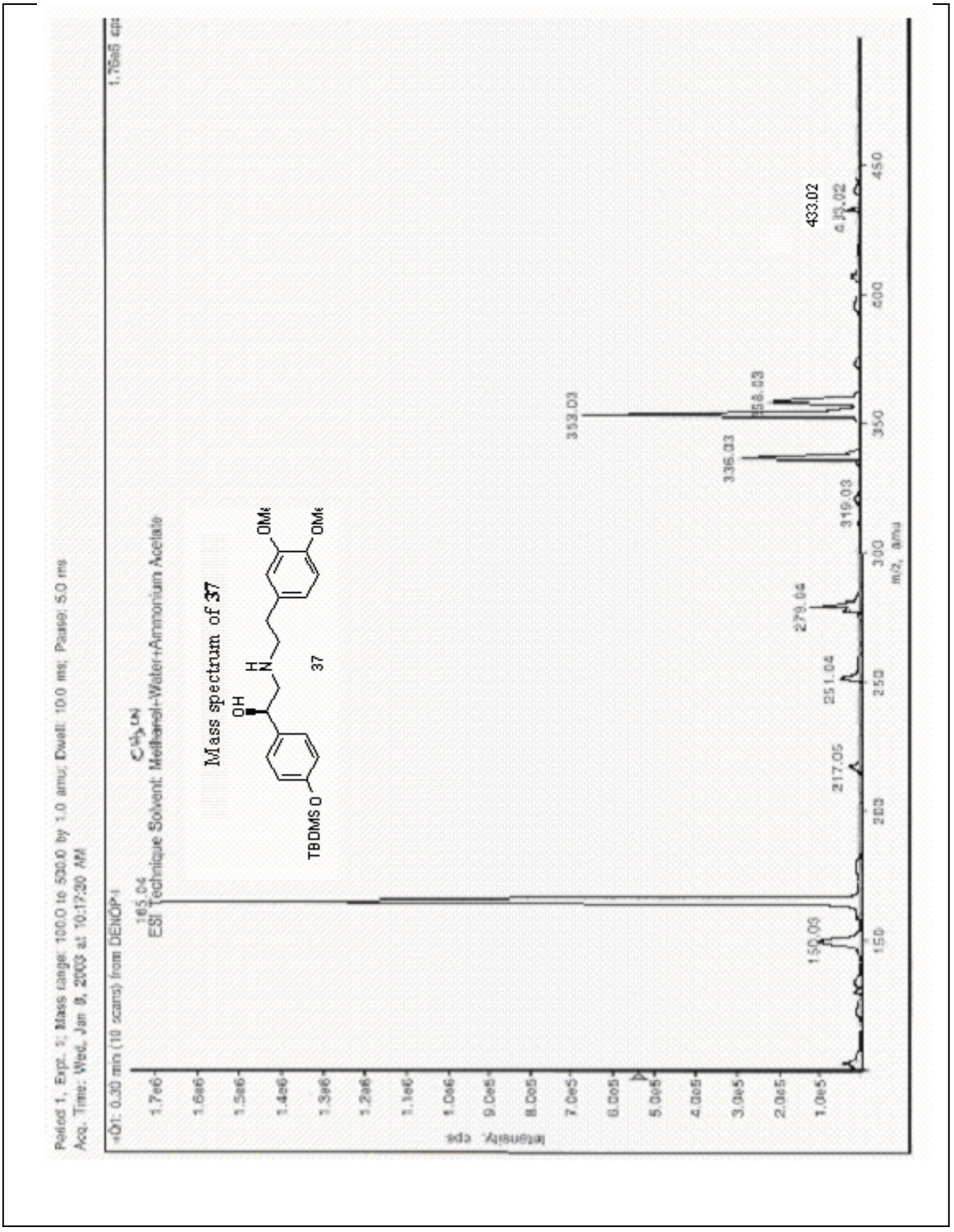


^{1}HNMR spectrum of **37**

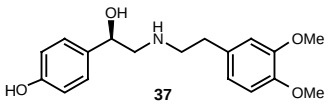

OH
H
N
OMe
TBDMSO
OMe

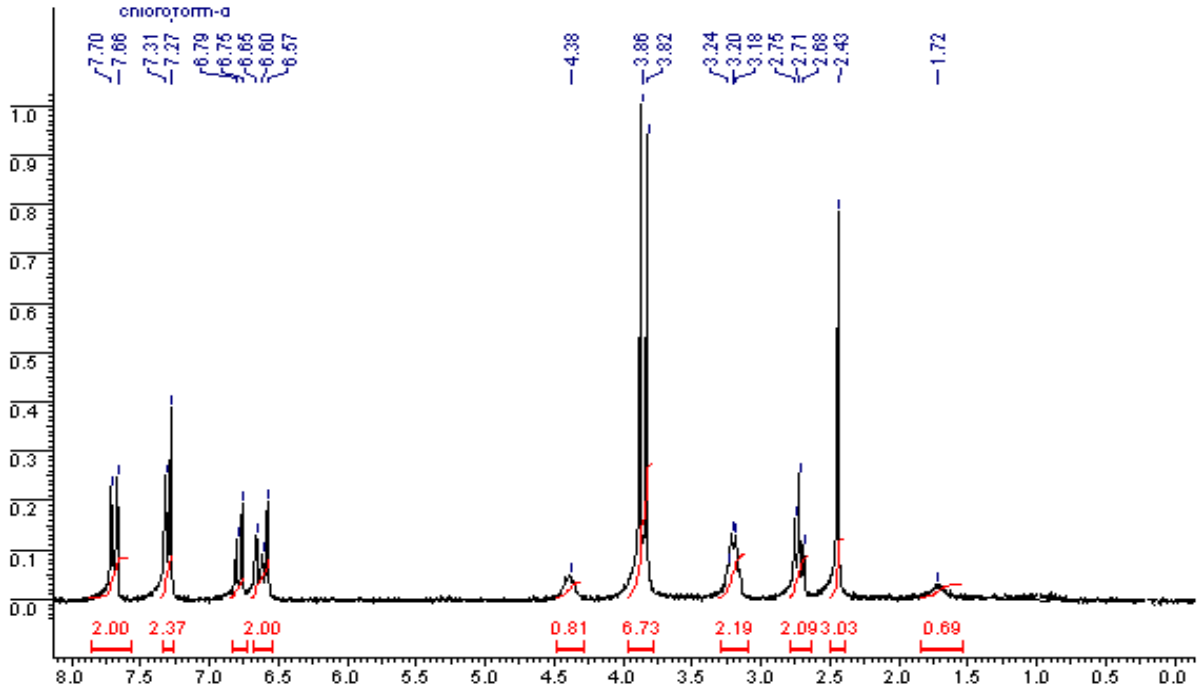
37


chloroform-d
7.89
7.85
7.29
7.27
7.26
6.77
6.73
6.64
6.63
5.00
4.99
4.74
4.71
4.66
3.84
3.81
3.21
3.18
3.16
3.11
2.73
2.70
2.67
1.41
0.87
0.18
2.00
2.13
1.99
6.50
2.07
3.08
3.05
2.21
1.71

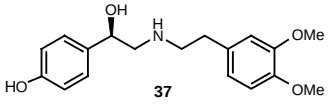

Mass spectrum of 37
37
TBDMSO
OMe
OMe
OH
H
N
ESI Technique Solvent: Methanol+Water+Ammonium Acetate
Intensity, cps
m/z, amu
433.02
353.03
336.03
319.03
279.04
251.04
217.05
165.04
150.03

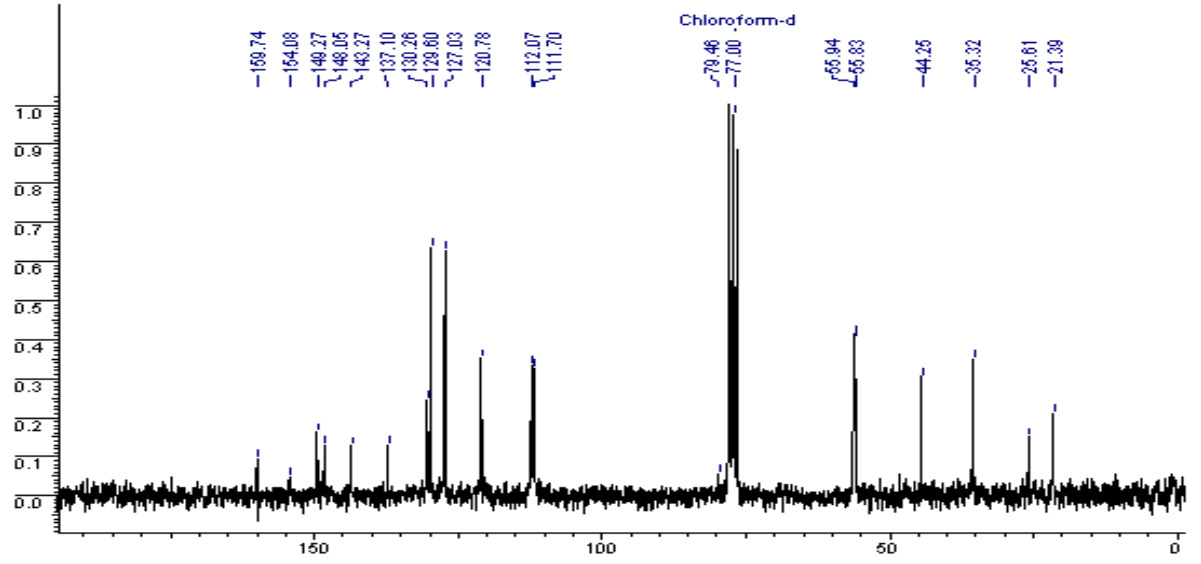
^{1}HNMR spectrum of **37**





^{13}CNMR spectrum of **37**

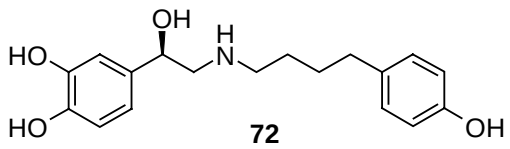




2.4 Section D Enantioselective synthesis of (*R*)-(-)-Arbutamine 72

2.4.1 Introduction

The important physiological roles that arylethanol amines play have led to many analogues being developed for coronary diseases. (*R*)-Arbutamine **72** is a new catecholamine which is being developed as a pharmacological stress agent (exercise stimulating agent ESA) for the diagnosis of coronary artery disease and myocardial ischemia. The pharmacology of **72** suggests that it is a mixed β_1-β_2 adrenoreceptor agonist with a significant affinity towards α_1-adrenoreceptors.[36] In view of the pharmacological properties of (*R*)-(-)-arbutamine, it has attracted the attention of organic chemist to develop a new chiral catalyst for the enantioselective synthesis of **72**. Till now only a few asymmetric synthesis of arbutamine has been reported. The earlier synthesis of (*R*)-(-)-arbutamine was accomplished from (*R*)-norepinephrine and 4-(*p*-benzyloxyphenyl) butanol, by the way of an imine forming reaction followed by reduction.[36] Shibasaki and coworkers used catalytic asymmetric nitroaldol reaction promoted by a heterobimetallic multifunctional catalyst as a key step.[37] Recently Trost and coworkers reported asymmetric synthesis of **72** using ligands modified dinuclear zinc catalyst[35] by nitro aldol (Henry) reactions. Though there are many reports of asymmetric synthesis (*R*)-(-)-arbutamine, surprisingly there has been no report in the literature using the well-established Sharpless asymmetric dihydroxylation procedure. As part of our research program aimed at developing enantioselective synthesis of naturally occurring lactones,[9] amino alcohols,[10] the Sharpless asymmetric dihydroxylation[11] was envisaged as a powerful tool to chiral dihydroxy compounds offering considerable opportunities for synthetic manipulations. We have developed a new and highly enantioselective synthesis of (*R*)-(-)-arbutamine **72** employing the sharpless asymmetric dihydroxylation as a key step and source of chirality.



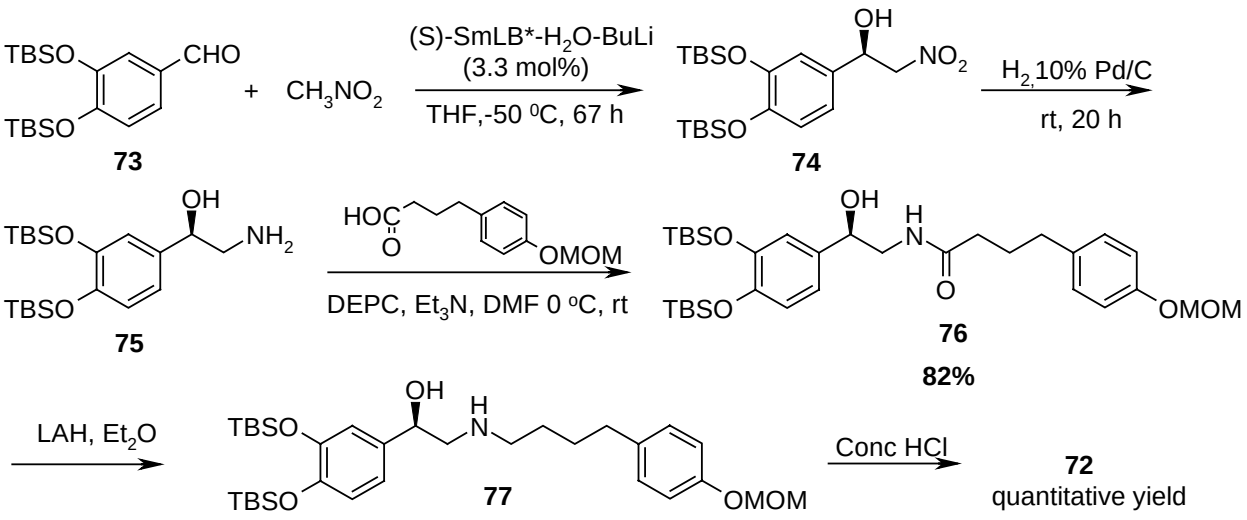
72

(*R*)-(-)-Arbutamine

2.4.2 Review of Literature

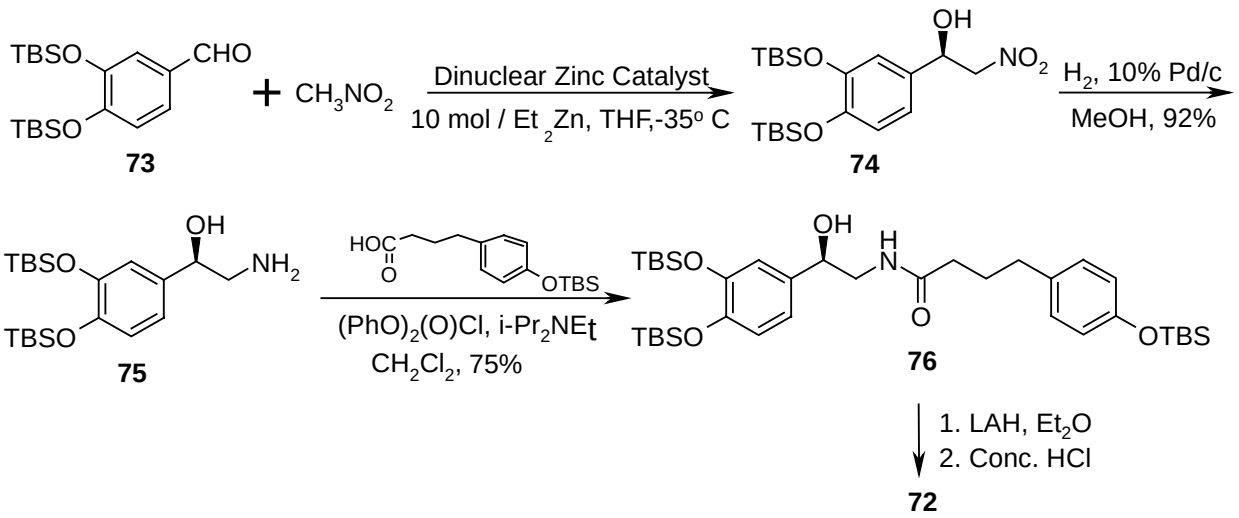
Shibasaki *et al.* (1997)[37] Scheme 19: (*S*)-$SmLi_3$ tri(binaphthoxide)(LnLB) or related heterobimetallic asymmetric complexes was used in Henry reaction as catalyst to synthesise (*R*)-(-)- arbutamine.

Scheme-19



Trost *et al.* (2002)[35] Scheme 20: In this process, various modified ligands were used with dinuclear zinc catalyst using Henry reaction to synthesise (*R*)-(-)-arbutamine **72**.

Scheme-20

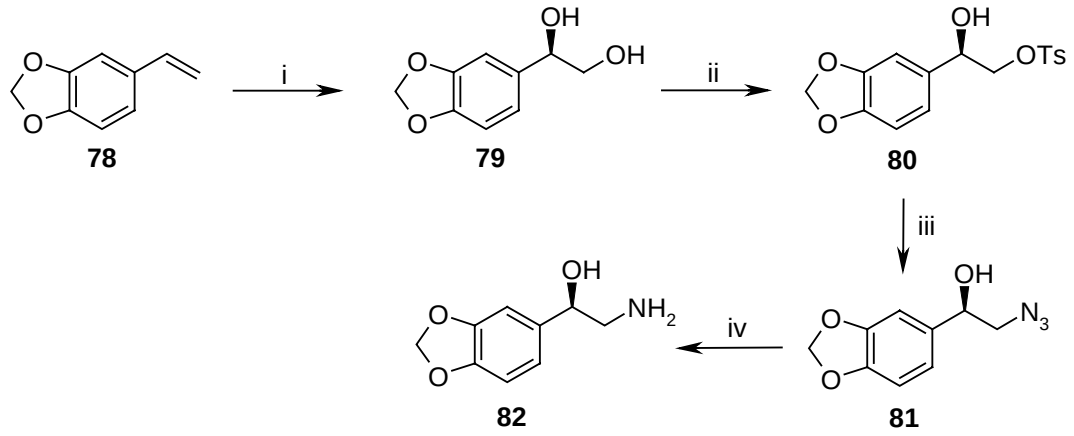


2.4.3 Present work

Objective

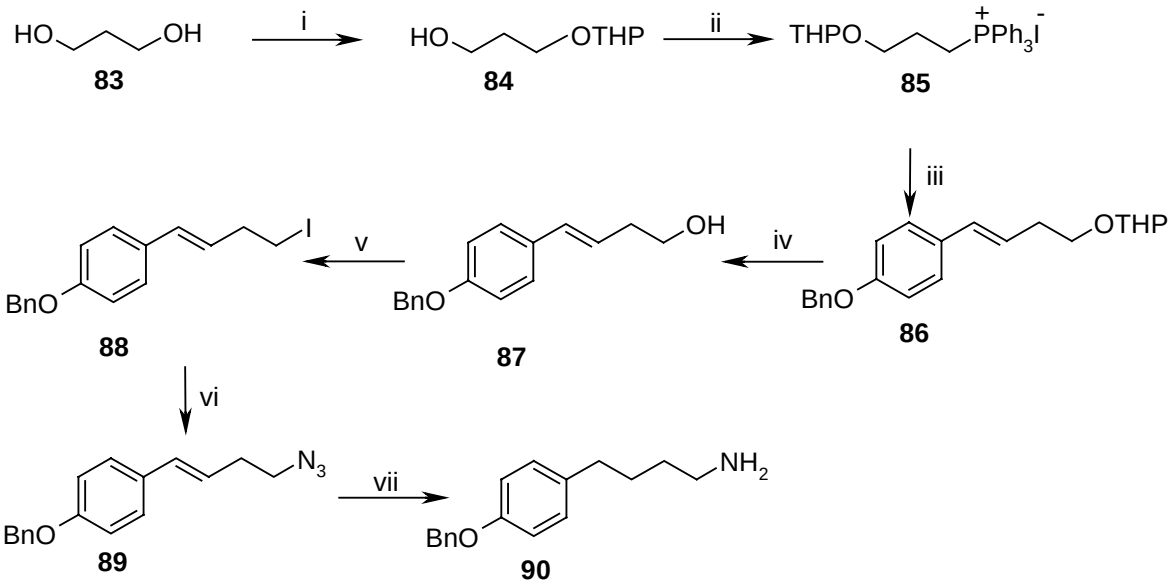
Despite the fact that the nitro aldol (Henry reaction) is an atom-economic approach to β-hydroxy nitroalkanes and arenes, an valuable synthetic intermediates, the catalysts used in the asymmetric version of this reaction requires either multistep synthesis or high cost starting materials. The objective of our work was to explore the chemistry of AD and develop a new route for the synthesis of (*R*)-(-)-arbutamine.

Scheme-21



Scheme 21 ***Reagents and conditions*****:** (i) $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, OsO_4, *t*-BuOH: H_2O (1:1), 0°C, 18 h, 95%; (ii) Bu_2SnO, TsCl, TEA, CH_2Cl_2, rt, 85%; (iii) NaN_3/DMF, 85-90°C, 95%; (iv) Pd/C, H_2, MeOH, 60 psi, 98%.

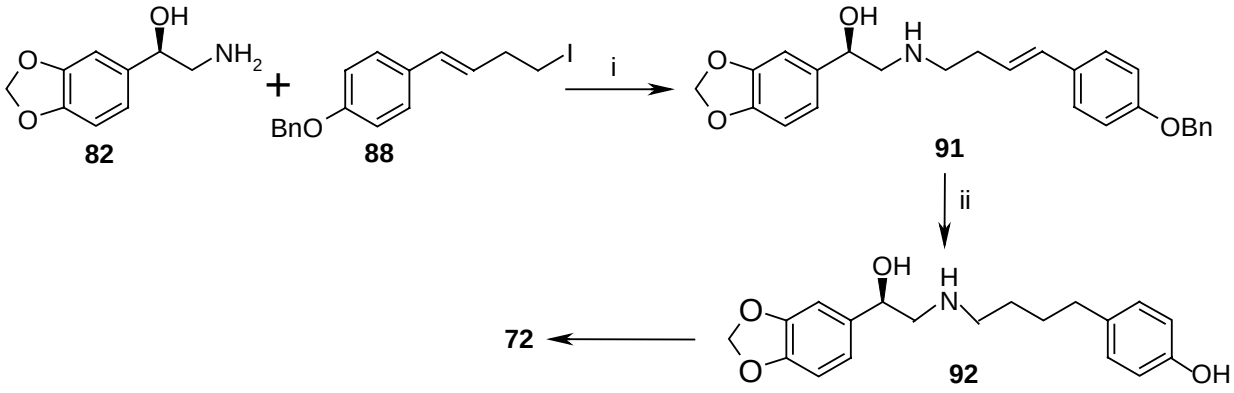
Scheme-22



Scheme 22 ***Reagents and conditions*****:**

(i) 3,4-tetrahydro-2*H*-pyran, I_2 (catalytic), CH_2Cl_2(dry), rt, 6 h, 95%; (ii) Imidazole, PPh_3, I_2, CH_2Cl_2, rt, 6 h, 98%; (iii) PPh_3, Benzene (dry), reflux, remove the benzene, add THF (dry), n-BuLi, at 0°C add 4-benzyloxystyrene at 0°C, 6 h, 70%; (iv) PTSA, CH_2Cl_2 (dry), 4 h, 99%; (v) Imidazole, PPh_3, I_2 CH_2Cl_2 (dry), rt, 6 h, 90%; (vi) NaN_3, DMF, 80°C, 4 h 98%; (vii) Pd-C, H_2, 60 psi, MeOH, 95%

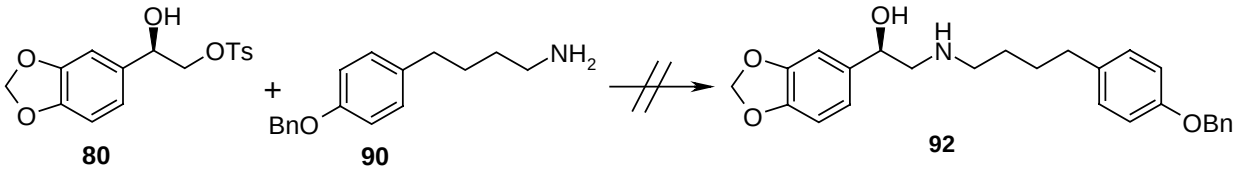
Scheme-23



Scheme 23 ***Reagents and conditions*****:**

(i) Et_3N, THF, 80°C, 3 h, 76%; (ii) Pd-C, H_2, MeOH, 60 psi, 10 h, 91%; (iii) EtOH, 2N NaOH Soln, 90°C, 1 h, 97%

Scheme-24



Scheme 24 ***Reagents and conditions:***

(i) Absolute EtOH, TEA, 80°C, 6h

2.4.4 Results and discussion

In our synthetic approach towards the synthesis of target compound **72**, we have planned to synthesise the fragment **82** (**Scheme-21**) (β-amino alcohol) and fragment **88** (**Scheme-22**) and then couple both the fragment by *N*-alkylation to give compound **91** which after hydrogenation and deprotection of methylene group would gives rise arbutamine **72**. Towards this end compound **78** was initially prepared from its aldehyde by the literature procedure.[10d] The dihydroxylation of styrene **78** using Sharpless asymmetric procedure gave the chiral diol **79**. The IR spectrum of **79** showed broad band at 3392 cm^{-1}, indicating the presence of hydroxyl groups. ^1H NMR spectrum showed the multiplet at δ 3.52-3.68 for CH_2 protons and a multiplet at δ 4.71 for CH proton. The ee was found to be as 97.77%. The optical rotation of the diol **79** was measured as $[\alpha]_D^{25}$ = - 39.08 (*c* 1, $CHCl_3$). When the diol was treated with TsCl, in the presence of Bu_2SnO, and TEA, it gave the monotosylate **80** in 85% yield. The IR spectrum of **80** showed a broad band at 3522 cm^{-1} and 3420 confirming the presence of hydroxyl groups. The ^1H NMR spectrum showed the presence of tosyl group at δ 2.36 (CH_3), 7.17 (d) and 7.67(d) for aromatic protons along with others protons of starting materials. The optical rotation was measured as $[\alpha]_D^{25}$ –37.35 (*c* 1, $CHCl_3$). Treatment of compound **80** with NaN_3 /DMF at 85-90°C gave **81**. The IR spectrum of **81** showed a broad band at 3443 cm^{-1}

and a peak at 2103 cm^{-1} indicating the presence of hydroxyl and azide functionalities. ^1H NMR spectrum showed the absence of tosyl group. The optical rotation of the compound **81** was measured as $[\alpha]_D^{25}$ – 34.07 (*c* 1, $CHCl_3$). **81** was converted into the corresponding β-amino alcohol **82** using Pd/C under H_2 atmosphere. The IR spectrum of **82** showed a broad band for amino group at 3334 cm^{-1}. The ^1H NMR spectrum of **82** showed a multiplet at δ 2.73-3.03 for CH_2 protons and a doublet of doublet at δ 4.58 for CH proton. The mass spectrum showed M^+ ion at 182. The optical rotation of **82** was measured as $[\alpha]_D^{20}$ – 36.54 (*c* 1, $CHCl_3$).

The fragments **88** and **90** were synthesized from mono-THP protected 1, 3-propanediol **84** which in turn was prepared from 1, 3-propanediol **83**. Treatment of **84** with imidazole, Ph_3P and iodine in CH_2Cl_2 (dry) at room temperature for 6 h, gave compound **85**. The compound **86** was prepared by reaction between triphenylphosphonium salt **85** with benzyloxybenzaldehyde in presence of *n*-BuLi, in dry THF at 0°C for 6 h. The ^1H NMR spectrum **86** showed a multiplet at δ 5.52-5.65 and a doublet at δ 5.87-5.95 for olefins. Treatment of compound **86** with *p*-TSA in dry CH_2Cl_2 at room temperature for 4 h gave compound **87**. The IR spectrum of **87** showed a broad peak at 3306 cm^{-1} and at 1596 cm^{-1} indicating the presence of hydroxy and olefin functionalities. The compound **87** was subsequently converted into **88** by reaction with imidiazole, PPh_3, iodine, in dry CH_2Cl_2 at room temperature for 6 h. On treating compound **88** with NaN_3 in DMF at 85°C for 4 h gave **89** which showed a peak at 2097 cm^{-1} for azide in the IR spectrum confirming the formation of compound **89**, which was further reduced to amine **90** by reacting with Pd/C in MeOH under H_2 atmosphere for 2 h. The structure of **90** was confirmed by its ^1H NMR spectrum. When compound **82** and **88** were stirred together in THF in presence of TEA, it gave compound **91**. The IR spectrum of **91** showed a broad band at 3360 cm^{-1}, 3310 cm^{-1} and peak at 1596 cm^{-1} indicating the presence of hydroxyl, -NH and olefin functionalities. Hydrogenation of **91** with Pd-C under H_2 atmosphere followed by treatment with 2N.NaOH solution at 90°C gave **72** in 91% yield. However, coupling of **80** and **90** in absolute ethanol under reflux condition in presence of triethylamine at 80^0C for 6 h failed to give the desired product **92**.

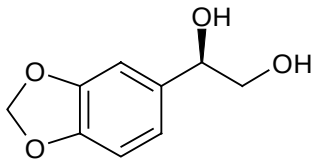
2.4.5 Conclusion

In summary, a highly practical enantioselective synthesis of (*R*)-(-)-arbutamine was achieved using Sharpless asymmetric dihydroxylation approach.

2.4.6 Experimental Section

3, 4-Methylenedihydroxystyrene (78): This was prepared by following the literature procedure.[10d]

(*R*)-1-(3,4-methylenedihydroxyphenyl)-1,2-ethanediol (79): To a solution of $K_3Fe(CN)_6$ (26.66 g, 81.28 mmol), K_2CO_3 (11.18 g, 81.28 mmol), $(DHQD)_2PHAL$ (209 mg, 270 mmol, 1 mol%) in 150 ml of *t*-BuOH:H_2O (1:1) was added OsO_4 (0.72 ml, 0.1 M solution in toluene, 0.5 mol%) at 0 °C. After stirring for 5 min., 3,4-methylenedihydroxy styrene **78** (4 g, 27.02 mmol) was added in one portion and the reaction mixture was stirred for 18 h at 0 °C. Solid Na_2SO_3 (4 g) was added and stirred for 1 h. The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 150 m). The combined organic layer were washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether: EtOAc (7:3) as eluent to give **79** (4.68g, 95%) as a colorless solid.



79

Yield: 95%

M.P: 61-62 ^{0}C

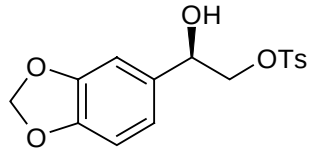
$[\alpha]_D^{20}$: -39.08 (*c* 1, $CHCl_3$)

IR (Neat, cm^{-1}): ν_{max} 3392, 2018, 2888, 1609, 1504, 1488, 1442, 1240, 1260

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.23 (brs, 2H), 3.52-3.68 (m, 2H), 4.67(dd, 1H, *J* = 4.40, 7.82Hz), 5.94 (s, 2H), 6.77 (s, 2H), 6.84 (s, 1H)

Mass: 182, 165, 149, 135, 121, 107, 79

(*R*)-2-(*O*-Tosyl)-1-(3,4-methylenedihydroxyphenyl)-1,2-ethanediol (80): To a solution of diol **79** (2 g, 10.98 mmol) in dry CH_2Cl_2 (150 ml) was added Bu_2SnO (4 mg, 0.2 mol%) and TEA (1.45 ml, 10.97 mol) and the mixture was stirred for 15 min. at room temperature, *p*-TsCl (2.05 g, 10.98 mmol) was added in three portion at a time interval of 20 min. The reaction mixture was stirred at room temperature under nitrogen atmosphere. The progress of the reaction was monitored by TLC. After the completion of the reaction (2 h), the reaction mixture was quenched by adding water (100 mL). The organic layer was separated, and the aqueous layer was again extracted with CH_2Cl_2 (2 x 75 ml). The combined organic layer were washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether: EtOAc (17:3) as eluent gave **80** as a colorless liquid (3.25 g, 85%).



80

Yield: 85%

$[\alpha]_D^{20}$: -37.35 (*c* 1, $CHCl_3$)

IR (Neat, cm^{-1}): ν_{max}3522, 3420, 3020, 2893, 1732, 1598, 1504, 1418, 1371, 1360

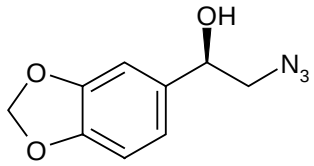
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10 (brs, 1H), 2.46 (s, 3H), 4.01 (m, 2H), 4.88 (dd, 1H, *J* = 3.30, 8.25 Hz), 5.95(s, 2H), 6.76 (s, 2H), 6.80 (s, 1H), 7.34(d, 2H, *J* = 8.25 Hz), 7.77(d, 2H, *J* = 8.25 Hz)

^{13}C NMR (200 MHz, $CDCl_3$): δ 21.61, 71.67, 74.21, 101,15, 106.63, 108.32, 119.79, 127.95, 129.89, 132.25, 132.75, 145.04, 147.69, 148

Mass: 354 (336+H_2O), 336, 319, 293, 279, 259, 227, 217, 199, 164

(*R*)-2-Azido-1-(3, 4-methylenedihydroxyphenyl)-ethan-1-ol (81): To a solution of **80** (1.12 g, 33.27 mmol) in dry DMF (10 mL) was added NaN_3 (1.29 mg, 199.38 mmol) and the mixture was stirred at 85-90°C for 4 h. The progress of the reaction was monitored by TLC. After reaction completion it was brought to room temperature and quenched with water (20

ml) and extracted with EtOAc (2x50 mL). The combined organic layer were washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether: EtOAc (17:3) as eluent to give the azido alcohol **81** (1.309 g, 95%) as a pale yellow oil.



81

Yield: 95%

$[\alpha]_D^{20}$: -34.07 (*c* l, $CHCl_3$)

IR (Neat, cm^{-1}): ν_{max} 3443, 2897, 2103, 1609, 1503, 1488, 1408, 1250

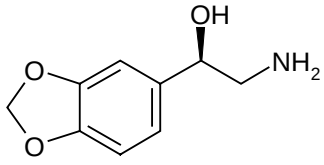
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.39 (b, 1H), 3.33-3.51 (m, 2H), 4.79(dd, 1H, *J* = 3.30Hz, 8.25Hz), 5.97 (s, 2H), 6.81 (s, 2H), 6.88 (s, 1H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 58.0, 73.1, 101.1, 106.4, 108.3, 119.4, 134.6, 147.5, 147.9.

Mass: 165 ($-N_3$), 149, 135, 118, 106

Analysis calcd for $C_9H_9N_3O_3$ (207.19): Found: C, 52.03; H, 4.26; N, 20.75 {Required C, 52.17; H 4.35; N, 20.85}

(*R*)-1-(3,4-Methylenedihydroxyphenyl)-2-amino-ethan-1-ol (82): A solution of azido alcohol **81** (1 g, 5 mmol) in methanol (25 ml) and Pd-C (10 mol%) was stirred at room temperature under H_2 atmosphere for 6 h to give **82** (0.857 g, 98%) as a thick brown oil.



82

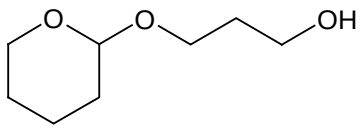
Yield: 98%

$[\alpha]_D^{20}$: -36.54 (*c* 1, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.44 (brs, 3H), 2.73-3.03 (m, 2H), 4.58(dd, 1H, *J* = 3.75, 8.25 Hz), 5.95 (s, 2H), 6.78 (s, 2H), 6.86 (s, 1H, *J* = 8 Hz), 5.95 (s, 2H), 6.78 (s, 2H), 6.86 (s, 1H)

Mass: 182 (M^++1), 178, 164, 149, 134, 106, 79, 59

3-(Tetrahydro-pyro-3yloxy)-propan-1-ol (84): A mixture of 1, 3-propanediol **83** (20 g, 263.15 mmol) and 3, 4-tetrahydro-2-pyran and iodine (25mg, catalytic) was stirred at room temperature in dry CH_2Cl_2 (250 ml) for 6 h. The reaction mixture was concentrated and passed through silica gel column chromatography using petroleum ether: EtOAc (98:2) as eluent to give **84** (40 g, 95%) as a colorless liquid.



84

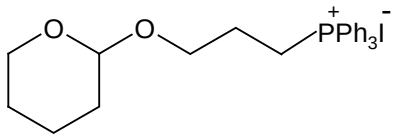
Colorless oil

Yield: 95%

IR (Neat, cm^{-1}): ν_{max} 3413, 2945, 2865, 1641, 1466

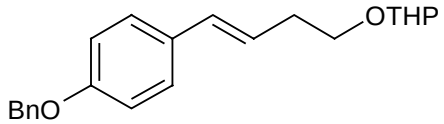
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36-1.80 (m, 8H), 3.37-4.11 (m, 6H), 4.47-4.53 (m, 1H).

3-(Triphenylphosphoniumiodo-propoxy)-tetrahydro-pyran (85): To a stirred solution of imidazole (3.06 g, 45.75 mmol), PPh_3 (9.12 g, 45.75 mmol) and iodine (11.42 g, 45.75 mmol) in dry CH_2Cl_2 (50 ml) at room temperature, was added a solution of alcohol **84** in CH_2Cl_2 (50 ml) and the mixture stirred for 6 h. The reaction mixture was monitored by TLC. After the completion of the reaction, the reaction mixture was quenched with water. The organic layer was separated, the aqueous portion was extracted with EtOAc (3 x 50 ml), and the combined organic layer was washed (brine), dried (Na_2SO_4), concentrated to give crude product which was washed with dry petroleum ether to give **85** (9.98 g, 98%) as a colorless liquid (phosphonium salt).



85

2-[4-(4Benzyloxyphenyl)-but-3-enyloxy]-tetrahydro-pyran (86): To a stirred solution of **85** (9 g, 16.90 mmol) in dry THF (150 mL), was added n-BuLi (25 ml, 1N solution in toluene) at 0°C. After 10 min. of stirring, 4-benzyloxybenzaldehyde (3.0 g, 14.14 mmol) in dry THF (25 ml) was added dropwise at 0°C, and stirring continued for 6 h at 0°C. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched by saturated ammonium chloride solution (50 ml) and stirred at 0°C for 1 h, and poured into water and extracted with EtOAc (3 x 100 ml), washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product with petroleum ether: EtOAc (95:5) as eluent gave **86** (3.29 g, 70%) as colorless oil.



86

Colorless oil

Yield: 70%

IR (Neat, cm^{-1}): ν_{max} 3443, 3064, 3033, 2941, 2868, 2741, 1886, 1694, 1601, 1577, 1509

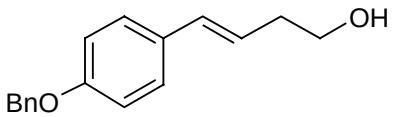
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27-1.92 (m, 8H), 3.40-3.50 (m, 2H), 3.71-3.90 (m, 2H), 4.55-4.63 (m, 1H), 5.08 (s, 2H), 5.96-6.20 (m, 1H), 6.3-6.45 (m, 1H), 6.91-6.95 (m, 2H), 7.07(d, 2H, *J* = 8.79 Hz), 7.30-7.43 (m, 3H), 7.84(d, 2H, *J* = 8.79Hz)

Mass: 276 {(338-85) + 23 (Na)}, 275, 265, 260, 181

Analysis cacl for $C_{22}H_{26}O_3$ (338.45): Found: C, 78.25; H, 7.69{Required C, 78.08; H, 7.74}

4-(4-Benzyloxyphenyl)-but-3-en-1-ol (87): To a stirred solution of **86** (2 g, 5.92 mmol) in dry CH_2Cl_2 (50 mL) was added, *p*-toluenesulphonic acid (50 mg, 0.33 mmol) and mixture stirred for 4 h.The reaction was monitored by TLC. After completion of reaction, it was

quenched with water and extracted with CH_2Cl_2 (2 x 50 ml). The combined organic layer was washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography with petroleum ether: EtOAc (80:20) as eluent, gave **87** (1.49 g, 99%) as thick colorless oil.



87

Colorless thick oil

Yield: 99%

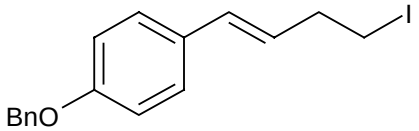
IR (Neat, cm^{-1}): ν_{max} 3450, 3019, 2867, 2400, 1954, 1891, 1606, 1575

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.71 (b, 1H), 2.46-2.83 (m, 2H), 3.68-3.84(m, 2H), 5.08 (s, 2H), 5.62-5.67 (m, 1H), 6.38-6.56 (m, 1H), 6.94 (d, 2H, *J* = 8.79 Hz), 7.25-7.44 (m, 7H).

Mass: 254, 236, 196, 163, 91, 72

Analysis cacld for $C_{17}H_{18}O_2$ (254.33): Found: C, 80.19; H, 7.23{Required C, 80.28; H, 7.13}

4-(4-Benzyloxyphenyl)-1-iodo-but-3-en (88): To a stirred solution of imidazole (0.45 g, 6.60 mmol), PPh_3 (1.73 g, 6.66 mmol), and iodine (1.68 g, 6.6141 mmol) in dry CH_2Cl_2 (30 ml), was added dropwise compound **87** in dry CH_2Cl_2 (20ml) at room temperature and stirred for 6 h. After the reaction completion, the reaction mixture was quenched with water, the organic layer was separated. The aqueous portion was again extracted with CH_2Cl_2 (3 x 30 ml), the combined organic layer was washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column purification with petroleum ether: EtOAc (95:5) as eluent gave **88** (1.81 g, 90%) as a colorless oil.



88

Colorless oil

Yield: 90%

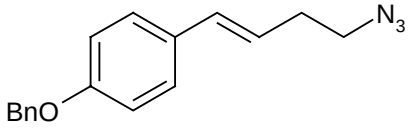
IR (Neat, cm^{-1}): ν_{max} 3361, 1601, 1592, 1452, 1423, 1278

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62-2.98 (m, 2H), 3.23 (t, 2H, *J* = 5.38Hz), 5.09 (s, 2H), 5.45-6.09 (m, 1H), 6.38-6.54 (m, 1H), 6.97(d, 2H, *J* = 8.79 Hz), 7.19(d, 2H, *J*= 8.79 Hz), 7.34-7.44(m, 5H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 28.2, 51.1, 55.4, 114.6, 114.9, 126.10, 127.4(2C), 128.0, 128.5(2C), 129.9(2C), 131.0, 132.2, 136.9, 157.1

Analysis calcd for $C_{17}H_{17}IO$ (364.22): Found: C, 77.03; H, 4.59{Required C, 77.28; H, 4.70}

4-(4-Benzyloxyphenyl)-1-azido-but-3-en (89): To a solution of 88 (200 mg, 0.549 mmol) in dry DMF (5 ml) was added NaN_3 (96 mg, 0.247 mmol) and the mixture was stirred at 80°C for 4 h under N_2 atmosphere. The reaction mixture was cooled to room temperature and diluted with water and EtOAc. The organic layer was separated the aqueous layer was again extracted with EtOAc (3 x 20 ml). The combined organic layers were washed (brine) dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether: EtOAc (17:3) as eluent to give 89 (0.15 g, 98%) as a colorless oil.



89

Colorless oil

Yield: 98%

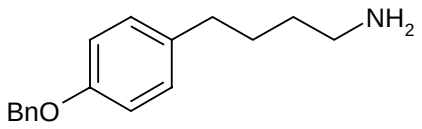
IR (Neat, cm^{-1}): ν_{max}3371, 3032, 2927, 2097, 1606, 1574, 1509, 1454, 1380, 1348, 1244, 1174

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62-2.98(m, 2H), 3.23(t, 2H, *J* = 5.38 Hz), 5.09 (s, 2H), 5.45-5.58(m, 1H), 6.38-6.54(m, 1H), 6.95(d, 2H, *J* = 8.79 Hz), 7.20-7.43(m, 7H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 28.2, 32.6, 51.1, 55.4, 69.9, 114.6, 114.9, 123.9, 126.1, 127.4, 128.0, 128.5, 129.9, 131.0, 132.2, 136.9, 157.7

Analysis calcd for $C_{17}H_{17}ON_3$ (279.34): Found: C, 72.90; H, 6.23; N, 15.22{Required C, 73.09; H, 6.13; N, 15.04}

4-(4-Benzyloxyphenyl)-1-amino-butane (90): Compound **89** was subjected to hydrogenation in the presence of Pd-C in methanol under hydrogen for 2 h to afford **90** (0.130 g, 95 %) as colorless oil.



90

Colorless oil

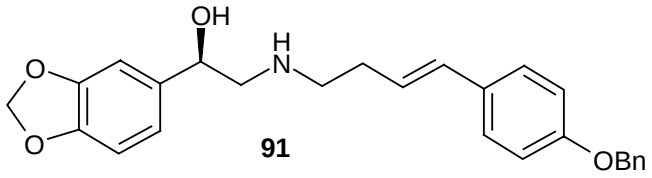
Yield: 95%

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (brs, 2H), 2.26-2.90 (m, 8H), 5.01 (s, 2H), 6.76 (d, 2H, *J* = 8.79 Hz), 7.06(d, 2H, *J* = 8.79 Hz), 7.26-7.39 (m, 5H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 33.5, 34.0, 56.6, 71.3, 78.7, 96.00, 101.8, 107.69, 127.7, 127.9, 128.4, 136.8, 176.1

Analysis calc for $C_{17}H_{21}NO$ (261.37): Found: C, 78.26; H, 7.93; N, 5.54{Required C, 78.12; H, 8.10; N, 5.39}

Benzo-[1, 3]-dioxol-5-yl-[3-(4-benzyloxy-phenyl-allylamino]-methanol (91): A soloution of compound **82 (**0.53 g, 2.93 mmol) and 88 (1.127 g, 3.22 mmol) in dry THF was heated under stirring at 80°C for 3 h. After completion of the reaction, the reaction mixture was cooled and poured into ice water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed (brine), dried (Na_2SO_4) and concentrated to give 91. Silica gel column chromatography using petroleum ether: EtOAc (70:30) gave **91** (0.93 g, 76%) as pale yellow semisolid.



91

Yield: 76%

Pale yellow semi solid

$[\alpha]_D^{20}$: -0.27 (*c* 1, $CHCl_3$)

IR (Neat, cm^{-1}): ν_{max}3430, 3312, 2914, 2810, 1604, 1516, 1413

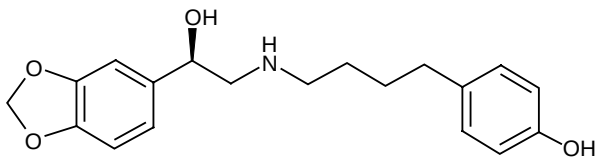
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.44-2.69 (m, 4H), 3.74(t, 2H, *J* = 5.38 Hz), 5.09 (s, 3H), 5.53-5.62 (m, 1H), 5.89-6.09 (m, 1H), 6.10(s, 2H), 6.53(m, 1H), 6.78(brs, 1H), 6.92-6.96 (m, 3H), 7.23-7.27 (d, 7H, *J* = 8.79Hz), 8.00 (s, 2H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 29.6, 31.9, 36.3, 62.0, 62.41, 69.9, 114.5, 114.8, 124.1, 126.7, 127.1, 127.4(2C), 127.9(2C), 128.5(2C), 129.9(2C), 130.0, 130.8, 132.0, 136.9, 157.5, 158.0

Mass: 655[832(Dimer)-2$PhCH_2$], 637, 538, 487, 446, 429, 418, 401, 340, 316, 272, 237, 188, 149.

Analysis calcd for $C_{26}H_{27}NO_4$ (417.50): Found: C, 74.80; H, 6.52; N, 3.35 {Required C, 74.71; H, 6.40; N, 3.26}

4-{3-(Benzo[1, 3]dioxl-5-yl-hydroxy-methyl)-amino]-propyl}-phenol (92): A mixture of compound **91** and Pd/C in absolute ethanol was stirred under hydrogen atmosphere for 10 h(60psi). The reaction mixture was filtered through celite and after concentration it was purified by coloumn chromatography to give **93** (0.287g, 91%) as a pale yellow solid.



92

Pale Yellow Solid

M.P: 63-65 ^{0}C

Yield: 91%

Optical Rotation $[\alpha]_D^{20}$**:** -17.87 (*c* 1 EtOH)

IR ($CHCl_3$, cm^{-1}): ν_{max}3425, 3350, 3015, 2105, 1955, 1601, 1575, 1425

^{1}H NMR (200MHz, $CDCl_3$): δ 1.47-1.54(m, 4H), 1.86-1.91(m, 2H), 2.22-2.25(m, 2H), 2.74(brs, 2H), 3.07-3.14(m, 2H), 5.04(m, 1H), 5.94(s, 2H), 6.65-6.90(m, 3H), 7.27 (d, 2H, *J* = 8.79Hz), 7.67(d, 2H, *J* = 8.31Hz)

Mass: 330(M^++ 1), 301, 275, 245, 227, 203, 188, 173, 155

Analysis calcd for $C_{19}H_{23}NO_4$ (329.39): Found: C, 69.17; H, 7.19; N, 4.13{Required C, 69.28; H, 7.04; N, 4.25}

(*R*)-(-)-Arbutamine (72): To a solution of compound **92** (0.20 g, 0.60 mmol) in ethanol (5ml) was added dropwise, 0.5ml of 2N NaOH Solution, and the mixture was stirred at 90°C for 60 minutes. The reaction mixture was cooled to room temperature and diluted with water and neutralized with dil HCl, and then extracted with EtOAc (3x50ml). The combined organic layers were washed (brine), and dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product, using $CHCl_3$: MeOH (8:2) as eluent gave (*R*)-(-)-arbutamine **72** as yellow solid (0.185g, 97%) with m.p 53-55C. The optical rotation $[\alpha]_D^{20}$ = -17.14(*c*, 0.97, EtOH){Lit.[35] $[\alpha]_D^{20}$ = - 17.3 (*c*, 1.03, EtOH). The physical and spectroscopic data were in full agreement with the literature data.[35]

2.4.7 Spectra

1. ^{1}HNMR spectrum of 79

2. HPLC analysis of Compound 79

3. ^{1}HNMR spectrum of 80

4. ^{13}CNMR spectrum of 80

5. ^{1}HNMR spectrum of 81

6. ^{13}CNMR spectrum of 81

7. ^{1}HNMR spectrum of 82

8. ^{1}HNMR spectrum of 86

9. ^{1}HNMR spectrum of 87

10. ^{1}HNMR spectrum of 88

11. ^{1}HNMR spectrum of 89

12. ^{13}CNMR spectrum of 89

13. ^{1}HNMR spectrum of 90

14. ^{13}CNMR spectrum of 90

15. ^{1}HNMR spectrum of 91

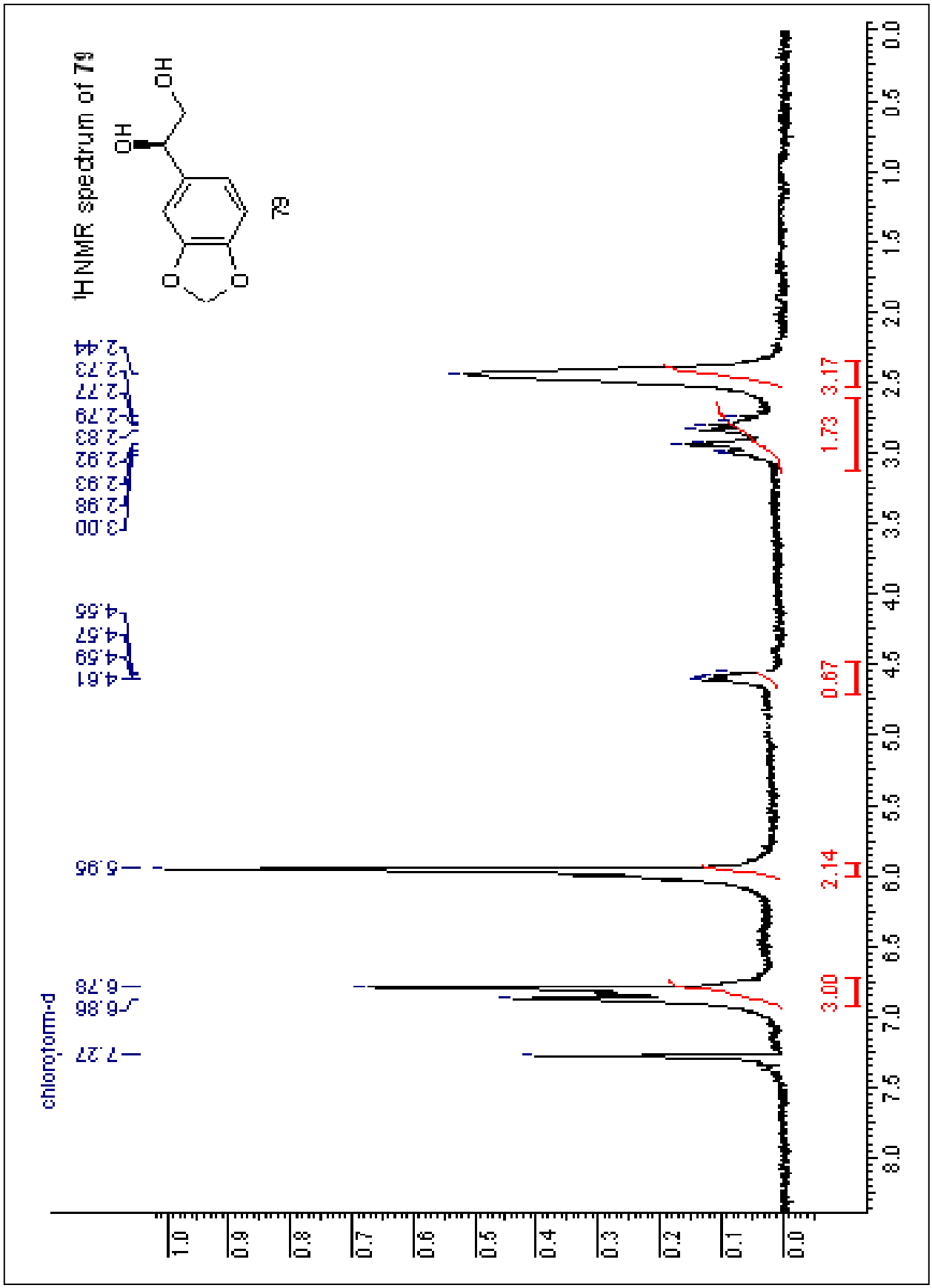
16. ^{13}CNMR spectrum of 91

17. Mass spectrum of 91

18. ^{1}HNMR spectrum of 92

19. Mass spectrum of 92

20. ^{1}HNMR spectrum of 72


^{1}H NMR spectrum of 79
79
OH
OH
O
O
chloroform-d
7.27
6.86
6.78
5.95
4.61
4.59
4.57
4.55
3.00
2.98
2.93
2.92
2.83
2.79
2.77
2.73
2.44
2.14
0.67
1.73
3.17

-7000 HSM: HPLC Series: 1047 Report: modified System: Sys 1

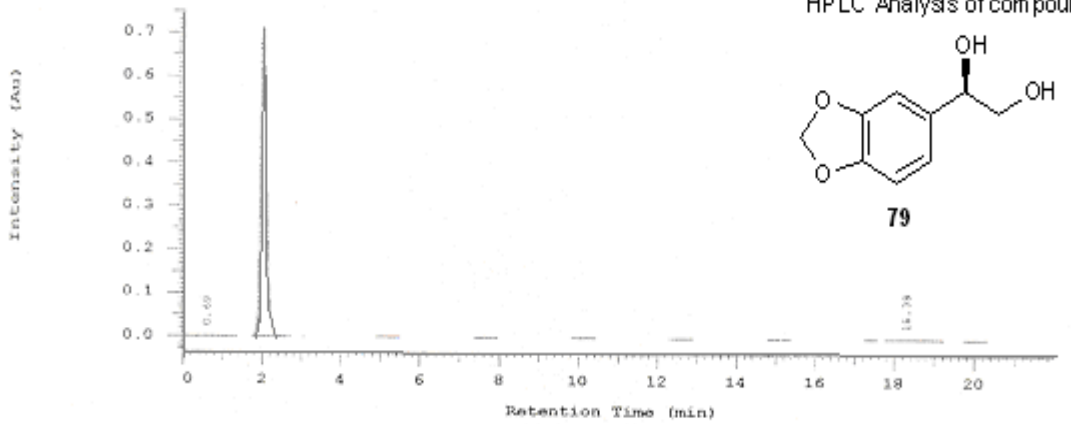
NATIONAL CHEMICAL LABORATORY

ORGANIC CHEMISTRY TECHNOLOGY

Analyzed: 07/10/03 11:14 AM Reported: 07/10/03 03:53 PM
Data Path: f:\Win32App\HSM\HPLC\DATA\1047\
Processing Method: Lichrosphere RP-18 (125-4) Acquisition Method: Lichrosphere RP-18 (125-4)
System(acquisition): Sys 1 Series:1047
Sample Name: MHP - OH Vial Number: 1
M. Phase :(MeOH:H2O) (40:60) Vial Type: UNK
Volume: 5.0 ul

Chrom Type: HPLC Channel : 1

HPLC Analysis of compound **79**



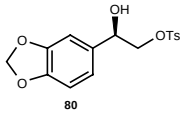
79

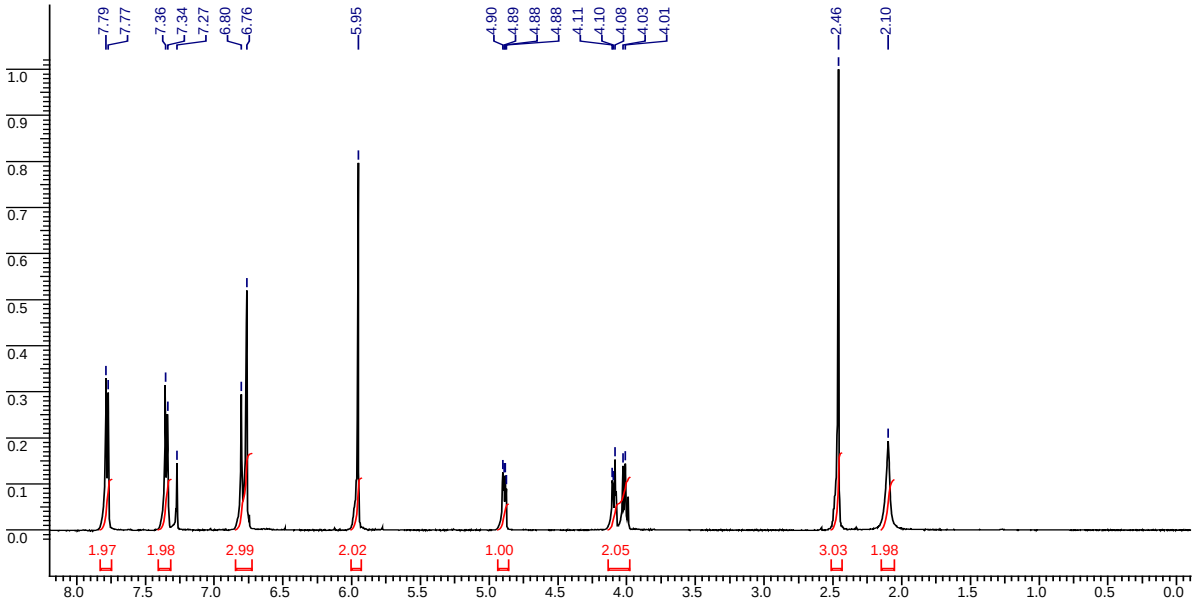
Peak Quantitation: AREA Calculation Method: AREA%

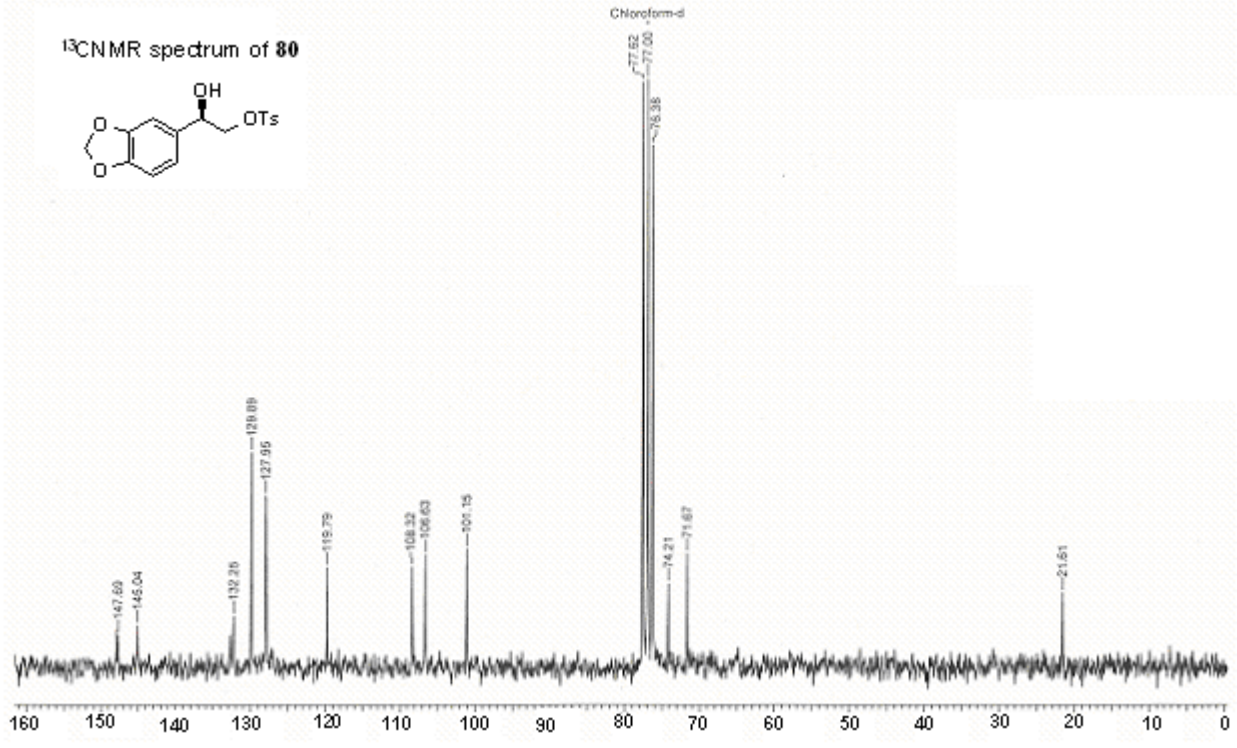
No.	RT	Height	Area	Area %
1	0.69	2190	22090	0.597
2	2.02	357735	3616521	97.777
3	18.38	1336	60130	1.626
		361261	3698741	100.000

Peak rejection level: 3000

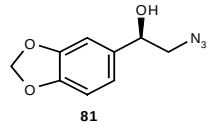
^{1}HNMR spectrum of 80



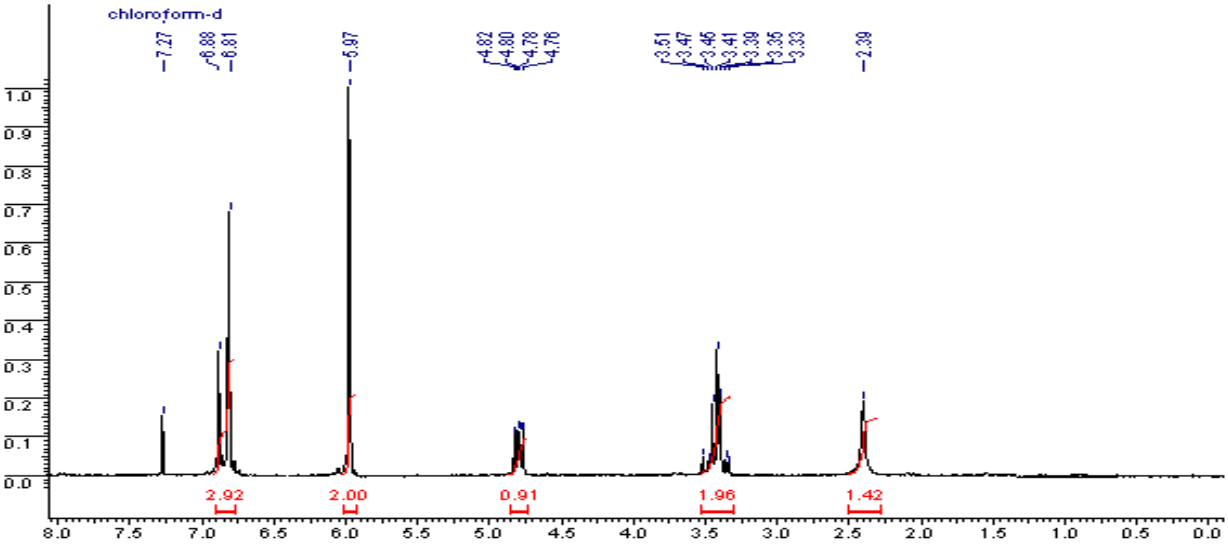




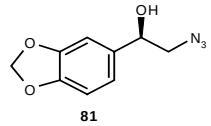
^{1}HNMR spectrum of 81



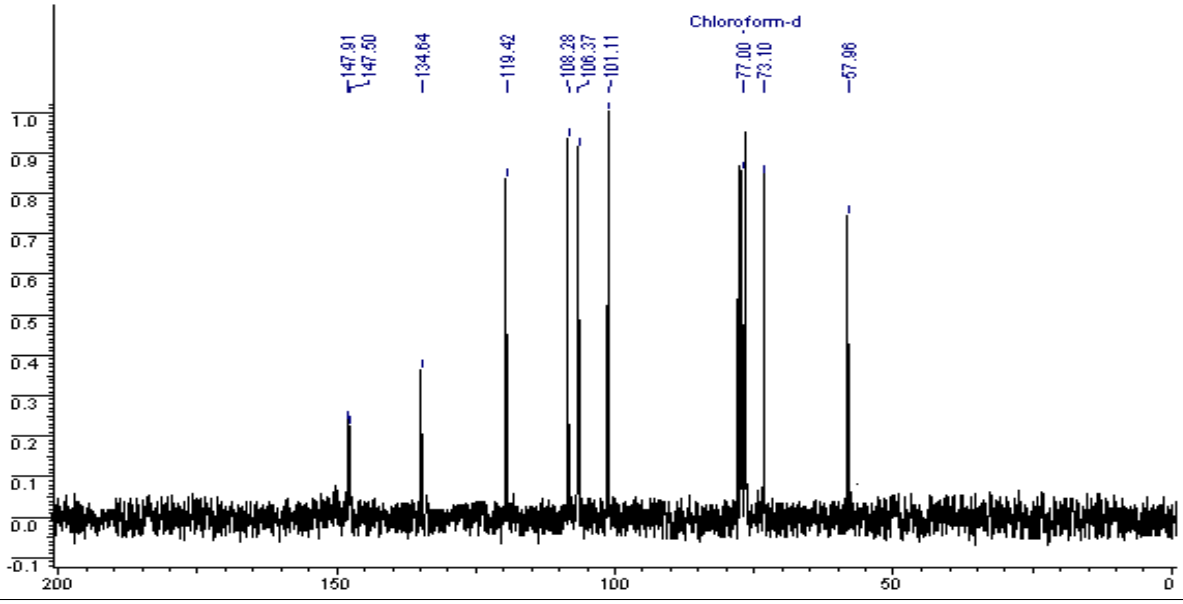
81

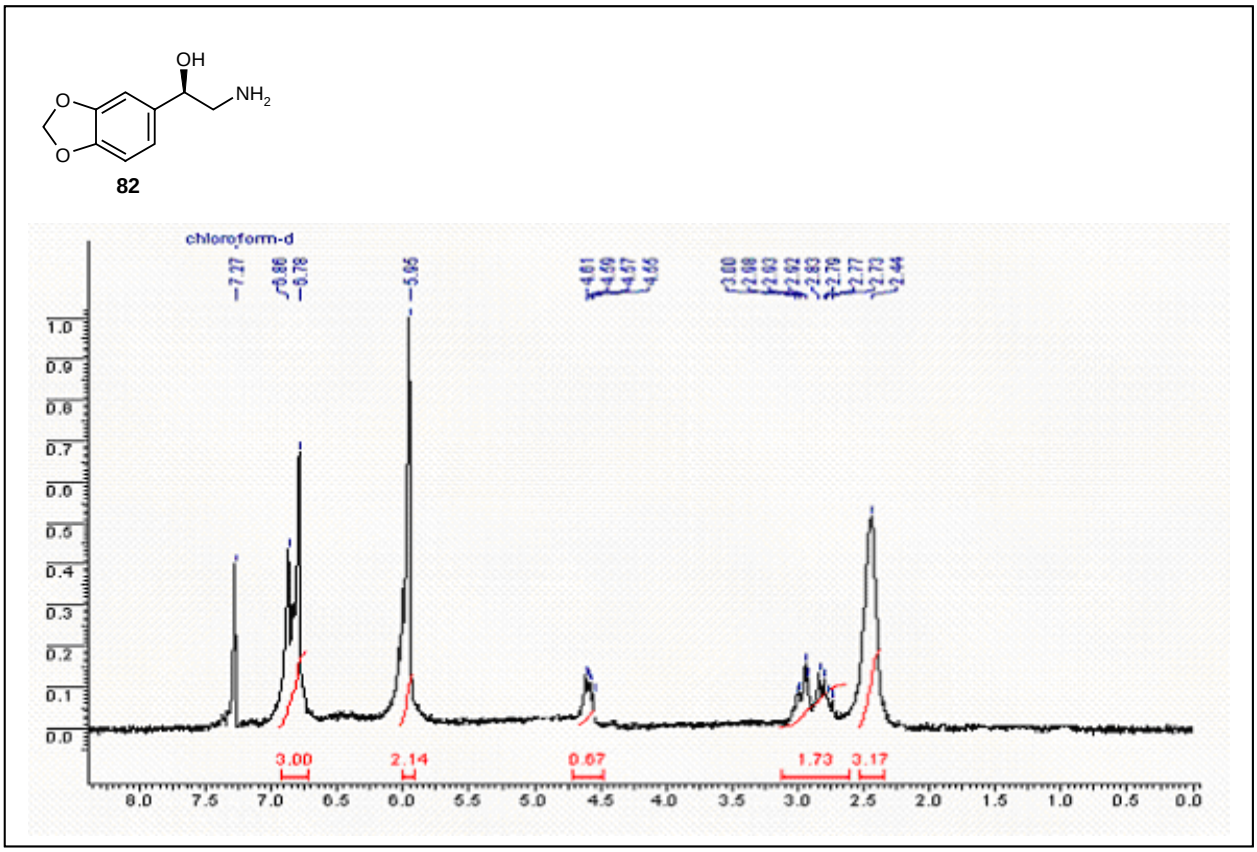


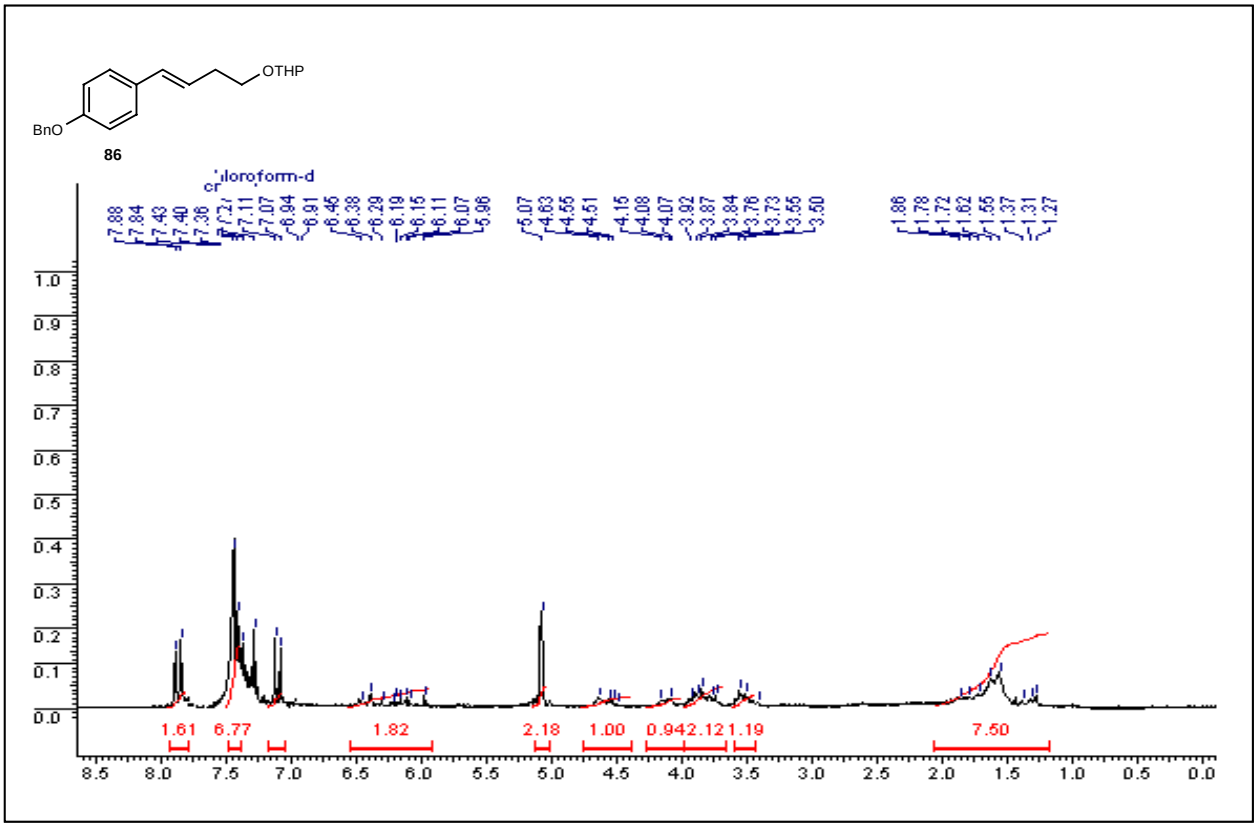
^{13}CNMR spectrum of **81**



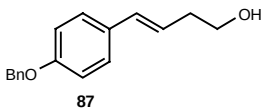
81



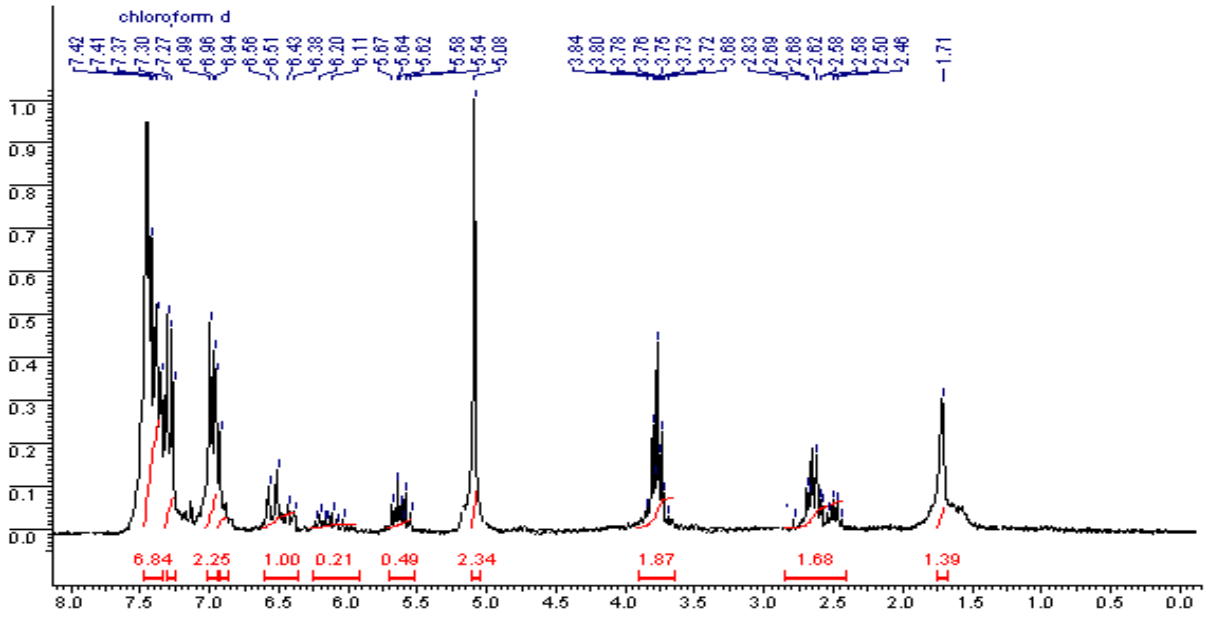

OH
NH2
O
O
82
chloroform-d
7.27
6.86
6.78
5.95
4.61
4.59
4.57
4.55
3.00
2.98
2.93
2.92
2.83
2.79
2.77
2.73
2.44
3.00
2.14
0.67
1.73
3.17

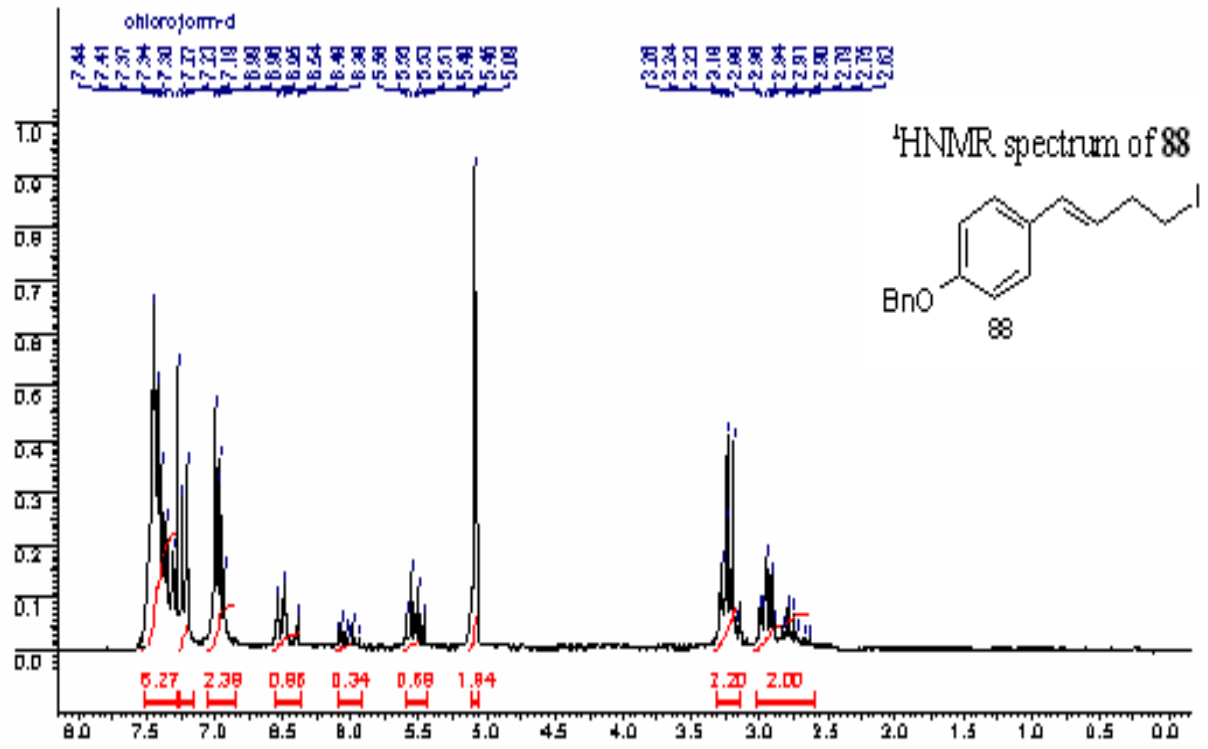

OTHP
BnO
86
chloroform-d
7.88
7.84
7.43
7.40
7.38
7.24
7.11
7.07
6.94
6.91
6.45
6.38
6.29
6.19
6.15
6.11
6.07
5.96
5.07
4.63
4.55
4.51
4.15
4.08
4.07
3.92
3.87
3.84
3.76
3.73
3.55
3.50
1.86
1.78
1.72
1.62
1.55
1.37
1.31
1.27
1.61
6.77
1.82
2.18
1.00
0.94
2.12
1.19
7.50

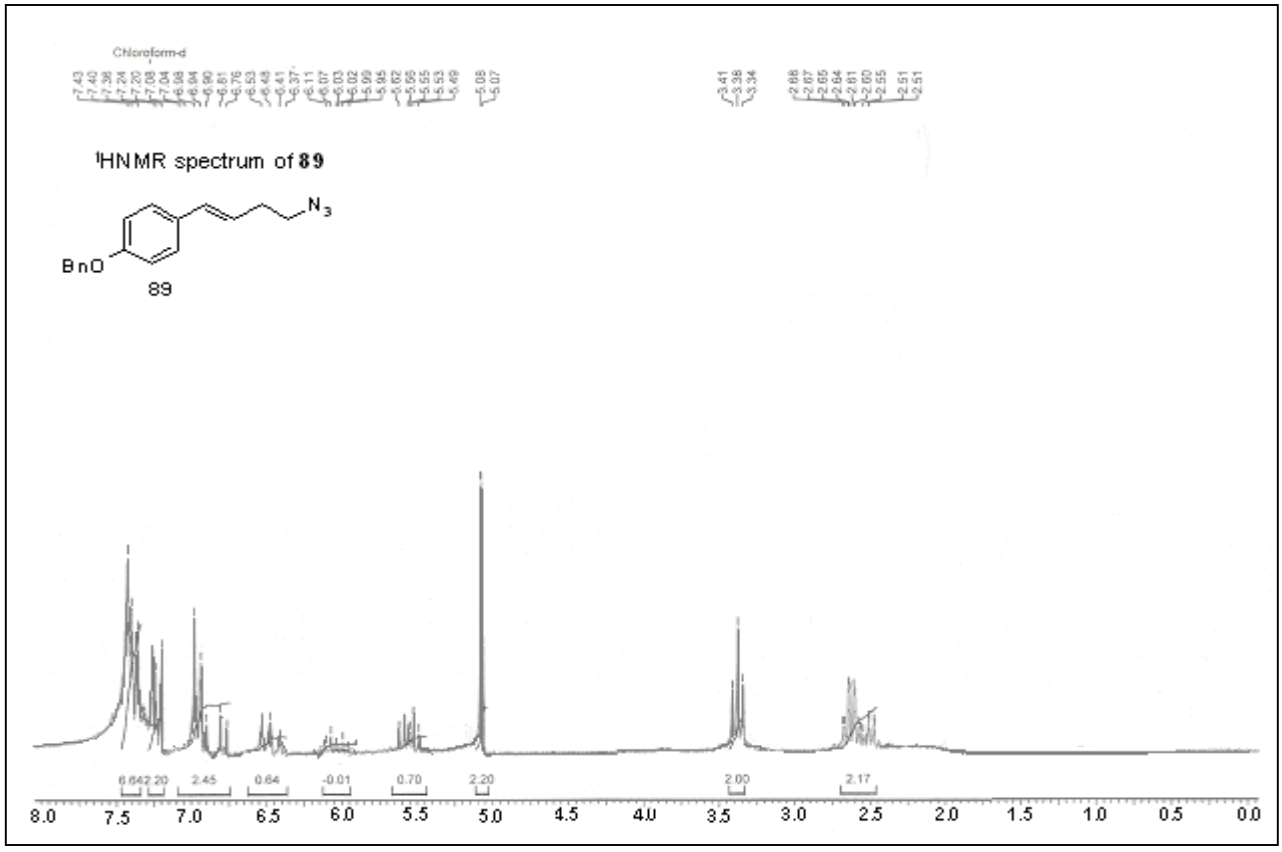
^{1}HNMR spectrum of 87

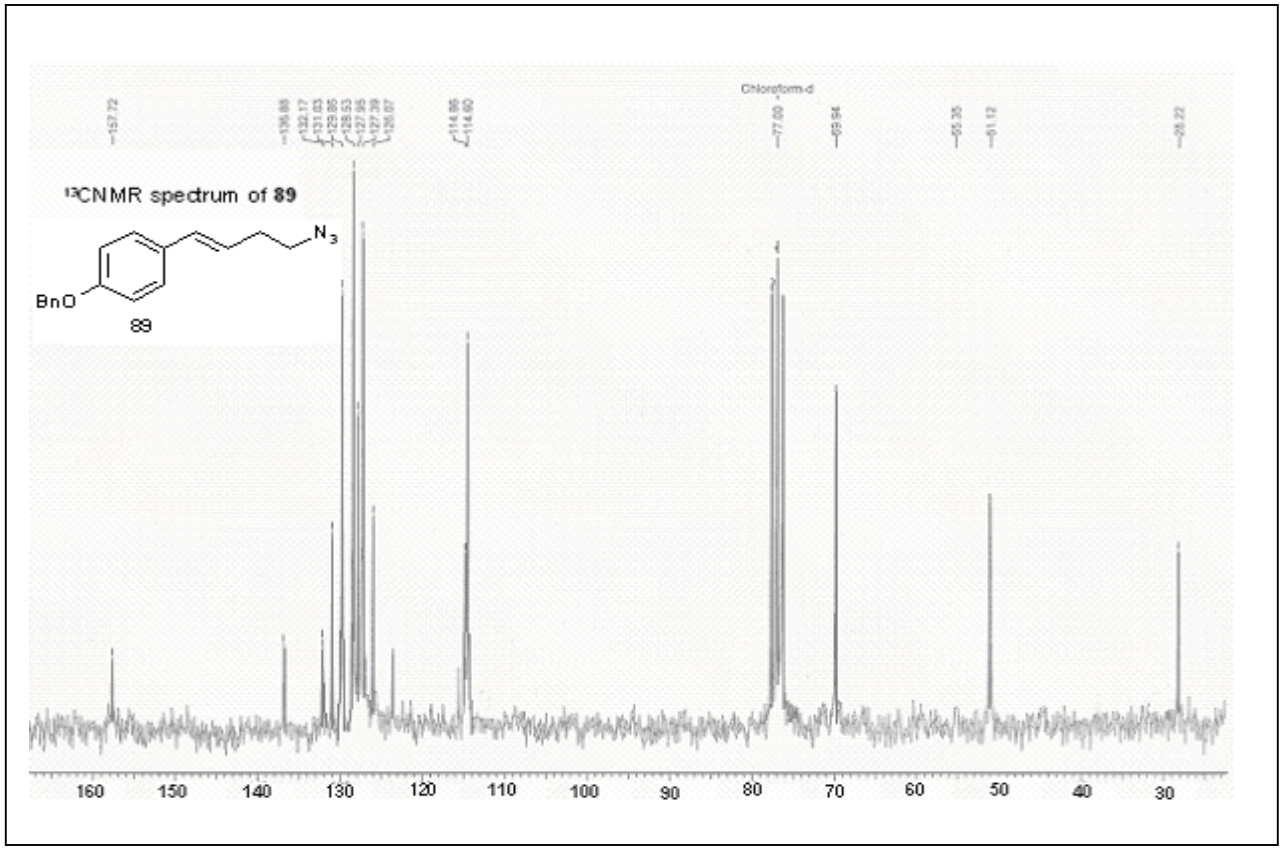


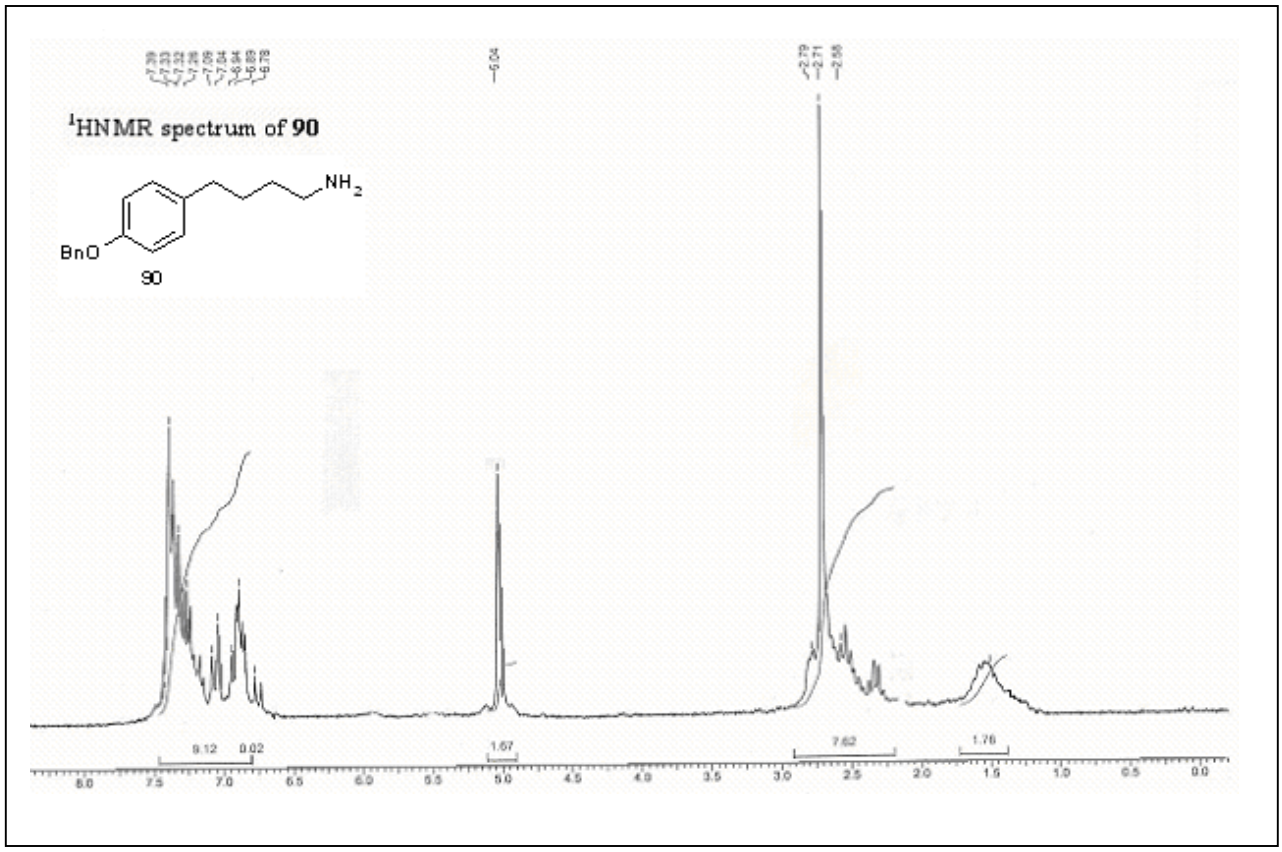
87

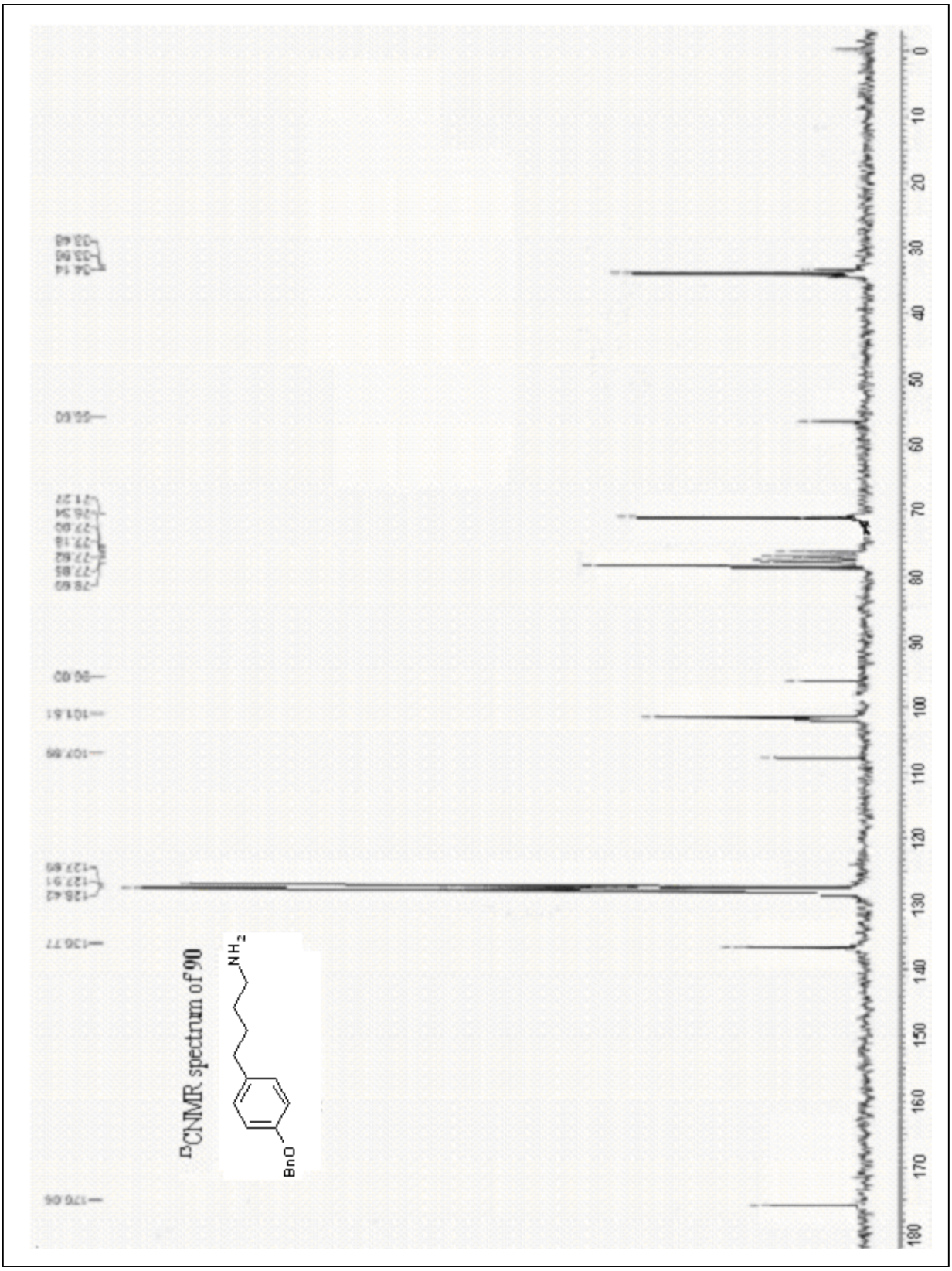


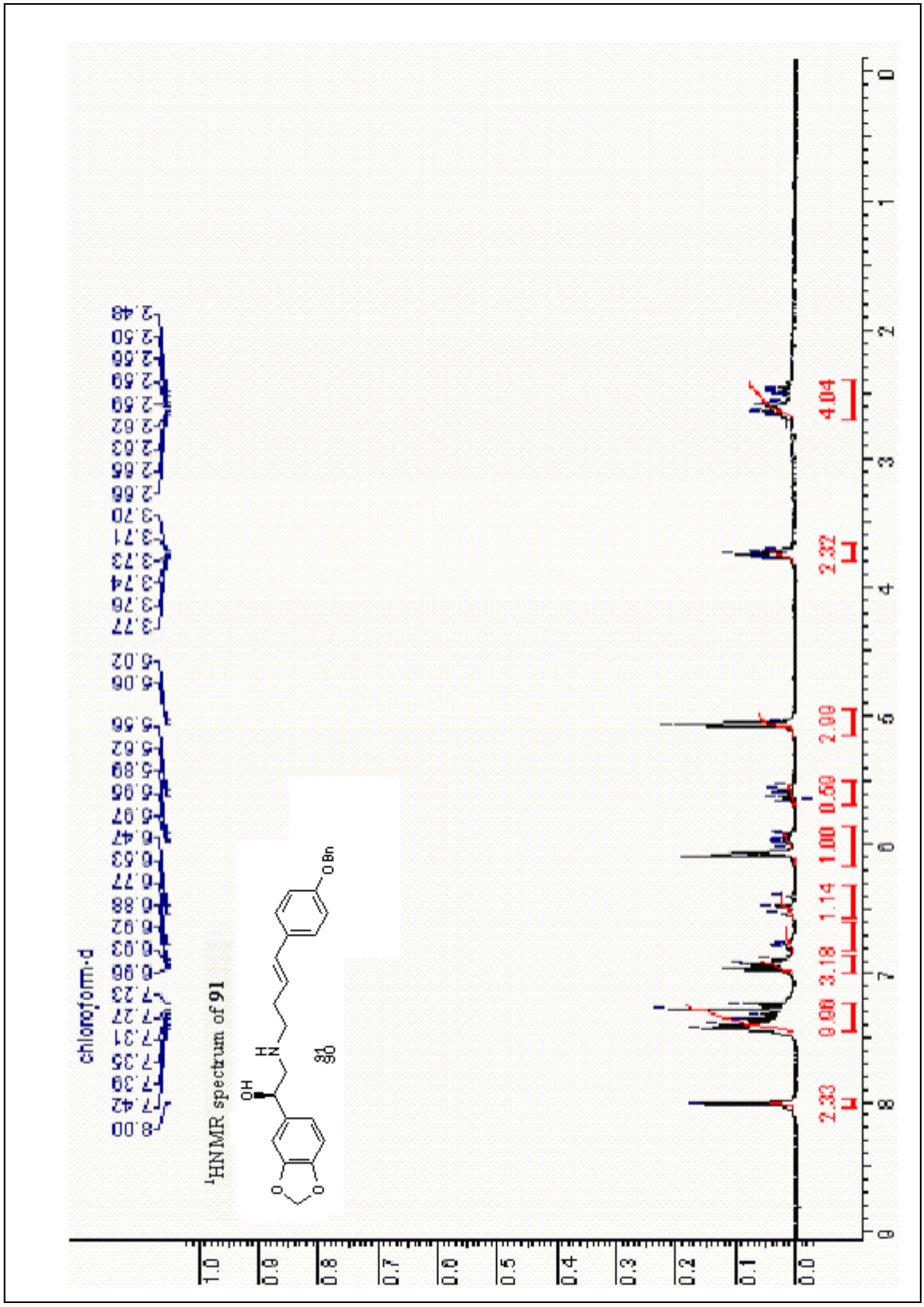



Chloroform-d
^{1}HNMR spectrum of **89**
N_3
BnO
89
6.64 2.20
2.45
0.64
-0.01
0.70
2.20
2.00
2.17
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

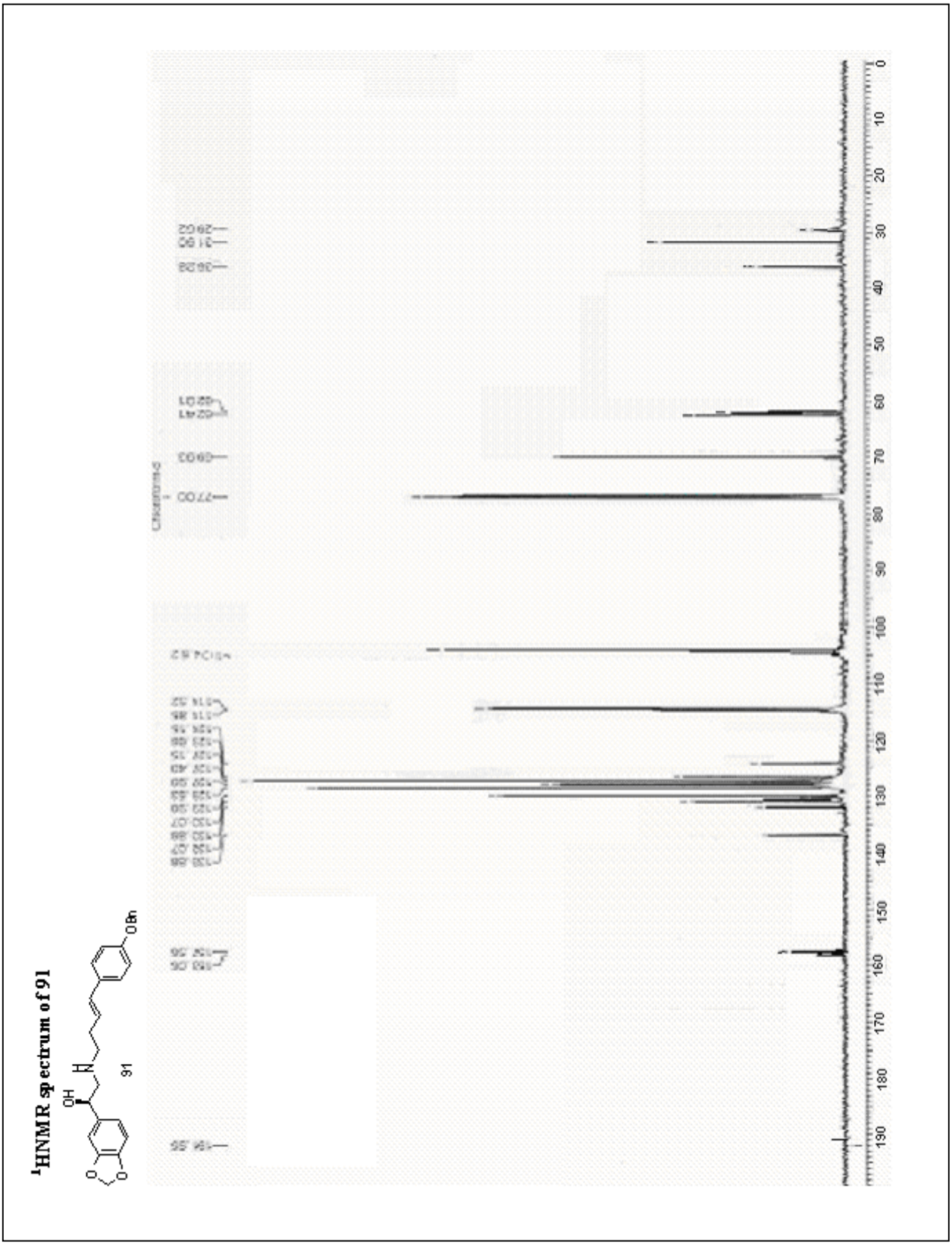

Chloroform-d
^{13}CNMR spectrum of **89**
N_3
BnO
89
160
150
140
130
120
110
100
90
80
70
60
50
40
30

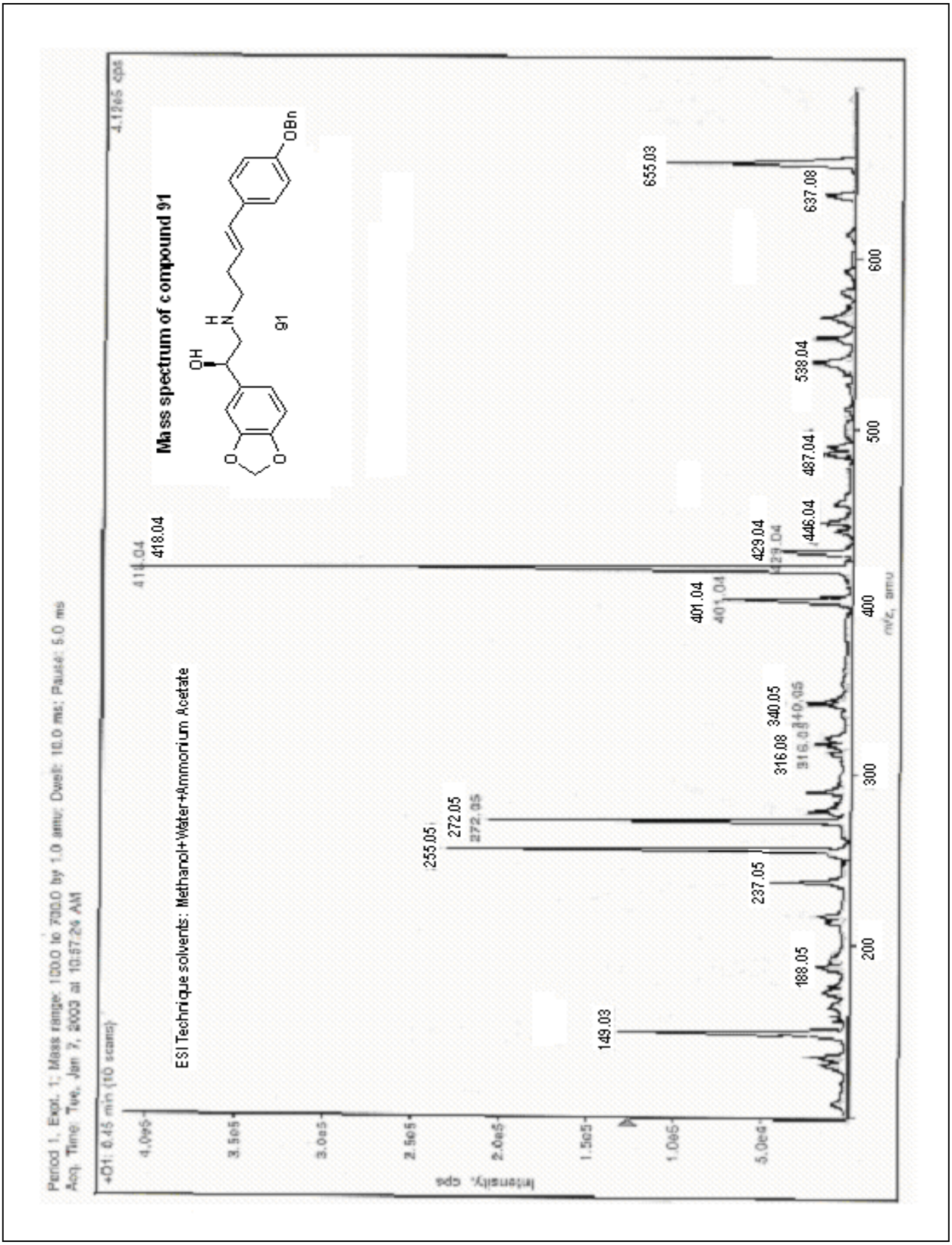

^{1}HNMR spectrum of **90**
NH$_2$
BnO
90

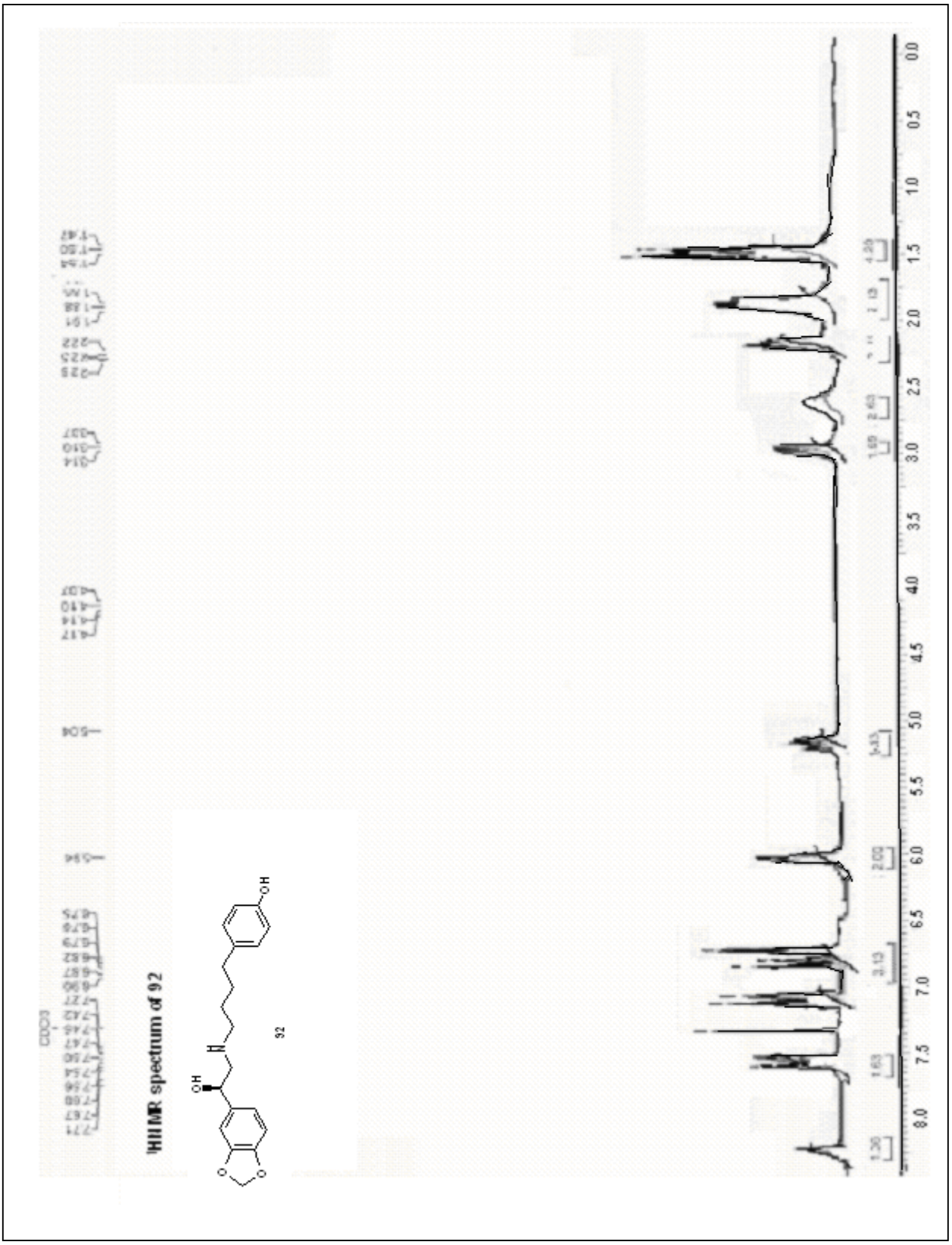

^{13}CNMR spectrum of 90
NH2
BnO

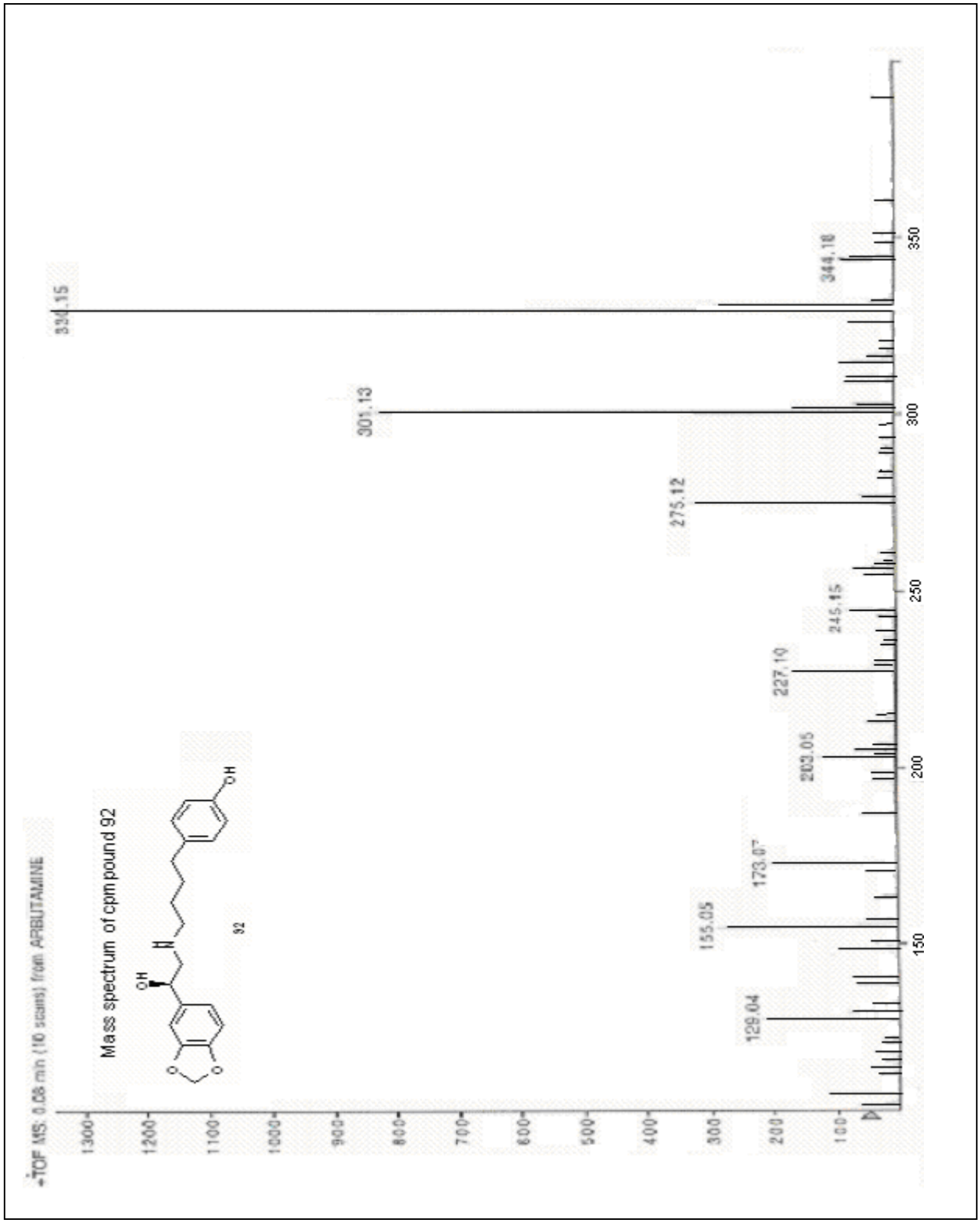

chloroform-d
^{1}HNMR spectrum of **91**
OH
H
N
OBn
91
90
O
O
8.00
7.42
7.39
7.35
7.31
7.27
7.23
6.98
6.93
6.92
6.88
6.77
6.63
6.47
6.07
6.05
5.89
5.62
5.56
5.06
5.02
3.77
3.76
3.74
3.73
3.71
3.70
2.66
2.66
2.63
2.62
2.59
2.59
2.56
2.50
2.48
2.33
0.96
3.18
1.14
1.00
0.59
2.00
2.32
4.04

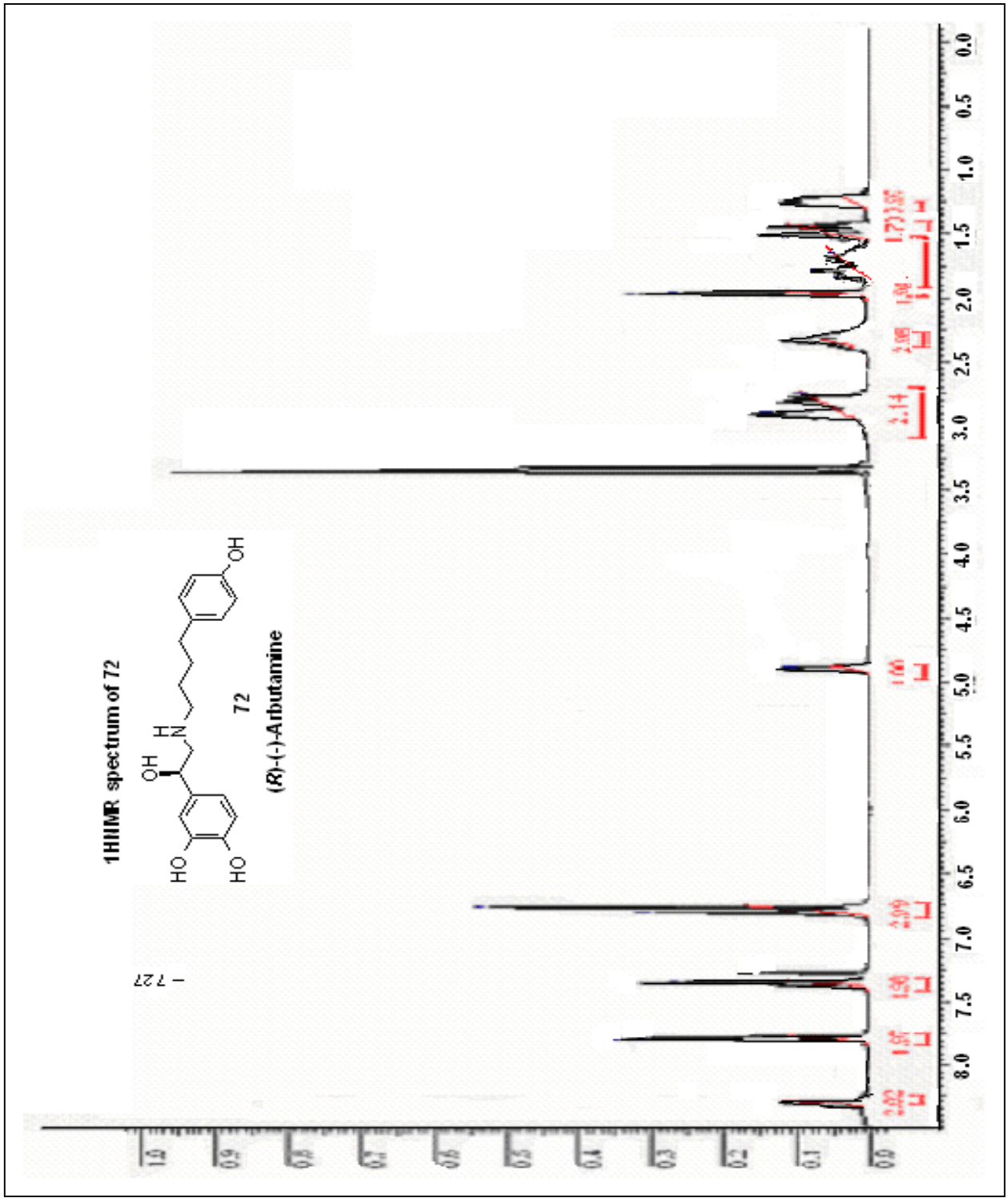
^{1}HNMR spectrum of 91




Mass spectrum of compound 91
ESI Technique solvents: Methanol+Water+Ammonium Acetate
91
OBn
OH
H
N
O
O
Period 1, Expt. 1: Mass range: 100.0 to 700.0 by 1.0 amu; Dwell: 10.0 ms; Pause: 5.0 ms
Acq. Time: Tue, Jan 2, 2003 at 10:57:26 AM
+Q1: 6.45 min (10 scans)
4.1965 cps
Intensity, cps
m/z, amu
149.03
188.05
237.05
255.05
272.05
316.08
340.05
401.04
418.04
429.04
446.04
487.04
538.04
637.08
655.03


^{1}HNMR spectrum of 92
92


+TOF MS: 0.08 min (10 scans) from APBUTAMINE
Mass spectrum of compound 92
92
334.15
301.13
275.12
245.15
227.10
203.05
173.07
155.05
129.04
344.18


1HNMR spectrum of 72
72
(R)-(-)-Arbutamine
OH
HO
HO
OH
H
N
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

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CHAPTER 3

Synthesis, characterization and application of MCM-41 based Palladacycle Pd-OMS(MCM-41) catalyst for C-C bond forming reactions

This chapter is divided into three sections.

3.1 Section A
3.1.1 Part 1 Palladacycle as catalyst

3.1.1.1 Introduction

Transition metal-catalyzed reactions have gained a steadily increasing importance in recent research and developments. Fine tuning of reaction parameters of known or newly discovered metal catalyzed transformations along with the catalyst development had a good impact on the synthesis of natural and non-natural biologically active compounds (valuable intermediates in the pharmaceutical and agrochemical industries) as well as theoretically interesting molecules. Among the process, palladium catalyzed transformations have played a leading role in developing and understanding totally new reaction types and the nucleophilic substitution of allylic substrates.Palladium catalysis has achieved the status of an indispensable tool for both common and state-of-the art in organic synthesis. Carbon-Carbon bond forming reactions represent the potential application of palladium catalysts. Among the basic type of palladium-catalyzed transformations, the Heck reaction and related chemistry occupy a special place and so it is considered as a sharpening stone of palladium catalysis.[1] Palladium complexes with or without phosphine ligands can catalyze the Heck reaction. The phosphine assisted approach is the classical and well established method, which gives excellent results in a majority of cases. Palladium catalyzed homogeneous reactions are often preferred for laboratory scale preparations and the majority of mechanistic elucidations and optimization studies have been carried out in solution phase. Frequently, however, problems are encountered when taking an optimized laboratory procedure and scaling it up. An obvious alternative is the use of heterogeneous catalysis where a polymeric ligand is employed. Such catalyst is easily separated from the reaction medium, and leaching into the reaction medium is often reduced. Heterogeneous catalytic systems which include polymer/dendrimer supported palladium catalyst,[2] palladium supported on carbon,[3] metal oxides,[4] clays,[5] molecular sieves[6] and nano palladium complexes, metal complexes of Ni, Co, Cu, Mn,[7] organically modified Pd-Silica heterogeneous catalysts[8], palladium supported on silico aluminophosphate-31,[9] bifunctional heterogeneous catalysts like palladium on zeolites[10] were reported in the literature catalytic system. Unfortunately, most of these are not efficient for reactions with aryl chlorides.

Among pool of palladium catalysts, carbometallated Pd-(II) compounds, especially palladacycles, have emerged as very promising catalysts for C-C bond forming reactions.[11] The discovery of Hermann and Beller *et al*. of the unique catalytic activity of a well known dimeric complex (Palladacvde) $Pd_2[(P(O\text{-}Tol)_3]_2$ $(\mu\text{-}OAc)_2$, as is now obvious, has set a milestone in palladium catalysts.[11b] The parental structure; which is now often referred to as Hermann's catalyst (*hc*) is definitely one of the most convenient forms of palladium complexes applied in homogeneous catalysis. Even if the palladacycle would have no specific properties (they are classified in the following paragraphs on the basis of their structure and its activity) but was equivalent to mixture of palladium salt and phosphine[12] is placed in the first row of catalysts due to exceptional ease of handling. Though palladium complexes incorporating cyclopalladated phosphines; phosphinites, chelated diphosphines are reported,[11] phosphine ligands are expensive, toxic and unrecoverable. In large-scale applications on industrial scale; the phosphines might be a more serious economical burden than palladium itself, which can be recovered by any stage of production or from wastes. Even catalyst like palladium complexes with carbene ligands and dimethyl glycine[13] have also been reported. Recently, silica supported imines and oxime based palladacycle catalyst anchored on MCM-41 have been studied as an excellent mechanistic probe in the Suzuki reaction.[14]

3.1.1.2 What do we mean by palladacycles?

Even if the palladacycle would have no specific properties, they are classified on the basis of its structure and its activity. The general structures of the complexes we will be concentrating on are shown in Fig.1.

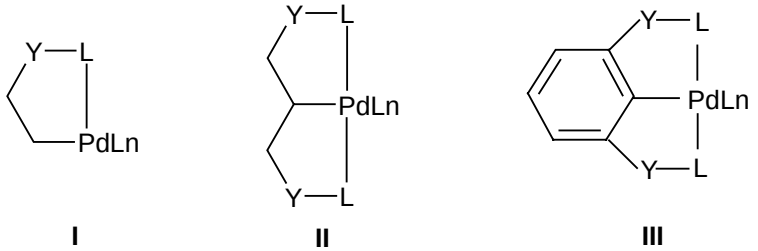


Figure 1. Generalised Palladacyclic structure L= donor, Y=linker group

Palladacycles, the most active catalysts in the Heck type C-C bond forming and related C-hetero atom bond forming reactions, have recently emerged as showing the highest activity in

Suzuki coupling of electronically challenging aryl chloride substrates, fall into two general classes: the first are simple palladacycles (I) where one ligand co-ordinates to the palladium center in k^2-*L,C* manner (*L*= donor) to form a stable, five membered chelate; the second are so called 'Pincer' complexes (II) where the metallated carbon is supported by two donor groups in a k^3-*L,C,L* fashion. The donor group'*L*'are typically PR_2, NR, NR_2 or SR and there is usually some degree of unsaturation between the metallated C and the donor group '*L*'. In nearly all the cases in this article the carbon donor is an orthometallated aryl ring (structure-III). The study of palladacycle catalysts, is almost hampered by the misconception that such species are likely to be deactivation product was dismissed by Heck who observed their formation in the coupling of dienes with aryl halides.

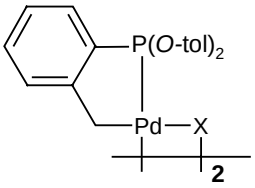
k^2 *L,C*-palladacyclic catalysis

k^2 *P,C* palladacycle

The *P, C*-version of palladacycle was first initiated by *Hermann*[11c] and *co-workers* and they reported the complex of the type **1** (ortho metallated complex). They found that the catalyst **1c** shows a TON[15] of 1,000000 with electronically activated aryl bromide, 4-bromoacetophenone with n-butylacrylate. It was also demonstrated that the catalyst **1c** can activate to couple aryl chlorides, albeit electronically activated chloroarenes for examples such as 4-chloroacetophenone. This class of substrates is particularly relevant from an industrial point of view as they are generally cheaper and more widely available than their bromide or iodide counterparts. They described that the performance with aryl chloride can be enhanced by the use of appropriate additives such as $[NBu_4]^+Br^-$ or PPh_4Cl with TON of 190 even in the case of electronically deactivated 4-chloro anisole. Beller demonstrated that the application of the catalyst **1** is not limited to Heck reaction, the catalyst **1c** could be used effectively in the Suzuki birayl coupling with TONs of 74,000, 7600, 2100 in the coupling of phenyl boronic acid with 4-bromoacetophenone, 4-bromoanisole and 4-chloroacetophenone[11b] respectively. Complex **1c** can also be used in Stille coupling of aryl bromide[16a,b] with allyl, aryl stannanes and allyl, aryl silanes, along with Sonogashira coupling of aryl bromide[16] with phenyl acetylene and other related couplings of aryl Grignard or Zinc reagent (Kumada and Negishi couplings)[16] and the amination of aryl bromides and chlorides (Buchwald-Hartwig amination).[16] Shaw and co-workers demonstrated that the palladated naphthyl complexes **2**

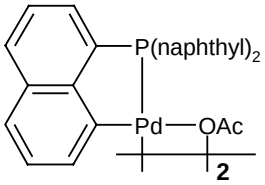
and **3** are the modified version of Hermann's system **4**. They have shown a TON of 1.2 million in the Heck coupling of methyl acrylate and iodobenzene. Bedford and co-workers[14a] synthesized the orthometallated triarylphosphite complex **5**, which shows the highest activity in the Suzuki coupling of aryl bromides (4-bromoacetophenone) with the complex **5a,** with TON upto 1 million and in the case of Stille coupling of aryl bromides (4-bromoacetophenone) with TON upto 830000. It is interesting to note that the high activity noted with complex **5** is despite the fact that it is π-acidic, orthometallated ligand renders the palladium center electron deficient with respect to the palladacyclic phosphine systems described below. The activity was also related to the size of the substituents on the orthometallated ring with **5b** showed significantly lower activity than the bulky analogue **5c**. However **5b** is still far more active than the bulky phosphite complex **5a**. They also observed that increasing the electron density on the palladium when using π-acidic phosphite-phosphenite based palladacycle increases the catalytic activity. However, it is important to strike the right electronic balance. Cole-Hamilton and co-workers found no activity with compound **8a**. They found good activity with the catalyst **8b, 8c f**or the Heck coupling of aryl bromide (TON of 3.6 millions) with n-butyl acrylates. Bedford and co-workers again synthesised the platinum based *P,C* catalyst and observed with poor or no activity due to the higher oxidation states of platinum which are more stable than those for palladium, and disfavours reductive elimination process. But they found that substitution with phenyl instead of 2, 4-*tert*-butyl substituted phenyl such as complex **9b** had shown good activity with Suzuki coupling aryl bromides[17] with TON 2.5 million, while its non-cyclometallated complex **6** showed less activity in the Suzuki coupling of arylbromides. In 2000, Dupont[18] and coworkers found sulfur-containing (*S, C*) palladacycle as catalyst precursors for the Heck reaction, with highest TON of 1,85000 with aryl iodide and with aryl chlorides (4-$NO_2C_6H_5Cl$) with reasonable TON of 5000.

P, C Palladacycle



1a X=Br
1b X=I
1c X=OAc
1d X=Cl

1



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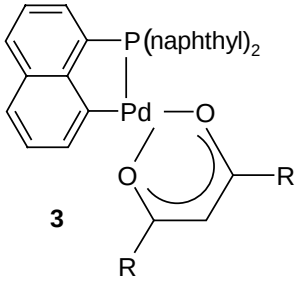
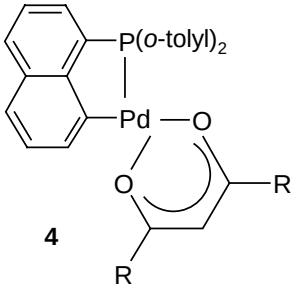


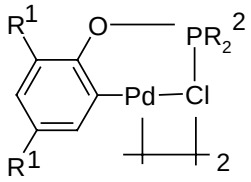
3

R=Me,CF_3



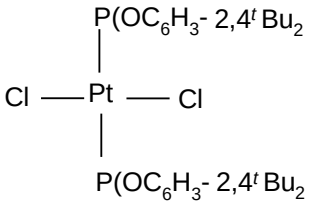
4

R=Me,CF_3

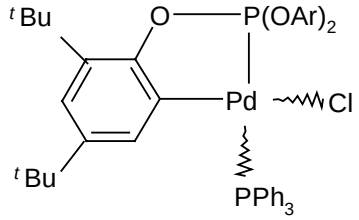


5

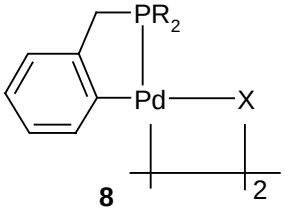
5a $R^1 = {}^t$Bu, R^2 = -OCH_3, 2,4-$^t Bu_2$
5b R^1 = H, R^2 = Ph
5c $R^1 = {}^t$Bu, R^2 = Ph
5d $R^1 = {}^t$Bu, $R^2 = {}^i$Pr



6

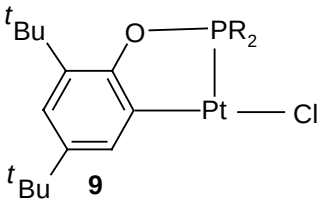


7 Ar = C_6H_3 -2,3-^{t}Bu



8

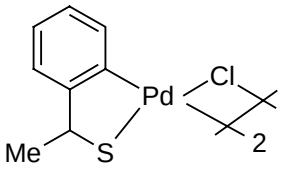
8a: R= Ph; X= Cl
8b: R= Ph; X= Br
8c: R= ^{t} Bu; X= Br



9

9a : R= -OC_6H_3-2,4-$^t Bu_2$
9b : R= Ph
9c : R= *i* Pr

***S, C* Palladacycle**



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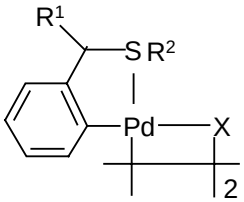
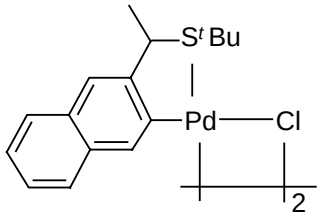


11a : R^1 = Me; R^2 = ^{t}Bu; X=Cl
11b : R^1 = Me; R^2 = Me; X=Cl
11c : R^1 = H; R^2 = ^{t}Bu; X=Cl
11d : R^1 =Me; R^2 = ^{t}Bu; X=OAc



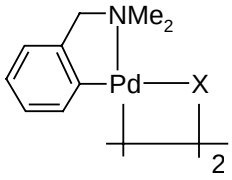
12

k^2 *N, C* Palladacycle

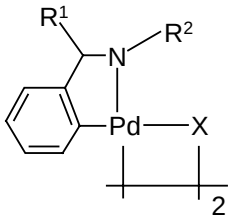
In 1998 Bedford, in 2001, Iyer, in 2002, Beletskaya, and Yang with their co-workers have demonstrated separately the catalytic activity of *N, C* palladacycles[19] (orthopalladated, *N, N*-dimethyl benzylamine complex **13**) for Heck coupling of aryl bromides. Milstein and co-workers[20] demonstrated the imine based *N, C* palladacycle, **14** and **15** for Heck reaction of aryl iodides and bromides with TON of 1.4 million with aryl iodides and half of the iodides for bromo benzene. They also proved that catalyst **14a** shows good activity in the Suzuki coupling of aryl bromides with TON upto 840000 and 1,36,000 for the coupling of phenyl boronic acid with 4-bromoacetophenone.[21] On his extended work on imine based *N, C* palladacycle they demonstrated the catalytic activity of triphenyl phosphenic adduct **16** of the dimeric of the complex **14** which shows increased activity in the Suzuki coupling compared with parent dimer.[22] Complex **14a** gives a TON of 3,20,000 in the coupling of 4-bromo anisole with phenyl boronic acid. Phosphine complex **16a** gives TON of 4,80000 for the same reaction. In 2002, Gladyse[23] and co-workers demonstrated ananother imine based highly active thermomorphic fluorous palladacycle catalyst precursor[17] for the Heck reaction (Palladium nono particle pathway) of aryl iodo, bromo compound with highest TON of 1286000 with iodo benzene. In the year 2003 Dupont[24] and co-workers demonstrated the activity of chloropalladated propargyl amine based, phosphine free *N, C* palladacycle catalyst precursor[18] for the Heck reaction of aryl chlorides with highest TON of 1,00,0000 with ary iodides was achived. 4-Chloroanisole and 4-chloronitrobenzene gave TON 330 and 1000. Bedford[22] also explained that the changing ketimine ligand for an aldimine analogue is beneficial to catalyst performance with the complex **16b**. In the year 1999, Leung[25] and co-

workers explained the activity of chiral amine based *N, C* Palladacycle **19a, 19b, 19c** in the asymmetric Claisen rearrangement with catalyst which act as Lewis acid and do not undergo any redox process. In addition he also demonstrated activity of pyrazole, benzothiazole based *N, C* Palladacycle in the Heck coupling of iodobenzene.

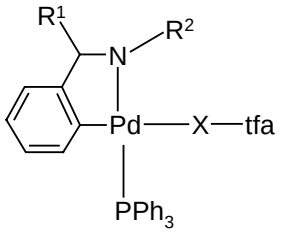
***N, C,* Palladacycle**



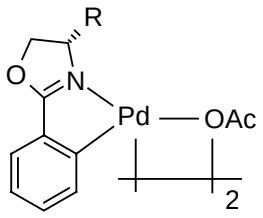
13: X= Cl



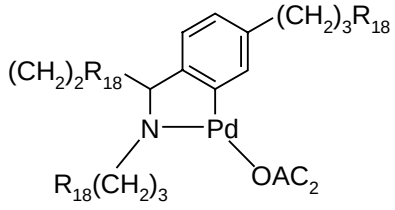
14a : R^1 = Me;R^2 = ^{i}Pr; X= TFA
14b : R^1 = H; R^2 = ^{i}Pr ; X= TFA



16a : R^1 = Me;R^2 = ^{i}Pr; X= TFA
16b : R^1 = H; R^2 = ^{i}Pr ; X= TFA

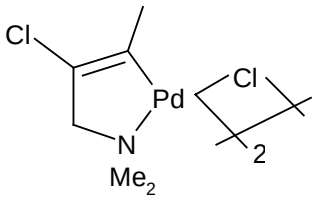


15a : R = H
15b : R = $CH_2{}^i$Pr
15c : R = ^{i}Pr

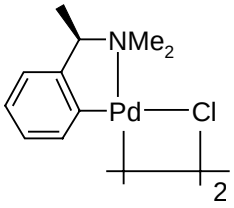


17

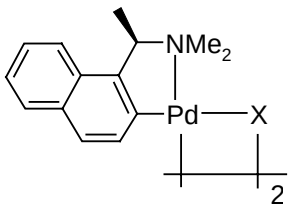
R_{18}=$CF_3CF_2CF_2CF_2CF_2CF_2CF_2CF_2$



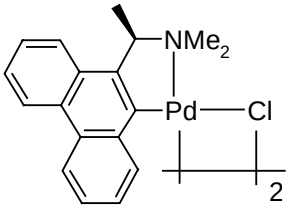
18



19a



19b

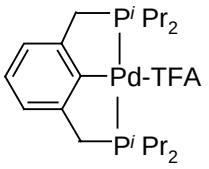


19c

k^3 *L,C,L* Palladacycles

k^3 *P,C,P* paladacycles

Shortly after the development of k^2 *P, C* palladacycle catalyst k^3 *P,C,P*-pincer complexes were shown to be active by Milstein and co-worker.[26] They demonstrated that the complexes **20** and **21** could be used effectively at low catalyst loadings in the Heck reaction of aryl iodides and activated aryl bromides with TON of 528700 with **21a**, the TON dropped to 713300 for 4-bromobenzaldehyde. On its further work by U.C. Andersson and co-workers on metallation of a saturated ring, they developed a chiral catalyst **22** which shows good activity in the Heck reaction of aryl iodides and activated, non-activated aryl bromides.[27] They observed that the performance was better than that obtained with related unsaturated system. A chiral bis(phosphine) pincer complex **23** has been synthesized, but it proved to be a poor catalyst for the asymmetric Heck reaction.[28] Silimar logic of how π-acidic ligands systems enhanced activity of k^2 *P,C* palladacyclic catalysts, Shibasaki and co-workers developed bis (phosphite) *P,C,P* pincer-based complex **24** that gives TON of 8.9 million in the Heck coupling of aryl iodides.[29] Since more π-acidic ligand systems seem to be beneficial to the performance of k^2 *P,C* palladacyclic catalysts, it may be logical to assume that more π-acidic *P,C,P*-pincer ligands should also show enhanced activity. This indeed appears to be the case when Shibasaki and co-workers showed that the bis-(phosphite)-*P,C,P* pincer based complex **24** gives TON upto 8.9 million in the Heck coupling of n-butyl acrylate with iodobenzene and 980 000 with the more electron rich iodide, 4-iodoanisole. As seen with the *P,C*-palladacycle, while phosphate-based systems show better activity than very electron rich phosphine analogues; 'fine-tuning' of the electronic properties can have a further beneficial effect on the performance of pincer complex **25a** and **25b** that not only show good activity in the Suzuki coupling of deactivated and activated aryl bromides but also with activated aryl chlorides.[30] **25c** can be used for Heck coupling of deactivated aryl chlorides with 4-chloroanisole.[31] Bergbreiter and co-workers[32] demonstrated that the *P,C,P*-pincer complex **26** not only failed as a catalyst in the intra molecular Heck reaction but also that the catalyst is inhibited by the presence of substrates. Longmire and coworkers[33] had demonstrated that the chiral *P, C, P* pincer complexes **27** shows reasonable enantio- selectivity in the aldol reaction with 77% ee.



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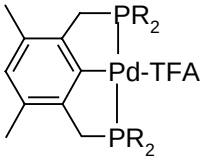
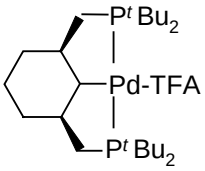


21a : R= iPr
21b : R= ^{t}Bu



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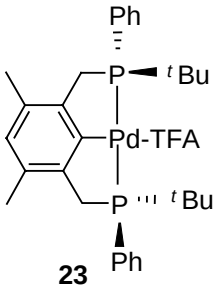

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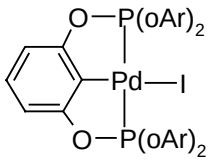
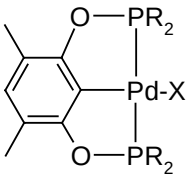
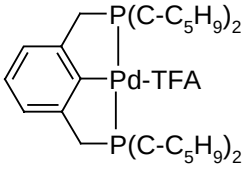


24 Ar = C_6H_4- 4-OMe



25a R^1=H; R^2=Ph; X=TFA
25b R^1=Me; R^2=Ph; X=TFA
25c R^1=H; R^2=^{i}Pr; X=TFA



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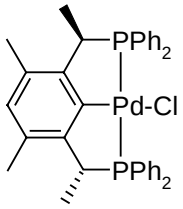
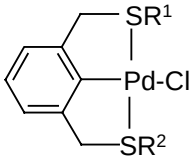


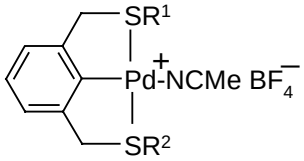
27

***S, C, S* piner palladacyclic catalyst**

Bergbreiter demonstrated that the *S,C,S*-pincer complexes **28a** and **29** could be used as a catalyst for the Heck Coupling of aryl iodides, but no activity was observed with aryl bromides.[34] In contrast Dupont *et al.* showed that the more electron-rich system **28b** could be used effectively in the coupling of the deactivated 4-bromoanisole in Suzuki coupling[35] reactions.



28a : R^1 = NHAc; R^2 =Ph
28b : R^1 = H; R^2 = ^{t}Bu

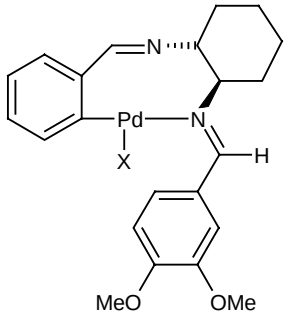


29

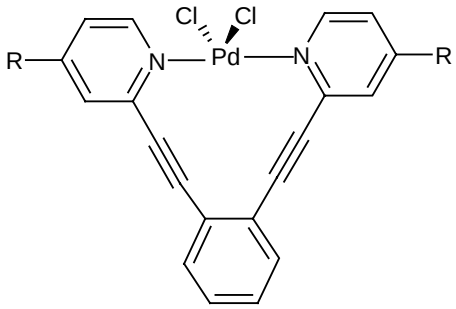
***N, C, N* pincer palladacyclic catalyst**

Nevarrao and co-workers synthesized the chiral *N, C, N* complexe **30**[36a] and successfully applied to the Heck reaction of aryl iodides and activated arylbromides but poor activity was obtained with the non-activated bromobenzene. Kawano and coworkers synthesized, highly active Pd(II) catalysts with trans-bidentate pyridine Ligands **31**[36] for the Heck reaction of iodo

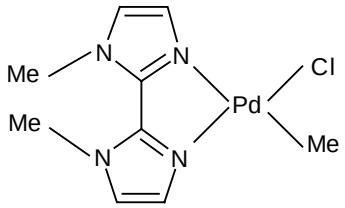
and bromo aromatics with highest TON with 79630 in aryl iodides.[36] Imidazole based *N,C,N* palladacycles **32a** was synthesised by Alper[37] and applied to the Heck reaction in ionic liquids. Di-2-pyridylmethylamine based palladium complexes **32b** reported by Najera[38] and co-workers had shown good activity towards Heck, Suzuki, Sonogashira reaction in aqueous medium.



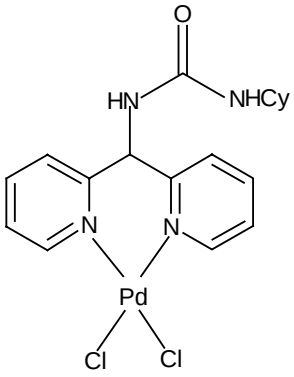
30 a : X = OAc
30 b : X = Cl



31 R = H, Me



32a

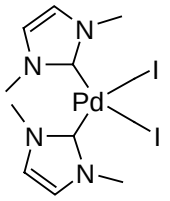


32b

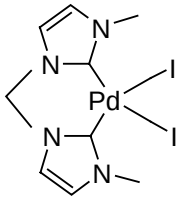
3.1.1.3 Carbene complexes

Alongwith the development of k^2 *L, C* palladacyclic systems and k^3 *L,C, L* palladacyclic systems, a new principle for designing catalysts for palladium-catalyzed reaction has been proposed by Hermann *et al*.[39] Stable heterocyclic carbenes (the derivatives of imidazoles and 1,2,4-triazoles) turned out to be excellent ligands in forming a wide range of complexes.[40] Carbene ligands are strong σ-donors which lack any appreaciable ability of π-acceptor back-bonding, and in this respect these ligands resemble donor phosphines, though with somewhat lower steric bulk. There are different carbene based palladium complexes that were developed.[41] Complexes with both mono carbenes and chelating bis carbene systems were

developed.[42] Hermann and Enders individually developed biscarbene palladium complexes for Heck reaction such as **33** and **34**.[42,43] They also developed mixed carbenes based Pd(0) complexes for Heck reaction. Bellar and co-workers investigated Heck coupling of activated and unactivated aryl chloride in the presence of defined carbene palladium(0)complexes **36** and **37**.[44] Anna Roglans and co-workers developed Pd(0) based 15 membered macrocyclic triolefin catalyst for Heck coupling of arenediazonium salts.[45]



33



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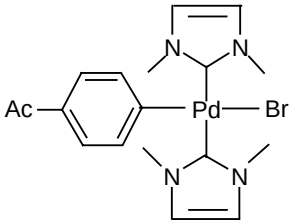

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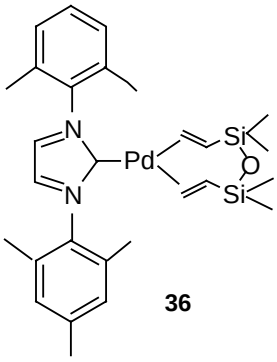

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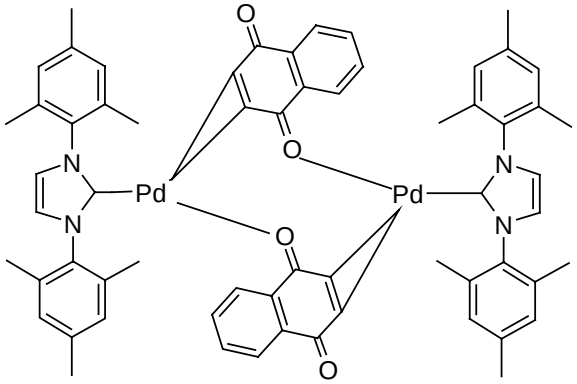
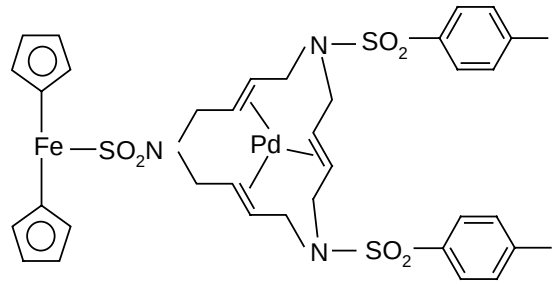


37



38

3.1.1.4 Recyclable catalysts

Development of phosphine free recyclable catalytic systems is of importance for the Heck reaction.[39, 46, 47] There are significant economical and environmental reasons for developing recyclable catalytic systems from both academic and industrial perspectives. Several goals has to be achieved for industrial applications such as the use of aryl chloride[48] as substrates, with high TON, the possibility of using aqueous conditions and the recovery of catalyst with diverse application, high thermal stability of a catalyst combined with their high activity in presence of air, moisture insensitivity in the coupling reactions makes them obvious candidate for recycling to moisture protocols.[49] While some systems do appear to be recyclable, they only work for the coupling reactions of the 'easy' substrates, aryl iodides, while applying to more challenging reactions then invariably no real recyclability was observed.

Route to recyclable palladium catalyst

Solid liquid system

The recent trend in catalysis related with environmental and economic concerns is the transformation of a homogeneous catalytic system into a heterogeneous system in which the Pd is immobilized on a solid support, making the catalyst easily recoverable from the reaction mixture with the possibility of reuse and waste minimization. For this reason the activity of Pd on its metallic complexes supported over variety of solid supports, particularly over active charcoal[3], inorganic oxides with bonded ligands,[4] molecular sieves,[5] and nanopalladium complexes,[6] polymeric materials,[2] silco-aluminophosphate[9] over mesoporous zeolites[10] have been studied for C-C coupling reactions.

Along with the development of reusable, highly active, solid supported Pd catalyst, there are many reports of recyclable palladacyclic catalysts (carbometallated) stable towards air, water and high temperature, for electron rich system, have been developed. Sulfur containing recyclable palladacycles had been reported by Dupont[18] and co-workers. Beller and co-workers introduced carbene ligand based reusable palladium carbene catalyst for aryl chloride in ionic liquids.[44] An efficient palladacycle will be those where the release of active Pd is neither too fast (typical of poorly thermally stable palladacycles that preferentially result in the formation of inactive metallic palladium) nor too slow (typically of thermally rebust palladacycles which would require higher temperature to start the reaction in order to

maintain a reasonable rate). Najera and co-workers[38] reported di-2-pyridyl methylamine based palladium complexes as new reusable catalysts for Heck, Suzuki, Sonogashira reaction, even with less active aryl chloride. Some of the above reported recyclable catalysts are built on the basis of immobilising liquid on solid support are called solid-liquid modes.

Liquid-Liquid Systems

In biphasic liquid-liquid system, the reagents and products are held in the organic phase while the catalyst is held in a different nonmiscible phase like water or other polar hydroxylic solvents, of which ethylene glycol is the most popular.[50] The reaction in a biphasic system may be thought to proceed at the interface, but this is hardly so because of too severe mass-transfer restrictions. As the interfacial tension between water and low-polar organic liquids is very high, the area of the interface is small even with vigorous stirring. Actually, the reaction proceeds in the polar phase and the rate depends on the solubility of organic reagents in this phase. Therefore, the separation and catalytic efficiency come to a contradiction.

A biphasic toluene-ethylene glycol system based on the TPPTS [$P(C_6H_4$-*m*-$SO_3Na)_3$] ligand has been reported for the standard Heck reaction of PhI with acrylates and styrene.[51] Liquid CO_2 at pressures both below and above the critical point has been used to form the second nonpolar phase in biphasic catalysis with TPPTS as ligand and water or ethylene glycol as the catalyst containing phase for the reaction of PhI with n-butylacrylate.[52] In biphasic systems, the increase in yields depends on two ways (a) designing system in which phase-separation can be controlled by e.g, temperature and (b) increasing the area of contact between phases. Controllable phase separation is achieved (i) by selecting solvents with temperature dependent, miscibility and (ii) by designing thermomorphic ligands with temperature-dependent solubility.[53a]

3.1.1.5 Unusual ways in doing Heck chemistry

(1) Less usual means of activation

(a) **Microwave Heating**: Very fast heating by means of microwave leads to shortening of the reaction time, while the yields and selectivity do not greatly differ from the same reactions carried out using conventional heating.[53b] Microwave heating is associated

with direct and uniform input of energy to the reaction media. Heck reactions are very well-known to run better at higher temperatures, naturally if reagents, products, and catalyst can survive such a harsh treatment. In conventional heating the energy is transferred by heat transfer through walls of the reaction vessel and further on through convention causing non-uniform distribution of heat. Local overheating at the walls leads to decomposition of catalyst. Uniform deployment of heat directly to the reacting molecules by means of absorption of microwave energy by a polar solvent effectively affords higher temperatures than those achievable through conventional heating.

(b) **High pressure:** They key steps of the Heck cycle oxidative addition and migratory insertion have negative activation volume and thus are likely to be accelerated by pressure. Pressure extends the lifetime of palladium catalyst. A huge increase in catalyst stability has been accounted for by the inhibition of de-ligation of palladium catalyst. The increase of oxidative addition with pressure rate makes it possible to perform reactions with substrates.[55]

(c) **Less usual Media for Heck Chemistry:** Though virtually all solvents seems to have been used for Heck reactions, the most useful are polar aprotic solvents having an ability to additionally support palladium complexes by weak co-ordination such as MeCN, DMF, NMP etc. In recent years improvement in Heck reaction were achieved through aqueous media, molten salts supercritical and subcritical fluids and fluorous system.[54a, d]

(d) **Phase-transfer agents in Heck Chemistry:** As in any other reaction requiring basic catalysis, the Heck reaction is responsive to phase-transfer phenomena. There were many referred effects of phase-transfer agents in the rate of Heck and its related chemistry.[54a, b, c] The beneficial effect of quarternary ammonium salts was first n oted by Jeffery. Despite a unifying feature of the presence of quarternary ammonium salts, there is actually not a single but several distinct protocols in which quarternary salt may play the following roles. It can act as a solid-liquid phase-transfer agents in the reactions catalyzed by solid salts such as sodium or potassium acetates, carbonates, hydrocarbonates, phosphates etc, are practically insoluble in solvents used in Heck chemistry. It can act as a liquid-liquid phase transfer agents e.g. in the reactions in

aqueous solvents in which base is soluble while the substrate is not. Halides, acetates and possibly other anions can serve as promoters to increase the rates of some steps of the catalytic cycle. This effect has been unveiled in fundamental studies of Amatore and Jutand *et al.*[54g]

3.1.2 Part II
Synthesis and characterization of aliphatic C-metallated Pd-OMS(MCM-41) Palladacycle

3.1.2.1 Introduction

After the resurge of recyclable heterogeneous phosphine free palladium catalysts, the trend in the palladium mediated reactions have been changed vastly. As we know already that a homogeneous catalytic system can be transformed into a heterogeneous catalytic system by immobilization of active center in the homogeneous system on a solid support. There were many reports of transformation of a homogeneous catalytic system into heterogeneous catalytic sytems.[6-10] The discovery of mesoporous molecular sieves has stimulated a renewed interest in developing adsorbent, sensors and the design of catalysts due to their high surface areas with narrow pore size distribution (2-20 nm).[56,57] Kosslick *et al*. have studied the anchoring of alkylsilyl sulfonic acid into the walls of Al-MCM-41 to stabilize the catalytically active palladium complex that was found during the course of the reaction.[58] Silica supported palladacycle catalysts have been studied for C-C coupling reactions.[14b,59] Corma *et al*. have reported an oxime carbopalladacycle complex covalently anchored to silica as an active and reusable heterogeneous catalyst for Suzuki cross-coupling in water.[60] Various attempts towards the immobilization of organometallic complexes have been made previously, such as attachment to supporting materials by chemisorption, immobilization by steric hindrance in zeolite micropores or supported liquid phase catalyst.[61]

Ortho-palladation with the weakest of palladation agents (Li_2PdCl_4) under very mild conditions, due to steric promotion of an aromatic C-H bond activation was studied by Dunia *et al.*[62] In this study, carbometallation was used to immobilize the palladium catalysts on MCM-41 support. Carbometallation of anchored ligands with palladium metal center enhanced by steric constraint of mesopores have been exploited to get the heterogeneous palladium catalyst. Recently the synthesis and preliminary application of the C-metallated palladacycle (MCM-41) was reported in our laboratory.[63] Herein we report the detailed study of its application in various C-C bond forming reactions.

3.1.2.2 Immobilization of homogeneous system into heterogeneous system

In order to immobilize the homogeneous catalyst on a heterogeneous solid surface, an organic linker group is needed. Organic functionalization of the internal surfaces of MCM-41 can be achieved, either by covalently grafting various organic species onto the surface, or by incorporating the functionalities directly during preparation. The organo silane having ligands, such as chlorine or amine is directly grafted to the silica surface by an in-situ silylation procedure. The chlorine functional group gets hydrolysed into hydroxyl group either at synthesis condition or at post synthesis hydrolysis treatment. These types of ligands permit formation of complexes through co-ordination bond with metal center.[64] There are three types of -SiOH groups over siliceous MCM-41 surface,[65] e.g. isolated single hydrogen bonds and geminal -SiOH groups, of which only the single and geminal -SiOH groups are responsible for active silylation. The hydrolysis of required composition of ClPTS and TEOS (0.03 – 0.3 and 0.095-0.7 respectively) in the presence TMAOH enriches the mother liquor with single and geminal -SiOH monomer silica species. Co-condensation of symmetrical $Si(OH)_4$ and unsymmetrical $RSi(OH)_3$ species results in the formation of uniformly distributed organo functionalized silica.

Six different molar ratio of TEOS to ClPTS in the synthesis mixture have been taken while synthesis to obtain materials with a range of different concentration of ClPTS functional groups over MCM-41. Six different samples are designated as Cl-MI, Cl-M2, Cl-M3, Cl-M4 Cl-M5 and Cl-M6 and the respective hydrolysed samples are designated as OH-M1, OH-M2, OH-M3, O-M4, OH-M5 and OH-M6. The fraction of the functionalized silicon in the synthesis gel (x) was set in the range of 0.025 to 0.3 as it was reported that material prepared with fraction of silicon atom in that range is more stable and hydrophobic in nature because of hydrophobisation of all the silanol groups. The higher fraction of functionalized silicon atoms obtained in the synthesized material was 0.2 (Table 1). From C, H elemental analysis it was observed that effective loading of ClPTS groups into the coupling agent, TEOS was about 60 wt. % with respect to amount of ClPTS taken in the synthesis gel.

Recently, the aliphatic C-metallated palladacycle **44** was synthesized in our laboratory for the first time by functionalising the pores of MCM-41 using 3-hydroxypropyltriethoxy silane in

the pores of 3-hydroxypropyl triethoxysilane functionalised MCM-41 which was found as an active and stable catalyst for Heck alkenylation reaction. Herein we elaborate on the synthesis and characterization of the aliphatic C-metallated palladacycle Pd-OMS(MCM-41) materials along with catalysts textural properties. The influence of synthesis condition on the performance has also been examined.

3.1.2.3 Synthesis of catalyst

Experimental procedure

Synthesis of Cl-MCM-41(Cl-M)/OH-MCM-41 (OH-M)

3-Chloropropyltriethoxy silane (3-ClPTS) functionalised MCM-41 was prepared by co-condensation of tetraethyl-orthosilicate (TEOS) with 3-ClPTS. Synthesis gels of the general molar composition [(1-X) TEOS: X 3-ClPTS:0.25C_{16}TAB; 0.3TMAOH:10 MeOH: 90 H_2O] were prepared. In a typical synthesis procedure, TEOS: (25.0 g) and 3 ClPTS (0.84g) in methanol were added dropwise with stirring to an aq. solution (25%) of tetramethyl ammonium hydroxide (TMAOH, 13.5 g) and cetyltrimethyl ammonium bromide (C_{16}TAB, 11.24 g). The mixture was stirred at room temperature for 5 h, then transferred into a glass reactor and refluxed at 373k for 48 h. The product was filtered, washed with excess deionized water and dried at 373k for 10 h. The organic surfactant molecules were removed by refluxing with acid solvent mixture 100 mL methanol + 5 mL HCl/g of solid material) at 343K for 24 h. Chlorine groups in Cl-M sample were hydrolysed into hydroxyl groups by treating 1g of the extracted sample with 10 mL of H_2O and 10 ml of MeOH at 338K for 2 h. The hydrolyzed material (OH-M) was filtered and dried at 373K to give mesoporoous materials with the molar composition [(1-X) TEOS: X3-CIPTS: 0.25 C_{16}TAB; 0.3 TMAOH: 10 MeOH: 90H_2O].

Preparation of palladacycle MCM-41(Pd-OMS)

Palladation was carried out over the samples OH-M (1.0g) with the palladation reagent, Li_2PdCl_4 (2.8 x 10^{-4} mol, 3.0 % Pd), NaOAc (0.05 g) in methanol at reflux temperature for 24 h. After palladation, the grey color material was washed thoroughly with aqueous methanol to remove all unreacted palladium salt and the inorganic base and dried at 383K for 12 h. The Pd

content present in the catalyst was measured by Inductively Coupled Plasma-Optical Emission Spectrum(ICP-OES)analysis, 1.68% Pd.

Table 1 Molar composition of silylating agent an coupling agents in the synthesis of mesoporous materials with molar composition [(1-X)REOS: X3-CLPTS:0.25 C_{16} TAB; 0.3 TMAOH: 10MeOH: 90H_2O

Catalysts	TEOs (Mol)	CLPTS (mol)	X		CLPTS (mmol/g)		% of Loading	Surface area (m^2/g)
			In put	Out Put[a]	In Put	Out Put		
Cl-MO	0.100	0	0	0	-	-	-	1050
Cl-M1	0.120	0.003	0.024	0.016	0.42	0.27	64	760
Cl-M2	0.107	0.007	0.061	0.036	1.08	0.60	56	735
Cl-M3	0.093	0.010	0.097	0.059	1.78	0.99	56	855
Cl-M4	0.080	0.013	0.140	0.100	2.70	1.67	62	614
Cl-M5	0.067	0.017	0.202	0.159	4.21	2.65	68	726
Cl-M6	0.050	0.020	0.286	0.196	6.66	3.26	49	715

[a]Calculated from the data obtained from C,H analysis.

Table 2 Physical Characteristics of catalysts (OH-M)

Catalysts	2θ	$D_{100}(A^o)$	Unit cell parameter, $a_o(A^o)$	BET surface area (m^2/g)
OH-M1	2.57	34.26	39.68	547
OH-M2	2.49	35.47	40.96	578
OH-M3	2.47	35.75	41.29	862
OH-M4	2.48	35.61	41.12	624
OH-M5	2.34	37.74	43.58	732
OH-M6	2.40	35.90	41.46	712

Table 3 Physico-chemical characteristics of the catalysts (Pd-OMs)

Catalysts	2θ	D_{100} (A^o)	Unit-cell parameter a_o (A^o)	BET surface are (m^2/g)	Pd content (%)	Conversion of bromo-benzene (w%)	Yield trans-stilbene	TON[h]
Pd-OMS1[a]	2.62	33.71	38.93	351	0.44	5.8	100	93
Pd-OMS2[b]	2.76	32.00	36.95	384	0.88	27.3	95	1205
Pd-OMS3[c]	2.77	32.88	36.82	632	0.94	33.8	90	213
Pd-OMS4[d]	2.40	36.83	42.53	640	1.12	42.4	89	340
Pd-OMS5[e]	2.49	39.42	40.96	862	1.05	57.8	90	389
Pd-OMS6[f]	2.40	35.90	41.46	722	1.05	38.5	92	280

a-f = OH-M1, OH-M2, OH-M3, OH-M4, OH-M5, OH-M6 and OH-SiO_2 respectively = 1 g; $LiPdCl_4$ = 1.4 x 10^{-4} mol (1.5% Pd); NaOAc = 50 mg; methanol = 20 mL; reaction temperature = 335K; reaction time = 24 h; j = TON (Turn over number) = moles of BB converted per mole of Pd.

Table 4 Effect of different synthesis conditions:

Catalysts	2θ	d100(A^o)	Unit-cell Parameter a^o (A^o)	BET Surface area(m^2/g)	Pd-content(%)	Conversion of Bromobenzene (wt%)	Yield trans-Stilbene	TON[J]
Pd-OMS51[a]	2.32	38.07	43.96	590	0.32	71.1	90.0	1570
Pd-OMS52[b]	2.36	37.42	43.21	605	0.35	86.6	90.0	1748
Pd-OMS53[c]	2.34	37.74	43.58	723	0.26	76.6	90.0	2082
Pd-OMS54[d]	2.38	37.10	42.85	894	0.38	53.6	90.0	997
Pd-OMS55[e]	2.44	36.20	41.80	802	0.71	74.0	91.0	736
P-Si-MCM-41[f]	2.86	30.90	35.66	1020	0.14	No reaction	-	-
SiO2-Pd[g]	-	-	-	255	0.26	5.60	100	152
Am-PdMS	2.56	34.50	39.85	261	1.26	85.5	91	477

a = preparation of Pd-OMS51
OH-M5 = 1.0g: $Li_2PdCl_4 = 1.4x10^{-4}$ mol; NaOAc = 0.05g; Methanol = 20ml;
reaction temperature = 303K; reaction time = 24h

b = preparation of Pd-OMS52
OH-M5 = 1.0g; $Li_2PdCl_4 = 1.4x10^{-4}$ mol; Methanol = 20ml;
Reaction temperature=335K; Reaction time = 24h

c = preparation of Pd-o=OMS53
OH-M5 = 1.0g; $Li_2PdCl_4 = 1.4x10^{-4}$ mol; Aectone = 20ml; Reaction temperature = 335K;
Reaction time = 24h

d = preparatopn of Pd-OMS54
OH-M5 = 1.0g; $Pd(OAc)_2 = 1.4x10^{-4}$mol; Chloroform = 20ml; Reaction temperature = 335K;
Reaction time = 24h

e = preparation of Pd-OMS55
OH-M5 = 1.0g; $Pd(OAc)_2 = 1.4x10^{-4}$mol; Methanol = 20ml; Reaction temperature = 335K;
Reaction time = 24h

f = preparation of Pd-Si-MCM-41
Si-MCM-41/OH – SiO_2 = 1.0g; $Li_2PdCl_4 = 1.4x10^{-4}$mol; Chloroform = 20ml;
Reaction temperature = 335K; Reaction time = 24h

h = Am-MCM-41= 1.0g; $Pd(OAc)_2$ = 1.4x10^{-4}mol; Chloroform = 20ml;
Reaction temperature = 335K; Reaction time = 24h

i = Bromobenzene = 2mmol; Styrene = 3mmol; K_2CO_3 = 2.4mmol; NMP = 5.0ml;
Reaction temperature = 335K; Reaction time = 24h

j = TON (Turn over number) = moles of Bromobenzene converted per mole of Pd

Table 5 Effect of Pd loading (%)

Catalyst[a]	Surface area (m^2/g)	Pd content (%)[b]		Conversion of bromobenzene (w%)[c]	Yield trans Stillbene%	TON
		In put	Out put			
Pd-OMs(0.38)	911	0.48	0.33	18.8	100	403
Pd-OMs(0.62)	866	0.90	0.62	37.8	91.0	431
Pd-OMs(1.05)	862	1.50	1.05	57.8	92.0	389
Pd-OMs(1.40)	763	3.00	1.40	90.1	91.0	455
Pd-OMs(1.68)	887	6.00	1.68	70.0	100	291

a= number in brackets denotes the Pd content present in the catalyst.
b=Input is based on the amount of Pd in solution during palladation reaction; out put is based on the ICP-OES analysis.
c= bromobenzene (BB)=2 mmol; styrene=3 mmol; K_2CO_3 = 2.4 mmol; DMF= 5.0 mL; temp = 423K; catalyst = 30 mg; reaction time = 5h.

3.1.2.4 Influence of synthesis condition on the performance of the catalyst

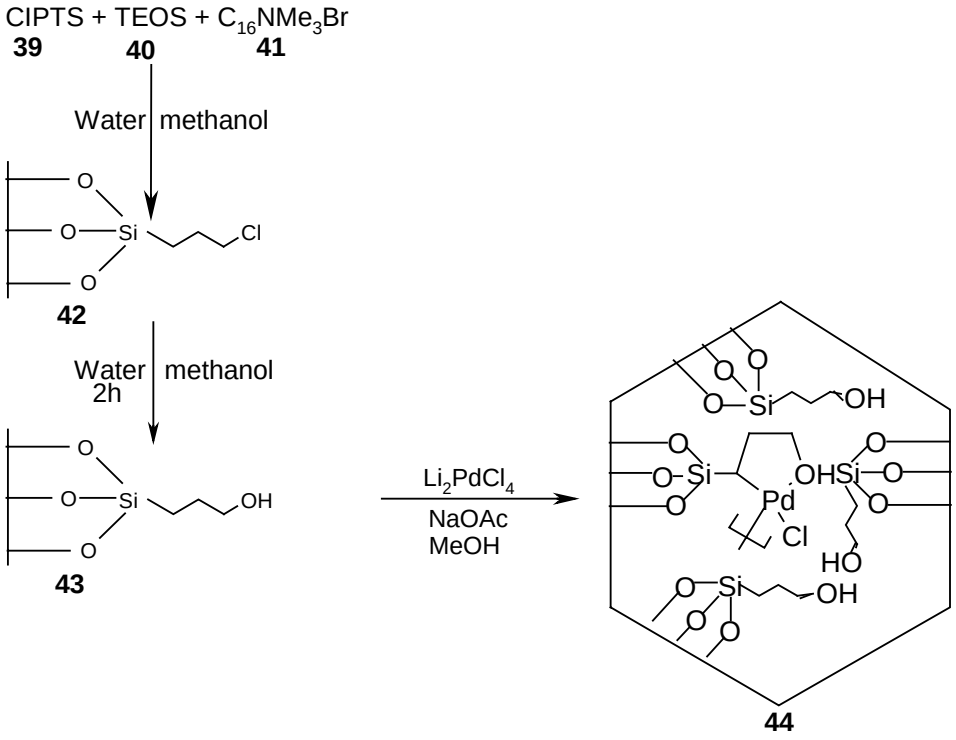
Palladation was carried out over the samples of OH-M (1.0 g) with palladation reagent Li_2PdCl_4 (2.8 x 10^{-4} mol, 3.0% Pd), NaOAc (0.05g) in methanol at reflux temperature for 24 h. The hydrolysed samples are designated as OH-M1, OH-M2, OH-M3, OH-M4, OH-M5 and OH-M6. The fraction of functionalized silicon atoms in the synthesis gel (x) was set in the range of 0.025 to 0.3, is more stable and hydrophobic in nature because of hydrophobisation of all the silanol groups. The higher fraction of functionalized silicon atoms obtained in the synthesized material was 0.2 (Table 1). From C, H elemental analysis it was observed that effective loading of ClPTS groups into the coupling agent TEOS was about 60 wt.% with respect to the amount of ClPTS taken in the synthesis gel. The physical properties of OH-M samples are given in Table 2, palladation was carried out over OH-M1, OH-M2,

OH-M3, OH-M4, OH-M5 and OH-M6. Samples under similar reaction conditions to obtain Pd-OMS1, Pd-OMS2, Pd-OMS4, Pd-OMS5 and Pd-OMS6 respectively. All the palladations were carried out at 335k in methanol and with sodium acetate (Table 3). Dunia *et al*. have achieved best results when ortho-palladation of sterically crowded primary benzylamine, α-phenyl-neopentylamine, was performed with $LiPdCl_4$ and excess sodium acetate in methanol.[66] Polar solvents have some advantages over non-polar solvents in the palladation reactions due to their strong solvating effect that assists in the generation of three-co-ordinate intermediate of the [L_2pd x_2 (Solv)] – type required for subsequent C-H bond activation.[67] Here the same steric effect due to the organo functionalized mesoporous structure has been utilized for the activation of aliphatic C-H activation. Formation of a quasi-immobilised palladium complex inside the mesopores when the anchored 3-hydroxypropyltriethoxy silane is treated with palladium source creates a steric constraint which might be expected to cause aliphatic C-H bond activation and hence carbometallation occurs with weakest of palladation reagents and weak ligands under mild conditions. While incorporating the organic functionalities on porous catalyst , the pore itself is considered to potentially cause constraint in addition to the constraint already present on the surface, resulting in an larger constraint.[68] The spatial confinement induced by the pore walls forces the propyl group to cyclize in the presence of electrophilic metal center. Two main possible factors determine the easier aliphatic carbometallation with weakest palladation reagents are (1) a large effective volume of ligand (3-hydroxypropyltriethyoxysilane) incorporated into MCM-41 pore walls must increase an internal energy of the intermediate binuclear co-ordination compounds due to a set of unfavourable non-bonding interaction,[69] thus stimulating an intermediate dissociation to form reactive three co-ordinate species, (ii) the same steric effect must result in a weakening of Pd-O bond in the co-ordination intermediate to make the Pd(II) center more electrophilic. Both effects essentially facilitate the C-H bond activation.[70]

The palladation results obtained with the weak palladation reagents, Li_2PdCl_4, in methanol in the presence of sodium acetate at room temperature may be considered as the most convincing evidence for the mesoporous structure promoted aliphatic C-H bond activation. Few samples were prepared with or without addition of base at room temperature to study the effect of base on synthesis. Chloroform or acetone has also been used instead of methanol but since it was found that Li_2PdCl_4 was not dissolving in chloroform, palladium acetate was

taken as palladium source in chloroform. The different conditions in the preparation of different palladacycle catalysts are also given in Table 4. For comparison; 3-aminopropylated MCM-41 (AM-MCM-41) have been palladated with $Pd(OAc)_2$ under similar reaction conditions to get Am-PdMS catalyst and the characterization data are compared with Pd-OMS catalysts. Liquid phase palladation of 3-aminopropyl ethoxysilane with $Pd(OAc)_2$ in $CDCl_3$ has been done and analysed by liquid phase ^{13}C-NMR spectra and diffuse reflectance UV-Vis spectra. The results are compared with the solid sample prepared with Am-MCM-41.

Scheme-1



3.1.2.5 Physico-chemical characterization of the catalyst

X-ray diffraction

The d_{100} spacing (intense reflection) at 2θ between 2.0 and 2.5 and d_{110}, d_{200}, and d_{210} spacing (weaker reflection) at 2θ between 2.0 and 2.5 reveals the hexagonal symmetry of MCM-41. It also shows the decrease in peak intensity when the changes take place from the samples Cl-M1 and Cl-M2 to OH-M1, OH-M2 and further to Pd-OMS1 and Pd-OMS2 (**Figure 1**). X-ray diffraction study also envisages changes in long-range spacing order of the structure during acid treatment of intermediate sample. It also discloses the retaining of the long-range order of

its palladated materials Pd-OMS3, Pd-OMS4, Pd-OMS5 after base treatment and their unit cell parameter ($90\text{-}2d_{100}/\sqrt{3}$) in close to 40A°(**Figure 2, Table 2**).

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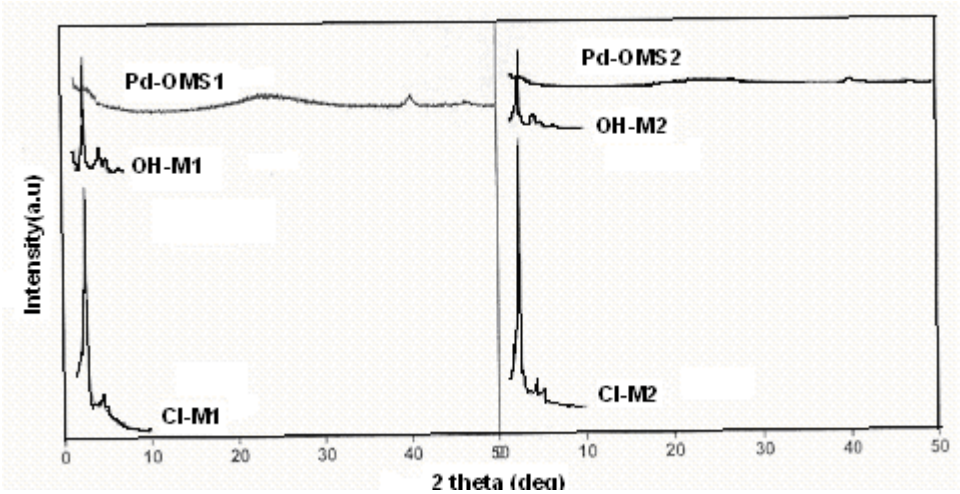
- 

- **Figure 1. X-ray diffraction pattern of Cl-M, OH-M, and Pd-OMS**

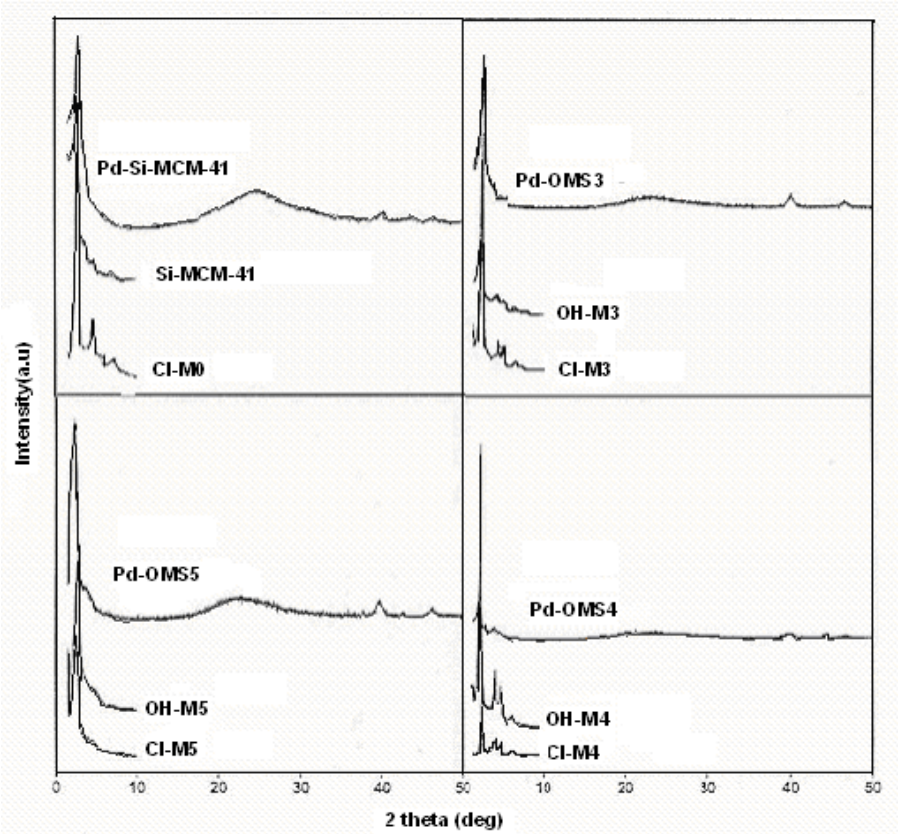


Figure 2. X-ray diffraction of Cl-M, OH-M, Si-MCM-41, Pd-OMS and Pd-Si- MCM-41

The major diffraction peak at 2θ = 40.0(III) and 46.5° (200) of Pd-OMS catalysts prepared with Li_2PdCl_4 and NaOAC in methanol at 335K confirms the presence of bulk Pd on the surface apart from metallated Palladium (**Figure 3**). One can also see from X-ray diffraction study, the absence of diffraction pattern of metallic Pd, when the loading of Pd is lower and its vis-versa (**Figure 4**). Peak intensity corresponding to Pd diffraction and so the peak intensity is higher when the loading of Pd[Pd-OMS, 1.4), Pd-OMS, 1.68)] is high.

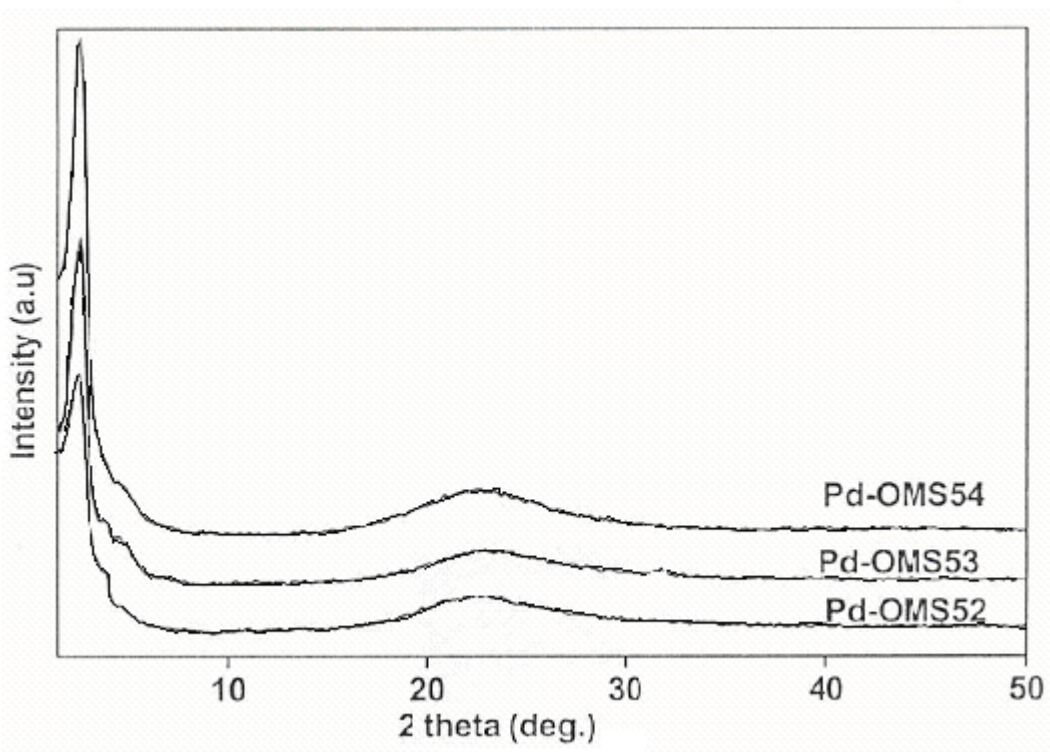


Figure 3. X-ray diffraction patterns of Pd-OMS catalysts

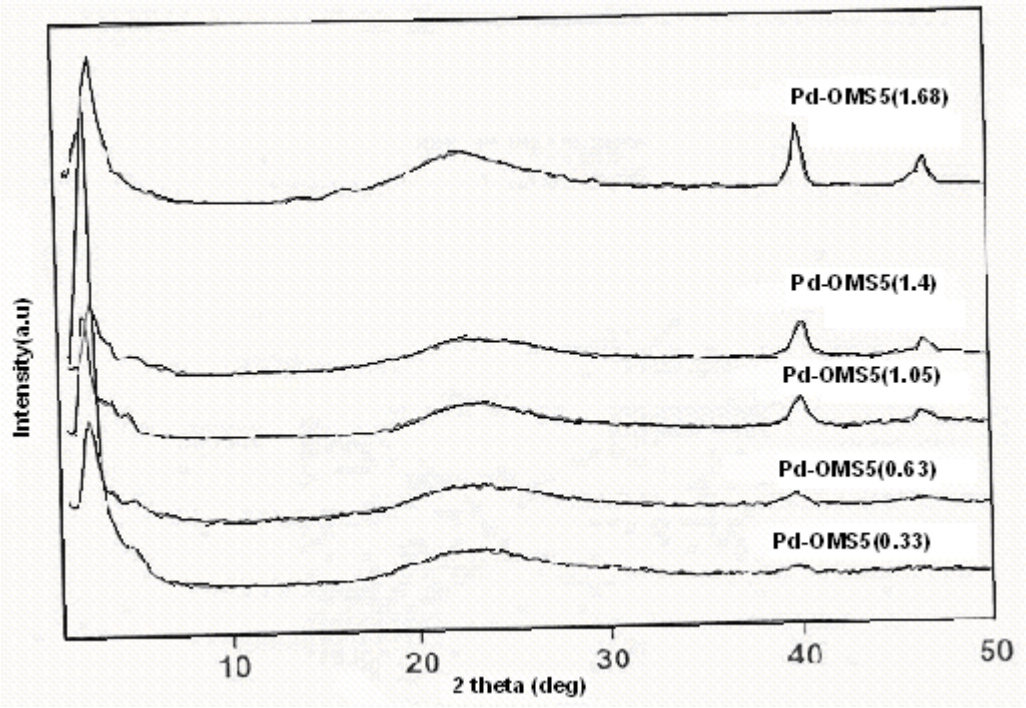


Figure 4. X-ray diffraction patterns of Pd-OMS5 catalysts

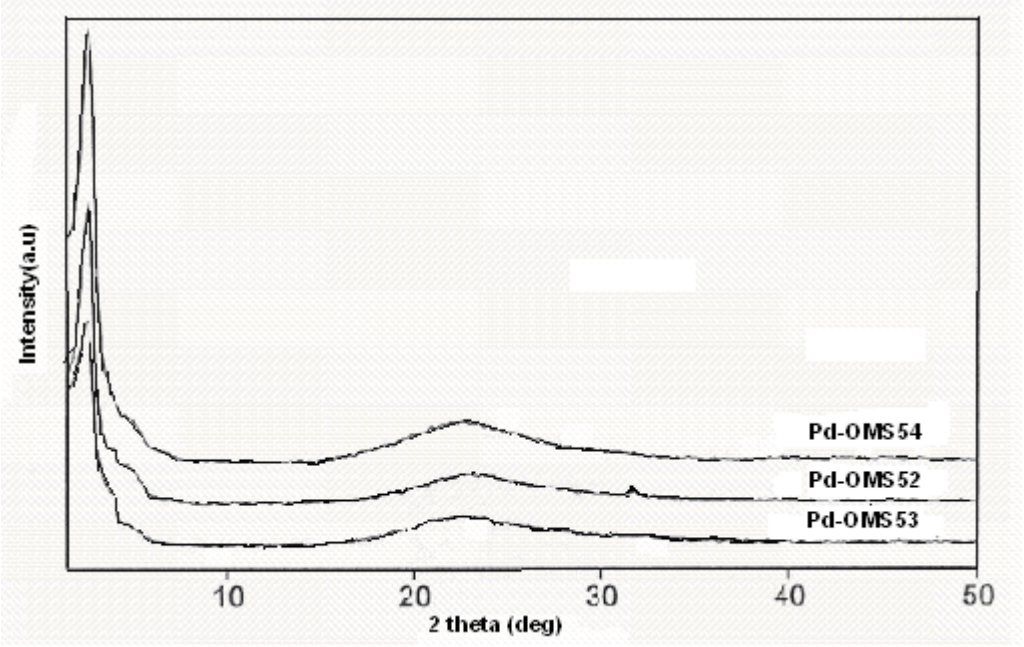


Figure 5. X-ray diffraction patterns of Pd-OMS52, Pd-OMS53 and Pd-OMS54

ICP-OES and CHN analyses

The total Pd content in the synthesized materials was achieved in the range of 0.4 to 1.12 % which was determined by ICP-OES analysis (Table 3). The various factors which play on the uptake of Pd through the co-ordination of ligands such as (1) Concentration of ligands (ClPTS) in the material which proportionally increases the palladation when the same concentration of Pd was treated with OH-M samples with different concentration of CLPTS. (2)When the Pd concentration used in the reaction solution increases, the uptake of Pd increases and then levels off when similar concentration of ligands expose to different concentration of Pd. (3) How the Pd content in the synthesis material varies by temperature, (room temp and at 33k) with and without addition of base, change of solvent, non-polar solvent less favours palladation), revealed by X-ray diffraction studies. The XRD study also tells how the reaction temperature and base enhances the formation of palladacycle and reduction of palladium salt into Pd, and how the propyl alcohol plays the role in stabilizing Pd as Pd(II) in the palladacycle complex. The XRD also reveals why the low Pd uptake happens in its relation with slow palladation process over OH-SiO_2 and no spatial confinement. C, H, N analysis of the sample shows that there is always increase in carbon content as we go from Cl-M1 to Cl-M6 samples (Figure 9c).

Adsorption studies

The surface area of functionalised MCM-41 materials were in the range of 500-900 m^2/g which are comparable to the previously reported organo functionalized MCM-41 with organo functional groups.[63] The adsorption studies reveals, how the higher order samples (OH-M3, OHM4, OH-M5 and OH-M6) retain their surface areas as the concentration of functionalised silicon atom increases (the passive character of silica walls towards acidic or basic condition) than the lower order sample (surface areas OH-M1 and OH-M2, were 547 and 578 m^2/g respectively are lower than their corresponding parent samples Cl-M1 (760m^2/g) and Cl-M2 (735 m^2/g) (where the collapsing long-range order in the lower order samples which attributed to lower surface area is evident from XRD pattern). Since the higher order OH-M samples does not show much difference in surface area therefore respective palladated catalysts show similar or little higher surface areas. The cyclisation of Pd with propyl group is also attributed to the increase in pore diameter as well as pore volume (Figure 6). The BJH (Braunauer-

Joyner-Halenda) pore size distribution of Pd-OMS5 illustrates a narrow peak centred at 28.8A° for pore diameter and pore volume measure as 0.63cc/g.

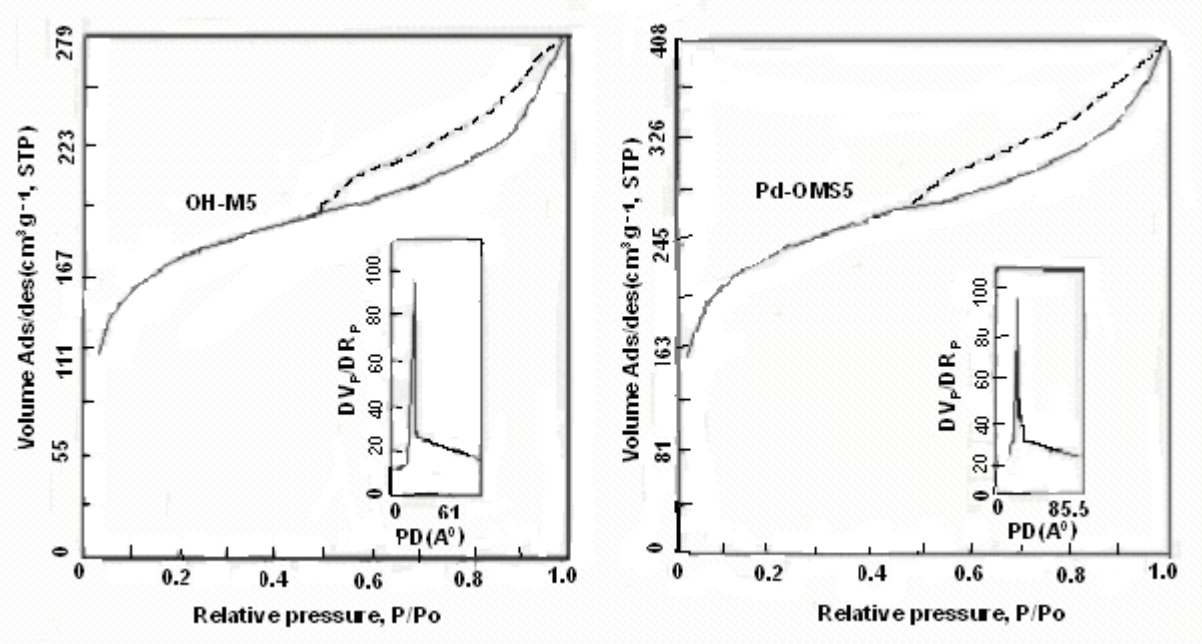


Figure 6.Nitrogen adsorption-desorption isotherms and pore size distribution(inset) for OH-5 and Pd-OMS5

Fourier Transform Infra Red Spectra (FTIR)

The FTIR spectroscopy of the (FTIR) samples Cl-M5, OH-M5 and Pd-OMs5 were taken. In Cl-M5 sample, bands at 2950-2850 cm^{-1} (str) and 1400-1420 cm^{-1} (def) were observed. In OH-M5 samples (containing poly alcohol group) had shown strong band at 1300, 800 cm^{-1} (C-O str) and at 3600-2500 cm^{-1} (O-H str), methylene stretching bands of propyl at 2950-2850 cm^{-1}. and deformation at 1414cm^{-1} 1440cm^{-1} and at 1475cm^{-1} (weak) (Three distant methylene groups) (Figure 7). The deformation band at 1414cm^{-1} is assigned to the methylene directly bonded to silicon atom. In the palladated samples the intensity O-H str.vib. also decreased. The C-H str. band also shifted from 2887, 2949 cm^{-1} to 2894, 2951 cm^{-1} and one more extra band at 2851 cm^{-1} were also seen in Pd-OMS5.[71] The shift towards higher energy side indicates the change of bonding behaviour of C-H bond. These data provides the supplementary evidence of the cyclometallation of propyl alcohol group which anchored on the walls of MCM-41 in presence of Palladation reagents.

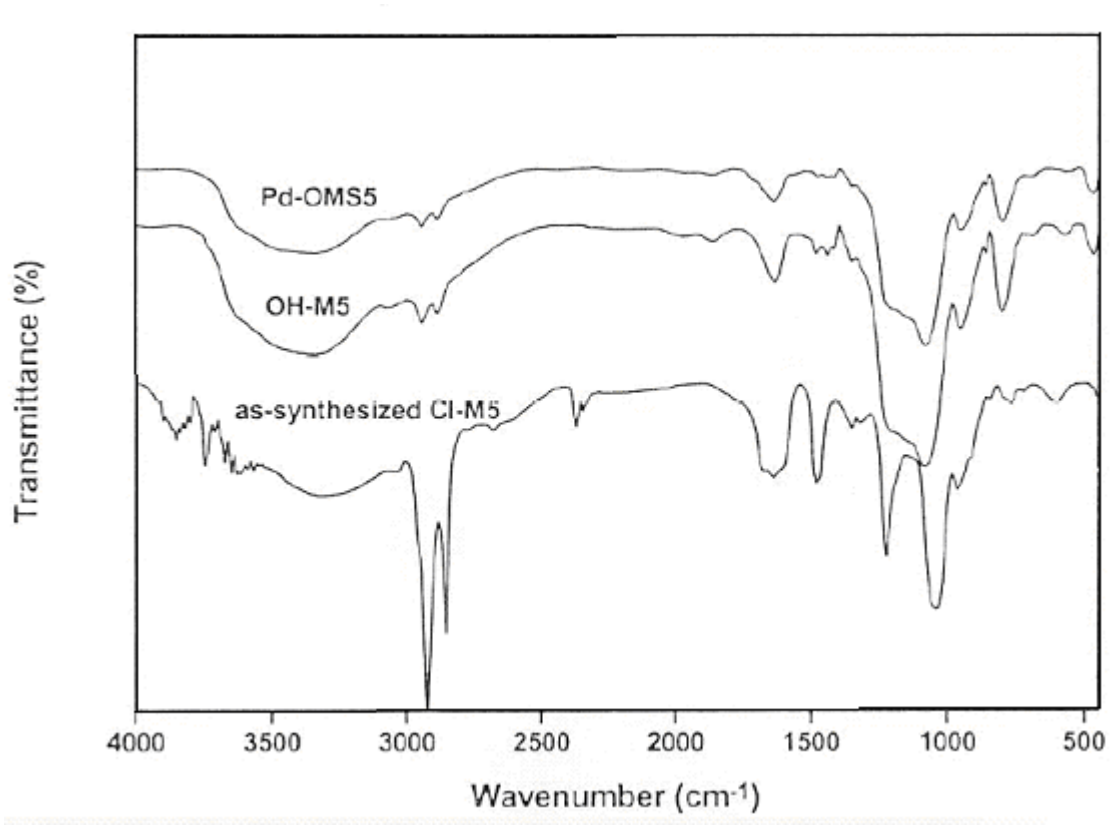


Figure 7. **FT-IR spectra of synthesized Cl-M5, OH-M5 AND Pd-OMS5**

TGA-DTA Analysis

The thermal stability of the palladated catalysts could be measured by TGA-DTA analysis. TGA-DTA analysis graph shows the two exothermic peaks at 450 and 500° C for Pd-OMS5; (Figure 8) gave an interpretation that the formation of palladium complex with ligands takes place in two different ways. The formation of palladacycles predominates over addition complex (exothermic peak at 500°C) PdX_2L_2 (the exothermic peak a $t450^0C$) where L = ligand and X=Cl or OAc) observed at lower Pd concentration, when similar concentration of ligands was treated with different concentration of Pd, whereas at higher concentration of Pd, favours formation of both addition complex as well as palladacycle(Figure 9). TGA-DTA analysis also reveals importance of addition of base for the formation of palladacycle and its stability. It describes how addition complex predominates over palladacycle when OH-M sample was treated with $LiPdCl_4$ without addition of a base (Figure 10). It also tells about how polar solvents favour the formation of palladacycle.

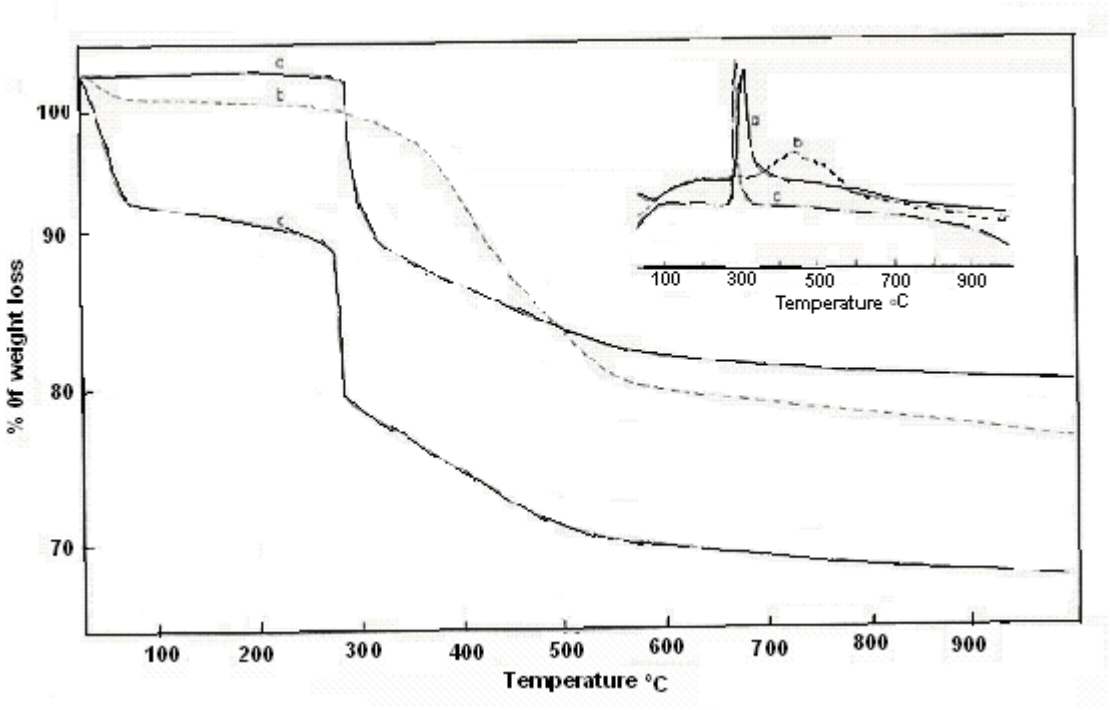


Figure 8. TGA-DTA curves of (a) Cl-M5 (b) OH-M5 and (c) Pd-OMS5

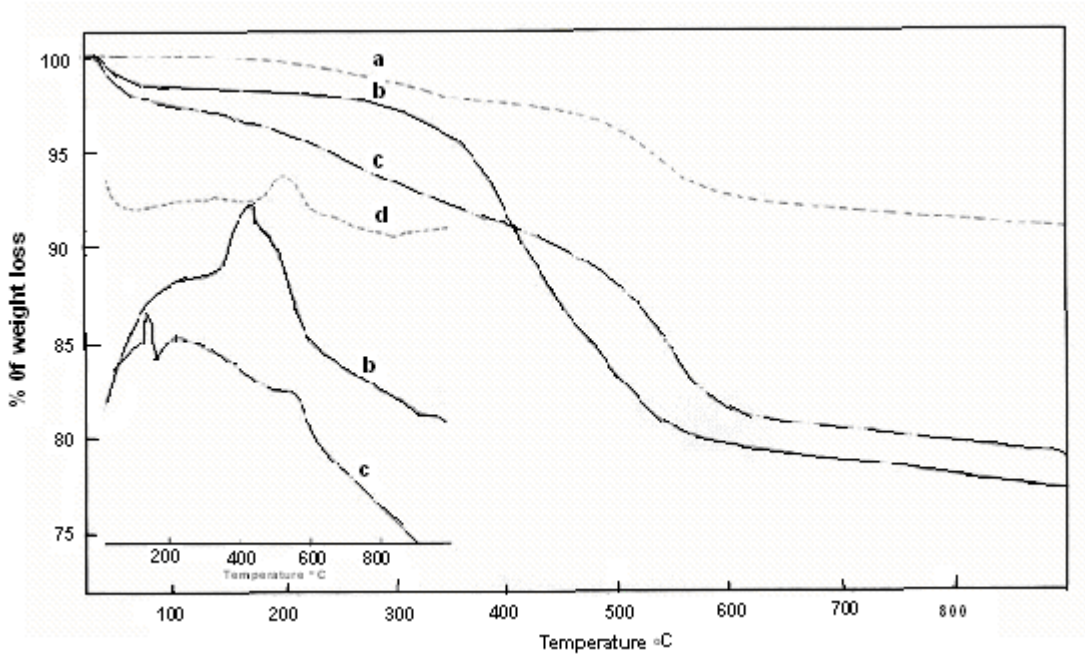


Figure 9. TGA-DTA curves of (a) Pd-OMS5(0.33) (b) Pd-OMS(1.68)and (c) Pd-OMS5(1.05)

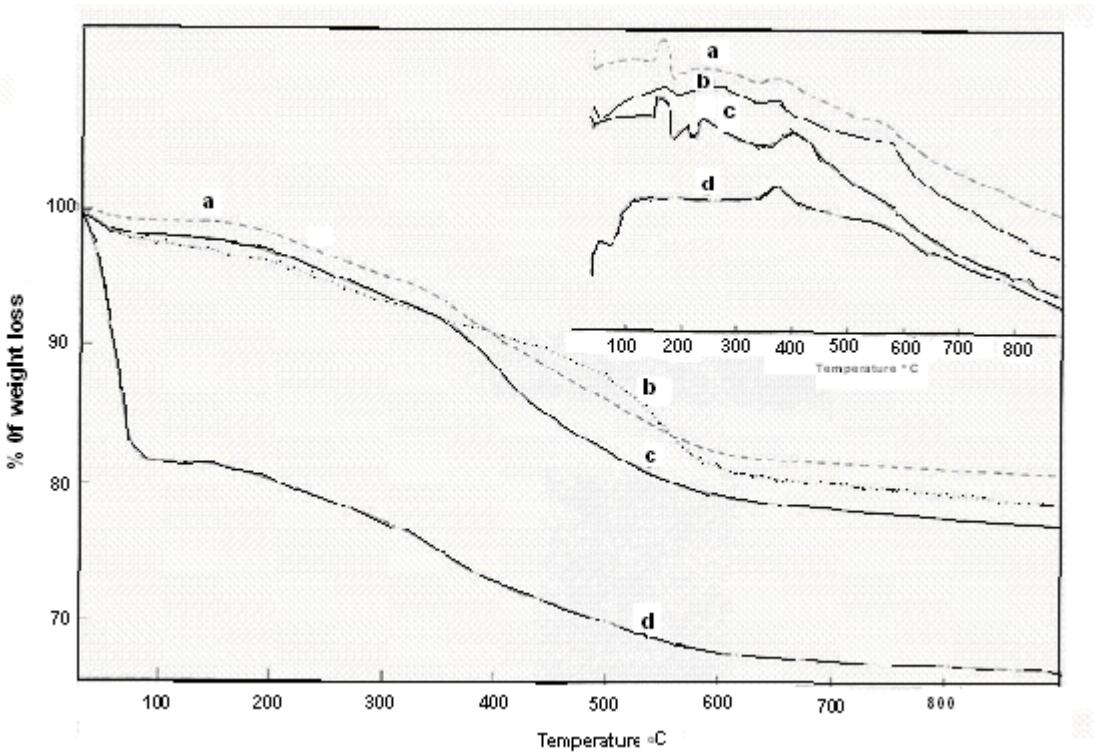


Figure 10. TGA-DTA curves of (a) Pd-OMS5 (b) Pd-OMS51 (c0 Pd-OMS52 and (d) Pd-OMS53

Electron Microscopy

The particle morphology of the sample was detected by Electron microscopy. Scanning electron micrographs(SEM) of OH-M5 samples shows about its uniform particle sizes (1-2/nm) for Pd-OMS5 samples and the particle sizes in the range of 1-3 nm(Figure 11).

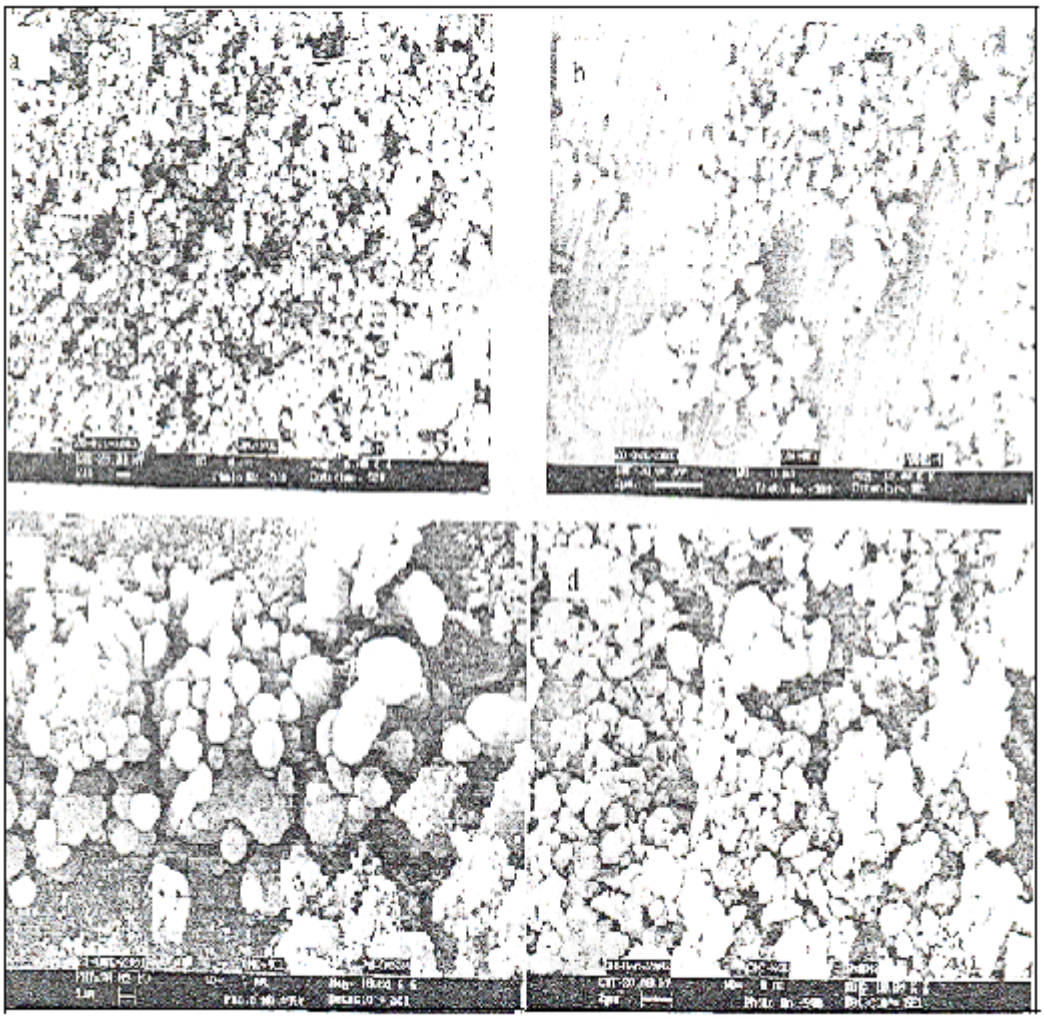


Figure 11. SEM Photograps of (a) OH-M5 (b) Pd-OMS5 (c) Pd-OMS53 (d) Am-PdOMS

NMR-Studies

The peak at 67.0 ppm of ^{29}Si NMR spectra of Pd-OMS5 indicates cross-linking of silicon atom (Figure 12). The cyclic palladation with aliphatic carbon and oxygen of OH group was confirmed by 125.76 MHz solid state ^{13}C CP/MAS spectra of OH-MCM-41 and Pd-OMS recorded on Brucker DRX 500 MHz. Spectrometer spun at 10 and 8 KHz, respectively are shown in the (Figure 13). The three main peaks of OH-M5 observed at δ 8.67, 25.28 and 63.63 ppm have been shifted to 8.33, 25.368 and 63.65 ppm, respectively, in Pd-OMS5. The shift of methylene carbon next to the silyl silicon towards high field is sufficiently higher,

0.34 ppm, compared to that of the middle carbon and carbon atom next to the OH group in Pd-OMS5. The shift of the signal corresponding to methylene carbon next to silyl silicon to high field confirms that the carbon exhibited different environment after palladation, while other two carbon are not showing much difference. The shift towards higher field confirms the complexation of the ligands with Pd-centre.

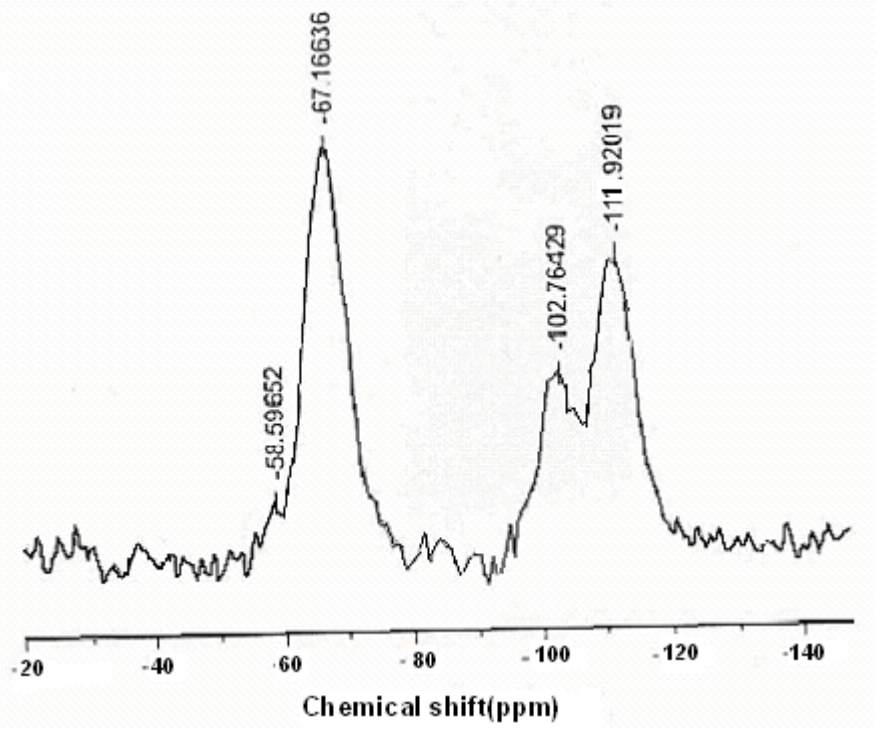


Figure 12. **^{29}Si NMR Spectra of Pd-OMS5 catalyst**

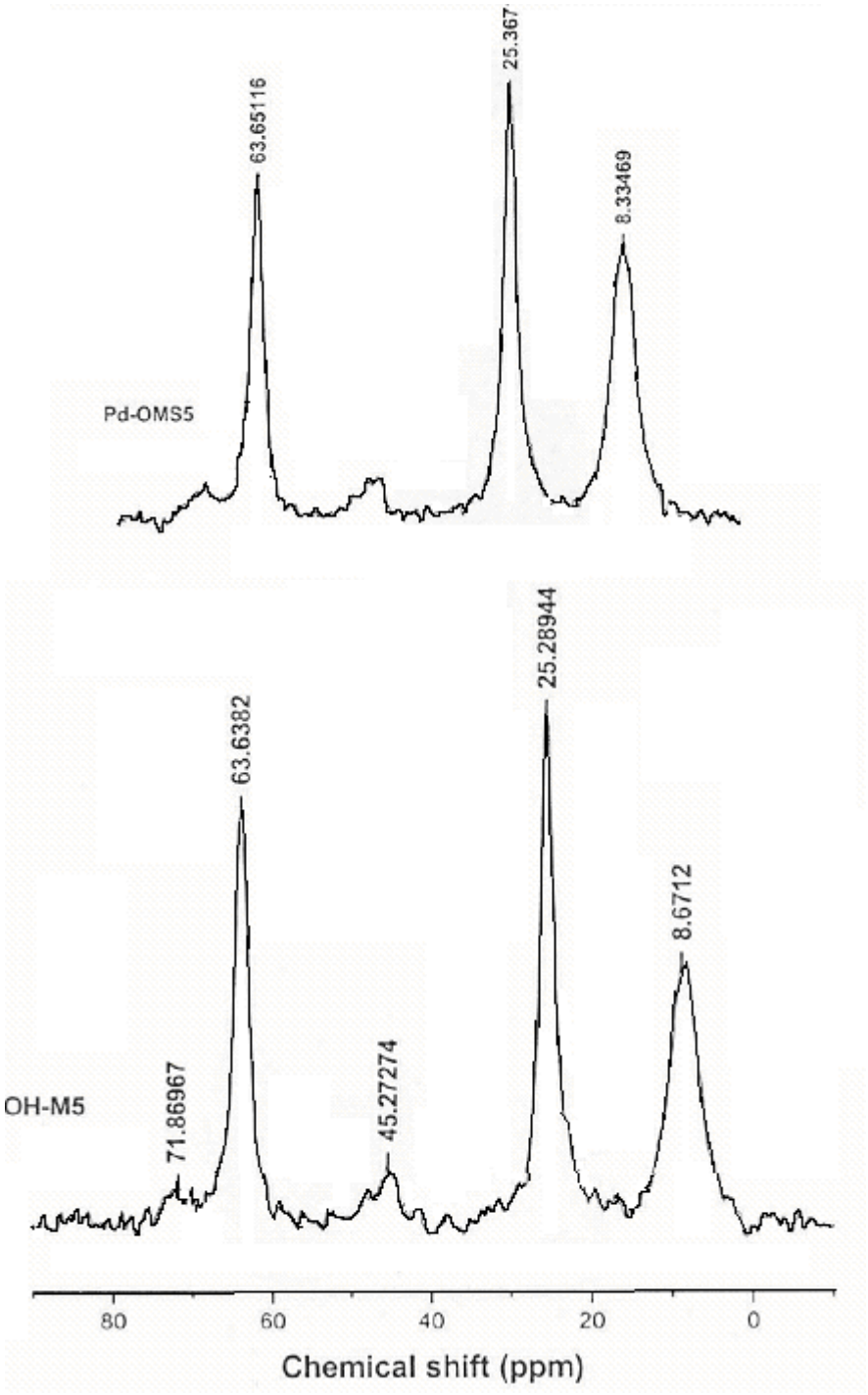


Figure 13. ^{13}C CP MAS NMR Spectrum of OH-M5 and Pd- OMS5.

XPS-Studies

The formation of palladacycles are again evidenced by Pd (3d) XPS spectra studies of Pd-OMS5 1.4), Pd-OMS51, Pd-OMS54 (Figure 14). The binding energy of adventitious C 1s core level, which is 284ev[72] was used to correct for the energy shift due to the surface changing. The accuracy of measured B.E was ± 2 eV. The peak maximum of the Pd II 3d5/2 line for Pd-OMS5 (1.4) Pd-OMS5, Pd-OMS54 is centred around 336ev. Pd-OMS5 (1.4) shows a weak Pd(O) $3d_{5/2}$ line at a B.E. of 334 7eV. Palladium present in palladacycle is in Pd (II) form and the binding energy is slightly lower compared to Pd(O) (335.6ev). Pd-OMs54 prepared with $Pd(OAc)_2$ shows no shoulder corresponding to Pd(O) on its surface whereas Pd-OMS5 (1.4) prepared with $LiPdCl_4$ as Pd source at 333K with methanol as a solvent and sodium acetate as a base shows weaker band at 334.7 eV, which is characteristic of B.E of Pd(O). Pd-OMS51 prepared at room temperature shows clear peak to Pd (II) at 336.4 eV.

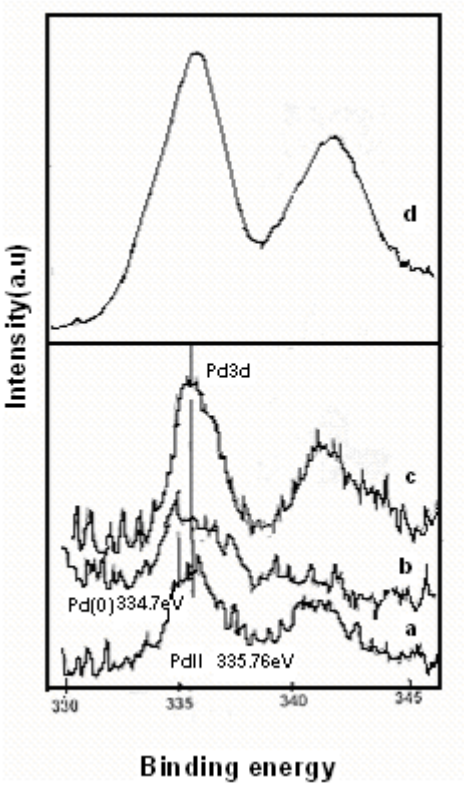


Figure 14. XPS Spectra of (a) Pd-OMS5 (1.4) (b) Pd-OMS53 (c) Pd-OMS51 and Am-PdOMS

UV-vis Spectral Studies

The diffuse reflectance spectra (200-800 nm) of Pd-OMS catalysis display three adsorption bands in the UV region in the range 260 and 450 nm, with reference to $BaSO_4$ standard (Figure 15). Pd-OMS5 shows a characteristic absorption band at 284 nm corresponding to metal-ligand charge transfer d-p transition. The shift towards high energy value was resulted from metallation.

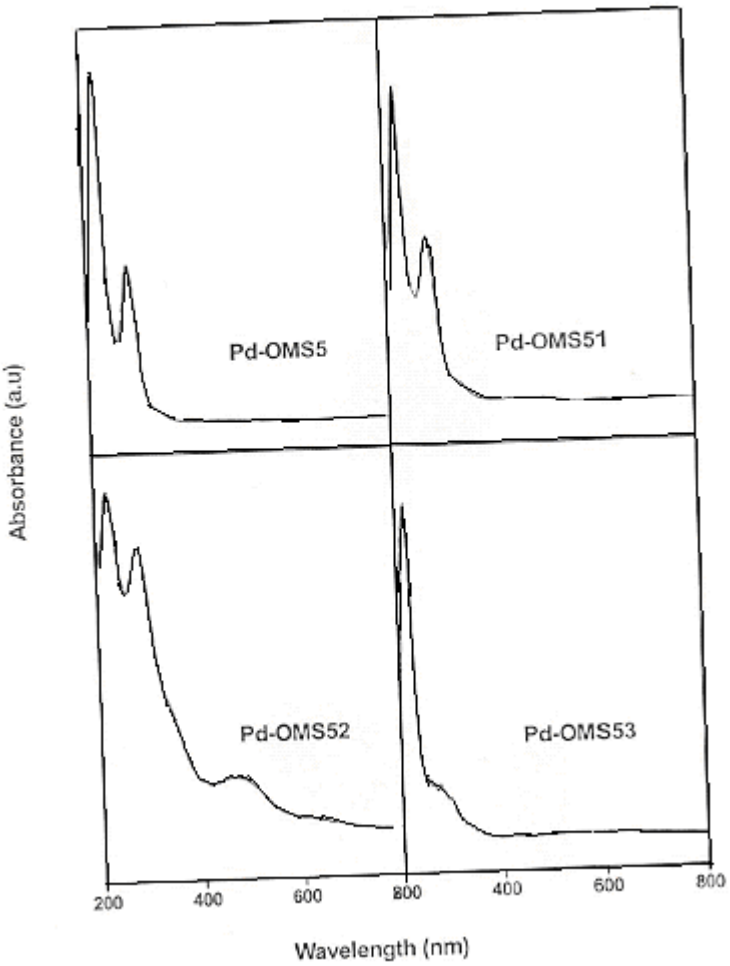


Figure 15. UV-Vis Spectra of Pd-OMS catalysts

3.2 Section B

Application of Pd-OMS(MCM-41) palladacycle catalyst to C-C bond forming reactions

3.2.1 Part 1. Pd-OMS(MCM-41) palladacycle catalyzed reactions of aryl halides with olefins (Heck reaction)

3.2.1.1 Introduction

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 compound.[74] As shown in the scheme 2 and 3, styrenes, dienes, α,β-unsaturated esters, α,β-unsaturated ketones, can be prepared from the corresponding alkene and aryl or vinyl halo compounds substituted with a leaving group X=Cl, Br, I. The other less usual leaving groups used in Heck chemistry are N_2BF_4, OTf, $I^+BF^-_4$ (iodonium salts) and COCl or $-(CO)_2O$. 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 quarternary 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. For the last two decades after mid eighties many research groups focused on developing and exploring the scope and limitations of the reaction.

In a typical experimental procedure, 1.2 equiv. of ethyl acrylate (0.120 g, 1.2 mmol) was added to a solution of 4-nitrobromobenzene (0.202 g, 1mmol) in 5 mL of DMF followed by the addition of a 1.4 eq. of base (K_2CO_3). After addition of 0.075 mol% palladacycle Pd-OMS(MCM-41) in DMF, the reaction mixture is stirred at 140°C for the desired time (5h). The reaction completion was identified by GC analysis and TLC. The products were identified by spectroscopic methods and the yield was calculated on the basis of amount of 4-nitrobromobenzene was taken. The results of various aryl halides reactions with different olefins are summarized in the Table 7.

3.2.1.2 Effects of temperature, base, solvents, leaving groups and catalyst loading on the performance of the catalyst

In an experimental protocol to evaluate the performance of the catalysts prepared under different conditions, Heck alkenylation of bromobenzene with styrene has been performed. While we were using the catalysts Pd-OMS1 to Pd-OMS5 (prepared under different conditions) for the above reaction, under similar conditions, the conversion and TON increases linearly from Pd-OMS1 to Pd-OMS5. The uptake of Pd consequently signified in the Heck alkenylation reaction. The Pd uptake increases proportional to the amount of ligand (3-hydroxypropyl triethoxysilane) present in the mesoporous walls of MCM-41 and so the rate of the reaction (TON) increases accordingly. As we can see from the Table 3, though the Pd content is higher in the Pd-OMS1 and Pd-OMS2 than the Pd-OMS3, Pd-OMS4 and Pd-OMS5, the activity was shown lower which might be attributed to formation of bulky Pd in Pd-OMS1 and Pd-OMS2, which is catalytically inactive for such reaction. We can co-relate this formation of inactive bulk Pd species with the collapsing of long range order in OH-M1 and OH-M2 samples during acidic or basic treatment, in consequence decrease in amount of ligand (3-hydroxy-propyl triethoxyl silane) in the pore walls of MCM-41, leads to decrease in Pd-species which actually involves in carbometallation. On the contrary, the palladated materials Pd-OMS3, Pd-OMS4, and Pd-OMS5 retain their longer range order after palladation as seen in X-ray diffraction (Figure 3), which favours the increase in the concentration of organo-functional group (ClPTS) in the surfaces of the silica walls which in turn strengthens the Pd-O co-ordination. From this experiment it was clearly seen that whenever there are less number of ligands available for the formation of palladacycle, the excess palladium present in the solution tends to deposit at the surface of silica near to the anchoring point of functional group. In order to study the effect of temperature and base in the preparation of Pd-OMS (MCM-41) on Heck alkenylation reactions, the palladation was performed with and without addition of base at room temperature or at 333K. Palladacycle prepared at room temperature shows lower Pd content but moderate activity. Catalytic activity of Pd-OMS54 prepared with palladium acetate in chloroform was found to be less when compared to the one prepared with base at 333K (Pd-OMS55). Table 4 shows effect of Pd(%) loading over OH-5 in the Heck alkenylation reaction when OH-M5 was treated with different concentration of Pd containing solution, the uptake of Pd increases upto 70% and then started decreasing. Conversion of

bromobenzene increases as the Pd content increases in the catalyst. A maximum of 1.68% Pd content in the catalyst Pd-OMS5(1.68) was achieved but at the same time the catalysts show less activity in the conversion of bromobenzene than Pd-OMS5(1.4) containing 1.4% Pd. This result confirms that activity of Pd will arise only from Pd present as Pd(II) in palladacycle and not from the bulk Pd deposited on the surface.

From the above spectral and experimental studies it is evident that though catalytic activity of Pd-OMS (MCM-41) palladacycle depends upon the Pd concentration during preparation, it is directly related to ligands available and its co-ordination to Pd. As we see from the experimental results, despite, a maximum of 1.68% Pd content in the catalyst [Pd-OMs 5(1.68)] was achieved, the catalyst shows less activity in the conversion of bromobenzene than the sample [Pd-OMS5 (1.4)] containing 1.4% Pd. After certain level when there are less number of ligands available for formation of palladacycle, the excess Pd present in the solution tends to deposit at surface, because of this reason the catalyst, Pd-OMs(1.4) containing 1.4% of Pd shows better activity than the catalyst Pd-OMS(1.68) containing 1.6% of Pd. In all the experiment carried out, catalysts Pd-OMS (1.4%) used as Pd-OMS (MCM-41) with inorganic base K_2CO_3 have been shown to give excellent yield.

Effect of Temperature and Time

In addition to the observation of catalytic activity of different Pd-OMS catalyst prepared under different condition, it is also inferred from different experiments that although the Heck reaction can be performed at lower temperature down to 110°C (in the case of aryl iodies and aryl bromides), 140°C is the best reaction temperature for the synthetic purpose).The unactivated and deactivated aryl require reaction temperature above 120°C. To study the effect of temperature on the conversion, the reaction was conducted by varying the temperature from 403K to 433K at fixed bromobenzene concentration of 2×10^{-3} mol, styrene concentration of 3×10^{-3} mol, potassium carbonate concentration of 2.4×10^{-3} mol and Pd at 4.8×10^{-6} mol. It was observed that at 403K temperature, the conversion was low. At initial hours of reaction, (0.5 h), the conversion of bromobenzene, yield of trans-stilbene and TON are 5.0 wt.%, 90%, 21 at 403K; 10.6 wt.%, 89% 45 at 413k; 17.5 wt%, 92%, 73 at 423K and 19.8 wt.% 91%, 83 at 433K respectively. As it can be seen there, initial reaction rate increases

gradually with reaction temperature. Selectivity to trans-stilbene remains about 90% in all cases. The conversion of bromobenzene, yield of trans-stilbene, and TON after 10 h of reaction time are 11.2 wt%, 90%, 47 at 403K; 20.9 wt.%, 90% 88 at 413K; 84.6 Wt.%, 94%, 355 at 423K and 98.9 wt.%, 90%, 416 at 433K respectively. The apparent activation energy calculated for initial rates of reaction of four different temperature was 112.7K/mol (Figure 16).

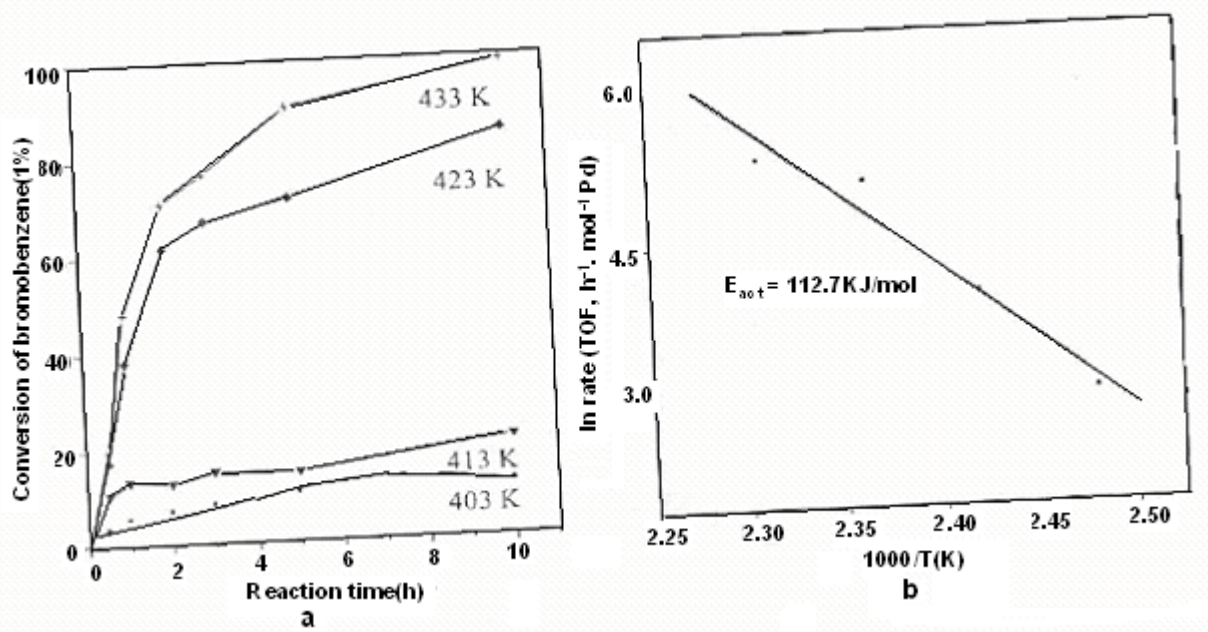


Figure16. (a) Effect of reaction temperature and reaction time on conversion of Bromo benzene (b) Arrhenius plot

Effect of different bases in the Heck alkenylation reaction

Among the various bases examined TEA, DEA, Bu_3N, (organic bases), NaOAc, Na_2CO_3, KOAc, K_2CO_3, K_3PO_4 (Inorganic bases), were screened, though K_3PO_4 seems to catalyze the reaction, K_2CO_3 was found suitable for the Heck alkenylation reaction with Pd-OMS(MCM-41) catalyst. The effect of different bases in Heck alkenylation of bromobenzene with benzyloxy styrene was conducted (Table 6). The reactions were conducted at a fixed bromobenzene concentration of 2 x 10^{-3}mole, styrene concentration of 3 x 10^{-3} mole, base concentration of 2.4 x 10^{-3} mol and Pd concentration of 4.8 x 10^{-6} mol. The reaction was performed at 423K for 12 h, and in the case of inorganic bases, potassium carbonate was

found to be effective in the conversion of bromobenzene with 90% selectivity (with 84% yield) to trans-stilbene. The other parameters have been optimized with K_2CO_3 as base. Organic bases triethylamine and tributyl amine showed lesser activity in alkenylation of bromobenzene.

Table 6 Effect of different bases on Heck alkenylation of bromobenzene

Base	Conversion of bromobenzene	Selectivity of trans-stilbene	TON
Triethylamine	20.9	91	88
Tributylamine	26.0	93	109
Sodium acetate	32.0	87	135
Sodium carbonate	56.5	88	238
Potassium carbonate	84.6	90	356

a = Reaction condition:
Bromobenzene = 2 mmol; styrene = 3mmol; base = 2.4 mmol; NMP 5.0 mL; catalyst = 0.2 mol% Pd; temperature = 423 K

Effect of solvent on Heck alkenylation reaction

To check the efficiency of the catalyst and to optimize reaction condition, different solvents have been checked. With K_2CO_3 as base, the reaction between 4-nitrobromobenzene and ethyl acrylate in presence of the carbometalled catalysts were conducted with different solvents. The reaction provided quantitative conversion with DMF. Even though other polar solvents like DMA, NMP can be used, DMF gave better results with unactivated and deactivated aryl bromides, and activated aryl chlorides. THF, CH_3CN gave lesser yield and required longer reaction time. Very low conversion was observed with solvent like toluene and dioxane.

Effect of substitution on aryl halides and olefins

The other parameteres like substitution on aryl halides, and on alkenes, the effect of loading of Pd mol% was also examined. The catalytic activity, as expected, depends on the substitutents on the aryl halides and olefin. Acrylates gave generally better yield. Electron withdrawing groups on the aryl ring increased the reaction rate. For example in a competitive

experiment, the reaction of 4-acetylbromobenzene, bromobenzene and 4-methoxybromobenzene (1:1:1) with 0.33 equivalent of ethyl acrylate and 1.4 equiv. of K_2CO_3 in DMF at 140°C after 12 h gave(100% conversion based on the ethyl acrylate) the substituted *trans*-cinnamates (4-acetylphenyl, phenyl, 4-methoxyphenyl) in the proportion 6:3:1 respectively.

Bromobenzene, a relatively inactive halide, gave 91% and 89% yield of *trans*-cinnamate and stilbene after reaction with acrylates and benzyloxy styrenes at the time interval of 8 and 12 h respectively. Bromobenzenes substituted with electron withdrawing or electron donating groups also gave good to excellentl yield (TOF), without addition of any additives. The highest TON, observed was 138700 in the case of aryl bromides (for the reaction of bromobenzene with ethylacrylate. With aryl iodides, the highest TON observed was119300 for the reaction of 4-iodotoluene with ethylacrylate. The styrenes with electron withdrawing or electron donating groups also reacted well and gave quantitative yield with aryl iodides and bromides (entry 4,6,13 of Table 7). The reaction of iodoarenes containing electron withdrawing or electron-donating groups with ethyl acrylates, styrenes was run under the optimized conditions (**entry 6, 7 of Table 7 and entry 12 of Table 8**). All the coupling reactions proceeded smoothly to give the corresponding (*E)*-cinnamates and stilbenes.

Heck alkenylation of reaction with aryl chloride

The real check of a catalyst activity and its performance lies with its activity with aryl chlorides. We were pleased to observe that activated aryl chlorides such as 4-chlorotoluene, 2-chloronitrotoluene, 4-bromoacetophenone, 2, 4-dinitrochlorobenzene (with electron withdrawing groups) gave reasonable yields in the coupling reaction with acrylates and styrenes (**entry No.14, 16, 17 of Table 7**) Non activated arylhalides such as 2-chlorotoluene, and chlorobenzene gave 42% and 32% yield of coupled product with styrenes with acrylates(Table 8, entry 7, 8 and 10). Higher temperatures (150-160°C) and additives (TBAB, CuI) enhanced the reaction rates and yields.

Heck alkenylation reaction of aryl halides with methyl vinyl ketones

In another appealing features of this carbometallated palladacycle Pd-OMS is the Heck alkenylation reaction between the aryl halides (Iodo, and Bromo) and methyl vinyl ketone. Bromo benzene substituted with electron withdrawing or electron donating groups also gave

moderate to good yields. Aryl iodides with both electron withdrawing and electron donating groups reacted with vinyl ketones to give the vinylated product.

Effect of catalyst loading

Although the aryl iodides and activated aryl bromides reacted well with faster reaction rate and conversion, non-activated and deactivated aryl bromides and aryl chlorides were sluggish when the catalyst loading is lower than the 0.075 mol% of Pd with respect to substrate. Aryl chlorides (activated and non-activated) give less than 10% yield, when catalyst is loading is 0.125 mol% of Pd, no reaction was observed when the catalyst loading was lower than 0.125 mol%. When the catalyst was increased to 0.24 mol% of Pd, the reaction rates and yield were increased almost 3 times. In the case of aryl iodides and aryl bromides, where the loading of the catalyst is reduced, it led to longer reaction times, but did not influence the reaction conversion. In typical experimental protocol; the reaction between bromobenzene and benzyloxystyrene, at 1.5 x 10^{-6} mol% Pd concentration (0.075 mol% of Pd with respect to substrates), the conversion of bromobenzene at 0.5 h reaction time was found very low (4.2 wt%) and it was found to increase to 14.6 wt.% when the Pd concentration was further increased from 1.5 x 10^{-6} and 2.5 x 10^{-6} mol. The initial reaction rates increases proportionally with Pd content but at the same time the increase is not linear. When the Pd concentration increased from 2.5 x 10^{-6} to 3.2 x 10^{-6} mol, the activity increased almost four times. The sharp increase in initial conversions while the concentration of Pd was varying, evidently signifies the catalytic nature of Pd. This results show that Pd plays an important role in activating the Heck alkenylation reaction and activity varies with the Pd concentration (**Figure 17**).

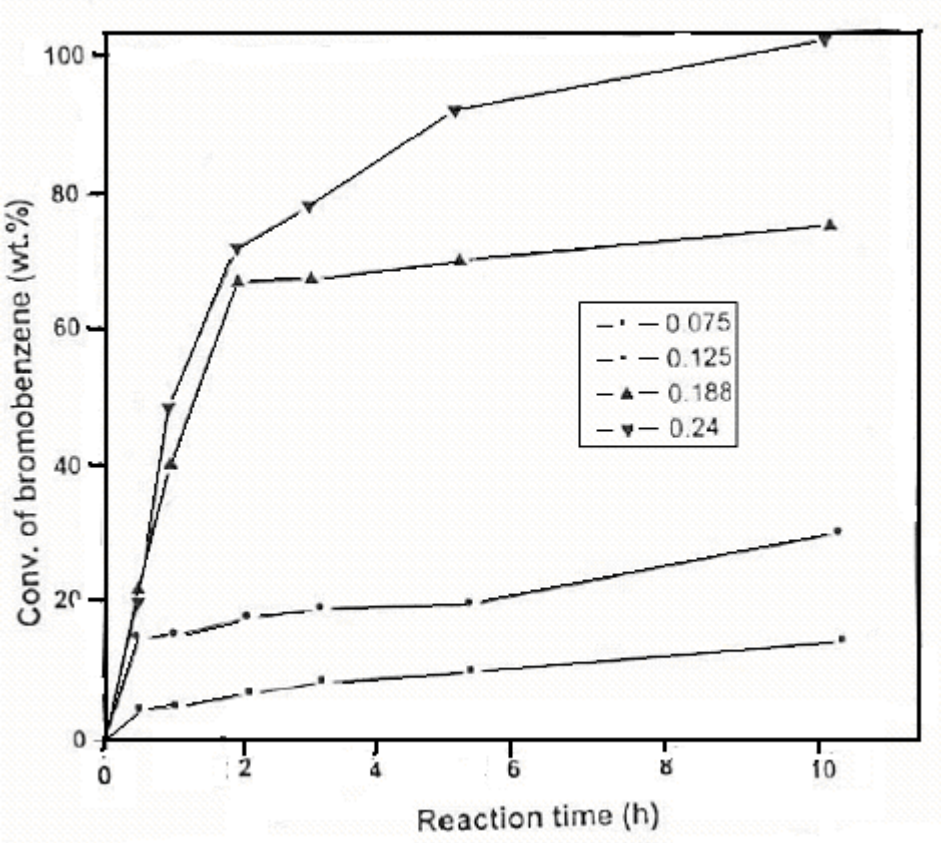


Figure 17. Effect of Pd mol % and reaction time on conversion of Bromobenzene

1.5 x 10^{-6} mol % Pd concentration (0.075 mol% of Pd with respect to substrates), the conversion of bromobenzene at 0.5 h reaction time was found very low (4.2 wt%) and it was found to increase to 14.6 wt.% when the Pd concentration was further increased from 1.5 x 10^{-6} and 2.5 x 10^{-6} mol. The initial reaction rates increases proportionally with Pd content but at the same time the increase is not linear. When the Pd concentration increased from 2.5 x 10^{-6} to 3.2 x 10^{-6} mol, the activity increased almost four times. The sharp increase in initial conversions while the concentration of Pd was varying, evidently signifies the catalytic nature of Pd. This results show that Pd plays an important role in activating the Heck alkenylation reaction and activity varies with the Pd concentration (Figure 17).

Stability of the carbometalled palladacycle

It is interesting to find the characteristic features of this catalyst that the complex are insensitive to oxygen or moisture. No change of their activity was observed, when they were exposed to an open air system. When $Pd(OAc)_2$ or $Pd(dba)_3$ was employed, the formation of palladium black or an insoluble solid material was observed.

Heterogeneity of carbometallated palladacycle Pd-OMS(MCM-41)

There are two divergent school of thought as how Heck olefination reaction is mediated by the heterogeneous catalyst. Blackmond[75a] and Reetz[75b] disclosed that the reaction occurs at the heterogeneous surface, involving nanopalladium particles. On the other hand, Arai[75c] and Brffis[75d]independently made detailed studies recently on the heterogeneity of the palladium supported systems and found that the reactivity is proportional to leached palladium, which indicates the heterogeneous palladium is source of homogeneous palladium species that actually perform the catalytic homogeneous reactions. The heterogeneity of the catalyst was analysed with Pd-OMS5 catalyst as depicted in Fig 18. After attaining 20% conversion of bromobenzene 5ml of reaction mixture was filtered and performed reaction in a separate set up. After filtering the sample, the reaction was continued further up to 24 h. A higher conversion of 36% of bromobenzene could be achieved with tributylamine as a base.The conversion of bromobenzene could be achieved with tributylamine as a base. The conversion of bromobenzene was lower when tributylamine was used as a base. Even though K_2CO_3 gave more than 90% coversion, tributylamine was chosen to study the leaching of Pd at slower conversion rate and also organic bases will be equally mixed with reaction mixture rather than K_2CO_3. The Pd content present in the solution was measured by ICP-OES analysis and a negligible amount of Pd was found in ppm level present in the solution. However, this Pd can be accounted for the bulk Pd present in the catalyst surface which may get leached out during the reaction. The fact was also confirmed by the reaction performed with the reaction mixture which was separated after 5 h, shows no increase in conversion (Figure 18).

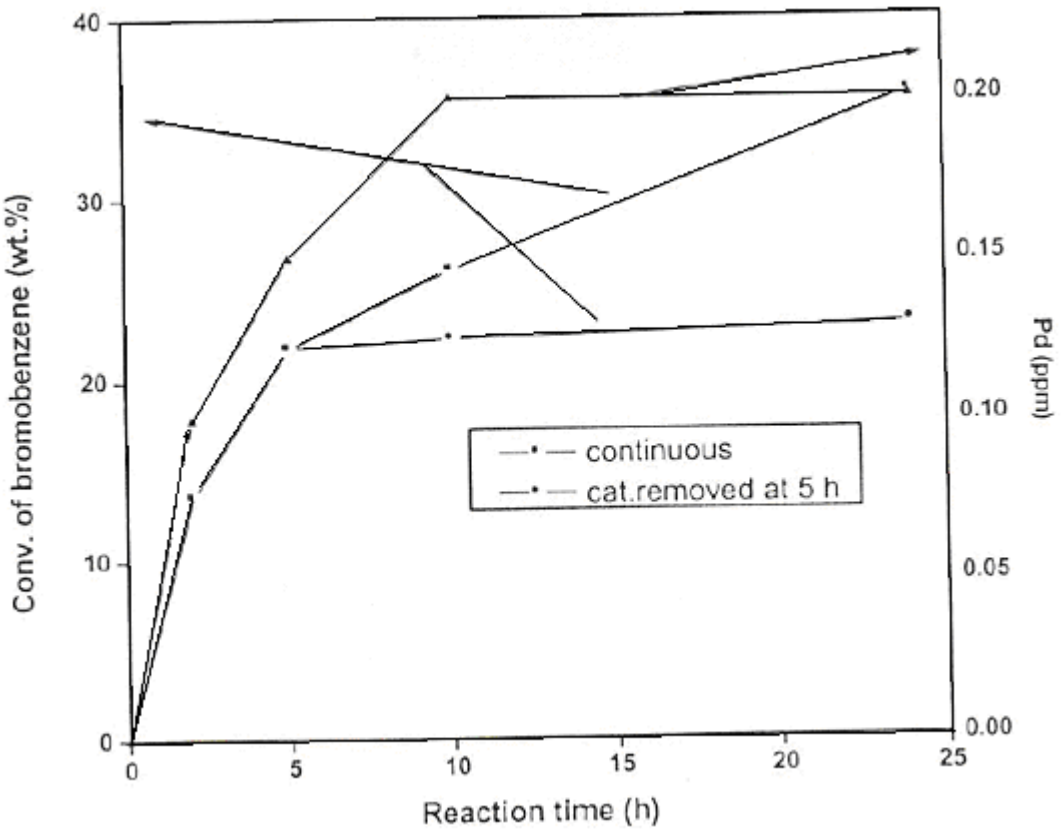


Figure18. Heck alkenylation of Bromobenzene; BB = 1x 10^{-2} mol; styrene = 1.5x 10^{-2}; tributylamine = 1.2x 10^{-2} mol; DMF = 25ml; temperature = 423 K; Catalyst = 0.1g

3.2.1.3 Results and Discussion:

when the aryl halides were treated with substituted alkenes, substituted aryl(styrenes), acyl,(vinyl ketones), esters(acrylates) in the presence of catalytic amount of Pd-OMS(MCM-41) catalyst, and K_2CO_3 as base, in DMF at 140^o C it gave the corresponding arylated olefins in good to excellent yield (**Table 7 and 8**). Thus 4-iodotoluene on reaction with 4-nitrostyrene in the presence of Pd-OMS(MCM-41) as catalyst, furnished the corresponding stilbene **47c** in 84% yield. The IR Spectrum of **47c** shows bands at 1605cm^{-1}, indicates presence of C-C double bond. The ^{1}HNMR spectrum of the **47c** shows signals at δ 2.40, 7.10, 7.20 corresponding to three, one, one proton each, indicating the presence of methyl and olefinic protons. The four doublets at δ 7.22, 7.45, 7.67, 8.27 coresponding to two protons each indicated two aromatics substituted at para position. The ^{13}C spectrum of **47c** showed signals

at δ 21.2 for CH_3 carbon. The two carbons of olefins appeared at δ 125.2 and 133.2. Further the compound **47c** was confirmed by its mass spectrum which showed M^+ ion peak at 239. In another experiment 4-methoxy-3-carbomethoxy-iodobenzene reacts with 4-benzyloxystyrene in the presence of Pd-OMS(MCM-41) catalyst to give compound **47g**. The IR spectrum of the **47g** shows bands at 1738 cm^{-1} and 1606 cm^{-1} characteristic of ester carbonyl and olefin of the styrenes. The ^1H NMR of the **47g** shows signals 3.93 corresponding to six protons for the methoxy and methylester groups. The benzylic protons appeared as singlet at δ 5.10. The olefinic protons of styrenes appeared as doublets at δ 6.90 and at 6.97. The ^{13}C NMR spectrum of **47g** shows peaks at δ 52.0, 56.0, and 69.9 corresponding to methylester, methoxy and benzylic carbons. The olefinic carbon of styrene appeared at δ 125.0 and 131.0. The catalytic activity of Pd-OMS(MCM-41) palladacycle in Heck coupling was again demonstrated by cross coupling reaction between aryl halides with acrylates and vinyl ketones. For example when 2-iodo-methylbenzoate was treated with ethyl acrylate in the presence of Pd-OMS(MCM-41) catalyst, and K_2CO_3 in DMF at 140^o C, it gave the corresponding cinnamate **49b**. The IR spectrum of the **49b** shows peaks at 1596 cm^{-1} and at 1732 cm^{-1} corresponding to olefin and carbonyl functionalities. The ^1H NMR spectrum of **49b** showed two doublets at δ 6.18 and at δ 7.49, corresponding to two olefinic protons. The presence of other peaks in the ^1H NMR spectrum comfirmed the formation of the product. Pd-OMS (MCM-41) catalyst was successfully employed in the coupling of 4-iodotoluene with vinyl ketone to give the product **49i**. The IR spectrum of **49i** showed peaks at 1601 cm^{-1} and 1665 cm^{-1} showing the presence of olefinic and carbonyl functionalities. The ^1H NMR Spectrum of **49i** shows two doublets at δ 6.68 and δ 7.49, corresponding to one proton each of olefinic protons. The other signals of the ^1H NMR spectrum confirms the formation of **49**i, which was again substantiated by its ^{13}C NMR and Mass spectrum. The present procedure is quite general as a wide range of aryl halides can be coupled under the reaction condition. [with Halide X= I, Br, Cl (except aryl chlorides with electron-donating groups)]. The electronically varied groups reacted well with various substituted styrenes, acrylates, vinyl ketones to give the corresponding stilbenes, cinnamates and vinylated products. This procedure allows us to use aryl iodide substituted with both electron-donating and electron-withdrawing group, and ortho substituted arylhalides successfully. A noteworthy feacture of this methodology is the survival of acid sensitive functionalities in styrenes (**Table 7, entry 2,**

8, 11, 16), and successful coupling of less reactive vinyl ketones with aryl iodides and aryl bromides and aryl chlorides with electron with-drawing groups. Though there are various palladacyclic catalyst developed for the Heck coupling, our protocol is advantageous as it can be applied to less reactive aryl chlorides (with electronically activated and nonactivated), styrenes with acid sensitive functionalities, less reactive vinyl ketones. The catalytic activity even with low catalyst loading(0.125mol%), reusability (with aryl iodides, aryl bromides and activated aryl chlorides) and quantitative conversion are another some noteworthy feature of this protocol .

3.2.1.4 Conclusion

Inconclusion we have developed a new and useful method for Heck coupling of aryl halides(with Halide X=I, Br, Cl) with styrenes, acrylates, and vinyl ketones

3.2.1.5 Experimental Section

Experimental Procedure

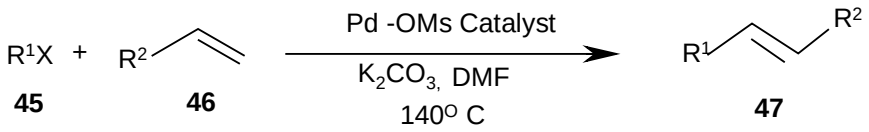
In a typical experimental procedure, 1.2 equiv. of ethyl acrylate (0.120 g, 1.2 mmol) was added to a solution of 4-nitrobromobenzene (0.202 g, 1mmol) in 5 mL of DMF followed by the addition of a 1.4 eq. of base (K_2CO_3). After addition of 0.075 mol% palladacycle Pd-OMS (MCM-41) in DMF, the reaction mixture is stirred at 140°C for the desired time (5h). The reaction completion was identified by GC analysis and TLC. The products were identified by spectroscopic methods and the yield was calculated on the basis of amount 4-nitrobromobenzene taken. The results of reaction of various aryl halides with different olefins are summarized in the Table 7 and 8.

General Procedure for Heck Olefination: In a experimental procedure, ethyl acrylate (1.2 mmol) was added to a solution of 4-nitrobromobenzene (1mmol) in 5ml of dry DMF, followed by addition of 1.4 eq of K_2CO_3. After addition of 0.24 mol% of palladacycle Pd-OMS (MCM-41), the reaction mixture was stirred at 140^{o}C for the indicated duration of time (Table 7). The reaction completion was monitored by GC and TLC analysis. After completion of the reaction, the catalyst was filtered and thoroughly washed with diethyl ether (50ml).The filtrate was washed with water and brine solution and dried over anhydrous sodium sulfate.

Evaporation of solvent gave the crude product, which was purified by silica gel (60-120 Mess) column chromatography using petroleum ether: ethyl aecetate(95:05) as eluent to give the pure product.

Table 7. Pd-OMS(MCM-41) catalysed Heck Reaction of aryl halides with styrenes

Scheme-2

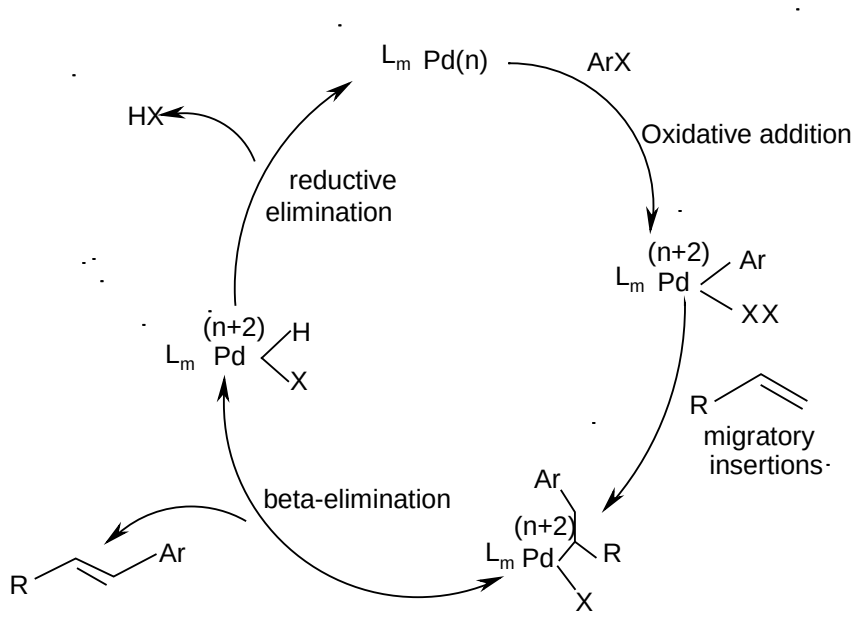


R^1 = Aromatics, Substituted aromatics

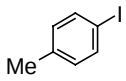
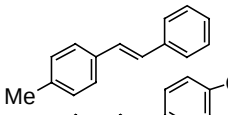
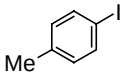
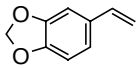
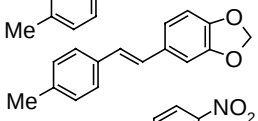
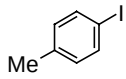
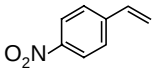
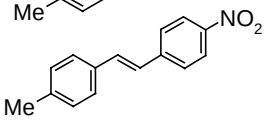
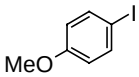
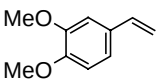
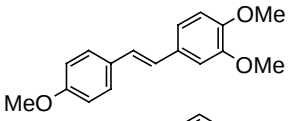
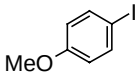
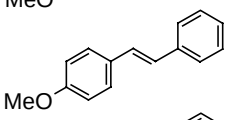
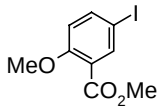
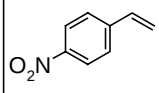
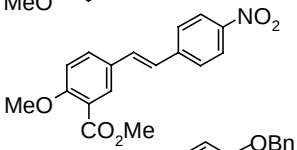
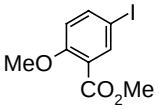
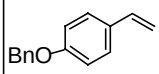
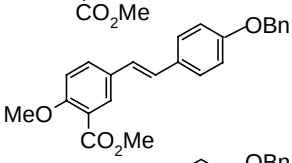
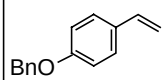
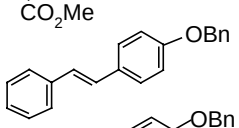
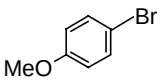
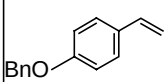
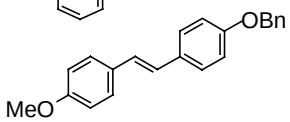
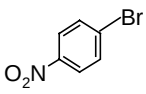
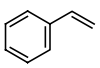
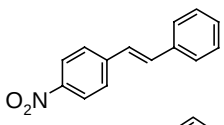
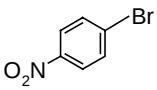
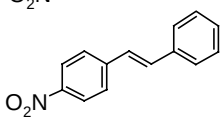
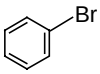
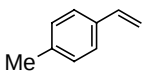
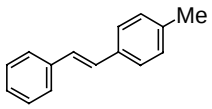
R^2 = Aromatics, Substituted aromatics, -COOMe, -COOEt, -COMe

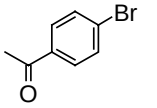
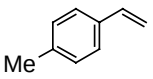
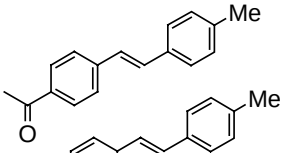
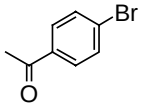
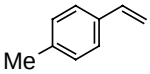
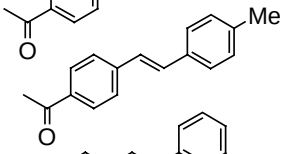
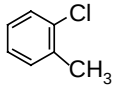
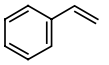
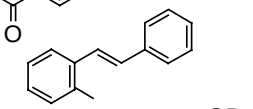
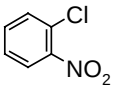
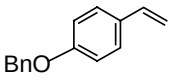
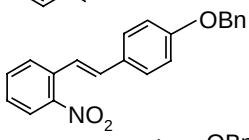
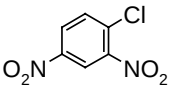
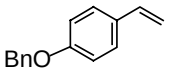
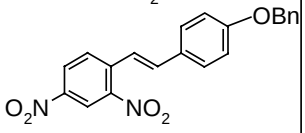
X = I, Br, Cl

Plausible mechanism for Heck reaction:

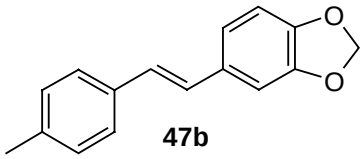


Highly simplified catalytic cycle for the Heck reaction.

Entry	Aryl halides	Styrenes	Product	Product number	Reaction Time (h)	Yield	TON
1				**47a**	6	94	96900
2				**47b**	6	85	88200
3				**47c**	8	84	84300
4				**47d**	5	87	82600
5				**47e**	7	75	55200
6				**47f**	8	75	59900
7				**47g**	9	89	62800
8				**47h**	12	89	84200
9				**47i**	15	87	103200
10				**47j**	2	86	89900
11				**47k**	4	83	77100
12				**47l**	12	76	79900

Entry	Aryl halides	Styrenes	Product	Product number	Reaction Time (h)	Yield %	TON
13				**47m**	5h	63	66700
14				**47n**	4h	87	86300
15				**47o**	22h	31	5400
16				**47p**	18h	42	6100
17				**47q**	16h	43	7500

5--(2-*p*-Tolyl-vinyl)-benzo[1,3]dioxole (47b)



47b

Yield: 85%

White Solid.

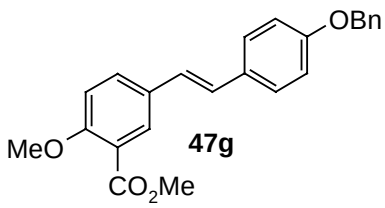
IR ($CHCl_3$ cm^{-1}): ν_{max} 3023, 2401(weak), 1596, 1512, 1493, 1216.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.67 (s, 3H), 6.28 (s, 2H), 7.09 (d, 1H, *J* = 8.79Hz), 7.19-7.25(m, 3H), 7.37 (d, 1H, *J* = 2.75 Hz), 7.45 (d, 2H, *J* = 8.79Hz), 7.68 (d, 2H, *J* = 7.31Hz)

^{13}C NMR (500 MHz, $CDCl_3$): δ 21.2, 101.0, 105.5, 108.4, 121.2, 126.2, 127.0, 127.4, 129.4, 131.1, 134.0, 137.2, 147.1, 148.1.

Analysis calcd for $C_{16}H_{14}O_2$ (238.284): Found C, 80.51; H, 5.79{Required C, 5.82; H, 5.92}

5-[2-(4-Benzyloxyphenyl)-vinyl]-2-methoxy-benzoic acid methyl ester (47g)



47g

Yield: 89%

Colorless Crystalline Solid

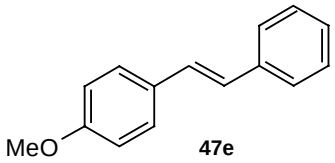
IR (CHCl3 cm^{-1}): ν_{max} 3020, 2983, 2963, 2943, 2887, 2855, 2029, 1738, 1606, 1576, 1510, 1491, 1496, 1460.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.93 (s, 6H), 5.10, (s, 2H), 6.90 (d, 1H, *J* = 16.04Hz), 6.97-7.00, (m, 4H), 7.33 (t, 1H, *J* = 7.34Hz), 7.39-7.46(m, 6H), 7.57-7.60 (dd, 1H, *J* = 2.29Hz, 8.71Hz), 7.94 (d, 1H, *J* = 5.7Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 52.0, 56.0, 69.9, 112.2, 115.0(2C), 120.0, 125.0, 127.2, 127.4(4C), 127.9, 128.5(2C), 129.3, 129.9, 130.2, 131.0, 136.8, 158.2, 158.3, 166.5

Analysis calcd for $C_{24}H_{22}O_4$ (374.43): Found C, 77.12; H, 6.09{Required C, 76.987; H, 5.922}

1-[2-Phenylvinyl]-4-methoxy benzene (47e)



47e

Yield: 87%

Colorless Solid

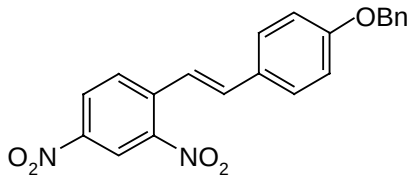
IR ($CHCl_3$, cm^{-1}): ν_{max} 3305, 3001, 2976, 2278, 1638, 1567, 1456, 1354, 1234, 1143.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89(s, 3H), 6.95-7.11 (m, 4H), 7.40 (m, 1H), 7.49 (t, 2H, *J* = 5.81Hz), 7.61-7.67 (m, 4H).

^{13}C NMR (500 MHz, $CDCl_3$): δ 55.3, 114.2(2C), 125.3(2C), 126.7, 126.2, 127.7(2C), 128.2, 128.6(2C), 130.2, 137.7, 159.4

Analysis cacld for $C_{15}H_{14}O$ (210.27): Found C, 85.83; H, 6.51{Required C, 85.60; H, 6.71}

1-[2-(4-Benzyloxy-phenyl)-vinyl]-2, 4-dinitrobenzene (47q)



47q

Yield: 43%

Colorless Solid

IR($CHCl_3$, cm^{-1}): ν_{max} 3423, 2388, 1610, 1555, 1485, 1218.

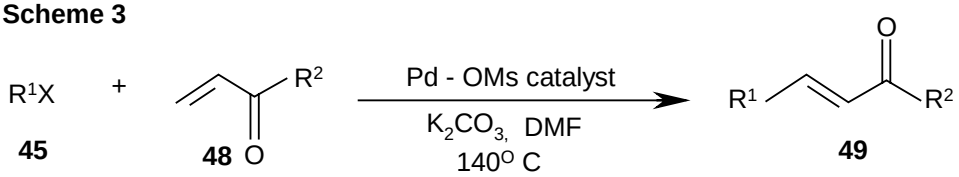
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.16 (s, 2H), 7.04 (dd, 1H, *J* = 2.29 Hz, 7.59Hz), 7.09 (d, 2H, *J* = 7.71Hz), 7.16 (dd, 1H, *J* = 2.31Hz, 7.72 Hz), 7.34-7.45 (m, 7H), 7.83 (d, 2H, *J* = 9.71Hz), 9.90 (s, 1H).

^{13}C NMR (500 MHz, $CDCl_3$): δ 46.1, 114.8, 115.0, 118.2, 123.7, 126.9, 127.3, 127.8, 128.2, 128.4, 131.8, 136.4, 137.0, 147.9, 190.7.

Analysis calcd for $C_{21}H_{16}N_2O_5$ (376.36): Found C, 67.23; H, 4.33{Required C, 67.02; H, 4.28}

Table 8. Pd-OMS(MCM-41) Catalyzed Heck Reaction of Aryl halides with acrylates and methyl vinyl ketones

Scheme 3

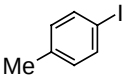
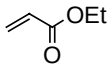
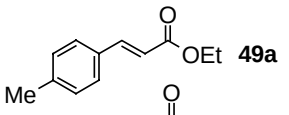
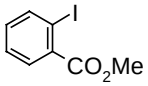
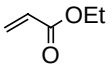
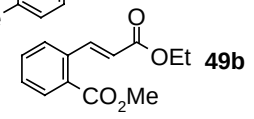
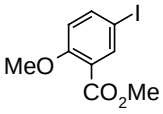
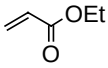
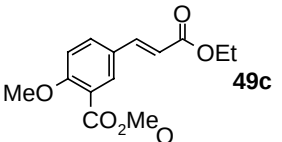
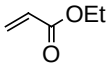
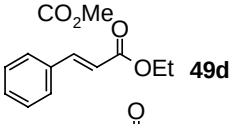
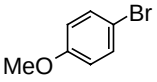
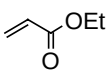
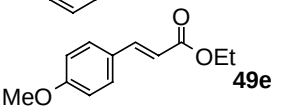
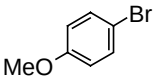
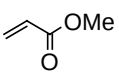
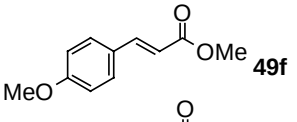
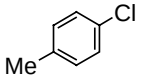
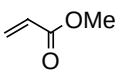
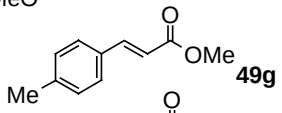
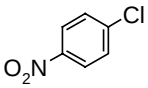
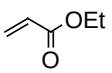
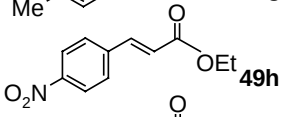
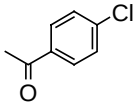
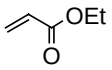
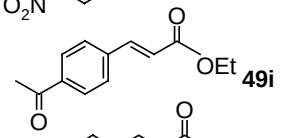
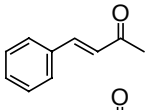
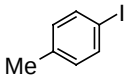
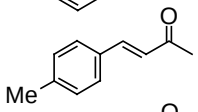
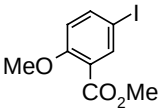
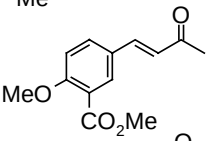
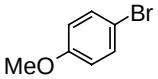
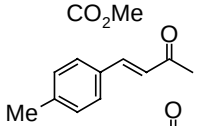
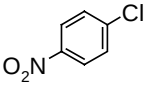


45 **48** **49**

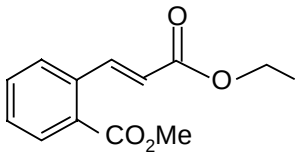
R^1 = Aromatics, Substituted aromatics

R^2 = OMe, OEt,

X = I, Br, Cl

Entry	Aryl halides	Styrenes	Product	Reaction Time	Yield	Tons
1			 **49a**	5	80	119300
2			 **49b**	8	82	87600
3			 **49c**	6	80	75700
4			 **49d**	8	91	138700
5			 **49e**	18	85	56900
6			 **49f**	22	76	59800
7			 **49g**	32	46	2100
8			 **49h**	28	47	9800
9			 **49i**	30	42	9400
10			 **49j**	5h	49	81400
11			 **49k**	8	43	80200
12			 **49l**	10	65	69400
13			 **49m**	15	67	104420
14			**49n**	24	43	3500

2-(2-Ethoxycarbonylvinyl)-benzoic acid methyl ester (49b)



49b

Yield: 82%

Colorless Oil

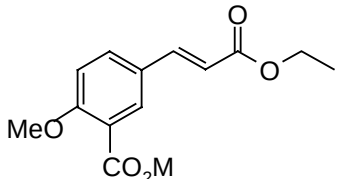
IR ($CHCl_3$ cm^{-1}): ν_{max} 3422, 3068, 2982, 2953, 1721(br), 1636, 1597, 1392

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H, *J* = 6.59Hz), 3.84 (s, 3H), 4.14 (q, 2H, *J* = 6.60Hz), 6.18 (d, 1H, *J* = 16.12Hz), 7.36 (t, 1H, *J* = 5.8Hz), 7.41 (t, 1H, *J* = 5.8Hz), 7.49 (d, 1H, *J* = 6.6Hz), 7.85 (d, 1H, *J* = 6.6Hz), 8.31 (d, 1H, *J* = 16.12Hz).

^{13}C NMR (500 MHz, $CDCl_3$): δ 14.0, 52.0, 60.3, 120.8, 127.6, 129.2, 129.6, 130.5, 132.0, 136.1, 143.3, 166.3, 166.8

Analysis calcd for $C_{13}H_{14}O_4$ (234.249): Found C, 66.73; H, 6.09{Required C, 66.65; H, 6.02}

5-(2-Ethoxycarbonylvinyl)-2-methoxy-benzoic acid methyl ester (49c)



49c

Yield: 80%

Colorless Oil

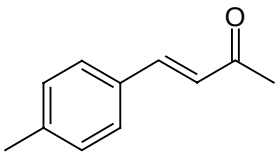
IR ($CHCl_3$, cm^{-1}): ν_{max} 3442, 3051, 2971, 2217, 1718, 1706, 1643, 1607

^{1}H NMR (300 MHz, $CDCl_3$): δ1.30 (t, 3H, *J* = 7.15Hz), 3.80 (s, 6H), 4.25(q, 2H, *J* = 7.15 Hz), 6.66 (d, 1H, *J* = 8.75Hz), 6.90 (d, 1H *J* = 7.15Hz), 7.40(m, 1H), 7.64(d, 1H, *J* = 7.15 Hz), 7.96 (d, 1H *J* = 8.75 Hz)

^{13}C NMR (500 MHz, $CDCl_3$): δ14.0, 52.1, 56.1, 61.0, 112.2, 114.4, 120.1, 131.5, 133.4, 141.7, 143.0, 159.0, 164.6, 165.0

Analysis calcld for $C_{14}H_{16}O_5$ (264.275): Found C, 63.71; H, 5.91 {Required C, 63.63; H, 6.10}

4-Tolyl-but-3-en-2-one(49g)



49g

Yield: 46%

Colorless Oil

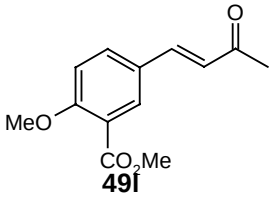
IR ($CHCl_3$, cm^{-1}): ν_{max} 3041, 2269, 1692, 1600, 1590, 1481, 1355, 1249

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.38(s, 3H), 6.66 (d, 1H, *J* = 16.29Hz), 7.20 (d, 2H, *J* = 7.94 Hz), 7.43 (d, 2H, *J* = 8.75Hz), 7.48 (d, 1H, *J* = 16.89Hz)

^{13}C NMR (500 MHz, $CDCl_3$): δ 21.3, 27.3, 126.2, 128.2(2C), 129.6(2C), 131.7, 140.8, 143.3, 198.0

Analysis calcd for $C_{11}H_{12}O$ (160.215): Found C, 82.52; H, 7.67{Required C, 82.46; H, 7.55}

2-Methoxy-5-(3-oxo-but-enyl)-benzoic acid methyl ester (49l)



49l

Yield: 65%

Colorless Oil

IR ($CHCl_3$, cm^{-1}): ν_{max} 3412, 2482, 1719, 1599, 1548, 1467, 1391, 1271

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H), 3.87 (s, 6H), 6.74 (d, 1H, *J* = 8.74 Hz), 7.22 (dd, 1H, *J* = 7.94Hz, 16,29Hz), 7.47 (d, 1H, *J* = 8.75Hz), 7.71(dd, 1H, *J* = 2.38Hz, 8.74 Hz), 8.06 (s, 1H)

^{13}C NMR (500 MHz, $CDCl_3$): δ 14.2, 52.0, 56.1, 112.3, 117.1, 120.5, 126.4, 131.3, 132.9, 142.9, 160.3, 165.9, 166.8

Analysis cacld for $C_{13}H_{14}O_4$ (234.25): Found C, 66.57; H, 5.96{Required C, 66.65; H, 6.02}

3.3.1.6 Spectra

1. ^{1}HNMR spectrum of 47b

2. ^{13}CNMR spectrum of 47b

3. ^{1}HNMR spectrum of 47g

4. ^{13}CNMR spectrum of 47g

5. ^{1}HNMR spectrum of 47e

6. ^{1}HNMR spectrum of 47q

7. ^{13}CNMR spectrum of 47e

8. ^{13}CNMR spectrum of 47q

9. ^{1}HNMR spectrum of 49b

10. ^{13}CNMR spectrum of 49b

11. ^{1}HNMR spectrum of 49c

12. ^{13}CNMR spectrum of 49c

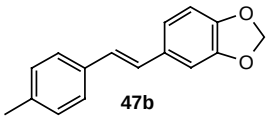
13. ^{1}HNMR spectrum of 49g

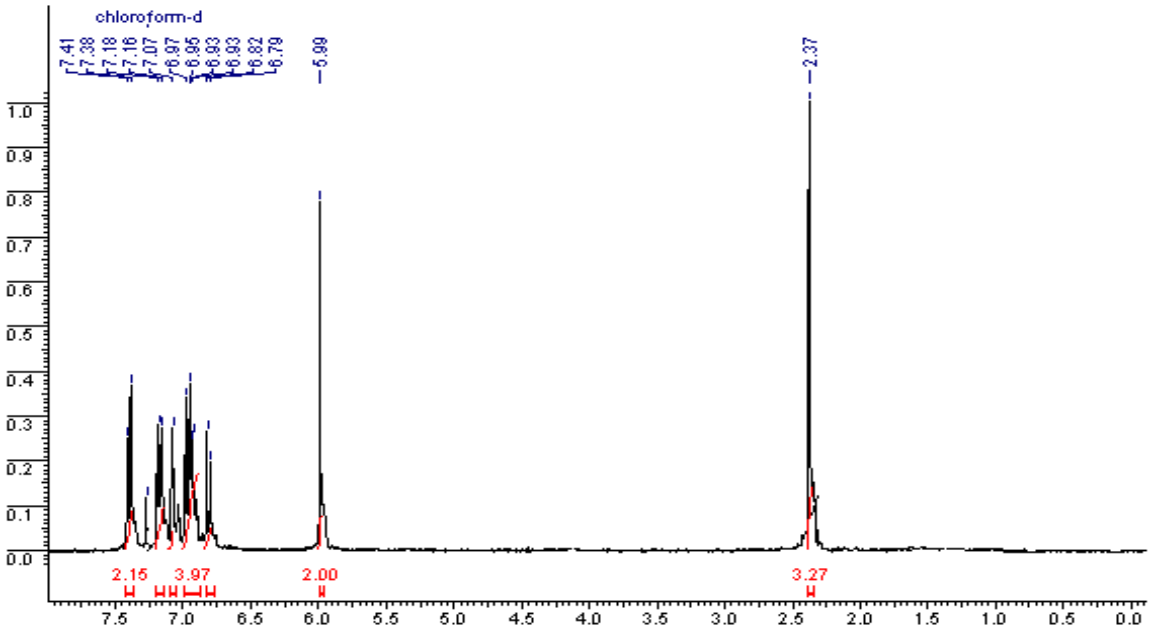
14. ^{13}CNMR spectrum of 49g

15. ^{1}HNMR spectrum of 49l

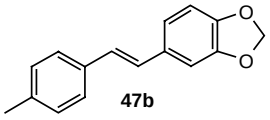
16. ^{13}CNMR spectrum of 49l

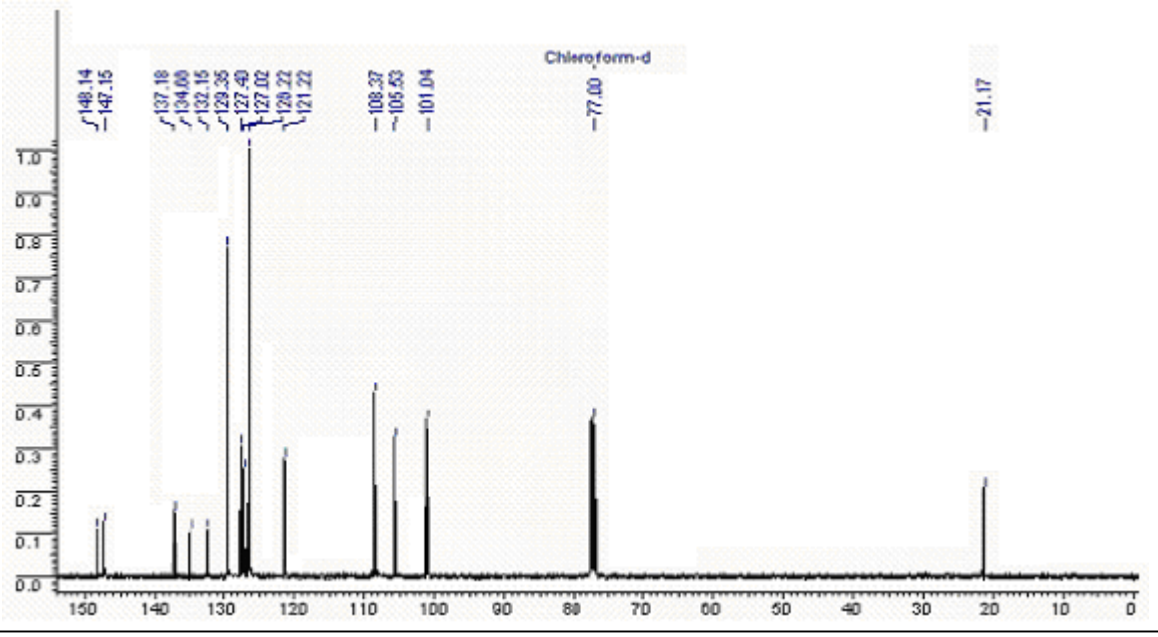
^{1}HNMR spectrum of **47b**



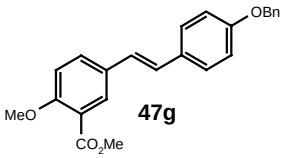


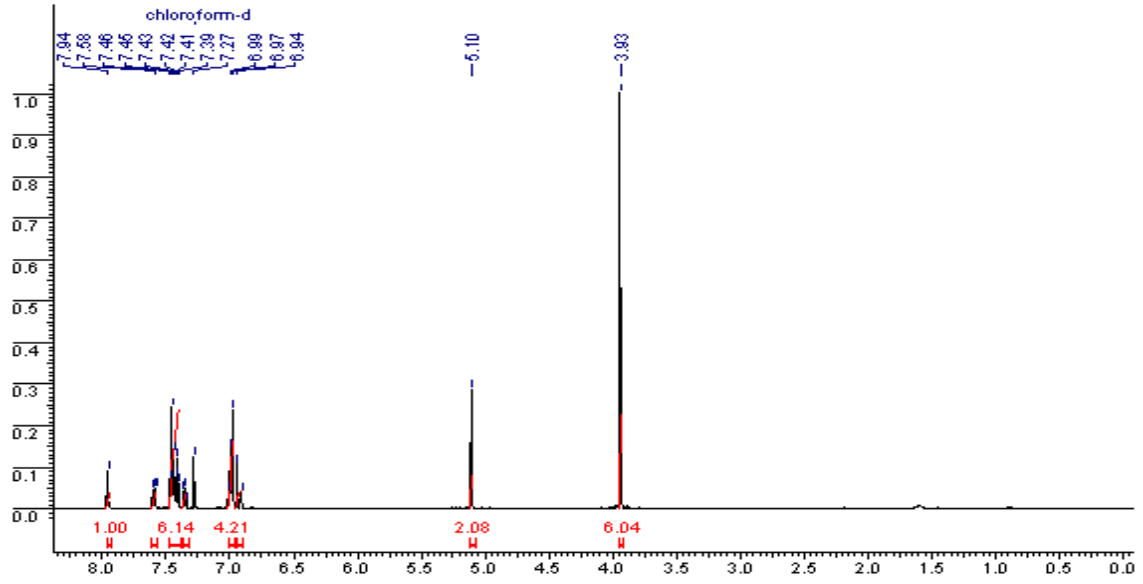
^{13}CNMR spectrum of **47b**



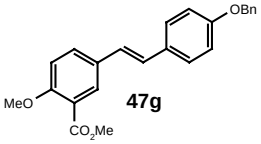


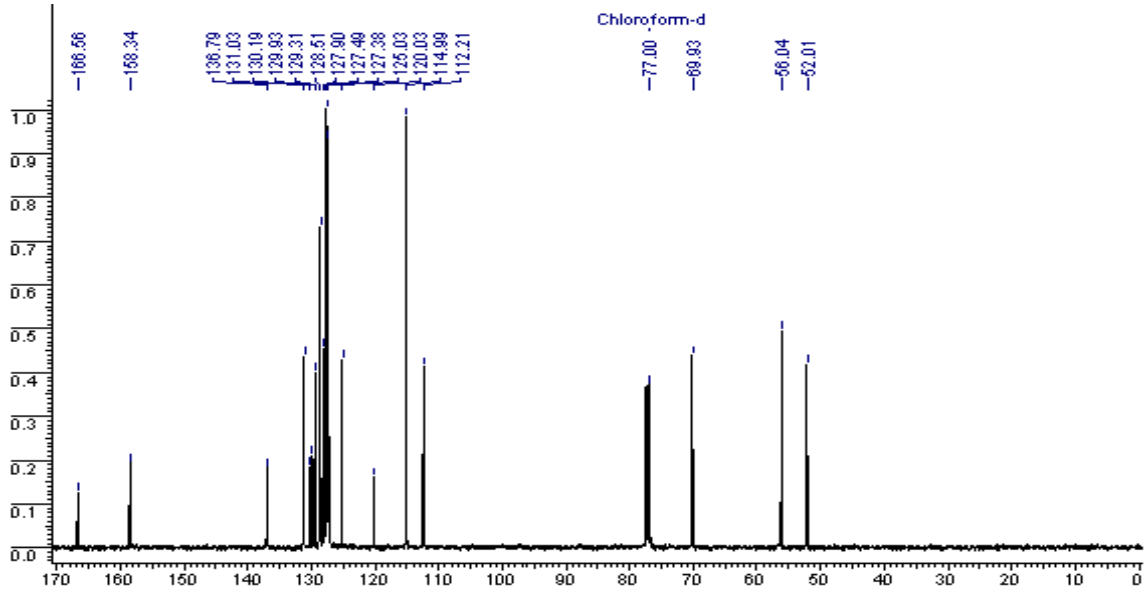
^{1}HNMR spectrum of **47g**

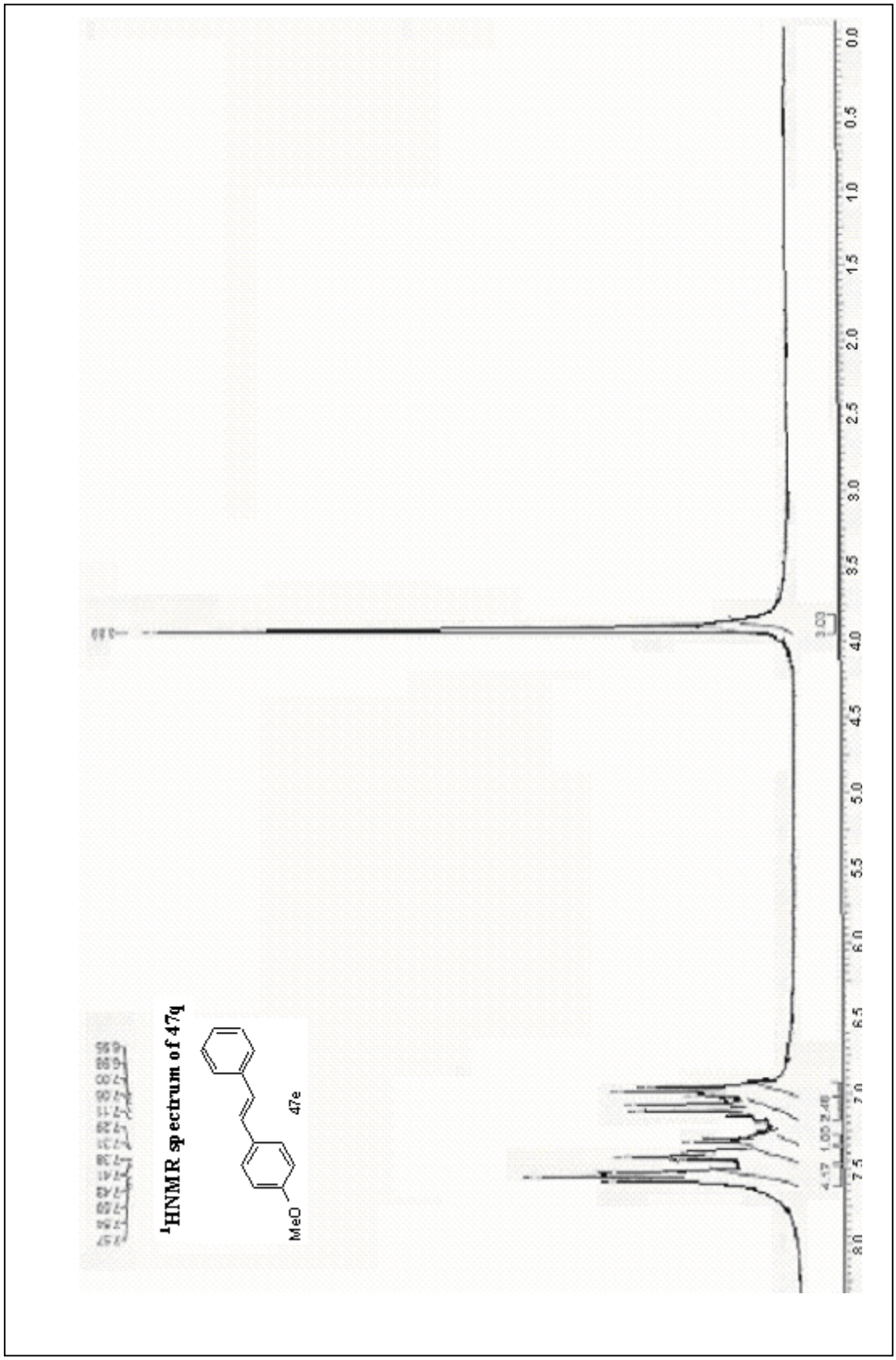


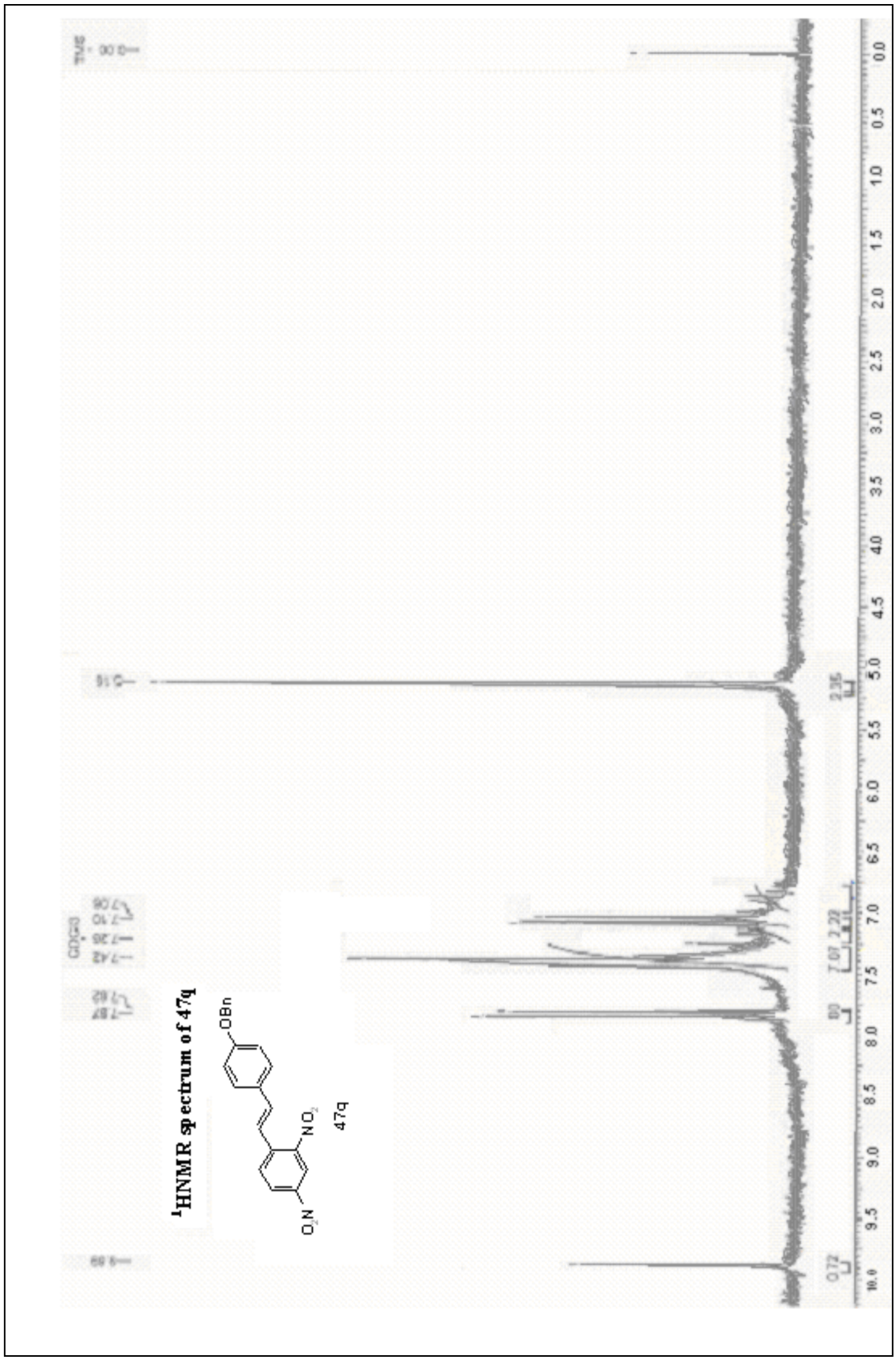


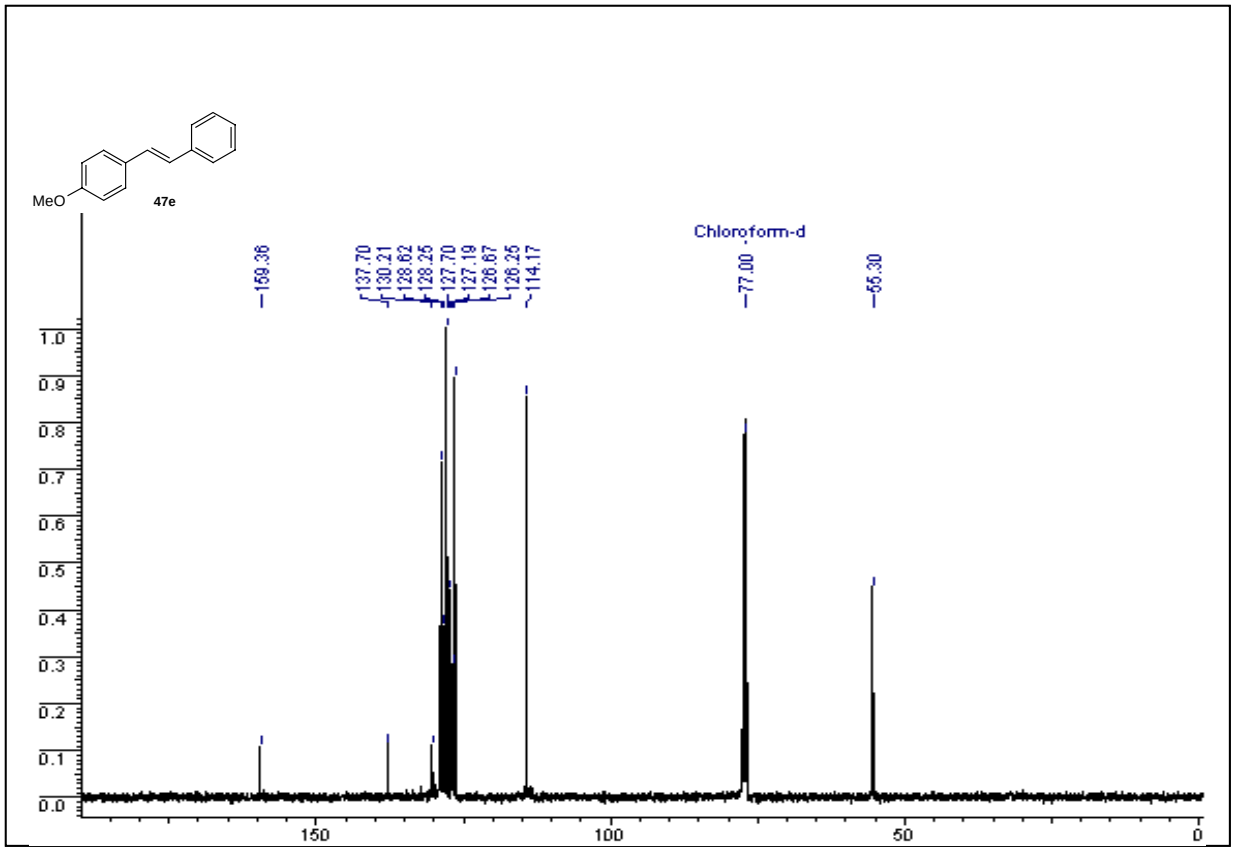
^{13}CNMR spectrum of **47g**

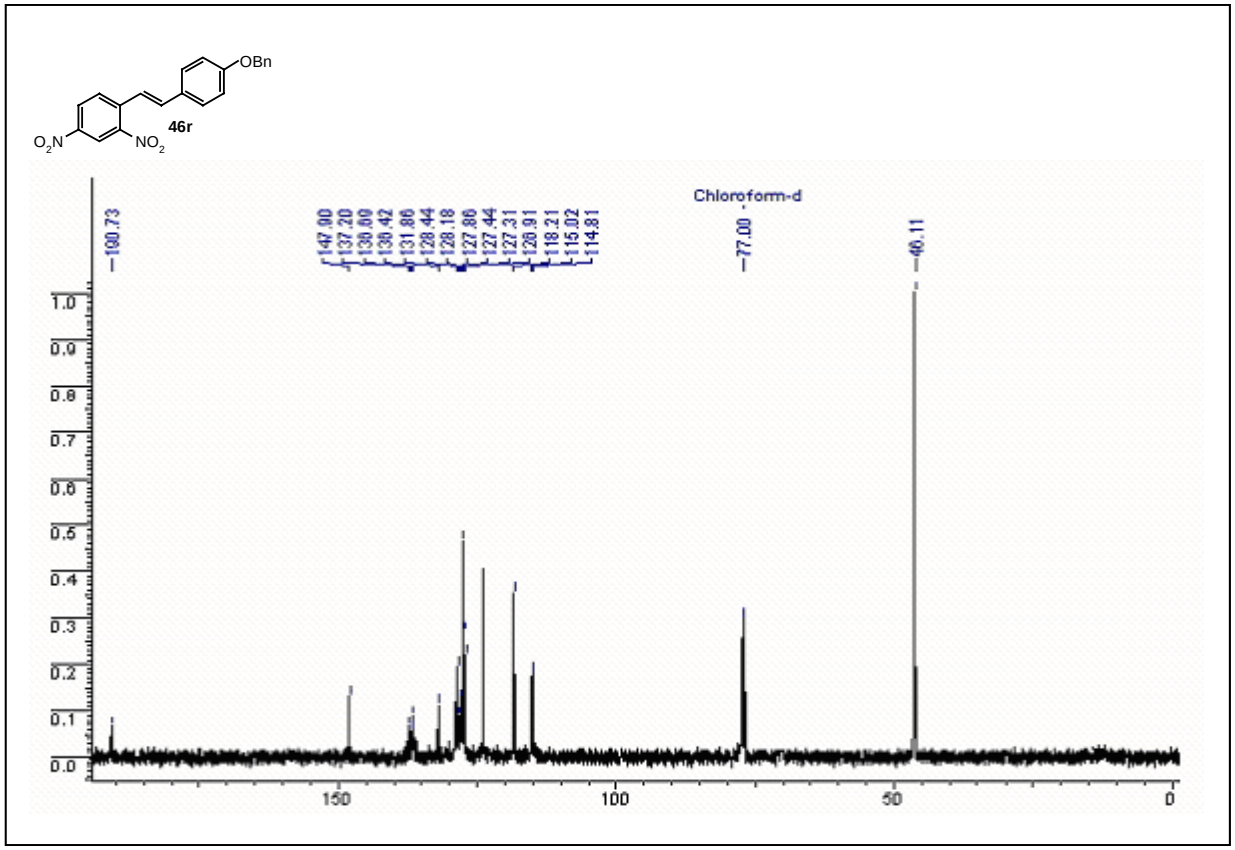




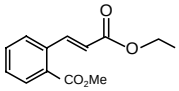

^{1}HNMR spectrum of 47q
MeO
47e


^{1}HNMR spectrum of 47q
OBn
NO$_2$
O$_2$N
47q
CDCl3
TMS

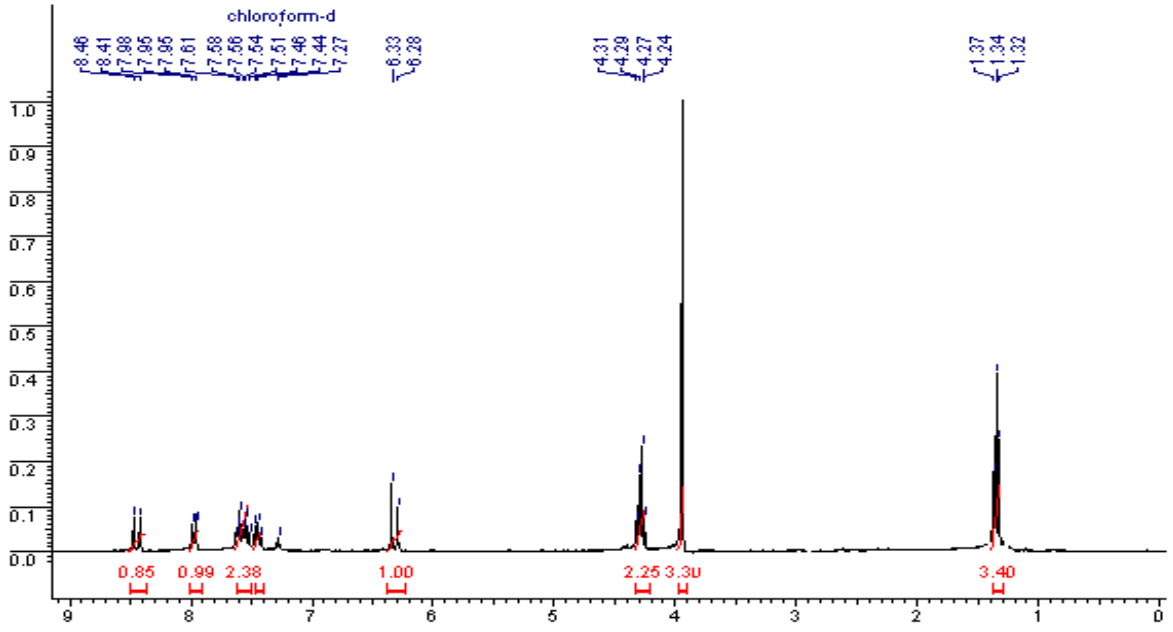

MeO
47e
Chloroform-d
159.36
137.70
130.21
128.62
128.25
127.70
127.19
126.67
126.25
114.17
77.00
55.30
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
150
100
50
0


OBn
O2N
NO2
46r
Chloroform-d
190.73
147.90
137.20
136.80
136.42
131.86
128.44
128.18
127.86
127.44
127.31
126.91
118.21
115.02
114.81
77.00
46.11
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
150
100
50
0

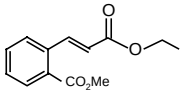
^{1}HNMR spectrum of **49b**



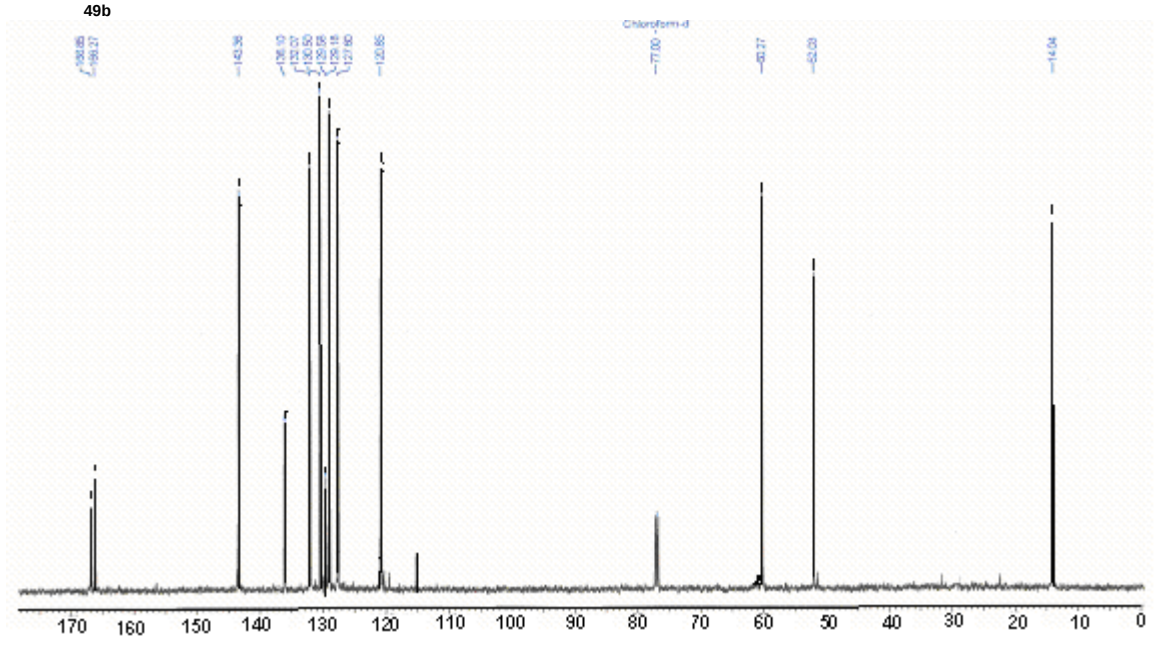
49b



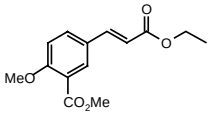
^{13}CNMR spectrum of **49b**



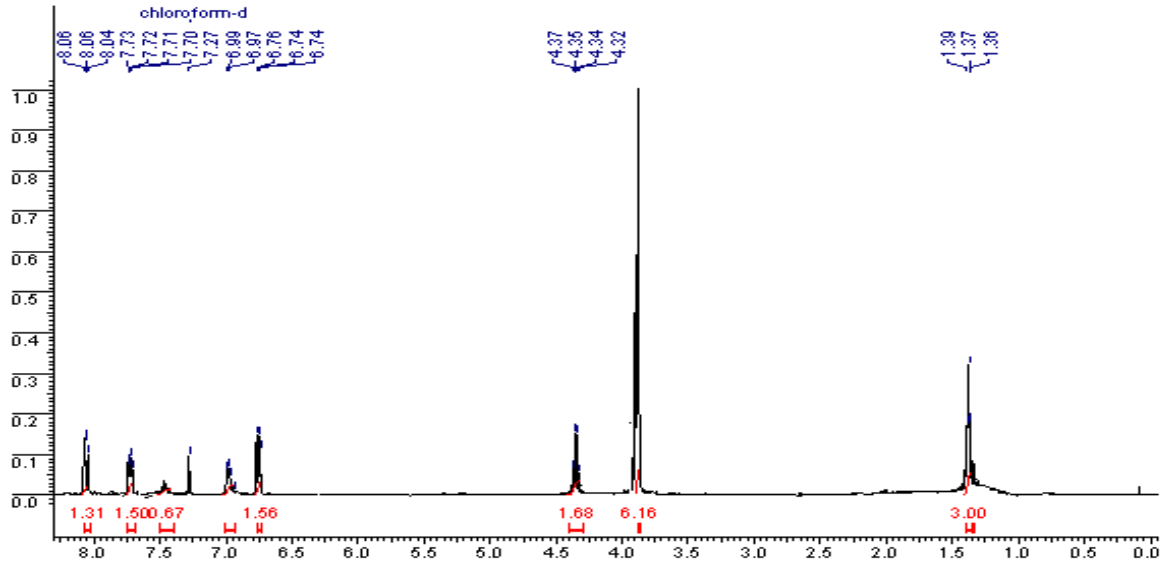
49b



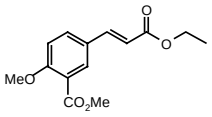
^{1}HNMR spectrum of **49c**



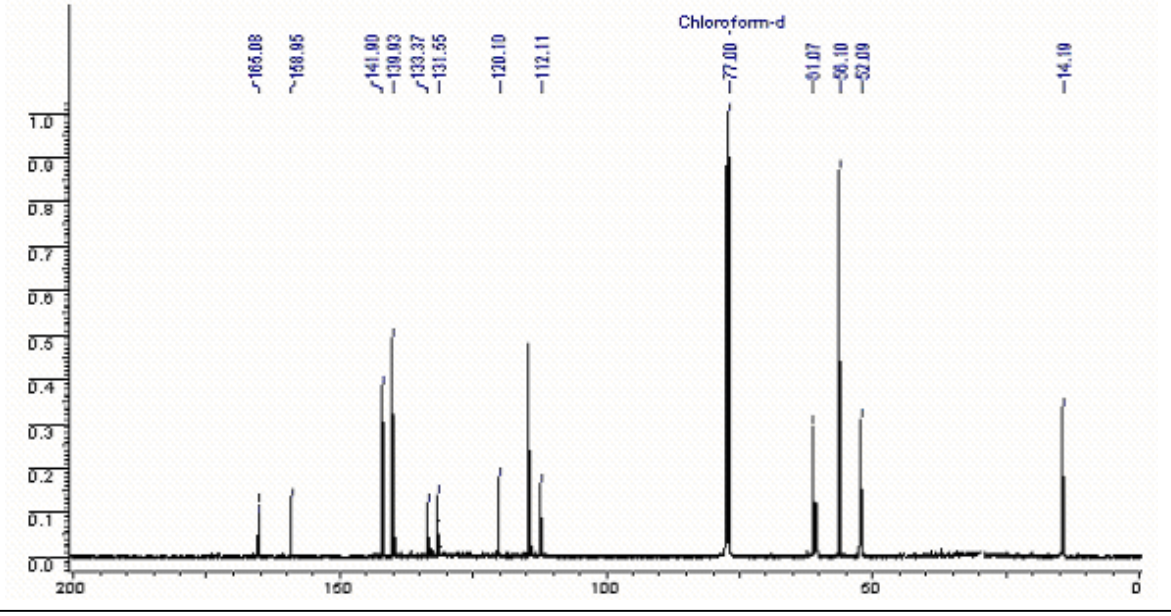
49c



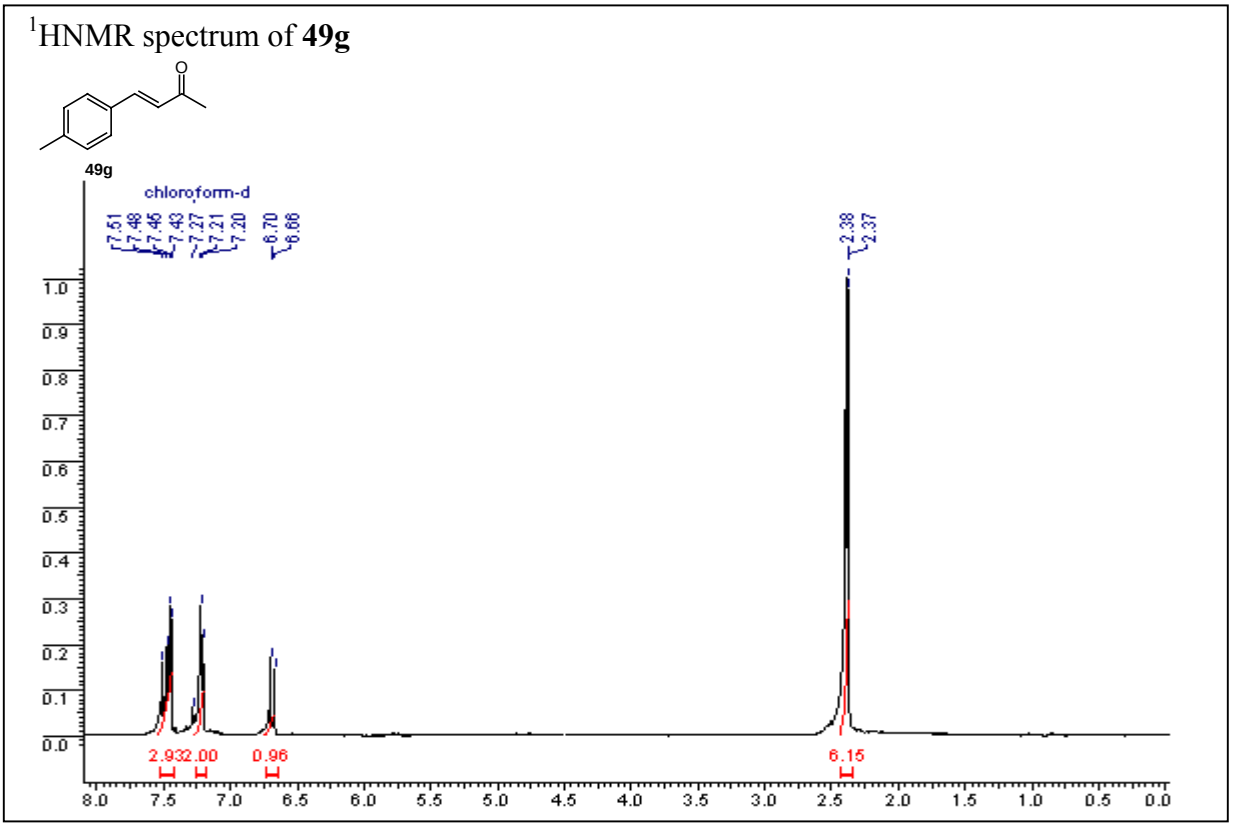
^{13}CNMR spectrum of **49c**



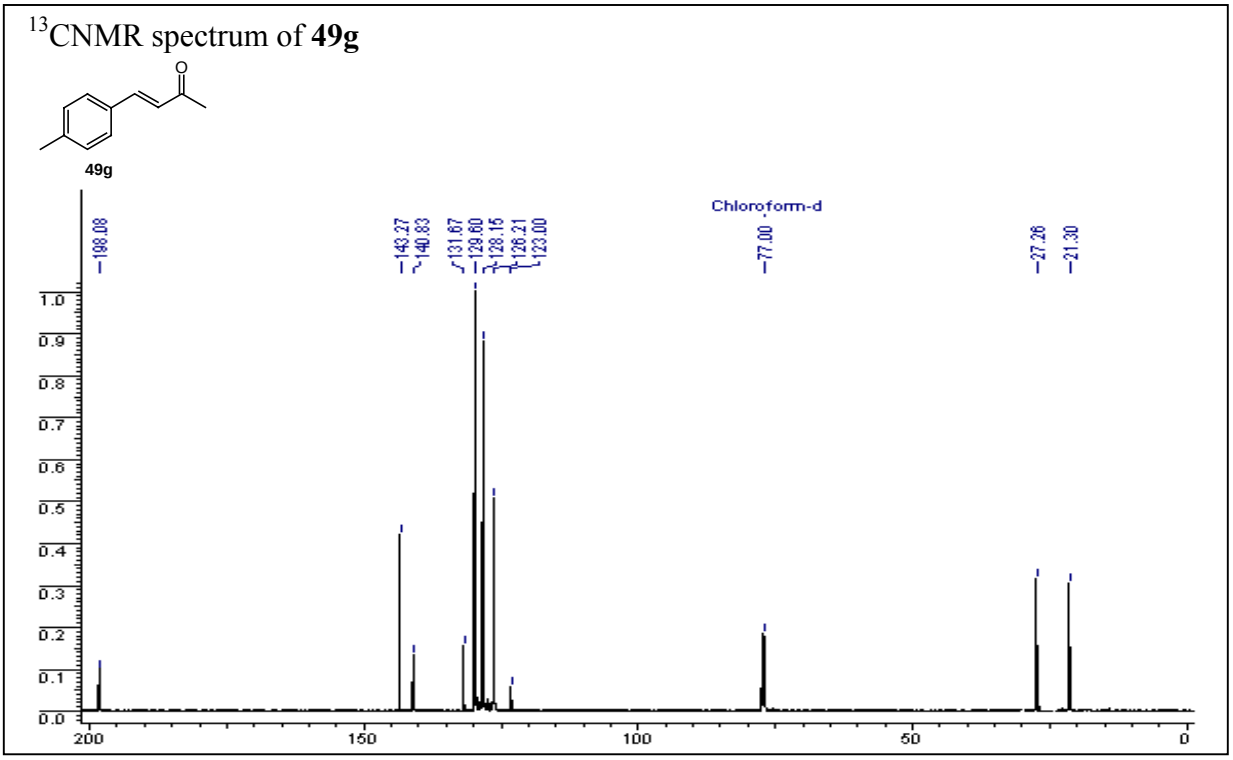
49c



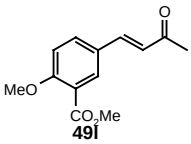
^{1}HNMR spectrum of **49g**



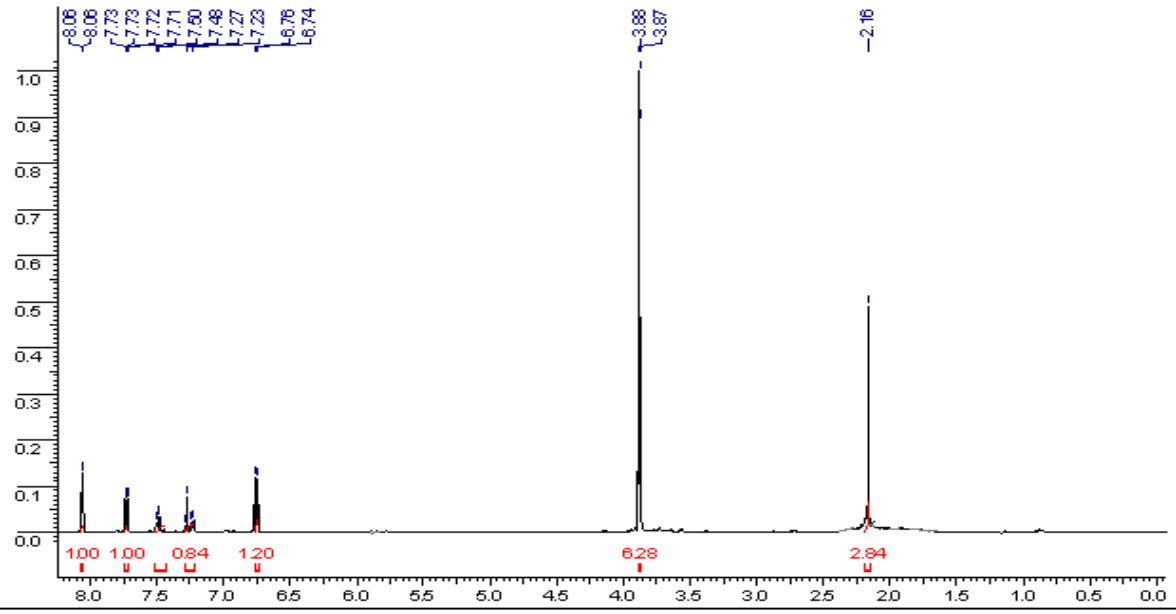
^{13}CNMR spectrum of **49g**



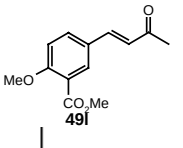
^{1}HNMR spectrum of **49l**



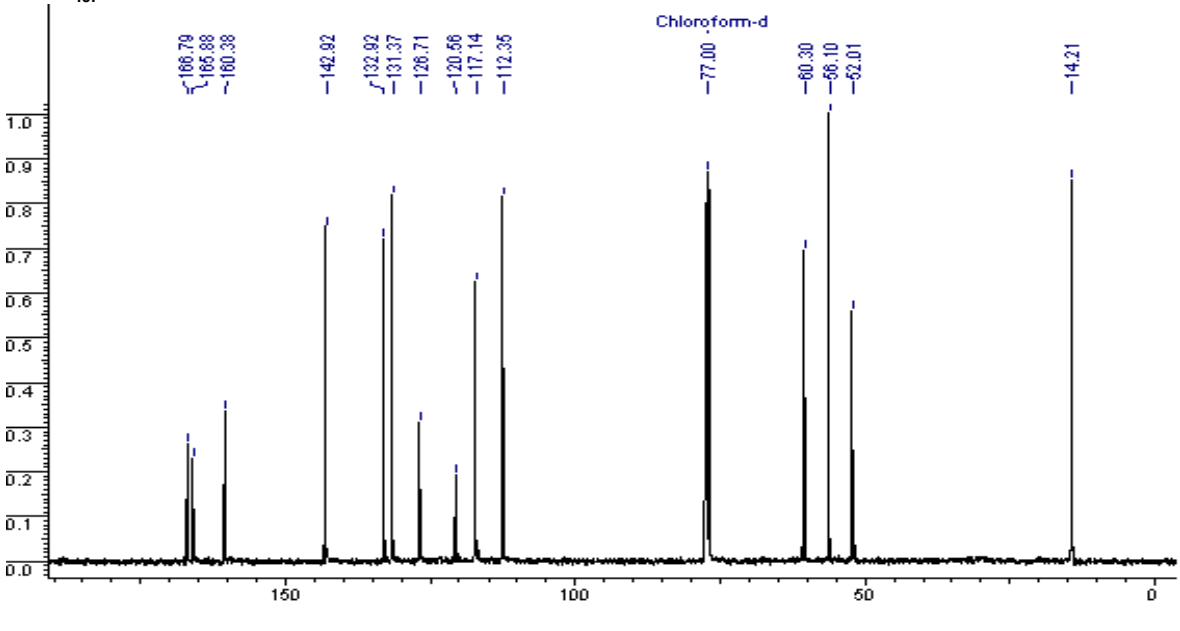
49l



^{13}CNMR spectrum of **49l**



49l



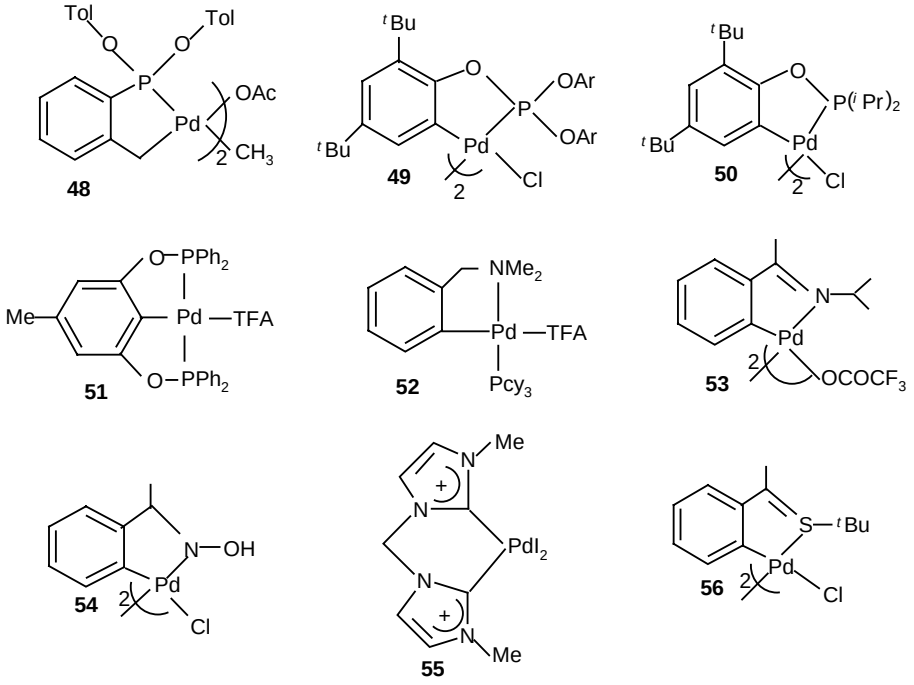
3.3.2 Part II
Carbometallated Palladacycle, Pd-OMS(MCM-41) catalyzed Suzuki-Miyaura coupling

3.3.2.1 Introduction

The Suzuki-Miyaura coupling, the palladium-catalyzed cross-coupling of Sp^2 hybridised halides, triflates, N_2BF_4, BF_3K, sulfonates with Sp^2 hybridised boronic acids or their esters, is one of the most important, and versatile tools for the synthesis of biaryls and liquid crystals.[76] Its tolerance to a wide range of functional groups on both substrates extended its scope to wide variety of biologically active compounds. The ease of separation of the non-toxic boron containing reaction byproduct from the desired product has ensured that the reaction has found extensive use in the pharmaceutical industry.

There are many masterful reviews available to cover Suzuki-Miyaura coupling upto 1998.[77] Kotha and co-workers[78] reviewed the recent development in Suzuki coupling from 1999 to late 2001. During the last 5 years, a number of advances have taken place with reference to the catalyst development. In recent years trends were directed towards the development of catalyst to use the electronically rich aryl halides, particularly aryl chlorides. Among this some catalyst were developed on the basis of anchoring of homogeneous system on the solid support to make heterogeneous catalyst.[79] Recently Ganesan and co-workers[80] have reported ionic liquid accelerated solid-phase Suzuki-Miyaura coupling reactions. Tertiary phosphane ligands based on phospha-adamantane framework for Suzuki-Miyaura coupling was reported by Alfredo Capretta and co-workers.[81] Air stable planar chiral ferrocenyl monophosphine ligand for Suzuki Miyaura coupling reactions were reported by Johannsen and co-workers.[82] Wu Yang and co-workers[83] regioselectively synthesized 2-aryl-6-chloronicotinamides via $PXPd_2$ catalyst. Hollis[84] and co-workers used imidazolylbenzene based bidentate carbenes in Suzuki-Miyaura coupling reaction. Chan *et al*.[85] explored ionic liquids as soluble support for Suzuki-Miyaura coupling. Fu and co-workers[86] reported the Suzuki-Miyaura coupling of electronically deactivated aryl chloride using air and moisture stable triaryl phosphine based catalyst. Ley *et al.*[87] have reported palladium-containing perovskities for Suzuki-Miyaura coupling of aryl bromides. Arentsen and co-workers[88] reported palladium/imidazolium salt protocols for Suzuki-Miyaura coupling of aryl chlorides.

There were many palladacyclic catalyst developed for Suzuki-Miyaura coupling of deactivated aryl chlorides. In 1995, Beller and co-workers[89] reported the use of metallated tris (2-methylphenyl) phosphine palladium (II) **48** as an efficient catalyst for the Suzuki Miyaura cross coupling reaction. Bedford and co-workers[90] later prepared the ortho-metallated Pd (II) triarylphosphite complex **49** which proved to be an extremely active catalyst for the Suzuki-Miyaura cross-coupling reaction, giving very high TON of 100000 at 110°C. The complex **48** gave a TON of 74000 at a higher temperature of 130°C over 16 h. The complex **49** showed an extremely high activity with both electronically activated and deactivated aryl bromides, considerably higher than the activity reported for **48**.



Palladacyclic phosphinite complexes of the type[91] **50** and **51** are suitable catalysts for the coupling of deactivated and sterically hindered aryl bromides, as they are comparatively inexpensive, easily synthesized and give high conversions at extremely low concentration of the catalyst. The low-cost tricyclohexylphosphine adduct of a Pd complex with an ortho-metallated N-donor ligand **52**[92] showed the highest activity in Suzuki-Miyaura coupling of aryl chlorides, regardless of whether the substrates are electron-rich or electron-poor. An additional high activity was observed with the catalyst formed in situ and when the reaction was carried out in the air. The phosphine free-imine complex **53,**[93] the oxime palladacycle

54,[94] and the imidazole palladacycle **55,**[95] are excellent catalyst for the Suzuki-Miyaura reaction leading to a high TON (100-1000000) with unactivated aryl bromides. The catalyst is both air and thermally stable. The sulfur containing palladacycle **56**[96] stable to air and water, can be prepared easily and that promotes effectively the Suzuki-Miyaura coupling of aryl bromides and chlorides at room temperature in excellent isolated yield (>90%) to give the biaryl products. However for reactions involving electron-rich and electron-neutral aryl chlorides, only low conversions, was observed even at high temperatures. The phosphine-free palladacycle **56** can also efficiently promote the cross-coupling reactions with sterically demanding substrates. The most efficient catalyst precursor generally contains one *t*-BuS moiety bonded to the Pd atom and a lower concentration of the palladacycle catalyst could be employed, leading to a TON of 37,000. The use of $n Bu_4N^+Br^-$ as a promoter increases the cross-coupling product. Najera and co workers[97] again reported, a new palladium-dipyridylmethylamines complex for the SM coupling of non activated aryl chloride.

3.3.2.2 Result and discussion

In this section we have investigated the, carbometallated Pd-OMS(MCM-41) catalyzed Suzuki Miyaura coupling of aryl halides. In a typical experimental procedure, 4-bromoanisole (0.157 g, 1 mmol) was treated with phenylboric acid (0.146g, 1.2 mmole), in the presence of K_2CO_3 (0.1932g, 1.4 mmol) and Pd-OMS5 catalyst (0.034g, 0.2 mmole) in 5mL of DMF/H_2O (98: 2) and stirred at 120°C for the indicated length of time. The reaction was monitored by GC analysis. The usual workup gave 173 mg of product (94%).

Initial investigations were focused on screening of solvents and it is found that DMF, methanol, ethanol with some amount of water were effective (anhydrous DMF or alcohol requires the temperature above 140^{o}C) at 120^{o}C under these conditions, for the coupling of aryl bromides and aryl iodides in the presence of 0.02 mol% catalyst and K_2CO_3 as base (K_3PO_4 and Cs_2CO_3 were also effective) proceeded smoothly to afford the requisite biaryls in high yields (Table 9). The addition more than 2% of water of water causes the catalyst deactivation. The catalyst can be removed from the reaction mixture by simple filtration or by decantation. Aryl iodides with both electron donating and electron withdrawing groups were successfully used in Suzuki- Miyaura coupling using this catalyst. Bromides with electron donating or electron with drawing groups were successfully coupled with boronic acid to give

biaryls. Substitution in the ortho position of aryl halides and boronic acid were tolerated without any undue increase in the reaction time or decrease in yields. To evaluate the real check of the catalyst activity, the reaction was carried out with 2-nitrochlorobenzene and phenylboronic acid at different temperature using K_2CO_3 as base in DMF/H_2O (98: 2) as solvent, at 120°C, however there was no traces of product formed. When the reaction temperature raised above 140°C, only trace of product was formed but when the reaction was carried out under identical condition with addition of TBAB, the reaction rates increased along with yield. Reaction with 4-acetyl-chlorobenzene, 4-nitro-chlorobenzene, 4-chloroanisole were carried out smoothly with addition of TBAB. The reaction with 4-chlorotoluene failed to give the required product. 4-Chlorobenzaldehyde was used successfully in Suzuki-Miyaura coupling at elevated temperature (at 140^0C) with TBAB.

In the case of aryl iodides and activated aryl bromide, the reaction proceeded smoothly even at low catalyst loading (0.15 mmol). But with electronically deactivated aryl bromides and aryl chloride, the catalyst loading has to be increased to 0.3 mmol. The catalyst recovered from aryl iodide and bromide (activated aryl halide) as substrates, can be recycled for 2 times but in the case of aryl chloride, the catalyst was found to be deactivated with higher temperature. Higher TON of 317800 was achieved with catalyst loading of 0.048 mol% in the case of reaction of 4-nitrobromobenzene with phenylboronic acid. The other activated aryl bromides also gave reasonable TON.

A variety of aryl iodides, aryl bromides and aryl chloride (electronically activated and neutral) were treated with phenylboronic acid and 4-methoxyphenylboronic acid in the presence of Pd-OMS(MCM-41) catalyst, K_2CO_3, in DMF at 140^oC to afford the corresponding biphenyl compounds in good to excellent yields, and the results obtained are summarized in **Table 9**. Thus when 4-iodotoluene was treated with phenylboronic acid in the presence of Pd-OMS(MCM-41), it gave the corresponding biphenyl in 78% yield (**Table 9**, **59a**). The ^{1}H NMR spectrum of **59a** showed a singlet at δ 2.46 for the CH_3 protons. The aromatic protons appeared at δ 7.31 (d), 7.56 (dd), 7.65 (dd) corresponding to nine protons. The ^{13}C NMR spectrum showed signal at δ 21.0 for CH_3 carbon. The quarternary carbon appeared at δ 136.9, 138.3, 141.1. The other aromatic carbons were seen at δ 126.9, 128.7, 129.4. The molecular ion peak at 168 in the mass spectrum of **59a** confirmed the formation of the

biphenyl compounds. A noteworthy feature of this methodology is aryl iodides with both electron withdrawing and electron donating groups (Table **9**, entry **3**, **4**, **7** and **14**) and ortho substituted aryl chlorides reacted to give product with moderate to good yield. 4-Chlorobenzadehyde reacted with phenylboronic acid to give the corresponding biphenyl. Aryl iodides and aryl bromides with electron withdrawing groups reacted faster and took less reaction time than the aryl bromides with electron-donating groups and aryl chlorides.

3.3.2.3 Conclusion

n conclusion we have developed a method for the synthesis of biphenyls catalyzed by Pd-OMS(MCM-41) catalyst using Suzuki-Miyura coupling. Aryl halides (with X=I, Br, Cl) were used to couple with phenylboronic acid to give the corresponding biphenyl in good yields. The catalyst was successfully applied to both electronically rich or poor systems, in the case of aryl iodides and aryl bromides. Aryl chlorides having electron withdrawing groups (-NO_2, -$COCH_3$) were successfully cross coupled using Pd-OMS(MCM-41) catalyst. Unactivated aryl chlorides (Table 9, entry 14, 15), were also coupled to give the Suzuki-Miyaura cross coupled product.

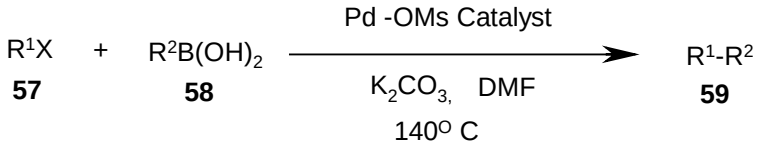
3.3.2.4 Experimental Section

General Procedure for the Suzuki-Miyaura cross coupling reactions (using Pd-OMS (MCM-41) catalyst:

Preparation of biphenyls: A slurry of aryl halide (1mmol), aryl boronic acid (1.2mmol), K_2CO_3 (1.4 eq) and 0.24 mol% of the palladium catalyst Pd-OMS(MCM-41) was stirred at 120^o C for the indicated duration of time (Table 9). The reaction was monitored by GC and TLC analysis. After completion of the reaction, the catalyst was filtered and washed thoroughly with diethyl ether. The filtrate was washed with water and brine solution and dried over anhy. Na_2SO_4. Removal of solvent followed by silica gel column chromography using petroleum ether: EtOAc(95:5), as eluent afforded the pure biphenyl 59 which was analyzed by IR, ^1H, ^{13}C-NMR and Mass spectra and elemental analysis.

Table 9: PdOMS (MCM-41) Catalyzed Suzuki cross coupling reaction

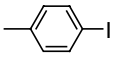
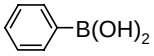
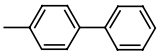
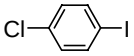
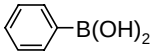
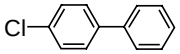
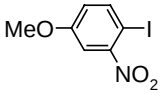
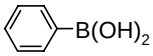
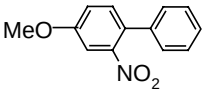
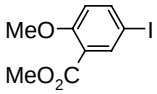
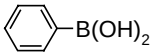
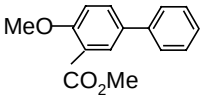
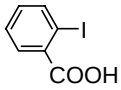
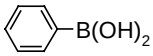
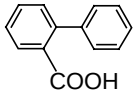
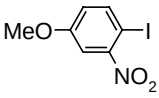
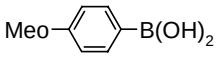
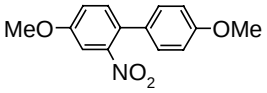
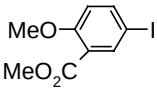
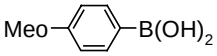
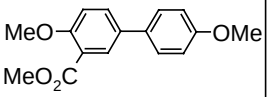
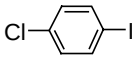
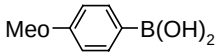
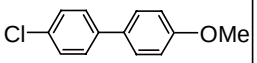
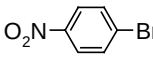
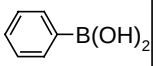
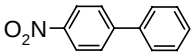
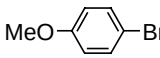
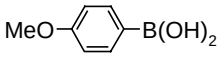
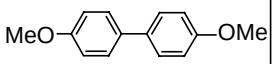
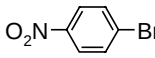
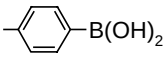
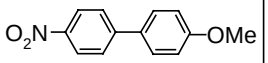
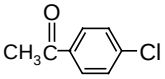
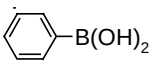
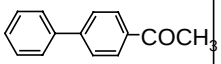
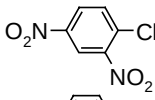
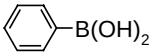
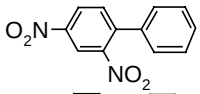
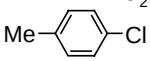
Scheme - 4



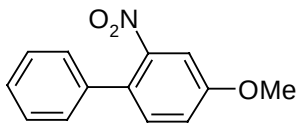
R^1 = Aromatics, Substituted aromatics

R^2 = Aromatics, Substitued aromatics

X = I, Br, Cl

Entry	Aryl halides	Boronic acid	Product	Product number	Reaction Time(h)	Yield in %	Ton
1				**59a**	10	78	116000
2				**59b**	12	84	131400
3				**59c**	13	89	108500
4				**59d**	15	96	91900
5				**59e**	15	36	12400
6				**59f**	14	91	107800
7				**59g**	15	93	170900
8				**59h**	28	28	99700
9				**59i**	12	92	115500
10				**59j**	15	92	317800
11				**59k**	17	88	96000
12				**59l**	24	66	27500
13				**59m**	23	61	31200
14				**59n**	28	58	10300
15				**59o**	31	48	5400
16				**59p**	36	42	9500

4-Methoxy-2-nitrobiphenyl (59c)



59c

Yield: 89%

Light brown solid

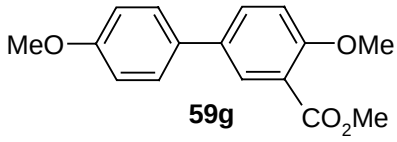
IR ($CHCl_3$, cm^{-1}): ν_{max} 3427, 1492, 1452, 1341, 1257, 1171

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.81 (s, 3H), 7.06 (dd, 1H, *J* = 2.75Hz, 8.24Hz), 7.20 (d, 2H, *J* = 6.42Hz), 7.26 (d, 1H, *J* = 8.21Hz), 7.28-7.35 (m, 4H)

^{13}C NMR (125MHz, $CDCl_3$): δ 55.8, 109.0, 118.4, 127.7, 127.9(2C), 128.4(3C), 132.6 137.2, 149.5, 159.0

Analysis calcd for $C_{13}H_{11}NO_3$ (229.23): Found C, 68.32; H, 4.91; N, 6.19{Required C**,** 68.12; H, 4.83; N, 6.19}

4, 4'-Dimethoxybiphenyl-3-carboxylic acid methyl ester (59g)



59g

Yield: 93%

Colorless Solid

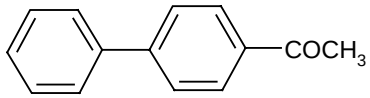
IR ($CHCl_3$, cm^{-1}): ν_{max} 3431, 3392, 3015, 1713, 1555, 1498, 1355, 1255, 1211, 1192

^{1}H NMR (300MHz, $CDCl_3$): δ 3.84 (s, 3H), 3.90(s, 3H), 3.93 (s, 3H), 6.93 (d, 2H, *J* = 8.79Hz), 7.12 (dd, 1H, *J* = 2.75Hz, 8.25Hz), 7.48 (d, 2H, *J* = 5.79Hz), 7.65 (dd, 1H, *J* = 3 Hz, 9 Hz), 8.00 (s, 1H)

^{13}C NMR (500 MHz, $CDCl_3$): δ 51.8, 55.1, 56.0, 112.5, 114.2(2C), 120.2, 127.6(2C), 129.6, 131.3, 132.2, 132.9, 158.0, 159.0, 166.6

Analysis calcd for $C_{16}H_{16}O_4$ (272.29): Found C, 70.65; H, 5.68{Required C, 70.58; H, 5.92}

4-Acetyl-biphenyl (59l)



59l

Yield: 66%

Colorless Solid

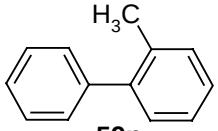
IR ($CHCl_3$, cm^{-1}): ν_{max}3012, 1673, 1515, 1492, 1357, 1211, 1187, 1092

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55 (s, 3H), 7.16 (t, 1H, *J* = 7.33Hz), 7.36(t, 2H, *J* = 7.34Hz), 7.53(d, 2H, *J* = 7.33Hz), 7.58 (d, 2H, *J* = 7.79Hz), 7.93 (d, 2H, *J* = 7.79Hz)

^{13}C NMR (125MHz, $CDCl_3$): δ 26.5, 127.2(4C), 128.2(2C), 128.9(3C), 135.9, 139.8, 145.7, 197.6

Analysis cacld for $C_{14}H_{12}O$ (196.248): Found C, 85.73; H, 6.24{Required C, 85.68; H, 6.16}

2-Methyl-biphenyl (59p)



59p

Yield: 42%

Colorless Solid

IR ($CHCl_3$, cm-1): ν_{max} 3023, 1562, 1495, 1465, 1401, 1352, 1262, 1105

^{1}H NMR (300MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.13-7.17 (m, 3H), 7.25(dd, 2H, *J* = 2.79Hz, 8.79Hz), 7.35 (dd, 2H, *J* = 2.79Hz, 7.31Hz), 7.49 (t, 1H, *J* = 5.75Hz), 7.61(d, 1H, *J* = 5.75Hz)

^{13}C NMR (300MHz, $CDCl_3$): δ 30.1, 126.5(2C), 127.1, 128.70, 129.0(3C), 130.9(3C), 134.4, 136.0

Analysis calc for $C_{13}H_{12}$ (168.23): Found C, 92.69; H, 7.05 {Required C, 92.81; H, 7.19}

3.3.2.5 Spectra

1.^{1}HNMR spectrum of 59c

2.^{13}CNMR spectrum of 59c

3. ^{1}HNMR spectrum of 59f

4. ^{13}CNMR spectrum of 59f

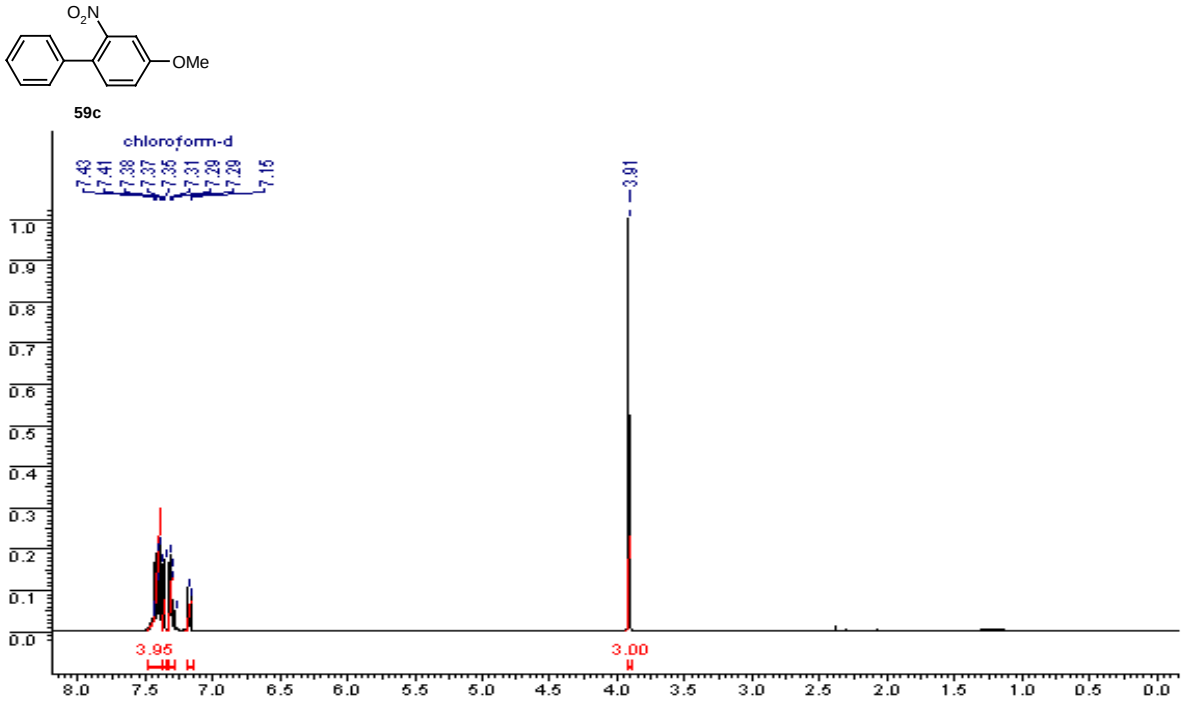
5. ^{1}HNMR spectrum of 59l

6. ^{13}CNMR spectrum of 59l

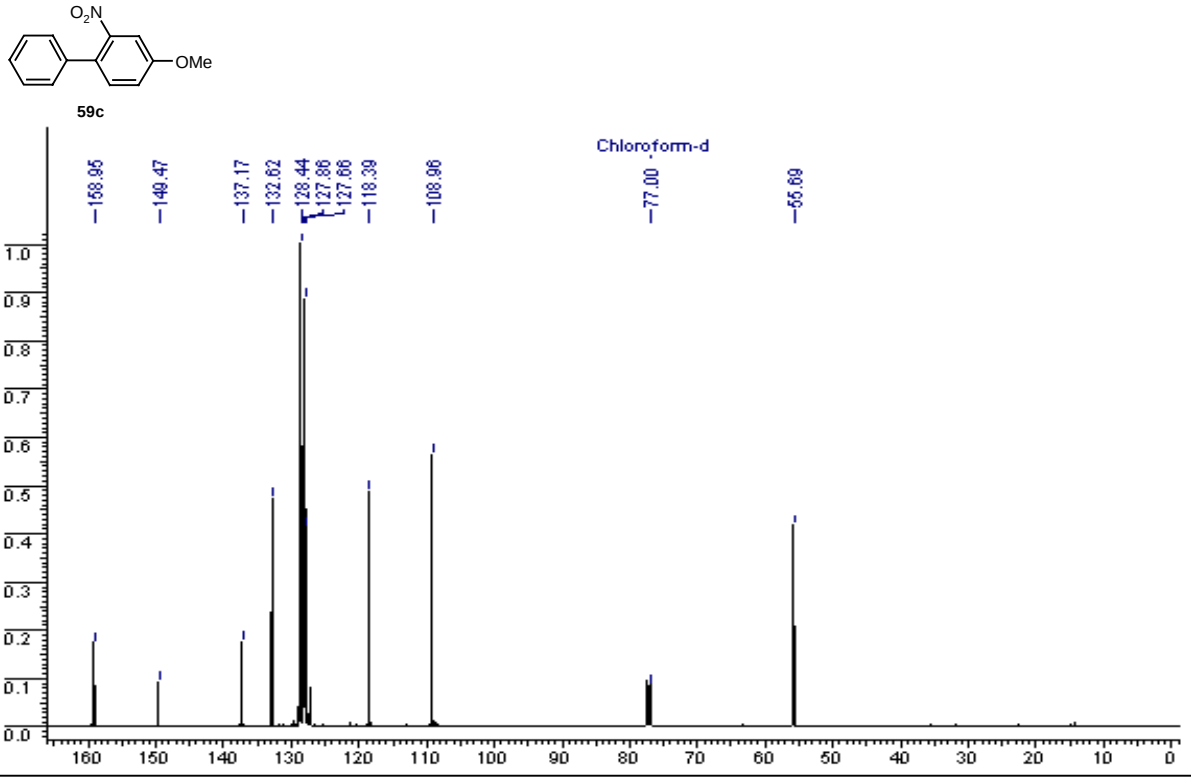
7. ^{1}HNMR spectrum of 59p

8. ^{13}CNMR spectrum of 59p

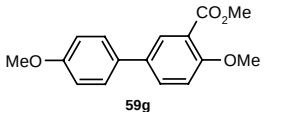
^{1}HNMR spectrum of **59c**



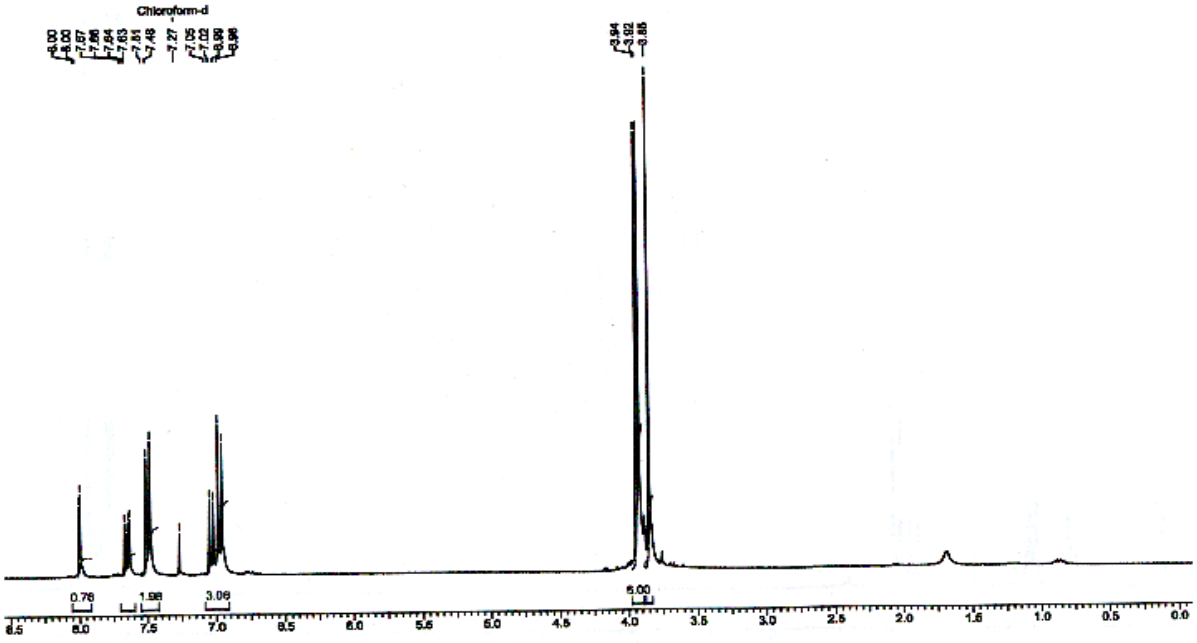
^{13}CNMR spectrum of **59c**



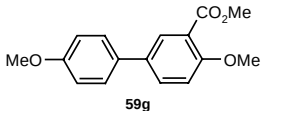
^{1}HNMR spectrum of **59g**



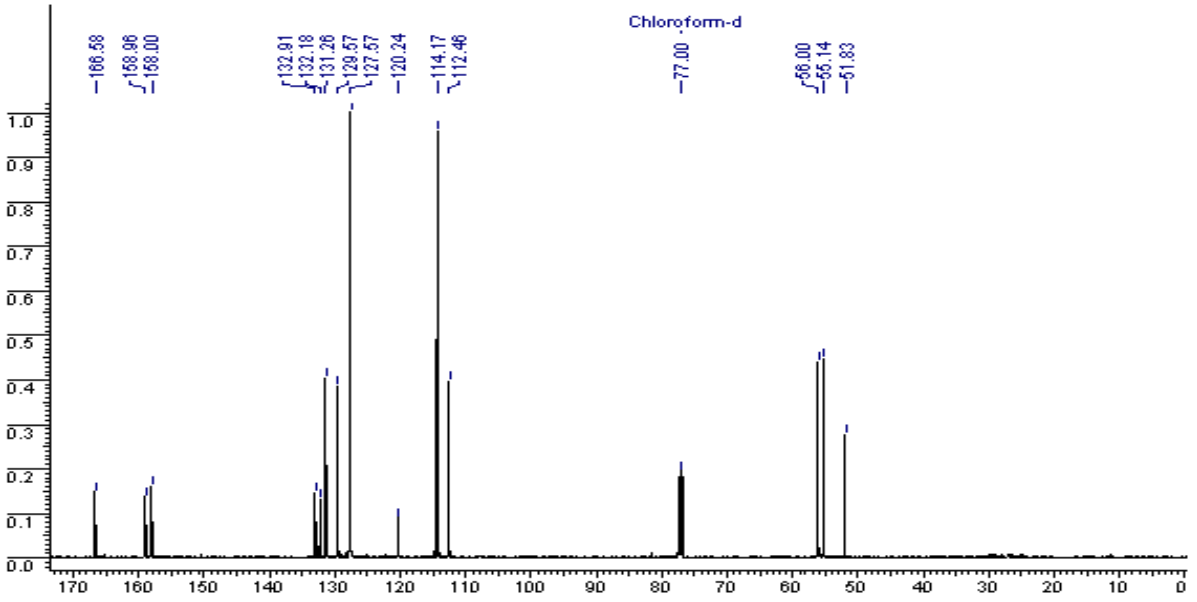
59g



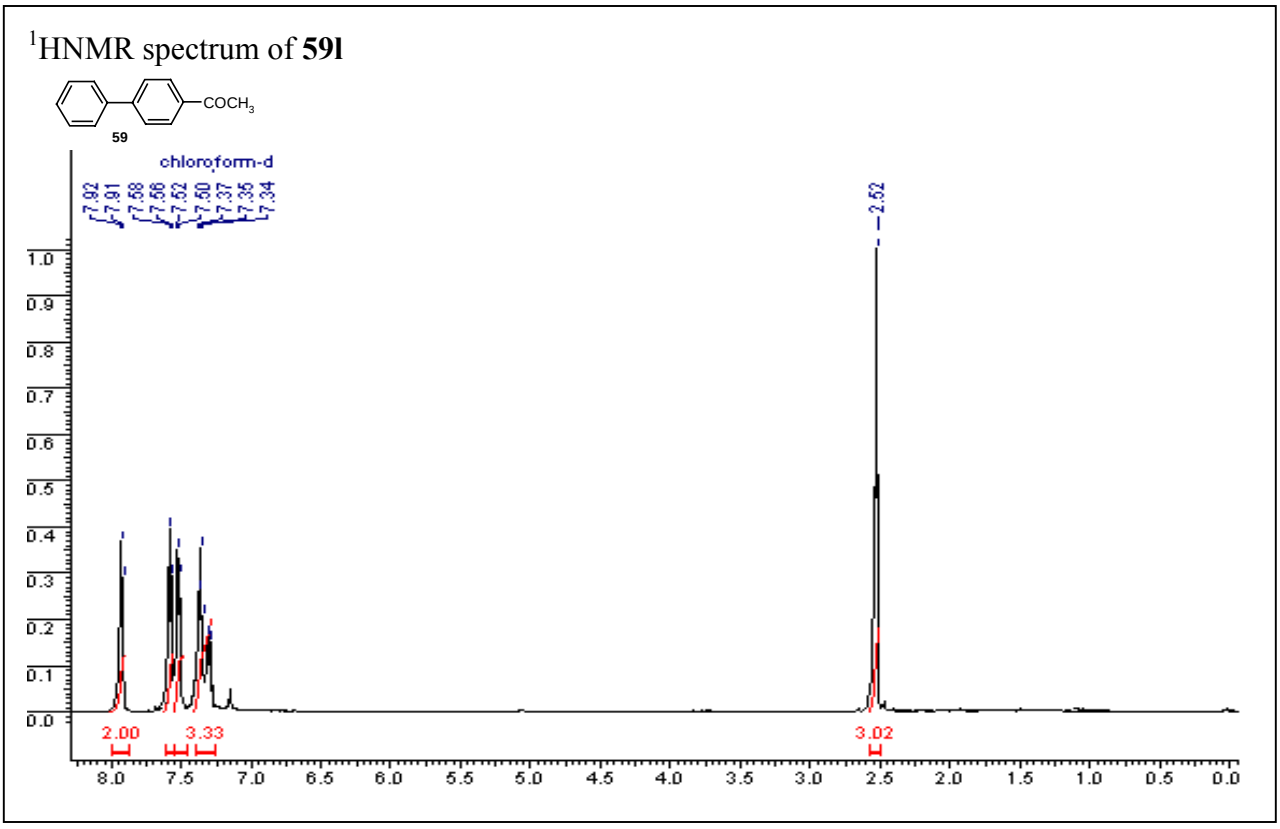
^{13}CNMR spectrum of **59g**



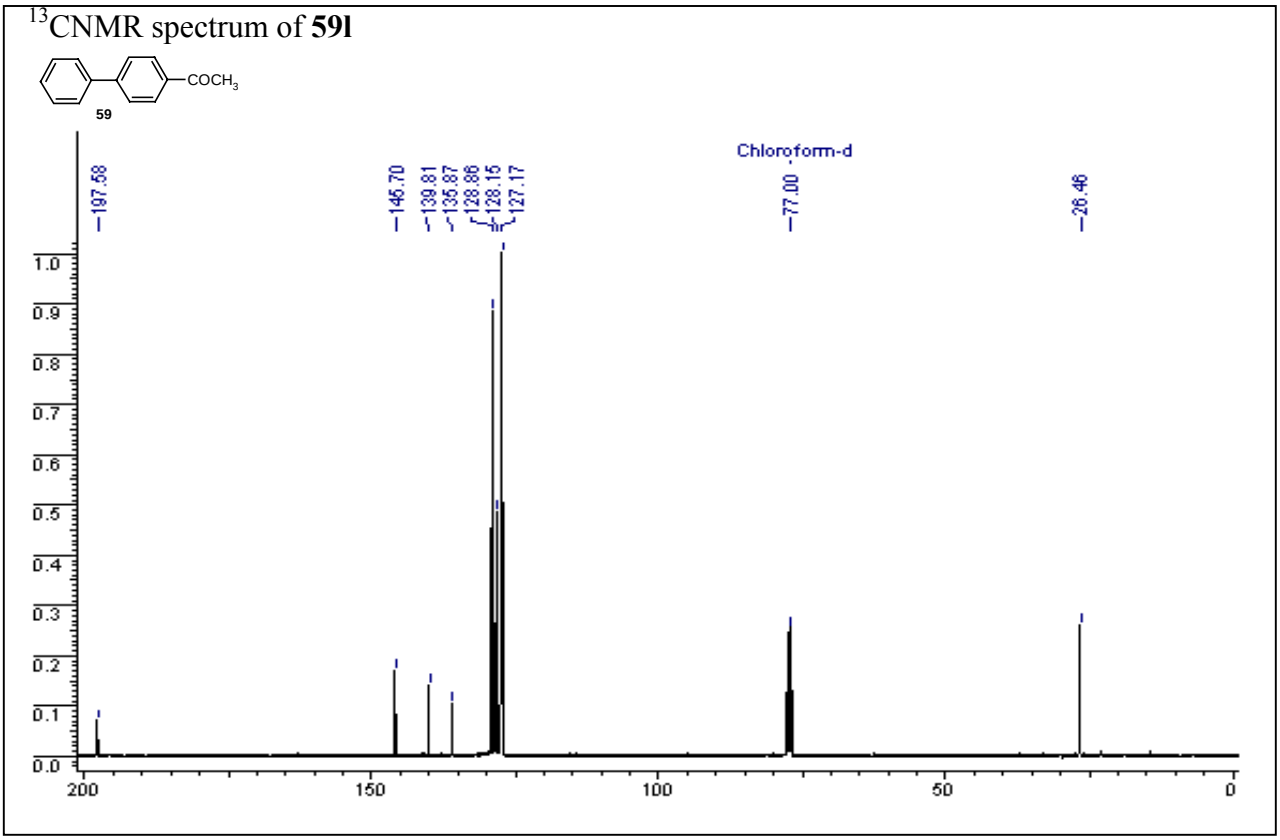
59g



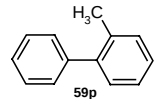
^{1}HNMR spectrum of **59l**

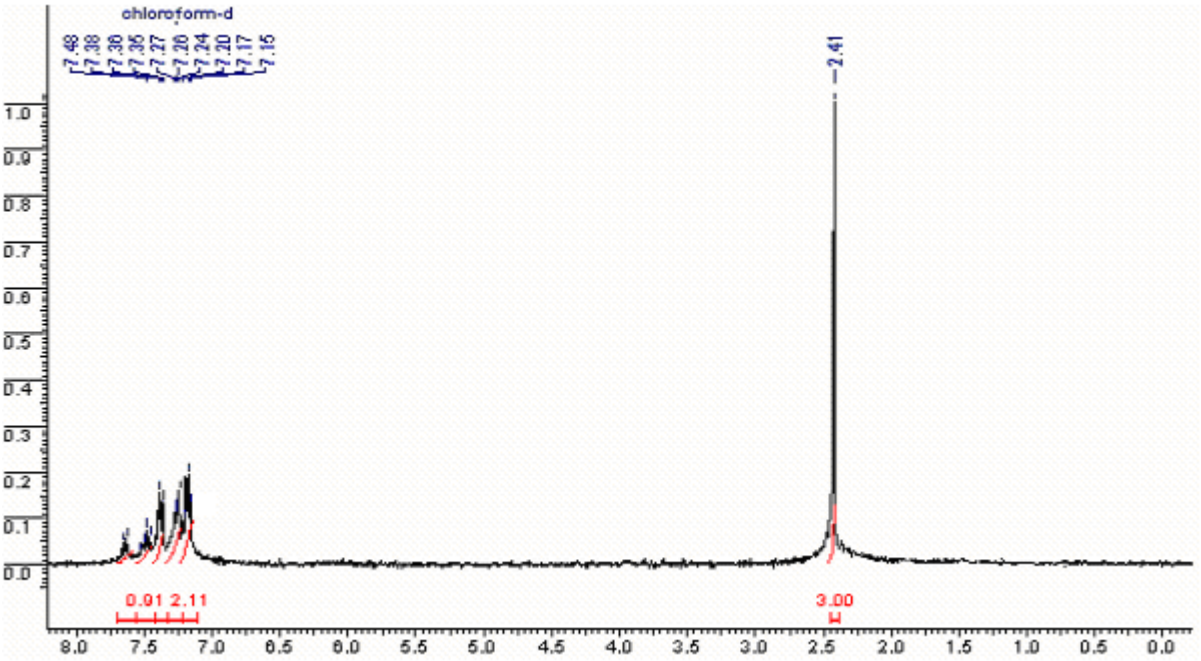


^{13}CNMR spectrum of **59l**

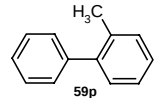


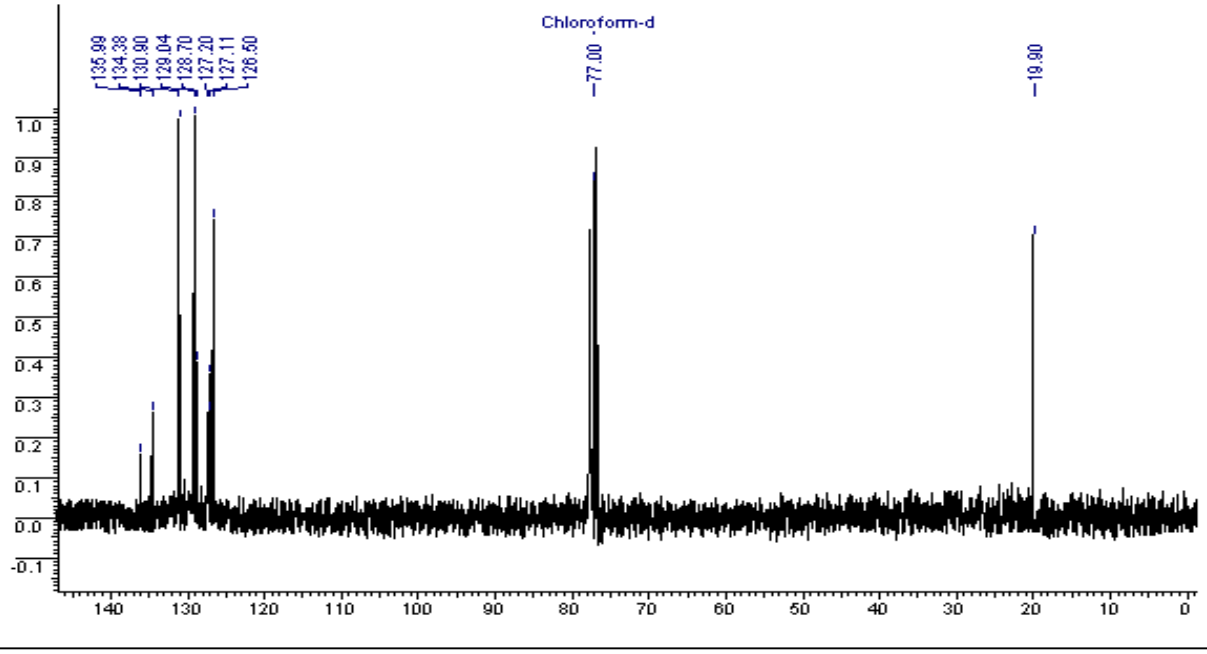
^{1}HNMR spectrum of **59p**





^{13}CNMR spectrum of **59p**





3.2.3 Part III
Application of carbometallated Pd-OMS(MCM-41) catalyst for Sonogashira coupling

3.3.3.1 Introduction

Sonogashira reaction is a well known coupling reaction of a Sp hybridised carbon (alkynes) with Sp^2-hybridised carbon (aryl or vinyl halide) in the presence of Pd(0) or Pd(II) complexes and excess of a base.[98] This is a reaction of construction of π-conjugated aromatic compounds which assumes significance in the wake of the application of these compounds in organic light-emitting diodes (OLEDS), generation of scaffolds leading to molecular electronic devices,[99a] in polymer LEDS as nonlinear optical materials,[99b] in carbohydrate sensing,[99c] in dendrimers,[99d] dehydrobenzannulenes.[99e] It is versatile to prepare several terminal and internal acetylenes. It is proven to be a reliable, high yielding reaction, and is tolerant to a wide variety of functional groups. Currently, palladium and copper co-catalyzed alkyne synthesis, the Sonogashira reaction, is the most straightforward and powerful method for construction of $C(Sp^2)$-$C(Sp^2)$ bonds. The original protocol[98] has been repeatedly modified and improved to overcome several significant limitations such as (a) the use of various palladacycles led to catalytic systems with high turnover numbers[100] (b) Copper-free[101] or silver co-catalyzed[102] protocols eliminated the undesired dimerisation of terminal alkynes.[103] (c) Sonogashira coupling of aryl bromides and iodides at room tempeature is now possible.[104] However unlike other cross coupling reactions, the use of aryl chlorides as a coupling partners for alkynes synthesis, until recently, had remained largely unexplored. Many reviews are available for Sonogashira reactions and its application. Sonogashira himself reviewed, how the organocopper reagents, alkynyl boranes, alkynyl zinc chlorides, alkynyl magnesium halides, alkynyl tin reagents, and the reactions of 1-alkenyl metals with 1-alkynyl halides, reactions of terminal alkynes acid (synthesis of terminal alkynes), play important role in this coupling reaction. He again elaborated about the stereospecific synthesis of alkynes, the utility of phase-transfer catalysis in Sonogashira coupling, and also explained how the coupling of aromatic and heteroaromatic rings via Sp^2-Sp coupling was effected. He also explained its application to synthesis of natural products.[105] In the year 2003, Negishi and co-workers reviewed the palladium catalysed alkylation reaction.[106] Grieco and co-workers[107] synthesised the unsymmetrical bis arylethynes by a modification of the Sonogashira reaction.

Ho and co-workers[108] demonstrated the Sonogashira coupling with diminished homo coupling of two terminal acetylenes. The room temperature, copper-free Sonogashira coupling of aryl bromides was reported by Soheili and co-workers.[109] Buchwald and co-workers[110] have reported the coupling of aryl chlorides with terminal alkynes using copper free conditions.

3.2.3.2. Results and Discussion

In this section we extended the utility of carbometallated palladacycle Pd-OMS(MCM-41) catalyst for the Sonogashira coupling, and explained how the catalyst is effective under various conditions. In a typical experimental procedure, 4-acetylbromobenzene (0.374g, 2 mmol) and phenyl acetylene (0.306 g, 3 mmol, 1.56 equiv) and catalyst Pd-OMS(MCM-41) (0.033g, 2 mmol) were heated at 100°C in DMF with K_2CO_3 (0.386 g, 2.0 mmol, 1.48 equivl) as a base. The GC analysis of the sample after 1h showed the formation of homo coupled product with no formation of required products. The GC analysis of the samples after 2 h, and 3 h had shown the complete conversion of phenyl acetylene to its dimer. In a modified reaction conditions, the reaction was carried out with slow addition of phenyl acetylene at 100°C. The GC analysis of the reaction mixture after a time interval of 1 h showed the formation of trace amount of product but after intervals of 2 to 3 h, the reaction mixture had shown improvement in the conversion of required product to homo coupled product ratio. After 15 h the reaction mixture had shown 100% conversion of 4-acetyl bromobenzene with 94% of cross coupled product with less than 2% of homo coupled product. Although the reaction can be carried out successfully in polar solvents like THF, CH_3CN, only DMF was found to be superior. The highest TON of 190900 was observed with cross coupling reaction between 4-acetylbromobenzene with phenyl acetylene with low catalyst loading of 0.048 mol%. Among the bases screened, inorganic bases were found to be superior over their organic counterpart. In the case of inorganic bases screened, K_2CO_3, K_3PO_4 were found to give best results. Though the reaction of aryl iodides and aryl bromides with electron withdrawing groups proceeded well with the optimized reaction conditions, the electronically rich aryl bromides and aryl chlorides required elevated temperature (140°C) under identical conditions with DMF and K_2CO_3 combination.

Under the optimized reaction condition, the coupling reaction with aryl iodides and activated aryl bromides proceeded with faster reaction rates and with low catalyst loading. On the other hand electronically deactivated aryl bromide (4-bromoanisole, 4-carbomethoxybromobenzene)- and aryl chlorides proceeded with slower reaction rates. The faster reaction rates of aryl iodides were examined by coupling of 4-chloro-iodobenzene with phenyl acetylene under identical optimized condition to give 1-(4-chlorophenyl)-1′-phenyl acetylene. In addition, heterocyclic compounds such as 2-bromopyridine, protected 2-iodoquinoline carboxaldehyde successfully coupled with phenyl acetylene and propargyl alcohol in excellent yield. The product obtained between 2-iodoquinoline carboxaldehyde and propargyl alcohol is an important intermediate for synthesis of camptothecin, an important anticancer drug. We have also investigated the coupling of activated and neutral aryl chlorides, 2-nitro chlorobenzene, 2-methyl chlorobenzene with phenyl acetylene and observed that the reaction can proceed at 100°C with slow addition of phenyl acetylene. Decomposition of alkyne is currently a limitation of this methodology for coupling of aryl chlorides. Aryl iodides with both electron withdrawing and electron donating groups were successfully employed for cross-coupling reaction with phenyl acetylene. We also found that the addition of phase transfer catalyst, TBAB (2 mol %) enhances the reaction rates and yields.

With a viable protocol in hand, we turned our attention towards mechanism of this reaction. Although, the mechanism of copper co-catalysed Sonogashira reaction has been investigated,[103] the mechanism of the copper-free variant has not been described. Drawing from the literature, we envisioned the following catalytic cycle (**Scheme 5**)

As shown in Table **10** a variety of aryl iodides, aryl bromides and aryl chlorides can be coupled with phenyl acetylene or propargyl alcohol to give the corresponding π-conjugated aromatic compounds in good to excellent yield. In a typical experiment, 2-carbomethoxy iodobenzene was treated with phenyl acetylene in the presence of Pd-OMS(MCM-41) catalyst, with K_2CO_3 CuI in DMF at 100^0 C for 22h to give the cross coupled product in 93% yield (**Table 10, entry 3**). The IR Spectrum of the compund **61c** showed bands at 1584cm^{-1}, 2400cm^{-1} and at 2950cm^{-1} corresponding to acetylene strectching frequencies. The IR bands at 1729 cm^{-1} confirms the presence of ester carbonyl. The ^{1}H NMR spectrum

showed 3 protons corresponding to ester **61c** at δ 3.93. The triplet at δ 7.15 (for one proton), the multiplets at δ 7.34-7.54 (for five protons), doublet at δ 7.81(for one proton) and a multiplet at δ 7.98-8.60 (for two protons) confirmed presence of all 9 aromatic protons of the product. In the ^{13}C NMR spectrum of the **61c** two aceylenic carbons appeared at δ 65.0 and at 93.9. The other carbons resonated as usual. Mass Spectrum with M^+ ion at 236 further confirmed the formation of product. The aryl iodides with both functionalities (electron withdrawing and electron donating), (Table **10**, entry **1** and **4**) worked well to give the required product in good yield. The self coupling of phenyl acetylene was avoided by addition of CuI. The aryl chlorides (activated and neutral) were used successfully to give the required cross coupled product in moderate yields. Ortho substituted aryl halides also worked well using Pd-OMS(MCM-41) catalyst to give moderate to good yield. The heteroaromatic halides also worked well by this protocol to give cross coupled products (Table **10**, entry **11**, **12**). The propargyl alcohol was used as one of the coupling partner suceessfully to prepare the cross coupled π-conjugated systems.

3.2.3.3 Conclusion

In conclusion, a new palladium based mesoporous catalyst was developed and successfully applied for the Sonogashira coupling reaction. The coupling of aryl halides (with Halogen X=I, Br, Cl) with different coupling partners (Phenyl acetylene, Propargyl alcohol etc) gave the corresponding cross coupled π-conjugated system in moderate to good yield.

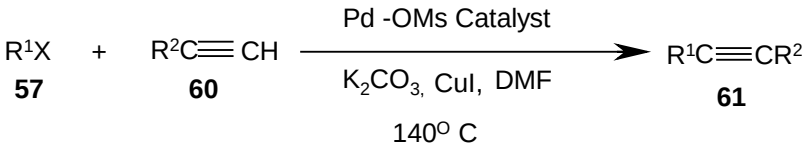
3.2.3.4 Experimental Section

General Procedure for Sonogashira coupling: To a stirred solution of aryl halide(1mmol) in 5 ml of DMF, K_2CO_3(1.4 mmol) and palladacycle Pd-OMS(MCM-41) 0.24mol %, was added dropwise phenyl acetylene and the reaction was heated at 100° C for the indicated duration of time(Table 10).The reaction was monitored by TLC and GC analysis. After the reaction completion, the reaction mixture was filtered for the catalyst reacovery, and the filtrate was thoroughly washed with diethyl ether. The combined organic filtrate was washed with water and brine solution, and dried over anhyd.sodium sulfate. Removal of solvent gave the crude product, which was purified by silica gel column chromatography using petroleum

ether: ethyl acetate (96:4) as eluent to give the pure product. The compound was characterised by IR, ^{1}H and ^{13}C NMR, and Mass spectra.

Table10: Pd-OMS (MCM-41) Catalyzed Sonogashira reaction

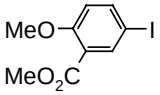
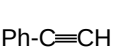
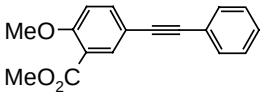
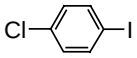
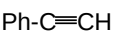
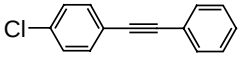
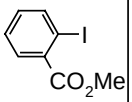
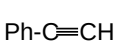
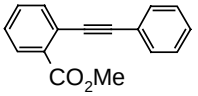
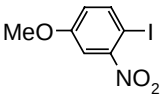
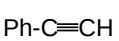
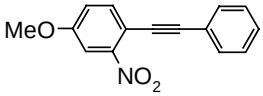
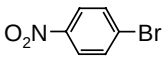
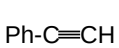
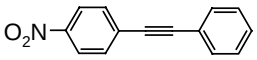
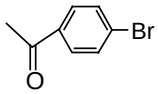
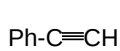
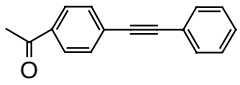
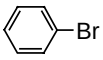
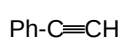
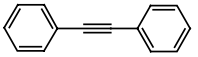
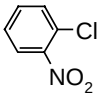
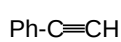
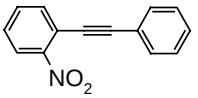
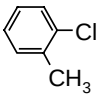
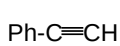
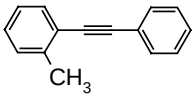
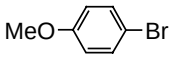
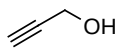
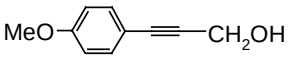
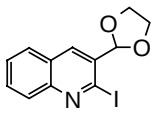
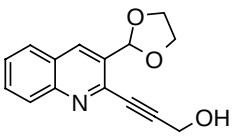
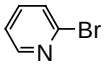
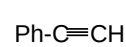
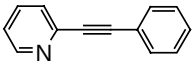
Scheme - 5



R^1 = Aromatics, Substituted aromatics

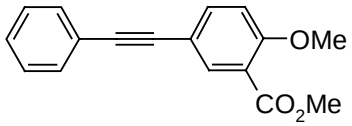
R^2 = Aromatics, $-CH_2OH$

X = I, Br, Cl

Entry	Aryl halides	Alkyne	Product	Product number	Reaction Time (h)	Yield* (%)	Ton
1				**61a**	18	92	172900
2				**61b**	28	89	127200
3				**61c**	22	93	82000
4				**61d**	40	83	164000
5				**61e**	18	80	89600
6				**61f**	20	84	190900
7				**61g**	10	90	113300
8				**61h**	24	74	50200
9				**61i**	36	62	48900
10				**61j**	24	58	54200
11				**61k**	18	64	38027
12				**61l**	23	68	59200

*** Isolated yield after column chromatography.**

2-Methoxy-5-phenylethynyl-benzoic acid methyl ester (61a)



61a

Yield: 92%

Pale Yellow Oil

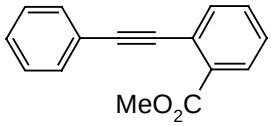
IR (Neat, cm^{-1}): ν_{max} 3447, 3020, 2951, 2851, 2400, 2190, 1725, 1596, 1502, 1462, 1437

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.91 (s, 3H), 3.94 (s, 3H), 6.96 (d, 1H, *J* = 8.71Hz), 7.34-7.40 (m, 3H), 7.51 (d, 2H, *J* = 7.79Hz), 7.63 (dd, 1H, *J* = 2Hz, 8.71Hz), 8.00 (s, 1H)

^{13}C NMR (500 MHz, $CDCl_3$): δ 52.0, 56.1, 88.2, 88.8, 112.1, 115.4, 120.4, 123.3, 128.3(3C), 131.5(2C), 131.5, 131.1, 135.1, 136.4, 158.9, 165.8

Analysis cacld for $C_{17}H_{14}O_3$ (266.29): Found C, 76.59; H, 5.18{Required C, 76.68; H, 5.30}

2-Phenylethynylbenzoic acid methyl ester (61c)



61c

Yield: 93%

Thick brown oil

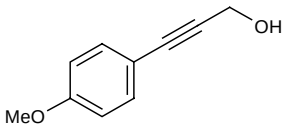
IR ($CHCl_3$, cm^{-1}): ν_{max} 3440, 3021, 2953, 2927, 2400(br), 1945, 1935, 1729, 1584, 1562, 1486, 1465, 1435, 1340, 1291, 1255, 1215

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (s, 3H), 7.15(t, 1H, *J* = 8.79Hz), 7.34-7.54 (m, 5H), 7.79 (d, 1H *J* = 8.31Hz), 7.98(d, 1H, *J* = 5.75Hz), 8.03(d, 1H, *J* = 8.79Hz)

^{13}C NMR (125 MHz, $CDCl_3$): δ 52.3, 65.1, 94.0, 127.8(2C), 128.2, 129.4, 130.8(2C), 132.0, 132.4, 132.5(2C), 135.0, 141.2, 166.5

Analysis cacld for $C_{16}H_{12}O_2$ (235.260): Found C, 81.77; H, 4.84{Required C, 81.69; H, 4.77}

3-(4-Methoxyphenyl)-prop-2yn-1-ol (61i)



61i

Yield: 58%

Brown Oil

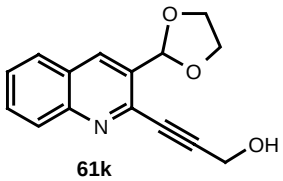
IR($CHCl_3$, cm^{-1}): ν_{max} 3431, 2429, 1634, 1597, 1542, 1492, 1267, 1192

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78-3.92 (m, 5H), 6.95 (d, 2H, *J* = 6Hz), 7.47 (d, 2H, *J* = 6Hz)

Mass: 181 (162(M^++1 +H_2O), 149 (162-CH_3), 132, 120

Anayalsis cacld for $C_{10}H_{10}O_2$ (162.187): Found C, 73.98; H, 6.18{Required C, 74.05; H, 6.21}

3-(3-[1,3]Dioxolan-2yl-quinolin-2-yl)-prop-2-yn-1ol (61k)



61k

Yield: 64%

Pale Yellow Solid

IR ($CHCl_3$, cm^{-1}): ν_{max} 3422, 3020, 2984, 2896, 2400, 2239, 1731, 1620, 1601

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.90(brs, 1H), 4.12-4.23 (m, 4H), 4.64 (s, 2H), 6.34 (s, 1H), 7.53 (t, 1H, *J* = 6.95Hz), 7.71 (t, 1H, *J* = 6.95Hz), 7.82(d, 1H, *J* = 8.21Hz) 8.08 (d, 1H, *J* = 7.95Hz), 8.37 (s, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 51.2, 65.6, 82.5, 92.8, 101.0, 126.9, 127.5, 127.9, 128.7, 130.6, 132.0, 134.3, 141.7, 147.9.

Analysis cacld for $C_{15}H_{13}NO_3$ (255.271): Found C, 70.77; H, 4.9 3; N, 5.37 {Required C, 70.60; H, 5.13; N, 5.48}

3.2.3.5 Spectra

1. ^{1}HNMR spectrum of 61a

2. ^{13}CNMR spectrum of 61a

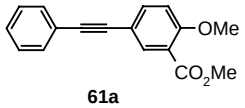
3. ^{1}HNMR spectrum of 61c

4. ^{13}CNMR spectrum of 61c

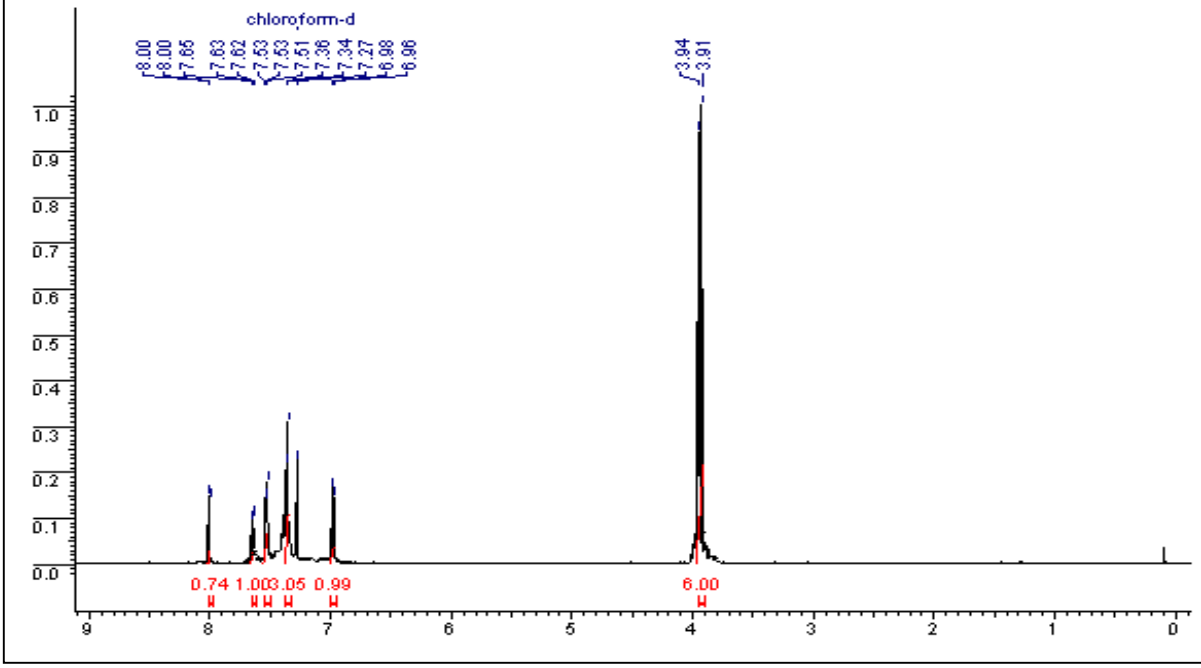
5. ^{1}HNMR spectrum of 61k

6. ^{13}CNMR spectrum of 61k

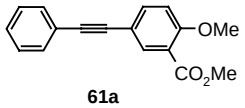
^{1}HNMR spectrum of **61a**



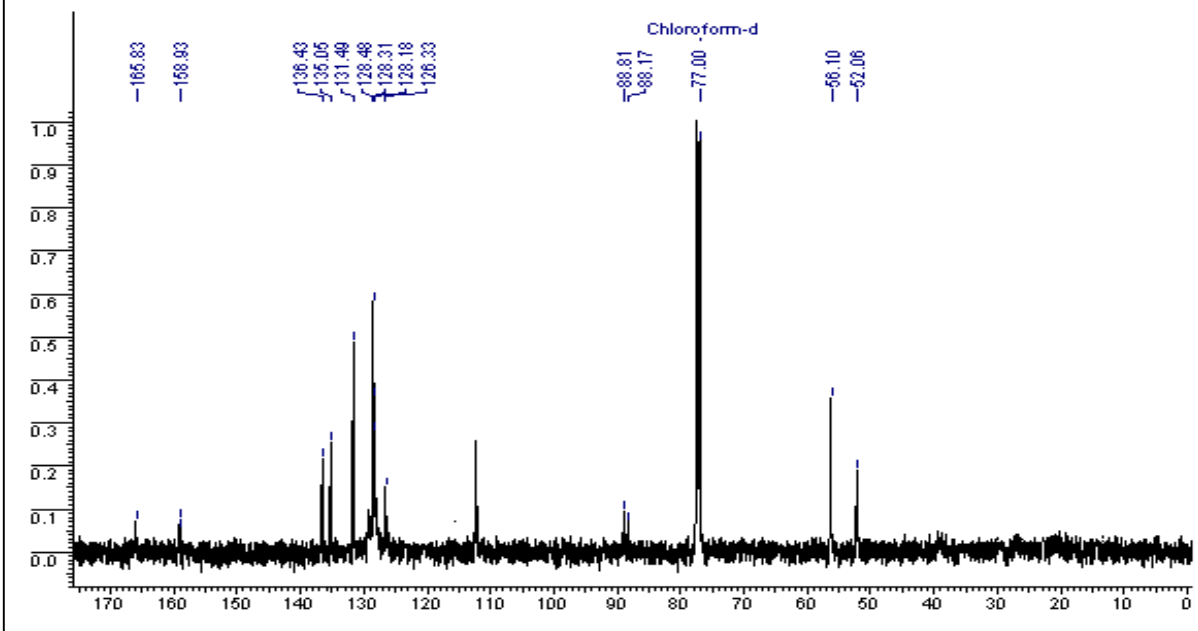
61a



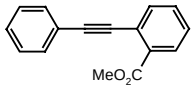
^{13}CNMR spectrum of **61a**



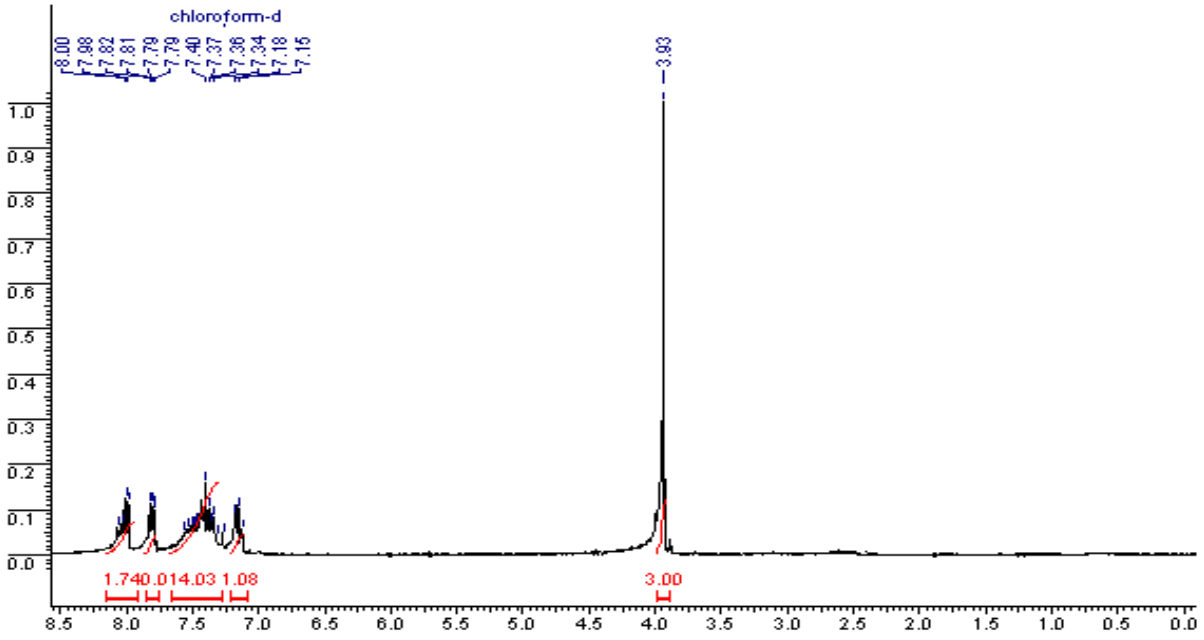
61a



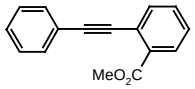
^{1}HNMR spectrum of **61c**



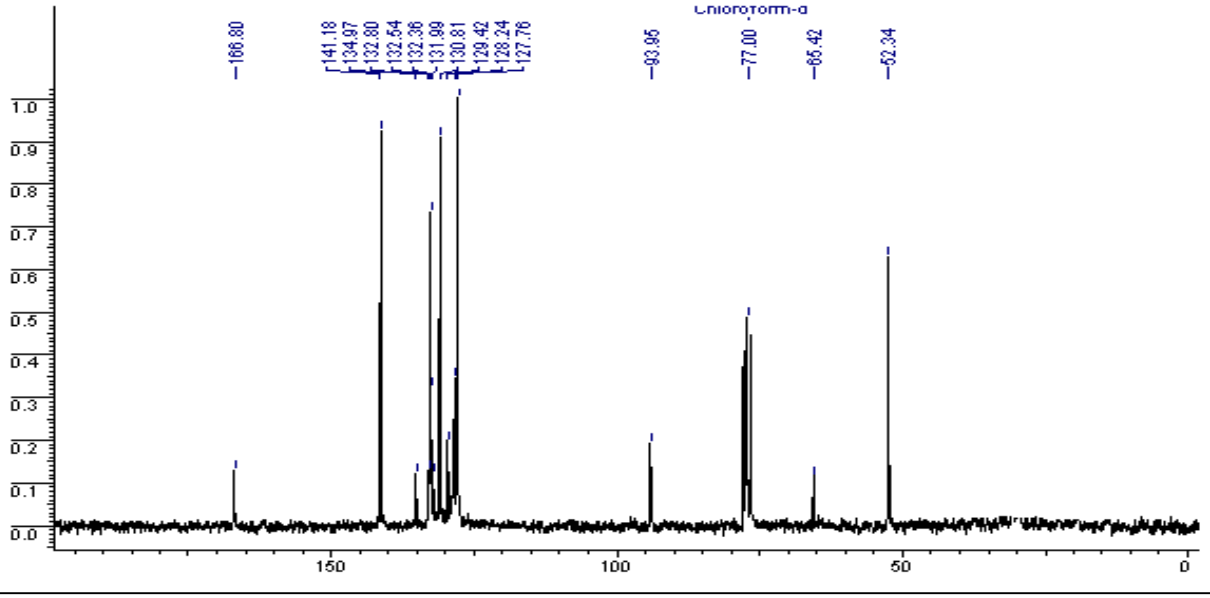
61c



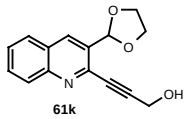
^{13}CNMR spectrum of **61c**



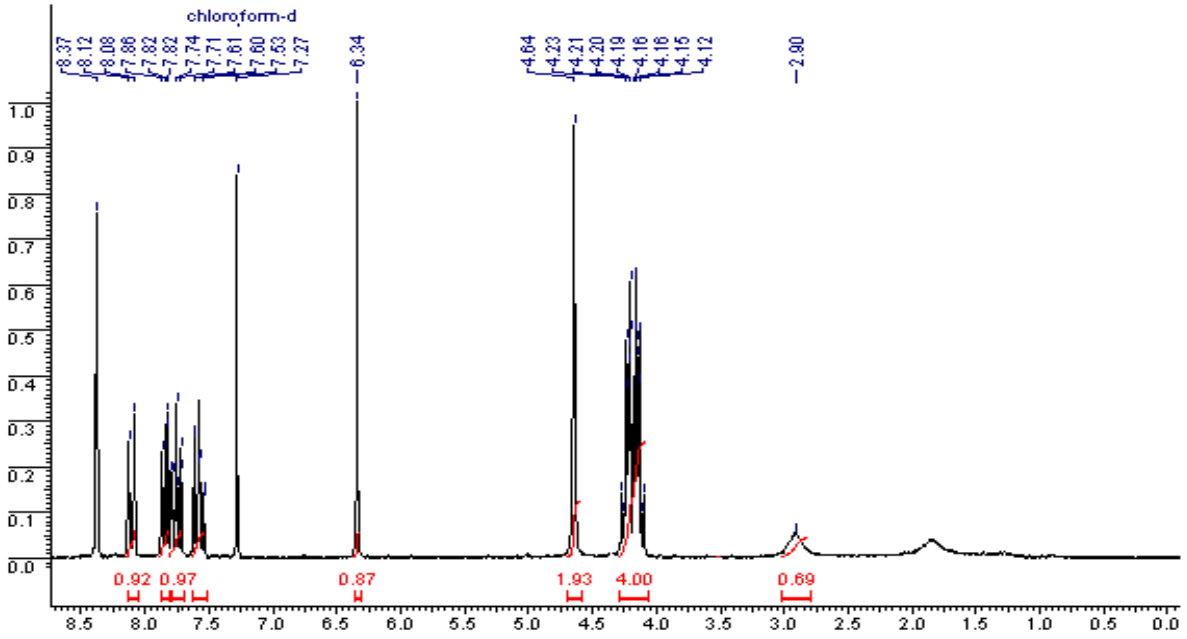
61c



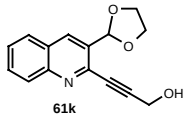
^{1}HNMR spectrum of **61k**



61k



^{13}CNMR spectrum of **61k**



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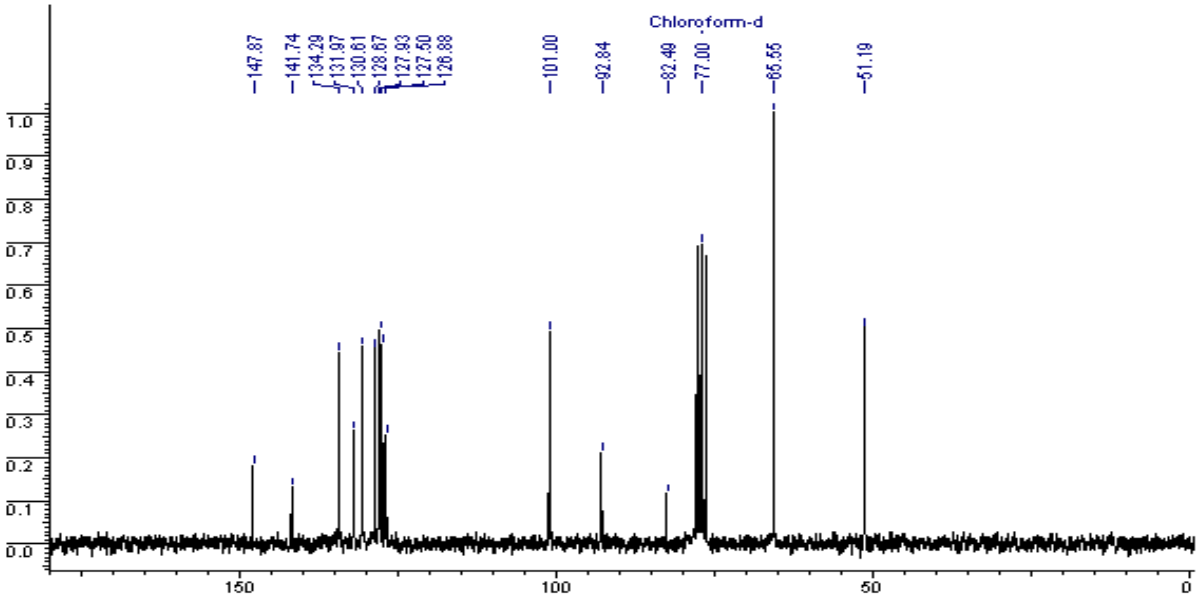


3.2.4. Part IV
Application of Carbometallated, Pd-OMS(MCM-41) Palladacycle catalyst to Stille Coupling reaction

3.3.4.1 Introduction

Cross-coupling reactions represent an extremely versatile tool in organic synthesis.[75] The Stille reaction[111] where tin reagent is employed as a coupling partner with aryl, vinyl or allyl halides (or pseudohalides) to form C-C bonds; belongs to a large family of palladium and nickel-catalyzed reaction. Albeit the difficulties associated with removal of tin from the product, tin toxicity represents major limitation/concerns associated, with the Stille reaction, still it has attracted much attention as a result of availability of various organo stannanes, and its stability towards air and moisture, as well as compatibility with variety of functional groups. Because of its versatility, Stille coupling has enjoyed widespread popularity and use in the synthesis of biphenyls and allylation of vinyl and aryl halides, because the biaryl structure exhibits a common motif in pharmaceuticals and other biologically active compounds. Alternatively, these coupling reactions make use of a variety of other transmetallating agents such as organoboron,[112] organomagnesium,[113] organosilicon,[114] and organozinc reagents. Usually metal-phosphine complexes are commonly employed as auxillary ligands in such systems.[75, 117] Nevertheless, significant room for improvement remains. For example, increasing the scope of the reaction and developing more versatile catalyst that operates under milder conditions would represent important advances. With regards to scope, one of the most apparent limitations in the palladium-catalyzed Stille cross coupling reaction has been the inability to couple unactivated aryl chlorides.[111b, 111c, 118] In recent years, many transition metal complexes were developed for coupling electron rich aryl chlorides. Fu and his coworkers[119] in his pioneering studies, reported palladium catalyst based on sterically hindered electron-rich $(Pt\text{-}Bu)_3$ for the Stille-cross coupling of aryl chlorides. This method, although in general, requires a highly air-sensitive and pyrophoric ligand that requires special handling technique. Though the air-stable $Pd[P(t\text{-}Bu)_3]_2$[120] complex was recommended as an alternative to $Pd_2(dba)_3$. For this process, its high cost is a deterrent to its widespread use. Nolan and coworkers[121] reported a Pd/N-heterocyclic/carbene system for the Stille reaction of aryl chlorides. However, this protocol provided good yields only for electron deficient aryl chlorides. In the case of electron-neutral and electron rich aryl

chlorides, only poor to moderate yields were obtained. In an elegant work, Choudhary and co-workers[79] reported a layered double-hydroxy supported nono-palladium catalyst which works even with electron rich aryl chlorides. However, for the Stille reaction of aryl chlorides, including electron rich aryl chlorides under mild condition (50°C), the generality of the process remains to be explored. More recently, the Stille reaction of aryl chlorides in water utilizing palladium-phosphinous acid complexes was described by Wolf and coworkers.[122] This methodologies required very high temperatures (135-140°C), and no examples of electron rich aryl chlorides were reported, and important functional groups such as esters and aldehydes were not compatible.

3.2.4.2 Results and Discussion

Based on our previous results, using heterogeneous carbo-metallated palladacycle Pd-OMS (MCM-41) for Heck, Suzuki-Miyaura and Sonogashira coupling, we attempted to apply this complex to Stille cross coupling of aryl bromides (with both electron donating and electron withdrawing groups) and activated and electron neutral aryl chlorides. In order to establish the standard reaction conditions, Stille coupling of 4-chlorotoluene with allyl tributyl stannanes in DMF at 110°C was chosen as a model reaction with K_2CO_3 as a base to give only 5% of cross coupled product.

It is well-known that, like silicon,[123] tin is fluorophilic,[124] consequently, the resulting hypervalent organostannane species generated in the reaction of the organostannane with fluoride anion are more labile with regard to the transmetallation reaction.[125] The studies by both Fu's[119] and Nolan's[121] on the Stille reaction have revealed the importance of a fluoride source in activating organo tin compounds for the transmetallation step. Kosugi *et al*. have reported that $Pd(dba)_2/PPh_3$/TBAF does not catalyze the Stille coupling of aryl chlorides. In an effort to overcome the limitations of the Still reaction e.g. slow transmetallation step and removal of tin byproducts, the use of hypervalent stannate species was investigated. Thus we carried out reactions with TBAF, (nBu_4NF), CSF, KF as various fluoride additives and we found that on reaction of 1.1equiv. of allyltributyl stannanes with 1 equiv of 4-chlorotoluene with K_2CO_3 as base and TBAF(2 equiv) as additive at 110^{o}C in DMF gave moderate to good yields of cross coupled product (46%). In turn CSF, a very effective additive with $Pd_2(dba)_3$

catalyzed Stille reaction but proved to be less effective. Attempts to couple other aryl halides using CSF/KF as an additive/base were unsuccessful. Other bases such KO^tBu_4 and NaOH proved to be ineffective for the cross-coupling of 4-chlorotoluene with allyltributylstannes. Using K_2CO_3 as additive in the reaction gave cross coupled product with aryl iodides and bromides, but the yields were not encouraging.

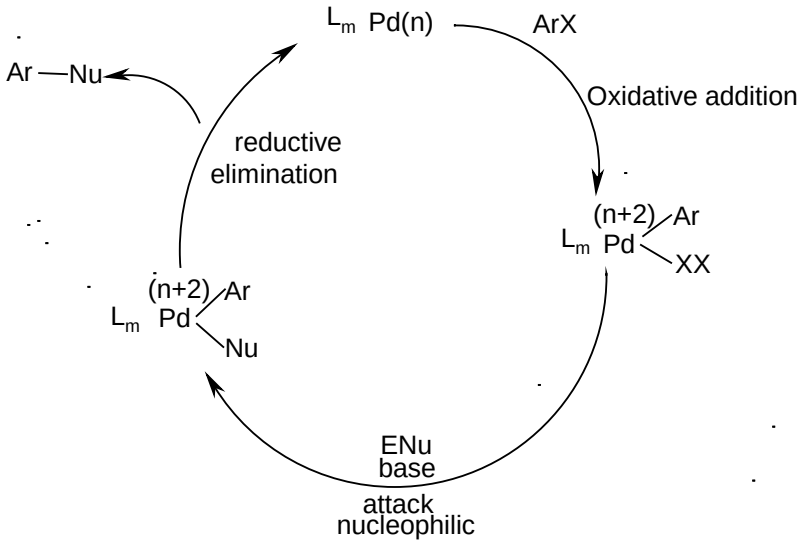
On investigating the solvent effect on the reaction rate and yield, we changed the solvent from DMF to 1, 4-dioxane, the reaction proceeded with enhanced reaction rate and yield (68%) with catalyst kept at 0.48 mol% of Pd. Although aryl iodides and bromides give cross coupled product in DMF with K_2CO_3 as a base at 0.48 mol% of Pd loading, the yields were not encouraging. But in presence of TBAF, we were pleased to observe the carbometallated palladacycle Pd-OMS(MCM-41) which was found to be effective catalytic systems for the cross-coupling of electron neutral and electron-deficient and electron rich aryl bromides with $PhSn(^nBu)_3$. On surveying the catalytic cross-coupling of aryl chlorides with aryl stannanes using the carbometallated palladacycle Pd-OMS(MCM-41), the catalytic system was found to be effective for electron-neutral and electron deficient aryl chlorides. The system was unable to effect the coupling of electron rich aryl chlorides such as 4-chloroanisole and 4-carbomethoxy chlorobenzene. On the other hand, the electron deficient aryl chlorides and electron neutral aryl halides, such as 4-chlorotoluene, 4-chloroacetophenone and 4-methylchlorobenzene and 2-nitrochlorobenzene were effectively coupled with $PhSn(^nBu)_3$ to give the respective biaryl compounds. Ortho-substituted aryl bromides require longer reaction times when reacted with $PhSn(^tBu)_3$. The results in Table **11** suggest that the coupling of aryl chlorides require more vigorous conditions and is facilitated by electron-withdrawing substituents.

Stille cross-coupling is frequently used as a key step in the synthesis of pharmaceuticals. Simple catalyst isolation and recycling are important features of synthetic methodologies with practical industrial applications. We therefore chose to recycle Pd-OMS(MCM-41) for 4-nitrobromobenzene and $PhSn(^tBu)_3$. After completion of each reaction the reaction mixture was decanted and diluted with water and extracted with EtOAc to get product. In the first two runs the results were encouraging. But on third and fourth, the yields were decreased

moderately. The major difficulty in working up reaction mixtures from Stille cross-coupling is the removal of tin byproducts. In the present case, TBAF serves not only as a base and tin transfer reagent but also as fluorous medium for tin extraction. This makes possible the removal of tin by simple water extraction.

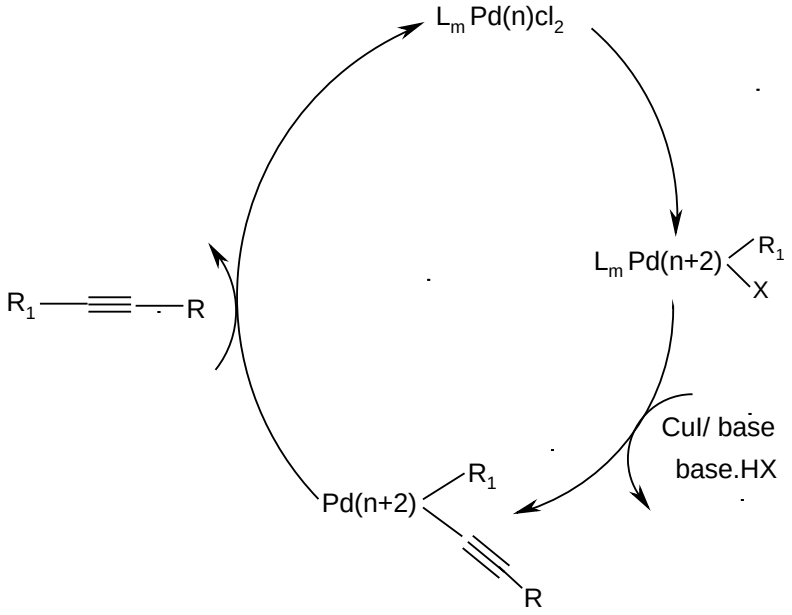
In a typical experimental procedure, 4-nitrobromobenzene (0.20g, 1 mmol) was stirred with allyltributylstannane (0.48g, 1.1mmol) in the presence of Pd-OMS(MCM-41)(0.24mol %) palladacycle with K_2CO_3(0.276g, 2eq) and CuI (additive), in 1,4 dioxane at 110 ^{0}C to give the corresponding cross coupled allylated product **63c**, in 85% yield. The IR spectrum of **63c** showed a peak at 1601cm $^{-1}$, the charcteristic of olefins. The ^{1}H NMR spectrum of **63c** showed peaks at δ3.75 as a doublet for the benzylic protons attached to terminal olefins. The doublet of doublet at δ 5.23 appeared for the CH_2 protons of the terminal olefins. The two doublets at δ 6.51 and at 7.26 showed the presence of aromatic protons. The ^{13}C NMR spectrum of compound shows the benzylic carbon at δ 46.4 and the carbons of the terminal olefin at δ 116.4 and 134.8. The formation of **63c** was again confirmed by its mass spectrum with molecular ion at 164. Aryl iodides having both electron withdrawing, and electron donating groups coupled successfully to give the cross coupled allylated products (Table **11,** entry **1** and **2**). Aryl halides were again successfully coupled with allyltributylstannanes to give biphenyls in good yield.

With a viable protocol in hand, we turned our attention towards mechanism of Suzuki, Sonogashira and Stille reactions. Although, the mechanism of copper co-catalysed Sonogashira reaction has been investigated,[103] the mechanism of the copper-free variant has not been described. Drawing from the literature, we envisioned the following catalytic cycle.



Catalyric cycle for Suzuki (ENu = $ArB(OH)_2$), Stille (ENu = R_1SnBu_3 Where R_1 = aryls) and Sonogashira (ENu = $HC{\equiv}CR_2$ Where R_2 = Phenyl, $-CH_2OH$)

Mechanism for copper catalyzed reaction:



3.2.4.3 Conclusion

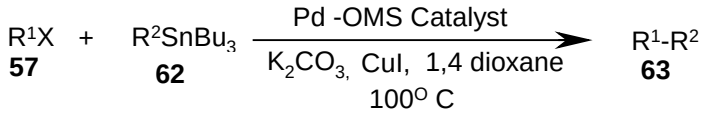
In conclusion a new, efficient catalytic procedure was developed for the Stille coupling reaction. Thus aryl halides (with Halogen X=I, Br, Cl) were successfully coupled with allyl and arylstannanes to give the corresponding cross coupled products usuing Pd-OMS (MCM-41) palladacycle.

3.2.4.4 Experimental Section

General Procedure for the Stille coupling: To a stirred solution of aryl halide (1mmol), K_2CO_3(1.4eq), TBAF (additive, 0.1mmol), and 0.24 mol% of palladacycle Pd-OMS(MCM-41), in 5ml of 1,4 dioxane, allyltributylstannane(1.1eq), at 110^oC was added dropwise (1.1eq), and the reaction was continued for the indicated duration of time. The reaction was monitored by GC and TLC analysis. After the reaction completion the reaction mixture was filtered for the catalyst recovery and the filtrate was thoroughly washed with dithyl ether. The combined organic filtrate was washed with water and brine solution and dried over anhyd. Na_2SO_4. Removal of solvent gave the crude product, which was purified by silica gel column chromography using petroleum ether: ethyl acetate (97:3) as eluent to give the pure product. The pure compound was charterized by IR, ^1H, and Mass spectra and elemental analysis.

Table 11: Pd-OMS(MCM-41) Catalyzed Stille Cross Coupling reaction

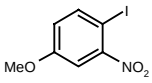
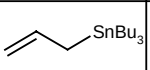
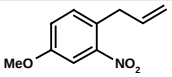
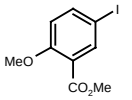
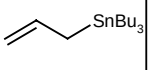
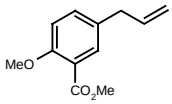
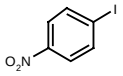
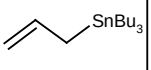
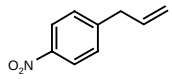
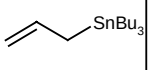
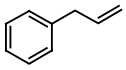
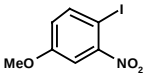
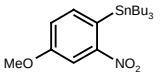
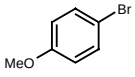
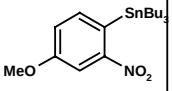
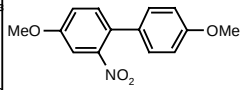
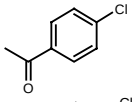
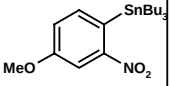
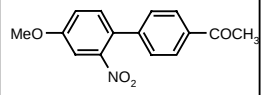
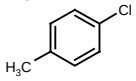
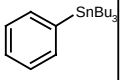
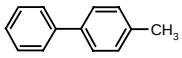
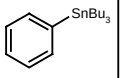
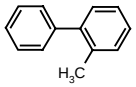
Scheme -6



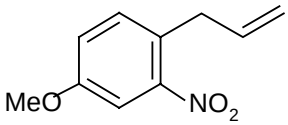
R^1 = Aromatics, Substituted atomatics

R^2 = Aromatics, Allyl.

X = I, Br, Cl

Entry	Aryl halides a	Stannanes b	Product c	Product No.:	Reaction Time(h)	Yield (%)	TON
1				**(63a)**	3	82	95300
2				**(63b)**	2.5	79	101500
3				**(63c)**	2	85	135600
4				**(63d)**	4	76	35800
5		Bu_3SnH		**(63e)**	3	86	98750
6				**(63f)**	4	77	68750
7				**(63g)**	10	46	5400
8				**(63h)**	12	49	1250
9				**(63i)**	11	58	850

1-Allyl-4-methoxy-2-nitro-benzene (63b)



63b

Pale Yellow Solid

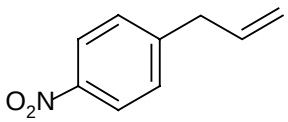
IR($CHCl_3$, cm^{-1}): ν_{max} 3452, 3102, 2231, 1752, 1625, 1599, 1557, 1487, 1383, 1281, 1104.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.75-3.89 (m, 5H), 5.19 (dd, 2H, *J* =15.31Hz, 30.21Hz), 5.90-6.00 (m, 1H), 7.09 (d, 1H, *J* = 6.31Hz), 7.50 (d, 1H, *J* = 9.21Hz), 7.55 (s, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) δ: 15.9, 30.7, 36.5, 56.0, 108.2, 115.7, 116.6, 121.2, 129.8, 132.7

Analysis cacld for $C_{10}H_{11}O_3$ (179.194): Found: C, 62.22; H, 5.61; N, 7.08 {Required C, 62.17; H, 5.74; N, 7.25}

1-Allyl-4-nitro-benzene (63c)



63c

Yield: 85%

Dark Brown Oil

IR ($CHCl_3$, cm^{-1}): ν_{max}3097, 2278, 1605, 1572, 1452, 1375, 1257, 1152, 1074.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (d, 2H, *J* = 5.75Hz), 5.23 (dd, 2H, *J* = 7.81Hz, 9.75Hz), 5.87-6.00 (m, 1H), 6.51(d, 2H, *J* = 5.74Hz), 7.25(d, 2H, *J* = 5.75Hz)

^{13}C NMR (500 MHz, $CDCl_3$): δ 30.9, 46.4, 55.0, 114.5, 116.4(2C), 131.8(2C), 134.9

Analysis cacl for $C_9H_9NO_2$163.175): C, 66.37; H, 5.64; N, 8.67{Found C, 66.25; H, 5.56; N, 8.58}

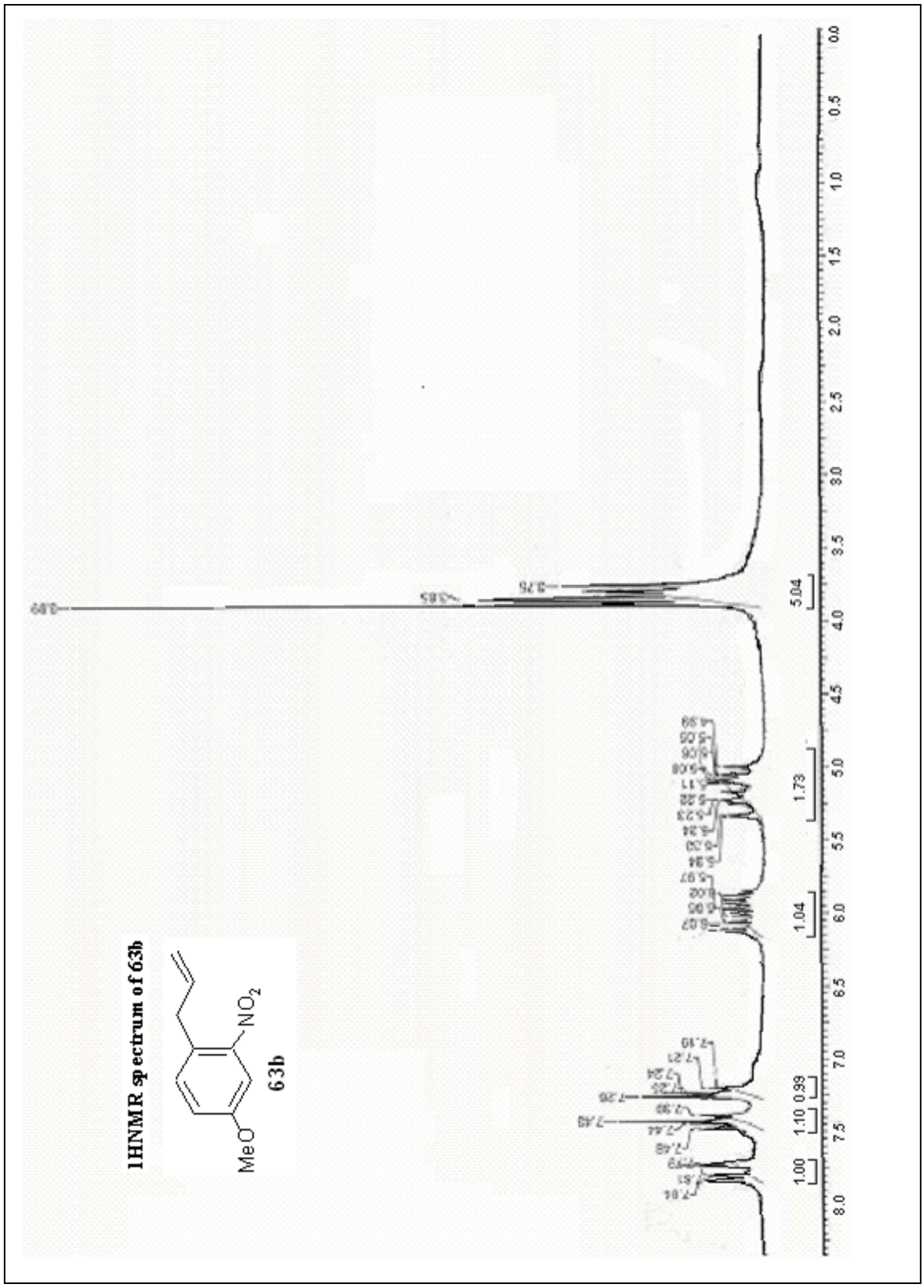
3.2.4.5 Spectra

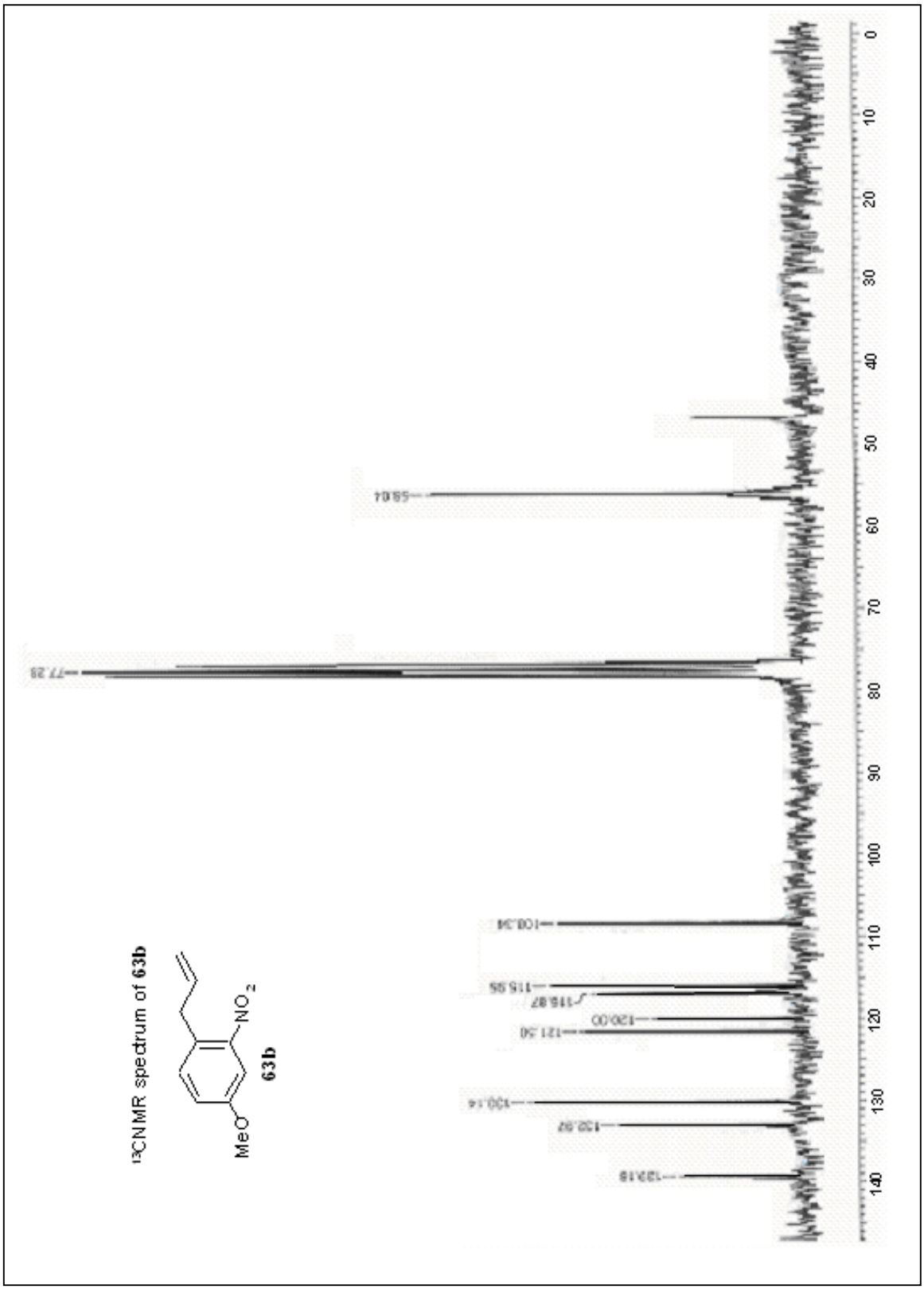
1. 1HNMR spectrum of 63b

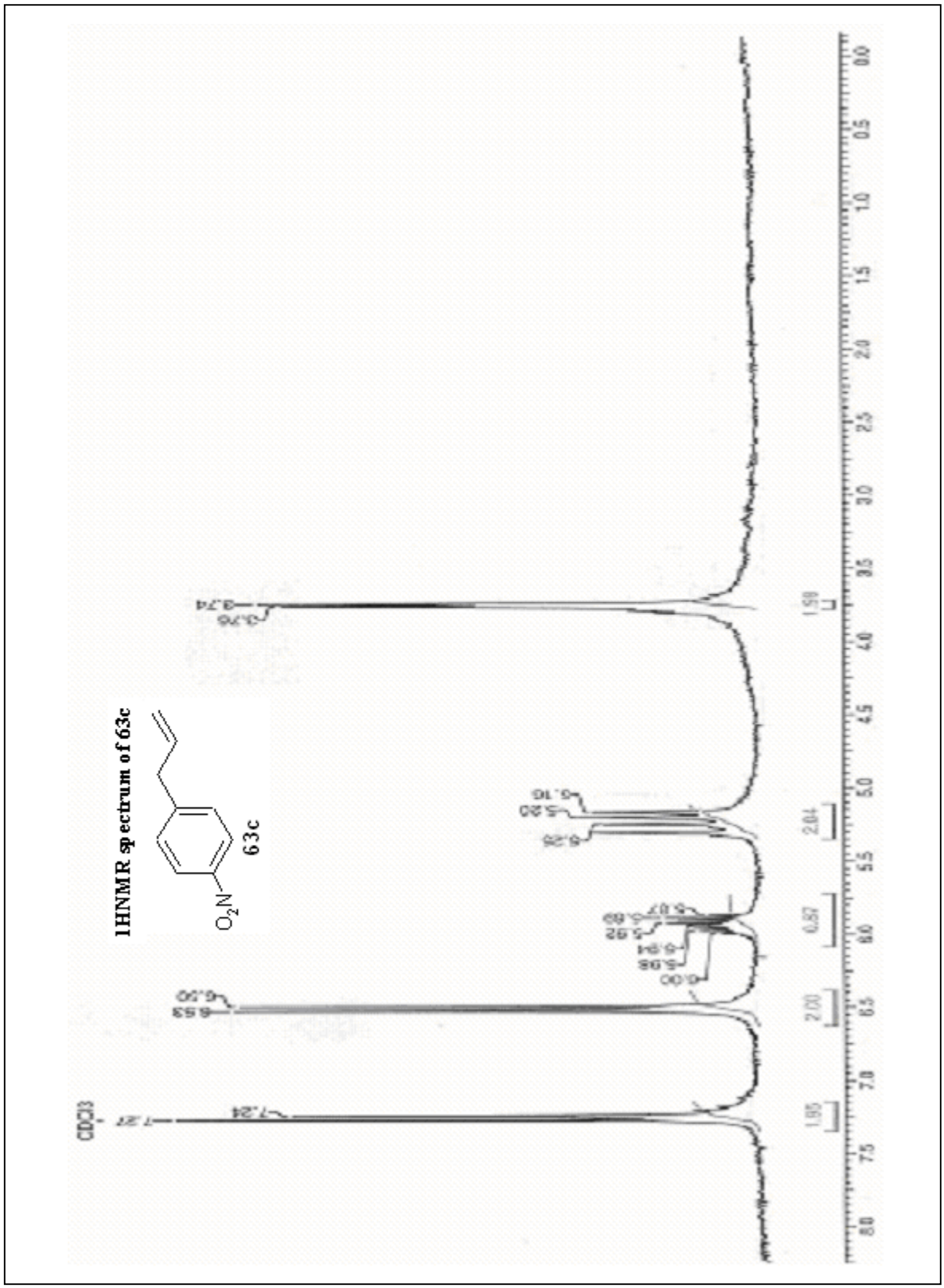
2. 13CNMR spectrum of 63b

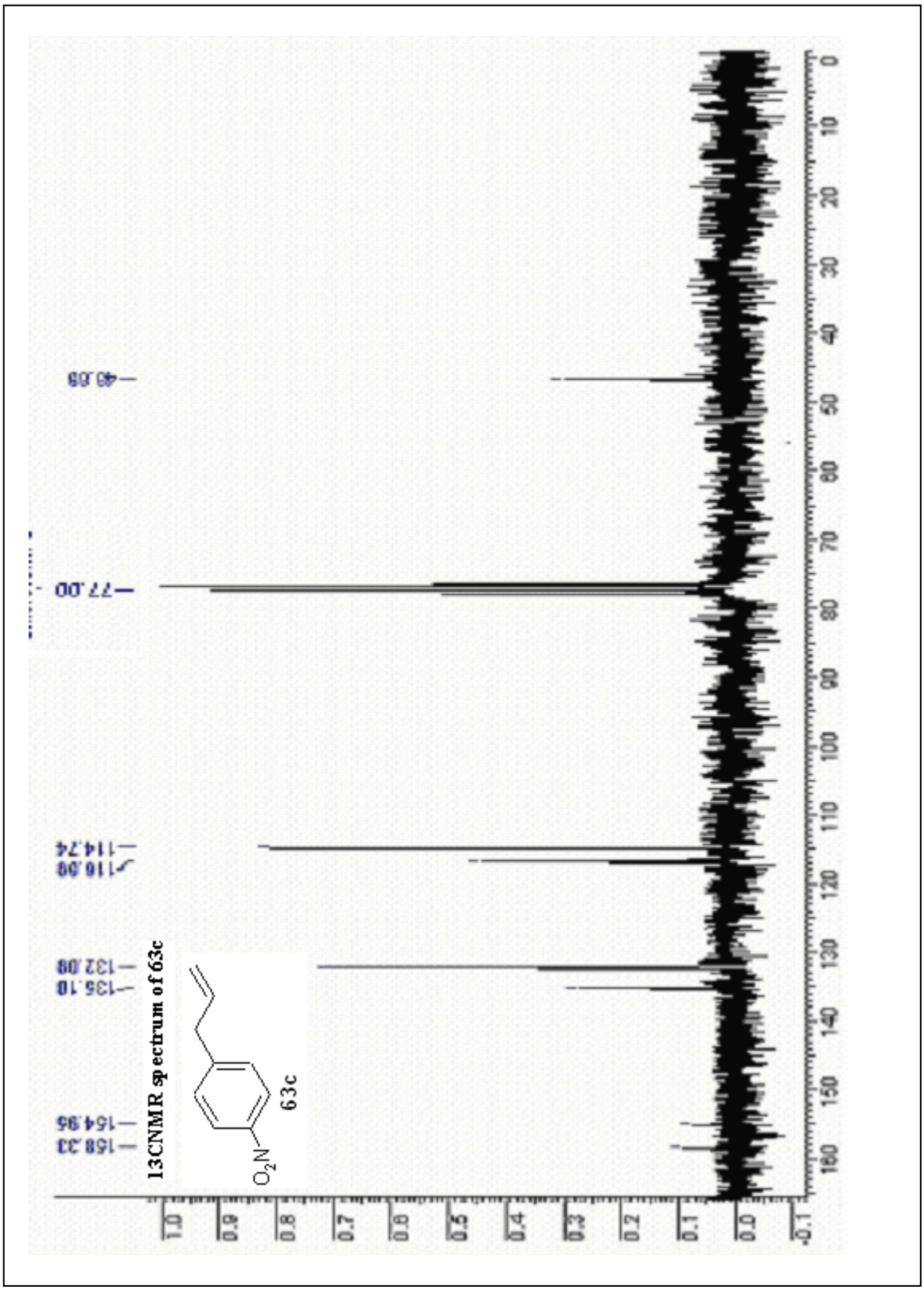
3. 1HNMR spectrum of 63c

4. 13CNMR spectrum of 63c


1HNMR spectrum of 63b
MeO
NO2
63b


^{13}CNMR spectrum of **63b**
MeO
NO_2
63b
77.23
59.61
108.34
116.95
116.87
120.00
121.50
130.14
132.97
133.19
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140


1HNMR spectrum of 63c
63c
O_2N
CDCl3
7.27
7.24
6.53
6.50
6.07
6.03
5.92
5.88
5.41
5.39
5.25
5.23
5.20
5.18
3.76
3.74
1.95
2.00
0.82
2.04
1.99


13CNMR spectrum of 63c
63c
O_2N
158.33
154.95
135.10
132.08
118.09
114.74
77.00
46.58

3.3 Section C

Pd-OMS(MCM-41) Palladacycle catalyzed allylation of aldehydes, ketones, imines and α-halo ketones

3.3.1 Introduction

The allylation of carbonyl compounds such as aldehydes, ketones and their derivatives (imines) is one of the most important C-C bond forming reactions, because of the versatility of homoallylic alcohols and amines as useful synthetic intermediates.[125] Although many methods have been developed, research in this field seeking new and more efficient methods are unabated. Among the various allyl metal reagents, allylstannanes and allylsilanes are very useful because of their modest reactivity, which in turn can be increased by catalyst activation. In recent years, development of allylation reactions in aqueous media has attracted greater attention, because of the easy handling, water-tolerance and unique reactivity of the methodology.[126] Albeit several kinds of Lewis acid or Bronsted acid catalyzed allylation reactions both in organic and aqueous media with allylstannanes and allylsilanes have been reported[127,128] these methods suffer from (1) requirement of stoichiometnic amount of catalyst and (2) pre-activation of imines (3) recyclability of the catalyst (4) substrate limitation and deactivation of catalyst by strong co-ordination of these catalyst with amine and its derivatives. Therefore, it is necessary to develop more active and efficient catalyst to overcome the above limitations. Though there are few reports of palladium catalyzed addition of carbonyls and imines with allyl-stannanes[129] there is no report on addition of allystannanes using heterogeneous palladium catalyst.[130] Our successful attempt for the Heck, Suzuki, Sonogashira, and Stille cross coupling reactions using Pd-OMS(MCM-41)-Palladacycle prompted us further to explore the catalytic activity of this palladacycle catalyst for the allylation of carbonyl compounds and imines with allyltributyltin and herein we describe the detailed study.

3.3.2 Results and Discussion

Allylation of aldehydes with allyl stannanes

The reaction of allylstannanes **65** with aldehydes **64** in aq. DMF (DMF: H_2O 9:1) in the presence of Pd-OMS (MCM-41) palladacycle (Pd-II complex) at 80°C, gave the

corresponding homoallylic alcohols **66** in high yields. The results are summarized in Table **12**. The addition of allyltributyl stannane **1a** to anisaldehyde (0.3g, 0.002 mole) proceeded very smoothly even with low catalyst loading (0.3mol %) at 80°C. When the reaction was carried out at room temperature, it took longer reaction time. While on comparing the performance of the Pd-OMS(MCM-41) palladacycle with Pd(0) catalyst $Pd(PPh_3)_4$, the Pd-OMS(MCM-41) gave better yield with less reactive subtrates without side product due to polymerization of unsaturated aldehydes. The formation of the product was confirmed by its spectral data. The IR spectrum of the compound **66c** (Table 12) showed a broad band at 3435cm^{-1} corresponding to the hydroxy functionality. The ^1H NMR spectrum of **66c** showed triplets at δ 2.50 for the allylic CH_2 protons. The CH_2 protons of the terminal olefins appeared as multiplet at δ 4.68-5.11. The benzylic proton of the allyl alcohol was seen as multiplet at δ 5.81. The two doublets at δ 6.87 and at δ 7.27 indicates para substituted aromatic system. ^{13}C spectrum showed signals at δ 43.4, 55.0, 72.8, 113.6, 117.6, 126.9, 136.1, 158.8 corresponding to all the carbons of the compound **66c**. The of M^+ ion at 168 in the mass spectrum confirmed the formation of the compound. Aromatic,α,β-unsaturated and aliphatic aldehydes underwent the allylation reaction smoothly to give the desired products in good yields. Polyaromatic and heteroaromatic aldehydes also underwent allylation smoothly to give the corresponding allylated product.

Allylation of ketones and α-haloaryl ketones with allylstannanes

Allylation of ketones and α-haloketones is an important C-C bond forming reaction. Very few reports of allylation of ketones[131] and α-halo ketones[132] are available in the literature. Further, the catalytic activity of palladacycle on allylation of ketones and α-haloaryl ketones was investigated using palladacycle catalyst. Aromatic ketones with electron withdrawing or donating groups do not affect the chemical yield but the ketones with electron donating groups took longer reaction time. Allylation of α-chloroacetophenones with allyl tributylstannane gave β, γ-unsaturated ketones as a exclusive aryl rearranged product. On the other hand α-chloro-α-methyl-4-isobutylacetophenone gave predominantly carbonyl addition product with allyl tributyltin and 10% of aryl rearranged product. In a typical experimental procedure when 4-chloro acetophenone (309 mg, 2.0 mmol), was stirred with

allyltributylstannanes(0.728, 1.1 equiv, 2.2 mmol)in presence of Pd-OMS(MCM-41), and K_2CO_3(0.333g, 1.2equiv, 2.4mmol) and CuI(catalytic) in aq DMF (DMF : H_2O, 9:1) at 80^oC, it gave the required product (Table 12, entry 13) in 98% yield. The formation of the product was confirmed by spectral data. The IR spectrum of the compound **66m** showed the broad band at 3449cm^{-1} indicating the presence of hydroxy functionalities. The band at 1595cm^{-1} showed the presence of olefinic functionalities. The ^{1}H NMR spectrum of **66m** showed a doublet of doublet at δ 2.56 corresponding to one proton each of the allylic -CH_2 protons coupling with other olefinic protons. The -CH_2 protons of the terminal olefins appeared as a doublet at δ 5.16. The multiplet at δ 5.60 corresponding to one proton indicated the coupling of olefinic proton with two –CH_2 groups. In another experiment the addition of allyltributylstannanes with α-chloroacetophenone (**Table 12, entry 16 and 17, 66q and 66p**) in the presence of the palladacycle Pd-OMS(MCM-41), K_2CO_3 and CuI in aq DMF (DMF:H2O, 9:1) at 80^oC gave exclusively the phenyl rearranged product β,γ-unsaturated ketones **66q** in 76% yield. The formation of **66q** was confirmed by IR, NMR, and its mass spectral data. The IR spectrum of the compound **66q** shows bands at 1601cm^{-1} and at 1678cm^{-1} indicating the presence of the olefinic and carbonyl functionalities. The ^{1}H NMR spectrum of **66q** showed a quartet at δ 2.54 corresponding to two –CH_2 protons adjacent to the terminal olefins. The benzylic –CH_2 protons adjacent to the carbonyl group appeared as triplet at δ 3.10. The olefinic –CH_2 protons was seen as a multiplet at δ 5.96. The Molecular ion peak at 161 confirmed the formation of the rearranged product.

3.3.3 Allylation of imines with allyl stannanes:

In general, homoallylic amines are prepared either by addition of allylsilane, allyltin, allylboron or allylgermane reagents to imines in the presence of acid catalysts. However, these reactions can not be carried out in a one-pot operation with aldehydes, amine and allyl metal reagent because the amines and water that exist during imine formation can decompose or deactivate the Lewis acid. We have now successfully employed Pd-OMS (MCM-41) palladacycle to the one-pot synthesis of homoallylic amines. Thus a mixture of anisaldehyde, 4-chloroaniline, and allyltributylstannanes were reacted in the presence of palladacycle Pd-OMS(MCM-41), K_2CO_3, CuI, in aq DMF (DMF:H_2O, 9:1) to give the corresponding allylamine in 88% yiled. The IR spectrum of the **69a** (**Table 13 entry 1**), shows a band at

3415cm^{-1} and at 1600cm^{-1} indicating the presence of –NH and olefinic functionalities. The ^{1}H NMR spectrum of the compound **69a** shows a multiplet at 2.50 for the CH_2 protons adjacent to the C-C double bond. The benzylic protons attached to –NH functionality and adjacent to –CH_2 groups appeared as a quartet at δ 4.31. The olefinic –CH_2 protons was seen as multiplet at δ 5.18. The olefinic -CH protons was seen as multiplet at δ 5.73. The formation of **69a** was again confirmed by its ^{13}C NMR spectral data. Different aldehydes and amines were coupled successfully with allylstannanes to give the corresponding homoallylic amines. Both aromatic and aliphatic aldehydes afforded excellent yields of products. Aldehydes bearing electron-withdrawing substitutent also worked effectively. Acid sensitive aldehydes such as furfuraldehyde and cinnamaldehyde, were converted into its corresponding homoallylic amines without any decomposition. In all cases, no homoallylic alcohol was obtained under the reaction conditions. This is because of the rapid formation and activation of imines in presence of Pd catalyst. All the products were characterized by ^{1}H NMR, IR and mass spectral data.

3.3.3 Conclusion

In conclusion, we have successfully employed our palladacycle catalyst for the preparation synthetically useful homoallylic alcohol and homoallylic amines. A variety of aldehydes and imines were successfully coupled with allylstannanes reagents. Acid-sensitive aldehydes were successfully coupled to give the desired product. Polyaromatic aldehydes were also successfully coupled with allylstannanes. Another noteworthy feature of our method lies in the application of palladacycle catalyst for the synthesis of β, γ-unsaturated ketones by aryl rearrangements.

3.3.4 Experimental Section

General experimental procedure:

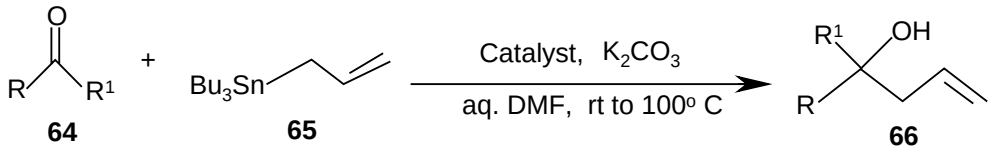
Allylation of aldehydes: A mixture of 2.0 mmol of aldehyde **64,** 2.2 mmole of allyltributylstannane **65,** 0.2 mole% of Pd-OMS(MCM-41) palladacycle and 2.4 mmol of K_2CO_3 in 1ml aq. DMF (9:1; DMF: H_2O) was stirred at 80°C for the indicated length of time(**Table 12**). The reaction was monitored by TLC. After completion of the reaction, the mixture was filtered for the catalyst recovery and thoroughly washed with diethyl ether. The

filtrate after washing with water, brine, dried over anhy. Na_2SO_4. Evaporation of solvent and purification, through a short silica gel column-chromatography gave the required product.

Allylation of imines: A typical procedure for Pd-OMS(MCM-41) palladacycle catalyzed allylation of imine is as follows. A mixture of 2.0 mmol of aldehyde, 2.0 mmol of amine and 2.2 mmol of allyltributyltin, 2.4 mmol of K_2CO_3 and 0.2 mol % of catalyst were stirred together in 1 ml of aq. DMF (DMF:H2O 9:1) at 80°C for the indicated time(**Table 13**). The reaction was monitored by TLC. After completion of the reaction, the reaction was filtered for the catalyst and thoroughly washed with diethyl ether. The combined organic filtrate was washed with water, brine, and dried over Na_2SO_4. After concentrating the filtrate the residue was purified through a short silica-gel column chromatography using petroleum ether: EtOAc (80:20) to give the pure allyl amines.

Table12. Pd-OMS(MCM-41) catalyzed allylation of aldehydes and ketones using allyltributyltin

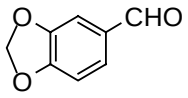
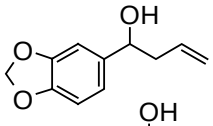
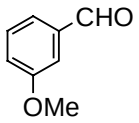
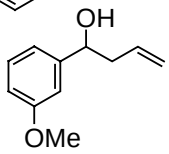
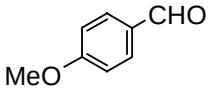
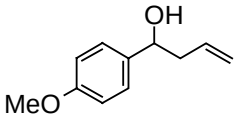
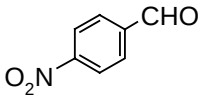
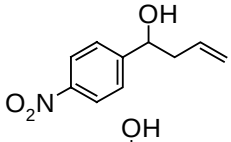
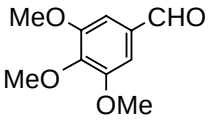
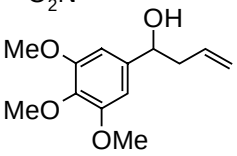
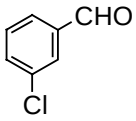
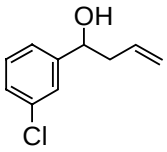
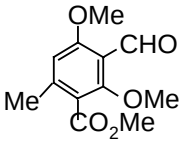
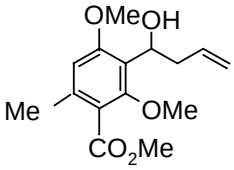
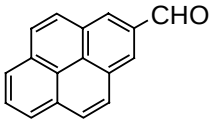
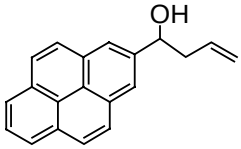
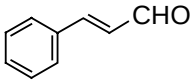
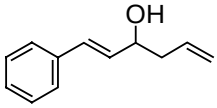
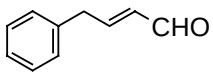
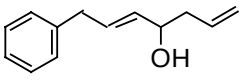
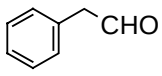
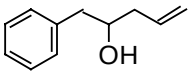
Scheme 7



64 **65** **66**

R = 4-OMe-C_6H_4, 3-OMe-C_6H_4, 3,4,5-$(OMe)_3$−C_6H_2, Cinnamyl. 3,4-OCH_2O-C_6H_3 , 3-Cl-C_6H_4 etc.

R^1 = H, CH_3CHCl, etc.

Entry	Substrate	Product	Product number	Reaction Time in hrs	Yield
1			66a	3	91
2			**66b**	4	92
3			**66c**	2	94
4			**66d**	4.5	85
5			**66e**	3.5	93
6			**66f**	4	90
7			**66g**	3	89
8			**66h**	2	84
9			**66i**	5	78
10			**66j**	7	66
11			**66k**	2	96

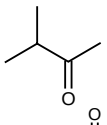
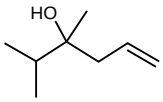
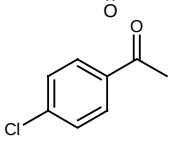
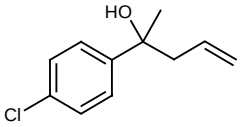
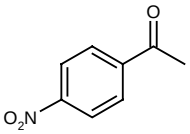
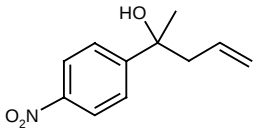
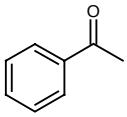
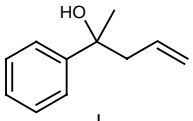
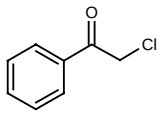
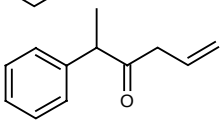
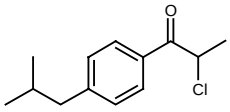
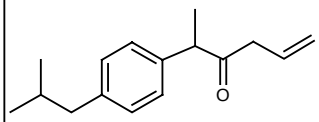
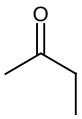
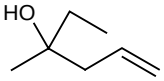
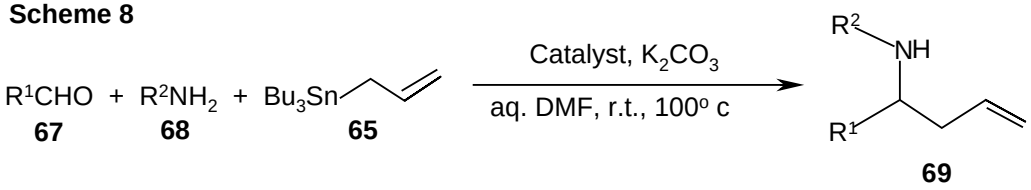
Entry	Substrate	Product	Product number	Reaction Time(h)	Yield %
12			**66l**	7	66
13			**66m**	1.5	98
14			**66n**	2	97
15			**66o**	2	93
16			**66p**	3	72
17			**66q**	2.5	76
18			**66r**	2	56

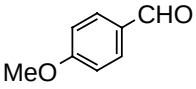
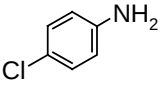
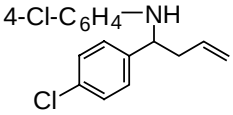
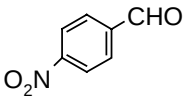
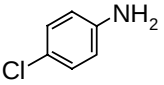
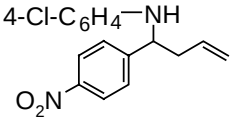
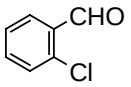
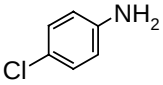
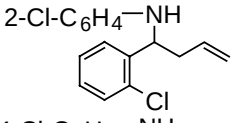
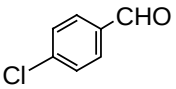
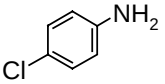
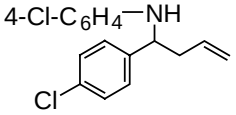
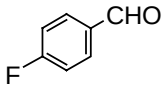
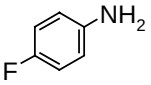
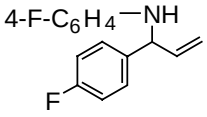
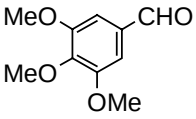
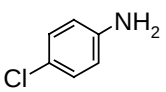
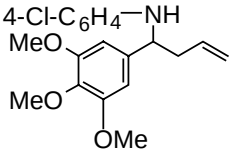
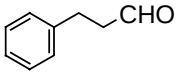
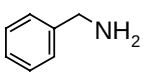
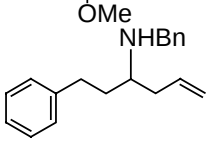
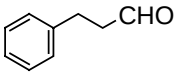
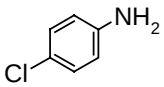
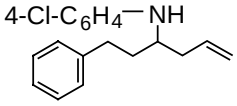
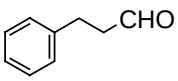
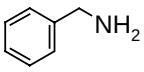
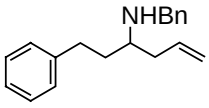
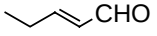
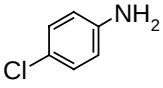
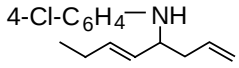
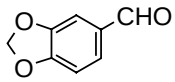
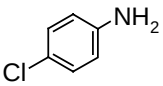
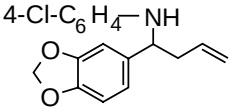
Table 13. Pd-OMS(MCM-41) Catalysed preparation of Homoallylic amines using allyltributyltin

Scheme 8



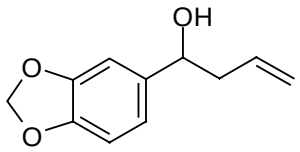
R1 = 4-MeO-C_6H_4, 4-NO_2-C_6H_4, Ph-CH=CH-, 2-Cl-C_6H_4-, 4-Cl-C_6H_4, 3,4,5-$(OMe)_3$-C_6H_2, CH_3CH_2CH=CH, $PhCH_2CH_2$, $PhCH_2$

R^2 = 4-Cl-C_6H_4, $PhCH_2$

Entry	Aldehyde	Amine	Product	Product no.	Reaction Time hrs	Yield in %
1				**69a**	6	88
2				**69b**	5	96
3				**69c**	7	94
4				**69d**	4.5	90
5				**69e**	4	86
6				**69f**	3	87
7				**69g**	2	81
8				**69h**	8	71
9				**69i**	7.5	70
10				**69j**	6	52
11				**69k**	5	94

Allylation of aldehydes, and ketones and α-halo ketones:

1-Benzo[1,3]dioxol-5-yl-but-3-en-1-ol (66a)



66a

Yield: 91%

Pale Yellow Liquid

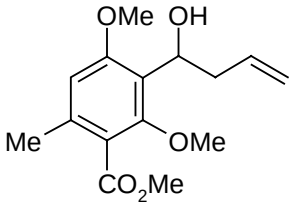
IR (Neat, cm-1): ν_{max} 3444, 3010, 2958, 2927, 2872, 1721, 1673, 1493

^{1}H NMR(200 MHz, $CDCl_3$): δ 2.37(brs, 1H), 2.46 (t, 2H, *J* = 5.75Hz), 4.62 (t, 1H, *J* = 5.74Hz), 5.09 (s, 1H), 5.14(d, 1H, *J* = 5.75Hz), 5.67-5.84 (m, 1H), 5.92 (s, 2H), 6.77 (s, 2H), 6.86 (s, 1H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 46.0, 74.4, 111.4, 116.2, 117.2, 118.5, 125.4, 127.0, 133.0, 134.7, 143.8

Analysis cacld for $C_{11}H_{12}O_3$ (192.21): Found C, 68.52; H, 6.44{Found C, 68.74; H, 6.29}

3-(1-Hydroxy-but-3-enyl)-2, 4-dimethoxy-6-methyl-benzoic acid methyl ester(66g)



66g

Yield: 89%

Pale Yellow Solid

M.P.: 45-47^0 C

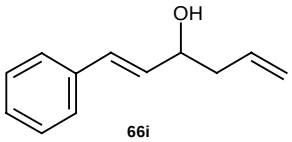
IR ($CHCl_3$, cm^{-1}): ν_{max} 3455, 3109, 2259, 1610, 1567, 1492, 1354, 1249, 1123

^{1}H NMR : (200 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.42-2.53 (m, 1H), 2.67-2.76 (m, 1H), 3.41-3.44 (m, 1H), 3.79 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 5.03 (s, 1H), 5.06 (d, 2H, *J* = 8.71Hz)), 5.80-5.91 (m, 1H), 6.52 (s, 1H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 19.9, 42.1, 52.0, 55.6, 63.0, 67.9, 108.8, 116.6, 121.1, 122.2, 135.4, 137.3, 156.0, 158.9, 168.4

Analysis calcd for $C_{15}H_{20}O_5$ (280.31): Found C, 64.03; H, 6.92 {Required C, C, 64.27; H, 7.19}

1-Phenyl-hexa-1, 5-dien-3-ol (66i)



66i

Yield: 78%

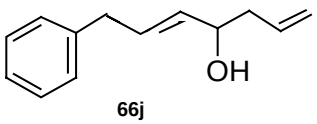
Thick Brown Oil

IR (Neat,cm^{-1}): ν_{max}3379, 3078, 3026, 2977, 2957, 2927, 2856, 1947, 1875, 1806, 1712, 1640, 1599, 1577

^{1}H NMR(200 MHz,$CDCl_3$): δ 1.95(brs, 1H), 2.37-2.46 (m, 2H), 4.38(dd, 1H, *J* = 4.31Hz, 7.78Hz), 5.14(s, 1H), 5.20(d, 1H, *J* = 7.79Hz), 5.76-5.97 (m, 1H), 6.25 (dd, 1H, *J* = 5.71Hz, 16.81Hz), 6.58 (d, 1H, *J* = 16.81Hz), 7.50-7.66 (m, 5H)

Analysis calcd for $C_{12}H_{14}O$ (172.24): Found C, 80.71; H, 7.98{Required C, 80.98; H, 8.10}

7-Phenyl-hepta-1, 5-dien-4-ol (66j)



66j

Yiled: 66%

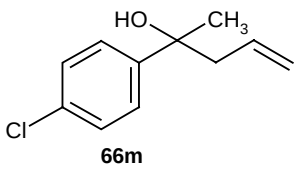
Brown Oil

IR ($CHCl_3$, cm^{-1}): ν_{max}3450, 3107, 2281, 1625, 1607, 1581, 1487, 1351, 1249, 1101

^{1}H NMR 200 MHz, $CDCl_3$): δ 2.11(brs, 1H), 2.38(t, 2H, *J* = 9Hz)), 3.49(d, 1H, *J* = 15Hz), 3.61(t, 1H, *J* = 9 Hz), 3.66(d, 1H, J = 15Hz), 5.02-5.09(m, 2H), 5.61-5.75(m, 1H), 6.93 (d, 1H, J = 9Hz), 7.27-7.42 (m, 6H)

Analysis cacld for $C_{13}H_{16}O$ (188.268): C, 83.08; H, 8.64{Found C, 82.94; H, 8.56}

2-(4-Chlorophenyl)-pent-4-en-2-ol (66m)



66m

Yield: 98%

Pale yellow oil

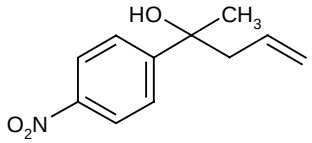
IR ($CHCl_3$, cm^{-1}): ν_{max}3449, 3076, 2977, 2929, 1903, 1850, 1639, 1595, 1490, 1453, 1400, 1374, 1264

^{1}H NMR (200 MHz, $CDCl_3$): δ1.53 (s, 3H), 2.49 (dd,1H, *J* = 8.79Hz, 13.92Hz), 2.62 (dd, 1H, *J* = 6.51Hz, 13.92Hz), 5.12 (d, 2H, *J* = 13.93Hz), 5.54-5.64 (m, 1H), 7.29 (d, 2H, *J* = 8.80Hz), 7.37 (d, 2H, *J* = 8.80Hz)

^{13}C NMR (200 MHz, $CDCl_3$): δ 29.6, 48.3, 73.3, 119.4, 126.3(2C), 128.1(2C), 132.3, 133.2, 146.2

Analysis cacld for $C_{11}H_{13}ClO$ (196.68): C, 67.24; H, 6.71{Found C, 67.18; H, 6.66}

2-(4-nitrophenyl)-pent-4-en-2-ol (66n)



66n

Yield: 72%

Dark Brown Oil

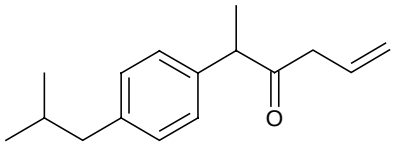
IR (Neat, cm^{-1}): ν_{max}3426, 3078, 2978, 2930, 2857, 1934, 1713, 1641, 1598, 1519, 1454.

^{1}H NMR (200 MHz, $CDCl_3$): δ1.56 (s, 4H, OH+CH_3), 2.53 (d, 1H, *J* = 9Hz), 2.63 (d, 1H, *J* = 13.92Hz), 5.11(d, 1H, *J* = 6.51Hz), 5.16(s, 1H), 5.50-5.64 (m, 1H), 7.59 (d, 2H, *J* = 8.79Hz), 8.16 (d, 2H, *J* = 8.79Hz).

^{13}C NMR (200 MHz, $CDCl_3$): δ 29.6, 48.2, 73.6, 120.3, 123.3, 125.9, 132.4, 146.6, 155.0

Analysis cacld for $C_{11}H_{13}NO_3$(207.228): Found C, 63.83; H, 6.45; N, 6.69{Required C, 63.75; H, 6.32; N, 6.76}

2-Chloro-3-(4-isobutylphenyl)-hex-5-en-3-ol (66p)



66P

Yield: 72%

Pale Yellow Oil

IR (Neat, cm^{-1}): ν_{max}3415, 3075, 3006, 2956, 2932, 2836, 1816, 1638, 1600, 1498, 1464, 1440

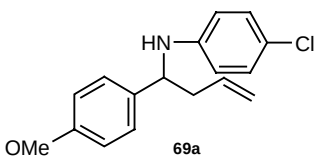
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (s, 3H), 0.93(s, 3H), 1.20(d, 3H, *J* = 6.60Hz)), 1.25-1.42 (m, 1H), 1.86-1.95 (m, 1H), 2.15-2.25 (m, 1H), 2.52 (d, 2H, *J* = 6.60Hz)), 3.47-3.59 (m 1H), 5.03(t, 2H, *J* = 16.81Hz), 5.73-5.86 (m, 1H), 7.23 (d, 2H, *J* = 8.07Hz)), 7.87 (d, 2H, *J* = 8.06Hz)

^{13}C NMR (200 MHz, $CDCl_3$): δ 17.0, 22.2, 30.0, 37.6, 40.3, 45.3, 116.4, 128.2(2C), 129.3(2C), 134.3, 135.9, 147.2, 203.0

Analysis cacld for $C_{16}H_{23}OCl$ (265.80): Found C, 72.44; H, 8.41{Required C, 72.30; H 8.34}

Allylation of Imines(Homoallylic amines):

(4-chlorophenyl)-[1-(4-methoxyphenyl)-but-3-enyl]-amine (69a)



69a

Yiled: 88%

Brown oil

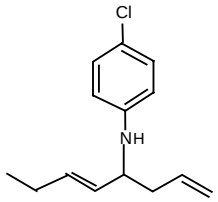
IR (Neat, cm^{-1}): ν_{max}3415, 3075, 3006, 2956, 2932, 2836, 1816, 1638, 1600, 1498, 1464, 1440

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 (m, 2H), 3.20 (br s, 1H), 3.80 (s, 3H), 4.30 (dd, 1H, J = 5.31Hz, 8.79Hz), 5.13-5.22 (m, 2H), 5.65-5.82 (m, 1H), 6.40 (d, 2H *J* = 8.31Hz), 6.84 (d, 2H *J* = 8.31Hz), 7.00 (d, 2H *J* = 8.79Hz), 7.22 (d, 2H *J* = 8.79Hz)

^{13}C NMR (200 MHz, $CDCl_3$): δ 43.1, 55.1, 56.7, 114.0, 114.6, 118.2, 121.9, 127.2, 128.8, 134.5, 134.9, 145.9, 158.7

Analysis cacld for $C_{17}H_{18}NOCl$ (287.788): Found C, 70.80; H, 6.18; N, 4.75{Required C, 70.95; H, 6.30; N, 4.86}

(1-Allyl-pent-3-enyl)-(4-chlorophenyl)-amine(66j)



69j

Yiled: 52%

Brown Oil.

IR (Neat, cm^{-1}): ν_{max}3418, 3078, 2959, 2923, 2777, 2252, 1861, 1711, 1686, 1639, 1599, 1499, **^{1}H NMR(200 MHz, $CDCl_3$):** δ 0.98-1.01 (t, 3H, *J* = 8Hz)), 1.98-2.05(t, 2H, *J* = 8Hz), 2.26-2.39 (m, 2H), 3.76-3.84 (m, 1H), 5.11-5.28 (m, 3H), 5.32-5.88 (m, 1H,), 5.65-5.88 (m, 2H), 6.48 (d, 2H, *J* = 7.71Hz), 7.07 (d, 2H, *J* = 7.72Hz)

^{13}C NMR (200 MHz, $CDCl_3$): δ13.6, 25.2, 40.4, 54.5, 114.1, 114.5, 117.9, 118.0, 121.6, 128.8, 129.0, 129.6, 133.5, 134.5, 146.1.

Analysis cacld for $C_{14}H_{18}NCl$ (235.756): Found C, 71.47; H, 7.73; N, 5.98{Required C, 71.328; H, 7.695; N, 5.941}

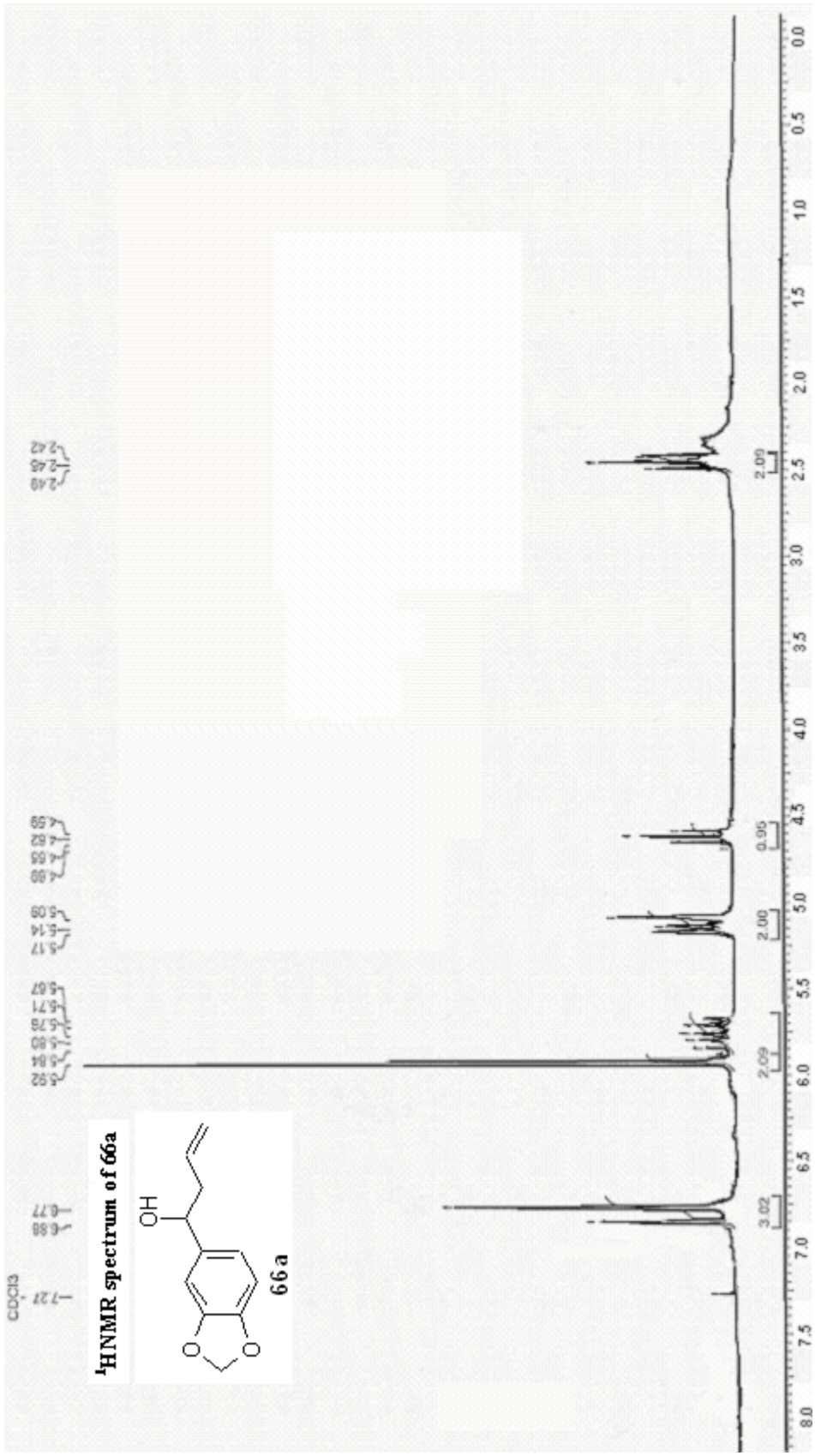
3.3.5 Spectra

Allylation of aldehydes and ketones

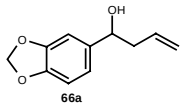
1. **^{1}HNMR spectrum of 66a**
2. **^{13}CNMR spectrum of 66a**
3. **^{1}HNMR spectrum of 66g**
4. **^{13}CNMR spectrum of 66g**
5. **^{1}HNMR spectrum of 66i**
6. **^{1}HNMR spectrum of 66j**
7. **^{1}HNMR spectrum of 66m**
8. **^{13}CNMR spectrum of 66m**
9. **^{1}HNMR soectrum of 66p**
10. **^{13}CNMR spectrum of 66p**

Allylation of imines

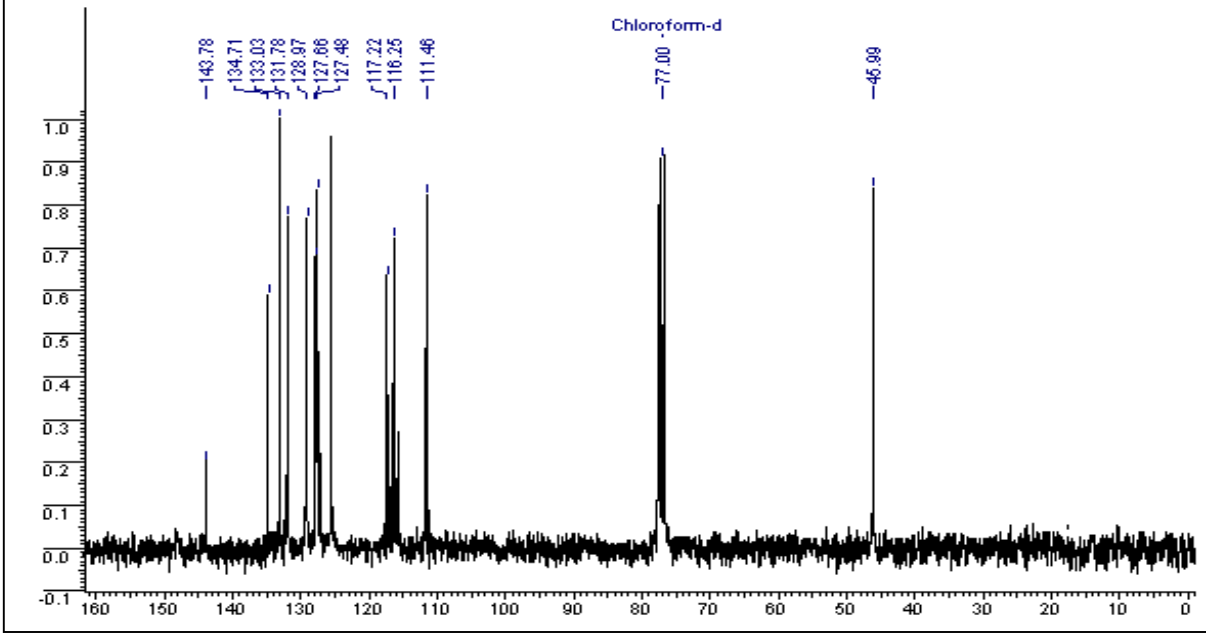
1. **^{1}HNMR spectrum of 69a**
2. **^{13}CNMR spectrum of 69a**
3. **^{1}HNMR spectrum of 69j**
4. **^{13}CNMR spectrum of 69j**


^{1}HNMR spectrum of 66a
OH
O
O
66a
CDCl3
7.27
6.88
6.77
5.92
5.84
5.80
5.76
5.71
5.67
5.17
5.14
5.09
4.68
4.65
4.62
4.59
2.49
2.46
2.42
3.02
2.09
2.00
0.95
2.09
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

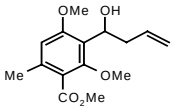
^{13}CNMR spectrum of **66a**



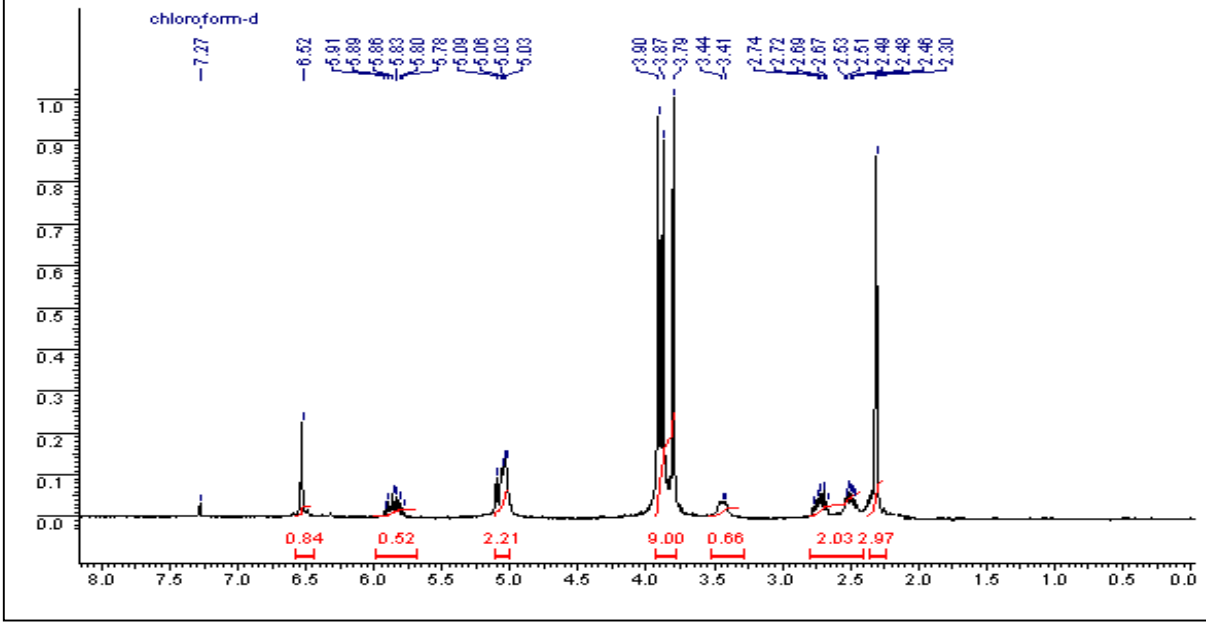
66a



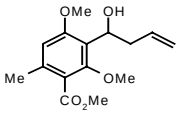
^{1}HNMR spectrum of **66g**



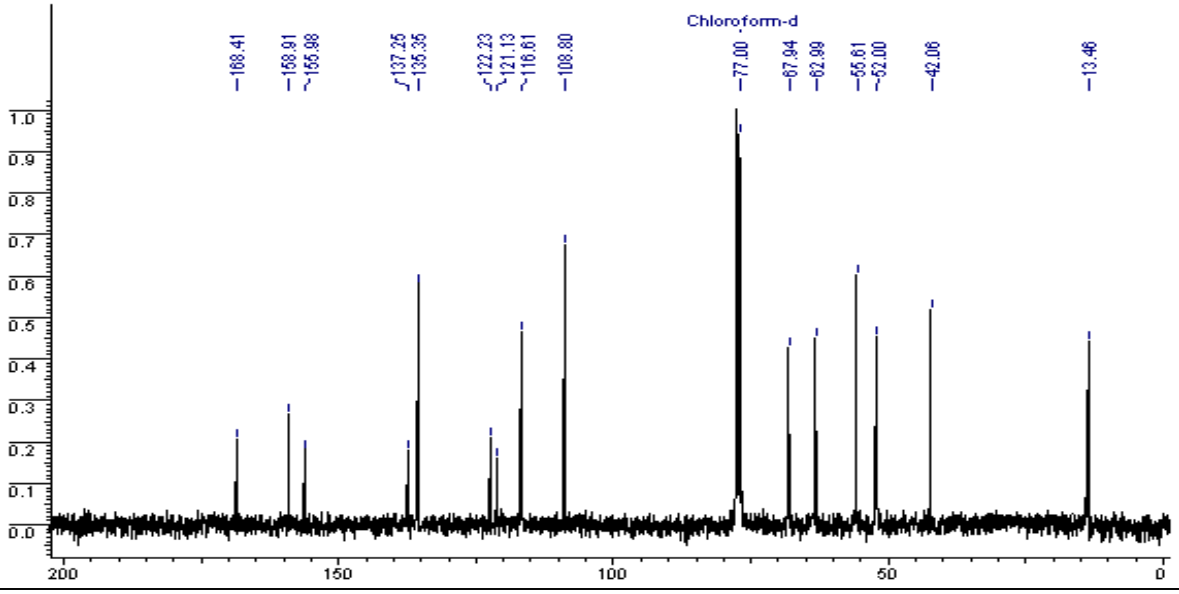
66g



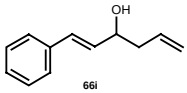
^{13}CNMR spectrum of **66g**



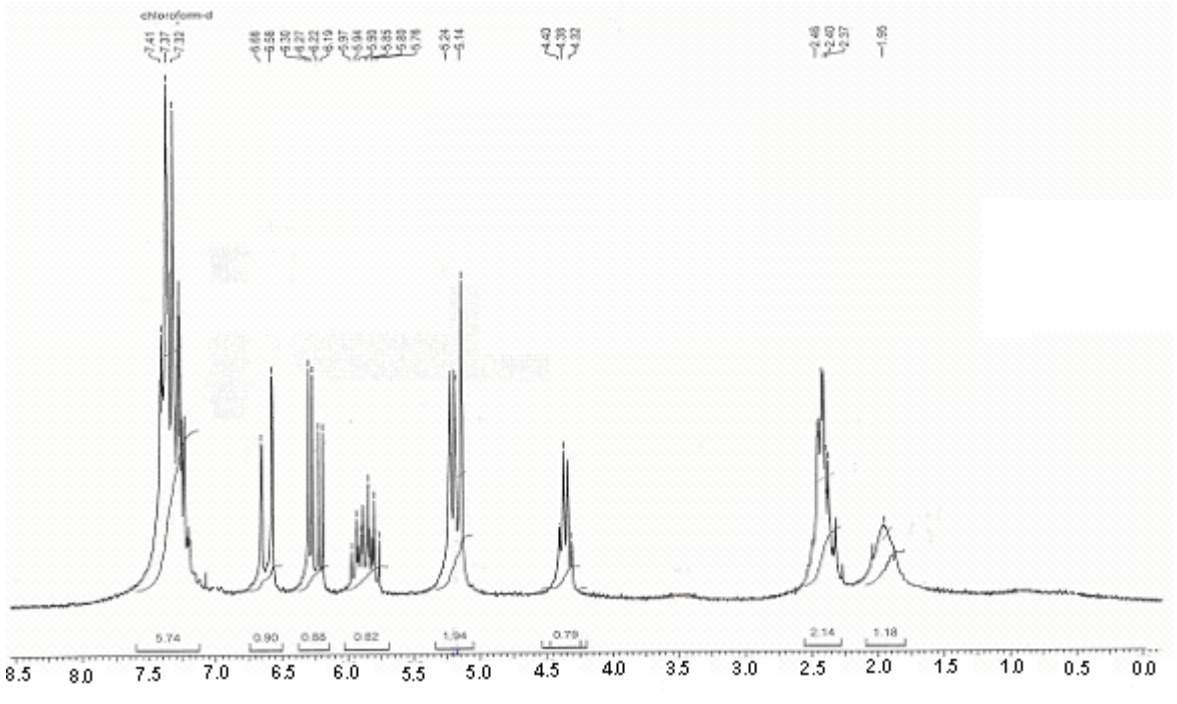
66g



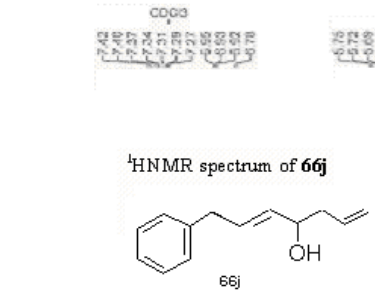
^{1}HNMR spectrum of **66i**



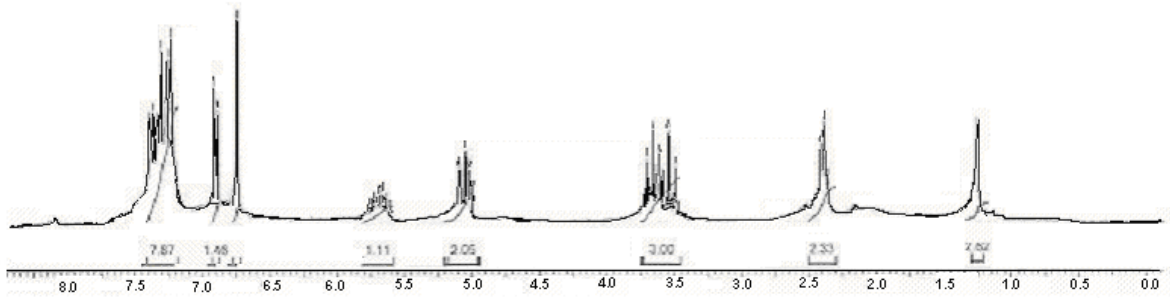
66i



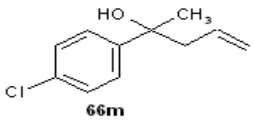
^{1}HNMR spectrum of **66j**



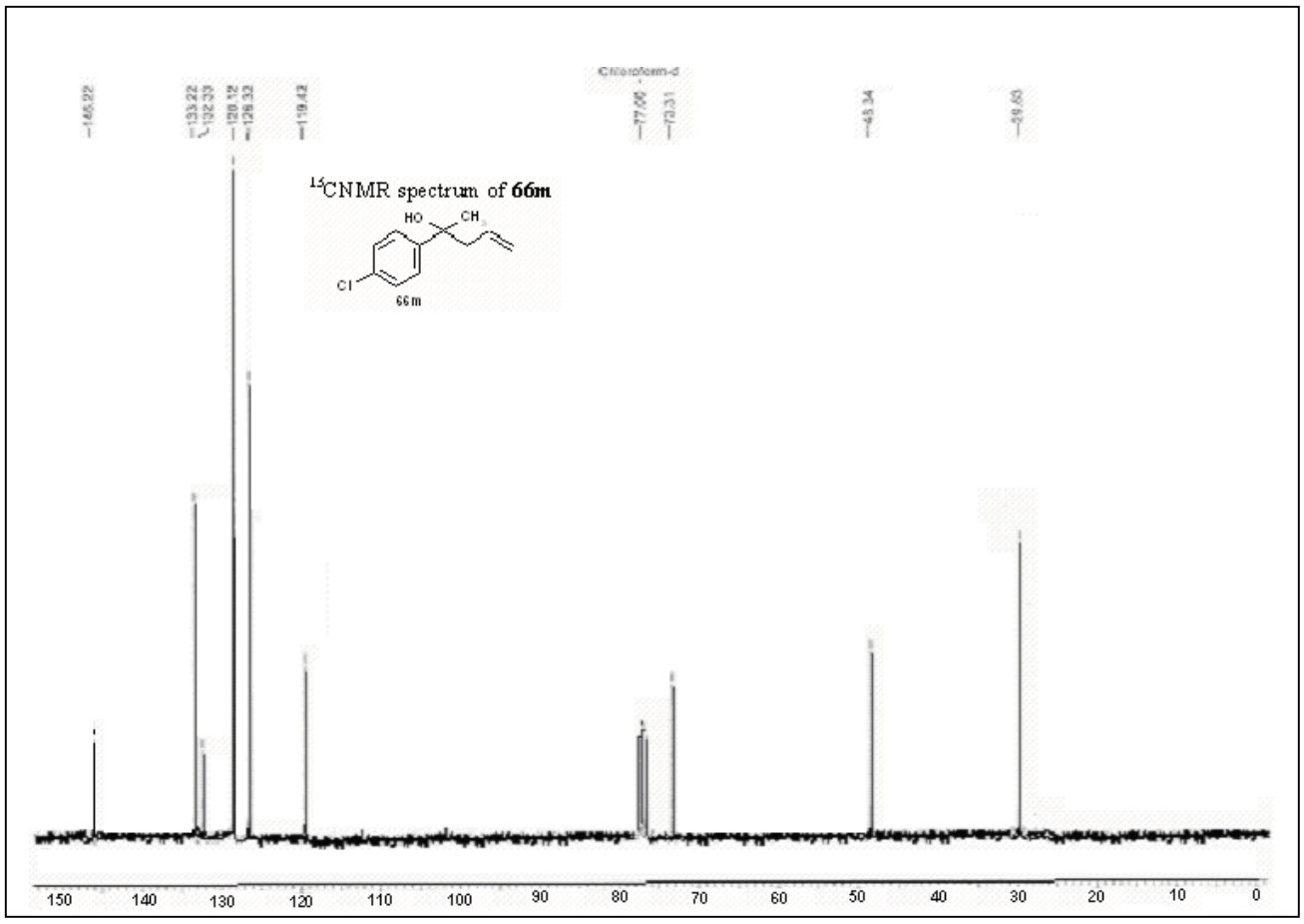
66j

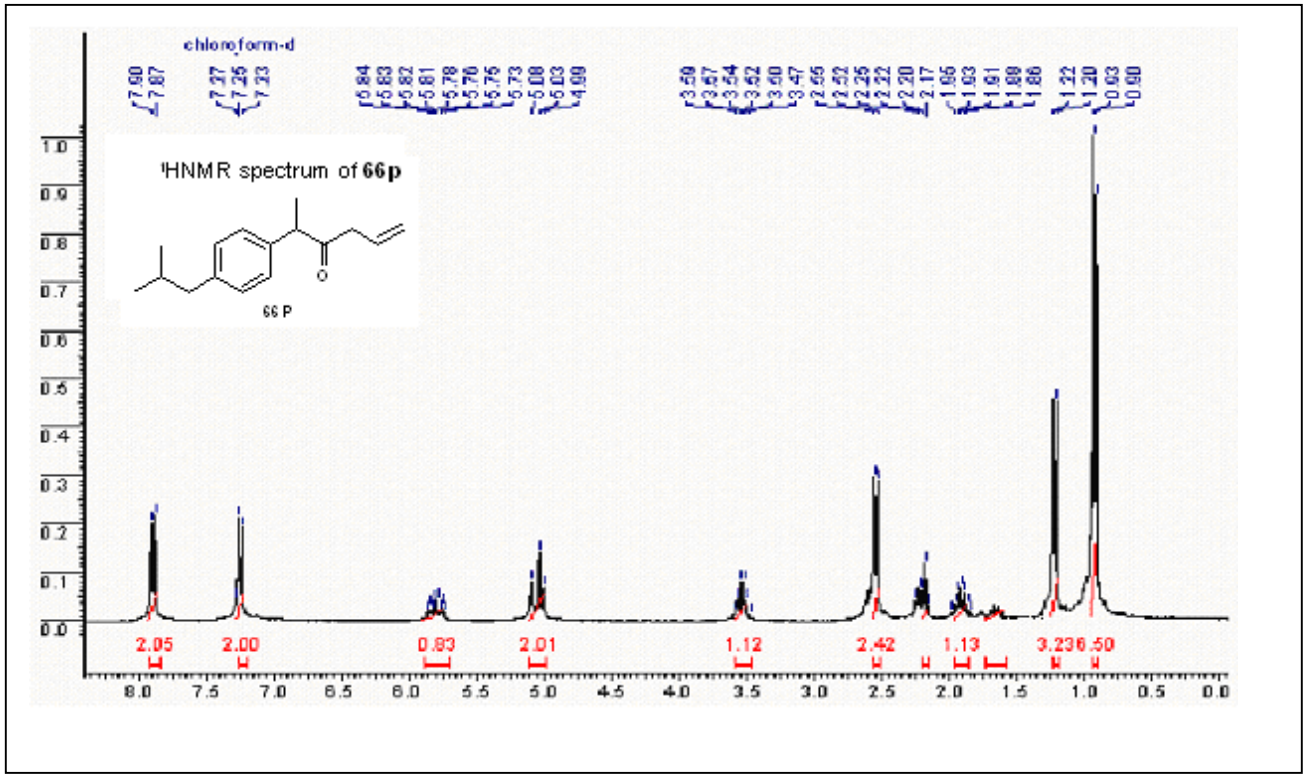


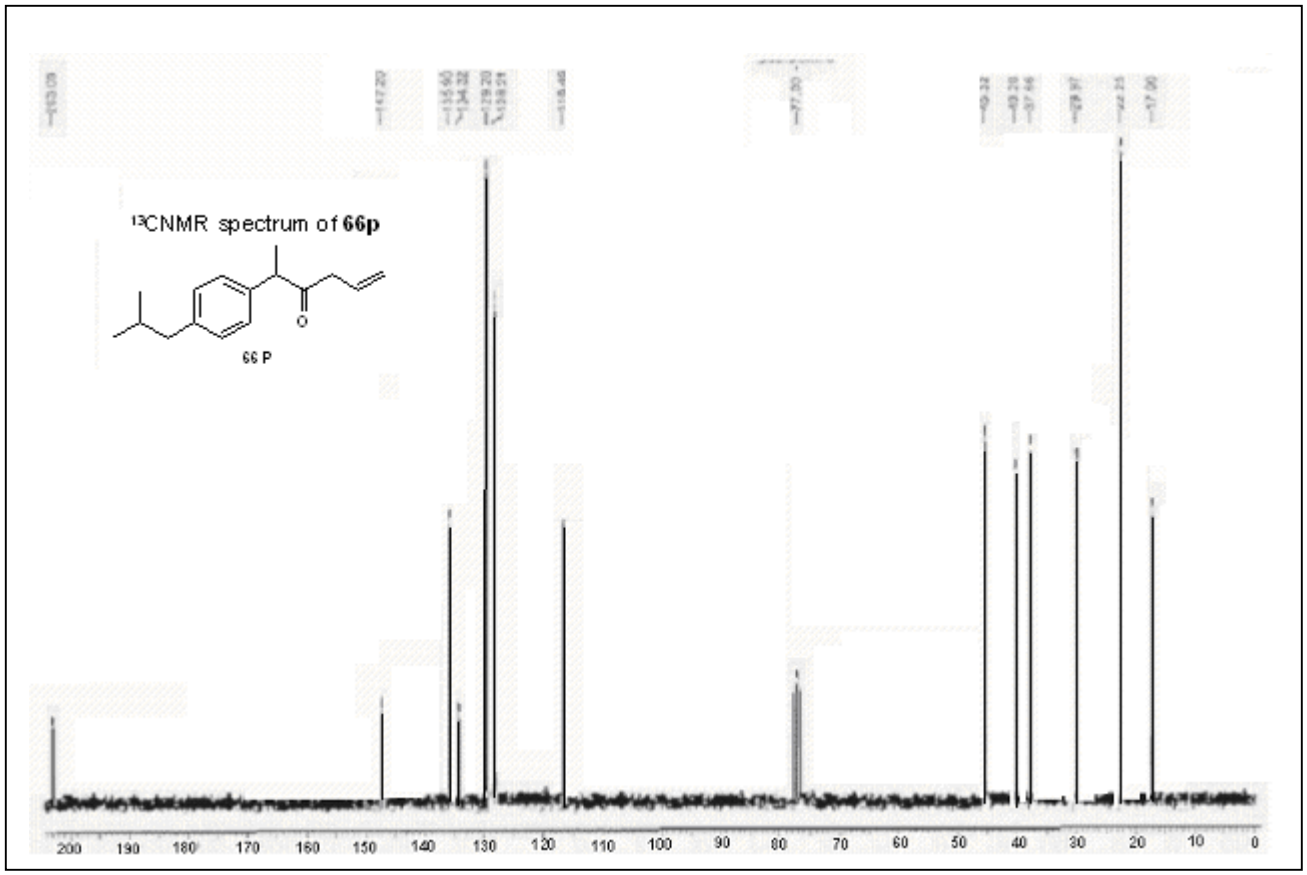
^{1}HNMR spectrum of **66m**

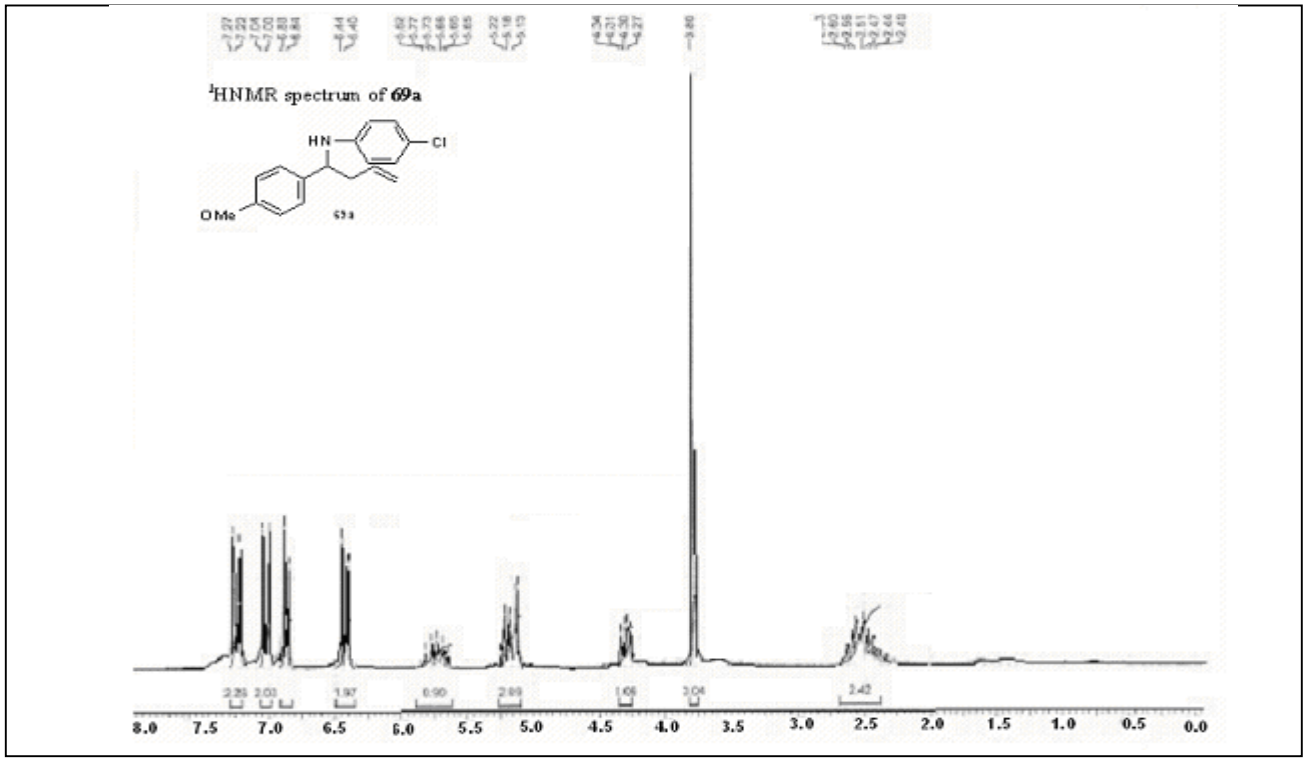


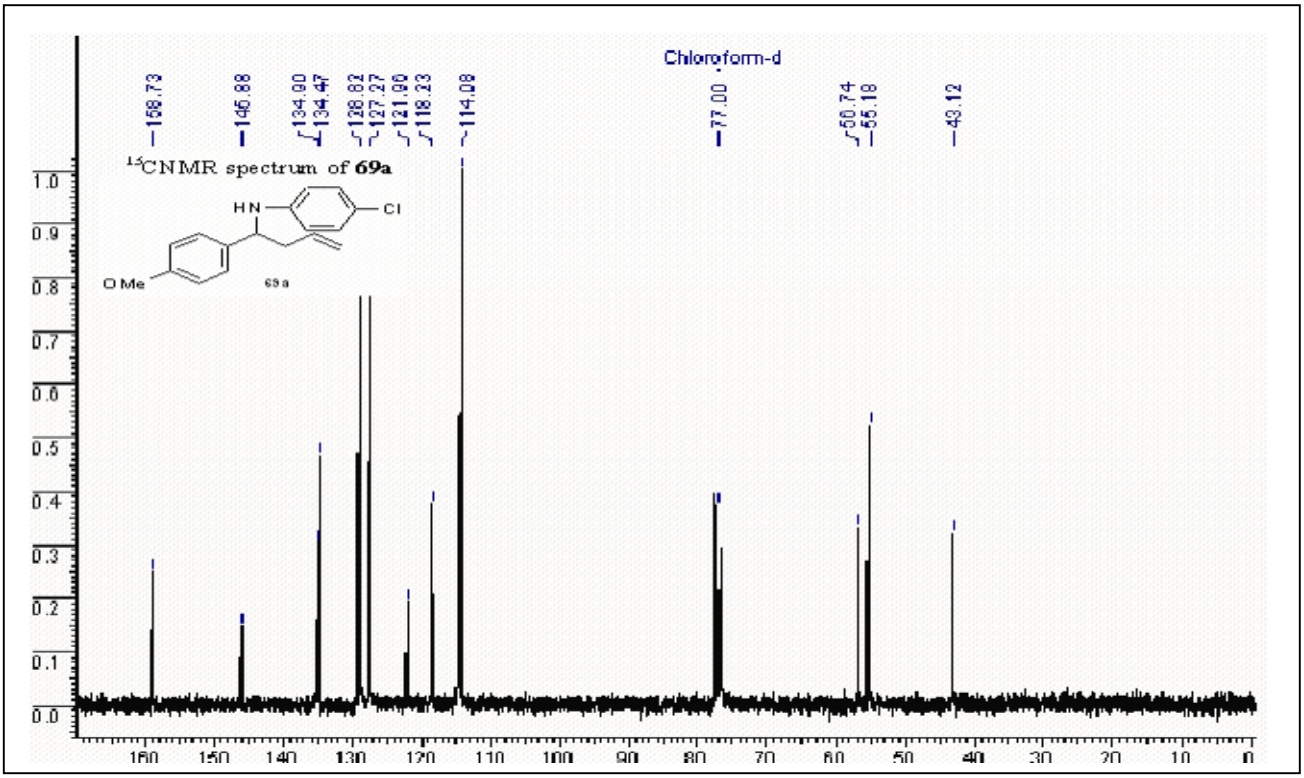
66m

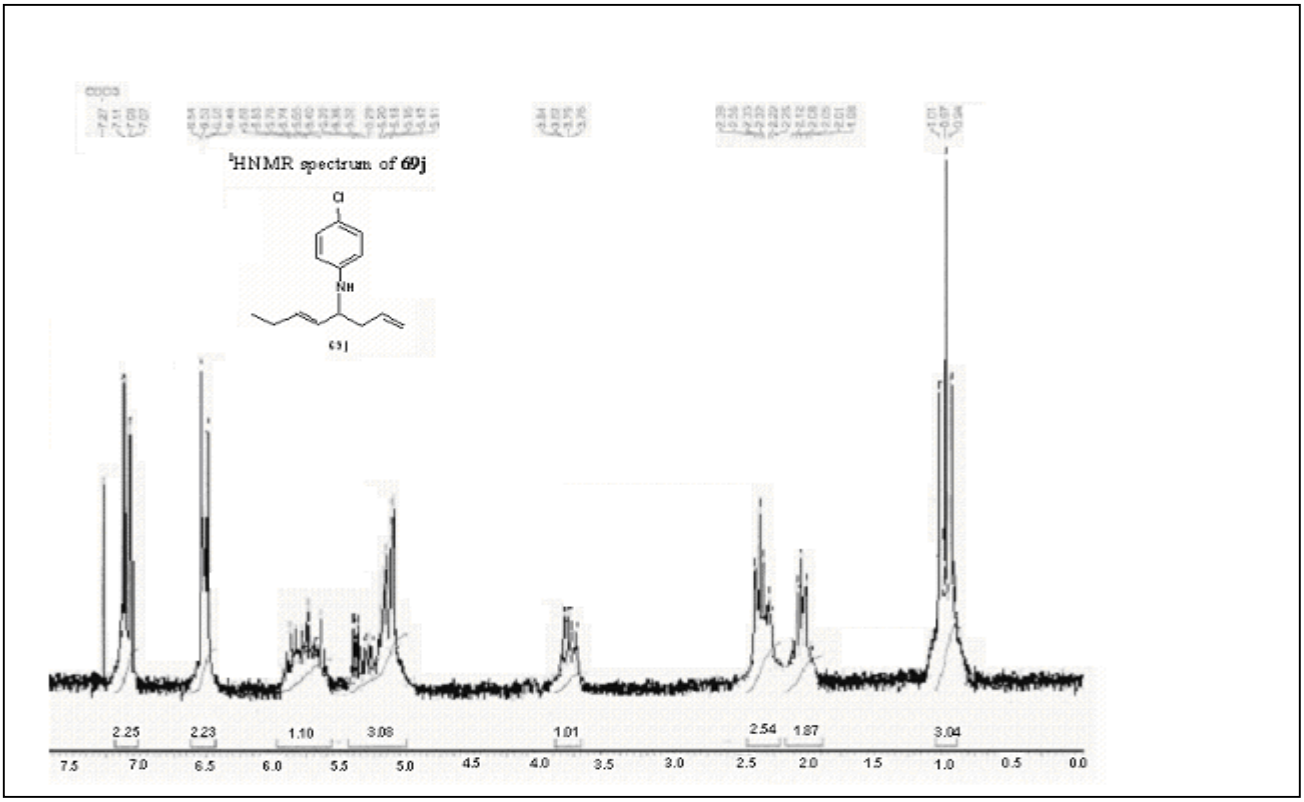

^{13}CNMR spectrum of **66m**
HO
CH
Cl
66m
Chloroform-d
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

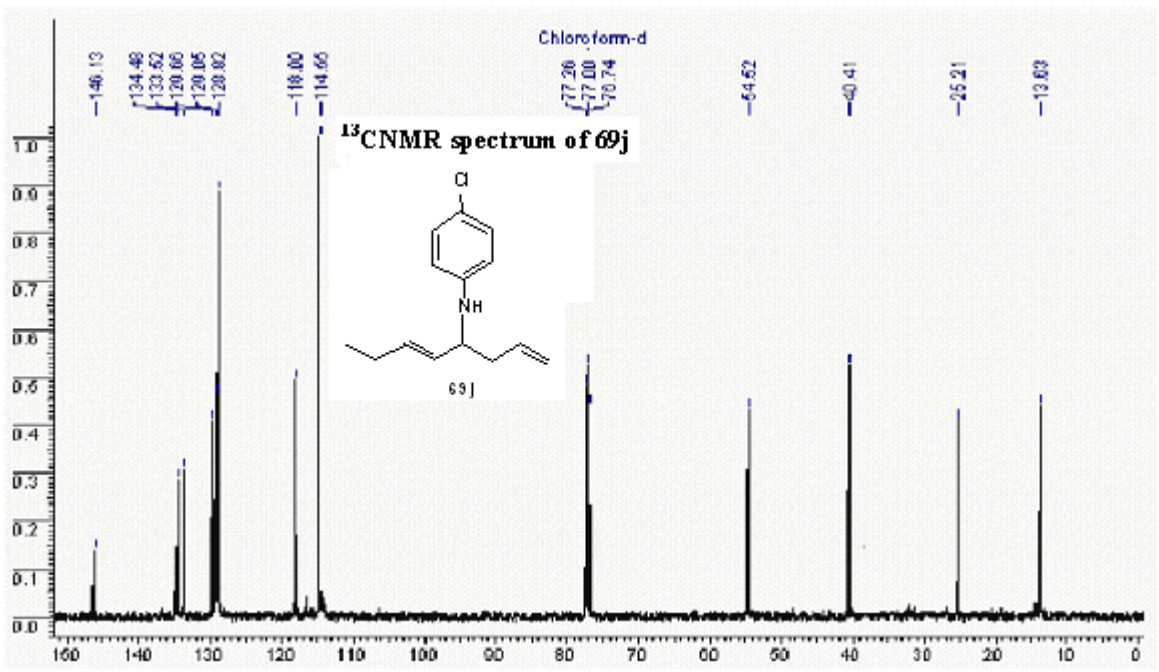

chloroform-d
^{1}HNMR spectrum of **66p**
O
66 P
2.05
2.00
0.83
2.01
1.12
2.42
1.13
3.23
6.50
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


^{13}CNMR spectrum of **66p**
66 P


^{1}HNMR spectrum of **69a**
HN
Cl
OMe
69 a


Chloroform-d
168.73
146.88
134.90
134.47
128.82
127.27
121.90
118.23
114.08
77.00
56.74
55.18
43.12
^{13}CNMR spectrum of **69a**
HN
Cl
OMe
69a


^{1}HNMR spectrum of **69j**
Cl
NH
69j
2.25
2.23
1.10
3.08
1.01
2.54
1.87
3.04



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CHAPTER 4

Synthesis, Characterization and Application of Sulfated Yttria-Zirconia Based Lewis Acid Catalyst for Organic Transformations

4.1 Section A

Synthesis and Physicochemical Characterisation of Yttria-Zirconia based Lewis acid Catalyst

4.1.1 Introduction

Heterogeneous catalysis is crucial to chemical technology. Innumerable chemical reactions are facilitated by catalysis. Chemical bonds are broken and new chemical bonds are formed during the catalytic process. These events occur repeatedly usually without a significant change of the catalyst. In the absence of the catalysts, this chemical transformation would either not occur or would take place with lower efficiencies of slower rates. The study of heterogeneous catalysis dates back to the early 1800s. Faraday was one of the first scientists to examine the ability of platinum to facilitate oxidation reactions. These catalytic reactions played a key role in the development of industrial revolution.

The ability of catalyst to crack long-chain hydrocarbons was critical for the emerging automobile industry. As we are now in 21st century, we would have difficulty in imagining the world without fruits of heterogeneous catalysis. The needs for the better catalysis will only increase as environmental and economic concerns motivate the development of more efficient catalysts.

Inorganic oxides and zeolites play an extremely important role in heterogeneous catalysis. We have been involved in the development of new heterogeneous catalysis and syntheses of new catalysts viz. zeolites and some metal oxides and its utility for some organic transformations and for auto exhaust emission control etc. In continuation of these efforts, we synthesized first time an yttria-zirconia based strong Lewis acid catalyst and its Lewis-acidity has been successfully exploited for the acceleration of Diels-Alder reaction (C-C bond formation reaction) under mild conditions. The possibility of using it for the other organic synthesis transformations has been investigated.

4.1.2 Synthesis of catalyst

The catalyst was prepared by mixing aq. solutions of yttrium nitrate and zirconyl nitrate in the mole ratio 16:84, to which aqueous ammonia (28%) was added under vigorous stirring until a pH of 8.5 was achieved and precipitate was formed. Washing with deionized water, drying at

110°C for 24 hours, treating with sulfuric acid (4M), drying at 120°C and subsequent programmed calcinations of 500°C for 3 hours at a heating rate of 2°C $min.^{-1}$ resulted in a highly acidic material. The chemical composition of the final catalyst (determined by XRF technique) was found to be 82.6 mole% Zr, 15.6 mole% Y and 1.8 mol% S. The physicochemical characterization of the catalyst was carried out by titration, temperature programmed desorption (TPD), scanning electron microscopy (SEM) and N_2 adsorption techniques.

4.1.3 Physicochemical characterization

The diffractogram of X-ray powder diffraction pattern was recorded on a Rigaku diffractometer model D/Max. IIIVC with N-filtered Cu-Kα radiation. FTIR spectrum of pyridine adsorbed on the yttrium-based catalyst was recorded on a Nicolet 60 SXB FTIR spectrometer. TPD profile (ammonia) of the cerium-based catalyst was recorded on a Sorbstar apparatus. Determination of specific surface area was carried out by BET (Brunner-Emmett-Teller) N_2 adsorption using a Omnisorp 100CX apparatus.

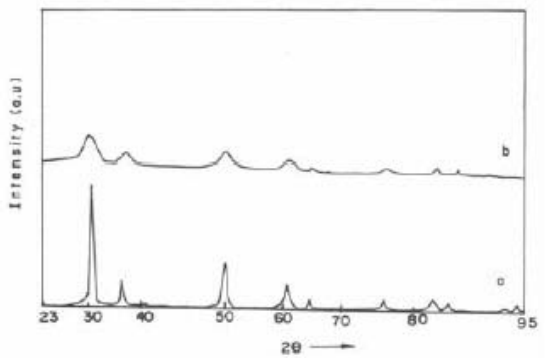


Figure 1. X- ray powder diffraction pattern of the yttrium based catalyst prior to (a) and after (b) sulfation. The diffractogram was recorded on a Rigaku diffractometer, model D/Max. IIIVC, with Ni-filtered $Ca_{k\alpha}$ radiation. I = intensity (arbitrary units).

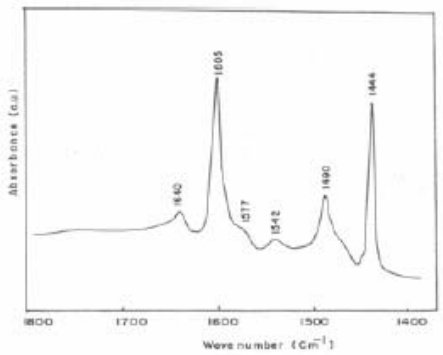


Figure 2. FTIR spectrum of pyridine adsorbed on the yttrium-based catalyst, recorded on a Nicolet 60 SXB FTIR spectrometer. A = absorption (arbitrary units).

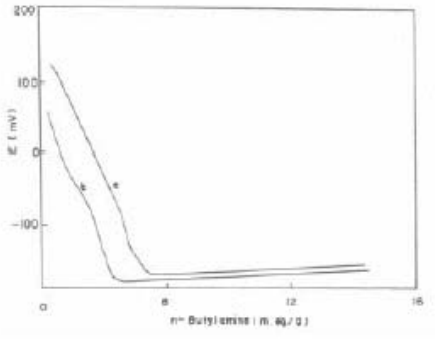


Figure 3. Potentiometric titration curves of the sulphated catalyst with yttrium (curve a) and without yttrium (curve b) in CH_3CN. For details see ref, [19]. n = number of molar equivalents of n-butylamine per g.

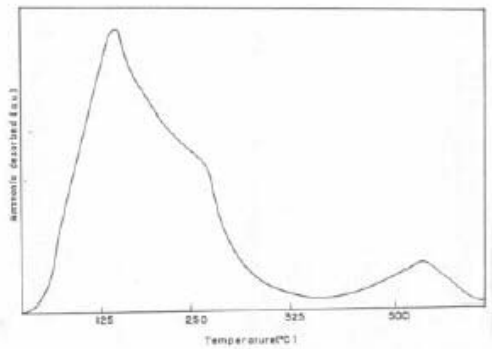


Figure 4. TPD profile (ammonia) of the yttrium-based catalyst, recorded on a Sorbstar apparatus, Institute of Isotopes, Hungary, with He as the carrier gas, a flow rate of 50 mL min^{-1}, and a heating rate of 10 K min^{-1} from room temperature to 625°C. NH_3 = amount of ammonia desorbed (arbitrary units).

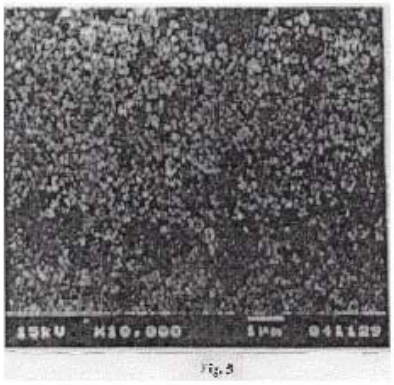


Figure 5. Scanning electron micrograph of the catalyst

4.1.4 Results and discussion

The physicochemical characterization of the catalyst was carried out by titration, temperature programmed desorption (TPD), scanning electron microscopy (SEM) and N_2 adsorption techniques. The X-ray powder diffraction profile of the catalyst shows the formation of a cubic phase (Figure 1). The IR spectra of pyridine adsorbed on the catalyst show absorption bands at 1640, 1605, 1577, 1542, 1490 and 1444 cm^{-1} (Figure 2). The strong absorption bands at 1605 and 1444 cm^{-1} indicate the presence of coordinated pyridine at the Lewis acid sites of the catalyst. The weak absorption at 1542 cm^{-1}, attributed to the pyridinium ion[1a] indicates the presence of a few Brönsted acid sites. The potentiometric titration of the acid sites with n-butylamine in nonaqueous medium(Figure 3) shows the influence of yttrium in enhancing the number of acid sites.[1b] The amount of n-butylamine consumed was 7.7 mol equiv g-1 for the yttrium-free catalyst. The presence of very strong acid sites in the catalysts is indicated by the peak maximum at 530°C in the TPD profile(Figure 4).[1c] The scanning electron micrograph of the sample shows the presence uniform-sized (around 0.3 μm) particles(Figure 5). The surface area of the sample determined by the BET method was 150m^2g^{-1}. The lattice defects caused by the incorporation of yttrium in the Zr^{4+} sites appear to enhance the number and strength of the Lewis acid sites of the catalyst.

4.1.5 Conclusion

In conclusion was have synthesized sulfated yttria-zirconia based strong Lewis acid catalyst for the first time which ws fully characterized by physicochemical characterization method such as XRD, SEM, TPD and FT-IR.

4.2 Section B

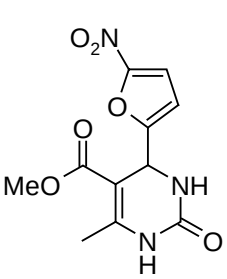
Application of sulfated Yttria-zirconia based Lewis acid catalyst for organic transformations

This section describes the application of Yttria-zirconia based Lewis acid catalyst for various organic transformations and is divided into four parts**.**

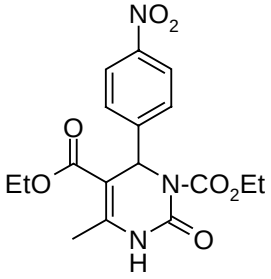
4.2.1 Part I. Yttria-zirconia based Lewis acid catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones in aqueous acetonitrile (Biginelli reaction)

4.2.1.1 Introduction

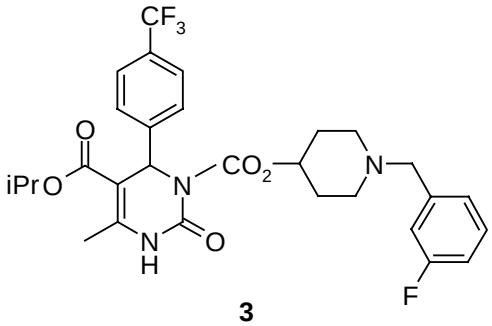
The fundamental target of modern organic synthesis is art of performing efficient chemical transformation of coupling three or more components in a single operation by a catalytic process avoiding stoichiometric toxic reagents, solvents and expensive purification technique.[1d] The discovery of new leads[2] and the preparation of libraries of small organic molecules is a rapidly evolving area of research.[3] The Biginelli reaction is constituted by a one-pot acid catalysed cyclocondensation of an aldehyde, a β-keto ester and urea leading to 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) (Scheme-1). DHPM derivatives have attracted considerable interest in recent times because of their promising therapeutic and pharmacological activities.[4] Several of them have been found to exhibit a wide spectrum of biological effects[5] including antiviral, antitumor, antibacterial and anti-inflammatory activities. In addition 4-aryl dihydropyrimidones have emerged as potent calcium channel blockers, antihypertensive, α_{1a}-adrenergic antagonists and neuro peptides antagonists.[6] For example dihydropyrimidines 1, 2, 3 were shown to have antiviral, calcium channel blocking and antihypertensive activity,[7] and DHPMs 4a and 4b (derivatives of 4-(3-hydroxyphenyl)-2-thiones) called monastrol[8] as cell permeable lead compounds for the development of new anticancer drugs, that specifically affects cell division (mitosis). Furthermore, dihydropyrimidinone-5-carboxylate core unit is found in many marine natural products[9] including batzelladine alkaloids which are found to be potent – HIV gb-120-CD_4 inhibitors.



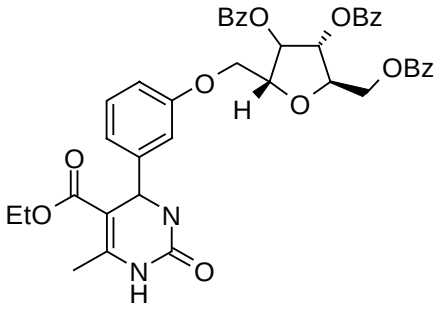
1
Antiviral



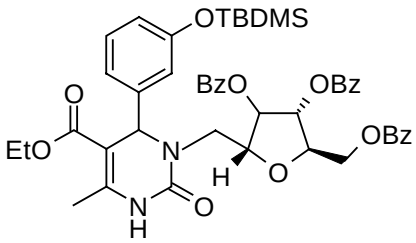
2
Calcium channel blocker



3
Antihypertensive



4a



4b

Monastral(±)

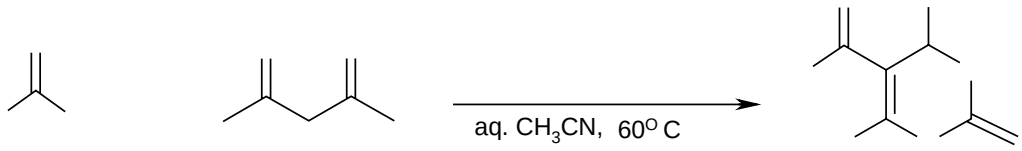
The most simple and straightforward procedure reported by Biginelli in 1893, involves one pot condensation of ethylacetoacetate, benzaldehyde and urea under strong acidic conditions.[10] However, low yields in the case of substituted aromatic and aliphatic aldehydes[6a,11] led to development of multistep strategies that produce somewhat higher overall yield but lack of simplicity of the one-pot synthesis.[12] Several methods for Biginelli's DHPM synthesis have been documented in the literature. These involve the use of Lewis acid catalysts such as BF_3 $-Et_2O$,[13a] $FeCl_3$ and HCl,[13b] $LaCl_3.7H_2O$,[13c] YbOTf,[13d] Protic acids such as AcOH,[13a] HCl,[13b] and additives,[13a,13e] $InCl_3$,[13f] InBr,[13g] $LiClO_4$,[13h] $NiCl_2.6H_2O$ or $FeCl_3.6H_2O$,[13i] Zirconium (iv)chloride,[13j] $Mn(OAc)_3.2H_{20}O$.[13k] Recently zeolites,[13l] ionic liquids,[13m] microwave irra-diation,[13n] ultrasound,[13o] and montmorillonite/KSF,[13p] have also been employed.

Furthermore La(OTf),[14a] $Cu(OTf)_2$,[14b] $Bi(OTf)_3$,[14c] LiBr,[14d] Silica and sulfuric acid,[14e] Boric acid,[14f] TFA,[14l] *N*-Butyl-*N*-*N*-dimethyl-α-phenyl-ethylammoniumbromide,[14m] Polyaniline-

bismoclite,[14n] Ammonium chloride,[14o] NBS,[4p] $CdCl_2$,[14q] $ZnCl_2$,[14r] $BiCl_3$[14s] and I_2[14t] were also employed in Biginelli reaction. Asymmetric version of the Biginelli reaction has also been reported using Garner aldehyde or from sugar derived aldehyde.[15] Recently environmentally benine approaches have been developed using solvent free condition.[16] Yadav *et al.* reported $Ag_3Pw_{12}O_{40}$ promoted Biginelli reaction in water.[17]

Despite their potential utility and green chemistry context, many of these methods suffer from using either elevated temperature or stoichiometric amounts of catalysts along with their longer reaction time. Therefore the development of new methods at moderate temperature would extend the scope of the Biginelli reaction. Recently our group employed yttria-zirconia based Lewis acid catalyst for various organic transformations.[18] In continuation we have developed an efficient synthesis of 2, 4-dihydropyrimidin-2(1*H*)-ones using yttria-zirconia based Lewis acid catalyst by Biginelli′s cyclocondensation reaction.

Scheme 1



α,β–

4.2.1.2 Results and Discussion

In a typical experimental procedure, when a mixture of β-keto ester (1eq), aldehyde (1eq) and urea (1.3eq) were reacted in the presence of catalytic amount of Yttria-zirconia catalyst in 10% aq. acetonitrile at 60°C, it underwent cyclocondensation to afford the corresponding dihydropyrimidones in good to excellent yields. A wide range of structurally varied β-dicarbonyl compound, aldehyde and urea are condensed by this procedure to produce the corresponding dihydropyrimidones, and the results are reported in Table 1. Both β-keto ester and β-diketone participated in this reaction readily. A wide variation of substitution in β-

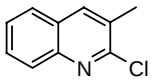
dicarbonyl compounds was tolerated in this procedure. A variety of substituted aromatic aldehydes and aliphatic, heteroaromatic aldehydes have been subjected to this condensation very efficiently. Less soluble heteroaromatic aldehydes such as 2-chloro-quinoline-3-carbaldehyde were also reacted very smoothly under the conditions, which failed to undergo reaction under solvent free conditions. Many of the pharmacologically relevant substituent patterns on the aromatic ring could be introduced with high efficiency. Aromatic aldehydes carrying either the electron-withdrawing or donating groups afforded high yields of products. Acid sensitive aldehydes such as furfural, phenylacetaldehyde and cinnamaldehyde worked well without the formation of any side products, which are normally observed either in the presence of protic or Lewis acids. In addition to its simplicity and milder reaction conditions, this method is effective even with aliphatic and α,β-unsaturated aldehydes which normally give poor yields in the presence of either protic or Lewis acids due to their decomposition or polymerization under acidic conditions. Another important feature of this procedure is the survival of a variety of functional groups such as olefins, ethers, esters, nitro and halides under the reaction conditions. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2-(1*H*)-thiones, which are also of great interest with regards to biological activity.[2] Thus variations in all three components have been accommodated very comfortably. Thus when a mixture of benzaldehyde (1.0 equiv.) , ethylacetoacetate (1.0 equiv.) and urea (1.3 equiv.) were stirred at 60°*C* in the presence of Yttria-zirconia (10 mol%) in 10% aq. acetonitrile for the indicated time, it gave the corresponding dihydropyrimidinones **8a** in 94% yield (**Table 1, entry 1**). The IR spectrum of **8a** showed bands at 3443 cm^{-1}, 3241 cm^{-1}, corresponding to the NH functionalities. The bands at 1730 cm^{-1} and 1703 cm^{-1}, indicated the presence of ester and ester carbonyl functionalities respectively. The ^{1}H NMR spectrum of **8a** showed a triplet at δ 1.17 and a quartet at δ 4.09 corresponding to ethyl group; the singlet at δ 5.45 corresponds to CH proton of the pyrimidinone ring. The NH protons resonated at δ 5.79 and at δ 8.13, while the peak at δ 2.35 indicated the presence of methyl protons. The aromatic protons appeared as multiplet at δ 7.30. The molecular ion peak at 260 shown in the mass spectrum confirmed the formation of the dihydropyrimidinones **8a**. In another example when cinnamaldehyde (1 eq.), acetylacetone (1 eq.), and urea were reacted together in the presence of yttria-zirconia catalyst at 60°C in 10% aq. acetonitrile, it afforded the corresponding dihydropyrimidinone 8i-1 in 88% yield(**Table 1, entry 35**). The IR

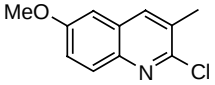
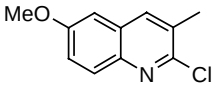
spectrum of **8i-1** shows bands at 3276 cm^{-1}, 3201 cm^{-1}, 1692 cm^{-1}, 1642 cm^{-1} and 1609 cm^{-1} indicating the presence of functionalities like NH, carbonyl of amide, ketones and C=C. The ^{1}H NMR spectrum, showed methyl protons at δ 2.32 and at δ 2.45. The CH proton of the pyrimidinone ring appeared as singlet at δ 5.03. The olefinic protons appeared as doublet of doublet (dd) at δ 6.18 and as doublet δ 6.52. The aromatic protons appeared at δ 7.09-7.52 as multiplet. The molecular ion peak at 256 in the mass spectrum confirmed the formation of dihydropyrimidinone.

4.2.1.3 Conclusion

In summary, the present procedure demonstrates an efficient Yttria-zirconia based Lewis acid catalysed cyclocondensation of 1, 3-dicarbonyl compound, aldehyde and urea/thiourea and depicts much improved modification of Biginelli reaction. In addition to its simplicity and milder reaction conditions, this method has the ability to tolerate a wide-variety of substitutions in all three components, which is lacking in many of the existing procedure. Thus, this procedure will offer an easy access to substituted dihydropyrimidin-2-(1*H*)-ones and thiones with varied substitution patterns in very high yields. The obvious advantage of heterogeneous catalysis in terms of simple operation coupled with the ease of workup and recyclability of the catalyst are noteworthy. We believe, our procedure will find important application in the synthesis of dihydropyrimidones to cater the needs of academia as well as pharmaceutical industries.

Table 1. Synthesis of substituted 3,4-dihydropyrimidones through the Biginelli cyclocondensation

Entry	R'	R''	R	X	DHPM	Time(h)	Yield* %	M.P (°C)	Reported M.P(°C)
1	Me	OEt	C_6H_5	O	**8a**	7	94	200-202	202-204[13a]
2	Me	OEt	4-CH_3-C_6H_4	O	**8b**	6	95	168-170	172[14s]
3	Me	OEt	4-OMe-C_6H_4	O	**8c**	6	92	202-204	201-203[13a]
4	Me	OEt	3-OMe-C_6H_4	O	**8d**	4	91	207-208	–
5	Me	OEt	2,4-$(OMe)_2$-C_6H_3	O	**8e**	6	81	158-160	158-160[13k]
6	Me	OEt	3,4,-$(OMe)_2$-C_6H_3	O	**8f**	10	80	175-177	178[13a]
7	Me	OEt	3,4,5-$(OMe)_3$-C_6H_2	O	**8g**	5	92	219	–
8	Me	OEt	2-OMe-6-Me-C_6H_3	O	**8h**	7	80	178-179	–
9	Me	OEt	4-OH-3-OMe-C_6H_3	O	**8i**	5	86	230-232	232-233[5b]
10	Me	OEt	2-OH-C_6H_4	O	**8j**	5	93	201-203	201-203[13c]
11	Me	OEt	2,6-$(OH)_2$-3-CO_2Me-4-Me-C_6H	O	**8k**	15	70	200-202	–
12	Me	OEt	4-Cl-C_6H_4	O	**8l**	6	90	213-215	213-215[13a]
13	Me	OEt	2-Cl-C_6H_4	O	**8m**	9	72	215-218	215-218[5d]
14	Me	OEt	C_6H_4-CH=CH(*E*)	O	**8n**	7	80	225-230	232-235[5d]
15	Me	OEt	4-[$N(Me)_2$] -C_6H_4	O	**8o**	8	95	256-257	256-257[13c]
16	Me	OEt		O	**8p**	16	67	261-263	–
17	Me	OEt	4-Me-C_6H_4	O	**8q**	5	80	204-205	–
18	Me	O^{t}Bu	C_6H_5	O	**8r**	7	94	207-208	–

Entry	R'	R''	R	X	DHPM	Time (h)	Yield* %	M.P (° C)	Reported M.P.(° C)
19	Me	OBn	C_6H_5	O	**8s**	8	56	165-166	165-167[14o]
20	Me	OEt	4-(OH)-C_6H_4	O	**8t**	5	88	227-229	227-229[13c]
21	Me	OMe		O	**8u**	7	86	203-205	205[13h]
22	Me	O^{t}Bu	4-OH-3-OMe-C_6H_3	O	**8v**	7	80	237-238	–
23	$C_6H_5CH_2$	OMe	C_6H_5	O	**8w**	16	82	183-184	–
24	Me	OEt	C_6H_5	S	**8x**	4	96	204-205	208-210[13g]
25	C_6H_5	OEt		S	**8y**	16	69	271(dec)	–
26	C_6H_5	OEt	C_6H_5	S	**8z**	12	62	153-155	–
27	C_6H_5	OEt	3,4-$(OMe)_2$-C_6H_3	S	**8a-1**	9	72	213-215	–
28	Me	Me	4-NO_2-C_6H_4	S	**8b-1**	15	75	229(dec)	–
29	Me	Me	4-OMe-C_6H_4	O	**8c-1**	6	92	170-172	168-170[13f]
30	Me	Me	3,4,-$(OMe)_2$-C_6H_3	O	**8d-1**	8	67	221-223	
31	Me	Me	3,4,5-$(OMe)_3$-C_6H_2	O	**8e-1**	10	84	224-225	217-219[4b]
32	Me	Me	4-OH-3-OMe-C_6H_3	O	**8f-1**	5	71	231-234	232-234[10]
33	Me	Me	2-Cl-C_6H_4	O	**8g-1**	9	71	258-259	–
34	Me	Me	2,6-$(OH)_2$-3-CO_2Me-4-Me-C_6H	O	**8h-1**	10	56	220-221	–
35	Me	OEt	C_6H_5-CH=CH(*E*)	O	**8i-1**	6	88	224-226	–
36	Me	OEt	Ethyl	O	**8j-1**	14	75	153-155	155-157[5b]
37	Me	OEt	*iso*-Propyl	O	**8k-1**	6	72	154	157-158[4]
38	Me	OEt		O	**8l-1**	13	70	258-259	–

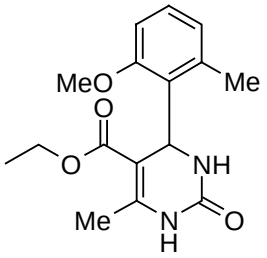
***Isolated yield after column purification**

4.2.1.4 Experimental Section

General procedure for the preparation of 3,4-dihydropyrimid-2-(1*H*)-one using yttria-zirconia Lewis acid catalyst.

A slurry of β-keto ester (1 mmol), aldehyde (1 mmol) and urea (1.3 mmol) in aq. CH_3CN (90:10) was stirred at 60°C in the presence of Yttria-zirconia (10mol%) for the indicated time(Table 1) under nitrogen atmosphere. After completion of the reaction as indicated by TLC, the reaction mixture was filtered under hot condition to remove the catalyst. The filtrate after cooling to room temperature was poured into crushed ice and the resulting solid was filtered under suction and recrystallized from hot methanol to afford the pure product.

Ethyl-6-methyl-2-oxo-4-(2-methyl-6-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8h)



8h

Yield: 80%

Pale Yellow Solid

M.P.: 178-179° C

IR ($CHCl_3$, cm^{-1}): ν_{max} 3432, 3257 (br), 1650, 2257, 2130, 1650(br), 1489, 1050

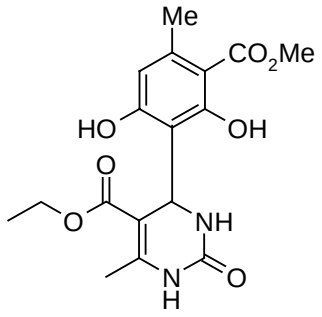
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13 (t, 3H, *J* = 6 Hz), 2.33 (s, 3H), 2.53 (s, 3H), 3.82 (s, 3H), 4.00(q, 2H, *J* = 6 Hz), 5.83 (s, 1H), 6.75-6.85 (m, 3H), 7.86 (s, 1H), 8.80 (s, 1H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 12.8, 17.0, 18.3, 48.2, 54.3, 57.7, 95.9, 108.5, 121.7, 126.6, 129.2, 136.3, 146.4, 150.0, 157.8, 164.9

Mass: 304(M^+), 289, 275, 257, 243, 231, 215, 201, 183, 155

Analysis calcd for $C_{16}H_{20}N_2O_4$ (304.34): Found C, 62.98; H, 6.75; N, 9.10{Required C, 63.14; H, 6.62; N, 9.20}

Ethyl-6-methyl-2-oxo-4-(4-methyl-3-carbomethoxy-2,6-dihydroxyphenyl)-1,2,3,4-tetra hydropyrimidine-5-carboxylate (8k)



8k

Yield: 70%

Colorless Soild

M.P.: 200-202° C

IR ($CHCl_3$, cm^{-1}): ν_{max} 3483, 3400, 3262, 3018, 1713, 1644, 1582, 1437, 136

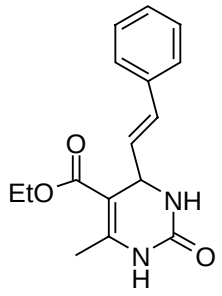
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (t, 3H, *J* = 6 Hz), 1.90 (s, 3H), 2.48 (s, 3H), 3.04 (s,1H), 3.95(s, 3H), 4.27 (q, 2H, *J* = 6 Hz), 4.99 (s, 1H), 5.52 (s, 1H), 5.60 (s, 1H), 6.24 (s, 1H), 2.22 (s, 1H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 20.5, 29.6, 57.1, 57.9, 60.1, 99.7, 103.4, 113.2, 113.7, 116.1, 116.5, 117.0, 118.5, 145.0, 149.0, 151.4, 152.7, 167.8, 169.9, 170.3

Mass: 365 (M^+ +1), 346, 335, 332, 318, 304, 291, 285, 274, 259, 235, 203, 183, 175, 150, 137, 105, 77

Analysis calcd for $C_{17}H_{20}N_2O_7$ (364.35): Found C, 55.89; H, 5.34; N, 7.85 {Required C, 56.04; H, 5.53; N, 7.69}

5-Ethyl-6-methyl-2-oxo-4-cinnamyl-1,2,3,4 –tetrahydropyrimidine carboxylate(8n)



8n

Yield: 80%

Pale Yellow Solid

M.P.: 225-230°C

IR ($CHCl_3$, cm^{-1}): ν_{max} 3239, 3106, 2867(br), 1715, 1649, 1461, 1374

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (t, 3H, *J* = 8.79 Hz), 2.20 (s, 3H), 4.06 (q, 2H, *J* =7.15Hz), 4.79(s, 1H), 6.10(dd, *J* = 6Hz, 16Hz), 6.32(d, 1H, *J* = 16Hz), 7.24(m, 5H), 7.89(s, 1H), 8.99(s, 1H)

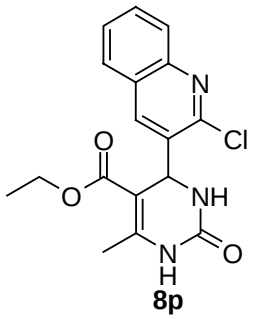
13CNMR (200 MHz, $CDCl_3$): δ 12.9, 16.6, 50.7, 57.9, 97.0, 124.8, 126.9, 127.1, 128.5, 135.1

143.7, 144.3, 147.0, 164.1, 191.83

Mass: 286(M^+), 257, 240, 213, 196, 183, 170, 155

Analysis calcd for $C_{16}H_{18}N_2O_3$ (286.33): Found C, 67.33; H, 6.12; N, 9.65 {Required C, 67.11; H, 6.34; N, 9.78}

4-(2-Chloro-quinolin-3-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (8p)



8p

Yield: 67%

White Solid.

M.P.: 261-263^{o} C

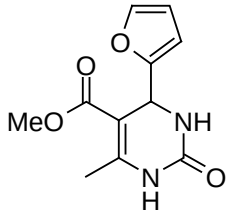
IR ($CHCl_3$, cm^{-1}): ν_{max} 3555, 3385, 3206, 3080, 1699, 1643, 1462, 1377

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.07 (t, 3H, *J* = 4 Hz), 1.85 (b, 1H), 2.55 (s, 3H), 4.07 (q, 2H, *J* = 8 Hz), 5.99 (s, 1H), 7.46 (t, 1H), 7.75 (t, 1H, *J* = 4 Hz), 7.79 (d, 1H, *J* = 4 Hz), 7.95 (s, 1H), 8.01 (d, 1H, *J* = 4 Hz), 8.46 (s, 1H)

Mass: 345(M^+), 330, 316, 310, 300, 280, 272

Analysis calcd for $C_{17}H_{16}ClN_3O_3$ (345.78): Found C, 58.79; H, 4.56; N, 12.31 {Required C, 59.05; H, 4.68; N, 12.15}

Methyl-6-methyl-2-oxo-4-furfuryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate(8u)



8u

Yield: 86%

White Solid

M.P.: 203-205°C

IR ($CHCl_3$, cm^{-1}): ν_{max} 3415, 3413, 2513, 1697, 1644, 1426, 1218

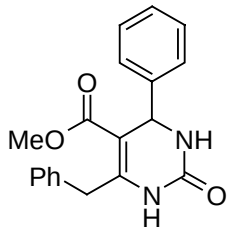
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.09 (s, 3H), 3.62 (s, 3H), 5.27 (s, 1H), 6.05 (s, 1H), 6.25 (s, 1H), 7.34 (s, 1H), 7.55 (s, 1H), 9.15 (s, 1H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 16.5, 29.1, 49.2, 95.9, 103.7, 108.7, 140.1, 147.9, 151.4, 154.5, 164.2

Mass: 236(M^+), 219, 208, 193, 182, 177

Analysis calcd for $C_{11}H_{12}N_2O_4$ (236.226): Found C, 55.79; H, 5.09; N, 8.52{Required C, 55.88; H, 5.12; N, 8.47}

Methyl-6-benzyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8w)



8w

Yield: 82%

Colorless Solid

M.P.: 183-184° C

IR ($CHCl_3$, cm^{-1}): ν_{max} 3523, 3424, 3238, 3088, 3018, 1700, 1643, 1432, 1229, 1217

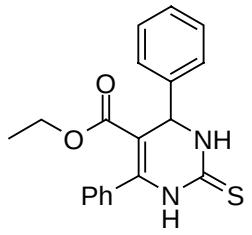
^{1}H NMR (200 MHz, $CDCl_3$): δ 3.61 (s, 3H), 4.00 (q, 2H, *J* = 12 Hz), 5.37 (s, 1H), 6.30 (s, 1H), 7.24 (s, 10 H), 7.89 (s, 1H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 30.7, 36.5, 51.1, 55.4, 101.8, 126.4, 126.9, 127.8, 128.7, 136.2, 143.6, 148.1, 153.5, 165.8

Mass: 304(M^+-H_2O), 276(304- CO), 231(322- $PhCH_2$), 216(231- CH_3), 200, 199, 187, 173**.**

Analysis calcd for $C_{19}H_{18}N_2O_3$ (322.36): Found C, 69.51; H, 5.99; N, 9.21{Required C, 69.66; H, 5.84; N, 9.06}

Ethyl-6-phenyl-2-thiooxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate(8z)



8z

Yield: 62%

Colorless Solid

M.P.: 153-155°C

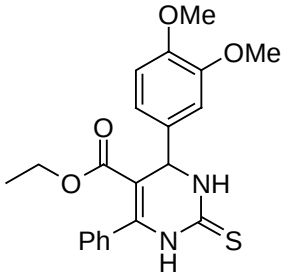
IR ($CHCl_3$, cm^{-1}): ν_{max} 3307, 3152, 3062, 2942, 2943, 2935, 2907, 2859, 1679, 1460, 1452, 204.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.84 (t, 3H, *J* = 6 Hz), 3.84 (q, 2H, *J* = 6Hz), 5.50 (d, 1H, *J* = 4Hz), 7.27-7.40 (m, 10H), 7.93 (b, 1H), 8.11 (b, 1H)

Mass: 338(M^+), 309, 293, 278, 265, 261, 250, 233, 215, 204, 187

Analysis calcd for $C_{19}H_{18}N_2O_2S$ (338.42): Found C, 67.26; H, 5,475; N, 8.015 {Required C, 67.43; H, 5.36; N, 8.27}

Ethyl-2-thiooxo-6-phenyl-4(3, 4-dimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-Carboxylate (8a-1)



8a-1

Yield: 72%

White Solid.

M.P.: 213-215^0 C

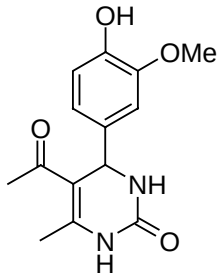
IR ($CHCl_3$, cm^{-1}): ν_{max} 3346, 3176, 3053, 2935, 2915, 1901, 1682, 1457.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83 (t, 3H, *J* = 6 Hz), 3.81-3.98 (m, 8H), 5.50 (d, 1H, *J* = 4 Hz), 6.84-7.00 (m, 3H), 7.35-7.44 (m, 5H), 7.71 (s, 1H), 7.88 (s, 1H)

Mass: 398(M^+), 369, 352, 325, 309, 293, 283, 261, 250, 220, 208, 165, 151, 129, 105, 91, 77, 65.

Analysis Calcd for $C_{21}H_{22}N_2O_4S$ (398.48): Found C, 63.43; H, 5.402; N, 6.915{Required C, 63.30; H, 5.56; N, 6.91}

5-Acetyl-6-methyl-2-oxo-4-(4-hydroxy-3-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine(8f-1)



8f-1

Yield: 71%

Pale Yellow Solid.

M.P.: 231-234° C

IR ($CHCl_3$, cm^{-1}): ν_{max} 3415, 3325, 3295, 1698, 1665, 1455

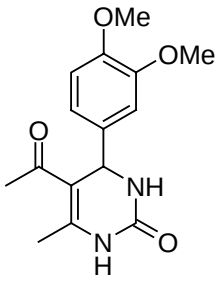
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.02 (s, 3H), 2.25 (s, 3H), 3.73 (s, 3H), 5.15 (s, 1H), 6.58 (d, 1H, *J* = 8 Hz), 6.67 (d, 1H, *J* = 8 Hz), 6.83 (s, 1H), 7.666 (s, 1H), 8.85 (b, 1H), 9.07 (b, 1H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 16.8, 28.0, 52.2, 53.9, 107.6, 109.6, 113.6, 116.9, 133.4, 144.3, 145.7, 145.8, 150.3, 192.7

Mass: 276(M^++1)275, 260, 243, 232, 271

Analysis calcd for $C_{14}H_{16}N_2O_4$ (276.29): Found C, 60.95; H, 5.38; N, 10.01{Required C, 60.86; H, 5.47; N, 10.14}

5-Acetyl-6-methyl-2-oxo-4-(3, 4-dimethoxy phenyl)-1,2,3,4-tetrahydropyrimidine(8d-1)



8d-1

Yield: 67%

Pale Yellow Solid

M.P.: 221-223 ^{0}C

IR ($CHCl_3$, cm^{-1}): ν_{max} 3445, 3281, 1658, 1554, 1461, 1377, 1265

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.33 (s, 3H), 3.85 (s, 6H), 5.40 (s, 1H), 6.36 (s, 1H), 6.80 (s, 3H), 8.66 (s, 1H)

Mass: 290 (M^+), 275, 259, 247, 231, 215, 203, 189, 173, 165, 153

Analysis calcd for $C_{15}H_{18}N_2O_4$ (290.31): Found C, 61.88; H, 6.01; N, 9.81{Required C, 62. 01; H, 6.24; N, 9.64}

4.2.1.5 Spectra

1. ^{1}HNMR spectrum of 8h

2. ^{13}CNMR spectrum of 8h

3. ^{1}HNMR spectrum of 8k

4. ^{13}CNMR spectrum of 8k

5. ^{1}HNMR spectrum of 8n

6. ^{13}CNMR spectrum of 8n

7. ^{1}HNMR spectrum of 8p

8. Mass spectrum of 8p

9. ^{1}HNMR spectrum of 8u

10. ^{13}CNMR spectrum of 8u

11. ^{1}HNMR spectrum of 8w

12. ^{13}CNMR spectrum of 8w

13. ^{1}HNMR spectrum of 8z

14. Mass spectrum of 8z

15. ^{1}HNMR spectrum of 8a-1

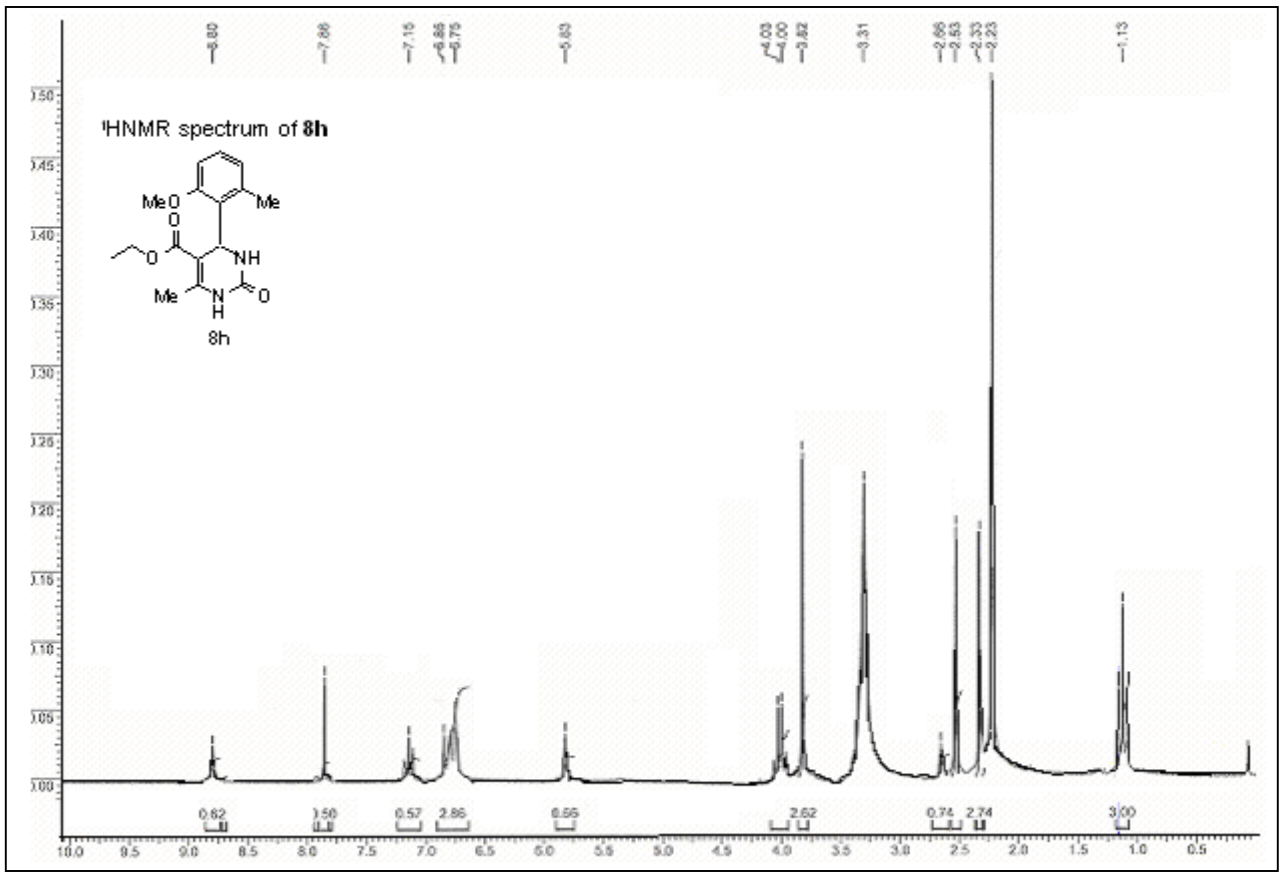
16. Mass spectrum of 8a-1

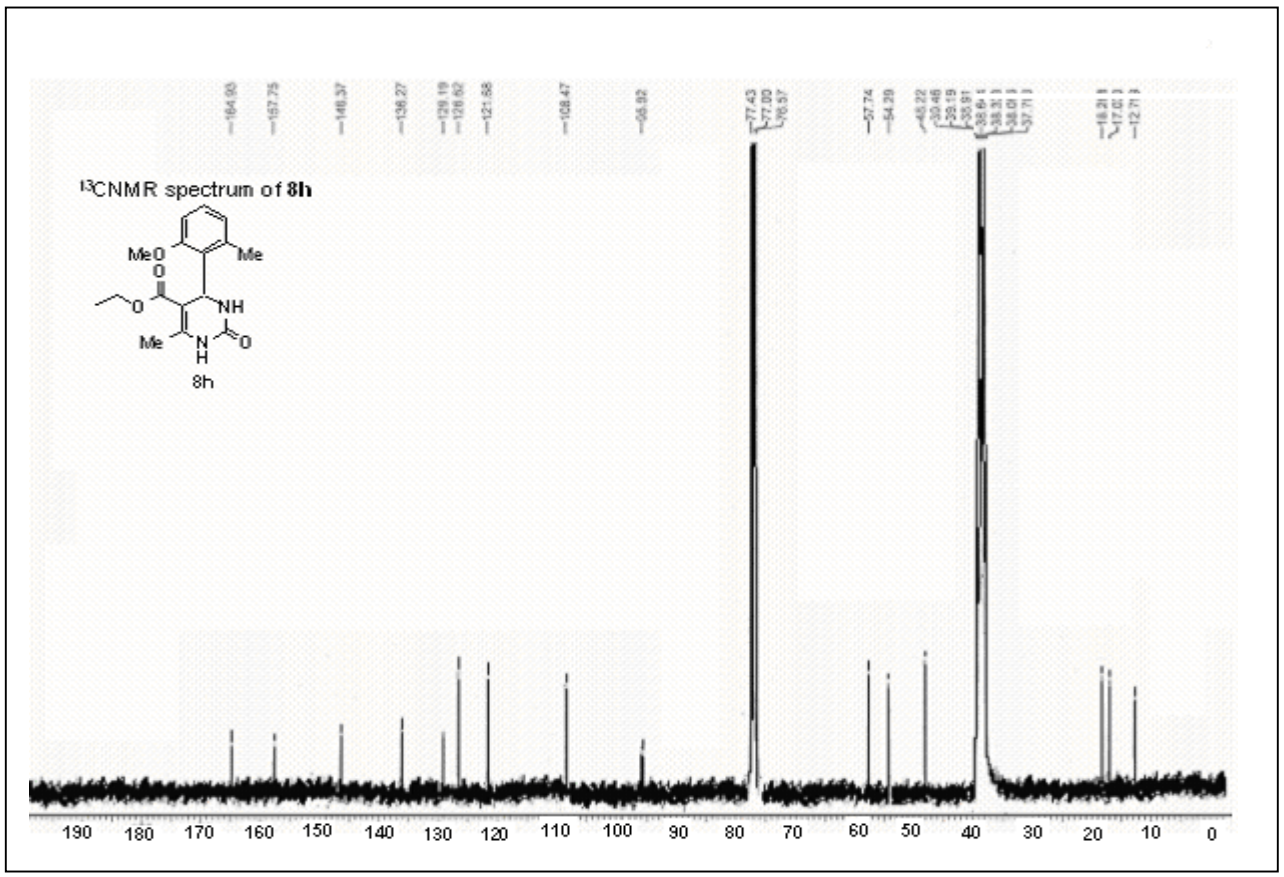
17. ^{1}HNMR spectrum 8f-1

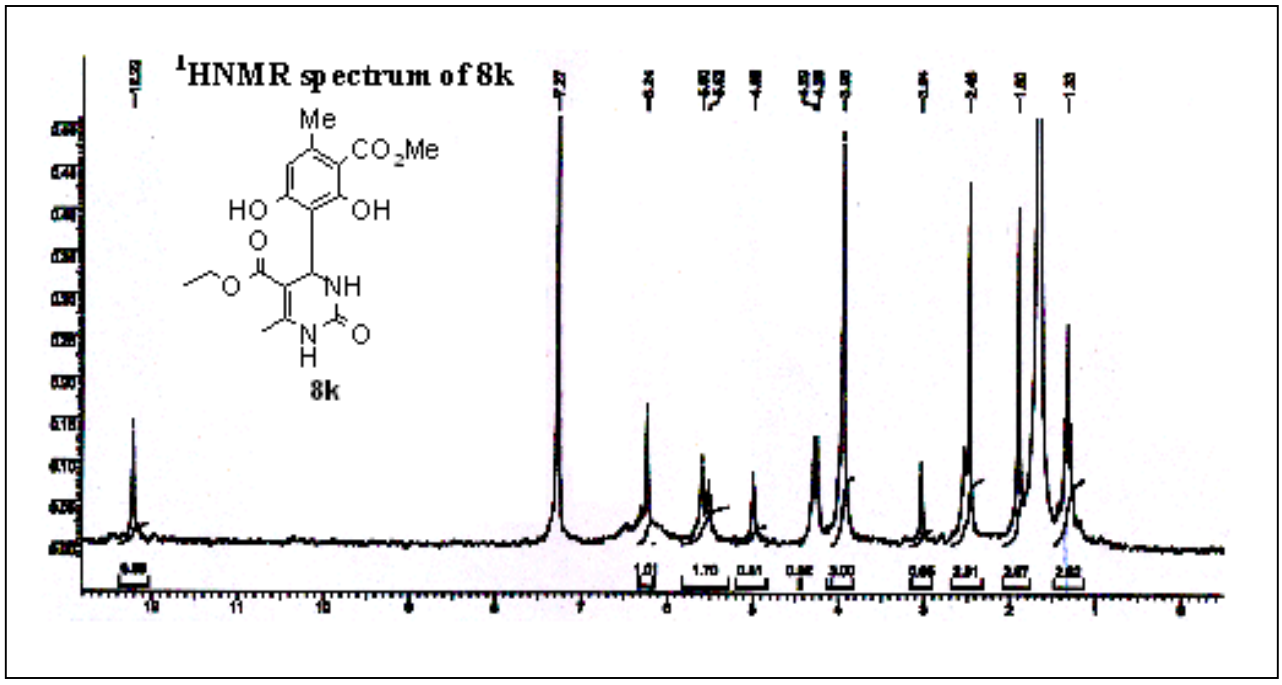
18. ^{13}CNMR spectrum of 8f-1

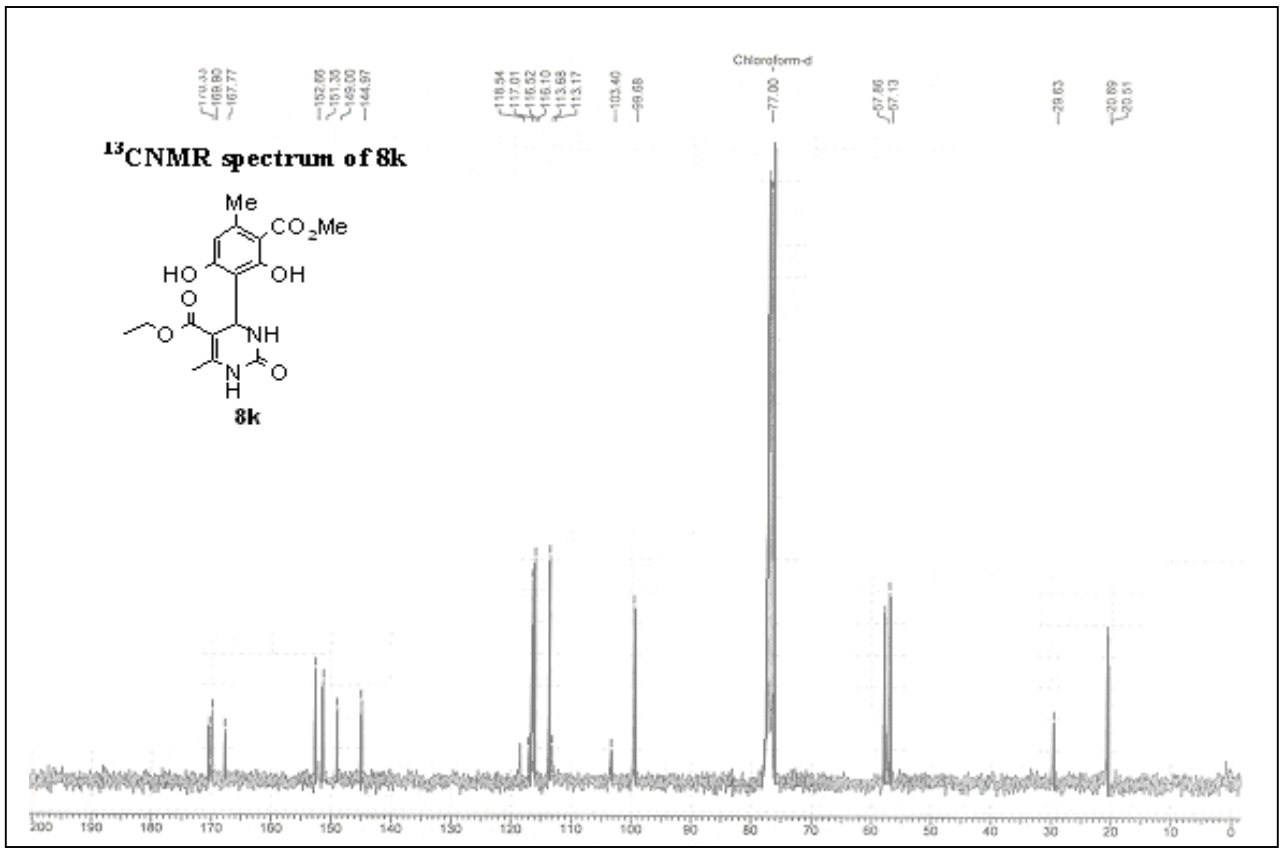
19. ^{1}HNMR spectrum of 8j-1

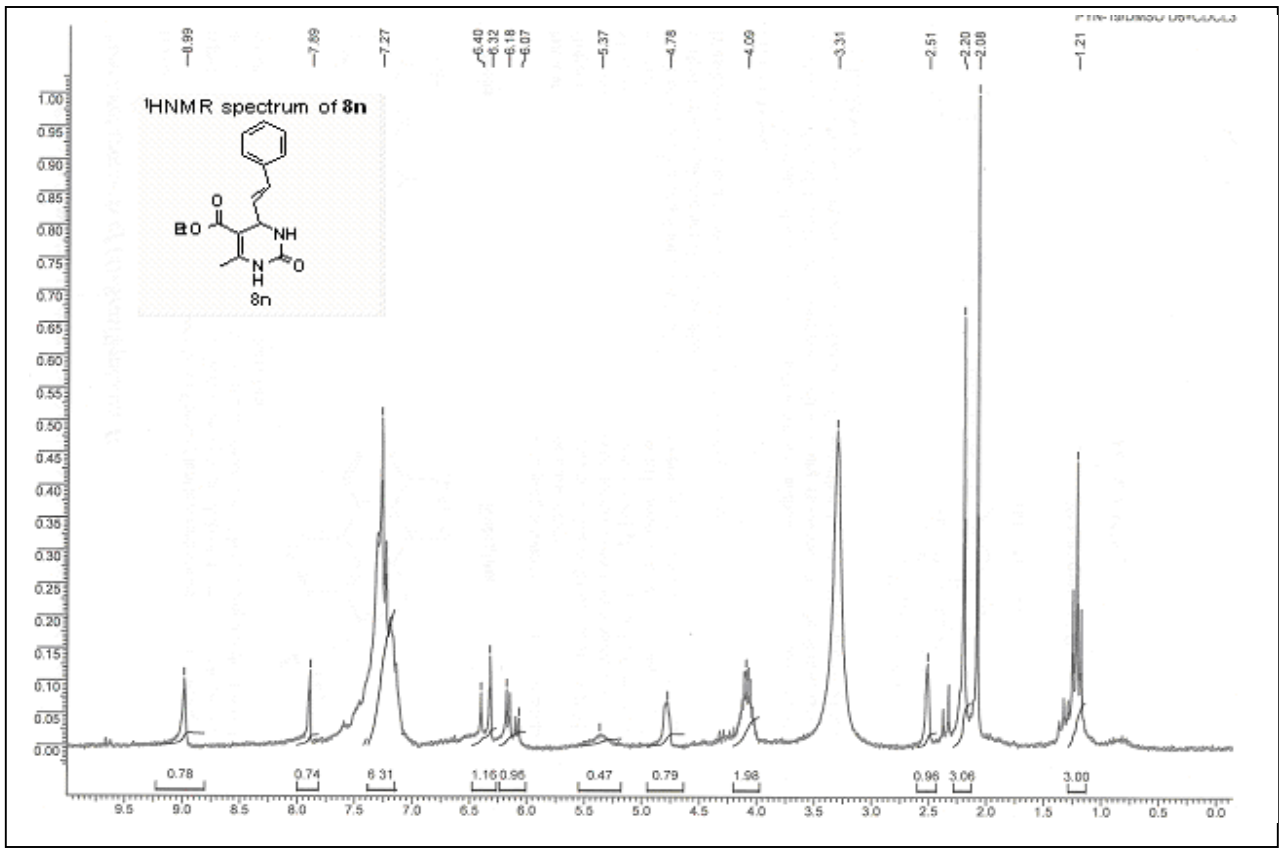
20. Mass spectrum of 8j-1

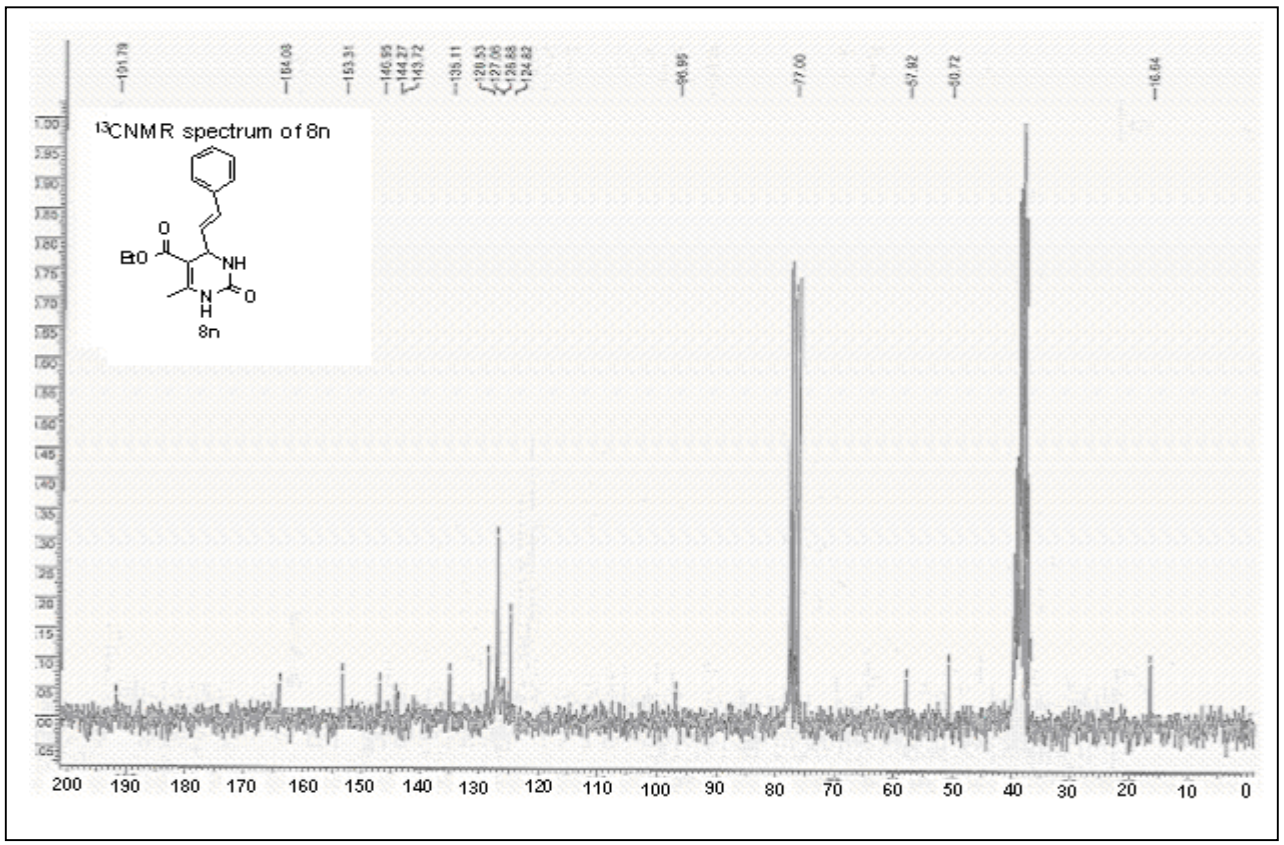

^{1}HNMR spectrum of **8h**
MeO
Me
O
O
NH
Me
N
H
O
8h

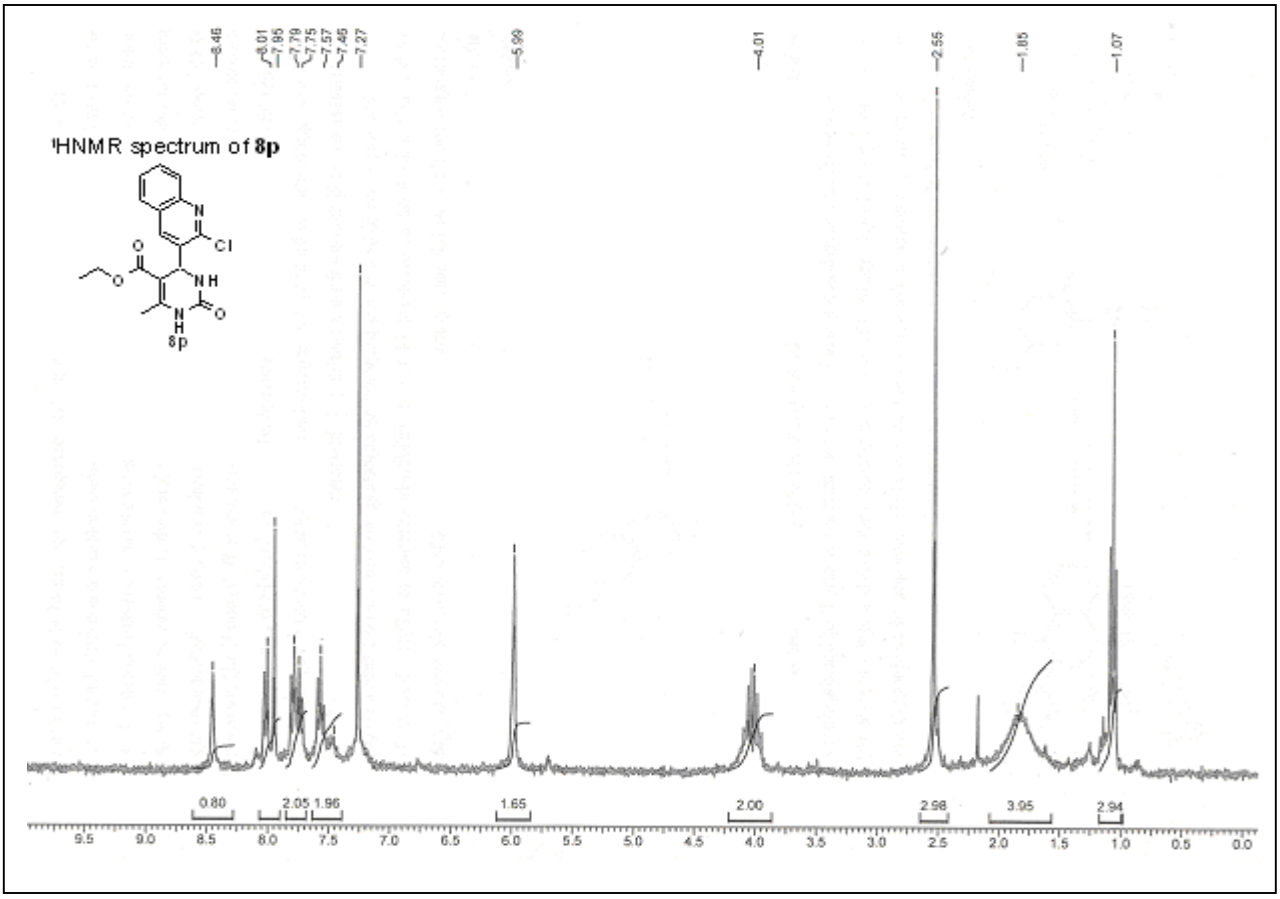

^{13}CNMR spectrum of **8h**
MeO
Me
O
O
NH
Me
N
H
O
8h

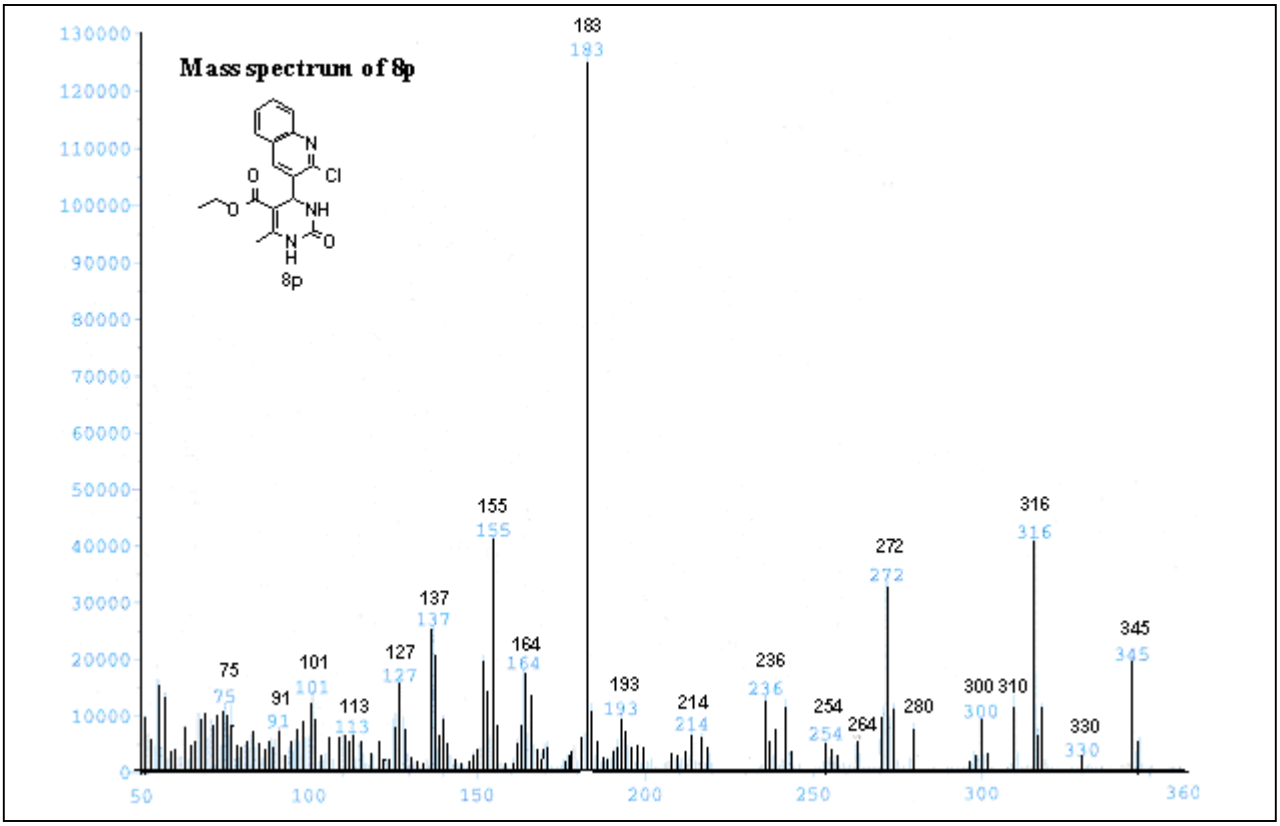

^{1}HNMR spectrum of 8k
Me
CO_2Me
HO
OH
O
O
NH
N
H
O
8k

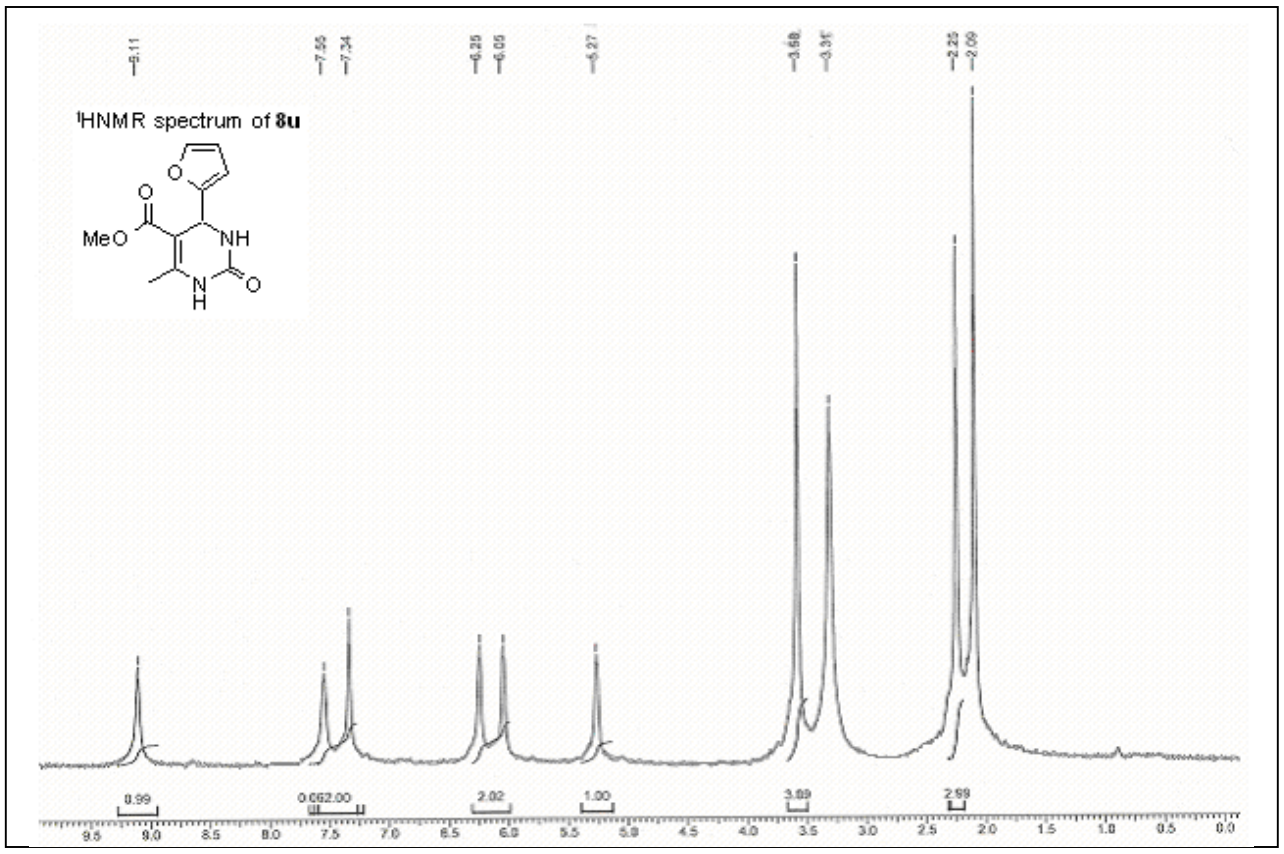

Chloroform-d
^{13}CNMR spectrum of 8k
Me
CO_2Me
HO
OH
O
O
NH
N
H
O
8k

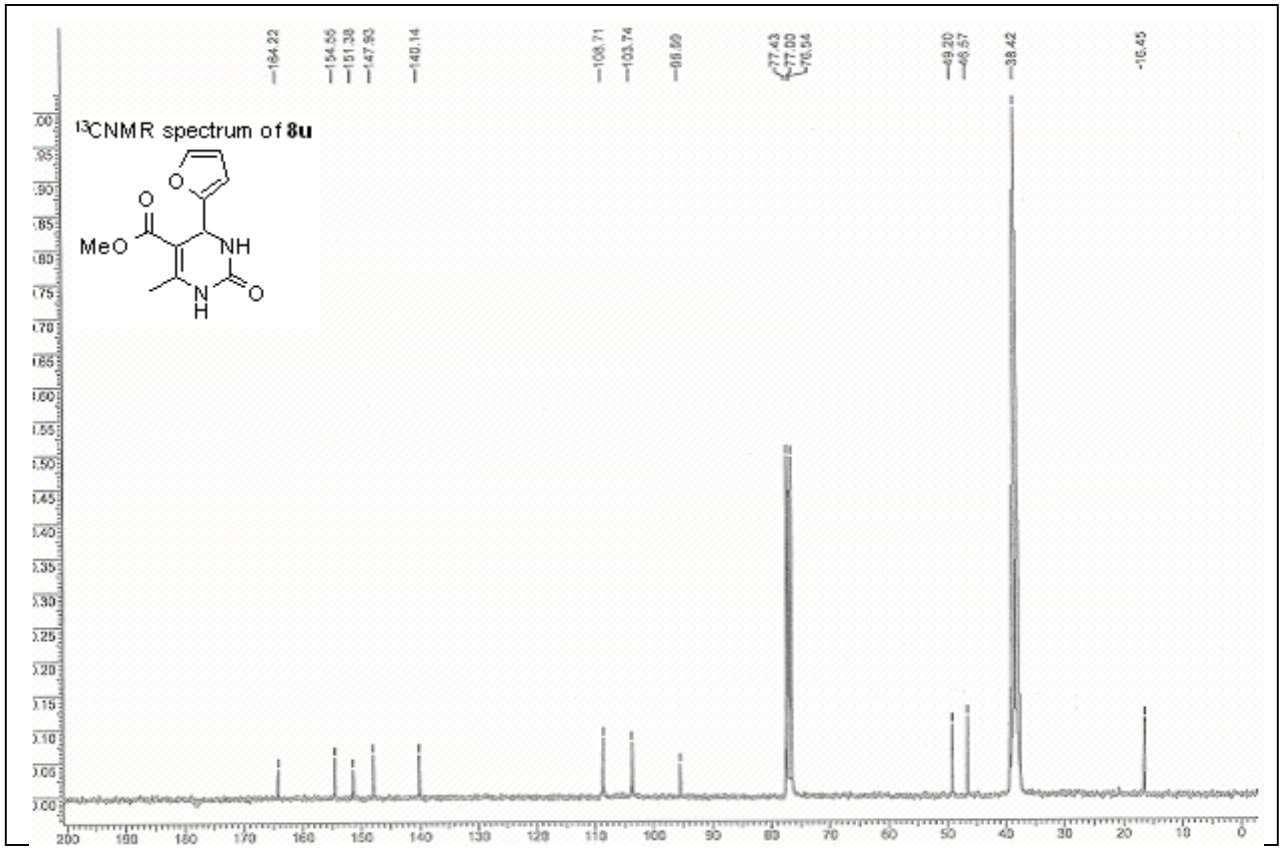

^{1}HNMR spectrum of **8n**
8n

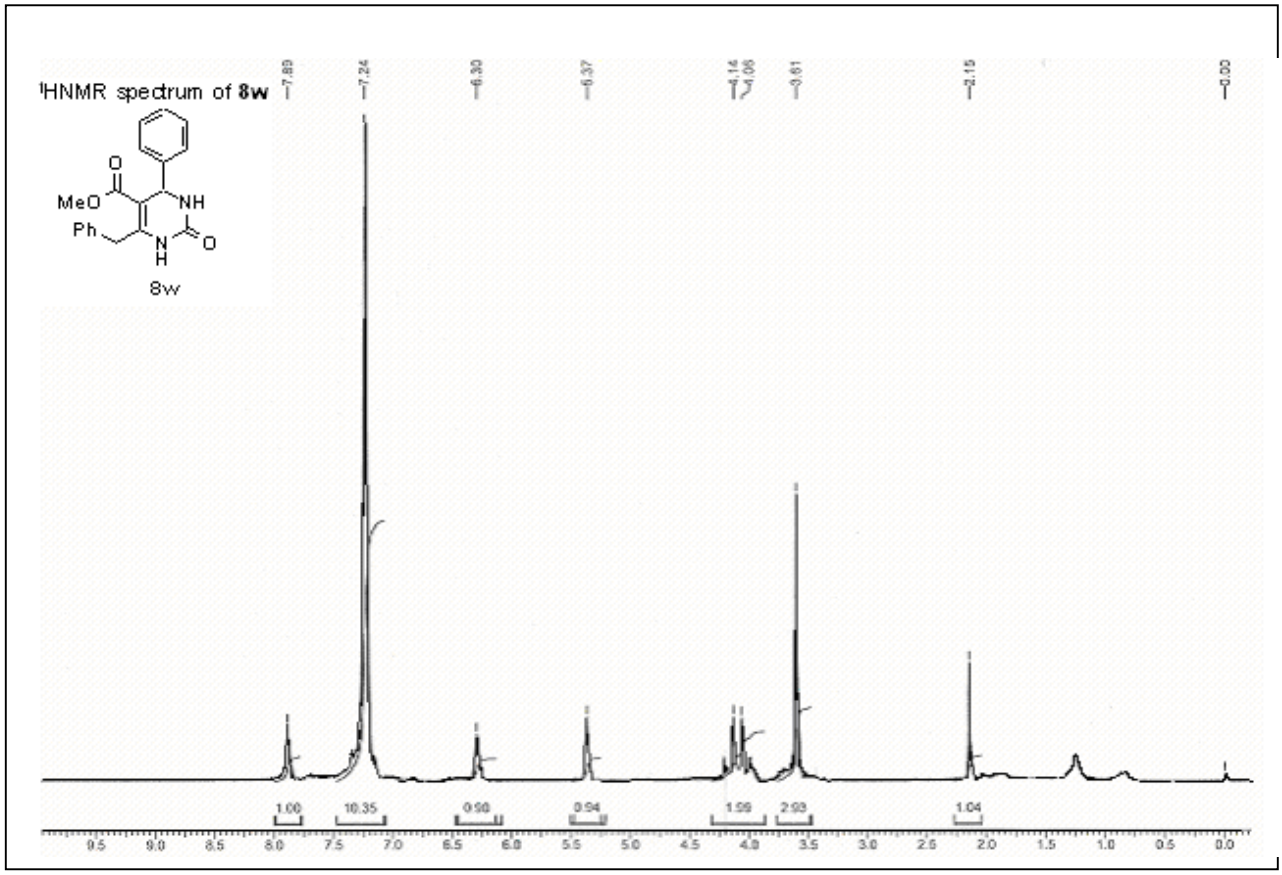

^{13}CNMR spectrum of 8n
8n

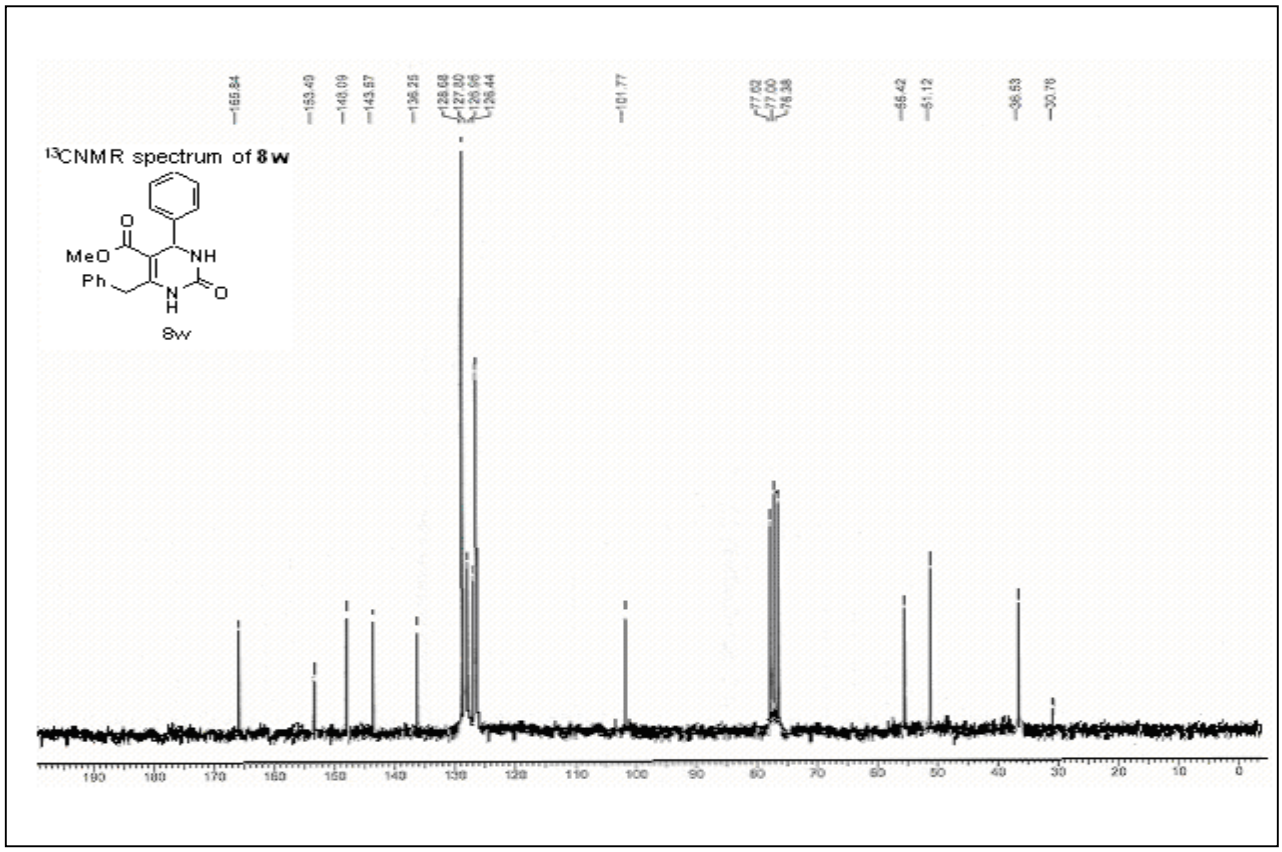

¹HNMR spectrum of 8p
8p
8.46
8.01
7.95
7.79
7.75
7.57
7.46
7.27
5.99
4.01
2.55
1.85
1.07
0.80
2.05
1.96
1.65
2.00
2.98
3.95
2.94

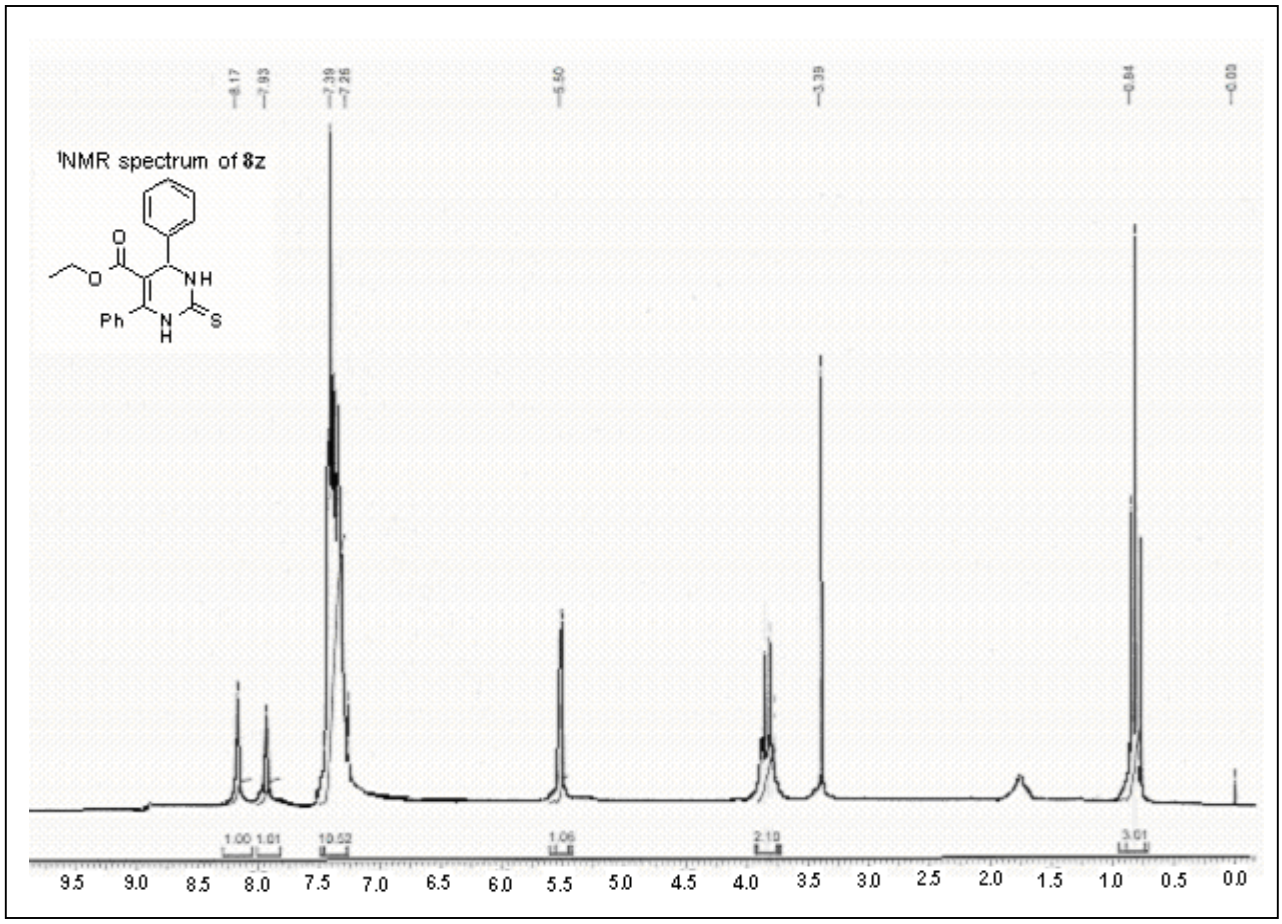

Mass spectrum of 8p
8p
183
155
137
316
272
345
75
101
91
113
127
164
193
214
236
254
264
280
300
310
330

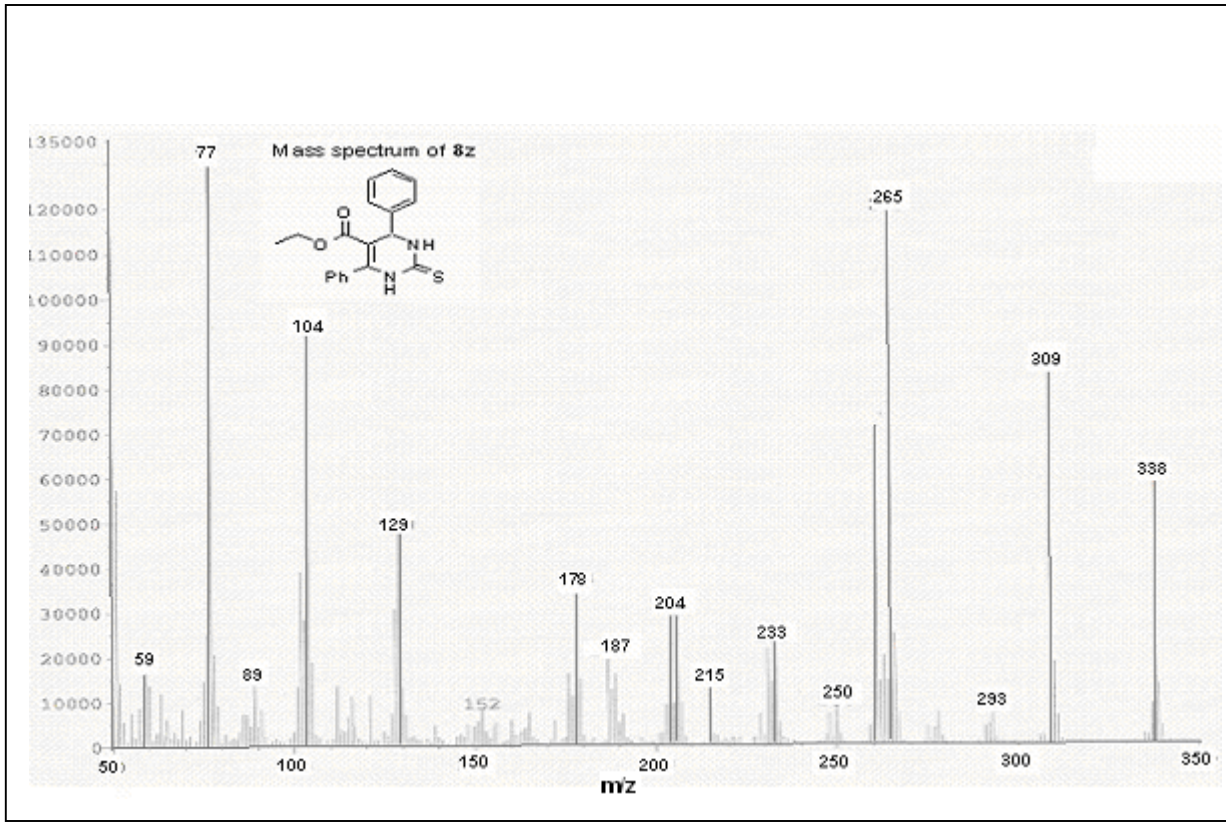

¹HNMR spectrum of 8u
MeO
NH
N
H
O
9.11
7.55
7.34
6.25
6.05
5.27
3.68
3.51
2.25
2.09
0.99
0.662.00
2.02
1.00
3.89
2.99

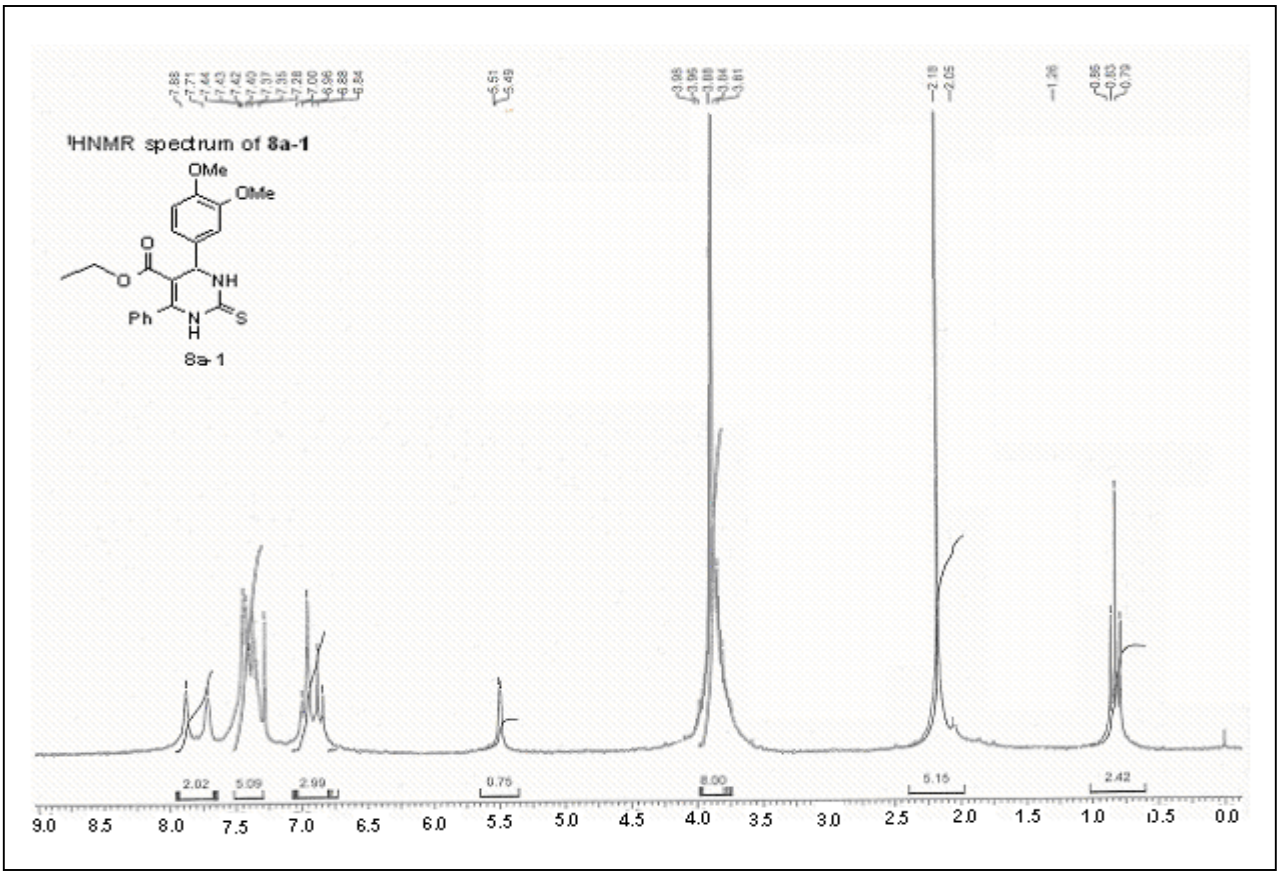

¹³CNMR spectrum of 8u
MeO
NH
N
H
O
164.22
154.59
151.38
147.93
140.14
108.71
103.74
88.99
77.43
77.00
76.54
69.20
49.57
38.42
16.45

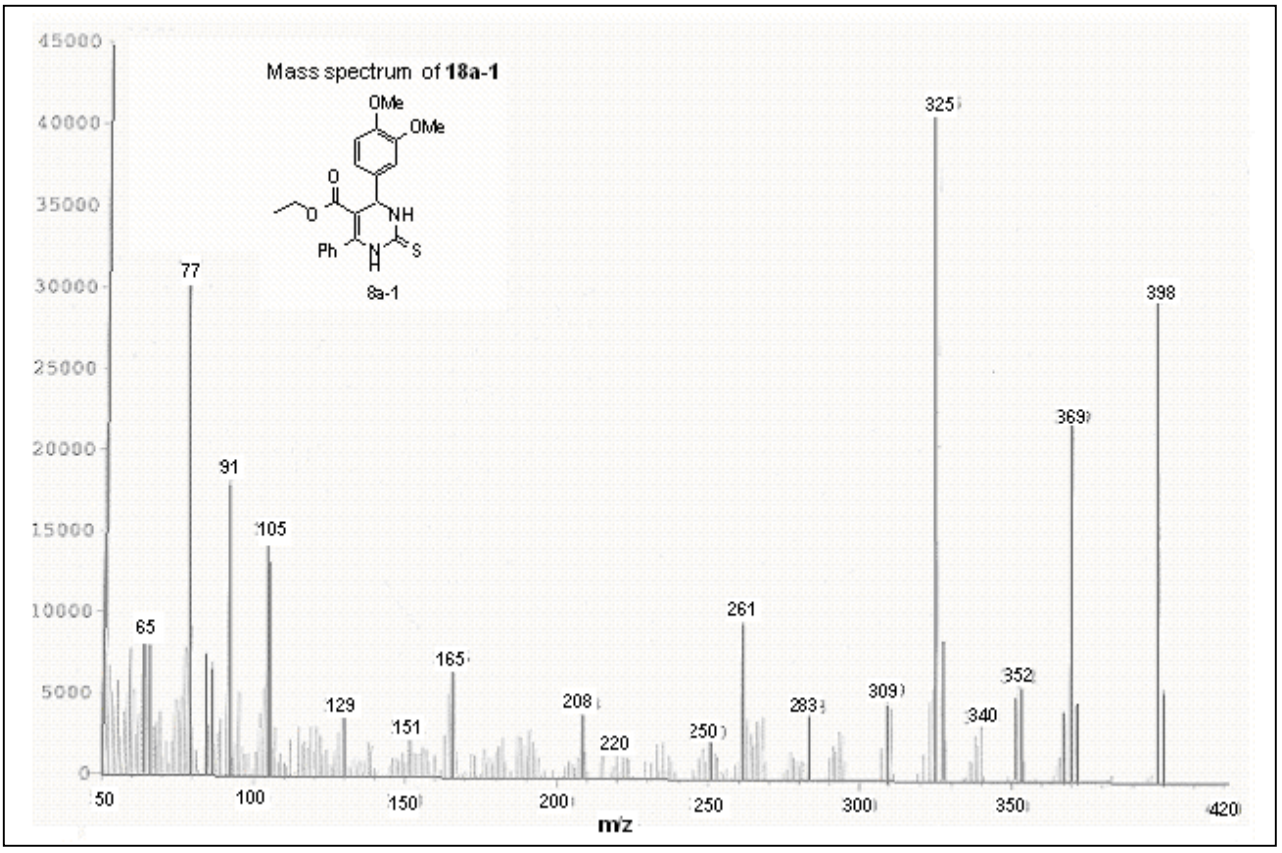

¹HNMR spectrum of 8w
MeO
Ph
NH
N
H
O
8w
7.89
7.24
6.30
6.37
4.14
4.06
3.61
2.15
0.00
1.00
10.35
0.98
0.94
1.09
2.03
1.04

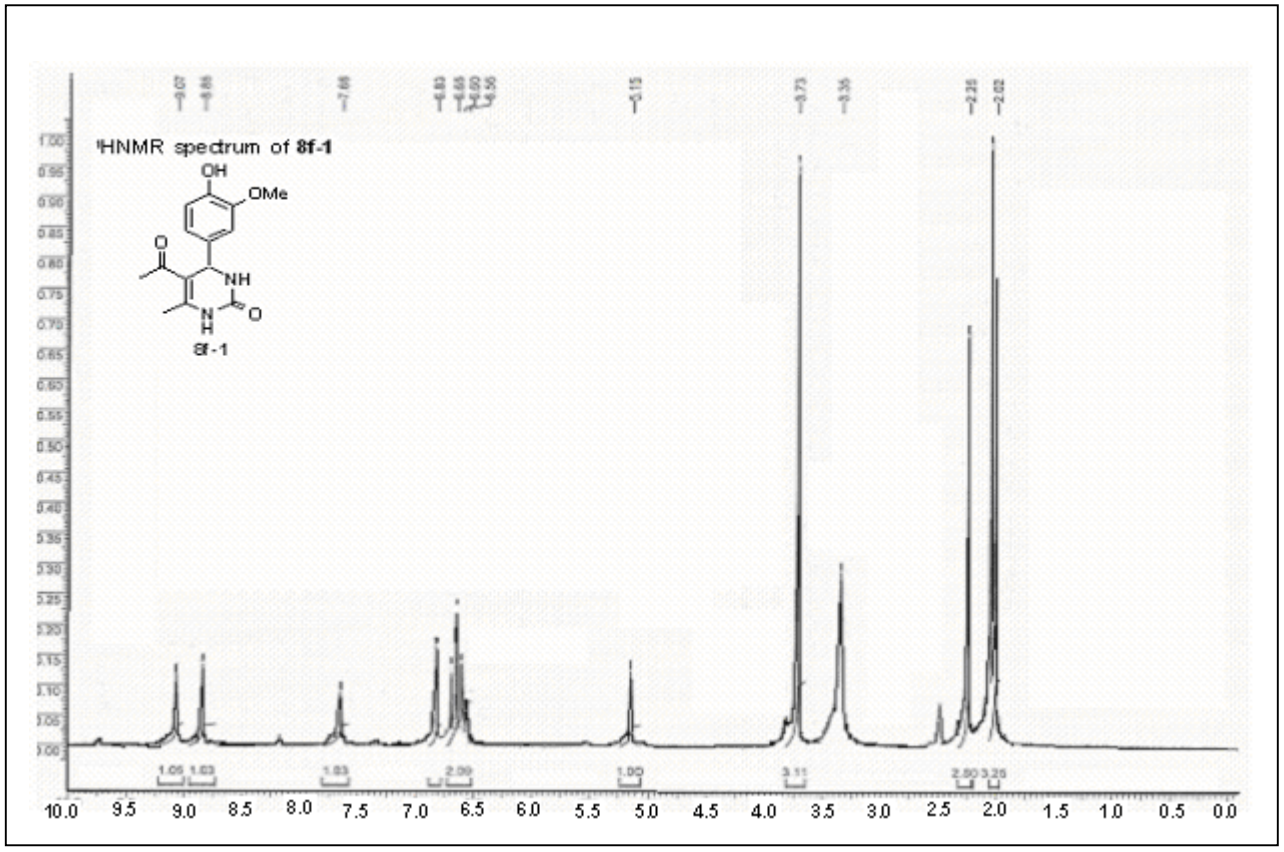

¹³CNMR spectrum of 8w
MeO
Ph
NH
N
H
O
8w
165.84
153.49
148.09
143.57
136.25
128.68
127.80
126.96
126.44
101.77
77.62
77.00
76.38
55.42
51.12
36.53
30.76

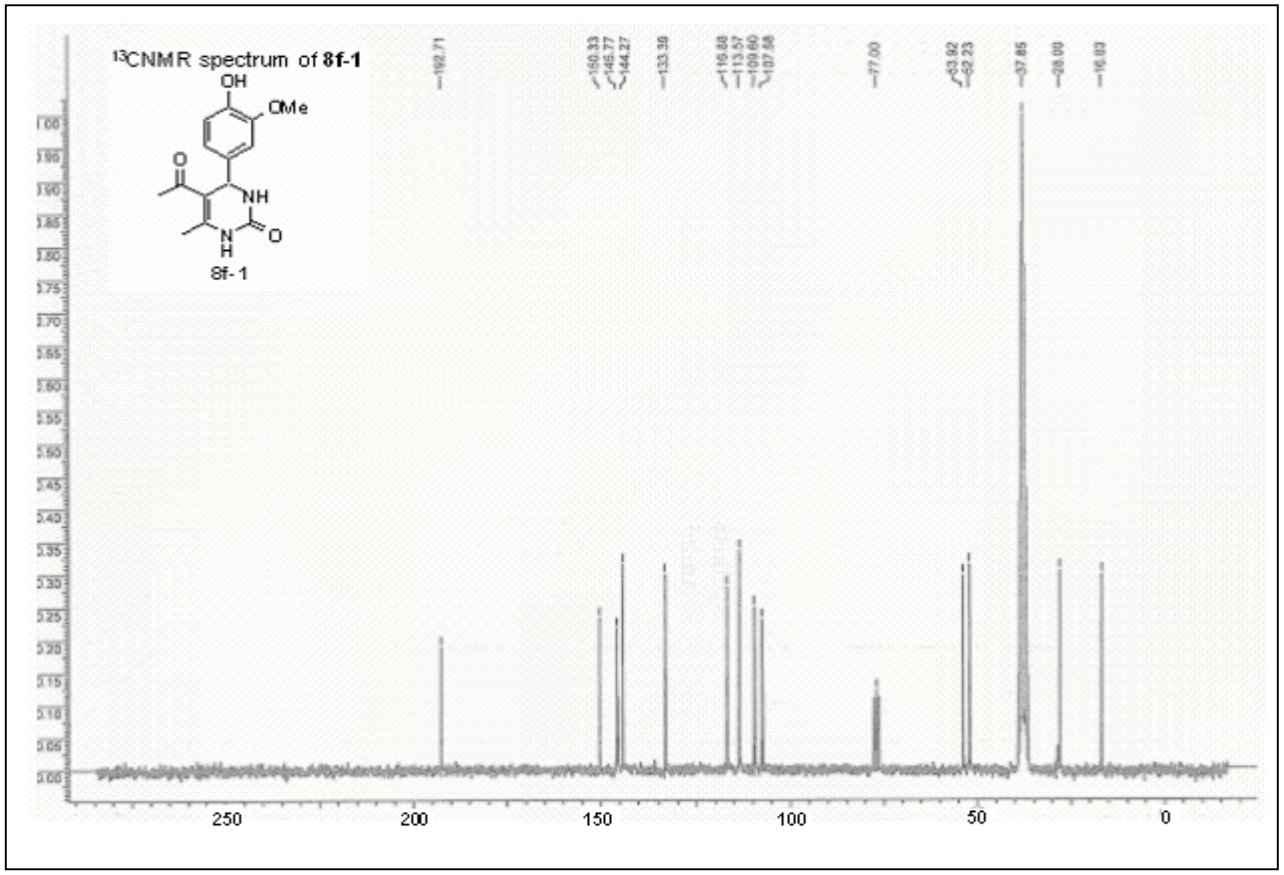

^{1}NMR spectrum of 8z
O
O
NH
Ph
N
H
S
8.17
7.93
7.39
7.26
6.50
3.39
0.84
0.03
1.00
1.01
10.52
1.06
2.10
3.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

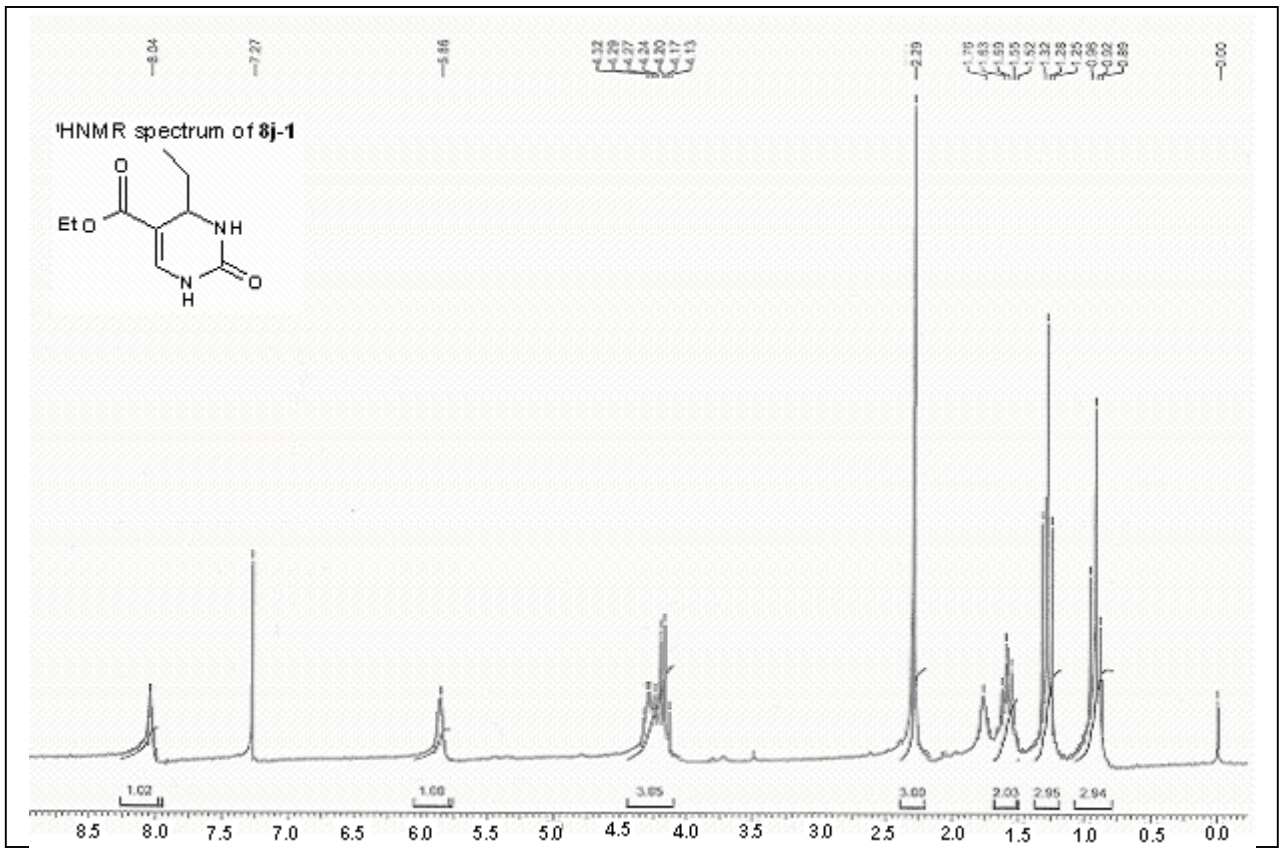

Mass spectrum of 8z
O
O
NH
Ph
N
H
S
135000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
77
104
129
178
204
265
309
338
59
89
152
187
215
233
250
293
50
100
150
200
250
300
350
m/z

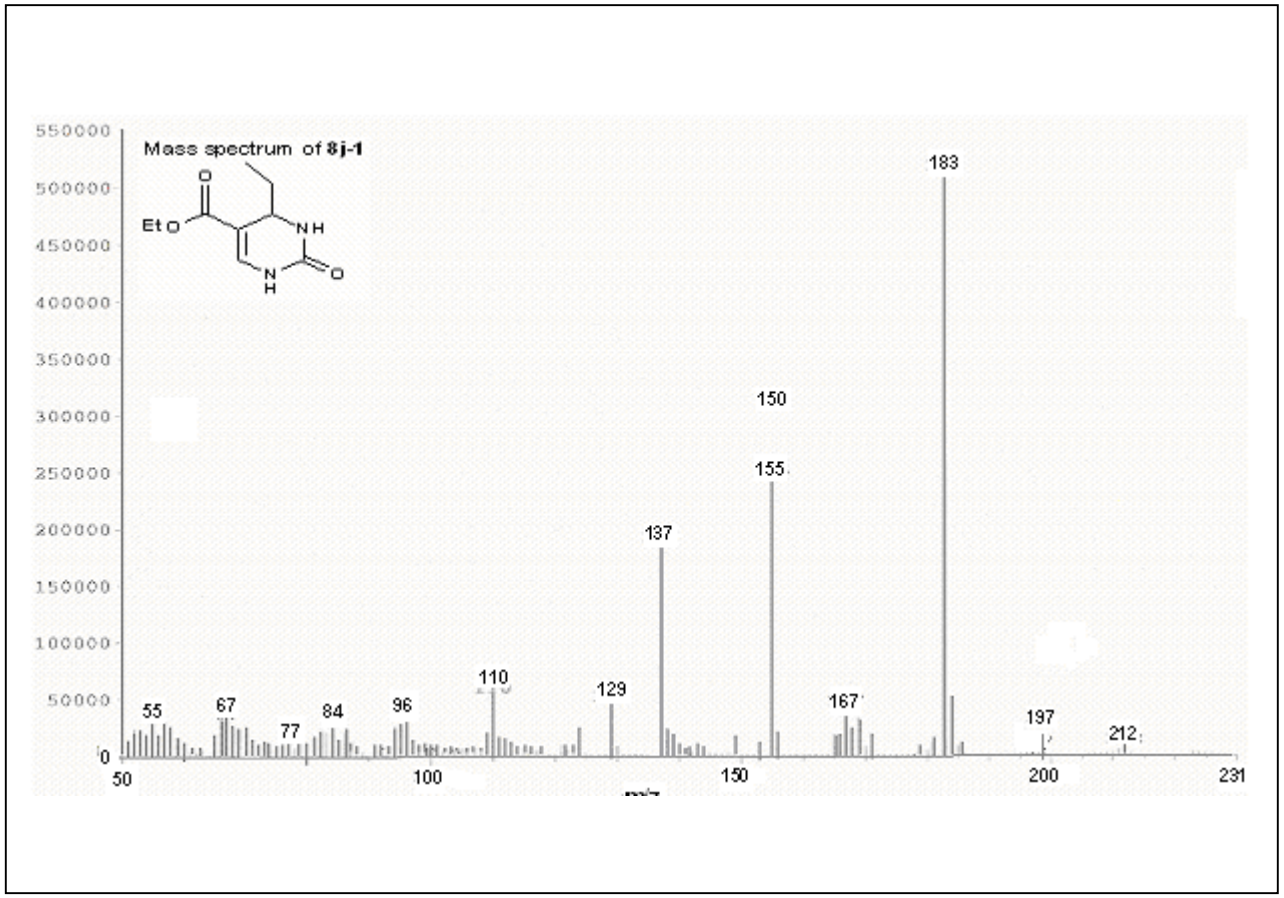

¹HNMR spectrum of 8a-1
OMe
OMe
O
O
NH
Ph
N
H
S
8a-1
2.02
5.09
2.99
0.75
8.00
5.15
2.42
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Mass spectrum of 18a-1
OMe
OMe
O
O
NH
Ph
N
H
S
8a-1
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
77
91
105
65
129
151
165
208
220
250
261
283
309
325
340
352
369
398
50
100
150
200
250
300
350
420
m/z


^{1}HNMR spectrum of **8f-1**
OH
OMe
O
NH
N
H
O
8f-1


^{13}CNMR spectrum of **8f-1**
OH
OMe
O
NH
N
H
O
8f-1


¹HNMR spectrum of 8j-1
Et O
NH
N
H
O
O
8.04
7.27
5.86
4.32
4.29
4.27
4.24
4.20
4.17
4.13
2.39
1.76
1.63
1.59
1.55
1.52
1.32
1.28
1.23
0.96
0.92
0.89
0.00
1.02
1.00
3.05
3.00
2.03
2.95
2.94
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

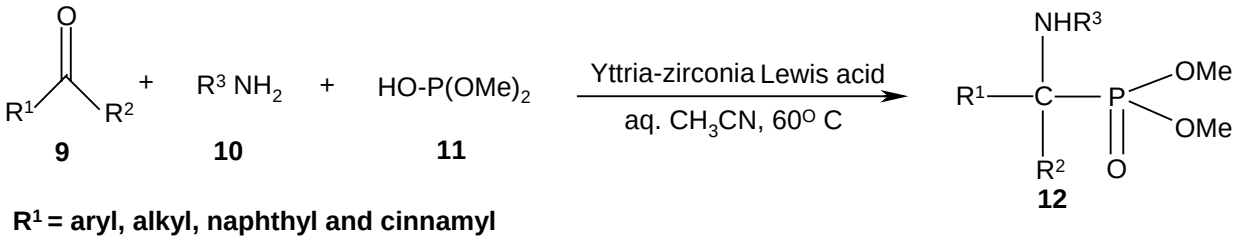

Mass spectrum of 8j-1
Et O
NH
N
H
O
O
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
183
150
155
137
110
129
167
197
212
55
67
77
84
96
50
100
150
200
231

4.2.2 Part II. Synthesis of α-aminophosphonates by three component condensation of carbonyl compounds, amine, and dialkyl phosphite using yttria-zirconia based Lewis acid

4.2.2.1 Introduction

α-Aminophosphosphonates, being structural analogs to α-amino acids, have shown considerable potentials as pharmacological agents,[19] peptide mimetics,[20] enzyme inhibitors[21] and also play an important role in hapten design for antibody generation.[22] Several synthetic methods for α-amino phosphonates have been developed during past two decades.[23] The general method involves the addition of phosphorus nucleophiles to imines, catalyzed by a base or an acid. Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3.Et_2O$,[23b] $TiCl_2$,[23c] $TaCl_3$-SiO_2,[23d] montmorillonite clay and $ZrCl_4$,[24] $ZnCl_2$/MgBr,[25] have been used earlier. However, these reactions can not be carried out in a one-pot operation with a carbonyl compound, amine and dialkyl phosphite, as the amine and water that exist during imine formation can decompose or deactivate when Lewis acids were used as catalyst. To circumvent the problems associated with these methods, one-pot procedure using lanthanide triflate[26a] and indium trichloride[26b] as catalyst has been developed. $LiClO_4$/LPDE or $LiClO_4$/TMSCl mediated synthesis of α-aminophosphonate are also available.[26c] Recently ionic liquids have also been employed for the synthesis of α-aminophosphonates in moderate yields.[27] Thus an efficient procedure for the synthesis of α-aminophosphonates from the aldehydes and ketones with aliphatic as well as aromatic amines is needed. In continuation of our ongoing research programme aimed at the application of Yttria-zirconia based Lewis acid catalyst for various organic transformations,[18] we have further explored the efficacy of this catalyst for the three component condensation of carbonyl compound, amine and dialkyl phosphite to yield α-amino phosphonates in good to excellent yields and selectivity (Table 2).

Scheme-2



9 **10** **11** **12**

R^1 = aryl, alkyl, naphthyl and cinnamyl
R^2 = H, CH_3
R^3 = aryl, alkyl

4.2.2.2. Results and Discussion

In a typical experimental procedure, a mixture of a carbonyl compound (1 mmol), an amine (1 mmol) and dialkyl phosphite (1mmol) was added to a slurry of Yttria-zirconia (10mol%) in acetonitrile (5 ml) and heated at 60^o C for the indicated length of time (**Table 2**) to afford the corresponding α-aminophosphonates in good to excellent yield. A wide range of structurally varied carbonyl compounds were subjected to this procedure and converted into the corresponding α-aminophosphonates in high yields. Thus when benzaldehyde (1mmol) benzylamine (1mmol) and dimethyl phosphite were heated at 60°C together with Yttria-zirconia based Lewis acid in 10% aqueous acetonitrile for the indicated time, it gave the corresponding α-amino phsophonates **12b** in 86% yield (**entry 2, Table 2**). The IR spectrum of **12b** showed a band at 3333 cm^{-1} indicating the presence of NH functionalities and band at 1246 cm^{-1} showed the P=O vibration. The ^{1}H NMR spectrum of **12b** showed doublets at δ 3.55 and at δ 3.75 with *J* value 10 Hz, corresponding to six protons of two methoxy groups of dimethylphosphite. The quartet at δ 3.73-3.88 with *J* value 10 Hz indicated the presence of two benzylic protons of the benzylamine. The doublet at δ 4.07 with *J* values 12 Hz confirmed the presence of one next phosphorus atom. The mass spectrum of compound 12b shows M^+ peak at 305 confirming the formation of the α-aminophosphonate **12b**. The results of other coupling reactions are reported in Table 2. A wide variety of aromatic, heteroaromatic and aliphatic aldehydes react with aromatic as well as aliphatic amines and dimethylphosphite to form the corresponding α-aminophosphonates. This procedure equally worked well for the conversion of aromatics ketones into α-amino phosphonates. As it is seen from the Table 2 (**entry 24, Compound 12x**), in the presence of both aldehyde and

ketone functionalities, aldehyde reacted faster and gave exclusively one product. We also succeeded in the reaction of β-keto esters with dimethylphosphite which led to the corresponding α-aminophosphonates. No difficulty was encountered with the reaction of conjugated aldehydes (**Entry 8 and 24**). The presence of electron withdrawing or electron donating substituents on aromatic rings does not make any difference in the course of reaction. Several sensitive functionalities such as OH, OMe, NO_2, Cl, F and C=C bond were unaffected under the present reaction conditions. The reactions were in general very fast, clean, no side product has been isolated in any reaction leading to a minimum waste.

4.2.2.3 Conclusion

In summary, the present procedure using Yttria-zirconia Lewis acid provides an efficient heterogeneous catalysis in the one-pot synthesis of α-aminophosphonates from the reaction of a carbonyl compound, amine and dialkylphosphites. The notable advantage of this procedure are (i) operational simplicity and requirement of no additives (ii) heterogeneous catalysis with easy workup and recyclability of the catalyst (iii) general applicability to aldehyde and ketones (both aromatic and aliphatic) (iv) both aromatic and aliphatic amines were used in the reaction, (v) survival of varied sensitive functional groups and (vi) good to excellent yields. We believe, our procedure will find important applications in the synthesis of α-aminophosphonates in a practical way as an alternative to existing methodologies.

4.2.2.4 Experimental Section

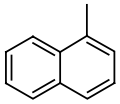
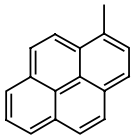
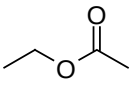
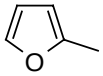
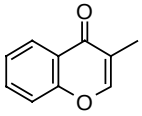
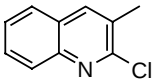
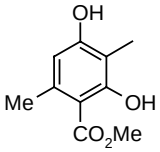
General experimental procedure for the synthesis of α-aminophosphonates using yttria-zirconia Lewis acid catalyst

A slurry of carbonyl compound (1 mmol), amine (1 mmol) and dialkyl phosphite (1 mmol) with yttria-zirconia (10mol%) in 10% aq. acetonitrile (5 mL) was stirred at 60°C for the indicated time (Table 2). The progress of reaction was monitored by TLC. After completion, the reaction mixture was filtered in hot condition and poured into cold water and extracted with CH_2Cl_2 (3 x 50 mL); washed (brine), dried (Na_2SO_4) and concentrated to afford the crude product which was purified by silica gel column chromatography using petroleum

ether: EtOAc (7:3) as eluent to give the pure product which was fully characterized by spectroscopic data.

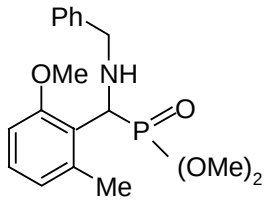
Table 2. One pot synthesis of α-aminophsophonates

Entry	R^1	R^2	R^3	Time (h)	Yield* (%)	MP ^oC	Product	Ref
1	Ph	H	Ph	2	99	181-183	**12a**	26a
2	Ph	H	$PhCH_2$	3	86	171-172	**12b**	26a
3	Ph	H	n-C_3H_7	4	95	168-169	**12c**	–
4	4-OMe-C_6H_4	H	Ph	3	95	184-185	**12d**	26b
5	4-Cl-C_6H_4	H	4-OMe-C_6H_4	7	82	155-158	**12e**	–
6	4-OMe-C_6H_4	H	4-OMe-C_6H_4	4	98	184-185	**12f**	–
7	4-Me-C_6H_4	H	Ph	7	79	174-175	**12g**	27b
8	Ph-CH=CH-(trans)	H	Ph	4	98	brown oil	**12h**	26a
9	2-OH-C_6H_4	H	4-Cl-C_6H_4	9	77	brown oil	**12i**	–
10	2-Me-6-OMe-C_6H_3	H	$PhCH_2$	5	55	162-163	**12j**	–
11	2-Cl-C_6H_4	H	$PhCH_2$	11	93	165-167	**12k**	–
12	3-OMe-C_6H_4	H	2,6-$(Me)_2$-C_6H_3	10	89	173-175	**12l**	–
13	3,4,5-$(OMe)_3$-C_6H_2	H	4-OMe-C_6H_4	3	89	191-194	**12m**	–
14	4-NO_2-C_6H_4	H	Ph	6	87	201-203	**12n**	–
15	4-$N(Me)_2$-C_6H_4	H	$PhCH_2$	7	84	218-220	**120**	–

Entry	R^1	R^2	R^3	Time (h)	Yield* %	MP °C	Product	Ref
16	2-OH-3-OMe-C_6H_3	H	2-Cl-3-F-C_6H_3	9	99	189-190	**12p**	–
17	3,4,-$(OMe)_2$-C_6H_3	H	2-NO_2-4-OMe-C_6H_3	9	98	198-200	**12q**	–
18		H	2,6-$(Me)_2$-C_6H_3	6	75	pale green oil	**12r**	–
19		H	$PhCH_2$	5	98	dark brown oil	**12s**	–
20	Ph	CH_3	$PhCH_2$	5	48	brown oil	**12t**	26b
21		CH_3	Ph	5	45	pale yellow oil	**12u**	–
22	Me_2CH	H	$PhCH_2$	7	88	dark brown oil	**12v**	26b
23		H	4-OMe-C_6H_4	3	83	brown oil	**12w**	–
24		H	$PhCH_2$	6	99	154-155	**12x**	–
25		H	Ph	12	75	224-226	**12y**	–
26		H	$PhCH_2$	6	42	167-169	**12z**	–

***Isolated yield after column purification**

α-(*N*-phenyl)-α-(2-methyl-6-methoxyphenyl)-phosphonate(12j)



12J

Yield: 55%

Dark Brown Solid

M.P.: 162-163°C

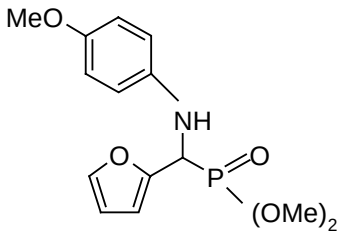
IR ($CHCl_3$, cm^{-1}): ν_{max} 3358, (br), 2957, 2852, 1709, 1607, 1503

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.03 (s, 3H), 3.65-4.00 (m, 11H), 4.40 (d, 1H, *J* = 23.93 Hz), 6.81 (t, 2H, *J* = 6.84 Hz), 7.15-7.45 (m, 7H)

Mass: 240 [-$PO(OMe)_2$], 224, 196, 165, 148, 143, 118, 105, 91, 79, 65

Analysis calcd for $C_{18}H_{24}NO_4P$ (349.36): Found C, 61.75; H, 6.80; N, 4.13{Required C, 61.88; H, 6.92; N, 4.45}

α-Furfuryl-α-*N*-(4-methoxyphenyl)-α-phosphonate (12w)



12w

Yield: 83%

Pale Brown Oil

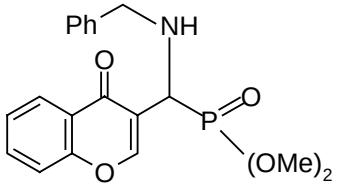
IR (Neat, cm^{-1}): ν_{max} 3343 (br), 2948, 2852, 1993, 1601, 1495.

^{1}H NMR : (200 MHz, $CDCl_3$): δ 3.61 (d, 3H, *J* = 12Hz), 3.72 (s, 3H), 3.80 (d, 3H, *J* = 11.92 Hz), 4.78 (d, 1H, *J* = 24 Hz), 6.30-6.40 (m, 2H), 6.63 (d, 2H, *J* = 8 Hz), 6.67(d, 2H *J* = 11.93 Hz), 7.40 (m, 1H), 8.45(s, 1H)

Mass: 311 (M^+), 246, 216, 202, 186, 173, 158, 134, 109, 93, 79, 64

Analysis calcd for $C_{14}H_{18}NO_5P$ (311.33): Found C, 74.47; H, 5.71; N, 4.48{Required C, 74.62; H, 5.84; N, 4.50}

α-2,3-Dihydro-benzopyran-4-one-α- (*N*-benzyl)-α-phosphonate (12x)



12x

Yield: 99%

White Solid

M.P.: 178-180°C

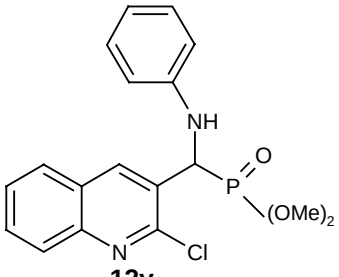
IR ($CHCl_3$, cm^{-1}): ν_{max} 3439, 3314, 3005, 2851, 1644, 1608, 1466, 1350

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.70-3.90 (m, 8H), 4.61-6.71 (d, 1H, *J* = 20 Hz), 6.9-7.4 (m, 10H), 8.24(m, 1H)

Mass: 373(M^+), 282, 264, 250, 234, 186, 172, 159, 148, 131, 120, 109, 89, 77, 65.

Analysis calcd for $C_{19}H_{20}NO_5P$ (373.34): Found C, 60.02; H, 5.22; N, 3.61{Required C, 61.12; H, 5.22; N, 3.61}

α-(2-Chloroquinolin-3-yl)-α-(*N*-phenyl)-α-phosphonate(12y)



12y

Yield: 75%

White solid

M.P.: 224-226^{0}C

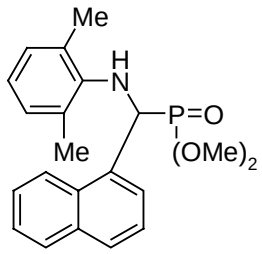
IR ($CHCl_3$, cm^{-1}): ν_{max} 3411, 3302, 3013, 1603, 1502, 1216, 1059

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.53 (d, 3H, *J* = 12 Hz), 3.92 (d, 3H, *J* = 12 Hz), 4.90 (b, 1H), 5.48 (d, 1H, *J* = 24 Hz), 6.64-6.90 (m, 3H), 7.12 (t, 2H, *J* = 8.91 Hz), 7.48(t, 1H, *J* = 8.92 Hz), 7.71(m, 2H), 8.01 (d, 1H *J* = 8.91 Hz), 8.44 (s, 1H)

Mass: 376(M^+), 267, 231, 203, 176, 153, 140, 128, 109, 77

Analysis calcd for $C_{18}H_{18}ClN_2O_3P$ (376.78): Found C, 57.21; H, 4.907; N, 7.31{Required C, 57.38, H, 4.81; N, 7.44}

α-Napthyl-α-(2,6-dimethylphenyl)-phosphonate(12r)



12r

Yield: 75%

Pale Green Oil

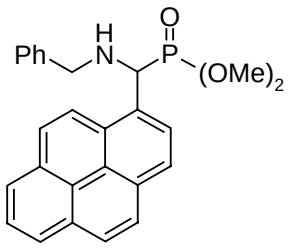
IR (Neat, cm^{-1}): ν_{max} 3385, 3048, 3010, 2952, 2852, 1594, 1471, 1246, 1055

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.23 (s, 6H), 3.10 (d, 3H, *J* = 9.79 Hz), 3.40 (brs, 1H), 3.76 (d, 3H, *J* = 11.93 Hz), 5.38(d, 1H, *J* = 21.71 Hz), 6.77 (t, 1H, *J* = 6.31 Hz), 6.94 (d, 2H, *J* = 7.81 Hz), 7.46-7.65 (m, 3H), 7.86-7.98 (m, 4H)

Mass: 369(M^+), 260, 249, 242, 236, 225, 120, 109

Analysis calcd for $C_{21}H_{24}NO_3P$ (369.40): Found C, 68.13; H, 6.49; N, 3.67{Required C, 68.28; H, 6.54; N, 3.79}

α-Pyrene- α-(*N*-benzyl)-phosphonates(12s)



12s

Yield: 98%

Dark Brown Oil.

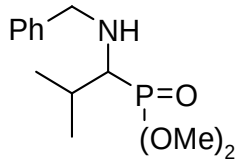
IR (Neat, cm^{-1}): ν_{max} 3507, 3002, 2995, 2850, 1711, 1607, 1499, 1362, 1223

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.30 (brs, 1H), 3.38 (d, 3H, *J* = 9.71 Hz), 3.60-3.96 (m, 5H), 5.27 (d, 1H, *J* = 19.92 Hz), 7.05-7.35 (m, 5H), 7.90-8.55 (m, 9H)

Mass: 339[-Bn], 319[-$PO(OMe)_2$], 239, 215, 151, 120, 91

Analysis calcd for $C_{26}H_{24}NO_3P$ (429.45): Found C, 72.79; H, 5.589; N, 3.31{Required C, 72.71; H, 5.63; N, 3.26}

α-Isopropyl-α-(*N*-benzyl)-α-phosphonate (12v)



Yield: 48%

Dark Brown Oil

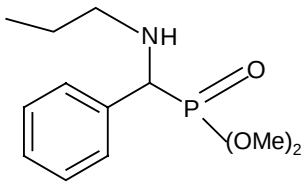
IR (Neat, cm^{-1}): ν_{max} 3437, 3298, 3013, 2872, 1673, 1216, 1040, 773, 667

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85-10.1 (m, 7H), 3.69-3.80 (m, 6H), 4.41(d, 1H, *J* = 2Hz), 4.45 (d, 2H, *J* = 6 Hz), 7.27 (m, 5H)

Mass: 271(M^+), 251, 242, 225, 208, 192, 170, 169, 134, 118

Analysis calcd for $C_{13}H_{22}NO_3P$ (271.29): Found C, 57.49; H, 8.05; N, 5.26 {Required C, 57.55; H, 8.17; N, 5.16}

α-Phenyl-α-N-Phenyl-α-Phhosphonate (12c)



12c

Yield: 95%

Pale yellow solid

IR ($CHCl_3$, cm^{-1}): ν_{max} 3299, 2970, 1624, 1525, 1475, 1215, 1056

^{1}HNMR (200MHz, $CDCl_3$): δ 0.90(t, 3H, *J* = 7.73 Hz), 1.46(m, 2H), 2.08(brs, 1H), 2.47(m, 2H), 3.52(d, 3H, *J* = 9.91Hz), 3.71(d, 3H, *J* = 9.92Hz), 4.01(d, 1H, *J* = 19.91 Hz), 7.33(m, 5H)

Analysis cacd for $C_{12}H_{20}N0_3P$ (256.23): Found C, 56.13; H, 7.72; N, 5.29 {Required C, 56.25; H, 7.87; N, 5.46}

4.2.2.5 Spectra

1. ^{1}HNMR spectrum of 12j

2. ^{1}HNMR spectrum of 12w

3. ^{1}HNMR spectrum of 12x

4. ^{1}HNMR spectrum of 12y

5. Mass spectrum of 12y

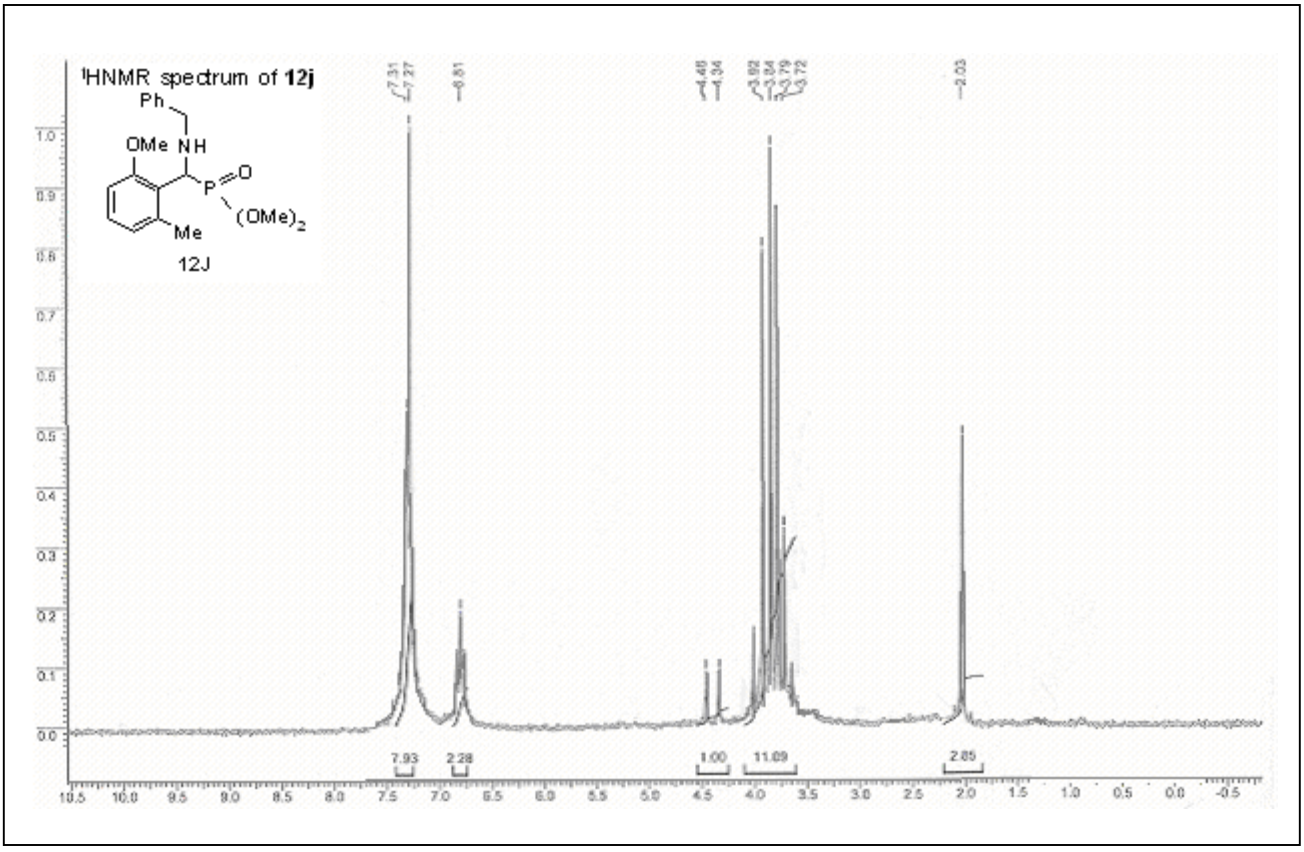
6. ^{1}HNMR spectrum of 12r

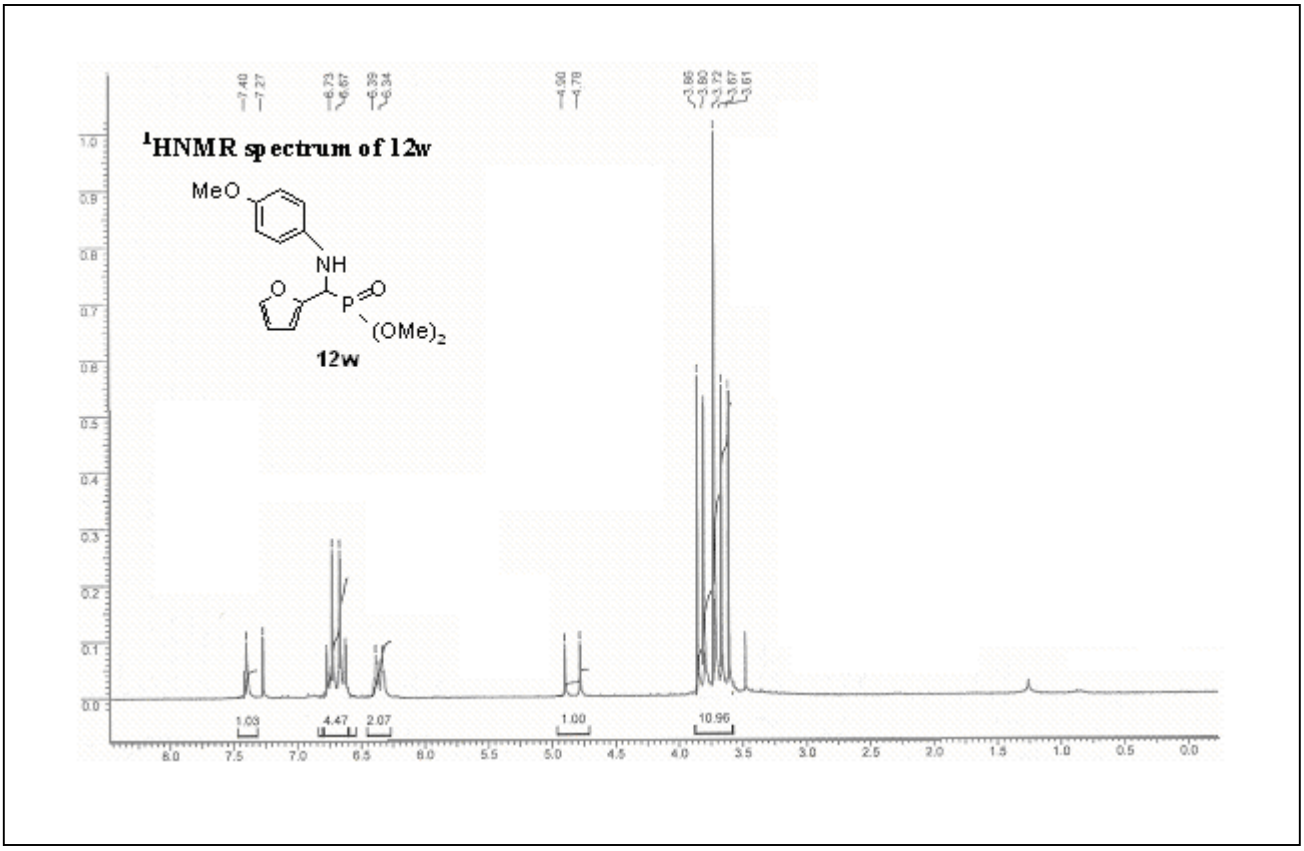
7. 1HNMR spectrum of 12s

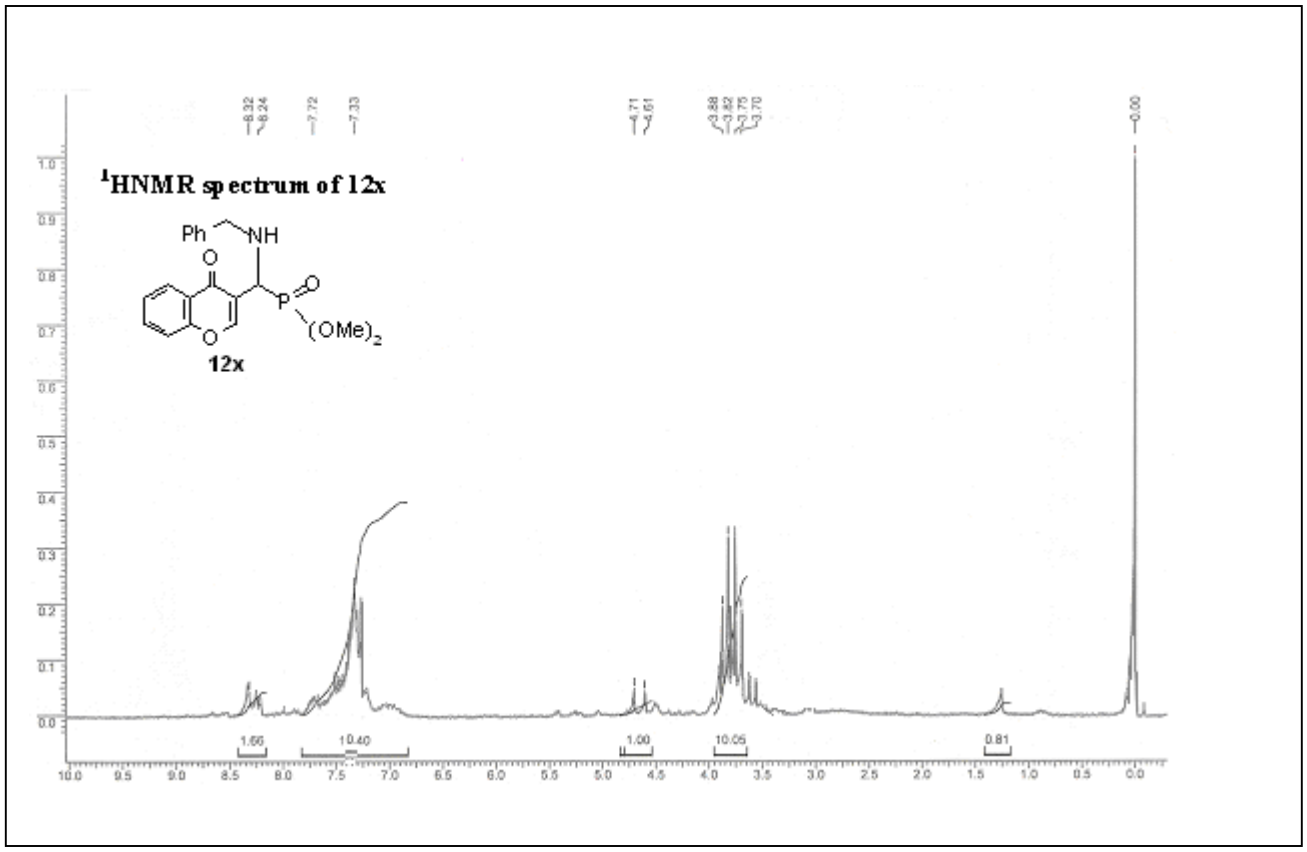
8. ^{1}HNMR spectrum of 12c

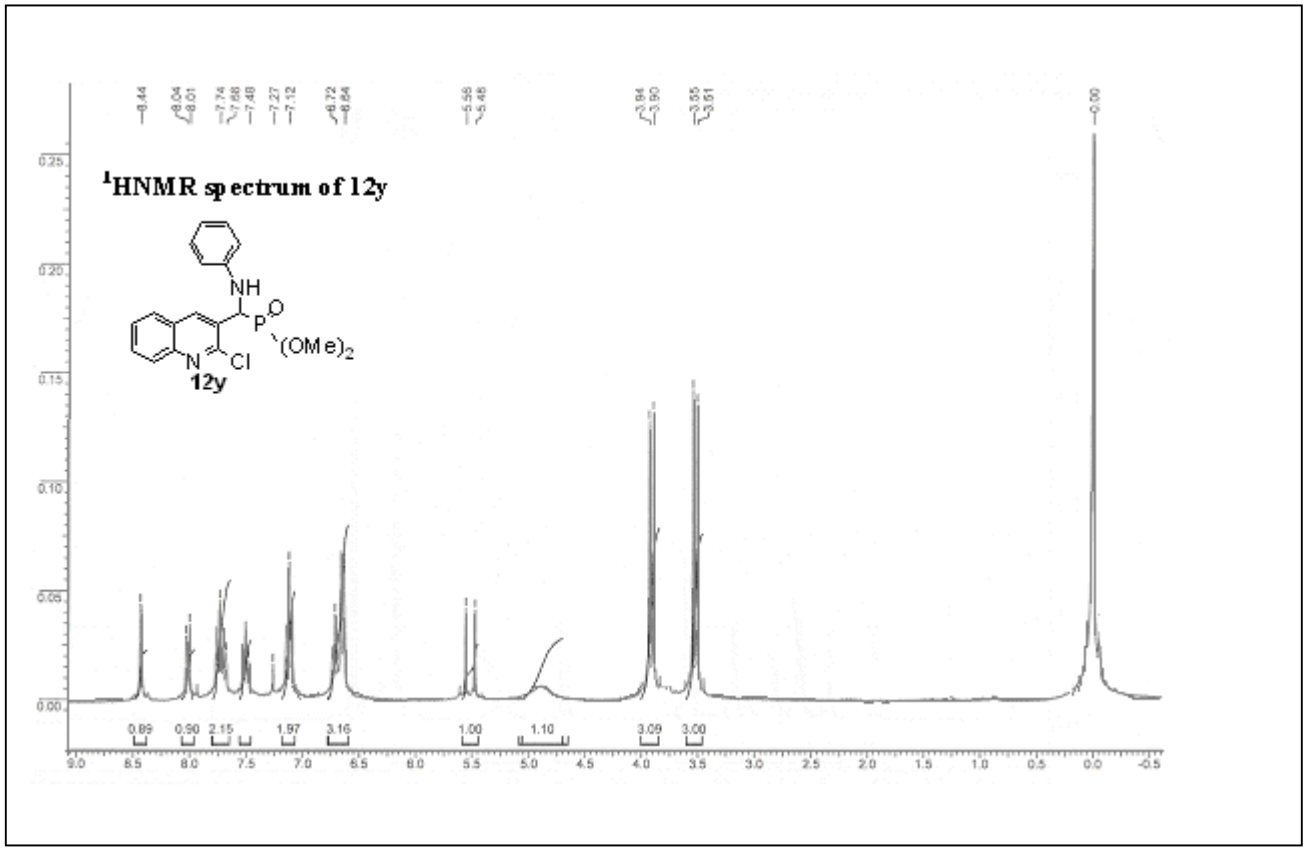
9. 1HNMR spectrum of 12t

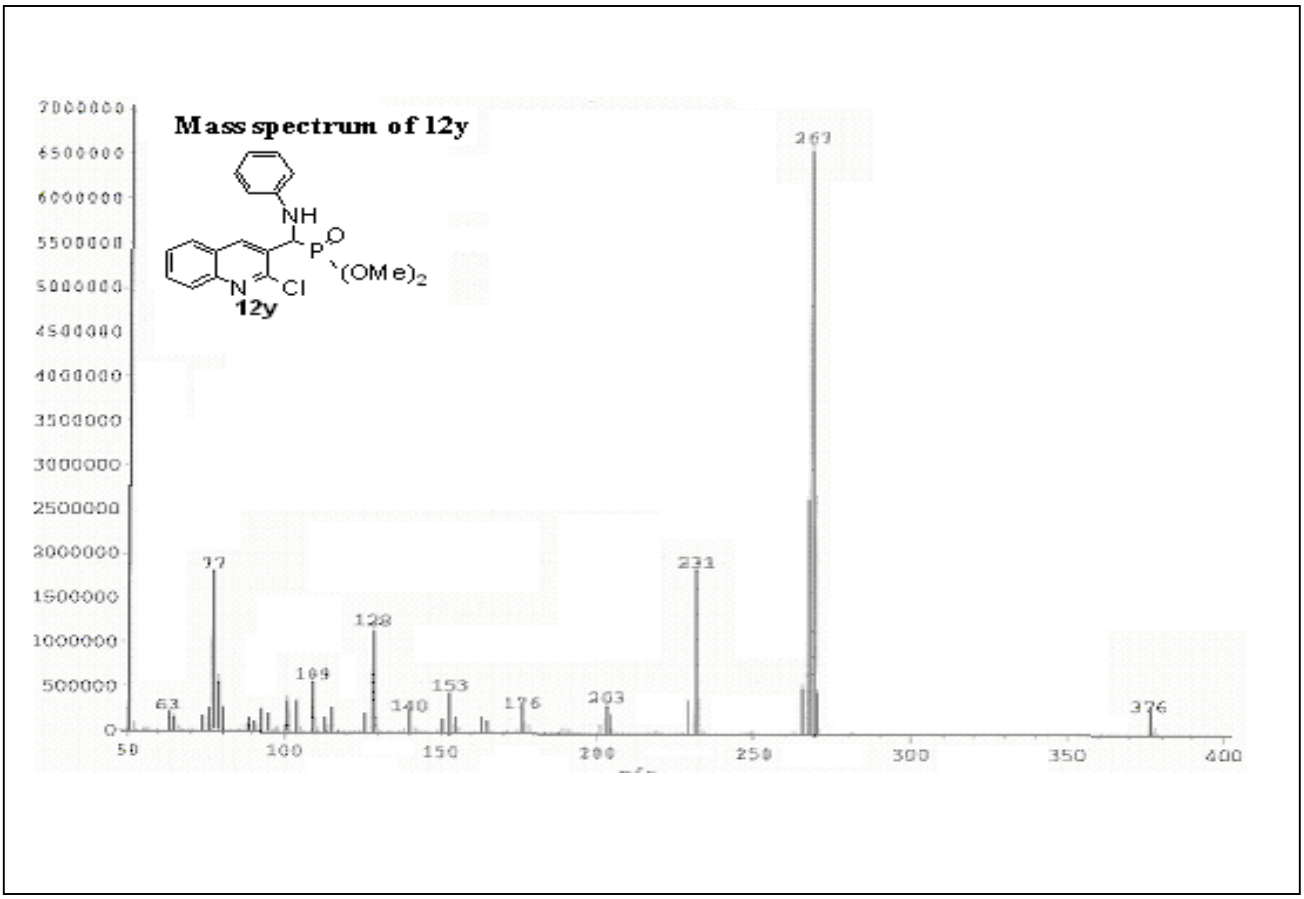
10. Mass spectrum of 12t

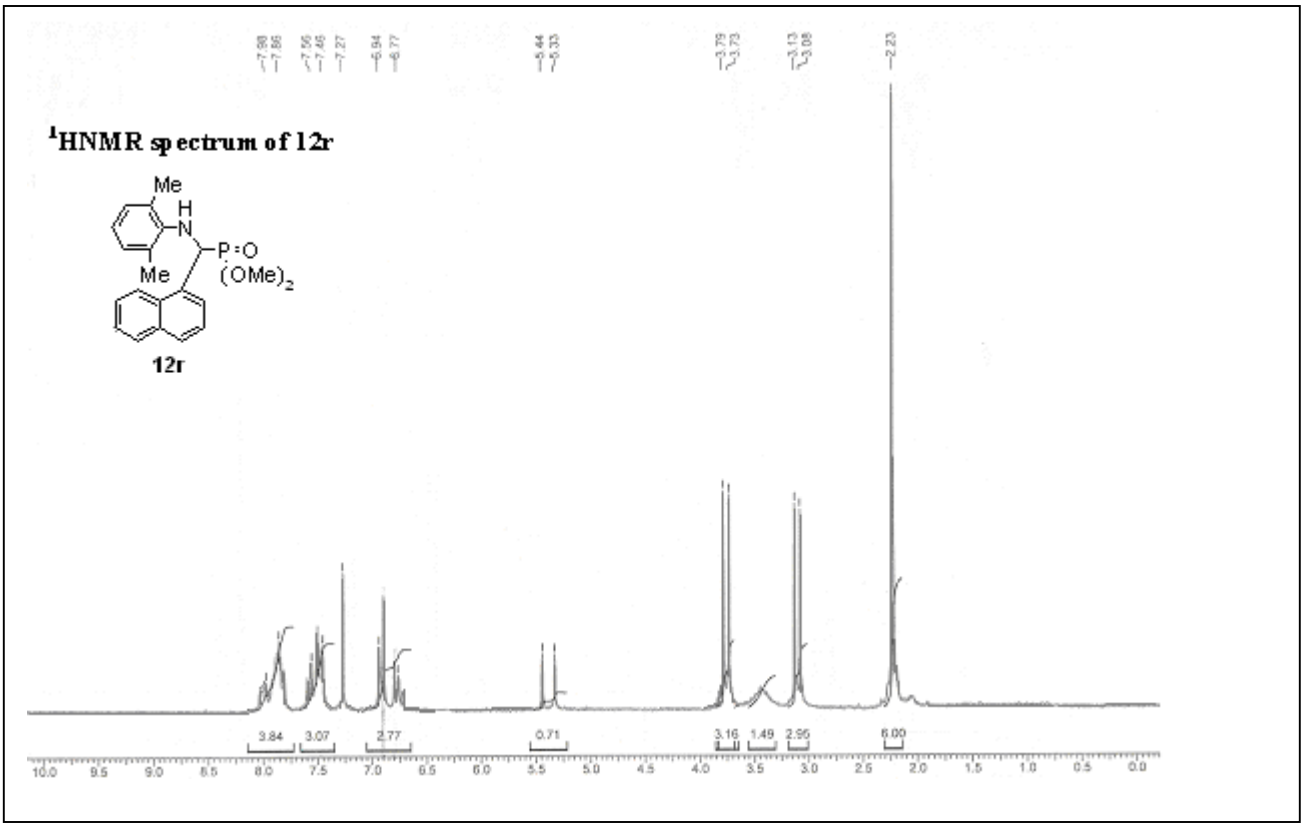

¹HNMR spectrum of 12j
Ph
OMe NH
P
O
(OMe)2
Me
12J
7.93
2.28
1.00
11.09
2.85

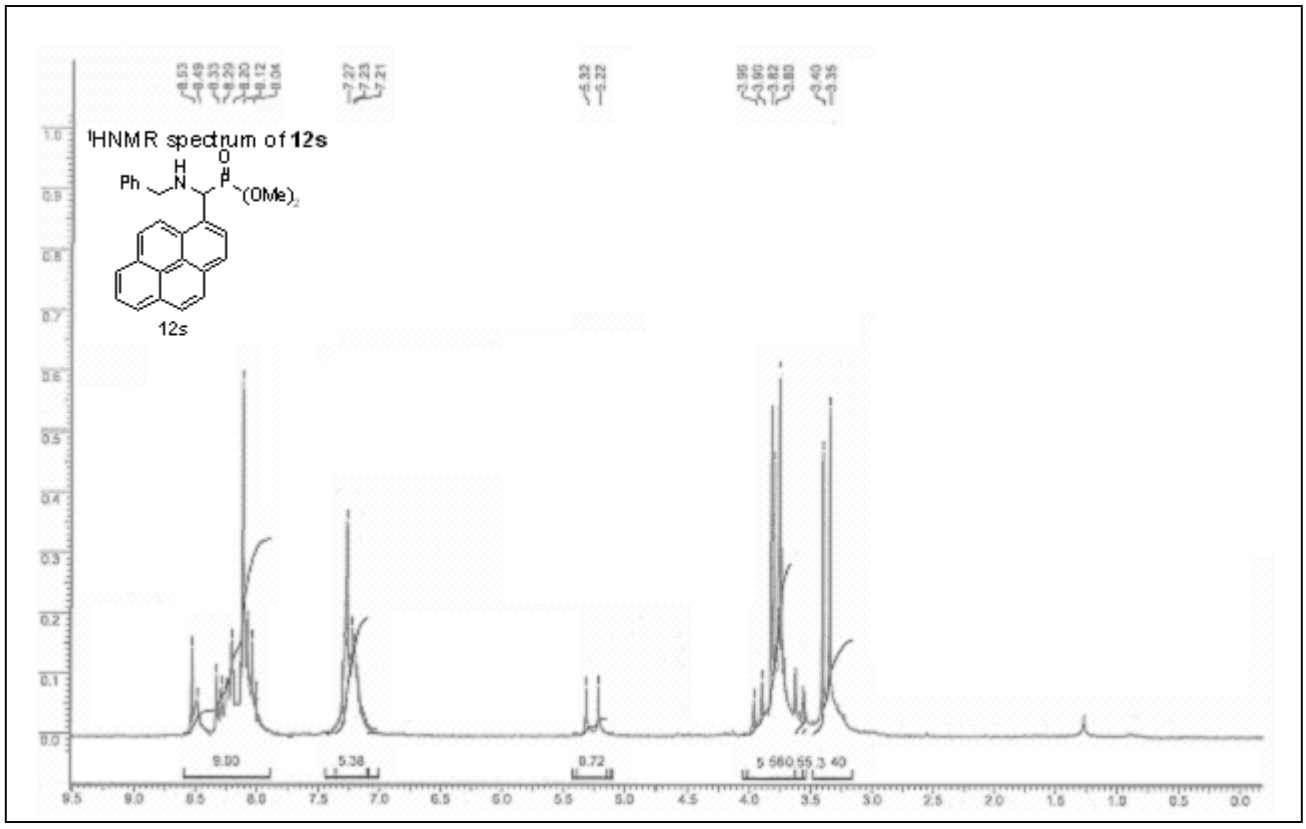

¹HNMR spectrum of 12w
MeO
NH
O
P
O
(OMe)2
12w
1.03
4.47
2.07
1.00
10.96

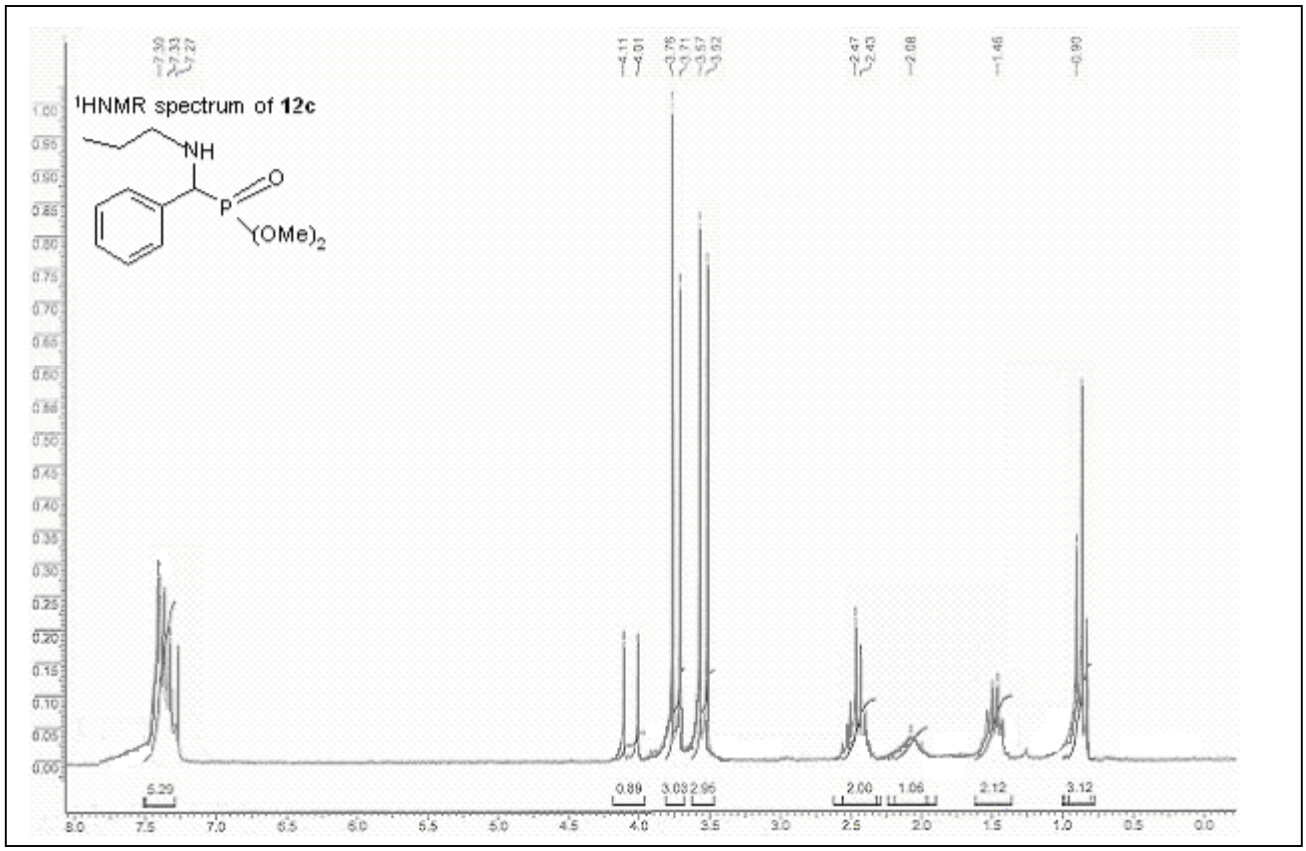

^{1}HNMR spectrum of 12x
Ph
NH
O
P
O
(OMe)$_2$
O
12x

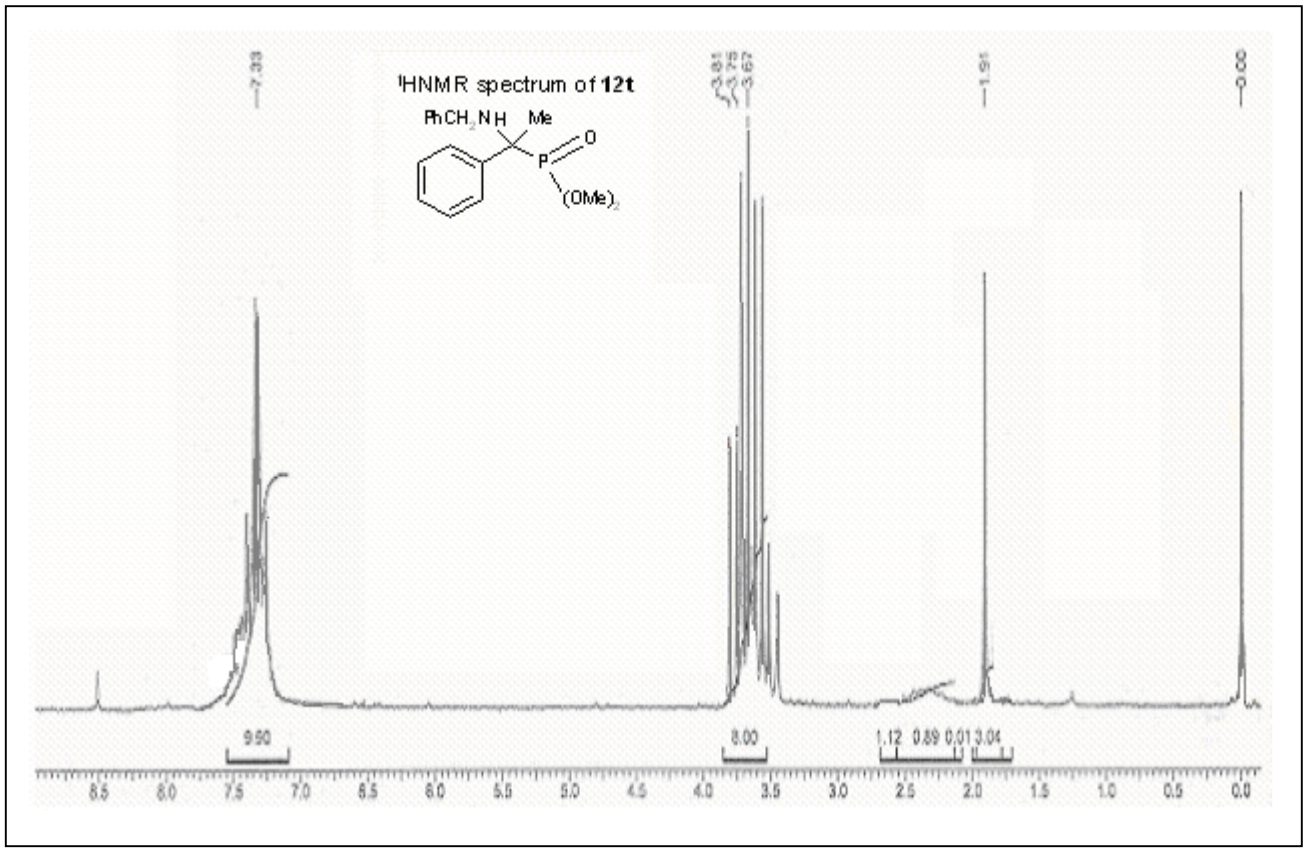

^{1}HNMR spectrum of 12y
NH
P
O
(OMe)$_2$
N
Cl
12y

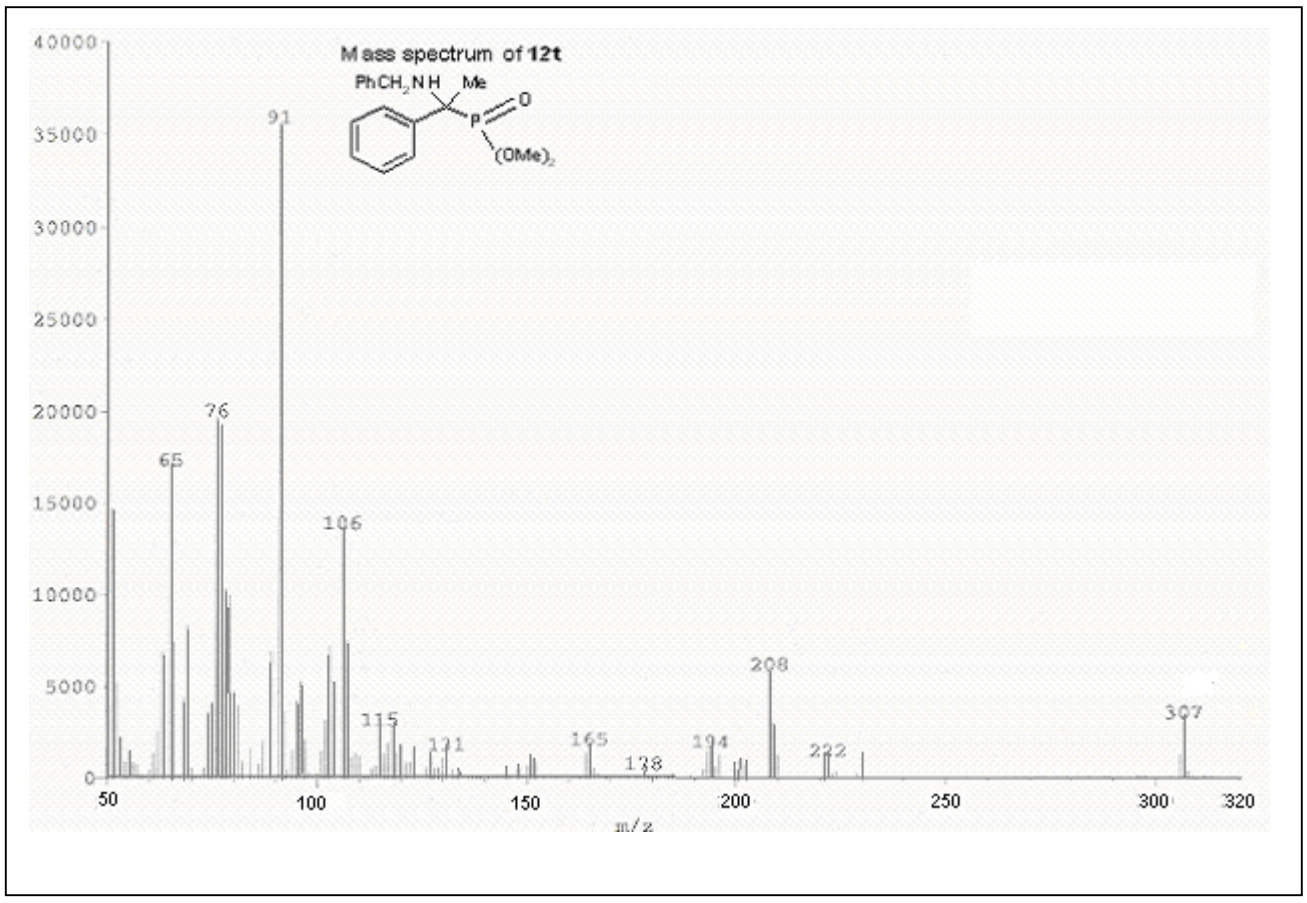

Mass spectrum of 12y
NH
P
O
(OMe)2
N
Cl
12y
263
231
77
128
109
153
140
176
203
63
376
7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
50
100
150
200
250
300
350
400


1HNMR spectrum of 12r
Me
H
N
P=O
(OMe)2
Me
12r
3.84
3.07
2.77
0.71
3.16
1.49
2.95
6.00


^{1}HNMR spectrum of **12s**
Ph
N
H
P
O
(OMe)$_2$
12*s*


^{1}HNMR spectrum of **12c**
NH
P
O
(OMe)$_2$


^{1}HNMR spectrum of **12t**
PhCH$_2$NH Me
P
O
(OMe)$_2$
7.33
3.81
3.75
3.67
1.91
0.00
9.50
8.00
1.12 0.89 0.01 3.04

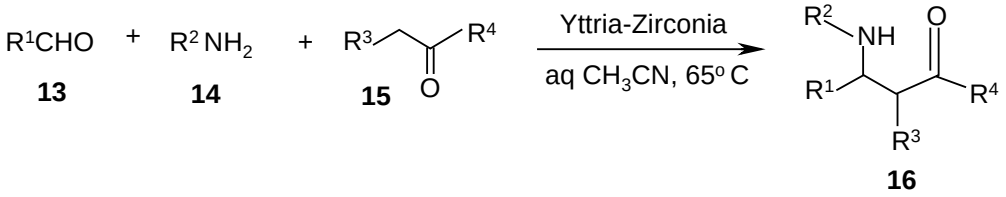

Mass spectrum of **12t**
PhCH$_2$NH Me
P
O
(OMe)$_2$
91
76
65
106
115
121
165
138
194
208
222
307
m/z

4.2.3 Part III. One Pot Synthesis of β-Amino carbonyls using Yttria-zirconia based Lewis acid

4.2.3.1 Introduction

Multicomponent reactions performed either on a solid or in solution[28] phase not only have emerged as a powerful tool in combinatorial chemistry but also has the power to rapidly build molecular complexity. Many unique structures can be attained rapidly when three or more reactants are combined in a single step to afford new compounds possessing the combined features of the building blocks.[29] The Mannich reaction provides one of the most basic and useful methods for the synthesis of such compound. In such a reaction, an amine, two carbonyl compounds in presence of acid (or base) catalysts are used to produce β-amino carbonyl compound.

Scheme 3



Mannich reaction, which produces β-amino carbonyls are important precursors for β-lactam and amino acid.[30] Numerous kinds of activators have been developed.[31] β-Amino carbonyls are versatile synthetic intermediate for various pharmaceuticals, and natural products. In the past, different methods have been developed to synthesise β-amino carbonyls based on the catalysts and solvents used. Some of the methods have been developed based on the kind of carbonyls used to react with aldimines (ketones or silyl enol ethers). In recent years, organic reactions in water or combination of water and organic solvents, without using harmful organic solvents are of great concern, especially in relation to today's environmental concerns.[32] On the other hand, organic reactions using reusable solid catalysts have also received much attention because of their practical advantage.[33] Therefore, organic reactions using solid lewis acid catalysts in water or the combination of water and organic solvents will be an ideal methodology, because of the deactivation of most of the solid acid catalysts, in water as solvent, the combination of water and organic solvents were preferred. There are

various methods available in the literature to prepare β-amino carbonyl in organic solvent. Many methods developed in aqueous media uses preformed aldimines and reactive silyl enolates to prepare β-amino carbonyl.[34] Though conventional protocols for three component Mannich type reaction of aldehydes, amines and ketones in organic solvents include some severe side reactions and have some substrate limitations, especially for enolizable aliphatic aldehydes. Kobayashi and co-workers reported the preparation of β-amino carbonyls by direct three component asymmetric Mannich reaction using different (amines, aldehydes and ketones) catalyst in aqueous media (colloidal dispersion system created by a Brönsted acid surfactant, *p*-dodecylbenzene sulfonic acid (DBSA) and polymer-supported sulfonic acid.[35] Jiang and co-workers reported the direct preparation of β-amino carbonyl from amines, aldehyde and ketones using acidic ionic liquids.[36a] List and co-workers reported the *L*-proline based three component coupling to prepare β-amino carbonyl compounds.[36b] Although Brönsted acid surfactant, proline catalysed direct three component coupling reaction to prepare β-amino carbonyls are known, the recyclability of these catalyst in water becomes a problem and also though the reaction system stated above has extended the substrate applicability in Mannich reactions in water, there is still drawback that the silyl enolates which is prepared from the corresponding carbonyl compounds usually under anhydrous conditions have to be used. From atom economy and practical points of view, it is desirable to develop an efficient reusable system for Mannich-type reactions in which the parent carbonyls compounds are directly used. In continuation of our exploration on Yttria-zirconia based Lewis acid catalysts on various organic transformations,[18] we have recently found that this catalyst is also effective for this transformation. In this section we describe the application of Yttria-zirconia based Lewis acid catalysts to the direct multi component coupling reaction to prepare β-amino carbonyls in aqueous acetonitrile or methanol. In three component Mannich type reactions in aqueous organic solvents, ketones instead of silyl enolates, was employed as nucleophilic component.

4.2.3.2 Results and Discussion

In a typical experimental procedure benzaldehyde, aniline and acetophenone in the presence of yttria-zirconia based Lewis acid in aq. CH_3CN (H_2O: CH_3CN, 1:9) was selected as a model reaction. The reaction mixture was stirred at 60-70°C, for 10 h (Table 3, entry 1) to give the

corresponding β-amino carbonyl **16a** in 83% yield. The IR spectrum of **16a** showed a peak at 3441cm^{-1} indicating the presence of NH group and another band at 1665 cm^{-1} showed the presence of keto carbonyl. The ^{1}H NMR spectrum of **16a** showed a quartet at δ 3.46 (J = 8 Hz) corresponding to two CH_2 protons and a triplet at δ 5.00 (with J = 8 Hz) corresponding to one CH proton. The molecular ion peak at 301 in the mass spectrum of **16a** gave additional evidence for the formation of β-amino carbonyls. Similarly the reaction between 3, 4, 5-tri methoxybenzaldehyde, 4-chloroaniline and acetophenone, in the presence of Yttria-zirconia based Lewis acid catalyst gave the product **16b** in 79% yield. The IR spectrum of **16b** showed a band at 1684 cm^{-1} indicating the presence of keto carbonyl group. The band at 3414 cm^{-1} showed the presence of NH functionality. The ^{1}H NMR spectrum of **16b** showed a doublet at δ 3.45 with J = 8 Hz corresponding to one CH proton attached to nitrogen atom. The singlet at δ 3.80 corresponding to 9 protons indicated the presence of three methoxy groups. The doublet at δ 6.48 (for 2H) singlet at δ 6.63 (for 2 H), doublet at δ 7.02 (for 2 H), multiplet at δ 7.40-7.58 (for 3H) and a doublet at 7.89 (for 2 H) indicated three different aromatics protons. The molecular ion peak at 425 of the mass spectrum confirmed the formation of the β-amino carbonyl **16b**.

Following are some noteworthy features of this methodology:

1. A 1:1:1 mixture of 4-methylbenzaldehyde; *p*-anisidine and *p*-hydroxyacetophenone with 2 mol% of yttria-zirconia based Lewis acid catalyst in aq. CH_3CN at 60-70°C gave the Mannich product in 57% yield (entry 7) in contrast to <5% yield with HCl catalysed reaction in EtOH (24h).[28]
2. In order to check the efficacy of the catalyst, various aldehydes were treated with 4 chloroaniline and acetophenone. We found that the reactivity order of the aldehydes is aromatic aldehydes>heteroaromatic aldehydes> aliphatic aldehydes. Aromatic aldehydes with electron withdrawing groups gave better yields than those having electron donating groups.
3. In case of amines, *p*-chloroanilines reacted efficiently with aldehydes and gave good yields than aniline, and anisidines, illustrating the importance of the electronic and steric nature of amines.

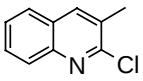
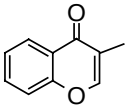
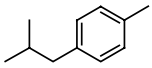
4. α,β-Unsaturated aldehydes, heteroaromatic aldehydes and aromatic aldehydes with chromophoric groups also reacted fairly to give moderate yield of the product. In order to evaluate the efficacy of the catalyst with aliphatic aldehydes, isovaleraldehyde and 2,3-pentenal were examined and when we followed the procedure of slow addition of aldehyde with amines in aq. CH_3CN, isovaleraldehyde gave only 35% of yield. On the other hand pentenal gave better yield (61%) with 4-chlorobenzaldehyde and 4-nitroacetophenone. Cyclohexanone gave moderate yield with 2 eq. of ketones. β-Keto esters and acetyl acetone did not give the required product. α-Halo aromatic ketones also reacted and gave the required product in 45% yield.

4.2.3.3 Conclusion

In summary, three component Mannich-type reaction of aldehyde, amines, and ketones is efficiently catalyzed by yttria-zirconia based Lewis acid in aq. CH_3CN. Aromatic, aliphatic and heteroaromatic aldehydes can be successfully used as the aldehyde component. Moreover, these reactions which proceed sluggishly in organic solvents, reacted faster when we add 5-10% of water. When the ratio of water increases beyond 20%, the recovery of the catalyst with original activity becomes a problem. The important features of this methodology is the easy preparation of the catalyst and its reactivation (by calcination) after the reaction.

Table 3

One pot synthesis of β-amino carbonyl compounds by three component coupling of amines, aldehydes and ketones

Entry	R^1	R^2	R^3	R^4	Ketone (equiv)	Time(h)	Yield* (%)	Product
1	C_6H_5	C_6H_5	H	C_6H_5	1.2	10	83	**16a**
2	3,4,5(-OMe)$_3$ -C_6H_2	4-Cl-C_6H_4	H	C_6H_5	1.2	12	79	**16b**
3	3,4,5(-OMe)$_3$ -C_6H_2	4-F-3-Cl-C_6H_3	H	C_6H_5	1.2	10	74	**16c**
4	3,4,5(-OMe)$_3$-C_6H_2	4-OMe-C_6H_4	H	C_6H_5	1.2	12	87	**16d**
5	3,4,5(-OMe)$_3$ -C_6H_2	2-Me-C_6H_4	H	2-Cl-C_6H_4	1.2	18	69	**16e**
6	Furfural	4-OMe-C_6H_4	H	C_6H_5	1.2	12	82	**16f**
7	4-Me-C_6H_4	4-OMe-C_6H_4	H	4-OH-C_6H_4	1.2	20	57	**16g**
8		C_6H_5	H	C_6H_5	1.2	22	45	**16h**
9		$C_6H_5CH_2$	H	C_6H_5	1.2	11	48	**16i**
10	C_6H_5	4-Cl-C_6H_4	H		1.1	24	32	**16j**
11	C_6H_5	C_6H_5	-$(CH_2)_4$ -	–	2	11	78	**16k**
12	2-Pentenal	4-Cl-C_6H_4	H	C_6H_5	1.2	24	35	**16l**
13	iso-valeraldehyde	4-Cl-C_6H_4	H	C_6H_5	1.2	12	61	**16m**

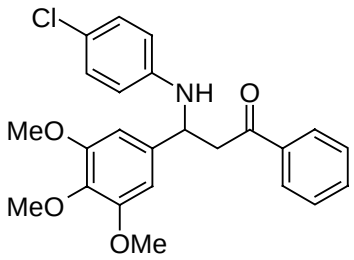
***Isolated yield after column purification**

4.2.3.4 Experimental Section

General procedure for the preparation of β- amino carbonyl compounds

A mixture of aldehyde (1mmol), amine (1mmol) and ketone (1.5mmol) was stirred at 65^0C in presence of 10 mol % of Yttria-zirconia Lewis acid catalyst in aq. CH_3CN (CH_3CN: H_2O, 9:1) for the indicated time mentioned in Table 3. The reaction completion was monitored by TLC. The reaction mixture was filtered in hot condition for the catalyst recovery, and the filterate was diluted with water and extracted with CH_2Cl_2 (3x25ml). The combined organic layer, was washed with water and brine solution, dried over anhy. Na_2SO_4 and concentrated to give the crude product, which was purified by silica gel column chromatography using petroleum ether: EtOAc(80:20) as eluent to give the pure β-aminocarbonyl.

3-(4-Chloro-phenylamino)-1-phenyl-3-(3,4,5-trimethoxyphenyl)-propan-1-one (16b)



16b

Yield: 79%

Light Brown solid

M.P.: 184-185°C

IR ($CHCl_3$, cm^{-1}): ν_{max} 3414, 3019, 2400, 1684, 1596, 1498, 1215

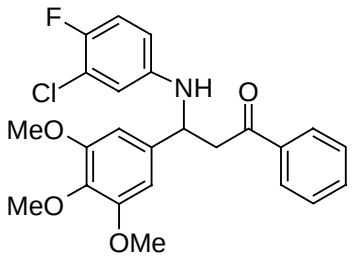
^{1}H NMR (200 MHz, $CDCl_3$): δ 3.45 (d, 2H, *J* = 4 Hz), 3.80 (s, 9H), 4.85 (t, 1H, *J* = 6 Hz), 6.48 (d, 2H, *J* = 10 Hz), 6.63 (s, 2H), 7.04(d, 2H, *J* = 10 Hz), 7.43 (t, 2H, *J* = 8 Hz), 7.53 (t, 1H, *J* = 6 Hz), 7.89 (d, 2H, *J* = 8 Hz)

^{13}C NMR (200 MHz, $CDCl_3$): δ 46.0, 55.3, 56.0(2C), 60.6, 103.4(2C), 115.0(2C), 122.4, 128.0(2C), 128.5(2C), 128.7(2C), 133.3, 136.7, 137.1, 138.2, 145.6, 153.5, 198.7

Mass: 425 (M^+), 306, 267, 236, 195, 179, 168, 154, 138, 127, 105, 91, 77

Analysis calcd for $C_{24}H_{24}ClNO_4$ (425.90): Found C, 67.75; H, 5.51; N, 3.17{Required C, 67.68; H, 5.68; N, 3.28}

3-(3-Chloro-4-fluoro-phenylamino)-1-phenyl-3-(3,4,5-trimethoxylphenyl)-propan-1-one(16c)



16c

Yield: 74%

Light Brown solid

M.P.: 187-188°C

IR (CHCl3, cm^{-1}): ν_{max} 3411, 3019, 2400, 1683, 1594, 1505, 1215

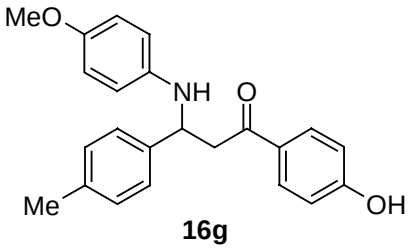
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (s, 1H), 3.49 (d, 2H, *J* = 6 Hz), 3.82 (s, 9H), 4.80 (t, 1H, *J* = 6 Hz), 6.44-6.50 (m, 1H), 6.63 (s, 3H), 6.89 (t, 1H, *J* = 8 Hz), 7.47(t, 2H, *J* = 6 Hz), 7.60 (t, 1H, *J* = 8 Hz), 7.90 (d, 2H, *J* = 8 Hz)

^{13}C NMR (200 MHz, $CDCl_3$): δ 46.1, 55.7, 56.1, 60.6, 103.4, 113.1, 115.2, 116.4, 116.7, 120.0, 128.0, 128.6, 133.4, 136.7, 137.9, 138.0, 144.0, 153.6, 198.1

Mass: 443 (M^+), 324, 299, 267, 222, 193, 156, 145, 129, 105, 91, 77

Analysis calcd for $C_{24}H_{23}NO_3ClF$ (443.89): Found C, 64.88; H, 517; N, 3.05{Found C, 64.93; H, 5.22; N, 3.15}

1-(4-Hydroxyl-phenyl)-3-(4-methoxy-phenylamino)-3-*p*-tolyl-propan-1-one (16g)



16g

Yield: 87%

White Solid

M.P.: 182-184^0 C

IR ($CHCl_3$, cm^{-1}): ν_{max} 3275, 3019, 2375, 1656, 1680, 1511, 1215

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.29 (s, 3H), 2.97 (b, 1H), 3.32 (d, 2H, *J* = 8 Hz), 3.66 (s, 3H), 4.67(brs 1H), 4.85 (t, 1H, *J* = 6 Hz), 6.49 (d, 2H, *J* = 10Hz), 6.63 (d, 2H, *J* = 6Hz), 6.84 (d, **2H,** *J* = 8 Hz), 7.09 (d, 2H, *J* = 6 Hz), 7.30 (d, 2H, *J* = 6Hz), 7.80 (d, 2H, *J* = 8 Hz)

^{13}C NMR (200 MHz, $CDCl_3$): δ 20.2, 30.8, 44.8, 54.6, 55.8, 113.9, 114.8, 115.4, 127.9, 128.5, 129.9, 135.9, 139.0, 152.0, 161.8, 195.6

Mass: 361(M^+), 238, 223, 210, 195, 171 165.

Analysis cacld for $C_{23}H_{23}NO_3$ (362.44): Found C, 76. 09; H, 6.71; N, 3.71{Required C, 76.22; H, 6.67; N, 3.86}

4.2.3.5. Spectra

1. ^{1}HNMR spectrum of 16b

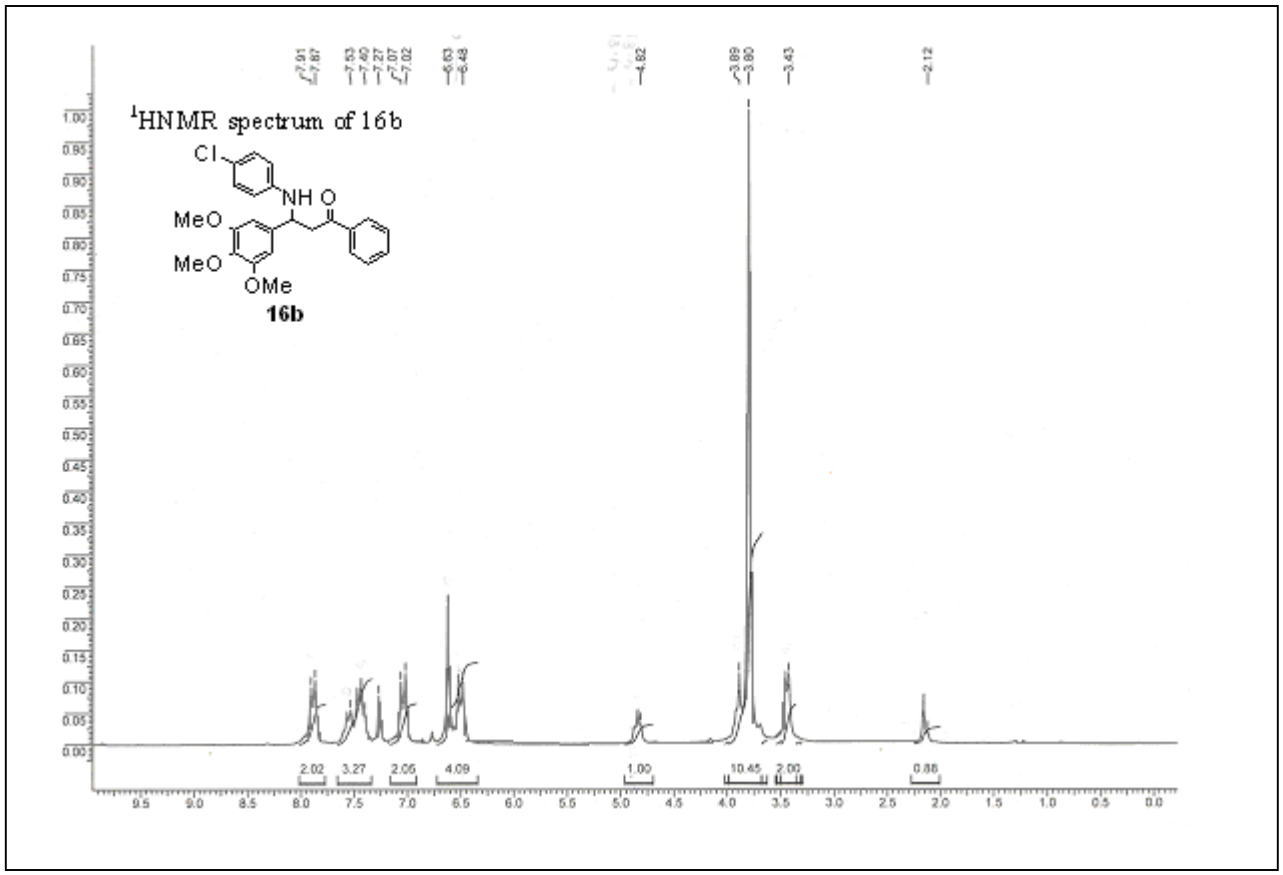
2. ^{13}CNMR spectrum of 16b

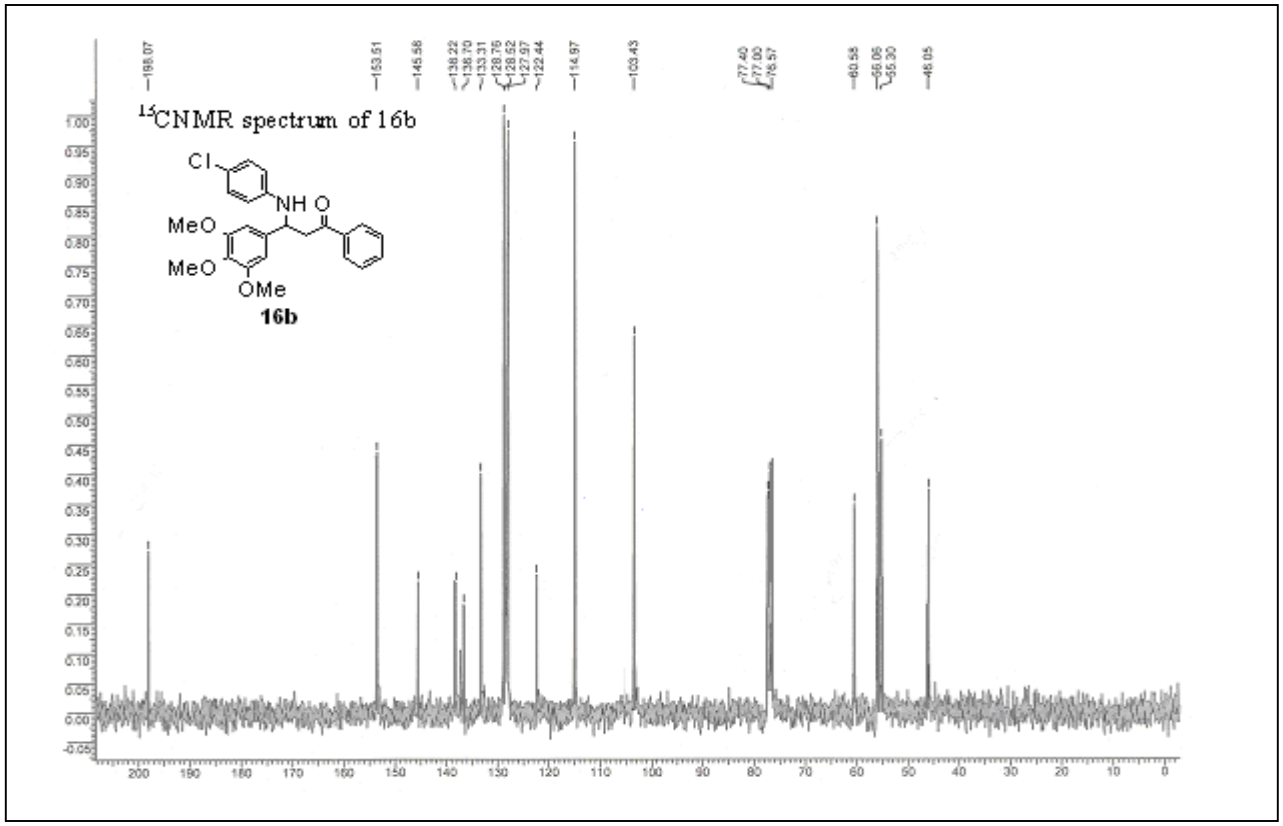
3. ^{1}HNMR spectrum of 16c

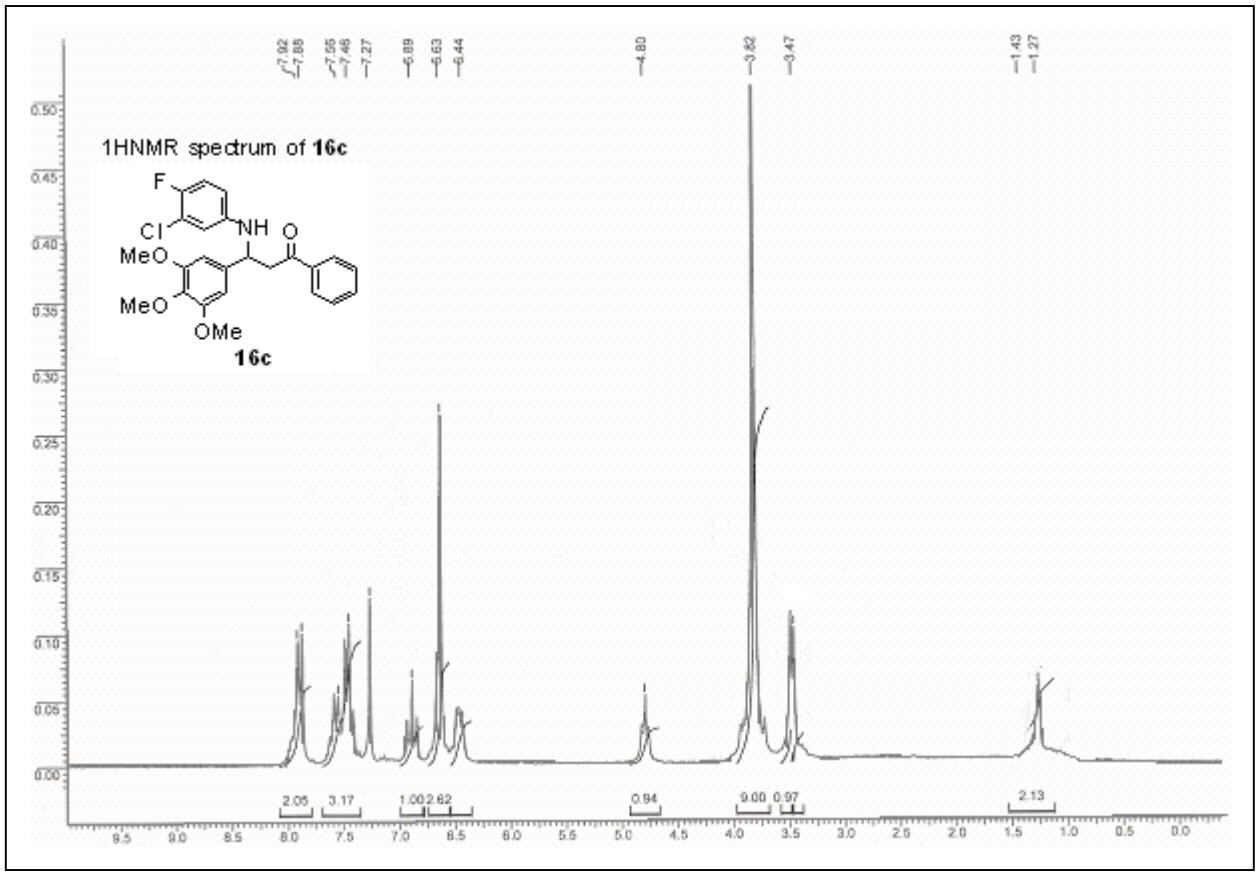
4. ^{13}CNMR spectrum of 16c

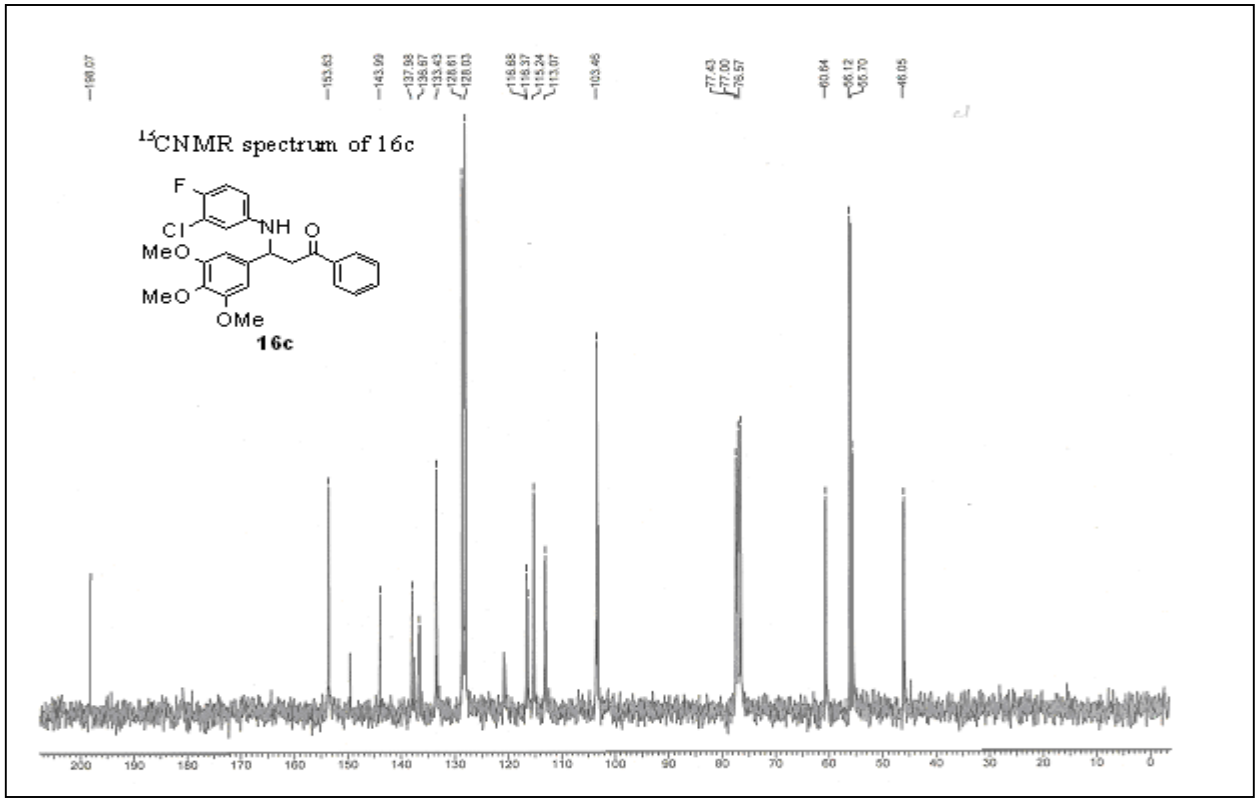
5. 1HNMR spectrum of 16g

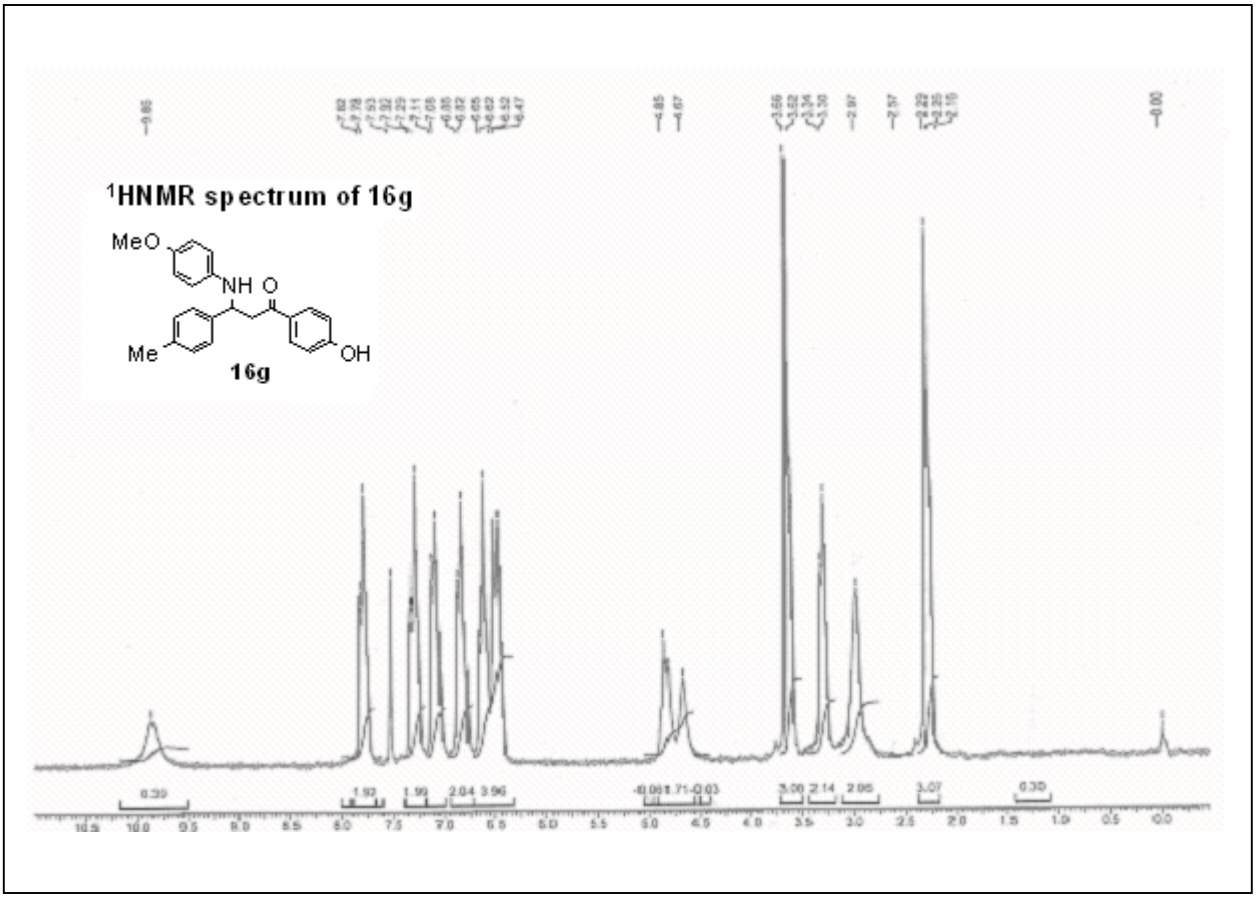
6. 13CNMR spectrum of 16g

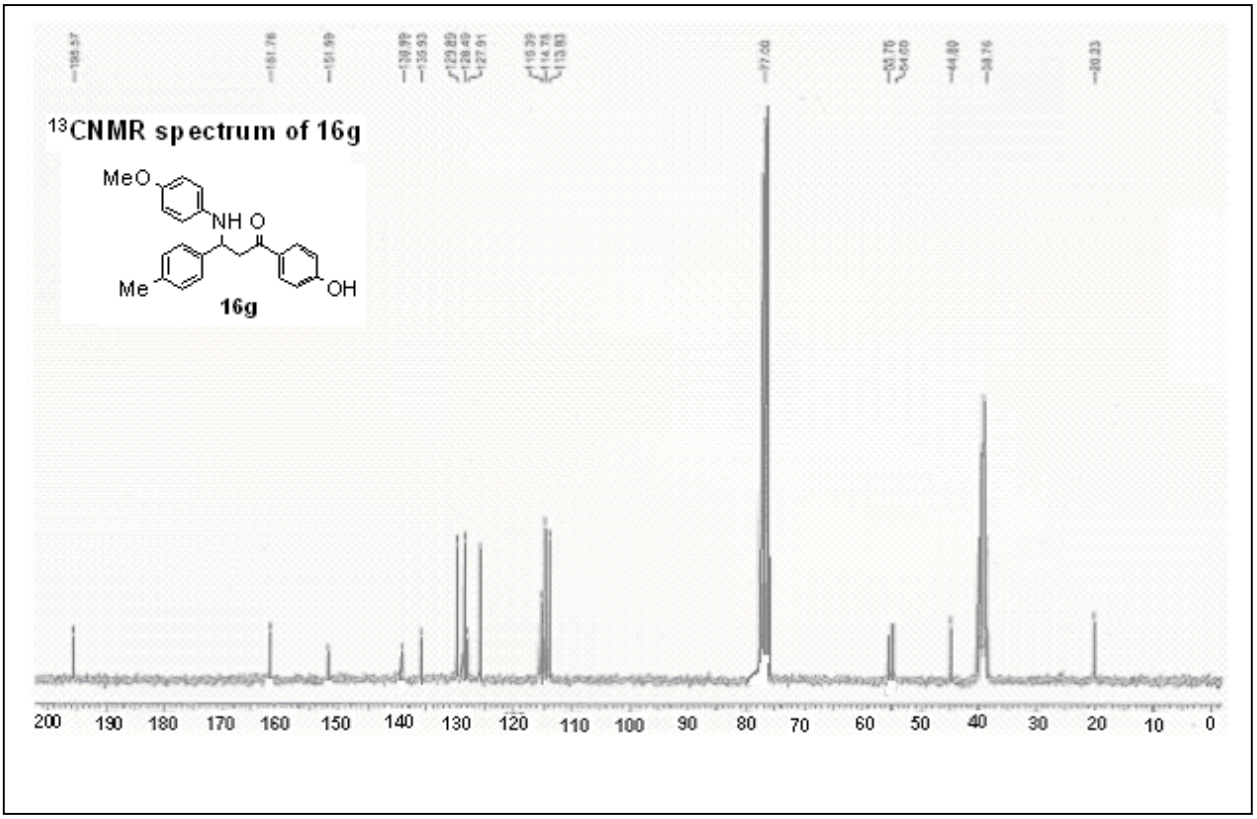

^{1}HNMR spectrum of 16b
Cl
NH O
MeO
MeO
OMe
16b


^{13}CNMR spectrum of 16b
Cl
NH O
MeO
MeO
OMe
16b


1HNMR spectrum of 16c
F
Cl
NH
O
MeO
MeO
OMe
16c


13CNMR spectrum of 16c
F
Cl
NH
O
MeO
MeO
OMe
16c


^{1}HNMR spectrum of 16g
MeO
NH O
Me
OH
16g


^{13}CNMR spectrum of 16g
MeO
NH O
Me
OH
16g

4.2.4 Part IV Yttria-zirconia based Lewis acid catalysed acylation of activated aromatic compounds

4.2.4.1 Introduction

Friedal-Crafts acylation reaction[39] is one of the most important reactions for preparation of various aromatic ketones by C-C bond formation and is generally carried out by using acylating reagents such as acyl chlorides, carboxylic anhydride or carboxylic acids in presence of an stoichiometric amount of acidic promotor, (due to consumption of the promoter by co-ordination to the produced aromatic ketones). The use of stoichiometric amount of acidic promotor, leads to an environmentally hostile process with gaseous effluents and mineral wastes. Catalysis by $FeCl_3$,[40] $ZnCl_2$,[41] and zeolites[42] have been reported for the acylation of activated aromatics. super acid[43] and sulfonic acid [44] (triflic acid) also catalyse the reaction, however the latter is extremely hygroscopic and soluble in reaction media, which seriously complicates its recovery in anhydrous form.[45] Triflates of boron, aluminium and gallium[46] also catalyse the reaction, however, these catalyst are sensitive to hydrolysis. Triflic acid[47] bis(trifluoromethyl sulfonyl)amide,[48] hafnium triflate,[49] bromopentacarbonylrhuthenium(I),[50] bismuth(III) trifluoromethanesulfonate[51] were recently employed in the last decades. Unlike bismuth (III) triflate,[52] $SbCl_5$-$LiClO_4$,[53] and HZSM-5[54] was found to be water stable with high catalytic activity. A combination of $TiCl(OTf)_3$ and TfOH,[55] hydrated Zirconia[56] were reported for the acylation of activated aromatics.

Recently gallium nonofluorobutanesulfonate[57] and yttribium tris(per)fluoroalkane sulfonyl)methide[58] are found to catalyse Friedal-Craft acylation in good to moderate yield. As part of our research program aimed at developing new solid catalyst and its subsequent application for various organic transformations, the yttria-zirconia based Lewis acid was found to be efficient catalyst for the Diels-Alder reaction, transesterification of β-keto esters, acylation of alcohols, amines and thiols.[18] This promoted us to use this catalyst for Friedal-Crafts acylation reactions, and herein we describe our findings on the yttria-zirconia based Lewis acid catalysed Friedel-Crafts acylation of activated arenes.

4.2.4.2 Results and discussion

A variety of activated aromatic compounds on reaction with acid chloride or anhydride (or) benzotrichloride in the presence of 10 mol% amount of Yttria-zirconia based catalyst gave aromatic ketones in moderate to good yield. A noteworthy feature of this methodology is that its application in the acylation of acetanilide with benzoyl chloride gave the aryl ketones without trans-acylation. The acylation or benzoylation of acetanilide went on regiospecifically in para position. Acylation of thiophene and cyclooctene has been successfully achieved with good yield. Mention must be made regarding regiospecific acylation of activated aromatic compound (**Table 1, entry 1 to 10**) with electron donating groups such methoxy, hydroxy and methyl groups. In all the above cases, the acylation was carried out regiospecifically at position para to methoxy, hydroxy, methyl groups. Another noteworthy feature of this methodology is that when benzoylation of 1,2-dimethylphenol was carried out with benzoyl chloride in presence of 10 mol % of catalyst, benzoylation was observed on aryl position instead of *O*-benzoylation. Acylation of 1, 3, 5-trichloroanisole gave only 15% of acylated product. When we treated anisole with neat acetyl chloride in presence of 10 mol% of Yttria-zirconia Lewis acid catalyst, it gave exclusively 4-methoxyacetophenone 18a in 93% yield. The IR spectrum of **18a** showed peak at 1673 cm^{-1} indicating the presence of aromatic carbonyl group. The ^1H NMR spectrum of 18a showed a singlet at δ 2.51 for acyl protons, and singlet at δ 3.82 for methoxy protons. The aromatic protons appeared as two doublets at δ 6.85-6.90 and at δ 7.86-7.90 indicating the regiospecific acylation at *para*-position. The molecular ion peak at 150 in the mass spectrum of **18a** also confirmed the formation of acylated product. The exclusive acylation at aryl position of acetanilide was confirmed by its spectral data. The IR spectrum of compound **18k** showed peaks at 1711cm^{-1} and 1664cm^{-1} corresponding to the carbonyl of amide and ketones. The ^1H NMR spectrum of **18k** showed a peak at δ 2.34 for 6 protons of the acyl group. The aromatic protons appeared as doublet at δ 7.18-7.22 and at δ 7.50-7.54. The presence of fragmentation peaks at 120 and at 105 (for $C_6H_5COCH_3$ and C_6H_5CO) in the mass spectrum confirmed the acylation at the aryl positions. Similarly when 2-nitro-4-methoxyacetanilide was acylated with acetyl chloride, it gave exclusively the corresponding acylated product. The IR spectrum of **18l** showed peak at 1709 cm^{-1} and 1672 cm^{-1} corresponding to the carbonyls of amide and aromatic ketones. The appearance of two aromatic protons, as singlet at δ 7.27 and at δ 7.70 gave an additional

evidence for the acylation at aryl positions. The peak at 164 of the mass spectrum (corresponding to $CH_3COC_6H_4NO_2$, since there is no other possibility for the fragmentation ion at 164) confirmed the acylation at aryl positions.

4.2.4.3 Conclusion

In conclusion, we have successfully applied the Yttria-zirconia based Lewis acid catalyst for acylation of activated aromatic compound in regionselective manner. Heteroaromatics like thiophene was acylated with moderate yields. Phenols were acylated at the aryl position, and no *O*-acylated product was obtained.

4.2.4.4 Experimental Section

Experimental Procedure

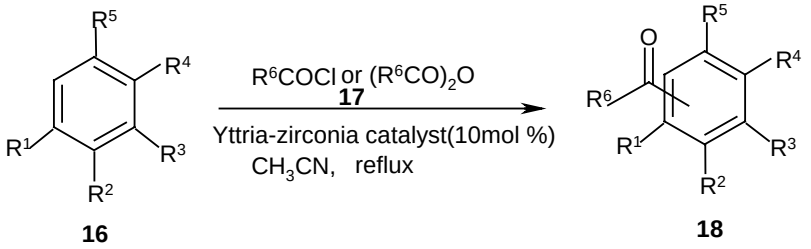
In a typical experimental procedure, a slurry of 2, 3-dimethoxytoluene (0.102 g) and acetyl chloride (15 eq.) and yttria-zirconia 10 mg (10mol%), in 10 ml of acetonitrile was stirred under reflux for 6 h. The progress of reaction was monitored by TLC. After completion of the reaction, it was cooled to 0^oC, and quenched with saturated aq. $NaHCO_3$ (10 ml) solution, and then the mixture was extracted with CH_2Cl_2 (20 ml x 3). The combined organic extracts were washed with water, brine solution and dried (anhydrous Na_2SO_4) and concentrated to give the crude product, which after column chromatography through silica gel using petroleum ether : EtOAc (9 : 5) gave 108 mg (85%) of pure acylated product.

General experimental proceure for acylation of activated aromatic compound using yttria-zirconia Lewis aci catalyst:

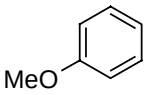
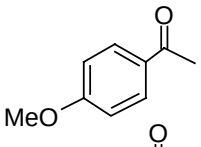
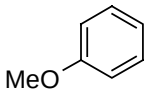
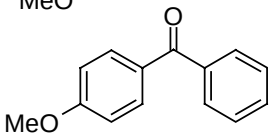
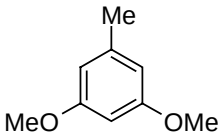
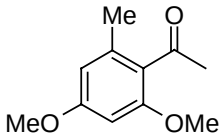
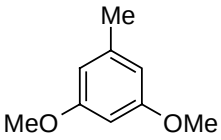
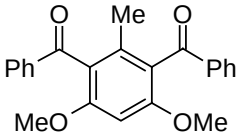
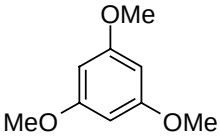
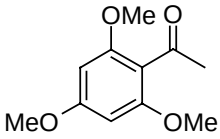
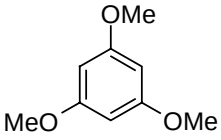
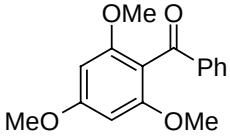
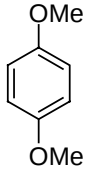
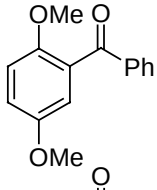
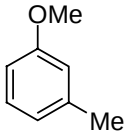
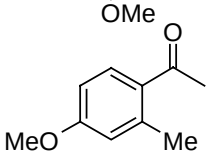
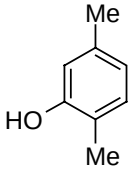
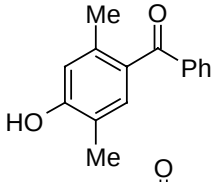
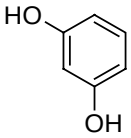
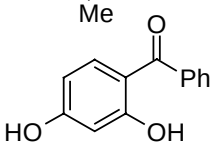
A slurry activated aromatics (1eq), acid chloride or acid anhydride (5eq) and yttria-zirconia (10 mol%) were stirred at reflux temperature in acetonitrile for the indicated time(Table 4). The reaction mixture was monitored by TLC. After completion, the reaction mixture was filtered and quenched with 10% sodium bicarbonate solution an extracted with ethyl acetate (2x50ml). After drying over anhy Na_2SO_4, the solvent was concentrated to give the corresponding acylated prouct as crude. Silica gel coloumn chromatography using petroleum ether: EtOAc (95:5) as eluent gave the required product in pure form.

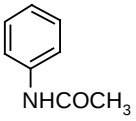
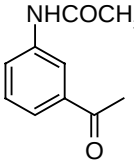
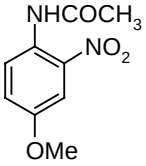
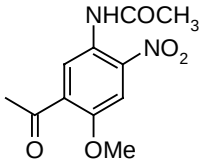
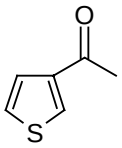
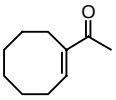
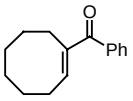
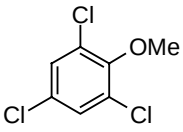
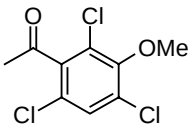
Table 4. Acylation of activated aromatic compound using Yttria-zirconia based Lewis acid

Scheme 5



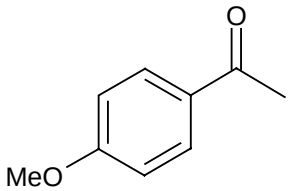
Entry	R^1	R^2	R^3	R^4	R^5	R^6
1	OMe	H	H	H	H	Me
2	OMe	H	H	H	H	Ph
3	OMe	H	OMe	H	Me	Me
4	OMe	H	OMe	H	Me	Ph
5	OMe	H	OMe	H	OMe	Me
6	OMe	H	OMe	H	H	Ph
7	OMe	H	H	OMe	H	Ph
8	H	H	Me	H	OMe	Me
9	OH	OMe	H	H	Me	Ph
10	H	OH	H	OH	H	Ph
11	$-NHCOCH_3$	H	H	H	H	Me
12	OMe	$-NO_2$	$-NHCOCH_3$	H	H	Me
16	Cl	H	Cl	OMe	Cl	Me

Entry	Aromatics used	Acylating agent used.	Product Formed	Reaction Time (h)	Yield* %	Product code
1		CH_3COCl		4	93	**18a**
2		C_6H_5COCl		3	91	**18b**
3		CH_3COCl		6	85	**18c**
4		C_6H_5COCl		6	87	**18d**
5		CH_3COCl		3.5	89	**18e**
6		C_6H_5COCl		7	95	**18f**
7		C_6H_5COCl		9	94	**18g**
8		CH_3COCl		18	92	**18h**
9		$C_6H_5CCl_3$		11	87	**18i**
10		$C_6H_5CCl_3$		12	76	**18j**

Entry	Aromatics used	Acylating agent used	Product Formed	Reaction Time (h)	Yield*	Product code
11		CH_3COCl		1	80	**18k**
12		CH_3COCl		8	83	**18l**
13		CH_3COCl		6	79	**18m**
14		CH_3COCl		1	49	**18n**
15		C_6H_5COCl		1	52	**18o**
16		CH_3COCl		2	45	**18p**

*** Isolated yield after column purification**

1-(4-Methoxy-phenyl)-ethanone (18a)



18a

Yield: 93%

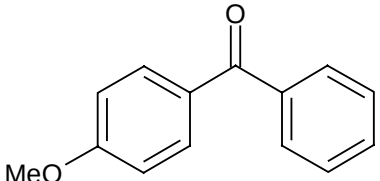
Yellow Oil

IR (Neat, cm^{-1}): ν_{max} 3487, 3334, 3100, 2950, 2840, 2550, 2410, 2070, 1950, 1673, 1600, 1508 **^{1}H NMR (200 MHz, $CDCl_3$):** δ 2.51 (s, 3H), 3.82 (s, 3H), 6.88 (d, 2H, *J* = 10Hz), 7.88 (d, 2H, *J* = 8 Hz)

Mass: 150 (M^+), 136, 135, 120, 107, 92, 77, 64

Analysis cacld for $C_9H_{10}O_2$ (150.17): Found C, 71.81; H, 6.56{Required C, 71.98; H, 6.71}

(4-Methoxy-phenyl)-phenyl-methanone (18b)



18b

Yield: 91%

Yellow oil.

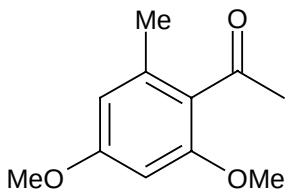
IR (Neat, cm^{-1}): ν_{max} 3420, 3067, 3035, 2671, 2552, 1918, 1693, 1650, 1599.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.96 (d, 2H, *J* = 10Hz), 7.40–7.64 (m, 5H), 8.15 (d, 2H, *J* = 8Hz)

Mass: 212 (M^+), 181, 169, 135, 122, 105, 92, 77

Analysis cacld for $C_{14}H_{12}O_2$ (212.24): Found C, 79.10; H, 5.76{Required C, 79.23; H, 5.70}

1-(2, 4-Dimethoxy-6-methyl-phenyl-ethanone (18c)



18c

Yield: 89%

Colorless oil

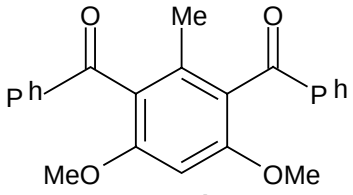
IR (Neat, cm^{-1}): ν_{max} 3449, 2933, 2843, 2395, 1752, 1690, 1602

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.25(s, 3H), 2.46 (s, 3H), 3.81 (s, 6H), 6.30 (s, 2H)

Mass: 194 (M^+), 180, 179, 171, 164, 150, 136, 135, 128, 122, 121, 105, 99, 93, 91, 83, 77, 69, 65

Analysis cacld for $C_{11}H_{14}O_3$ (194.22): Found C, 67.89; H, 7.17{Required C, 68.02; H, 7.26}

(3-Benzoyl-4,6-dimethoxy-2-methylphenyl)-phenyl-methanone (18d)



18d

Yield: 87%

Pale Yellow Oil

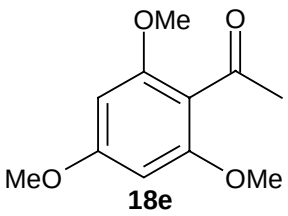
IR (Neat, cm^{-1}): ν_{max} 3454, 3019, 2910, 2900, 2850, 1665, 1588, 1464, 1449, 1323, 1280, 1245, 1215, 1174, 1122, 1085, 915

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.92 (s, 3H), 3.76 (s, 6H), 6.48 (s, 1H), 7.46 (t, 4H, J = 4 Hz), 7.60 (t, 2H, J = 4 Hz), 7.87 (d, 4H, J = 8 Hz)

Mass: 361(M^++1), 360, 359, 343, 315, 289, 283, 267, 254, 240, 225, 211, 198, 181, 165, 152, 122, 105, 77

Analysis cacld for $C_{23}H_{20}O_4$ (360.38): Found C, 76.56; H, 5.51{Required C, 76.65; H, 5.59}

1-(2,4,6-Trimethoxy-phenyl)-ethanone (18e)



18e

Yield: 89%

Colorless solid

M.P.: 72-75°C

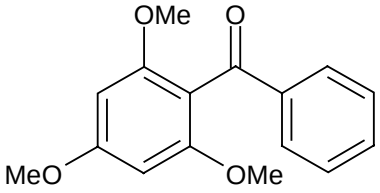
IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 2400, 1746, 1667, 1600, 1581, 1450, 1394

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.44(s, 3H), 3.79(s, 6H), 3.81(s, 3H), 6.08(s, 2H)

Mass: 211(M^++1), 196, 181, 168, 166, 122, 107, 92, 77

Analysis cacld for $C_{11}H_{14}O_4$ (210.227): Found C, 58.29; H, 6.12{Required C, 58.40; H, 6.24}

Phenyl-(2,4,6-trimethoxy-phenyl)-methanone (18f)



18f

Yield: 95%

Colorless Solid

M.P.: 110-112^{0}C

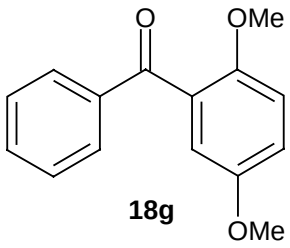
IR ($CHCl_3$, cm^{-1}): ν_{max} 3449, 3080, 2942, 2840, 1738, 1666, 1595, 1459, 1405

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.68 (s, 6H), 3.86 (s, 3H), 6.16 (s, 2H), 7.35-7.60 (m, 3H), 7.83 (d, 2H, J = 8 Hz)

Mass: 272, 255, 241, 227, 196, 195, 181, 180, 171, 152, 137, 122, 105, 91, 77, 69, 57.

Analysis cacld for $C_{16}H_{16}O_4$ (272.30): Found C, 70.68; H, 5.79{Required C, 70.58; H, 5.92}

(2,5-dimethoxy-phenyl)-phenyl-methanone (18g)



18g

Yield: 94%

Brown oil

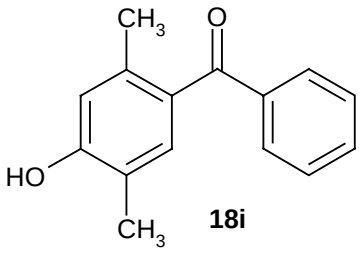
IR ($CHCl_3$, cm^{-1}): ν_{max} 3414, 3154, 3101, 3055, 2948, 2836, 2668.51, 2150, 1690, 1663, 1605, 1495

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.68 (s, 3H), 3.80 (s, 3H), 6.93 (d, 1H, *J* = 4 Hz), 7.01 (d, 1H, *J* = 4 Hz), 7.40-7.65 (m, 3H), 7.82 (d, 2H), 8.14 (d, 1H, *J* = 2 Hz)

Mass: 242 (M^+), 225, 211, 197, 181, 165, 151, 122, 105, 92, 77

Analysis cacld for $C_{15}H_{14}O_3$ (242.273): Found C, 74.41; H, 5.69{Required C, 74.36; H, 82}

(2,5-Dimethyl-phenyl)-phenyl-methanone (18i)



18i

Yield: 87%

Colorless solid.

M.P.: 98-99°C

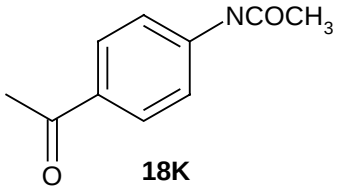
IR ($CHCl_3$, cm^{-1}): ν_{max} 3296, 1691, 1627, 1573, 1377, 1319, 1276, 1264

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.20 (s, 6H), 2.32 (s, 1H), 6.69 (s, 1H), 7.18 (s, 1H), 7.45-7.70 (m, 3H), 7.78 (d, 2H, *J* = 8 Hz)

Mass: 226, 210, 121, 105, 77

Analysis cacld for $C_{15}H_{14}O_2$ (226.271): Found C, 79.51; H, 6.09; {Required C, 79.62; H, 6.23}

***N*-(4-Acetyl-phenyl)-acetamide (18k)**



18K

Yield: 80%

Brown Oil

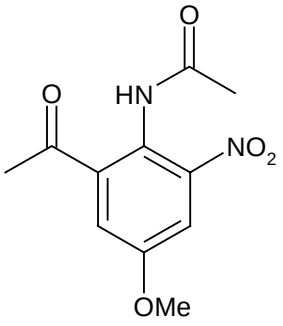
IR(Neat, cm^{-1}): ν_{max} 3410, 3950, 3294, 3197, 3136, 3020, 2400, 2100, 1950, 1711, 1664, 1601, 1545

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.34 (s, 6H), 7.22 (s, 1H), 7.34 (brs, 1H), 7.50 (m, 3H).

Mass: 177 (M^+), 136, 135, 120, 118, 105, 94, 93, 91, 77, 65

Analysis cacld for $C_{10}H_{11}O_2$ (171.192): Found C, 67.85; H, 6.07; N, 7.91{Required C, 67.79; H, 6.25; N, 8.12}

***N*-(2-Acetyl-4-methoxy-6-nitro-phenyl)-acetamide (18l)**



18l

Yield: 83%

Dark yellow solid

M.P.: 115-116^0 C

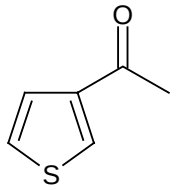
IR ($CHCl_3$, cm^{-1}): ν_{max} 3421, 2955, 1725, 1690, 1545, 1243

^1H NMR (200 MHz, $CDCl_3$): δ 2.31 (s, 6H), 3.93 (s, 3H), 7.21 (s, 1H), 7.63 (s, 1H)

Mass: 252 (M^+), 210, 194, 168,164, 153, 134, 122, 95, 77, 63

Analysis calcd for $C_{11}H_{12}N_2O_5$ (252.225): Found C, 52.19; H, 4.65{Required C, 52.38; H, 4.80}

1-Thiophen-3yl-ethanone (18m)



18m

Yield: 79%

Brown Oil.

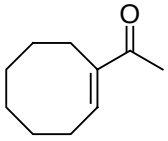
IR ($CHCl_3$, cm^{-1}): ν_{max} 3474, 3095, 2920, 1725, 1661, 1550

^1H NMR (200 MHz, $CDCl_3$): δ 2.71 (s, 3H), 7.27 (s, 1H), 7.79 (d, 2H, J = 8 Hz)

Mass: 126, 110, 83

Analysis cacld for C_6H_6OS (126.112): Found C, 57.05; H, 4.63{Required C, 57.14; H, 4.79}

1-Cyclo-oct-1-enyl-ethanone (18n)



18n

Yield: 49%

Pale Yellow Oil.

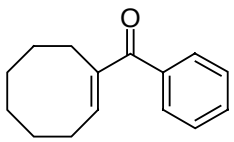
IR ($CHCl_3$, cm^{-1}): ν_{max} 3365, 2965, 1715, 1670, 1601, 1559

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25-2.65 (m, 15H), 5.52-5.77 (m, 1H)

Mass: 152, 136, 109

Analysis cacld for $C_{10}H_{16}O$ (152.2): Found C, 78.79; H, 10.39{Required C, 78.95; H, 10.52}

Cyclooct-1enyl-phenyl-methanone (18o)



18o

Yield: 52%

Yellow Oil.

IR (Neat,cm^{-1}): ν_{max} 3412, 2933, 1723, 1667, 1606, 1515, 1201.

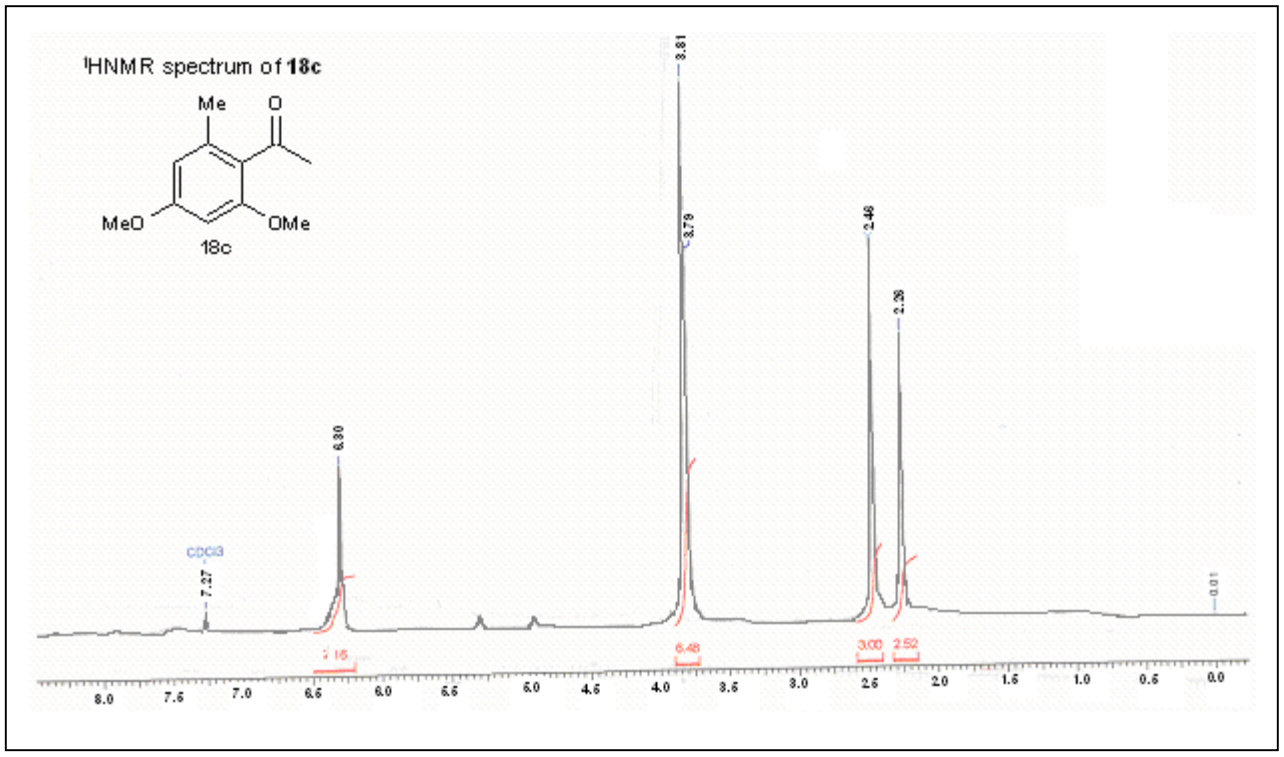
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27-2.70 (m, 12H), 5.65-5.85 (m, 1H), 7.40-7.95 (m, 5H)

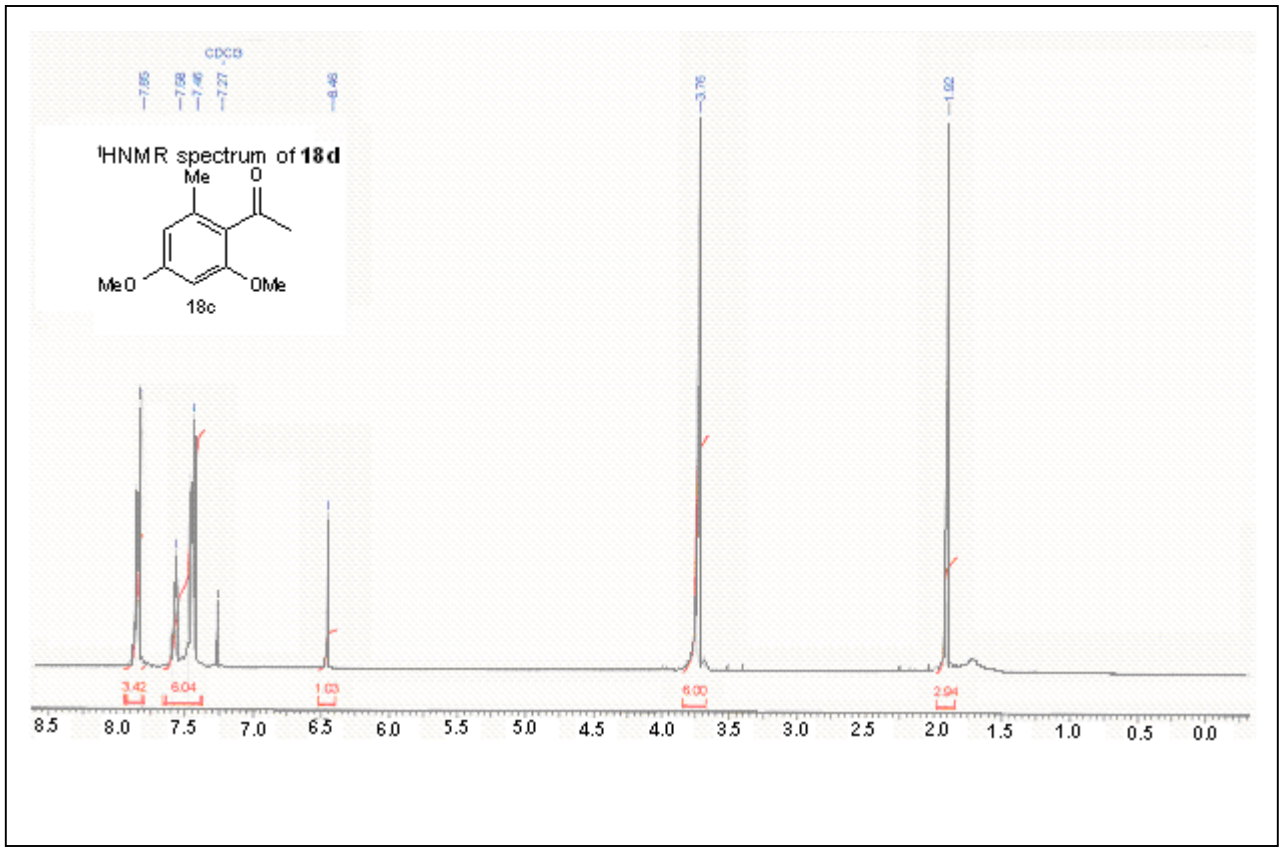
Mass: 214, 198, 137, 109, 105, 77

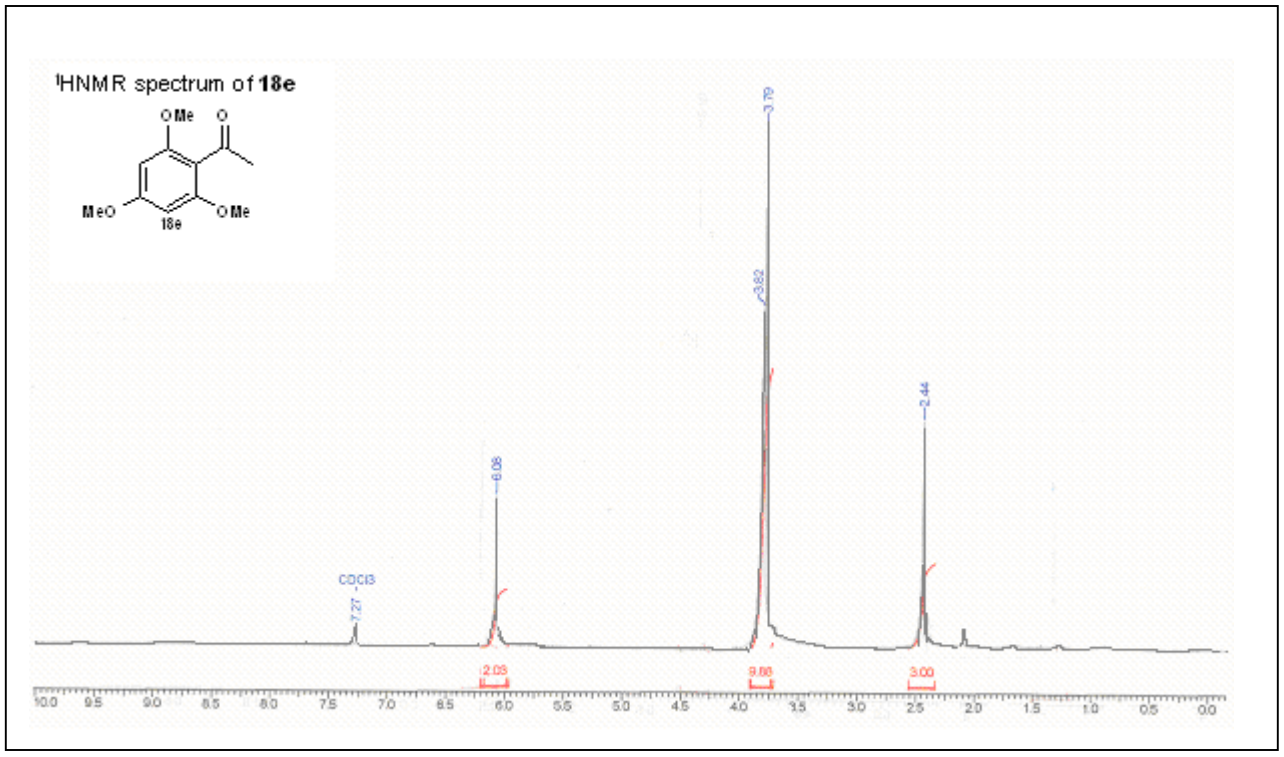
Analysis cacld for $C_{15}H_{18}O$ (214.23): Found C, 84.25; H, 8.79{Required C, 84.11; H, 8.88}

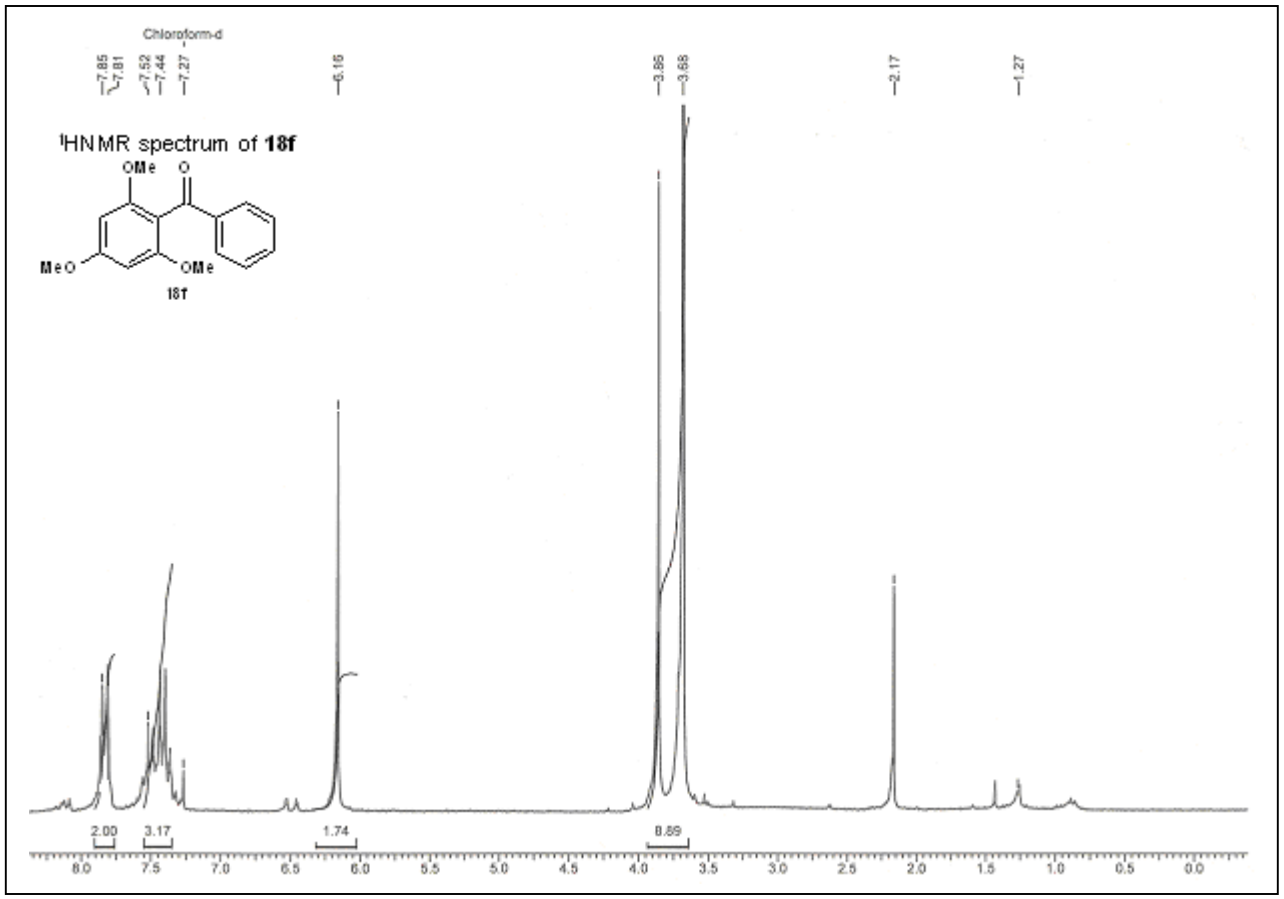
4.2.4.5 Spectra

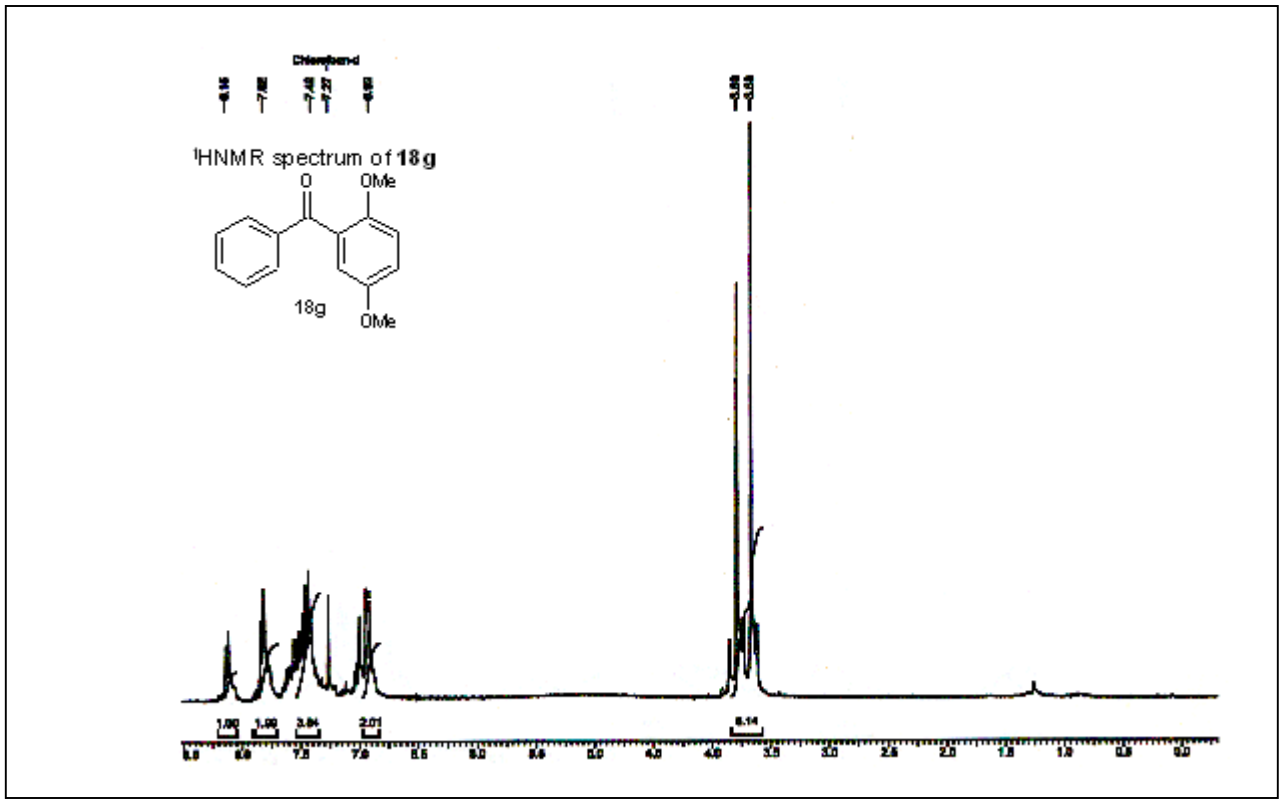
1. **^{1}HNMR spectrum of 18c**
2. **^{1}HNMR spectrum of 18d**
3. **^{1}HNMR spectrum of 18e**
4. **^{1}HNMR spectrum of 18f**
5. **^{1}HNMR spectrum of 18g**
6. **^{1}HNMR spectrum of 18i**
7. **^{1}HNMR spectrum of 18k**
8. **Mass spectrum of 18k**
9. **^{1}HNMR spectrum of 18l**
10. **Mass spectrum of 18l**
11. **^{1}HNMR spectrum of 18m**
12. **^{1}HNMR spectrum of 18n**
13. **^{1}HNMR spectrum of 18o**

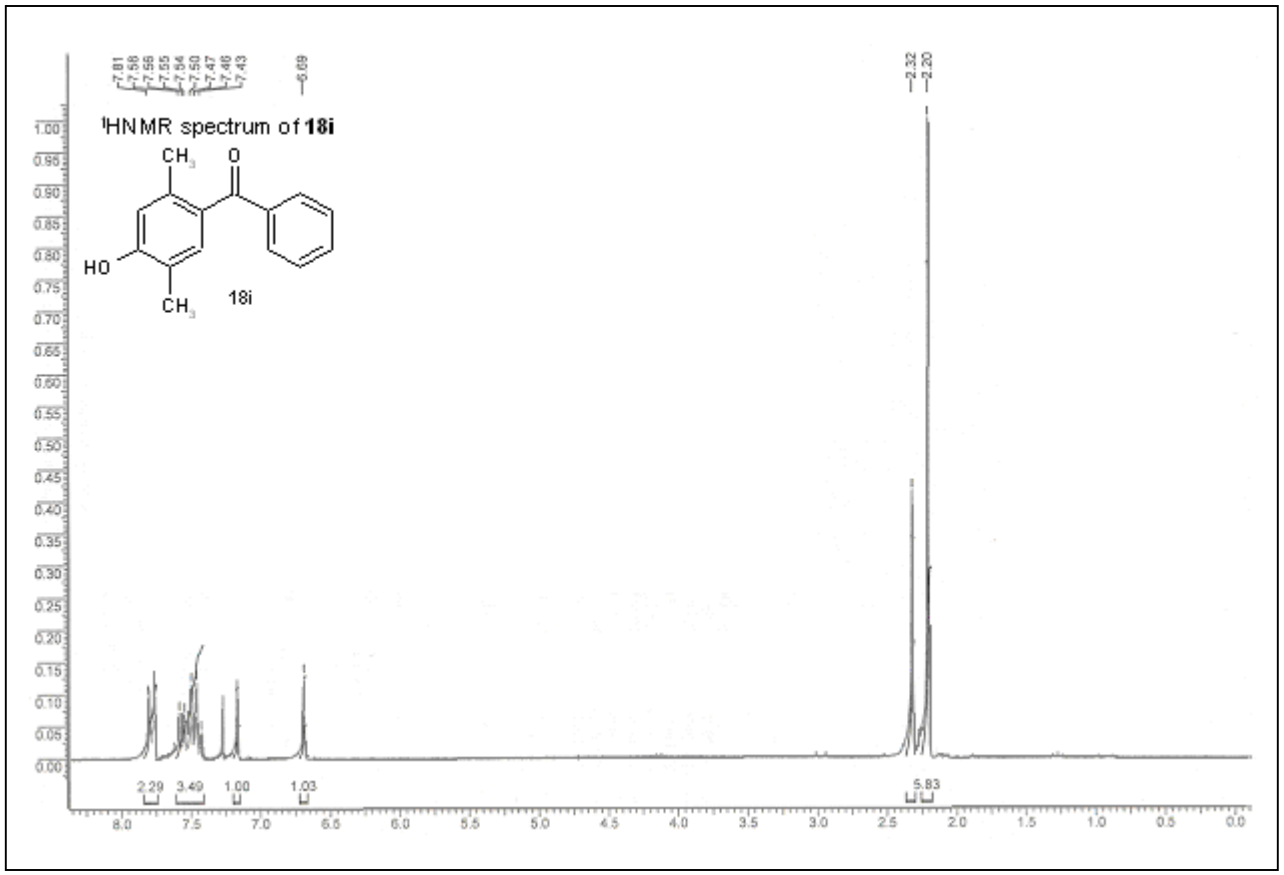

¹HNMR spectrum of 18c
Me
O
MeO
OMe
18c
CDCl3
7.27
6.80
3.81
3.79
2.46
2.26
0.01
2.16
6.48
3.00
2.52

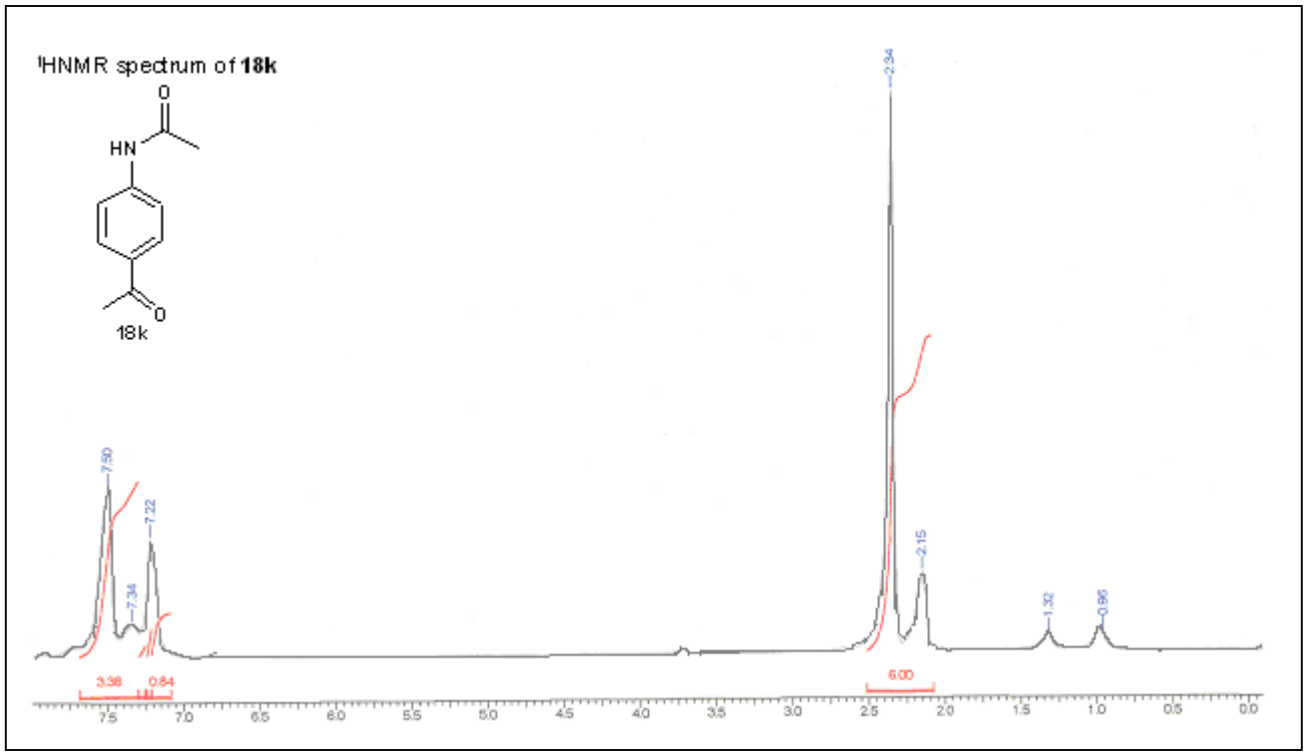

CDCl3
7.85
7.68
7.46
7.27
6.46
¹HNMR spectrum of 18d
Me
O
MeO
OMe
18c
3.76
1.92
3.42
6.04
1.03
6.00
2.94

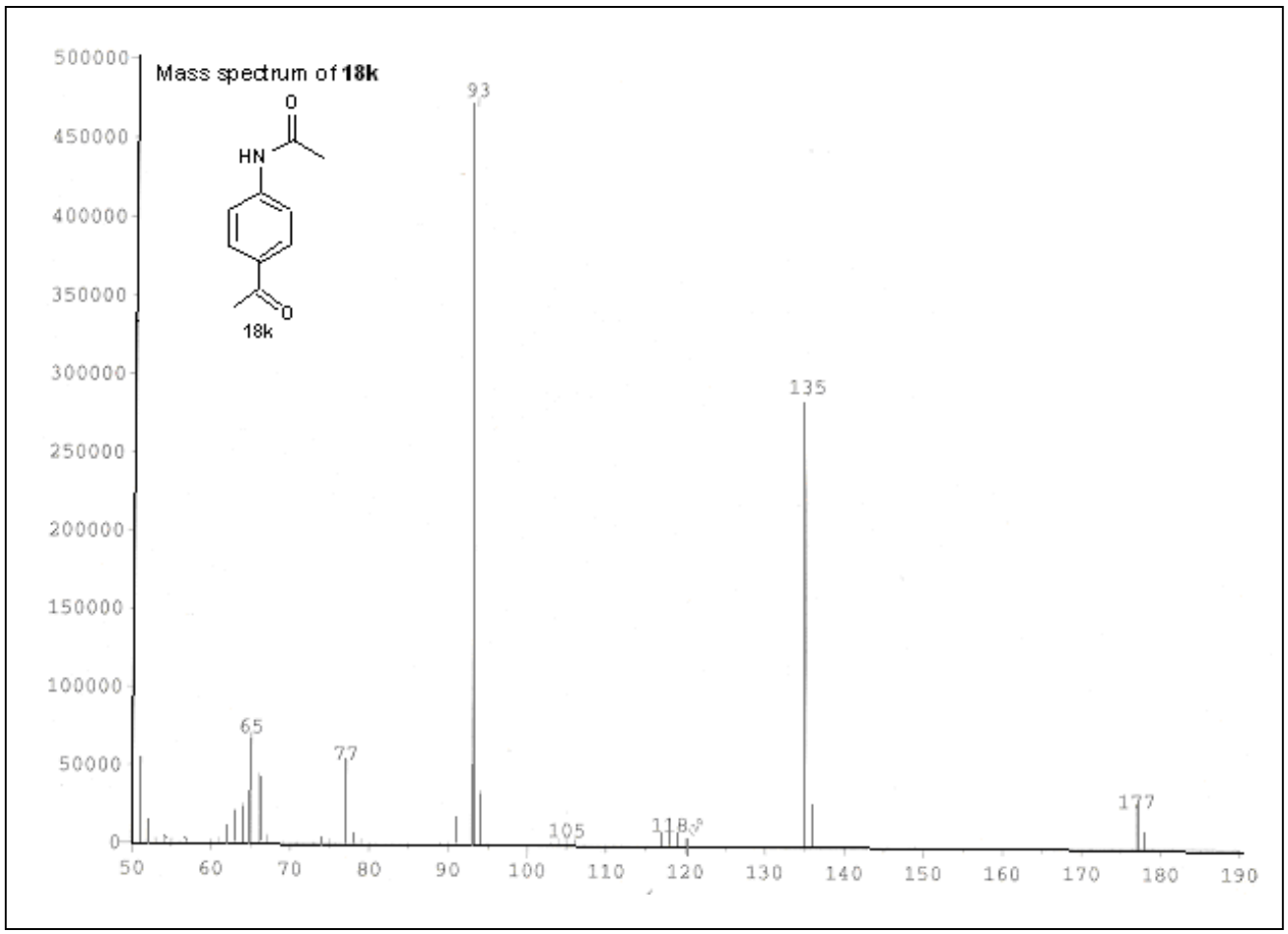

¹HNMR spectrum of 18e
OMe
O
MeO
OMe
18e
3.79
3.82
2.44
6.08
CDCl3
7.27
2.03
9.86
3.00

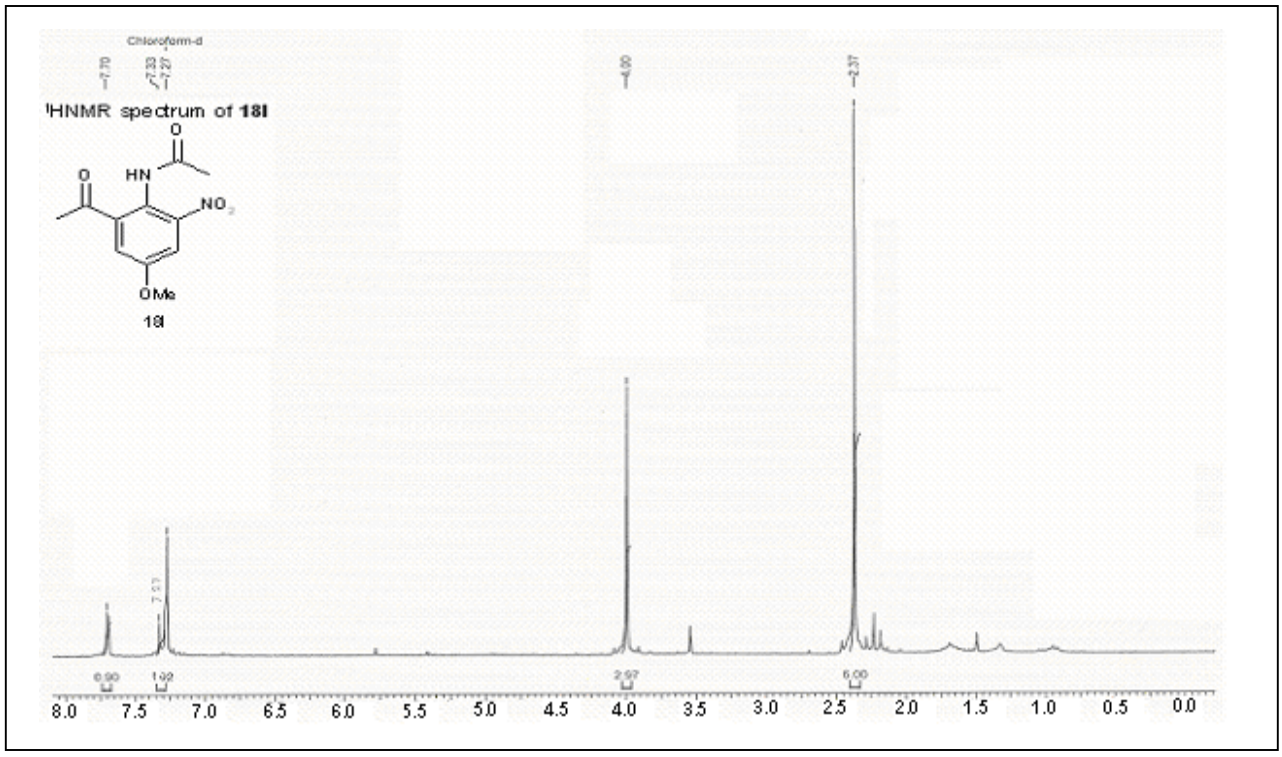

Chloroform-d
7.85
7.81
7.52
7.44
7.27
6.16
3.86
3.68
2.17
1.27
¹HNMR spectrum of 18f
OMe
O
MeO
OMe
18f
2.00
3.17
1.74
8.89

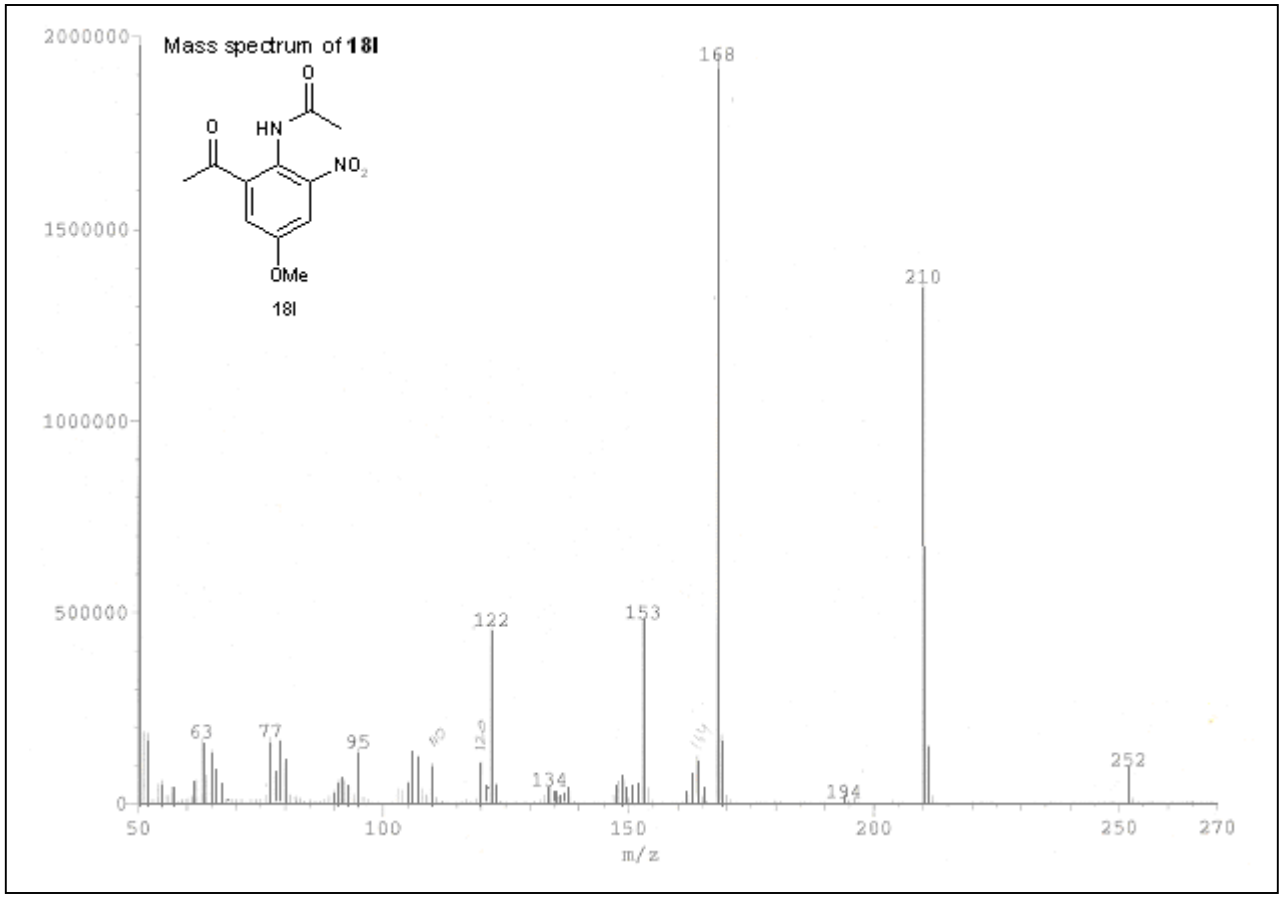

^{1}HNMR spectrum of **18g**
O
OMe
18g
OMe

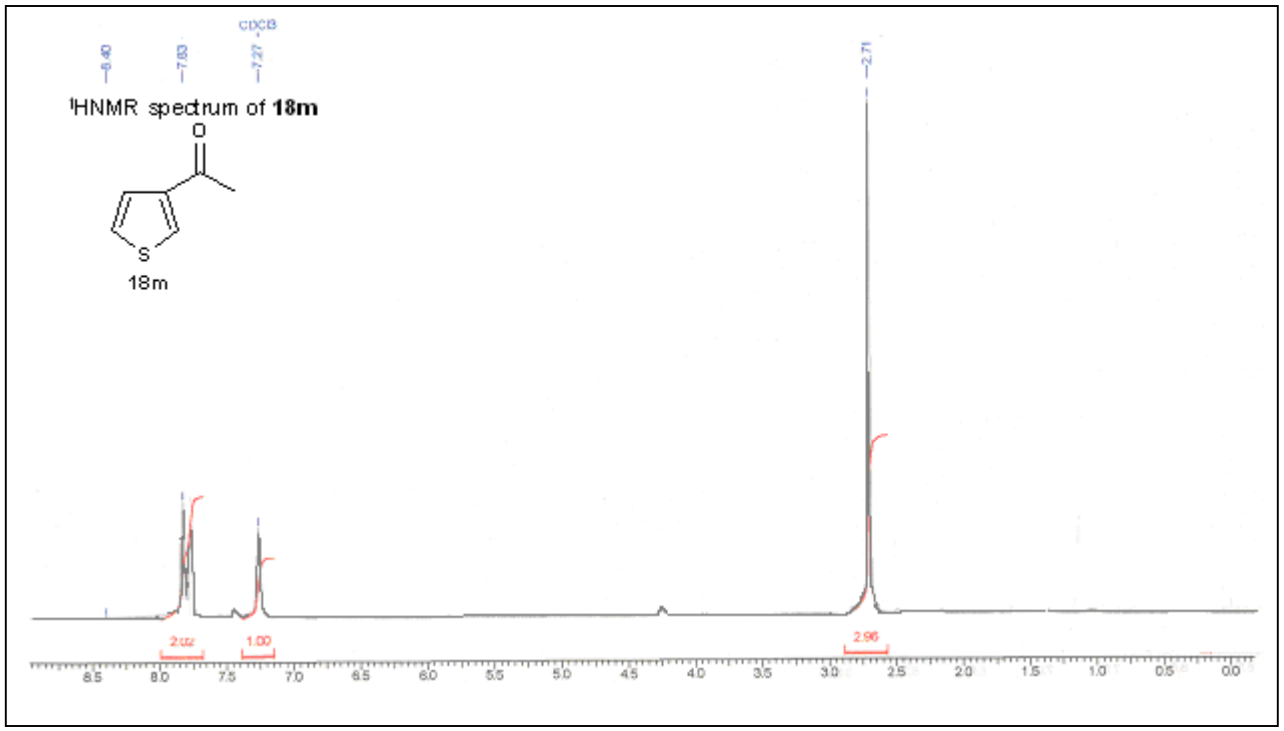

^{1}HNMR spectrum of **18i**
CH3
O
HO
CH3
18i
2.29
3.49
1.00
1.03
5.83

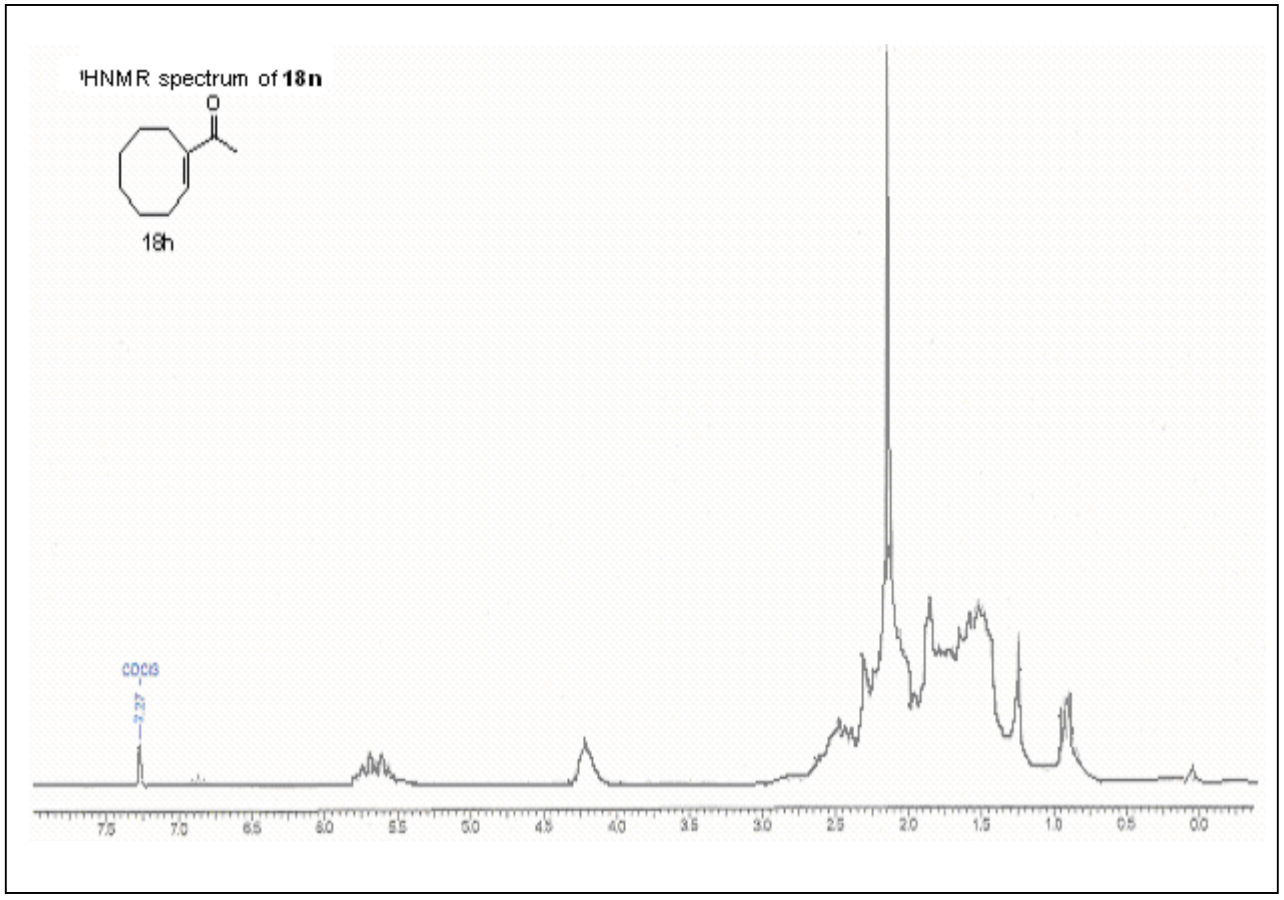

¹HNMR spectrum of 18k
HN
O
O
18k
2.34
7.50
7.22
7.34
2.15
1.32
0.95
3.38
0.84
6.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

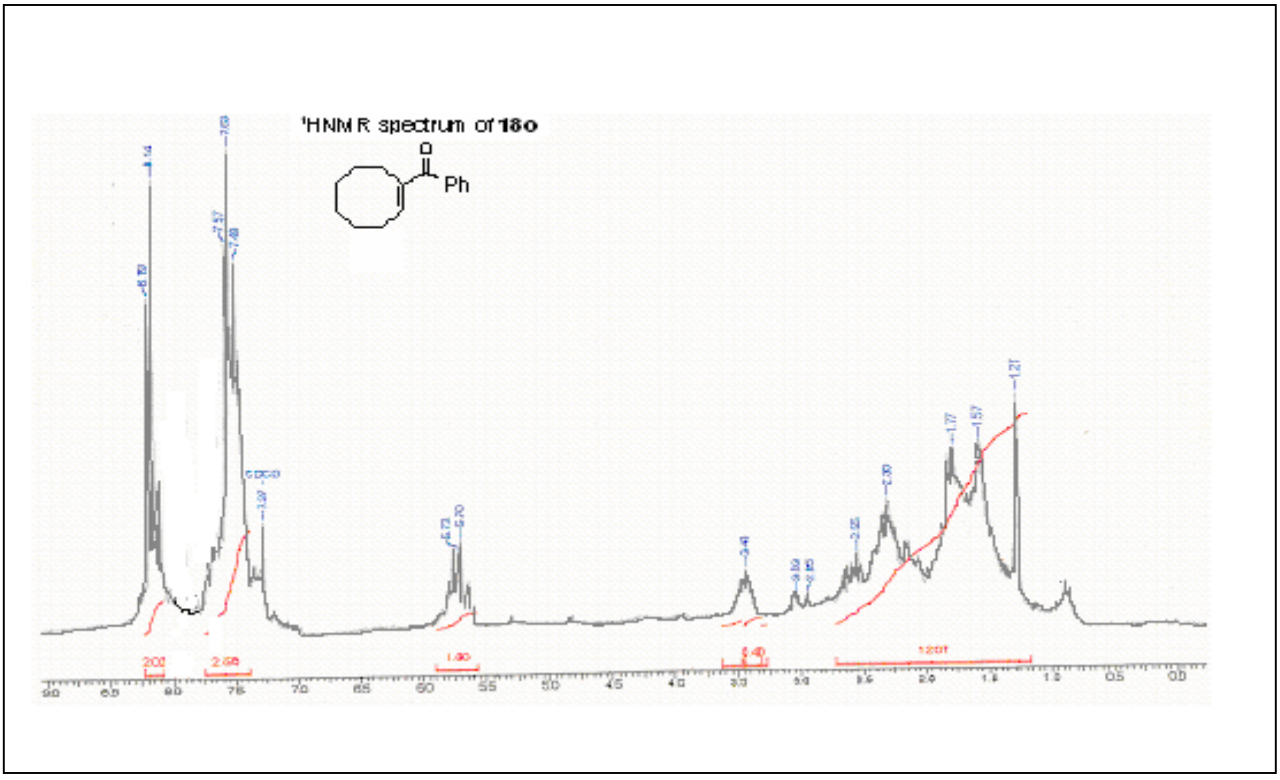

Mass spectrum of 18k
HN
O
O
18k
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
93
135
65
77
105
118
177
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190


Chloroform-d
7.70
7.33
7.27
4.00
2.37
¹HNMR spectrum of 18l
O
HN
NO2
O
OMe
18l
7.27
0.90
1.92
2.97
6.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Mass spectrum of 18l
O
HN
NO2
O
OMe
18l
2000000
1500000
1000000
500000
0
168
210
122
153
63
77
95
134
194
252
50
100
150
200
250
270
m/z


CDCl3
6.40
7.03
7.27
2.71
¹HNMR spectrum of 18m
O
S
18m
2.02
1.00
2.96


¹HNMR spectrum of 18n
O
18h
CDCl3
7.27


¹HNMR spectrum of 16o
O
Ph

4.3. References

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CHAPTER 5

Synthesis of Chiral Aza Building Block for Various Polyhydroxyl piperidine alkaloids.

5.1 Section A General Introduction about polyhydroxy piperidine alkaloids and its synthons

5.1.1 Introduction

Today it is widely apparent that all three major class of nature's bio-molecules play fundamental roles in life process. Out of these three classes of biopolymers (proteins, nucleic acids, and carbohydrates) it is the carbohydrates that are least exploited. Despite the important roles that saccharides play in numerous biological recognition events (e.g. bacterial and viral infection, cancer metastasis and inflammatory reactions), the molecular details of these recognition processes are generally not well understood. Carbohydrates were for many decades thought to be important mainly as source of metabolic energy. The other biochemical significance seemed limited to their roles as relatively inert structural polymers in plants, fungi, insects, and crustaceans until the advent of sophisticated analytical methods. The pace of development of carbohydrate based therapeutics, and the carbohydrates involvement in triggering of cell-cell communication, signalling and other metabolic phenomena becomes impossible until the development of practical synthetic and analytical methods. But the recent advances in the field, gaining molecular level of understanding of the language and syntax of oliegosaccharides signaling mechanism, use of carbohydrate mimetics promises to change the way many serious diseases are treated. Learning how to alter or intercept those chemical signals could prove useful in treating diabetes, metastatic cancer, and lysozomal storage diseases.

Carbohydrates are ubiquitous and important biomolecules. Besides their role in energy storage, they form much of the structural frame work of cells and tissues. As part of glycoproteins and glycolipids, and their conjugates, they are key elements in variety of process such as chemical signaling, cell-cell communication and molecular and cellular targeting.[1-3] These glycoconjugate (glycoproteins and glycolipids) are principal components of cell membranes and play prominent role not only in antigen-directed immune response, but also in other immune recognition phenomena such as lymphocyte recirculation, lymphocyte trafficking and cell-cell or cell-matric adhesion.

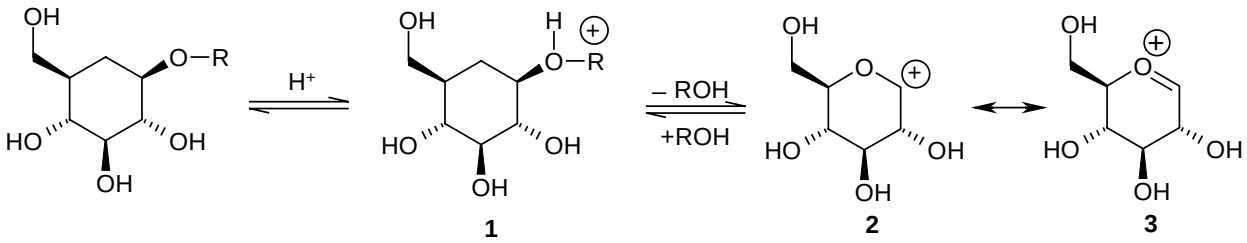
The very heart of the modern carbohydrate research is to understand the reactions that assemble, trim, and shape carbohydrates into bioactive glycoprotein and glycolipid conjugates. These reactions are called glycosyl group transfer reactions, catalyzed by two families of enzymes: glycosidases and glycosyl transferases.[4] Glcosidases are key enzymes that involve in the process of cleavage of glycoside bond linking a sugar's anomeric carbon with an oligo or polysaccharide or a nucleoside diphosphate group. In general, this is called biosynthesis and processing of glycoproteins and catabolism of glycoconjugates. These macromolecules are involved in cell-cell recognition and thus in the control of other biological mechanism (cell growth, cell-cell adhesion, inflammation, and metastasis). An important aspect of enzymatic catalysis was the ability of an enzyme to lower the energy of the transition state for the reaction it catalysed.[5] For a long time, the only real evidence for this theory was of the fact that stable compounds that resembled the transition state, or transition state analogues, were competitive inhibitors of the enzyme. It has also been used as haptens to raise antibodies with catalytic activity.[6]

The "carbohydrate mimetic" is frequently used term, refer to any carbohydrate derivative or other compound that has multiple hydroxy groups and thus looks like a sugar or saccharide.[7] Carbohydrate mimetics have a number of advantages over their parent structures as therapeutic agents. They can be designed such that they are (1) more stable towards endogeneous degradative enzymes (2) have improved bioavailability and reduced clearance rate and (3) have a higher affinity and selectivity for their cognate receptors by taking advantage of interactions that the natural saccharide does not. By constructing polymers or oligomers with multiple copies of the mimetic to allow for polyvalent interactions, the affinity can be increased further.[8] In the case of inhibitors of glycosyltransferases, glcosidases and carbohydrate-modifying enzymes (e.g sulfotransferase), mimetics can be designed in such a way that imitate the transition state of these reaction, rather than ground states and thus will inhibit the enzymes better than simple substrate analogues.

A fascinating aspect of this area of research is the controversy that has existed regarding the exact structure of the transition state of glycoside cleavage[9] and it has therefore not been straight forward to predict the structure of good transition state analogues. The generally

accepted mechanism, C-O cleavage is exocyclic and the transition state will be any of, or a hybrid of, the ions **1-3.** However, the alternative possibility, endocyclic C-O bond cleavage[10] is ignored in this treatment, as recent work[11a, b] suggests it does not occur to an extent in some other case[11c] however. Assuming this mechanism to occur in enzymatic glycoside cleavage, a compound that resemble any of these ions should be an inhibitor of glycosidases (glycoside hydrolases).

Scheme-1

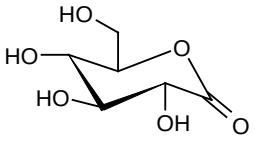


There are number of known compounds that fulfill these criteria. Numerous competitive inhibitors of glycosidases are known,[12, 10b] many of them are not good transition state analogues but resemble substrate or product in the ground state. The major goal of our research and of investigation in many other laboratories, has been to design and synthesis of new generations of glycosidase inhibitors with which chemists might exert more potent and effective control over glycoside hydrolysis.[13] Aside from their potential value in basic biochemical research, several synthetic glycosidase inhibitors have already demonstrated promising therapeutic applications, in the areas of both diabetes management[14] and antiviral chemotherapy.[15]

Inhibitors of Glycosidases

Inhibitors of glycosidases, have been attractive target compounds for synthetic chemists and biochemists, not only because they serve as useful biological tools for studying the biological functions of oligosaccharides[16] but also because they have great potential as drugs to treat a variety of carbohydrate mediated diseases.[17] This group of inhibitors, which are derivatives of naturally occurring azasugars, are now finding clinical application as anti-HIV,[18] anti-cancer[19] and antidiabetic agents,[20] and their effectiveness has made the development of additional glycosidase inhibitors a matter of considerable interest to synthetic chemist.[21,22]

Historically, the first glycosidase inhibitors were families of monosaccharide-derived δ-aldonolactones such as D-glucono-lactone **4** and glycosylamine (e.g., 1-amino-1-deoxypyranoses such as D-glycosylamine **5**. More recently, several polyhydroxylated piperidine, pyrrolidine, and indolizine alkaloids have been identified as naturally-occurring glycosidase inhibitors in plants and microorganisms.[4] Many of these structures (in particular polyhydroxy piperidines) for example nojrimycin **6**, 1-deoxynojirimycin **7**, and 1-deoxymannonojirimycin **13a** bear a striking resemblance to monosaccharides, and may be regarded as simple azasugar analogs of D-glucose and D-mannose, respectively in which the pyranose oxygen is replaced with a basic nitrogen. Later it was found that not only the naturally occurring (e.g., deoxynojirimycin **7,** fagomine **8**) but also the synthetic (e.g., miglitol **9,** isofagomine **10** and *epi*-isofagomine **12**) polyhydroxylated piperidines, pyrrolidines and indolizidine[23] alkaloids have been shown to be specific and potent inhibitors of glycosidase.



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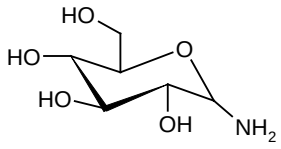

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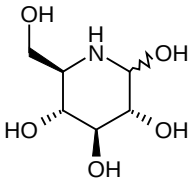
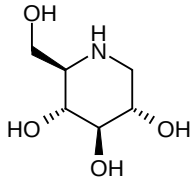
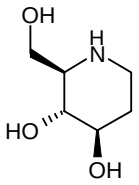


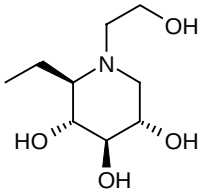
6
Nojirimycin



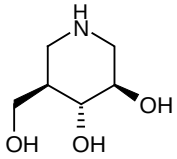
7
1-deoxynojirimycin



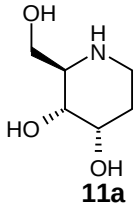
8
Fagomine



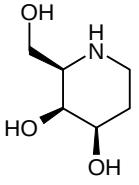
9
Miglitol



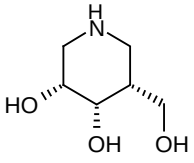
10
***Iso*-fagoamine**



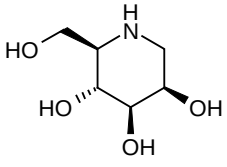
11a
3-*epi*- fagomine



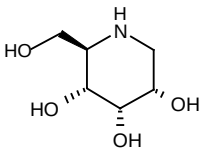
11b
4-*epi*- fagomine



12
***epi*- *iso*fagomine**



13a
Deoxymannonojirimycin



13b
Deoxyallonojirimycin

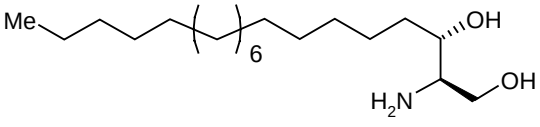
β-Glycosidase inhibitors

Although there are many natural as well as synthetic α-glycosidase inhibitors known, the development of anomer-selective β-glycosidase inhibitors took place only in the past decade, pioneered by studies from the groups of Bols[24] and Ichikawa.[25] In recent years, improved glycosidase in **4** and **5** and systematic data in the inhibition of β-glucosidases is documented in the literature.[26, 20d, 18a] In this aspect, it has been noted that removal of the hydroxy methyl substituent at C-5 in **5** had very little effect on enzyme substrate activity.[27] In view of this, Ganem *et al*. have first reported the synthesis of piperidine triols **10**, **11**, and **12** and referred these compounds as 1-aza-sugars or 1-*N*-imino sugars where in the nitrogen atom is considered to be at one position.[27] Genjiro and co-workers have isolated 1-aza-sugars **13a** and **13b** from *Eupatorium fortunei Turz*.[28] Since then a number of new derivatives of 5-dehydroxymethyl-1-deoxynojirimycin **10** with different stereochemical orientation of the OH-functionality at C-3/C-4/C-5 (**e.g 10**, **11** and **12**) as well as the replacement of the one of the –OH functionality at C-3/C-5 with hydroxy methyl substituent (**e.g**. **8**, **9**) have been synthesized and evaluated for β-glycosidase inhibition.[29]

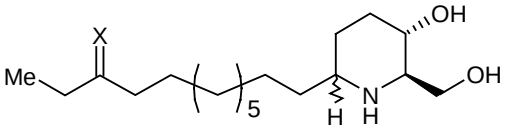
Polyhydroxy piperidine alkaloids

Polyhydroxylated piperidine alkaloids are frequently found in living system, and display a wide range of biological activities due to their ability to mimic carbohydrate substrates in a variety of enzymatic processes. Selective inhibition of a number of enzymes involved in the binding and processing of glycoproteins has rendered piperidine alkaloids important tools in the study of biochemical pathways. A number of piperidines and indolizidines bearing carbonaceous substituents at both α and α'- positions have been isolated from natural source and many of them have received much attention due to a variety of biological activities. 3-Piperidinol alkaloids having appendages at α and α'- position also have been isolated from plants. These 3-piperidinol alkaloids also exhibit a variety of pharmacological properties such as anesthetic and analgesic and antibiotic activities. Recently the alkaloids containing ring system were isolated from marine species and all of them showed substantial cytotoxic activity against human solid tumor cell lines. These 2,6-dialkylated piperidine alkaloids have been found abundantly in nature and are key structural units in medicinally important compounds.[30a]

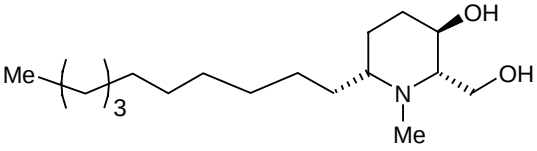
Prosopis alkaloids, isolated from *Prosopis africanan*, forms a subgroup possessing a characteristic 3-hydroxy function.[30b] Structurally theses compounds possessing a polar head group and a hydrophobic aliphatic tail, can be considered as cyclic analogues of membrane lipid sphingosine(**15-23**).[30c]



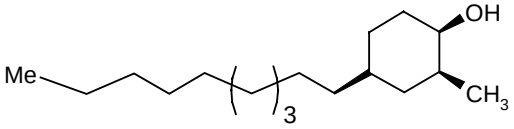
14 Sphingosine



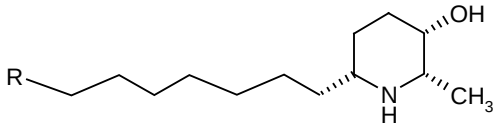
15X = O; β= H; Prosophine
16X = O ; α = H ; Prosophylline
17X = H ; β = H ; B=H
18X = H ; H ; α= H



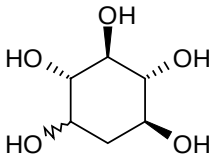
19 Micropine



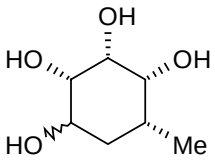
20 R = -CO_2Me ;Prosafrinine
21 R = -CH_2COMe ; Cassine



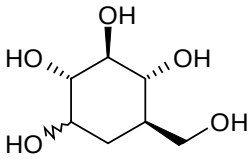
22 R = -CO_2H ; Carpamicacid
23 R = -$(CH_2)_5$COMe ; Spectaline



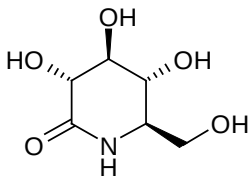
24 I-D-Glucose



25 Fucose



26 D-Mannose



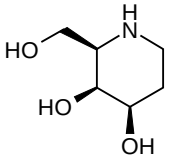
27 D-Mannonolactam

5.1.2 Review of Literature

In 1966, Inouye *et al.*[31a] discovered the first natural polyhydroxylated alkaloid, nojirimycin (NJ) **6**. Isolated from a *streptomyces* filtrate it was shown to actively inhibit α-and-β-glucosidase and was therefore the first natural glucosemimic. The first deoxy-derivative, 1-deoxynojirimycin (DNJ) [(2*S*)-hydroxymethyl]-(3*R*,4*R*,5*S*)-trihydroxypiperidine or 1,5-dideoxy-1,5-imino-D-glucitol **7** was synthesized by Inouye *et al*. by the reduction of the anomeric hydroxyl group.[31b] However, DNJ was soon isolated from Mulberry trees[32] as well as *streptomyces* cultures.[33]

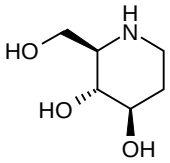
The analogue of 1-deoxynojirimycin is called fagomine **8** (1,2-dideoxynojirimycin) was found in the seeds of *Fagopyrum esculentum* (polygonaceae) seeds,[34] later it was discovered in the leaves and roots of Xanthocercis Zambesiaca (*Leguminosae*) together with 3-epifagomine

11a, 3,4-diepifagomine **28,** fagomine-4-*O*-β-D-glucopyranoside, and fagomine-3-*O*-β-D-glucopyranoside.[35a] Fagomine analogues, 6-deoxy-fagomine **29** and α-1-C-ethyl-fagomine **30** were isolated from *Lycium* Chinese (*Solanaceae*) roots[35b] and *campanulaceae* respectively.[36, 37]



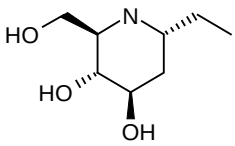
28

3,4-Di*epi*fagomine



29

6-Deoxy-fagomine



30

α-1-C-Ethyl-fagomine

Due to the various biological activities presented by polyhydroxy piperidine alkaloids, they have gained a huge attention by chemists to synthesize these kinds of alkaloids. There are various synthetic methods in the literature for the synthesis of these alkaloids and we can classify the methods for synthesis as follows:

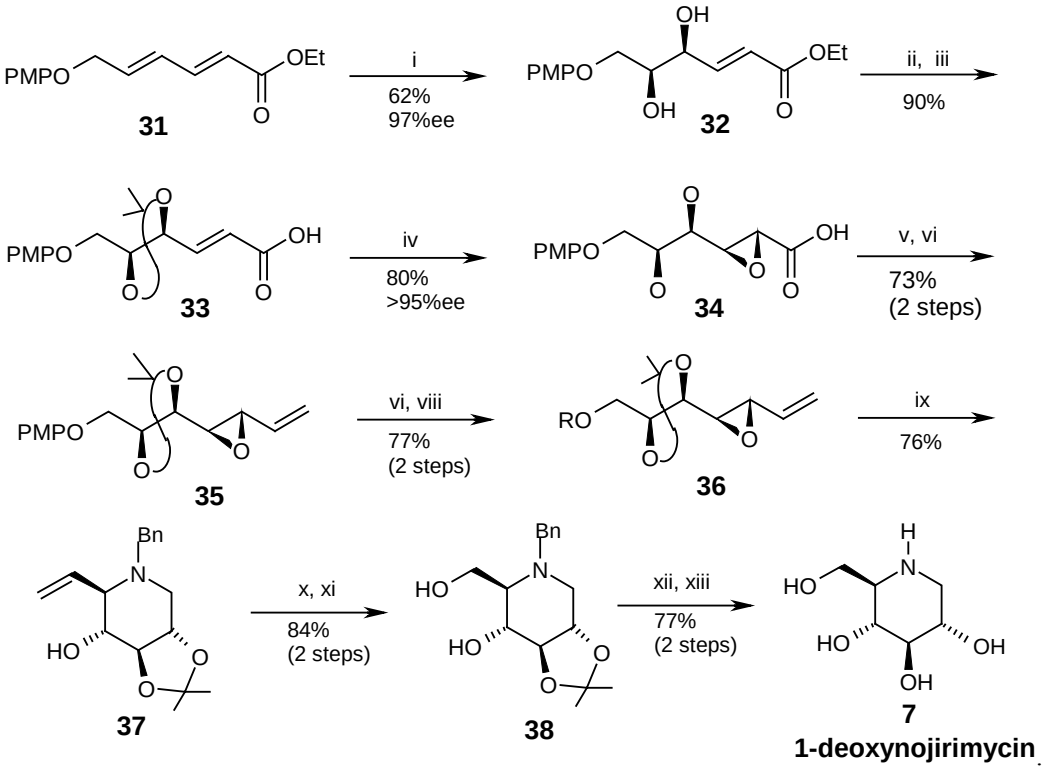
1. Carbohydrate substrate as a starting source and
2. Non-carbohydrate approach (achiral substrates and amino acids or chiral substrate)

Few selected literature reports of hydroxylated piperidine alkaloids based on these methods are described below.

Somfai *et al*. 1998[38a, b] Scheme 2

Followed here is, the regio-and stereoselective opening of epoxide at allylic position of the key intermediate,[38b] through amine nucleophiles and subsequent ring closure.

Scheme 2



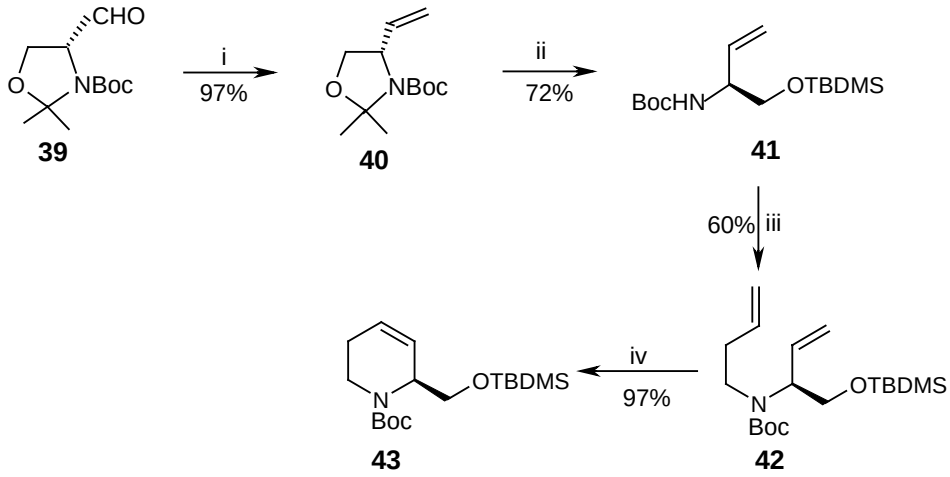
Seheme 2: Reagents and conditions: (i) $K_2OsO_4.2H_2O(DHQ)_2PHAL$, *t*-BuOH, H_2O; (ii) $(MeO)_2CMe_2$, DMF; (iii) DIBAL, CH_2Cl_2, -78°C; (iv) (+)-DIPT, $Ti(O\text{-}iPr)_4$, TBHP, CH_2Cl_2, -20°C; (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C; (vi) Ph_3PCH_3Br, KHMDS, THF, toluene; (vii) DDQ, CH_2Cl_2, H_2O; (viii) MsCl, *i*-Pr_2NEt, CH_2Cl_2, 0°C; (ix) $BnNH_2$, TsOH, DMSO, 120°C; (x) (a) OsO_4, NMO, *t*-BuOH, THF, H_2O; (b) $NaIO_4$, THF, H_2O; (xi) $LiAlH_4$, THF, 0°C; (xii) TFA, MeOH; (xiii), H_2, Pd/C, EtOH.

Fagomine and 3-epifagomine (1,2-dideoxyazasugars)

Takahata *et al*. 1998[39] Scheme 3, Scheme 4, Scheme 5

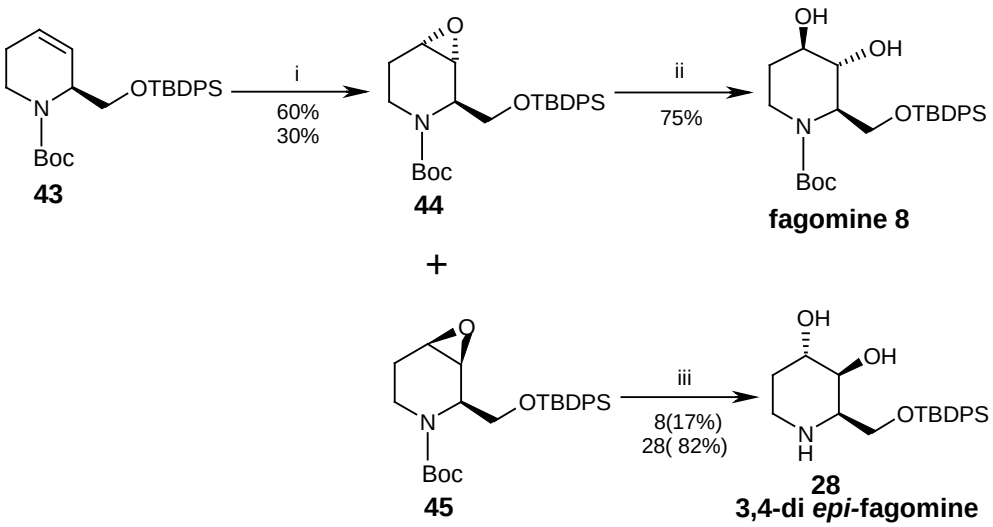
This approach involves the synthesis of common intermediate **43**, starting from Garner aldehyde **39**, using Wittig reaction and RCM as the key steps of the synthesis.

Scheme 3



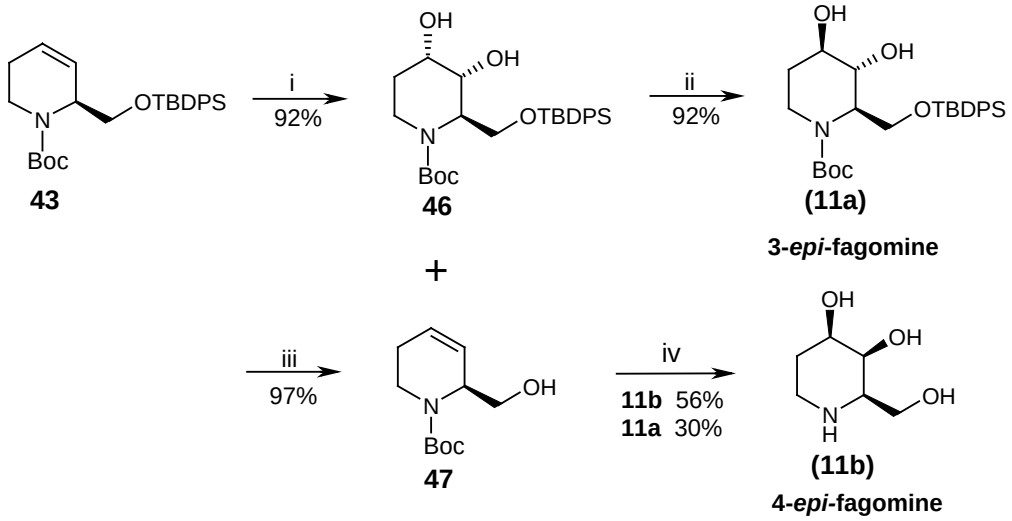
Scheme 3: ***Reagents and conditions*****:** (i) Ph_3PCH3I, $NaN(TMS)_2$, THF; (ii) $TsOH.H_2O$, MeOH, (b) TBDPSCl, DMAP, imidazole, CH_2Cl_2;(iii) (a) TFA, CH_2Cl_2, (b) 4-bromo-1-butene, K_2CO_3, MeCN; (c) $(Boc)_2O$, Et_3N, THF; (iv) Grubbs cat., CH_2Cl_2.

Scheme 4



Scheme 4: ***Reagents and conditions*****:** (i) Oxone®, CF_3COOCH_3, $NaHCO_3$, aq. Na_2EDTA, MeCN; (ii) H_2SO_4, dioxane, H_2O; (iii) KOH, dioxane, H_2O.

Scheme 5

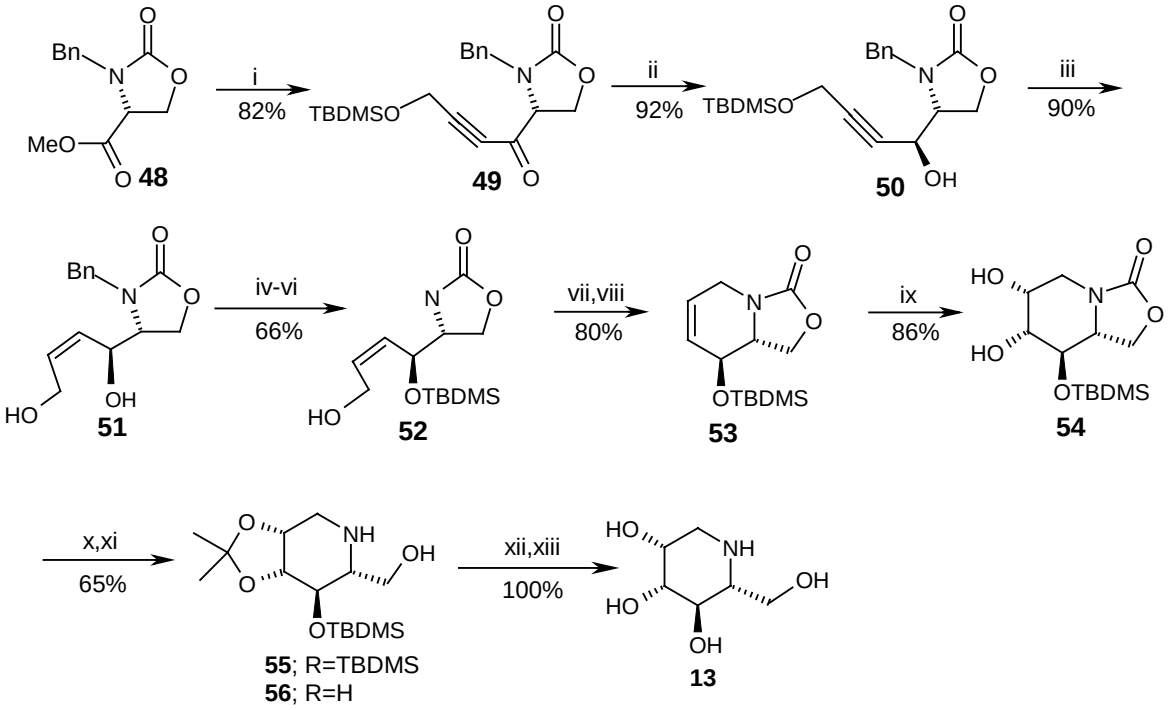


Scheme 5: ***Reagents and conditions*****:** (i) $K_2OsO_4.2H_2O$, NMO, H_2O, acetone; (ii) 10% aq. HCl, dioxane; (iii) TBAF, THF; (iv) (a) OsO_4, TMEDA, CH_2Cl_2; (b) 35% HCl, MeOH.

Katsumura *et al*. 1994 and 1999[40] Scheme 6

The synthesis utilized chiral building block (*R*)-(+)-4-carbomethoxyoxazolidinone as a chiral source. The approach involves the stereoselective reduction of the intermediate ketone with diisobutylaluminium 2, 6-di-*tert*-butyl-4-methylphenoxide to give the desired *anti*-alcohol in 92% yield. Oxazolidinonylpiperidine proved a key intermediate in the synthesis of other azasugars.

Scheme 6



Scheme 6: ***Reagents and conditions*****:** (i) $TBDMSOCH_2C{\equiv}CLi$, THF, -100°C; (ii) diisobutylaluminium 2,6-di-*tert*-butyl-4-methyl phenoxide, toluene, 0°C; (iii) Lindlar's cat., H_2, MeOH; (iv) Na, Liquid NH_3, -78°C; (v) TBDMSCl, imidazole, DMF; (vi) 55% aq. HF, MeCN, -20°C; (vii) MsCl, Et_3N, DMAP, DMF; (viii) NaH, DMF, 0°C, (ix) OsO_4, NMO, *t*-BuOH, H_2O; (x) $(MeO)_2C(Me)_2$, PPTS, acetone; (xi) 6 M NaOH, dioxane, reflux, 24 h; (xii) conc. HCl, MeOH, reflux, 4 h; (xiii) basic ion-exchange resin.

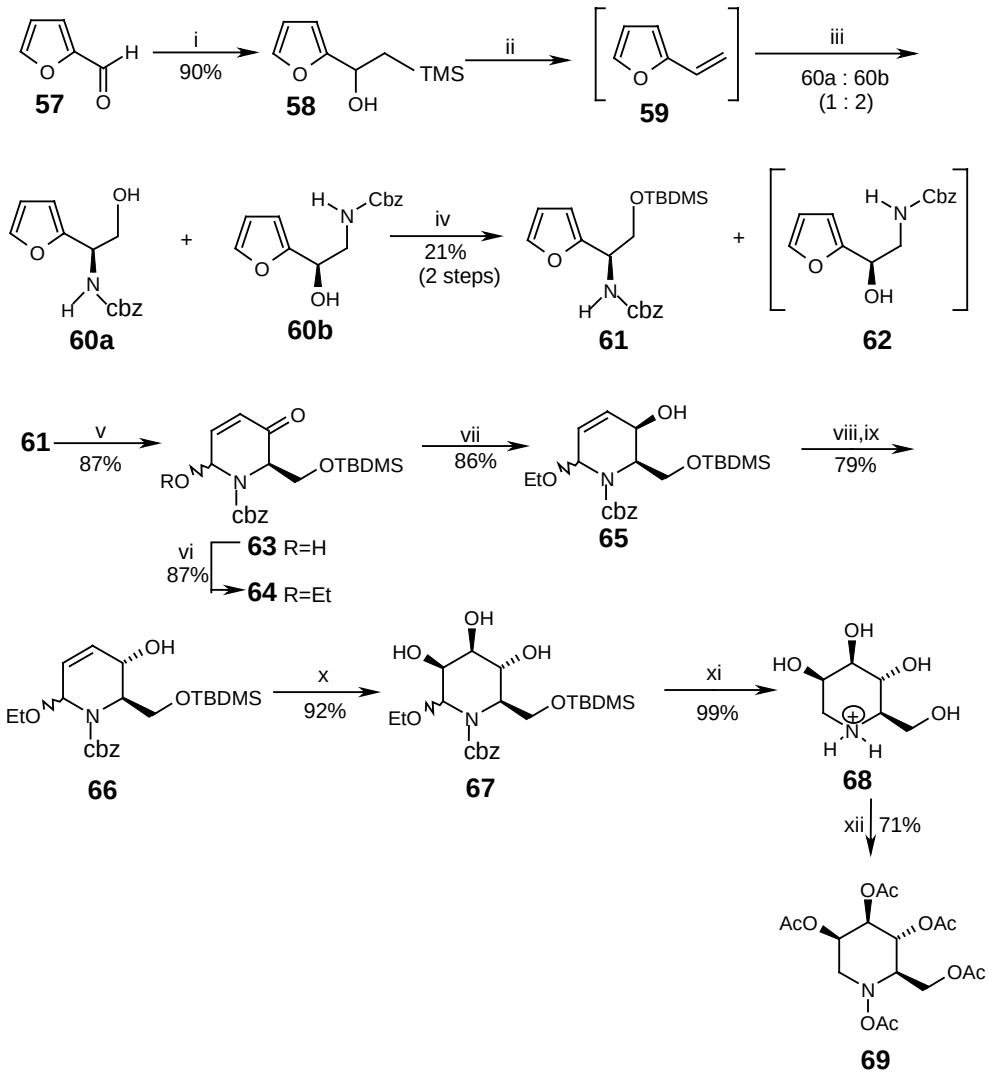
Both Ciufolini *et* al 1998[41] and Haukaas and O'Doherty 2001[42] have reported on an aza sugar synthesis via an asymmetric amino hydroxylation/aza-Achmatowicz approach.

O'Doherty *et al.* 2001[42] Scheme 7

His approach involves Sharpless asymmetric aminohydroxylation of 2-vinylfuran (prepared by Grignard of furan and chloromethyltrimethyl silane and further treatment with HCl). Regioisomers **60a** and **60b** were separated by selective protection of primary alcohol with TBDMSCl followed by silica gel chromatography. Treatment of the intermediate with NBS via aza-Achmatowicz rearrangement gave the cyclised product. Hemiaminal distereomers

were converted into ethylaminal using triethylchloroformate and TsOH. Luche reduction of ethylaminal gave the allylic alcohol. Under Mitsunobu condition the required manno-stereochemistry was obtained.

Scheme 7

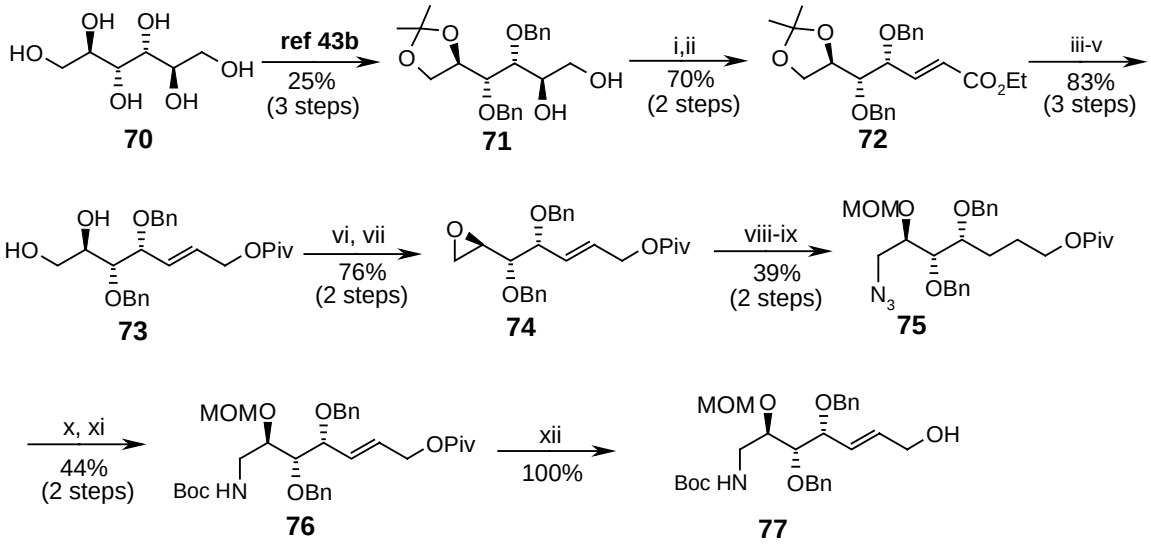


Scheme 7: ***Reagents and conditions*****:** (i) TMSCl, Mg, Et_2O, 0°C, 12 h; (ii) 1MHCl, Et_2O, rt, 1 h; (iii) $CbzNH_2$, NaOH, tert-butylhypochlorite, OsO_4, $(DHQ)_2PHAL$, *t*-BuOH, rt, 1h; (iv) DMAP, TBDMSCl, Et_3N, CH_2Cl_2, rt, 3 h; (v) *m*-CPBA, CH_2Cl_2, 0°C, 3 h; (vi) $HC(OEt)_3$, $TsOH.H_2O$, CH_2Cl_2, rt, 24 h; (vii) $CeCl_3$, $NaBH_4$, CH_2Cl_2/MeOH, -78°C, 2 h; (viii) PPh_3, DEAD, *p*-nitro benzoic acid THF, 0°C. 30 min. (ix) Et_3N, MeOH, rt 8 h (x) OsO_4, NMO, CH_2Cl_2, 0°C, 12 h. (xi) Pd/C (10%), H_2, MeOH, $TsOH.H_2O$, rt, 12 h; (xii) Ac_2O, DMAP, Py, CH_2Cl_2, rt, 12 h.

Hirai *et al*. 2000[43a] Scheme 8 and 9

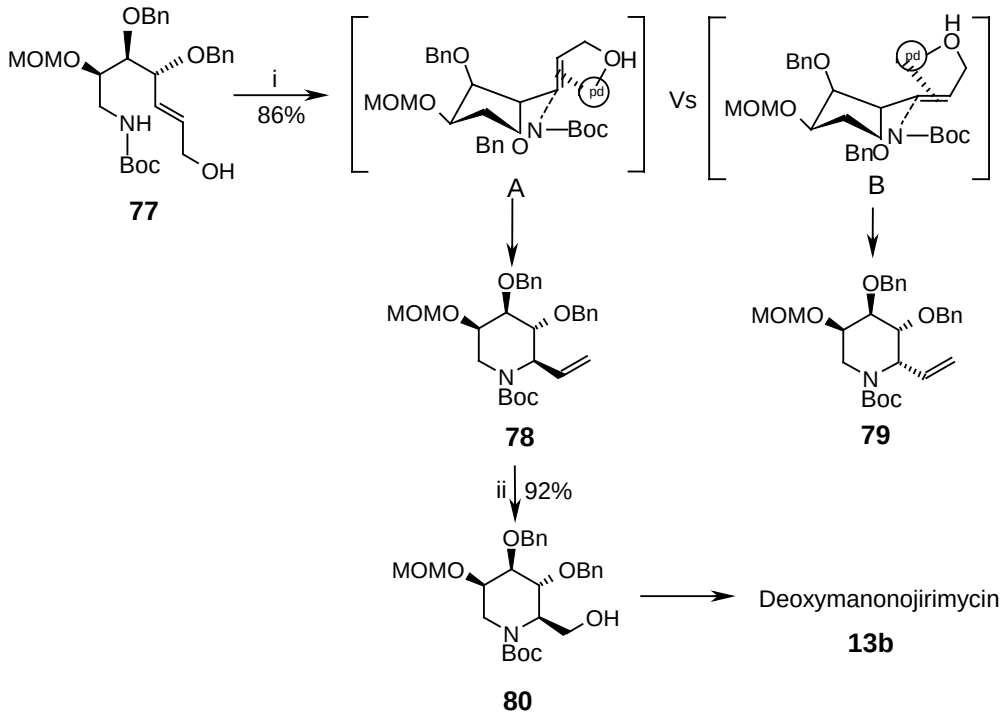
Hirai reported palladium catalysed cyclisation of urethane as a key steps to prepare DMJ (**Scheme 8**). The urethane itself was synthesized from readily available D-mannitol. Oxidative cleavage, followed by Horner-Wadsworth-Emmons olefination to α, β-unsaturated ester are the key steps towards urethane moiety. The ring cyclisation was achieved using 15 mol% $PdCl_2(CH_3CN)_2$ to give primarily one compound (151:152 > 26:1 ratio) in 86% yield (Scheme-13). The stereo-selectivity was explained by assuming cyclisation proceeding via the sterically favored transition state.

Scheme 8



Scheme 8 : ***Reagents and conditions*****:** (i) $NaIO_4$, H_2O/Et_2O, 0°C (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0°C (iii) DIBAL, THF, -78°C (iv) PivCl, THF, 0°C (v) 10% aq HCl, THF, 40°C (vi) TsCl, Py, CH_2Cl_2, 0°C (vii) K_2CO_3, MeOH, 0°C (viii) NaN_3, 15-Crown-5, 0°C, DMF, rt (ix) MOMCl, *i*-Pr_2NEt, 0°C (x) PPh_3, THF, rt (xi) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt (xii) K_2CO_3, MeOH, rt, THF, rt,

Scheme 9

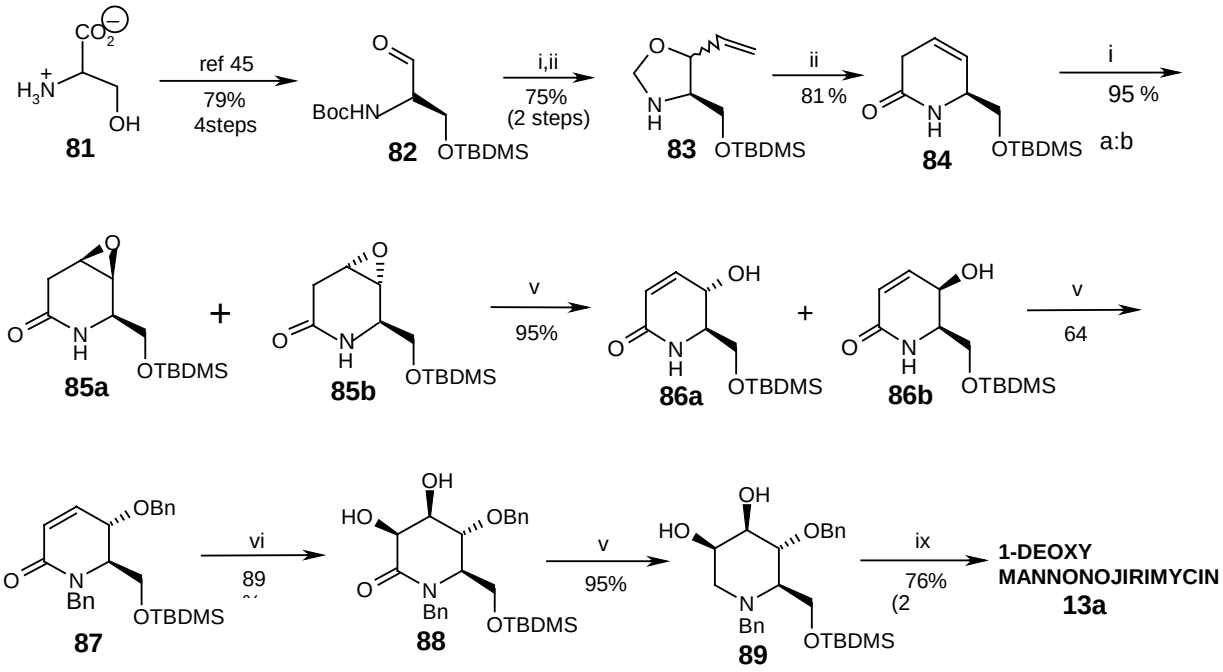


Scheme 9: ***Reagents and conditions*****:** (i) 15 mol%/$PdCl_2(MeCN)_2$, THF, rt; (ii) (a) O_3, CH_2Cl_2/MeOH, -78°C, (b) $NaBH_4$, -78°C; (iii) TFA, CH_2Cl_2, 0°C to rt; (iv) H_2; Pd/C, conc. HCl, EtOH, rt.

Knight *et al*. 2003[44] Scheme 10

Starting from D-serine, the palladium catalysed 'decarboxylative carbonylation' is the key step in this synthesis.

Scheme 10

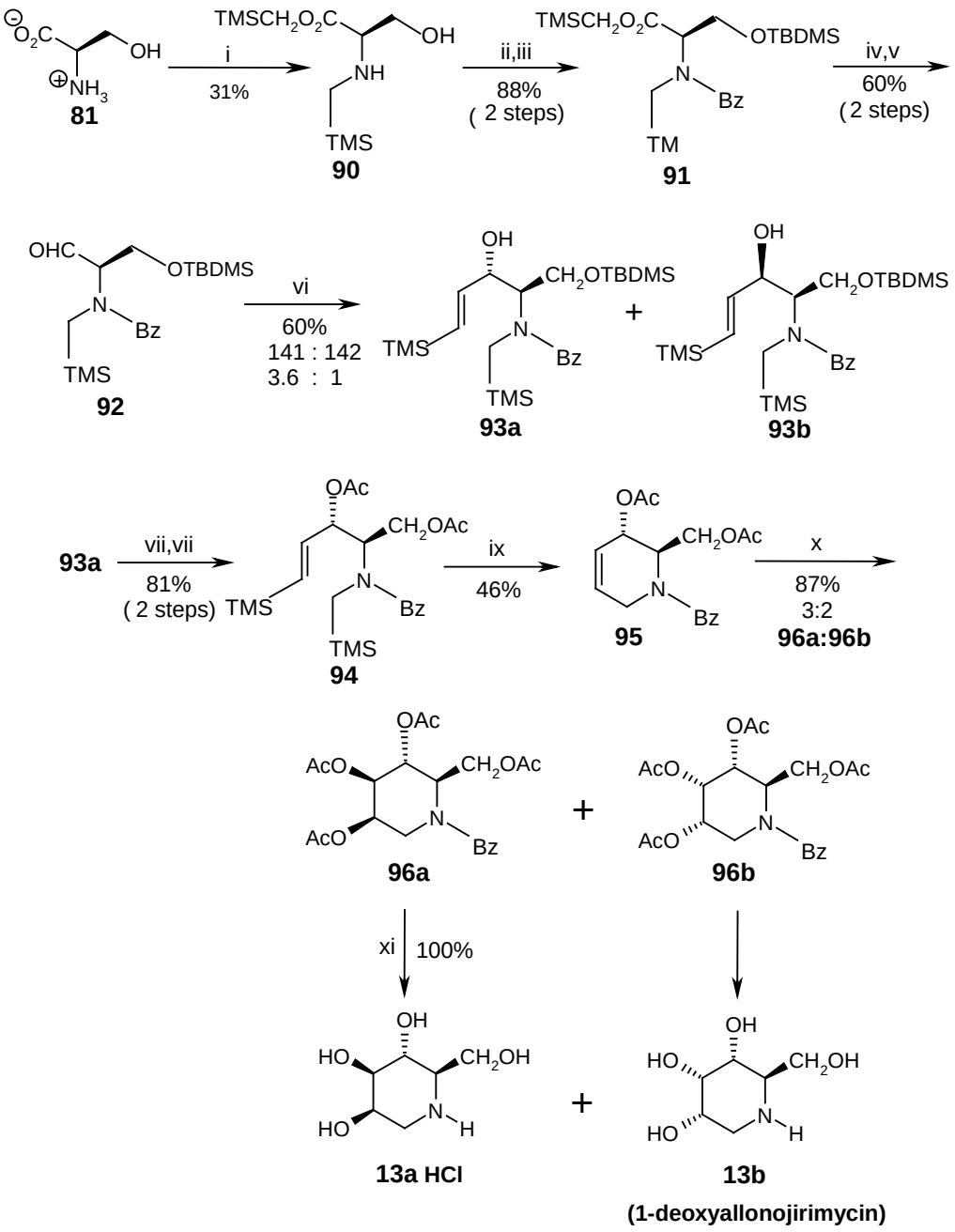


Scheme 10: ***Reagents and conditions*****:** (i) H_2C=CHMgBr, THF, -78°C to rt, 3 h; (ii) *t*-BuOK, THF, rt, 3 h; (iii) $PdCl_2(PPh_3)_2$, (10 mol%), CO (65 atm), EtOH, 60°C 32 h; (iv) Oxone®, $NaHCO_3$, acetone/H_2O, rt, 3 h; (v) DBU (2 equiv), CH_2Cl_2 reflux, 3 h; (vi) NaH (2 equiv), DMF, BnBr, 0°C to rt, 3 h; (vii) OsO_4, NMO, *t*-BuOH, rt, 3 h; (viii) $LiAlH_4$, Et_2O, rt, 3 h; (ix) Bu_4NF, THF, rt, 1h; (x) Pd/C. (10%), H_2, EtOH, HCl, rt, 2 h.

Mariano *et al*. 1998[46] Scheme 11

Starting from D-serine, this approach involves oxidative Mannich cyclisation of the intermediate. The distereomeric ratio of the alcohols was assigned on the basis of Felkin-Ahn model (70% ee).

Scheme 11

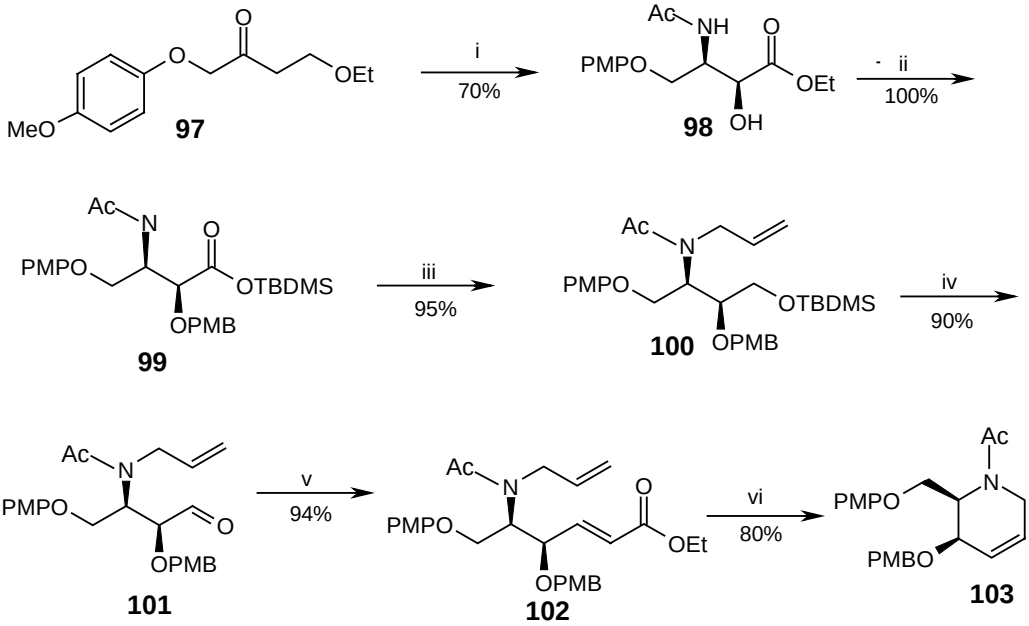


Scheme 11: ***Reagents and conditions*****:** (i) $TMSCH_2I$, K_2CO_3, DMF, 100°C, 17 h;(ii) imidazole, TBDMSCl, DMF, 25°C, 18 h; (iii) BzCl, Et_3N, CH_2Cl_2, 0°C, 15 min; (iv) $NaBH_4$, EtOH, 25°C, 6 h (v) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C, 2.5 h; (vi) (E)-1-(trimethylsilyl)-2-(tri-n-butylstannyl)ethane, n-BuLi, THF, -78 to 25°C 6.5 h; (vii) 48% HF/H_2O, MeCN, 25°C, 0.5 h; (viii) DMAP, Ac_2O, Py, 25°C, 17 h; (ix) CAN MeCN, 25-40°C, 20 h; (x) (a) OsO_4, NMO, acetone/H_2O, 0°C, 17 h, (b) DMAP, 25°C, 17 h; (xi), 6N HCl, reflux, 2 h; (xii) (a) 6M HCl, reflux, 5 h (b) ion-exchange chromatography.

Han *et al*. 2003[47] Scheme 12

A general strategy to synthesise the common olefin intermediate for different 1-deoxyazasugars was developed by Han using the olefin as starting material. Here it is believed that aryl-aryl stacking interaction between the olefin and the Sharpless asymmetric aminohydroxylation catalyst would proceed with improved selectivity. (gave the regio selectivity of >20:1 to furnish amino alcohol (>99% ee after recrystallisation). Horner-Wadsworth-Emmons olefination protocol to prepare the α, β-unsaturated ester and ring closing metathesis are the important reaction involved in this approach.

Scheme 12



Scheme 12: ***Reagents and conditions*****:** (i) $K_2OsO_4.2H_2O$, $(DHQD)_2PHAL$, LiOH, *N*-bromoacetamide, *t*-BuOH/H_2O, 4°C, 8 h; (ii) (a) NaOH, PMBCl, DMF, 0°C, 8 h, (b) $LiBH_4$, Et_2O, 15 min. (c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 25°C, 4 h; (iii) KH, 18-crown-ether, $H_2C{=}CHCH_2Br$, THF, 25°C, 5 h; (iv) (a) TBAF, THF, 25°C, 1 h (b) periodinanane, CH_2Cl_2, 25°C, 1 h (v) $(EtO)_2P(O)CH_2CO_2Et$, LiBr, DBU, THF, 25°C, 2 h; (vi) Grubbs' catalyst (10 mol%), toluene, 90°C, 2 h.

5.2 SECTION B
α-Amino Aldehydes as Synthons in the Syntheses of Aza Building Blocks for Hydroxylated Pyrrolidine and Piperidine Alkaloids

5.2.1 Introduction

The synthesis of optically active organic compounds is one of the most important problems of contemporary chemistry. Pure enantiomers attain increasing commercial interest, especially in the field of pharmaceutical products. During recent years, asymmetric synthesis has greatly contributed to progress in highly controlled formation of new chiral centers.[48] These processes still remain the basic problems in the total synthesis of natural products. Preparation of the latter in an optically pure form by application of chiral starting materials is very advantageous, enabling precise programming and efficient realization of synthetic pathways. Many monosaccharides and their readily available derivatives are versatile substrates for the synthesis of optically active target molecules.[49] α-Amino acids are the second important natural source of chiral substrates, useful in stereocontrolled organic synthesis.[49e, 50]

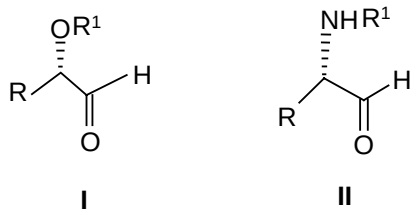
Naturally occurring amino acids constitute an attractive source of chiral, non-racemic starting materials for asymmetric synthesis. This is due to part to the commercial availability of these substances, which in many cases involve the unnatural antipode as well. Active esters of amino acid derivatives represent one of the most important classes of activation for peptide coupling.

In nature amino acids are combined to give proteins with hundreds or even thousands of amino acids in each one. Small assemblies of amino acids are known as peptides and the amide bond that links them is called a peptide bond. Longer peptides are called proteins, though where exactly the boundary occurs is difficult to say. Amino sugars one of the class of amino acid derivatives produce structure of remarkable variety and beauty.

Amino acids are particularly useful precursors for the asymmetric synthesis of piperidine alkaloids for several reasons. Firstly, many amino acids are cheap and homochiral; secondly, they already contain the nitrogen of the alkaloid target; thirdly, they usually lead to 2-substituted piperidines, which is the commonest position for substitution. Conformationally

constrained α-amino acids have gained significant attention in recent years. This may be due to the observations that incorporation of such amino acids into peptides induces the conformational change and thus may serve as useful means for obtaining information on receptor recognition. It also provides peptide mimetics that can be used as new drugs. This type of amino acids per se exhibits interesting biological activities. For designing such amino acids, construction of a proline or piperidine analogue with a functional group at a specific position of the pyrrolidine or piperidine framework has become a major strategy.

Aldehydes are important and versatile compounds, widely used in organic synthesis. In recent years there has been a growing interest in chiral nonracemic aldehydes because of the development of new and effective methods for controlling stereochemistry of several basic organic reactions, such as metalloorgnic addition to the carbonyl group,[51] aldol condensation,[52] [4+2] cycloaddition with carbonyl heterodienophiles[53] etc. Protected α-hydroxyl and α-amino aldeydes II (Figure 1) are of special interest, owing to their ready availability in both enantiomeric forms from natural sources (sugars and α-amino acids, respectively) and to pronounced versatility due to the presence of both the formyl group and suitably protected hydroxy or amino functionality in the molecule.

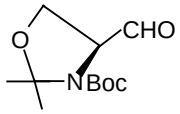


I **II**

Figure 1

Recently, several extensive reviews on the application of α-hydroxy aldehydes in organic synthesis has been published[49e, 52a, 52c] but there is no general survey concerning α-amino aldehyde.[54] On account of the increasing interest of chemists in α-amino aldehydes, reflected by an augmenting number of relevant publications, and in view of our belief that their further potential applications may be very important, we resolved to gather and present the actual knowledge concerning the use of optically pure *N*-protected α-amino aldehydes in stereocontrolled organic synthesis.

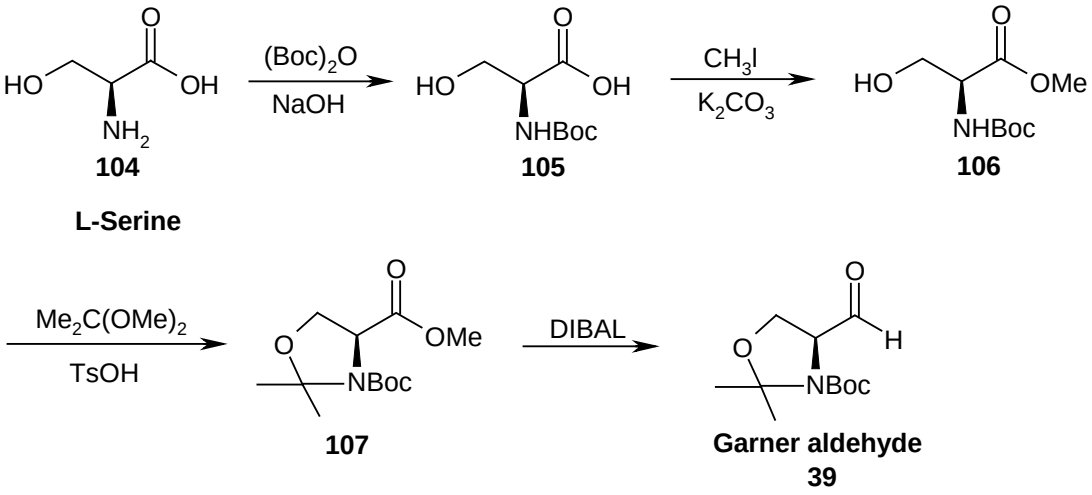
α-Amino aldehydes are versatile building blocks, frequently used in the syntheses of natural product.[55-63] Adducts of α-amino aldehydes and acetylenic compounds are easily transformable to a variety of chiral natural products containing many contiguous stereogenic carbon atoms. Among these products are cytostatics,[57]glycosidic antibiotics,[61] as well as anthelmintic[62] and antiviral[63] compounds. In 1984 Garner published[64] a method for preparing the configurationally stable 1, 1-dimethylethyl-4-formyl-2, 2-dimethyloxazolidine-3-carboxylate **39**, today called Garner's aldehyde. Since that time both enantiomers of **39** have been used extensively as chiral building blocks in asymmetric synthesis. Garner's aldehyde **39** is perhaps one of the most valuable chiral building blocks in recent time, as it has been employed in more than 200 reported studies since its discovery.



39

The first synthesis of **39** was as the compound's name implies, reported by Philip Garner.[55] His synthesis started with Boc protection of the L-serine **104** using di-*tert*-butyl dicarbonate [Boc_2O] at pH ≥ 10 to form *N*-Boc-serine **105**, which was converted to the methyl ester **106** either by diazomethane[65] or, more conveniently, with CH_3I and K_2CO_3 (**Scheme 23**).[66] Compound **106** was then treated with $Me_2C(OMe)_2$, and TsOH to give the oxazolidine ester **107** in 87-89% yield. Direct reduction of ester **107** with DIBAL in toluene then afforded the title Garner's aldehyde **39** in 76% yield.[67] Garner's original synthesis (**Scheme 13**) has been subject to a number of improvements.

Scheme 13



104 **105** **106**

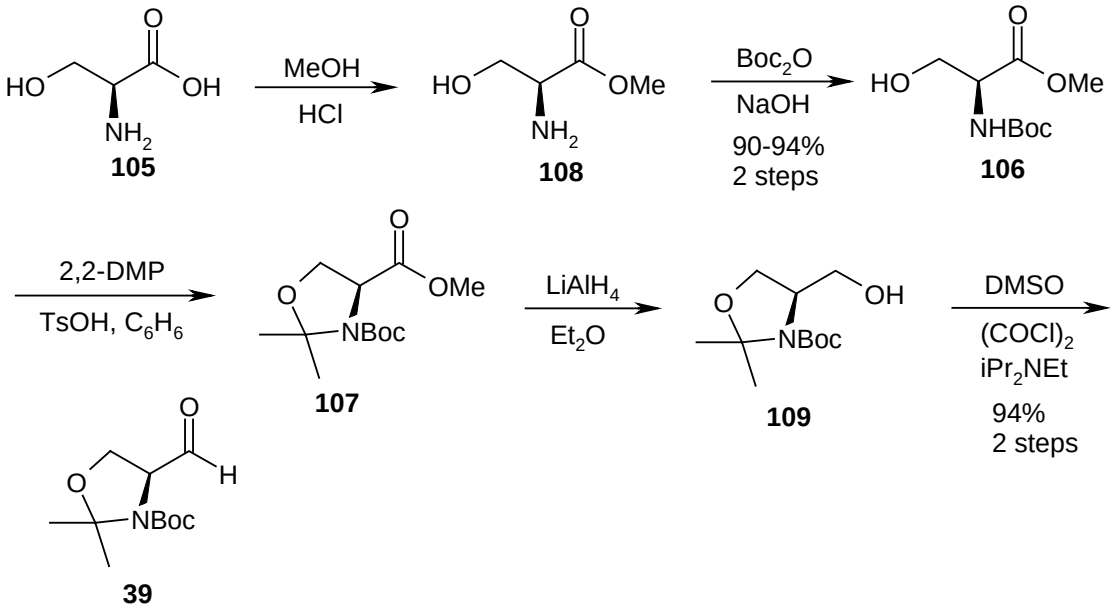
L-Serine

107 **Garner aldehyde 39**

The step that has been subjected to most attempts at improvement is the DIBAL reduction of **107** to aldehyde **39**. A more reliable procedure was to reduce the ester **107** to the alcohol **109** and then oxidize it back to **39** under Swern conditions (S**cheme 14**).[68- 73] Roush and Hunt noted that not only is the DIBAL reduction tricky, but the enantiomeric excess was also only 86-87% in their hands.[70] The reliability and yield of the synthesis was improved by replacing DIBAL with $LiAlH_4$-Swern protocol (**Scheme 14**), but not the enantiomeric purity of **39**. This was confirmed by Marshall *et al.*, who also obtained a product with 90% ee after the Swern oxidation.[69] This problem was solved by Dondoni *et al***.** by changing the base used in the Swern oxidation from Et_3N to Hünig's base.[73] Hünig's base is more hindered and therefore less likely to facilitate enolisation of **39** with the modification the enantiomeric purity of **39** was more than 97%.

Both steps of this sequence have also been carried out with other reagents. The reduction of **107** to **109** can be performed by $NaBH_4$-LiCl and proceeds in 96% yield.[74] The oxidation of 1**09** to **39** can also be performed via TEMPO-catalyzed oxidation, which proceeds in 90% yield and with 100% ee optical purity,[75] or with DMSO-triphosgene which gives 81% yield of a product with an optical purity similar to that reported by Garner.[76]

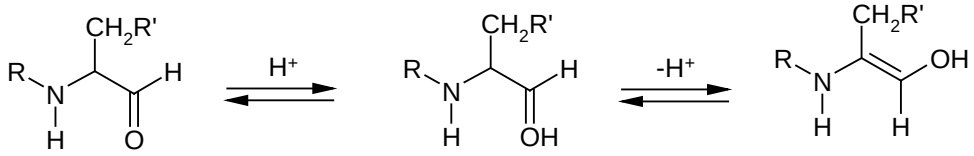
Scheme 14



5.2.2 Physical and Chemical properties of *N*-protected α-amino aldehydes

N-Protected α-amino aldehydes are usually colorless crystals or oils, well soluble in typical organic solvents. They are relatively unstable both chemically and configurationally, particularly in solution. For this reason their elemental analysis and optical rotation measurements should be considered as only approximate. Therefore, it is recommended to use these compounds immediately after preparation; however, if purification is necessary, two methods are available: flash chromatography on silica gel[77] of formation of much more stable semicarbazone[78] followed by simple chromatography and subsequent decomposition to return the pure aldehyde. The optical stability of some *N*-protected α-amino aldehydes during chromatography on silica gel was first studied by Ito *et al.*[79] (**Table 1, Scheme 15 and 16**). As shown in Table 1, the order of the extent of racemisation of Cbz-L-α-amino aldehydes on silica gel was as follows: Cbz-S-BZl-L-cysteinal >> Cbz-L-phenylalaninal > Cbz-L-leucinal >> Cbz-NG-nitro-L-argininal.

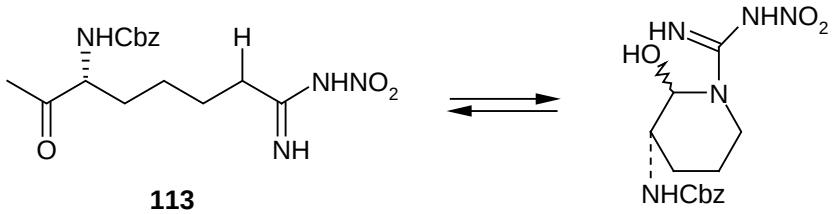
Scheme 15



110 **111** **112**

The authors[79] proposed a racemization mechanism for compounds **110** involving the protonated form **111** and enol **112 (Scheme 15).** Aldehyde **110** with an enol-stabilizing **R'** group, e.g. Cbz-*S*-Bzl-cysteinal, racemize extremely quickly during contact with silica gel.

Scheme 16



113 **114**

Limited racemization of Cbz-N^G-nitro-L-argininal **113** seems to be related to its cyclic carbinolamine structure **114 (Scheme 16)**, which probably prevents the nitroargininal derivative **113** from racemization due to keto-enol tautomerism. Further studies on the optical stability of *N*-protected α-amino aldehydes were carried out by Evans and and co-workers,[80]

Table 1: Optical Stability of Selected α-Amino aldehyde on Silica gel

	deg of racemization, %		
α-Amino Aldehyde	0 h[a]	6 h[a]	22 h[a]
Cbz-N^G-nitro-*L*-argininal	0	5	9
Cbz-*L*-leucinal	0	32	65
Cbz-*L*-phenylalaninal	0	53	85
Cbz-*S*-*L*-cysteinal	7	99	100

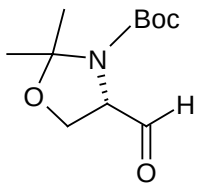
[a]Exposure time

found that the reduction-oxidation procedure (BH_3 THF-CrO_3/Py) generated Boc-α-amino aldehydes with completed retention of chiral integrity (>99.5%). The optical lability of the crude aldehydes depends on their structure. Thus as expected from previous studies,[78] Boc-*L*-phenylalaninal appeared to be much less stable than Boc-*L*-leucinal. Very illustrataive results of optical stability investigations of BOC-*L*-leucinal during storage at various temperatures are shown in **Table 2.**

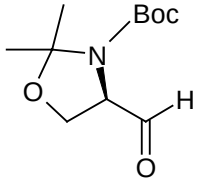
Table 2 : Optical Stability of Boc-*L*-Leucinal During Storage

Storage time, day	Storage temp.°C	$[\alpha]_D^{24}$, deg	L/L HPLC
0	-	+18.2	100
1	-30	+17.9	99/1
9	-30	+17.4	99/1
9	+24	+6.9	7/3

These studies led to the conclusion that even Boc-*L*-leucinal subjected to any prolonged treatment regimen, including drying, could no longer be regarded as optically pure unless otherwise verified as such.[80] Recently, two important reports on configurational stability of *N*-protected α-amino aldehydes have appeared. The first one by Lubell and Rapoport[81] describes the synthesis of *N*-(9-(9-phenylfluorenyl)-*L*-alaninal. Exposure to silica gel or to a non nucleophilic base caused no detectable racemization. The PhFI *N*-protecting group also maintains the configurational integrity of *L*-alaninal during C-C bond-forming reactions affording enantiomerically pure products from Wittig reactions, aldol condensations, and Grignard addition.[82] The second report by Garner and Park[66] describes the synthesis of N,O-diprotected *L*-serinal **39** and *L*-threoninal **threo 39**



39



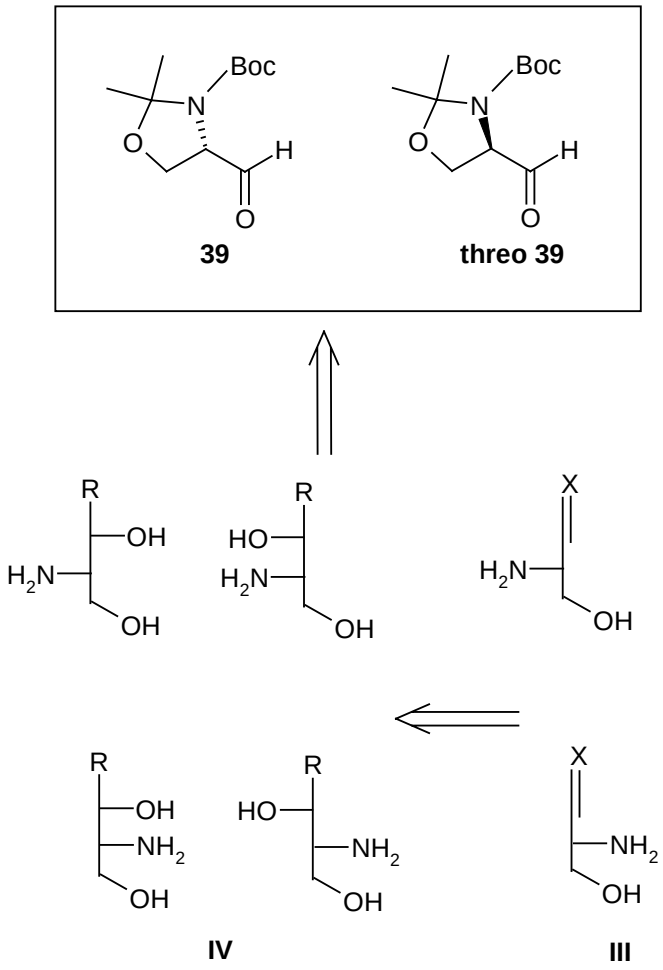
threo-39

These differentially protected β-hydroxy-α-amino aldehydes were shown to be produced in a 93-95% enantiomeric excess. The congifurational stability of compounds **39** and **threo 39** during their purification either by vacuum distillation or by flash chromatography was also demonstrated.[66]

Nucleophilic addition reaction of Garner's aldehyde

The addition of nucleophilic compounds to Garner's aldehyde **39** opens access to the 2-amino-1, 3-dihydroxypropyl structure motif which is widespread in natural products. The synthesis of azasugars, peptide antibiotics and sphingosines can be realized stereoselectively by this means. Nucleophilic additions to **III** lead first to the corresponding 2-amino-1, 3-dihydroxypropyl derivatives **IV** through the formation of a carbon-carbon or carbon-hetero atom bond (**Scheme 17**). Depending on the reaction conditions, subsequent elimination of water gives access to *D*- and *L*-2-amino-3-hydroxypropyl productrs **IV**. In most cases, the constitution of **39** prevents racemisation during nucleophilic addition reactions. Therefore, starting from **39** or *threo*-**39** all four possible isomers of the *D*-, *L-threo* and the *D*, *L-erythro* series are selectively available in moderate to excellent yields.[83]

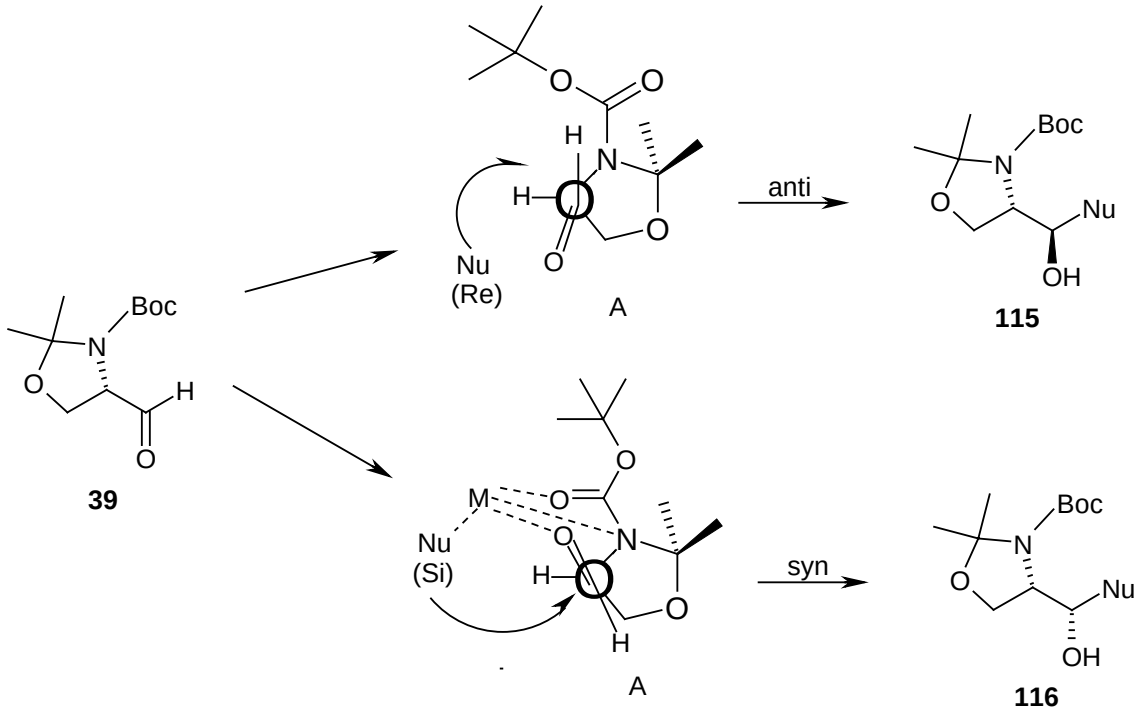
Scheme 17



Addition of Organometallic reagents

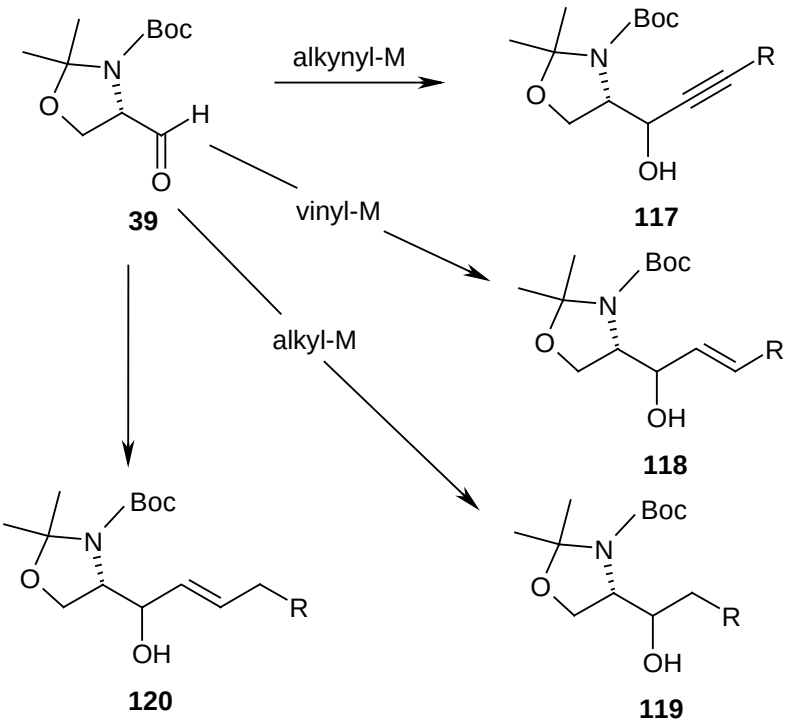
Addition of metal activated carbon nucleophiles to **39** leads, in most cases, to mixtures of two diastereomers, anti-addition gives the erythro-products, while syn-addition leads to the threo-products. Herold first reported that high asymmetric induction in both the directions could be achieved using different solvents and additives with chelation effects.[84] The formation of the reaction products is explained either with the Felkin-Ahn model **A** involving a non-chelating transition state and leading to the anti-adduct **115**, or with the Cram model **B** having a chelation-controlled transition state and leading to the syn-adduct **116** (**Scheme 28**).[85] Without chelation, the formation of *syn*-products is believed to be disfavoured because of repulsion between the electronegative O- and N-atoms. Efficient formation of *syn*-products can also be achieved by simple oxidation of the diastereoisomeric *anti-syn* mixture to the corresponding ketone followed

Scheme 18



by metallohydride reduction (with $NaBH_4$[86-95], $LiBH_4)_2$[96], $Zn(BH_4)_2$[97, 98] K-Selectride, DIBAL[99-101] or Bu_3BHK[102]), which is highly biased towards formation of the *syn*-product **116** It is possible to make almost equal mixture of **115** and **116**, which might be useful in combinatorial syntheses, since all four isomers of the *D-, L-threo* and the *DE-, L-erythro* 2-amino-1,3-dihydroxypropyl structure element would be obtained by this means. However, it is also possible to obtain enantiomerically pure compounds even on a solid phase. For instance, ω-aminosphingosine derivatives have been synthesized on a solid phase and used to purify sphingosine kinase, an enzyme involved in a variety of mammalian processes.[103, 104] Depending on the carbon nucleophile and the metal counterion different stereoselectivities are observed. One of the most important addition reaction is the alkynylation, which gives selective access to all possible stereoisomers of alkynl, vinyl and alkyl products **117-120** (**Scheme 19**).

Scheme 19

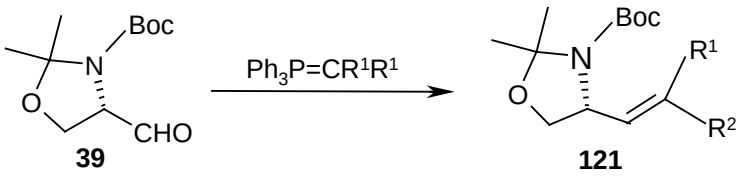


Wittig Reactions

Wittig Reaction of Garner's Aldehyde with Non-Stabilized Ylides

The Wittig reaction of **39** with non-stabilised ylides favours the formation of the corresponding *Z*-olefin. Beaulieu *et al.*[105] investigated such processes in detail. Thus, treatment of **39** with a variety of phosphorus ylides generated from the corresponding phosphonium salts provides alkenes (**Table 3**). In most instances, *Z*-olefins are formed exclusively. Glycosphingolipids and sphingomyelins that are biomembrane components play physiologically important roles in bioorganisms. As a consequences, sphingosines, dihydrosphingosines and phytosphingosines have been independently synthesized by many groups. Very recently, three different types of sphingosine derivative were prepared using **39** as starting material.[106] Wittig olefination of **39** using n-BuLi and pentadecyltriphenylphosphonium bromide ($C_{15}H_{31}PPh_3Br$) only resulted in low yields of the desired olefin. In contrast, by using $C_{15}H_{31}PPh_3Br$-LiHMDS in combination, a

Scheme 20



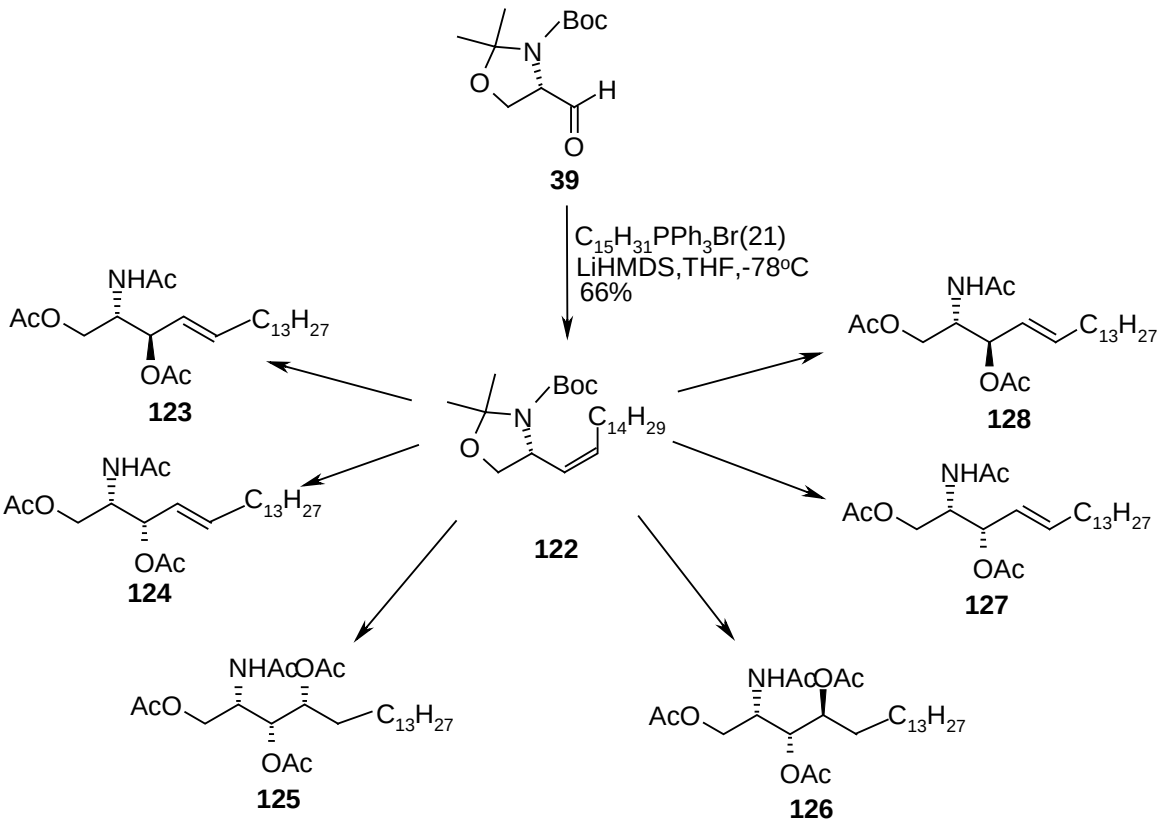
39 **121**

Table 3

Entry	Compound	R_1	R^2	Yield(%)	Z
1	a	Me	H	62	93
2	b	n-C_5H_{11}	H	78	>98
3	c	CH_2CH_2Ph	H	96	>98
4	d	$(CH_2)_2CO_2H$	H	73	>98
5	e	Et	Me	50	70

9:1 mixture of (*Z*)- and (*E*)-isomers was obtained in 83% total yield. Use of sodium hexamethyldisilazide (NaHMDS) as a base gave similar results. Column chromatographic purification then provided pure (*Z*)-**121(Scheme 20)**. Further functional group manipulation then afforded dihydrosphingosines **123, 124**, phytosphingosines **125, 126** and sphinogosines **127, 128** (**Scheme 31**). A similar approach to phytosphingosines has been described by Horikawa et al[107]. Reagent-controlled *cis*-dihydroxylation using AD-mix was investigated in detail.

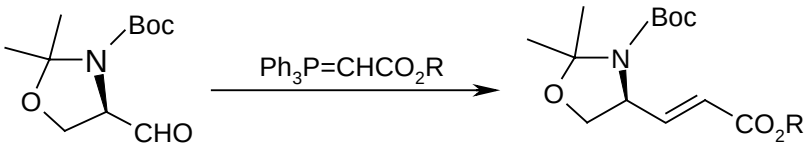
Scheme 21



Wittig Reaction of Garner's Aldehyde with Stabilized Ylides

Garner's aldehyde **39** has been used often in the synthesis of another important building block, compound **129**, which also offers many possibilities for chemical transformation. This α, β-unsaturated ester can undergo Michael type addition, cyclopropanation, [2,3]-cycloaddition, Diels-Alder reaction, epoxidation, dihydroxylation etc. Further functional group interconversions will pave the way to many other useful building blocks. Here, the preparation of **129** using the Wittig reagent is described and later some uses of this building block will be discussed. Wittig reaction of **39** with commercially available ylides proved to be a very convenient procedure for preparation of **129a**. Both reactants can be simply mixed in a solvent and stirred at room temperature, though the work up does involve chromatography. The stereochemical outcome of this reaction strongly depended on solvents. When the reaction was performed in methanol, poor *E/Z* ratios were observed, while in THF or benzene, high stereoselectivity was observed (**Table 4**).[108-115] Taylor and co-workers have developed a one pot procedure for the preparation of **129a**.

Scheme 22



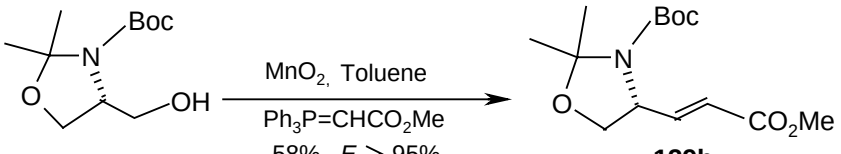
threo 39 **129**

Table 4

Entry	R	Solvent	Yield(%)	E:Z	Ref.
1	Me	MeOH	93	3:2	61
2	Me	MeOH	78	3:1	62
3	Et	THF	72	1:0	63
4	Et	Benzene	82	1:0	60,64
5	Me	Benzene	86	94:6	65
6	Et	Benzene	100	1:0	66
7	Me	Benzene	95	1:0	67

The corresponding alcohol **109** was oxidized using manganese dioxide, and in the presence of the ylide and the aldehyde **39** so formed was trapped to produce the α,β-unsaturated ester

Scheme 23



109 **129b**

directly. Even thoughthis *n-situ* oxidation-Wittig methodology proceeded in moderate yield, the stereoselectivity was very high (>95% *E*) (**Scheme 23**).[116] Due to the presence of the chiral oxazolidine moiety, Michael addition of organometallic reagents to compound 1**29** was expected to be diastereoselective.

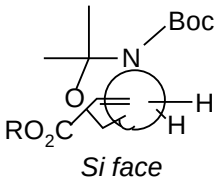


Figure 3

Yoda *et al.* Wermuth *et al.* and Hanessian *et al.* have systematically investigated the reactivity and stereochemical outcome of this reaction. The reaction conditions are similar in all three cases. Conjugate addition of organocuprates to esters 1**29** in the presence of trimethylsilyl chloride led to faster reaction and higher yield. The diastereoselectivities observed ranged from good to excellent.[117-120] The formation of the favored *syn*-isomer was rationalized by the Felkin-Ahn model wherein nucleophilic addition takes place preferencially from the *Si*-face (Fig. 3).[120]

5.2.3. Conclusion

As can be seen from the above-presented description, *N*-protected α-amino aldehydes are versatile chirons, widely recognized, inexpensive, and easily accessible from natural sources. However, the degree of stereoselectivity obtained in some reactions shown is not high enough to meet the present requirements, and thus more work has to be done to elucidate the nature of all factors responsible for asymmetric induction. Higher stereoselectivities will surely extend the utility of these values chiral synthons.

Garner's aldehyde, one of the major component of α-amino aldehydes has, in a very short time, proven an extremely useful chiral building block in organic synthesis. Its value is due to its simple structure that allows it to be used for many targets and because good methods exist for diastereoselective elaboration of aldehydes. It may be anticipated that similar simple chiral building blocks for alternative purposes are in demand and will develop in the future.

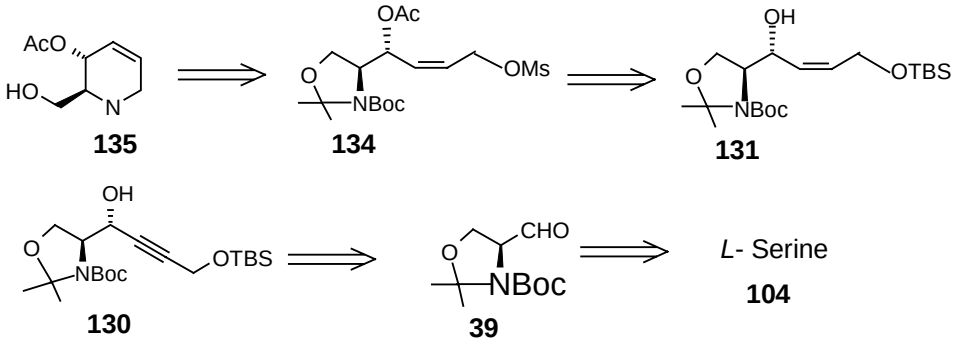
5.3 Section C Present work

5.3.1 Introduction

Recent years have witnessed an increasing interest in synthetic and naturally occurring polyhydroxylated piperidine alkaloids as biological tools and potential therapeutics. On the other hand, construction of a versatile chiral building block for biologically active natural products would provide us with powerful tools for the synthesis of target natural products.

As seen from the literature, the non-chiral approach towards synthesizing these chiral building block (for synthesis of 1-deoxymannojirimycin, 1-deoxyidonojirimycin, 1-deoxygulonojirimycin)[57] use highly expensive reagents. Though, there are few synthesis of chiral building blocks for hydroxylated piperidine derivatives with the use of α-amino aldehyde[43a, 43b] as the synthetic precursor, (1-deoxygalactonojirimycin, fagomine, 3,4-diepifagomine, 3-epifagomine and epiisofagomine) they are derived with use of some specific reagents or suffer from harsh reaction condition. Carbohydrates based approach towards these compounds, in general requires a large number of steps to reach a specific target. Because of the role of polyhydroxylated piperidines, as a potential drugs to treat a variety of carbohydrate-mediated diseases, and the exceptional usage of α-amino aldehyde as a building block, we thought of using Garner's aldehyde as starting material in synthesizing the chiral building block, which can be useful to synthesise different hydroxylated piperidine alkaloids and its congeners of biological interest.

Scheme 24

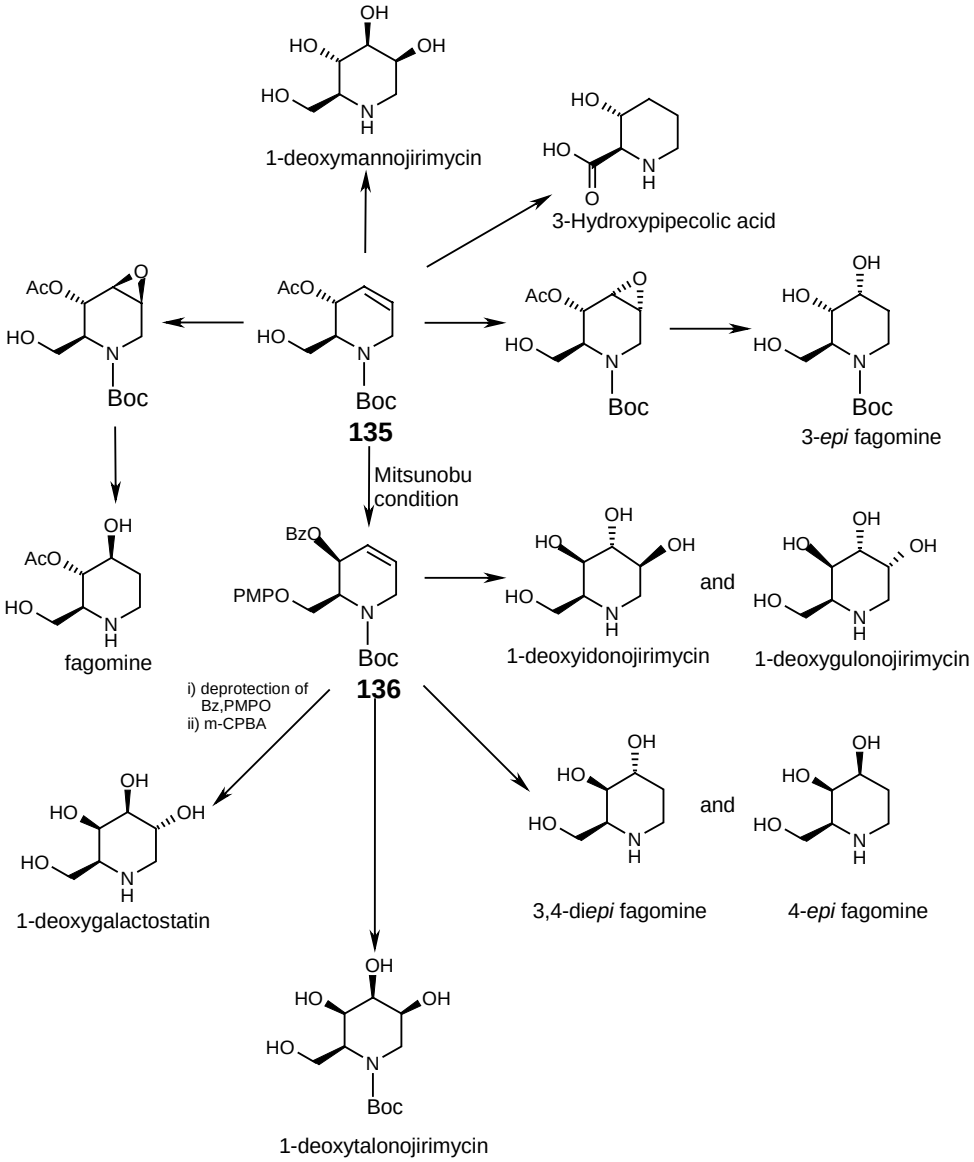


As seen from the **Scheme 24** desired building block could be obtained from Garner aldehyde **39**, which involves diastereoselective addition of lithium derivative of *tert*-butyldimethylsilyl propargyl ether to Garder aldehyde, followed by reduction of the double bond using Lindler's

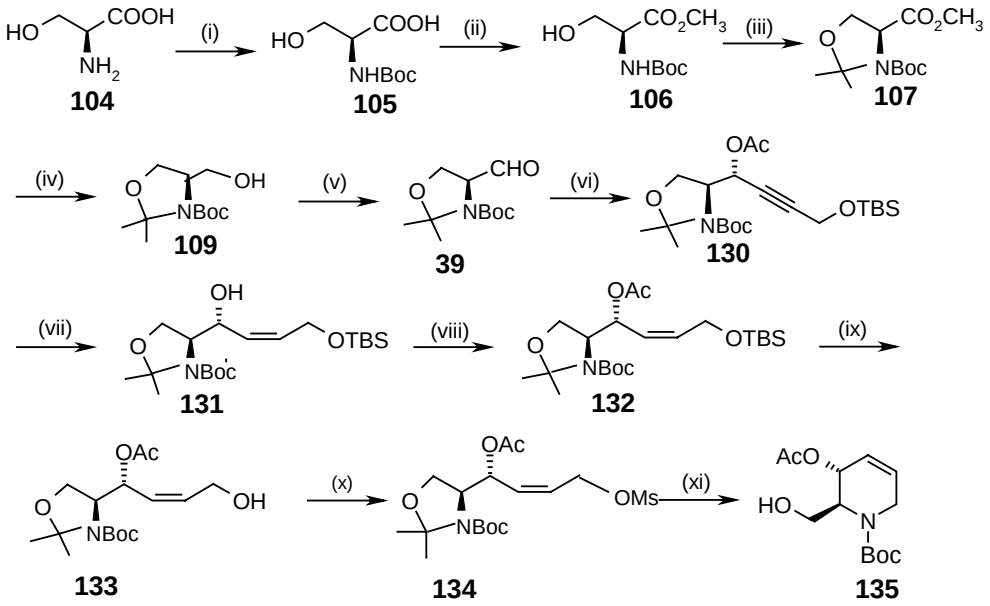
catalyst, to give the *cis* olefin **131** which could be easily transformed into the desired chiral building block **135.**

As seen from the retrosynthetic analysis, compound **130** is the key intermediate for the synthesis of desired chiral building blocks which could then be easily transformed into various polyhydroxypiperidine alkaloids and its congeners such as 1-deoxymannonojirimycin **13a**, 1-deoxyallonojirimycin **13b**, fagomine **8**, 3-*epi*fagomine **11a** and 3-hydroxypipecolic acid by direct asymmetric dihydroxylation reaction using different chiral ligands. Inversion at C-4 position using Mitsunobu condition gives the intermediate **136** which can be easily transformed into other polyhydroxylated piperidine alkaloids like 1-deoxygulonojirimycin, 1-deoxyidonojirimycin, 4-epifagomine and 3,4-di*epi*fagomine (**Scheme 25**), which renders our synthetic intermediate **135** as a powerful tool for the synthesis of various polyhydroxy piperidine alkaloids.

Scheme 25


1-deoxymannojirimycin
3-Hydroxypipecolic acid
Boc
135
3-epi fagomine
Mitsunobu condition
fagomine
PMPO
BzO
Boc
136
1-deoxyidonojirimycin
and
1-deoxygulonojirimycin
i) deprotection of Bz,PMPO
ii) m-CPBA
1-deoxygalactostatin
3,4-diepi fagomine
4-epi fagomine
1-deoxytalonojirimycin

Scheme 26



Scheme 26: *Reagents and conditions*: (i) $(Boc)_2O$, 1N NaOH, 1,4-dioxane, 0°C to rt, 12 h, 99% (ii) MeI, Dry DMF, K_2CO_3 , 0°C, 6 h, 96% (iii) 1,1-dimethoxypropane, PTSA, Benzene, reflux, 3 h, 82% (iv) LAH, dry THF, 0°C, 4 h, 80% (v) $(COCl)_2$, $(i\text{-}Pr)_2NEt$, DMSO, CH_2Cl_2 (vi) *t*-Butyldimethylsilylpropargyl ether, *n*-BuLi, HMPA, -78°C, 6-8 h, 71% (vii) Lindler's catalyst, dry ethyl acetate, H_2, 6-8 h, 99% (viii) Ac_2O, pyridine, DMAP, CH_2Cl_2 (dry), 0°C, 4 h, 97% (ix) TBAF/THF, 0°C, 8 h, 98% (x) MsCl, Et_3N, CH_2Cl_2 (dry), 0°C, 4 h, 97% (xi) *p*-TSA, CH_2Cl_2 (dry), 5 h, 98%

5.3.2. Results and discussion

As per our retrosynthetic analysis we started our approach towards the desired chiral building block, with α-amino acid, L-serine (**Scheme 26**) Following the literature procedure, the amino group of L-serine was protected using di-*tert*-butyldicarbonate (Boc_2O), as a Boc derivative and the acid functionality was esterified using methyl iodide to afford compound **106**, whose spectroscopic data matched with the literature data. The acetonide protection of **106** alcohol using 2,2-dimethoxypropane and LAH reduction of methyl ester followed by oxidation gave compound **39** (Garner aldehyde), which was immediately used (without column purification) to prepare the addition product **130**, in the ratio of 5:95 (syn:anti) with *tert* butyldimethylsilyl propargylether using *n*-butyl lithium/Et_2AlCl/HMPA in toluene at -

78°C. The IR spectrum of **130** showed a broad band at 3452 cm^{-1}, the characteristic of hydroxy functionality, and a peak 1734 and at at 1695 cm^{-1} corresponding to carbonyl functionality. The peak at 2971 cm^{-1} and the weak bands at 2310cm^{-1} and at 2210cm^{-1} indicated presence of C≡C. The ^{1}H NMR spectrum of **130** showed the multiplet for two CH protons belongings to two stereocentres at δ 3.9d and at δ 4.10 two CH_2 protons appearing as singlet at δ 4.34. TBS protons and the other remaining protons resonated as usual. The ^{13}C spectrum of **130** showed the peaks δ 108.7 indicating the presence of carbon-carbon triple bond. The δ value at 198 indicates the presence of carbonyl functionality. The mass spectrum of **130** showed peaks at 439, 423 and 401 corresponding to (M^{+}+ K), (M^{+}+ Na) and (M^{+}+H) peaks. These peaks confirmed the formation of the addition product **130.** The optical rotation of **130** was measured at $[\alpha]_D^{25}$ – 41.1 [*c* 1, $CHCl_3$] {lit[84]. $[\alpha]_D^{25}$ –4o.78 [*c* 1, $CHCl_3$]. Reduction of **130** with Lindler's catalyst gave the cis olefin **131** in 99% yield. The broad band at 3385 cm^{-1} and the peaks at 1690 cm^{-1} and 1606 cm^{-1} in the IR spectrum indicated the presence of hydroxyl, carbonyl and olefin functionalities. The ^{1}H NMR spectrum of **131** showed the multiplet at δ 5.50 and at δ 5.71 indicating the presence of the olefin functionality. The ^{13}C spectrum of **131** showed peaks at δ 124.9 and at 135.8 corresponding to the two olefinic carbons, and the carbonyl carbon at δ 169.5. The mass spectrum of **131** showed peak at 440, 424 and at 401 corresponding to molecular ions (M^{+}+K), (M^{+}+Na) and (M^{+}+1). The optical rotation of **131** measured as $[\alpha]_D^{20}$ –38.2 [*c* 0.98, $CHCl_3$]. The secondary hydroxyl group of **131** was converted into its acetate **132** in 92% yield using acetic anhydride/drypyridine in dry CH_2Cl_2. The IR spectrum of **132** showed two peaks at 1754 and at 1722 cm^{-1} corresponding to the carbonyls of Boc and acetyl groups. The ^{1}H NMR spectrum of **132** showed a peak at δ 2.05 for CH_3 protons of the acetate. The olefinic CH protons appeared as multiplets at δ 5.30 and at δ 5.75. The ^{13}C spectrum of **132** showed a peak at δ 20.9 corresponding to methyl carbon of the acetate in addition to the other carbons of the starting material. The mass spectrum of **132** showed the molecular ion peaks at 482, 466, and 444 corresponding to (M^{+}+K), (M^{+}+Na) and (M^{+}+1) ions. The optical rotation was measured as $[\alpha]_D^{20}$ –15.3 [*c* 1.04, $CHCl_3$]. The *t*-butyldimethylsilyl group of **132** was deprotected using TBAF in dry THF to give **133** in 89% yield. The IR spectrum of **133** showed a broad band at 3445cm^{-1}, the characteristic of hydroxy functionality arising out of deprotection of TBDMS.

The ^{1}H NMR spectrum of **133** showed disappearance of peaks corresponding to *t*-butyldimethylsilyl groups indicating the formation of the product. The ^{13}C spectrum of **133** showed disappearance of the carbons of the *t*-butyldimethylsilyl group. The mass spectrum of **133** showed molecular ion peaks at 368, 352, 330 corresponding to (M^{+}+K), (M^{+}+Na) and (M^{+}+1) ions. The optical rotation of **133** was measured as $[\alpha]_D^{20}$ –35.4 [*c* 1.02, $CHCl_3$]. The primary alcohol functionality of **133** was mesylated using methanesulphonyl chloride in presence triethylamine at 0°C to give **134** in 86% yield. The IR spectrum of **134** showed absence of broad band at 3400 cm^{-1} corresponding to the hydroxyl group which indicated the conversion of free hydroxy group into *O*-mesylate compound. The optical rotation of the **134** was measured as $[\alpha]_D^{20}$ + 18.21 The ^{1}H NMR spectrum of **134** showed a peak at δ 2.99 for methyl group of mesyl group of compound. The acetyl protons appeared at δ 2.07. Cyclisation of **134** under acidic condition in dry DCM furnished the required chiral building block **135** in 68% yield. The IR spectrum of **135** indicated a broad peak at 3431 cm^{-1} corresponding to the presence hydroxyl functionality. The ^{1}H NMR spectrum of **135** showed disappearance of acetonide and methanesulphonyl group. The ^{13}C spectrum of **135** showed peaks for the required carbons. The mass spectrum of **135** showed peaks at 294 [M^{+}+Na], 271 (M^{+}), 234 [294-$OCOCH_3$+1], 229 [271-$COCH_3$], 228 [272-$COCH_3$(43)], 212 [271-$OCOCH_3$(59)], 202, 198 [(M^{+}+1)-$CO(CH_3)_3$, (73)], 197 [271-($COCH_3$(43) + CH_2OH (31)], 196 (197-H), 195 (196-H), 190 (294-(*t*-BuO (73) + CH_2OH (31)], 173 (294-*t*-Bu-O-C-(101) and 172 corresponding to all fragmentation possibilities which further confirm the formation of the target compound **135**. The optical rotation of the compound was measured as $[\alpha]_D^{25}$ +17.44 [c,1, $CHCl_3$].

5.3.3 Conclusion:

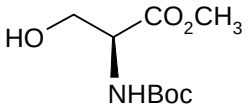
In conclusion, we have developed a simple, short and efficient route to the important chiral building which can be easily transformed into various polyhydroxy piperidine alkaloids.

5.3.4 Experimental Section

General information

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use. ^{1}H NMR spectra were recorded on 200 MHz, 300 MHz, NMR machine and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Optical rotations were measured using sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on ALI MATTISON RS-1 FT-IR spectrometer. Mass spectra were obtained with a Finnigan LCMS mass spectrometer. Elemental analysis were carried out on Carlo Erba CHNS-O analyzer. Column chromatography was performed on silica gel (60-120 mesh) using a mixture of petroleum ether and ethyl acetate as eluent.

Preparation of (2S)-2-*tert*-butoxycarbonyl amino-3-hydroxypropionic acid methyl ester (106)



106

A solution of di-*tert*-butyldicarbonate (24.93 g, 114.22 mmol) in dioxane (90 ml is added to an ice cold solution of *L*-serine (10.0g, 95.24 mmol) in 1*N* NaOH (7.61 g, in 190 ml of water) by means of an addition funnel. The two phase mixture is stirred at 5°C for 30 min., then allowed to warm to room temperature over 3.5 h at which TLC analysis shows the reaction to be complete. The mixture is concentrated to half of its original volume at 35°C, cooled in an ice bath, acidified to pH 2-3 by the slow addition of 1N $KHSO_4$ and then extracted with EtOAc (3 x 150 ml). The combined extracts were dried over anhy.Na_2SO_4, filtered and concentrated to give 18.7 g, (95% crude yield) of *N*-Boc-*L*-serine **106** as colorless, sticky foam which was used without further purification.

To an ice cold solution of *N*-Boc-*L*-serine (18.7 g, 95.01 mmol) in DMF (160 ml) was added solid K_2CO_3 (14.0 g, 101.44 mmol). After stirring for 10 min. in an ice bath, methyl iodide (26 g, 183.1 mmol) was added to the white suspension and stirring continued at 0°C for 30 min, where upon the mixture solidifies. The reaction is warmed to room temperature and stirred for additional 1 h or so at which point TLC analysis indicated complete formation of the methyl ester. The reaction mixture was filtered by suction and the filtrate partitioned between EtOAc and water. The organic phase was washed with brine, dried filtered and concentrated. Silica gel column chromatography of the crude product using petroleum ether: EtOAc (3:7) as eluent gave *N*-Boc-*L*-serine methyl ester **106** (17.13 g, 84%) as a thick liquid.

Yield: 17.13 g, 84% (2 steps)

$[\alpha]_D^{20}$: –17.15 (*c*, 5.0, MeOH) {Lit. $[\alpha]_D^{25}$ -17.5 (*c*, 5.0 MeOH)}

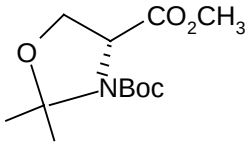
IR ($CHCl_3$ cm^{-1}): ν_{max} 3472, 3345, 1733, 1640, 1512, 1432, 1213

^{1}H NMR (300 MHz, $CDCl_3$): δ1.42 (s, 9H), 3.65-3.69 (m, 1H), 3.75 (s, 3H), 3.84-3.97 (m, 2H), 4.35 (brs, 1H)

13C NMR (125 MHz, $CDCl_3$): δ 28.1, 52.3, 55.6, 62.7, 80.0, 155.9, 171.5

Analysis calcd for $C_9H_{17}NO_5$(219.24): Found C 49.41, H 7.72, N 6.38{ Required C 49.30, H 7.80, N 6.42}

Preparation of (*S*)-2,2-Dimethyl oxazolidine-3,4-dicarboxylic acid 3-*tert*-buty ester 4-methyl ester (107)



107

To a solution of ester **106** (17 g, 82.12 mmol) in dry benzene (200 ml) was added 2,2-dimethoxy propane (12.81 g, 123.18 mmol) and TSOH (50 mg). The colorless solution was heated under reflux (110°C for 15 h). After completion of reaction, the reaction was cooled down to room temperature and concentrated to half of its volume. The reaction mixture was then partitioned between saturated $NaHCO_3$ (50 ml) and diethyl ether (150 ml). The organic layer is washed with brine, dried (Na_2SO_4), filtered and concentrated to give the crude product

as amber oil. Silica gel chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave **107** as colourless oil.

Yield: 17.85 g, 88%

$[\alpha]_D^{20}$: – 56.1 (*c*, 1.03, $CHCl_3$) {Lit.[67] $[\alpha]_D^{20}$ –57.0 [*c*, 1]}

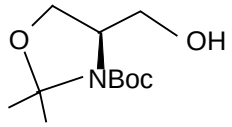
IR ($CHCl_3$, cm^{-1}): ν_{max} 3007, 2952, 2815, 1728, 1717, 1510, 1477

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38(s, 9H), 1.46(s, 6H), 3.72(s, 3H), 3.96-4.09(m, 2H), 4.32-4.46(m, 1H)

Analysis calcd for $C_{12}H_{21}NO_5$(259.3): Found C 55.83, H 7.95, N 5.21{Required C 55.59, H 8.16, N 5.40}

The spectroscopic data were in agreement with those reported.

Preparation of (2*S*)-4-Hydroxymethyl-2-2-dimethoxy-oxazolidine-3-carboxylic acid *tert*-butyl ester (109)



109

To a suspension of LAH (2.16 g, 57.0 mmol) in dry THF (100 ml) was added dropwise with vigorous stirring the compound **107** (9.91, 38.20 mmol) in dry THF at 0°C, over a period of 30 min. under N_2 atmosphere. The stirring is continued for 5 h at 0°C. After completion of the reaction the reaction mixture was quenched with 0.1N solution of NaOH and stirred for 1 h and filtered through celite. The filtrate after washing with phosphate buffer, was added to water and extracted with dichloromethane (3 x 100 ml) and dried over anhyd. Na_2SO_4. After removal of solvent and purification through silica gel column chromatography gave **109** (8.28 g, 93%) as colorless thick syrup which solidified after cooling. m.p. 33-35°C [Reported 35-38°C].

Yield: 93%

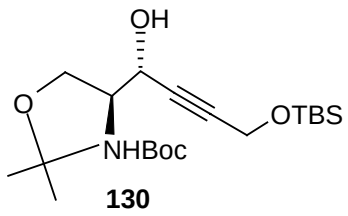
Colorless Syrup

$[\alpha]_D^{20}$: –23.4 (*c* 1, $CHCl_3$) {Lit.[73] $[\alpha]_D^{20}$ -23.9; *c* 1}

IR ($CHCl_3$ cm^{-1}): ν_{max} 3417,(brs), 3007, 2901, 1743, 1722, 1512, 1433,

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39(s, 9H), 1.48(s, 6H), 3.98-4.14(m, 4H), 4.40-4.48(M, 1H).

Preparation of 4-[4-(*tert*-Butyldimethylsilanyloxy)-1-hydroxy-but-2-ynyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester(130)



130

To a cooled (-78°C) stirred solution of oxalyl chloride [$(COCl)_2$, 6.58 g, 51.85 mmol)] in dry CH_2Cl_2 (75 ml) was added DMSO (8.10 g, 103.71 mmol) over 25 min. At the end of the addition, the mixture was allowed to warm to -60°C over a period of 20 min; then a solution of the crude *L*-serinol **109** (8.0 g, 34.57 mmol), was added dropwise over 50 min. The mixture was warmed to -45°C over 30 min., then a solution of *N*,*N*-diisopropylethyl amine (36 ml, 207 mmol) in CH_2Cl_2 (5 ml) was slowly added. The cooling bath was removed and the mixture was allowed to warm to 0°C over 10 min. and then transferred to separating funnel charged with ice-cold 1N HCl solution (130 mmol). The two phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 x 50 ml) and the combined organic phases were washed with aqueous phosphate buffer (pH 7, 4 x 80 ml), then dried (Na_2SO_4) and concentrated under reduced pressure to give the Garner's aldehyde **39** (7.90 g, 99.1% crude yield) as a clear yellow oil which is used for further reaction without purification.

A 250 ml flack containing tert-butyldimethylsilyl propargyl ether (10.41 g, 61.13 mmol) and toluene (100 ml) was cooled under argon -78°C, and then n-butyllithium (1.6 M in toluene 37.1 ml, 59.30 mmol) was added followed by HMPA (1.8 M in 10.37 ml, 59.57 mmol). The stirring was continued for another 2 h, then the solution of the protected serinal (7.9 g, 34 mmol) in toluene (30 ml) was added dropwise. After 3 h, the reaction mixture was allowed to warm to room temperature and after an additional 1 h of stirring it was poured into 1 M aqueous NaH_2PO_4 (20 mL). It was then extracted with ethyl acetate (3 x 100 ml), and the organic layer was worked up in a usual manner to yield 14.0 g of the adduct **130** (92% of

crude product) which after column chromatography using petroleum ether: ethyl acetate (95:5 to 85:15) afforded **130**, 12.3 g of anti and 0.70 g of syn product was obtained.

Pale Yellow Oil

$[\alpha]_D^{20}$: - 41.1 [*c*, 1, $CHCl_3$] {lit.[84] $[\alpha]_D^{20}$ - 40.7 (*c*, 1.2, $CHCl_3$)}

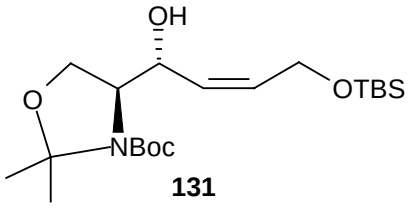
IR (Neat, cm^{-1}): ν_{max} 3447, 2310, 2207, 1734, 1695, 1472, 1368, 1252

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.89, (s, 9H), 1.50 (s, 12H); 1.60 (s, 3H), 1.72(brs, 1H), 3.87-3.97 (m, 1H), 4.00-4.10 (m, 1H), 4.10-4.19 (m, 1H), 4.34 (s, 2H), 4.58 (m, 0.5H), 4.81 (m, 0.5 H), 4.81 (m, 0.5 H)

^{13}C NMR (500 MHz, $CDCl_3$): δ -5.8, 17.9, 25.5, 26.7, 62.3, 63.4, 77.6, 79.4, 95.8, 108.7, 180.5

Mass: 439 (M^++K), 423 (M^++Na), 400 (M^+), 382, 345, 289

Preparation of 4-[4-(*tert*-Butydimethylsilanyloxy)-1-hydroxy-but-2-enyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester(131)



131

A solution of **130** (2 g, 5 mmol) and Lindler's catalyst (25 mg) in anhydrous ethyl acetate (50ml) was stirred under H_2 atmosphere for 6 h. After completion of the reaction, the reaction mixture was filtered under celite and concentrated to give **131** (2 g, 99.5%) as pale yellow oil.

Pale Yellow Oil.

$[\alpha]_D^{20}$: -38.19 [*c*, 0.98, $CHCl_3$]

IR (Neat, cm^{-1}): ν_{max} 3385, 3019, 2400, 1690, 1503, 1472, 1392, 1368, 1255, 1215

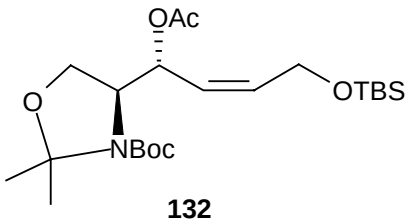
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.85 (s, 9H), 1.47 (s, 12H), 1.54 (s, 3H), 3.25-4.17 (m, 4H), 4.20-4.38 (m, 2H), 4.60 (s, 1H), 5.45- 5.56 (m, 1H), 5.65-5.75 (m, 1H).

13C NMR (75 MHz, CDCl3): δ 5.40(2C), 18.1(2C), 20.9, 25.8(3C), 28.3(4C), 59.6, 63.8, 68.8, 69.4, 80.3, 94.5, 124.9, 135.8, 152.4, 169.5

Mass: 440 (M^++K), 424 (M^++Na), 402 (M^+) 358, 301

Analysis calcd for $C_{20}H_{39}NO_5Si$ (401.758): Found C, 59.80; H, 9.20; N, 4.21{Required C, 59.56; H, 9.31; N, 4.40}

Preparation of 4-[1-Acetoxy-4-(*tert*-butyldimethylsilanyloxy)-but-2-enyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester(132)



132

To an ice cold stirring solution of compound **131** (1.8 g, 4.47 mmol) was added pyridine (0.32 ml, 3.7 mmol) and acetic anhydride (332 mg, 0.21 ml, 2.3 mmol) in 50 ml of dry CH_2Cl_2 and stirring was continued for 12 h. After the reaction completion, the reaction mixture was poured into 50 g of crushed ice. The organic layer after separation, was washed with dilute solution of $CuSO_4$. After drying over anhydrous Na_2SO_4 and concentration, the crude product was purified through silica gel column chromatography using petroleum ether: EtOAc (90:1; as eluent) to give compound **132** (1.62 g, 82%) as pale yellow oil.

Pale Yellow Oil.

$[\alpha]_D^{20}$: –15.26 [*c*, 1.04, $CHCl_3$]

IR (Neat, cm^{-1}): ν_{max} 3016, 1754, 1722, 1471, 1406, 1389, 1362, 1216, 1256, 1152, 1103

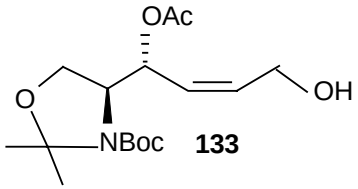
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.89 (s, 9H), 1.48 (s, 12H), 1.56 (s, 3H), 2.05 (s, 3H), 3.60-4.10 (m, 4H), 4.25-4.55 (m, 2H), 5.24-5.41 (m, 1H), 5.65 – 5.89 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 5.40, 18.1, 20.9, 25.6, 25.8, 28.3, 29.5, 59.6, 63.8, 68.8, 69.4, 80.3, 94.5, 124.9, 135.8, 152.4, 169.5

Mass: 482 (M^++K), 466 (M^++Na), 444 (M^++1), 343

Analysis calcd for $C_{20}H_{38}NO_5Si$ (443.653): Found C, 59.80; H, 9.31; N, 4.75{Required C, 59.56; H; 9.13; N, 4.40}

Preparation of 4-(1-Acetoxy-4-hydroxy-but-2-enyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester(133)



133

A mixture of compound **132** (1.40 g, 3.16 mmol) and TBAF (140 mg) in 25 ml of dry THF is stirred together at 0°C for a time period of 9 h under N_2 atmosphere. After completion of the reaction, it was quenched with water and concentrated to remove THF. The remaining aqueous phase was extracted with EtOAc (3 x 50 ml) to give crude compound **133**. Purification by silica gel column chromatography using petroleum ether: EtOAc (85:15) as eluent gave **133** (0.88 g, 85%) as colorless oil.

$[\alpha]_D^{20}$: – 35.36 [*c*, 1.02, $CHCl_3$]

IR (Neat, cm^{-1}): ν_{max}3401, 2989, 1742, 1716, 1475, 1375

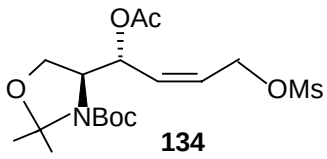
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46(s, 15H), 1.48(brs, 1H), 2.02(s, 3H), 3.90-4.38(m, 4H), 4.66-4.82(m, 2H), 5.62-5.66(m, 1H), 5.76-5.87(m, 1H)

^{13}C NMR (200 MHz, $CDCl_3$): δ 20.8, 26.4, 28.2, 60.3, 64.4, 68.7, 69.3, 80.9, 94.3, 126.5, 129.4, 170.8

Mass: 368(M^++K), 352(M^++Na), 330(M^++1), 274, 263, 246

Analysis calcd for $C_{17}H_{27}NO$ (329.39): Found C, 58.23; H, 8.03; N, 4.05 {Required C, 58.34; H, 8.26; N, 4.25}

Preparation of 4-(1-Acetoxy-4-methanesulfonyloxy-but-2-enyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester(134)



134

To a stirring ice cold solution of **133** (0.6 g, 1.82 mmol) and pyridine (1.27, 9.1 mmol) in anhydrous CH_2Cl_2, methanesulphonyl chloride (0.472 ml, 5.47 mmol) was added. The stirring was continued for 7 h. After completion of the reaction it was quenched with water and extracted with CH_2Cl_2 (3 x 25 ml), washed with $CuSO_4$ and brine solution, and dried over anhydrous Na_2SO_4. After concentration the crude product was passed through silica gel column chromatography to give **134** (0.64g, 86%) as pale yellow oil.

Yellow oil.

$[\alpha]_D^{20}$ + 18.21(*c*, 1.04; $CHCl_3$)

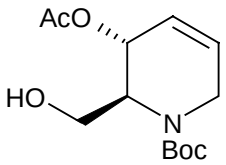
IR (Neat, cm^{-1}): ν_{max} 3012, 2973, 1737, 1713, 1608, 1556, 1375, 1215

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49(s, 12H), 1.51(s, 3H), 2.07(s, 3H), 2.99(s, 3H), 3.74(d, 2H, *J* = 6 Hz), 4.00(m, 1H), 4.13(d, 2H, *J* = 6Hz), 4.22(m, 1H), 5.51(m, 1H), 5.81(m, 1H)

Mass: 408(M^++1), 330(M^++1- SO_2CH_3), 316(M^+- OSO_2CH_3), 310(M^+ - COO^tBu), 301, 296, 272, 250, 217

Analysis calcd for $C_{17}H_{29}NO_8S$ (407.543): Found C, 50.34; H, 6. 95; N, 3.19 {Required C, 50.10; H, 7.19; N, 3.44}

Preparation of 3-Acetoxy-2-hydroxymethyl-3, 6-dihydro-*2H*-pyridine-1-carboxylic acid *tert*-butyl ester (135)



135

A solution of **134**(0.4g, 0.00098 mmol) in dry CH_2Cl_2 and *p*-TSA (20mg, 0.000116 mmol) were stirred together at 0° C for 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction the reaction mixtire was washed with water and brine solution, dried over anhydrous Na_2SO_4 and concentrated to give crude product, which after coloumn chromatography using petroleum ether : EtoAc (75 : 25) as eluent to give **135(** 0.182mg, 68%) as pale yellow oil

Pale yellow oil.

$[\alpha]_D^{20}$: + 17.44 (c, 1.05; $CHCl_3$)

IR (Neat, cm^{-1}): ν_{max} 3465(br), 3014, 2976, 2815, 1738, 1719, 1597, 1452, 1372, 1125.

^{1}H NMR (200MHz, $CDCl_3$): δ 1.48(s, 9H), 2.06(s, 3H), 3.94(m, 2H), 4.10-4.30(m, 4H), 5.47(q, 1H, *J* = 6.2Hz), 5.79(m, 2H)

^{13}C NMR (200MHz, $CDCl_3$): δ 21.1, 28.3, 39.0, 59.4, 63.8, 68.9, 80.9, 128.2, 130.4, 152.3, 169.9

Mass: 294(M^++Na), 272(M^++1), 234(294 - CH3COO), 229(M^++1 – $COCH_3$), 228(271-$COCH_3$), 212((M^+ - $OCOCH_3$), 203, 202, 197, 196, 195, 190, 173, 172

Analysis calcd for $C_{13}H_{21}NO_5$ (271.31): Found C, 57.43; H, 7.67; N, 4.95{Required C, 57.55; H, 7.80; N, 5.16}

5.4 Spectra

1.^{1}H NMR spectrum of 130

2. ^{13}C NMR spectrum of 130

3. ^{1}H NMR spectrum of 131

4. ^{13}C NMR spectrum of 131

5. ^{1}H NMR spectrum of 132

6. ^{13}C NMR spectrum of 132

7. ^{1}H NMR spectru of 133

8. ^{13}C NMR spectrum of 133

9. ^{1}H NMR soectrum of 134

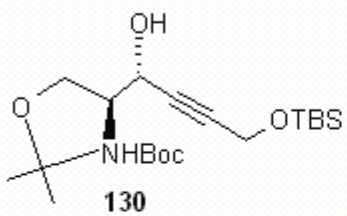
10. Mass spectra of 134

11.^{1}H NMR spectrum of 135

12. ^{13}C NMR spectrum of 135

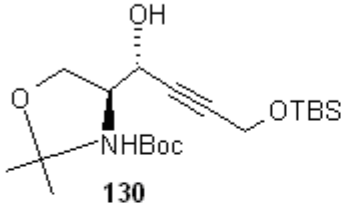
13. Mass spectra of 135

^{1}H NMR spectrum of **130**

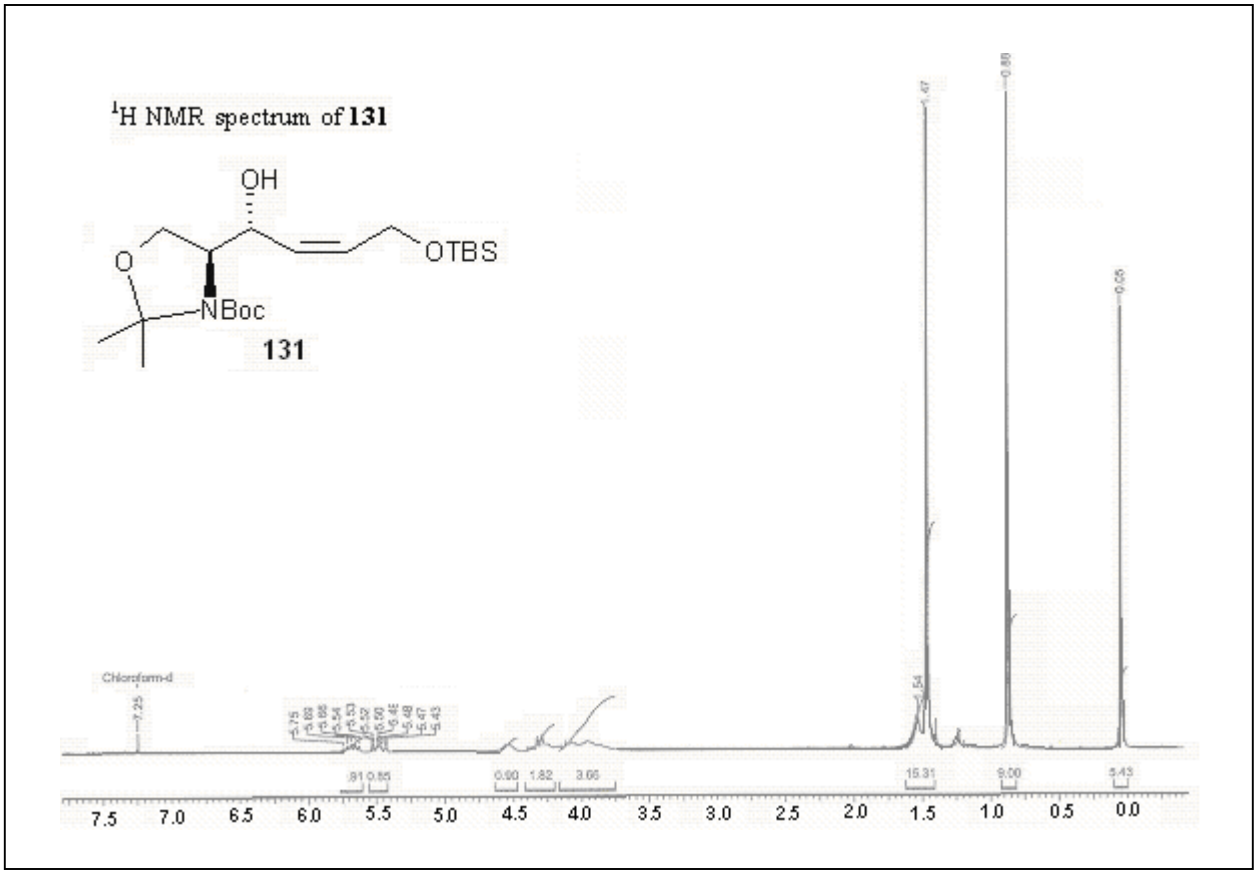


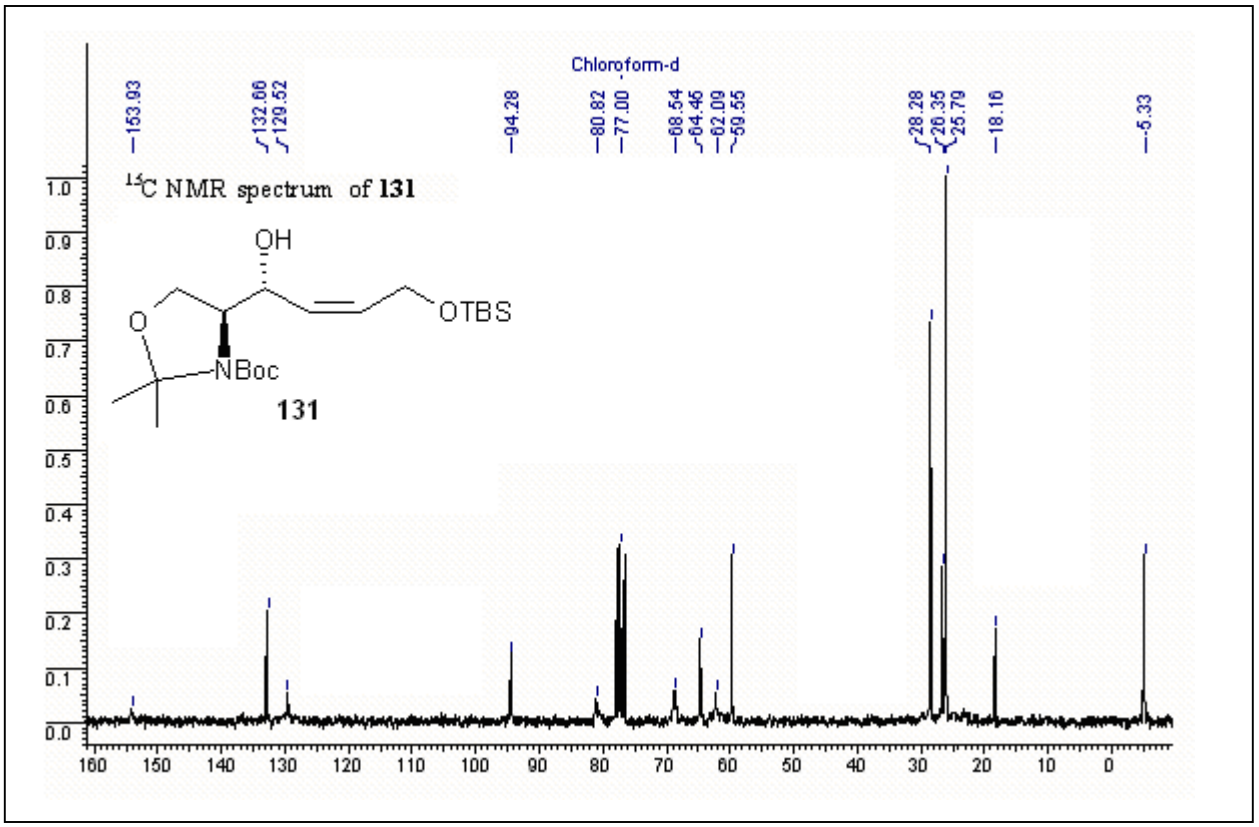
130

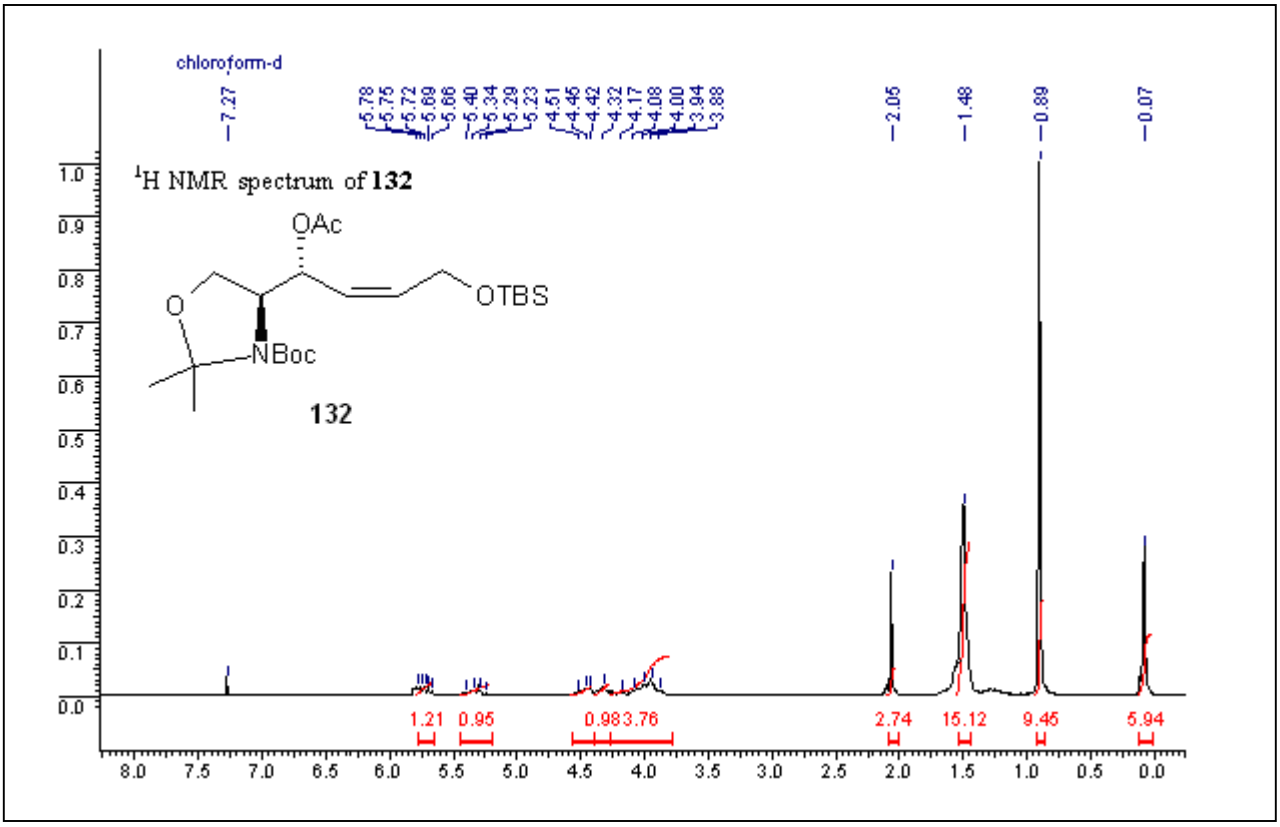
^{13}C NMR spectrum of **130**

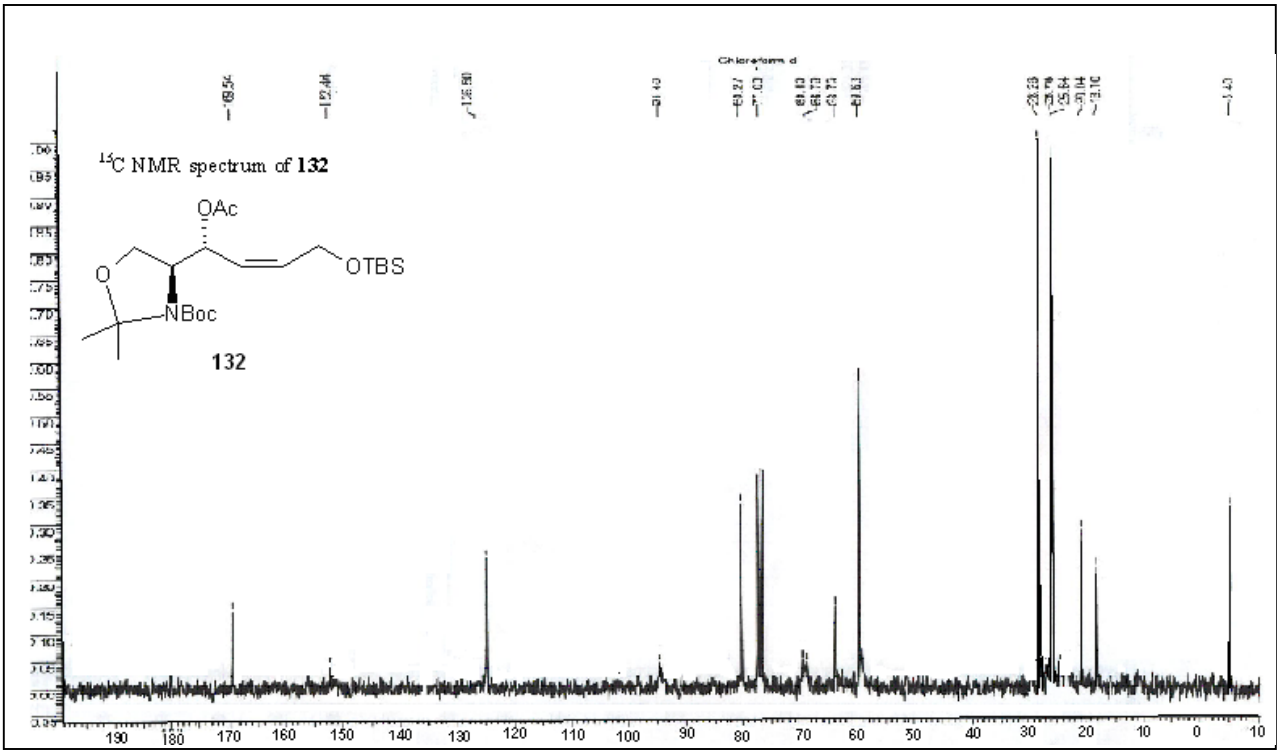


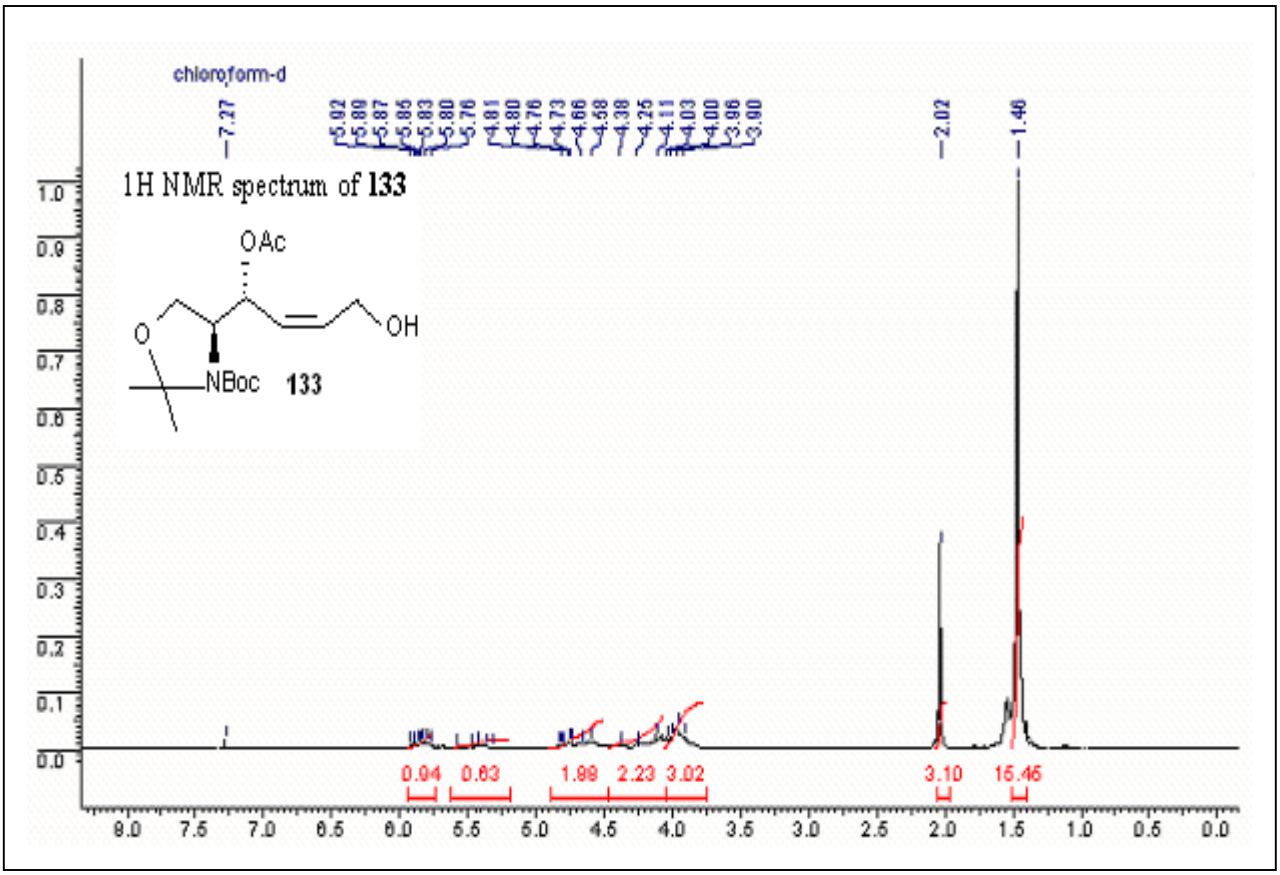
130

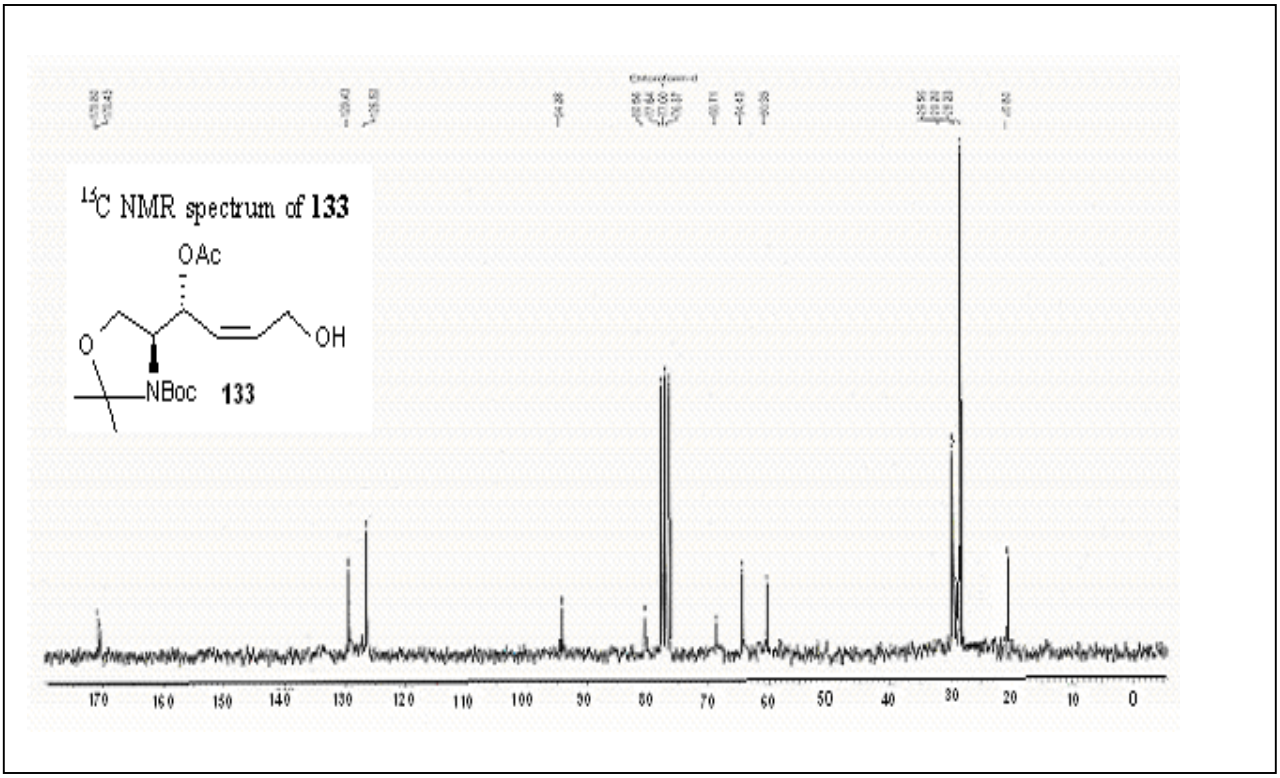

^{1}H NMR spectrum of **131**
OH
OTBS
O
NBoc
131
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

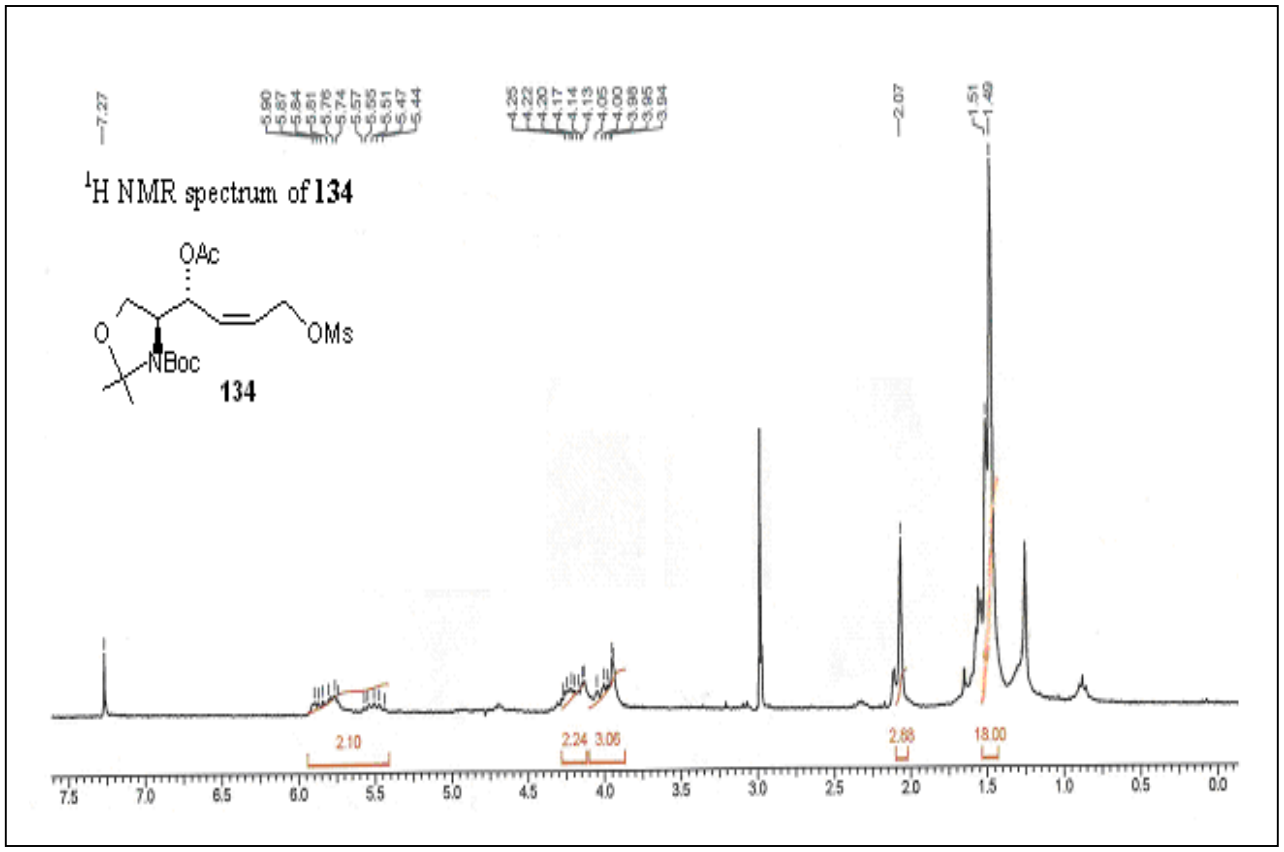

Chloroform-d
153.93
132.66
129.52
94.28
80.82
77.00
68.54
64.46
62.09
59.55
28.28
26.35
25.79
18.16
-5.33
^{13}C NMR spectrum of **131**
OH
OTBS
O
NBoc
131
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

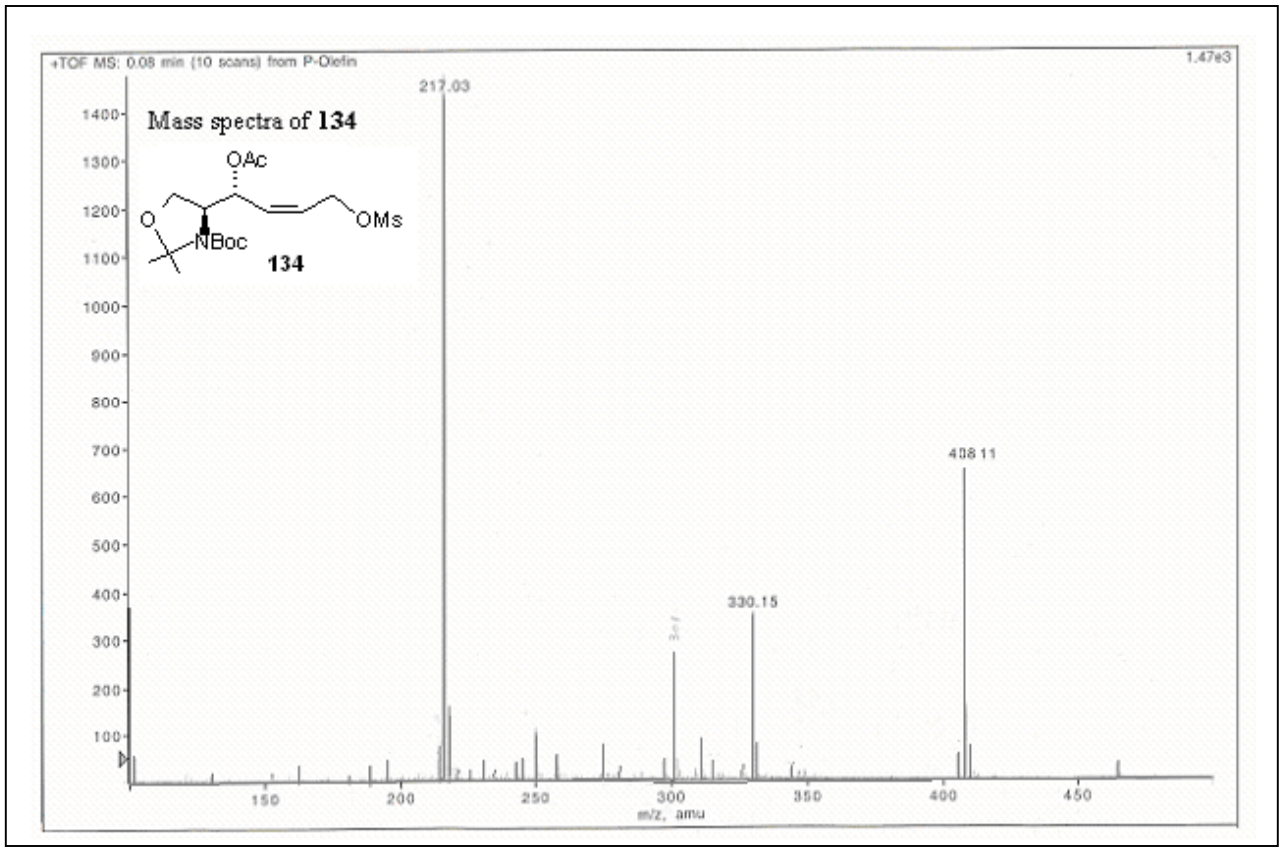

chloroform-d
7.27
5.78
5.75
5.72
5.69
5.66
5.40
5.34
5.29
5.23
4.51
4.46
4.42
4.32
4.17
4.08
4.00
3.94
3.88
2.05
1.48
0.89
0.07
^{1}H NMR spectrum of **132**
OAc
OTBS
O
NBoc
132
1.21
0.95
0.98
3.76
2.74
15.12
9.45
5.94


^{13}C NMR spectrum of **132**
OAc
OTBS
O
NBoc
132

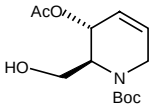

chloroform-d
1H NMR spectrum of 133
OAc
OH
O
NBoc
133
0.94
0.83
1.99
2.23
3.02
3.10
15.46

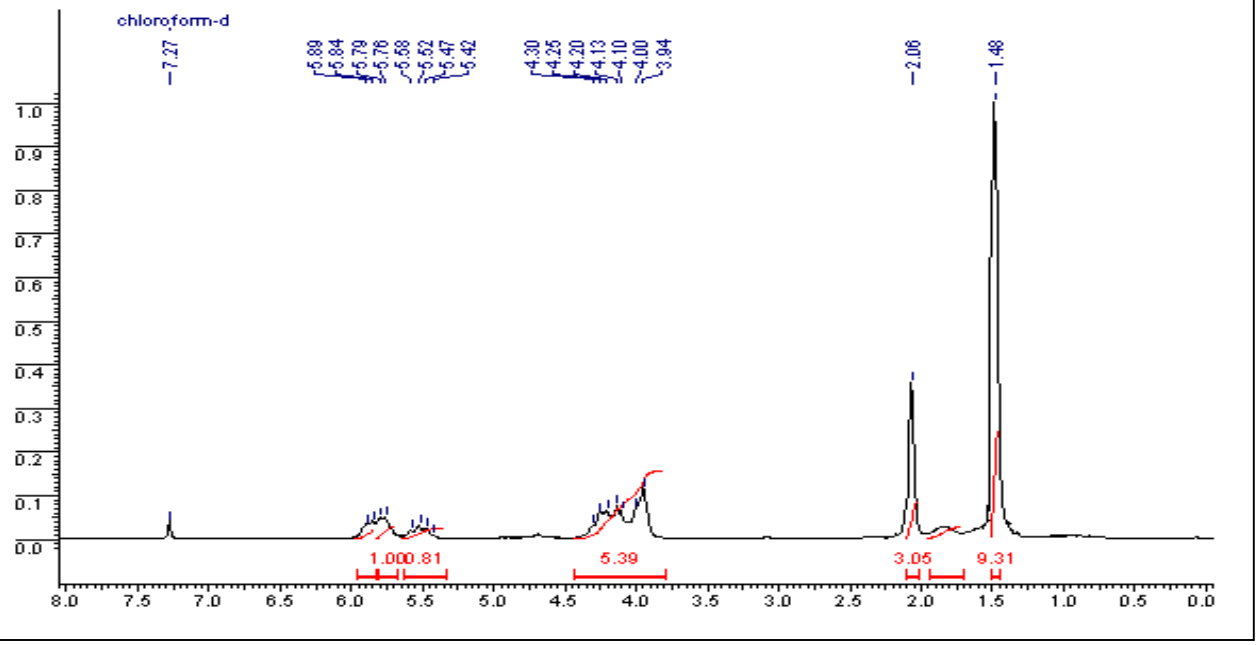

13C NMR spectrum of 133
OAc
OH
O
NBoc
133


^{1}H NMR spectrum of **134**
OAc
OMs
NBoc
O
134
7.27
5.90
5.87
5.84
5.81
5.78
5.74
5.57
5.55
5.51
5.47
5.44
4.25
4.22
4.20
4.17
4.14
4.13
4.05
4.00
3.98
3.95
3.94
2.07
1.51
1.49
2.10
2.24
3.06
2.68
18.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

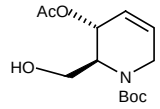

+TOF MS: 0.08 min (10 scans) from P-Olefin
1.47e3
Mass spectra of **134**
OAc
OMs
NBoc
O
134
217.03
408.11
330.15
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
150
200
250
300
350
400
450
m/z, amu

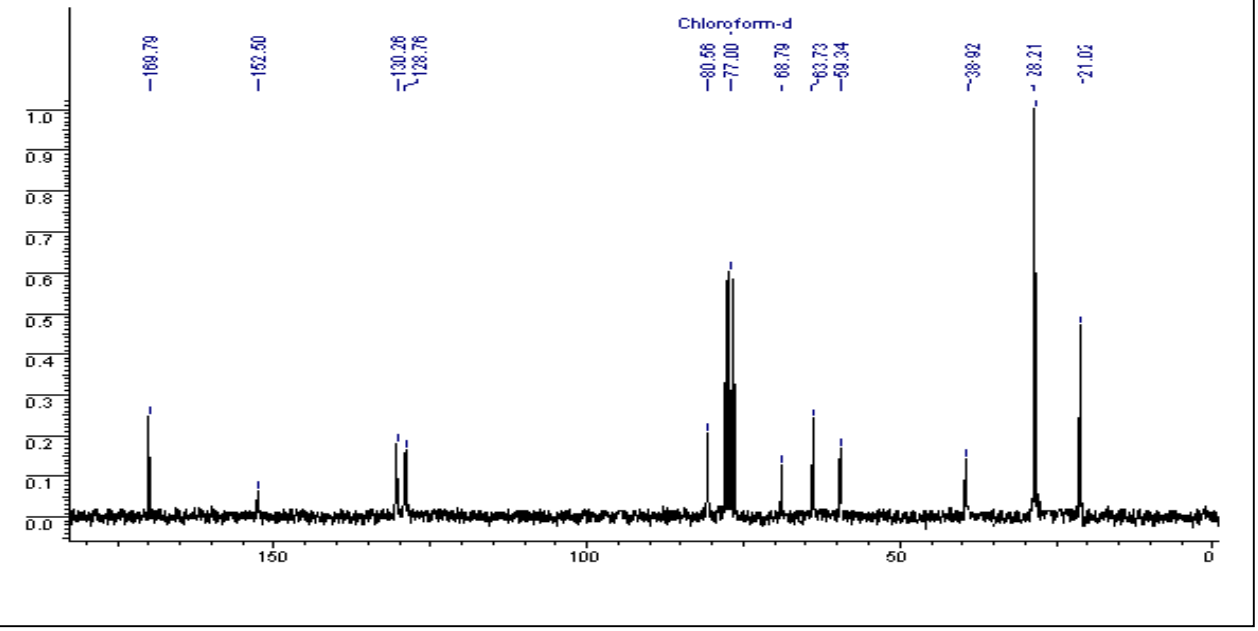
^{1}H NMR spectrum of **135**

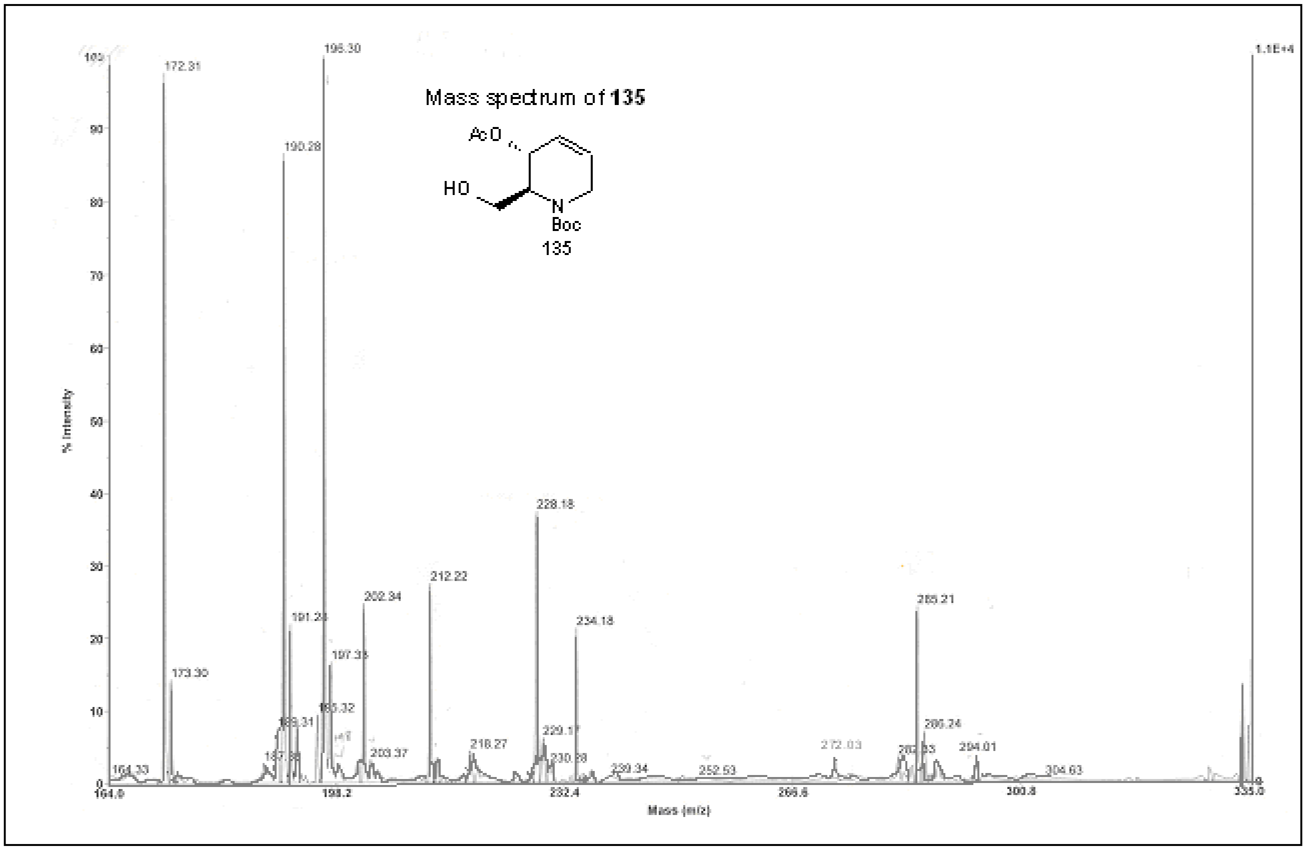




^{13}C NMR spectrum of **135**







Mass spectrum of 135
AcO
HO
N
Boc
135
% Intensity
Mass (m/z)
172.31
196.30
190.28
228.18
212.22
202.34
234.18
285.21
1.1E+4

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GENERAL REMARKS

1. All melting points and boiling points temperature are in centrigrade scale.

2. The compound numbers, scheme numbers and reference numbers given in each chapter refer to that particular chapter only.

3. All solvents were distilled prior to use. Petroleum ether refers to the fraction collected in boiling range 60-80°C

4. Organic layers were dried over anhydrous sodium sulfate.

5. TLC analyses were carried out on glass plate using silica gel, GF – 254 and the plates were developed in iodine stain.

6. In case where chromatographic separations were done, SiO_2 were used as the stationary phase.

7. The IR spectra were recorded on Perkin-Elmer spectrophotometer 683B or 1605FT-IR and adsorptions are expressed in cm^{-1}.

8. The ^{1}H and ^{13}C-NMR spectra were recorded on Brucker AC-200, MSL-300, DRX-500 MHz instruments using trimethyl siliane as the internal standard. The following abbreviations were used s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet and dd = doublet of doublet.

9. The mass spectra were recorded on Finnigan MAT-1020-B-7ev and mass spectrometer.

10. The optical rotations were done in Carlo ERBA EA110 B instrument.

G L O S S A R Y

Ac	Acetyl
Ac_2O	Acetic anhydride
aq.	Aqueous
AD	Asymmetric dihydroxylation
Ar	Aryl
BP	Boiling point
Boc_2O	Bi-*tert*-butyl dicarbonate
t-Bu	*tert*-Butyl
Bn	Benzyl
$CDCl_3$	Deuterated chloroform
D_2O	Deuterium oxide
$(DHQ)_2$-PHAL	1,4-Bis(dihydroquinin-9-*O*-yl)-phthalazine
$(DHQD)_2$-PHAL	1,4-Bis(dihydroquinin-9-*O*-yl)-phthalazine
DMAP	N,N-(Dimethylamino)pyridine
DMSO	Dimethylformamide
ee	Enantiomeric excess
EIMS	Electron impact mass spectrum
eq.	Equivalent
Et	Ethyl
EtOH	Ethyl alcohol
EtOAc	Ethyl acetate
Et_3N	Triethyl amine
gm	Grams
H	Hours
Hz	Hertz
IR	Infrared

LDA	Lithium diisopropulamide
ml	Milliliter
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligram
mmol	Millimol
min	Minutes
M.P.	Melting point
M+	Molecular ion
MS	Mass spectrum
NMR	Nuclear magnetic resonance
Pet. Ether	Petroleum ether
Ph	Phenyl
Piv.	Pivaloyl
Py	Pyridine
p-TSA	p-Toluene sulfonic acid
rt	Room temperature
SAD	Sharpless asymmetric dihydroxylation
TBDMS	Tert-Butyl dimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	p-Toluene sulfonyl

ABSTRACT

The thesis entitled **"Synthetic studies towards bioactive molecules using asymmetric dihydroxylation and organic transformations using yttria-zirconia and other heterogeneous catalyst"** is divided into five chapters.

Chapter 1: Explains briefly the various aspects of Sharpless asymmetric dihydroxylation (AD) reaction.

Chapter 2: Covers the application of Sharpless asymmetric dihydroxylation to the synthesis of enantiomerically pure octopamine, tembamide, aegeline, denopamine and arbutamine and is further divided into four sections.

Chapter 3: Constitutes the synthesis and characterization of heterogeneous palladacyclic catalyst and its application to C-C bond forming reactions (Heck, Suzuki, Sonogashira, Stille) and allylation of carbonyls and imines and is divided into three sections.

Chapter 4: Deals with the synthesis and characterization of sulphated yttrium based Lewis acid and its application to C-C bond forming and other reactions (Biginelli reaction, Mannich reaction, acylation of activated aromatics and synthesis of α-amino phsophonates) and is further divided into two sections.

Chapter 5: Includes studies towards the synthesis of six membered aza-compound, an important building block for variety of polyhydroxylated compounds of biological interest.

Chapter 1:

This chapter gives a brief introduction to Sharpless asymmetric dihydroxylation (AD) reaction. A catalytic asymmetric reaction provides an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents. Especially useful is the carbon-heteroatom bond forming reactions, since the resulting functionality can be readily

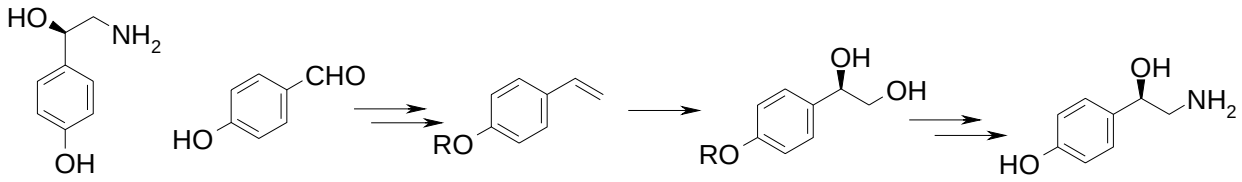
manipulated to produce many important classes of compounds. The AD reaction is one such reaction developed in early 1990.[1] It has evolved as one of the most powerful methods for enantioselective oxidation of olefins to optically active vicinal diols that are versatile and convenient building blocks in the synthesis of bioactive compounds.

Chapter 2:

In our synthetic endeavors we have employed the chiral diol compounds obtained by AD reaction towards the synthesis of some bioactive compounds. Thus, this chapter describes the application of Sharpless asymmetric dihydroxylation (AD) reaction to the synthesis of enantiopure *(R)*-(-)-octopamine *(R)*-(-)-tembamide, *(R)*-(-)aegeline, *(R)*-(-)-denopamine and *(R)*-(-)-arbutamine. This chapter is further divided into four sections.

SECTION A : Enantioselective synthesis of *(R)*-(-)-octopamine:

(R)-(-)-Octopamine, **1** is a potent chiral drug possessing β-adrenergic activity.[2] Recent studies have revealed that two enantiomers of a chiral drug usually display different biological activities.[3] and in most of the aryl ethanolamine drugs, the biological activity resides mainly in the *(R)*-enantiomer.[4] We have developed a short and efficient route for the synthesis of *(R)*-(-)-octopamine employing AD reaction as the key step (Scheme 1).



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

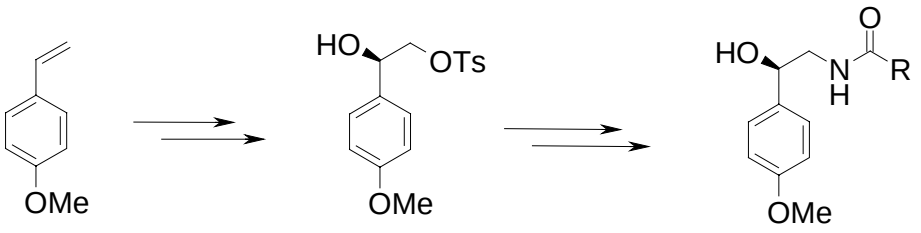
SCHEME -1

Thus, the asymmetric dihydroxylation of styrene 3 to the diol 4 followed by selective conversion of OH group into a tosylate and nucleophilic displacement with azide and subsequent reduction provided the target compound **1**.

Thus, a practical and highly enantio-selective synthesis of **1** has been achieved for the first time using AD as the source of chirality.

SECTION B: Enantioselective synthesis of *(R)*-(-)-tembamide and *(R)*-(-)-aegeline

(R)-(-)-Tembamide **5a** and *(R)*-(-)-aegeline **5b** are naturally occurring hydroxyamides isolated from various members of the family Rutaceae.[5] These hydroxyamides have been reported to have adrenaline-like and insecticidal activity[6] and extracts of Aegle marmelas corr., which contains tembamide **5a**, have been used in traditional Indian medicines and show hypoglycemic activity.[7] Our synthetic strategy features a Sharpless asymmetric dihydroxylation route to tembamide and aegeline (Scheme 2).



6 **7** **5**

5a : R =Ph, Tembamide

5b : R=(*E*)-Ph-CH=CH- , Aegeline

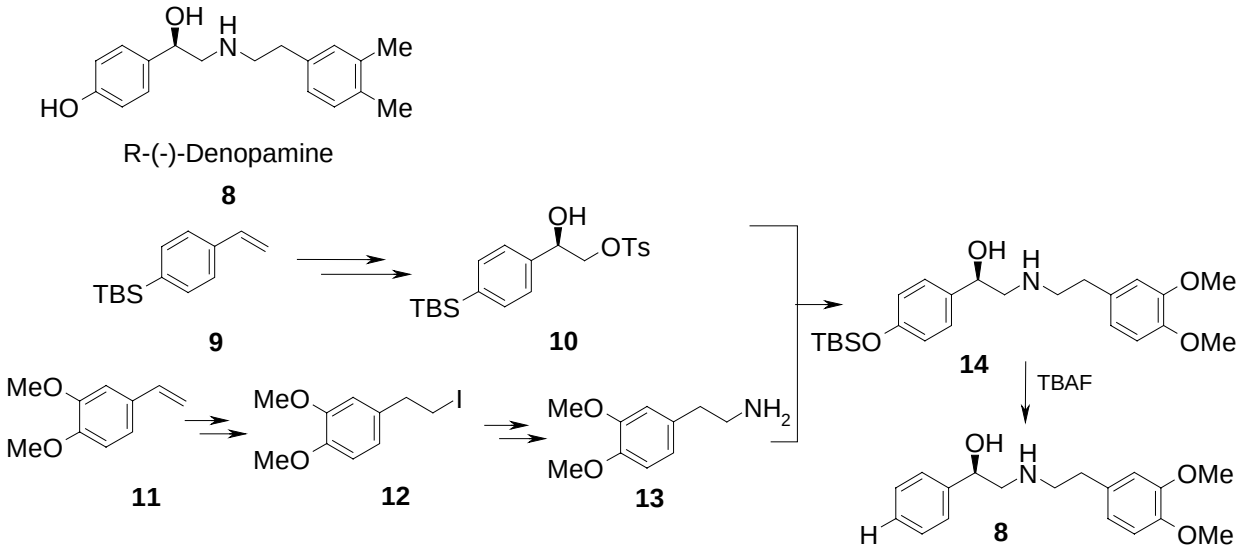
SCHEME - 2

Tembamide and aegeline were prepared by dihydroxylation of p-methoxy styrene and subsequent conversion of primary hydroxy group into amino followed by its acylation to afford the target compound **5a, 5b**.

SECTION C :

This section describes the enantioselective synthesis of *(R)*-(-)denopamine **8** using Sharpless asymmetric dihydroxylation. Denopamine, *(R)*-(-)-α-[(3,4-dimethoxyphenyl)-amino] methyl-4-hydroxybenzyl alcohol was the first orally active and long acting positive inotropic agent with a selective β-adrenoreceptor agonistic activity.[8] Potent positive inotropic activity was found to reside only in *(R)*-(-)-isomer. It is effective in the treatment of congestive heart failure.[9]

(Scheme 3)



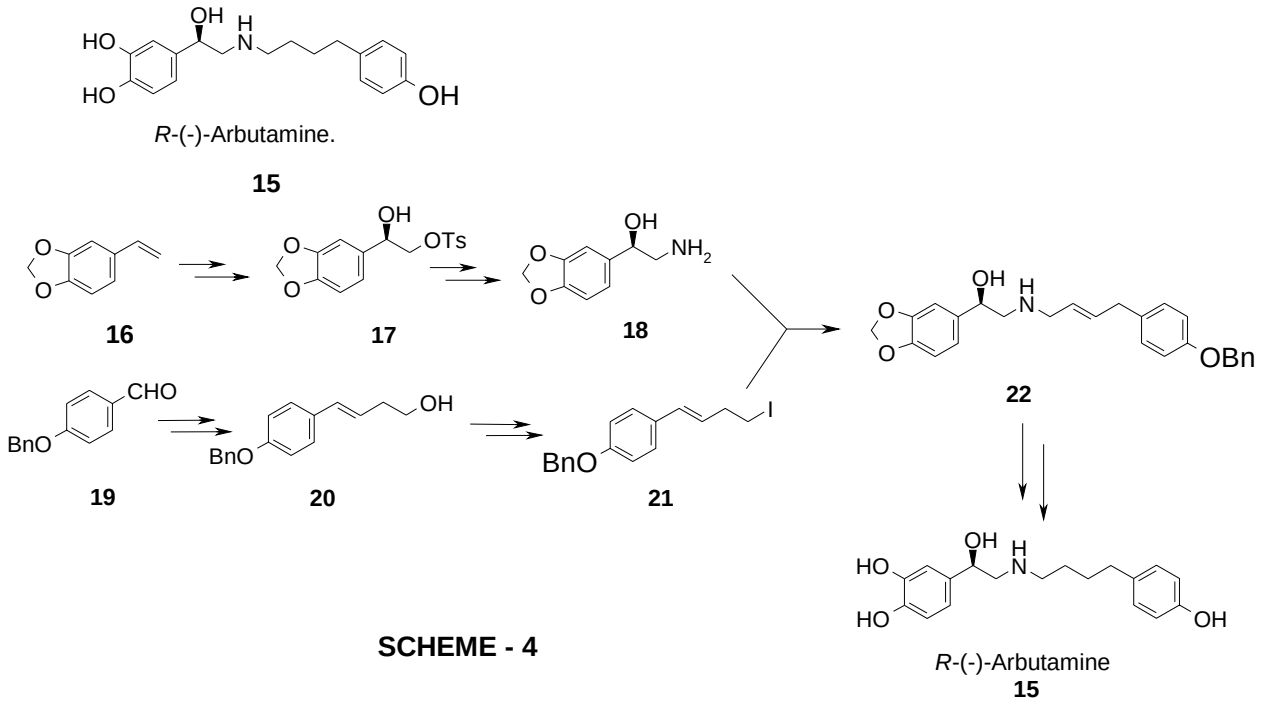
SCHEME - 3

The synthesis of *(R)*-(-)denopamine was achieved by coupling reaction of two fragments **10** & **13** (Scheme 3). The coupling partner **10** in turn was obtained from styrene derivative **9** while the other fragment **13** could be derived from 3,4-dimethoxy styrene compound **11**.

Thus, a practical and highly enantioselective synthesis of *(R)*-(-)-denopamine has been achieved for the first time using AD as the source of chirality.

SECTION D :

(R)-(-)-Arbutamine[10] **15,** a mixed β,β_2 adrenoreceptor agonist is useful as an exercise stimulating agent (ESA). So far only two chiral synthesis of this molecule is reported in literature. The Sharpless asymmetric dihydroxylation and Wittig olefination, are the key steps in the synthesis of *(R)*-(-)-arbutamine. The coupling of two fragments **18** & **21** followed by reduction yielded the target molecule **15**. (Scheme 4)



SCHEME - 4

Chapter 3:

Synthesis and characterization of new heterogeneous palladacycle catalyst and its applications for C-C bond forming reactions

This chapter deals with the synthesis and physicochemical characterization of a new heterogeneous palladacycle catalyst developed in our lab and its application for various C-C bond forming reactions. This is further divided into three sections.

SECTION A : Synthesis and physicochemical characterization of palladacycle catalyst (MCM-41(Pd-OMS).

Palladium catalysts have achieved the status of an indispensable tool for both common and state of organic synthesis. We have synthesized a new and heterogeneous palladium catalyst. Subsequently we have explored its application for a variety of organic transformations.

(i) Synthesis of Cl-MCM-41(Cl-M)/OH-MCM-41(OH-M)

3-Chloropropyltriethoxysilane (3-ClPTS) functionalised MCM-41 was prepared by co-condensation of tetraethylortho silicate (TEOS) with 3-ClPTS. Synthesised gels were of the general molar composition [(1-x)] TEOS: X 3-C1PTS: 0.25 C_{16}TAB: 0.3TMAOH: 10 MeOH:

90 H_2O. In a typical synthetic procedure, TEOS (25.0 g) and 3 ClPTS (0.84 g) in methanol were added dropwise with stirring to an aq. solution (25%) of tetramethyl ammonium hydroxide (TMAOH, 13.5 g) and cetyltrimethyl ammonium bromide (C_{16}TAB; 11.24 g). The mixture was stirred at room temperature for 5 h, then transferred into a glass reactor and refluxed at 373K for 48 h. The product was filtered, washed with excess deionized water and dried at 373 k for 10 h. The organic surfactant molecules were removed by refluxing with acid solvent mixture (100 mL methanol + 5 ml HCl/g of solid material) at 343 K for 24 h.
Chloride groups in Cl-M sample were hydrolysed into hydroxyl groups by treating 1 g of the extracted sample with 10 mL of H_2O and 10 mL of MeOH at 338 k for 2 h. The hydrolysed material (OH-M) was filtered and dried at 373 k for 10 h.

(ii) Preparation of palladacycle MCM-41 (Pd-OMS):

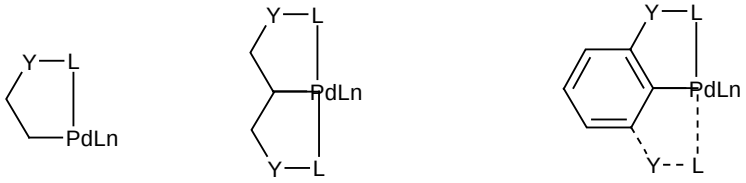
Palladation was carried out over the sample OH-M (1.0 g) with the palladation reagent; Li_2PdCl_4 (2.8×10^{-4} mol; 3.0% Pd); NaOAc, (0.05 g) in methanol at reflux temperature for 24 h. After palladation, the grey colour material was washed thoroughly with aqueous methanol to remove all unreacted palladium salt and the inorganic base and dried at 383K for 12 h. The Pd content present in the catalyst was measured by inductively coupled plasma-optical Emission spectrum (ICP-OES) analysis as 1.68% Pd.

(iii) The physiochemical characterization of catalyst was carried out by X-ray powder diffraction, FT-IR, potentiometric titration, temperature programmed desorption (TPD); scanning electron microscopy (SEM) and N_2 adsorption techniques.

SECTION B: Application of the palladacycle mcm-41 (pd-oms) catalyst for Heck, Suzuki, Sonogashira and Stille coupling reactions.

Palladacycles (metalla cycles) are among the most active catalysts in C-C bond forming reaction. They have recently emerged as powerful catalyst in the Heck, Suzuki, Sonogashira and Stille coupling reactions, and found to show the highest activity with electronically challenging aryl chloride substrates. In addition to the high activity they display, their ease of synthesis, facile modification and comparative stability all act to enhance their applicability.

Palladacycles are the structures where one or more ligands coordinates to the palladium centre, and is generalized by following structure I, II and III.



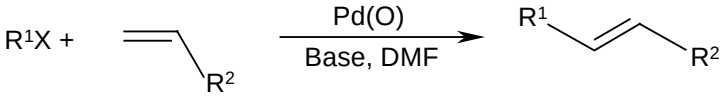
I **II** **III**

In palladacycle I where one ligand co-ordinates to the palladium center in K_2- L,C manner (L = donor) to form a stable five membered chelates; the second are so called 'Piner' complexes (II) where the metallated carbon is supported by two donor groups in a K_3 -L, C fashion. The donor group 'L' are typically PR_2, NR, NR_2 or SR and there is a degree of unsaturation between the metallated carbon and the donor group 'L'. In nearly all the cases in this catalysts the carbon donor is an orthometallated aryl ring (structure III).

The palladacycles which we synthesized was characterized and its Pd content in the palladacycles was measured by inductively coupled plasma-optical Emission Specturm (ICP-OES) analysis[9] as 1.68% Pd and its structure and its classification were examined as K_2 –L, C type.

Part I Heck Reaction:

SCHEME - 5



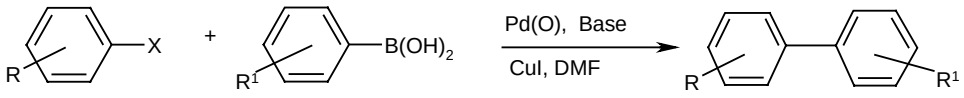
R^1 = aryl
R^2 = aryl, $COCH_3$, COOEt
X = I, Br, Cl

Among basic types of palladium-catalysed transformations, the Heck reaction and related chemistry occupy a special place. The synthesis of arylated and vinylated olefins is of fundamental importance in organic chemistry. The palladium catalysed coupling reactions of haloalkanes and haloarenes with alkenes; generally known as Heck reaction, provides an efficient gateway into such compounds.[11] Here we have successfully employed our palladacycles to the Heck reactions with variation of substitution in the leaving groups X=Cl, Br, I. The variation in alkenes for the Heck reaction was also investigated.

Part II Suzuki coupling:

Although several other methods (e.g. kharash coupling, Negishi coupling, Stille coupling, Himaya coupling Liebeskind – Srogl coupling and Kumuta coupling) are available for making biaryls, Suzuki coupling, a cross coupling reaction has proven to be most popular in recent times. The preference for Suzuki coupling over other Pd-catalysed cross couplings are due to the mild reaction condition and commercial availability of the diverse boronic acids that are environmentally safer than the other organometallic reagents.[12] In our attempt we have successfully employed our heterogeneous palladacycles to the synthesis of biaryls with variation of substitution both in aryl halides and in aryl boronic acids The method also works with less reactive aryl halides (aryl bromides, aryl chlorides).

SCHEME - 6



X = I, Br. Cl

R = Cl, -OMe, -CO_2Me, -NO_2, -COMe, -Me, -CHO, -COOH

R_1 = H, OMe

Part III Sonogashira coupling

Over the past few decades, the Pd-catalysed alkylation has emerged as one of the most general and reliable method for the synthesis of alkynes. Although there are various methods to effect alkylation, Sonogashira reaction (palladium and copper co-catalysed coupling of terminal alkynes with aryl and vinyl halides) is one of the most widely used C-C bond forming reactions.[13] It provides an efficient route to aryl alkynes, which are interesting intermediates for the preparation of a variety of target compounds with applications ranging from natural products and pharmaceuticals to molecular organic materials. Due to the use of these products, the development of new catalyst has received considerable attention.

In our efforts to apply our MCM-41 based palladacycles to Sonogashira reaction we have succeeded in the coupling of even the less reactive aryl bromides, aryl chloride (with electron donating groups), with various alkynes.

SCHEME - 7

R = H, Me, OMe, CO_2Me, COMe, NO_2, Cl,

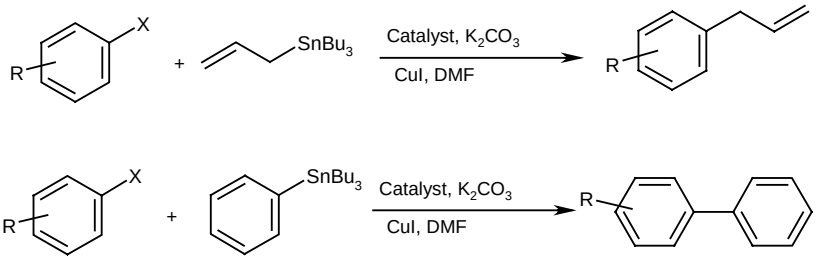
X = I, Br, Cl

R^1= Ph, - CH_2OH

Part V Stille coupling:

Stille coupling is a well established cross coupling reaction between aryl, vinyl or allyl halides and trialkyltin reagents to form biaryls and vinylated, allylated aromatics and aliphatic compounds.[14] Though these coupling reactions alternatively make use of organoboron[15a], organomagnesium[15b], organosilcon[15c], organozinc[15d], organoindium[15e] reagents, the Stille reaction is a potential C-C bond forming reaction in the syntheses of many natural products and pharmaceuticals. In continuation we have successfully employed our heterogeneous palladacycle for the Stille coupling reaction even with the less reactive substrates.

SCHEME - 8



R = NO_2, MeO, Me, CO_2Me

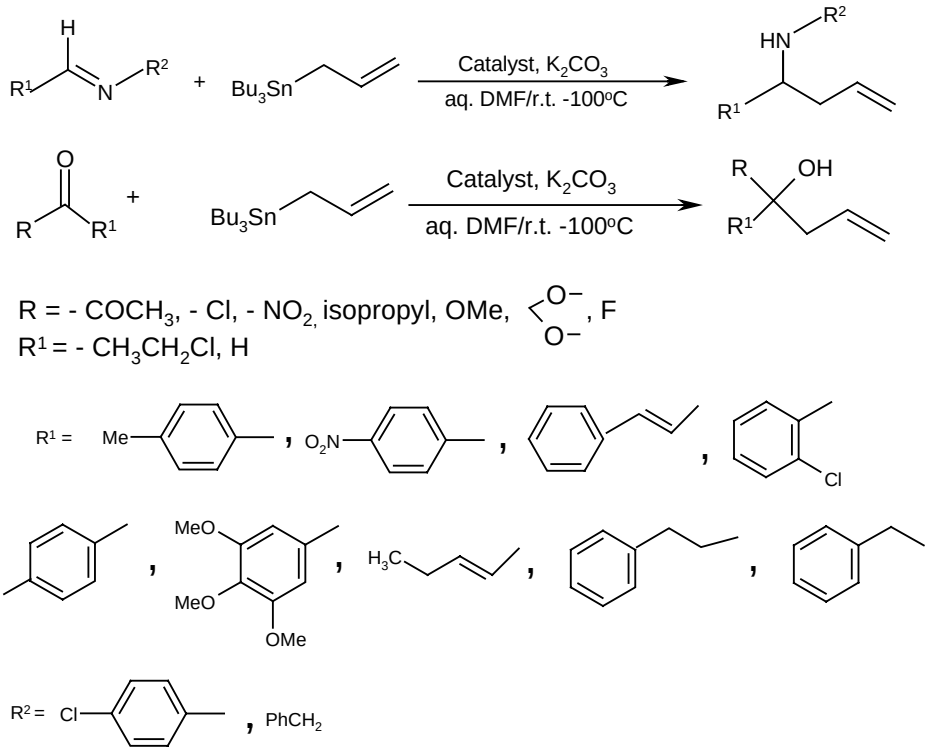
X = I, Br

SECTION C : Allylation of carbonyl and imines

Allylation of carbonyl compounds such as aldehydes, ketones, and their derivatives is one of the most important C-C bond forming reaction, because of the versatility of homoallylic alcohols and amines as useful synthetic intermediates.[16] Among the various allylmetal reagents, allyl stannans and allylsilanes are very useful because of their modest reactivity, which in turn can be increased by catalyst activation. Imine activation methods using Lewis

or Bronsted acids have also been developed. However, these acids co-ordinate strongly with amine products, making the catalyst inactive. Here we have successfully employed the heterogeneous recyclable palladacycle to the allylation of carbonyls and imines in aqueous DMF.

SCHEME - 10



Chapter 4 :

Synthesis and characaterisation of sulfated Yttria-Zirconia based Lewis acid catalyst and its applications for organic transformations:

Yttria-Zirconia based strong Lewis acid catalyst was recently developed in our group and application of this catalyst was explored for Diels-Alder reaction[17] and other transformations like transesterification, synthesis of β-ketoesters, acylation of alcohols, amines and thiols and carbamate synthesis.[18] This chapter deals with the synthesis and physiochemical characterization of sulfated yttrium based strong Lewis acid catalyst and its applications for various organic transformations. This is further divided into two sections.

SECTION A: Synthesis and Physiochemical Characterisation of Sulfated Yttrium-zirconia based Lewis acid

The catalyst was prepared by mixing aqueous yttrium nitrate to which aqueous ammonia was added under vigorous stirring until a *p*H of 8.5 was achieved and precipitate was formed. Washing, drying and treating with sulfuric acid, further drying and subsequent calcinations resulted in a highly acidic material. The chemical composition of the final catalyst was determined by XRF technique. The physiochemical characterization of catalyst was carried out by X-ray powder diffraction, FT-IR, potentiometric titration, temperature programmed desorption (TPD), scanning electron microscopy (SEM) and N_2 adsorption techniques.

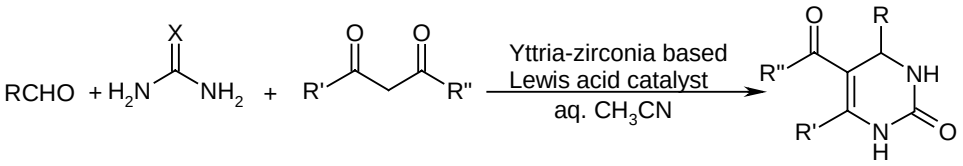
SECTION B: Application of sulfated Yttria-Zirconia based Lewis acid catalyst for organic transformations

This section describes the application of yttrium based Lewis acid catalyst for various organic transformations and is further divided into four parts.

Part I : Yttria-Zirconia based Lewis acid catalysed One-pot synthesis of 3,4-dihydro-pyrimidin-2-(1H)-ones (Biginelli reaction)

The fundamental target of modern organic synthesis is art of performing efficient chemical transformation by coupling three or more components in a single operation by a catalytic process avoiding stoichiometric toxic reagents, and solvents and expensive purification techniques.[19] The new leads using combinatorial chemistry and the preparation of libraries of small organic molecules is rapidly evolving area of research.[20] The Biginelli reaction is constituted by a one-pot acid catalysed cyclo-condensation of an aldehyde, β-keto ester and urea[21] leading to 3,4-dihydropyrimidine-2-(1H)-one (DHPM) (Scheme-11). DHDM derivatives have attracted considerable interest in recent times because of their promising therapeutic and pharmacological activities.[22] Several methods for Biginellis DHDMS synthesis have been decomented in the literature, using various Lewis acids, Brönsted acids, mineral acids, additives, ionic liquids, and clays etc. Even asymmetric version of DHDM synthesis has been reported using Garner aldehyde. We have explored the catalytic potential of yttria-zirconia catalyst for the synthesis of DHDMS.

SCHEME - 11



R' = aromatic, substituted aromatics with electron withdrawing and electron donating groups, hetero-aromatics, aliphatics, cinnamyl

R" = Me, C_6H_5 $C_6H_5CH_2$-

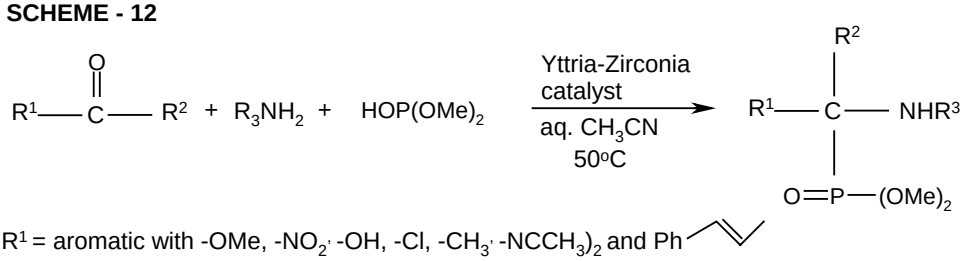
X = O, S

Thus, yttria-zirconia based Lewis acid has been successfully employed for an efficient cyclo condensation of 1,3-dicarbonyl compound, aldehyde, urea or thiourea. The generality of this reaction has been demonstrated with several examples.

Part II Synthesis of α-amino phosphonates by three component condensation of carbonyl compound, amine and dialkyl phosphite using Yttria-zirconia based Lewis Acid catalyst

α-Amino phosphonates, being structural analogs to α-amino acids, have shown considerable potentials as pharmacological agents, peptides mimetics and enzyme inhibitors.[23] Several synthetic methods for α-aminophosphonates have been developed during past two decades using various Lewis acids Brönsted acids, ionic liquids and triflates etc. Reports of solvent free and catalyst-free methods are also available. Even though solventless and catalyst free methods are available[24], these methods often suffer from drawbacks such as longer reaction time or elevated temperature. We have found that Yttira-zirconia based Lewis acid serves as an excellent catalyst for the synthesis of α-amino phosphonate (with methyl ester) in aqueous CH_3CN at moderate reaction temperature.

SCHEME - 12



R^1 = aromatic with -OMe, -NO_2, -OH, -Cl, -CH_3, -$NCCH_3)_2$ and Ph

R^2 = H, CH_3

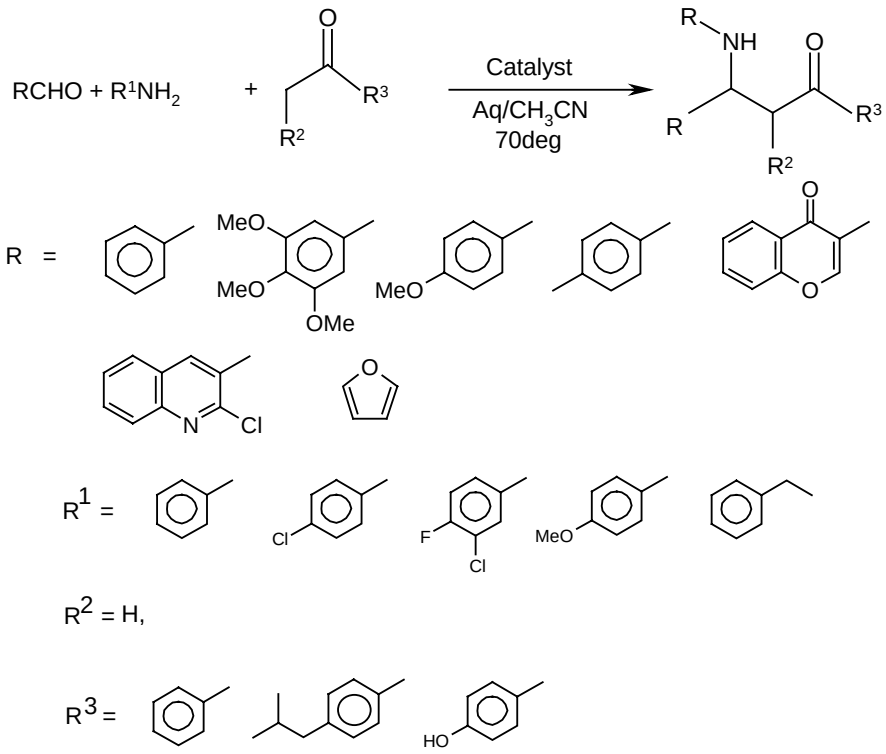
R^3 = Ph, $PhCH_2$ 4 -MeO-Ph, 4 -Cl- Ph, Propyl

Thus we have efficiently carried out the synthesis of α-amino phosphonate using recycable Lewis acid Yttria-zirconia under mild condition in high yields. The generality of reaction has been established with several examples.

Part III One pot synthesis of β-amino carbonyls using Yttria-zirconia based Lewis catalyst

Lewis acid-catalysed Mannich-type reaction of silylenol ether with aldimine are important synthetic reactions for the preparation of β-amino carbonyl compounds, which are precursors of β-lactam and amino acids.[25] Numerous kinds of activators have been developed. β-Amino carbonyls are versatile synthetic intermediates for various pharmaceuticals, and natural products. There are various methods available for the synthesis of β-amino carbonyls catalysed by $Sc(OTf)_3$, $InCl_3$, $TiCl_4$, Brönsted acid-surfactant mediated reactions.[26] Synthesis of β-amino carbonyl is always encountered with side reaction, especially with enolisable aliphatic aldehydes. Most of the reports involve reactive silylenol ethers. In this section we have successfully employed the yttria-zirconia based Lewis acid catalyst for Mannich reaction using less reactive aromatic carbonyl compounds.

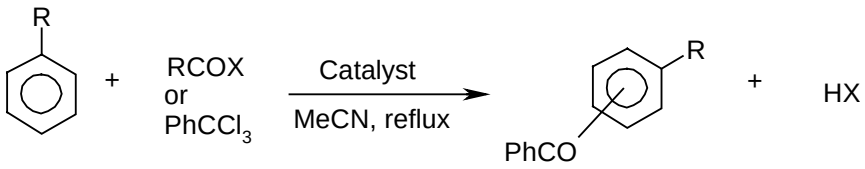
SCHEME-13



Part IV Friedel-Crafts acylation of activated aromatics using Yttria-zirconia based Lewis Acid catalyst

Friedel-Crafts acylation reaction is one of the most important reactions for preparation of various ketones by carbon-carbon bond forming reaction, and is one of the major methods for the synthesis of aromatic ketones and often employed in the industrial process.[26] Though, there are many methods available in the literature for acylation of activated and less activated aromatics, most of the methods suffer from using corrosive materials, and workup and effluent pollution.[28] We have successfully carried out regioselective acylation and benzylation of activated aromatics using Yttria-zirconia based Lewis acid catalyst.

SCHEME 14



R = Me, OMe, -NHCOCH$_3$

R^1 = CH$_3$, Ph

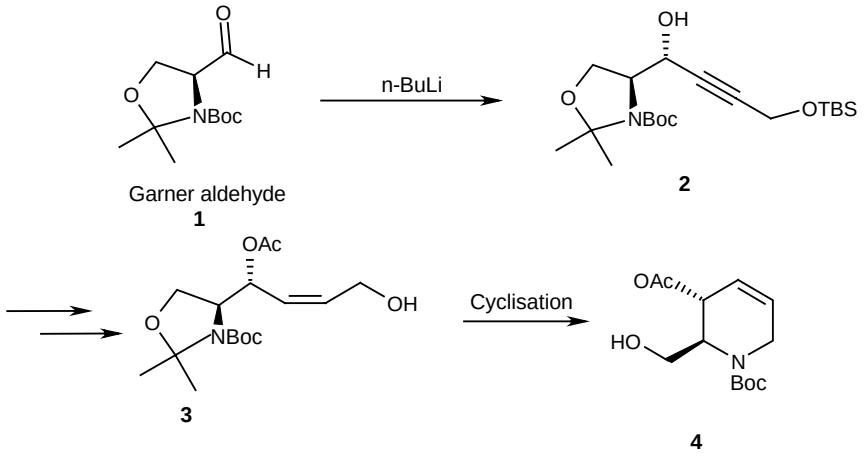
X = Cl, OCOCH$_3$, OCOPh

Chapter 5 :

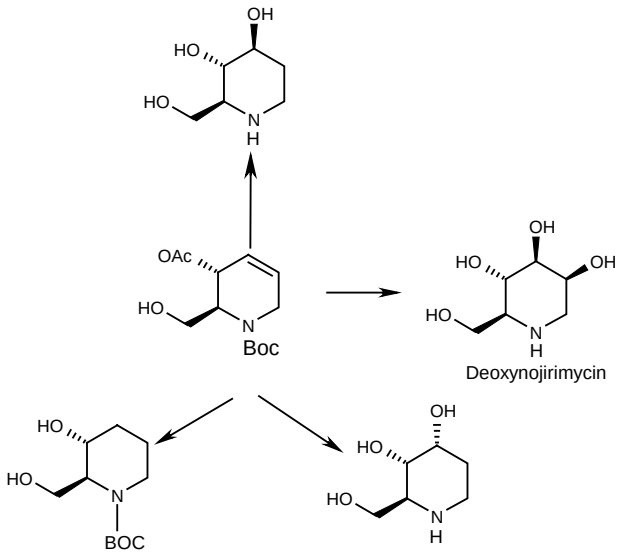
Synthesis of six membered aza compounds

Poly-hydroxylated piperidine alkaloids are frequently found in living system,[29] and display a wide range of biological activities due to their ability to mimic carbohydrate substrates in a variety of enzymatic processes.[30] Selective inhibition of a number of enzymes involved in the binding and processing of glycoproteins has rendered piperidine alkaloids important tools in the study of biochemical pathways.[31]

As shown in Scheme-15, we have investigated the addition of metal-activated carbon nucleophiles to 1 which led to a mixture of two diastereomers. The anti-addition is expected to give the erythro-product while *syn*-addition would lead to the threo-product. The lithium derivative (generated in-situ from *t*-BDMS propargyl ether & n-butyllithium) was reacted with Garner aldehyde **1** in a highly selective manner to afford compound **2** which was transformed easily into **3** and cyclised under mild condition to afford the piperidine derivatives **4**. The piperidine derivative **4** can serve as an important building block and can be used to synthesise a variety of poly hydroxylated compounds of biological interest as illustrated in Scheme-15.



SCHEME-15



3-Hydroxypipercolic acid

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