Chapter 5

Synthesis of 1,2,3-triazolyildene palladium complexes: Application as catalyst for Szuzuki-Miyaura coupling reaction and cytotoxic studies

5.1 Introduction

Carbenes are generally described as compounds having sp^2 hybridized divalent carbon atom with two nonbonding electrons and doesn't carry a formal charge. They can be classified as singlet or triplet depending on whether the nonbonding electrons are either paired (singlet) or unpaired (triplet) (**Fig 1).**

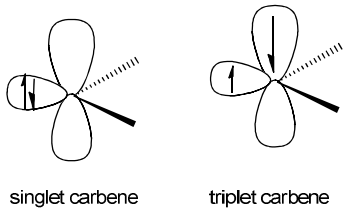
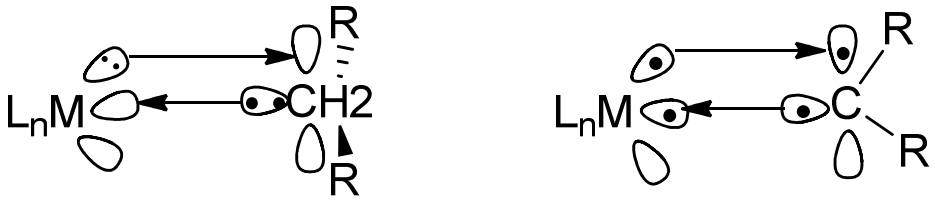


Fig 1

Depending on the structure and reactivity of carbenes toward metal ion they can also be classified as Fischer, Schrock and *N*-Heterocyclic Carbene (NHC). In general Fischer carbene forms complexes with metal center at low oxidation state[1] whereas Schrock carbene forms bond with metal centers having high oxidation state.[2] Metal-ligand multiple bond is present in both carbene complexes (**Fig 2).**



a) Fischer carbene b) Schrock carbene

Fig 2 Bonding in a) Fischer and b) Schrock carbenes

Apart from the above two types, *N*- heterocyclic carbene (NHC) represent a unique type of carbene in which carbene carbon is in a position α to a heteroatom typically nitrogen. General representation of NHC is shown in (**Fig 3**)**.**

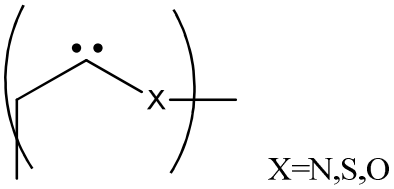


Fig. 3 General representation of NHC

NHC have advantages over the above two carbenes that the nitrogen atom adjacent to carbene carbon stabilize the carbene via σ and π bonding. Stability of NHC acquired by the interaction of π electrons of the substituents with the p_π orbital of carbon give rise to four-electron-three-center π system(**Fig.4).**

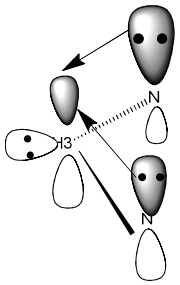


Fig.4

Common subclass of different types of NHCs is shown in **Fig 5.**

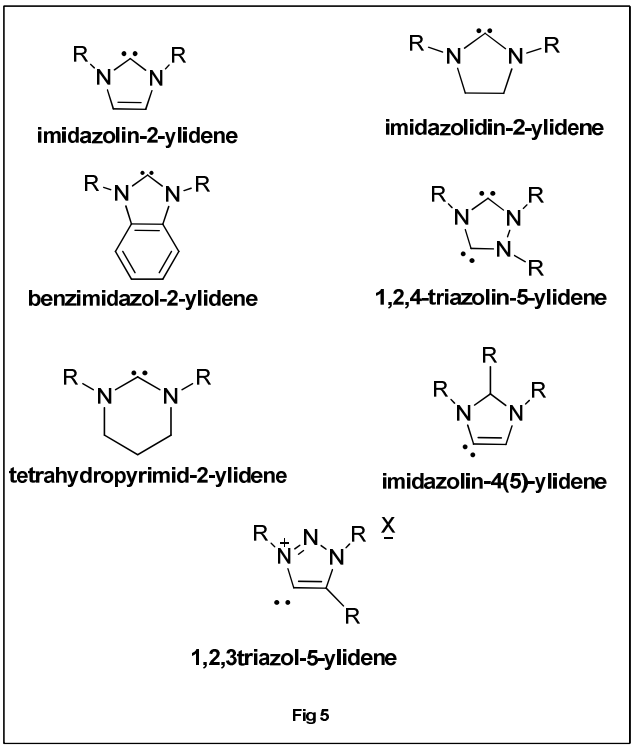


Fig 5

These carbenes are again classified as normal, remote and abnormal or mesoionic carbenes depending on the nature of the carbene species. In remote carbenes (rNHC) there is no heteroatom adjacent to carbene and in abnormal or mesoionic carbene (aNHCs or MICs), no uncharged resonance can be drawn (**Fig 6)**

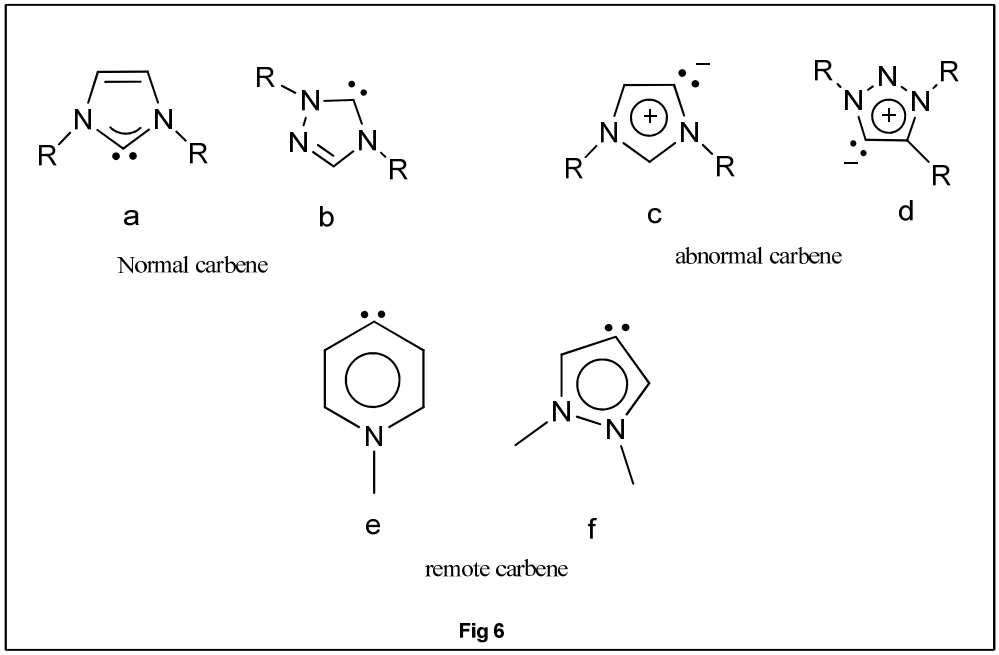
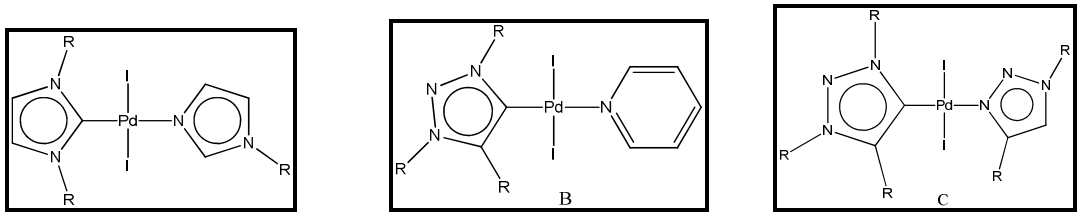


Fig 6

Synthesis of biaryls by palladium catalyzed Suzuki-Miyaura cross coupling reactions using organic halides and boronic acid as reactants attained more relevance.[3–5] Traditionally, air and thermal stable phosphine ligands and their complexes have been

employed as catalyst for such coupling reactions.[6] In recent times, nucelophilic N-heterocyclic carbene ligand are used as auxiliary ligands for the coupling reactions[7] and such reactions were usually carried out in organic solvents. However, due to environmental concerns green chemistry protocol demands for such reactions[8,9] which needs proper design of the catalyst to enable the use of water as reaction medium. Such a green protocol involves the use of water soluble ligands, micellar catalysis and hydrophilic ligand precursors.[10,11] Water soluble NHC complexes are used for C-C bond formation reactions such as Suzuki coupling.[12] Generally N-heterocyclic carbenes are neutral, strongly donating and covalently binding ligands and these type of ligands can be tuned for catalytic activity especially those catalysts containing palladium metal.[13]

In 2011, Karimi reported the synthesis of water soluble NHC-Pd catalyst.[14] Then arises a new way for the catalyst design like "throw away" ligand in which is a weakly coordinated ligand can leave the complex immediately before an oxidative addition takes place. Such catalytic systems contains imidazolylidene palladium core with N-donor labile ligands like PEPPSI (Pyridine Enhanced Precatalyst Preparation, Stabilization and Initiation), amine, (iso)quinoline, DABCO(1,4-diazabicyclo[2.2.2]octane etc. There are few reports on triazolyildene palladium complexes bearing throw away ligands that can be used for Suzuki-Miyaura cross coupling reactions.[15–17]



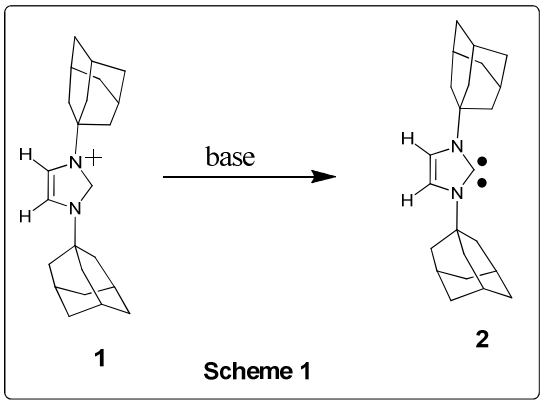
A[18–20] B[15–17] Present work

Fig.7 Development of "throw away" ligand concept in NHC-Pd complexes: C_{Im}-Pd(II)-N_{Im} complex (**A**), C_{tzl}-Pd(II)-N_{PEPPSI} complex (**B**) and C_{tzl}-Pd(II)-N_{tzl} complex(**C**)

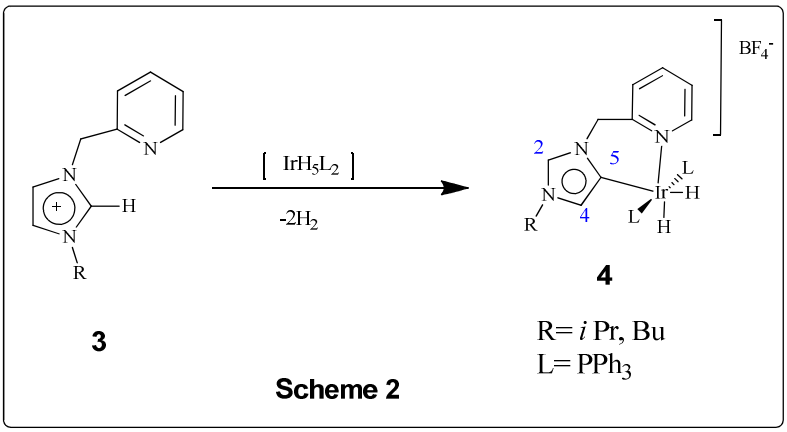
Compared to imidazolylidene counterpart triazolyildene ligands have stronger donor capacity which improves the catalytic activity of such palladium complexes.

5.2 Review of Literature

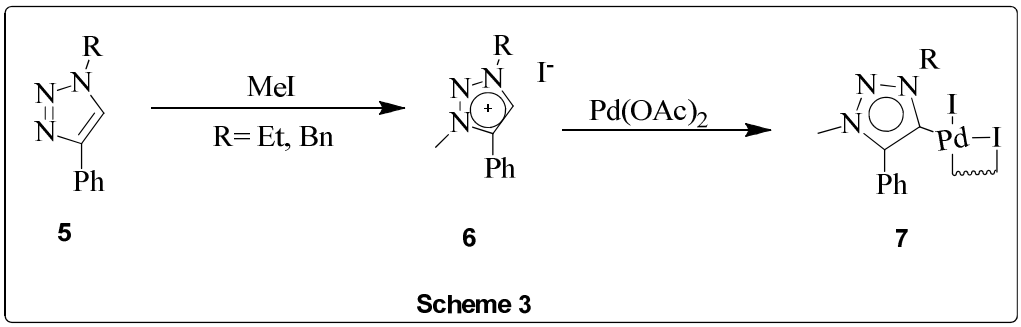
In 1968 Wanzlick synthesized carbene from N,N'-disubstituted imidazolines[21] but it could never be isolated. Arduengo isolated the first stable carbene by the deprotonation of 1,3-bis(adamantyl)imidaolin-2-yildene using sodium hydride in presence of DMSO[22]**(scheme 1).**



Abnormal imidazol-4-ylidenes with metal attached to C-5 carbon were first reported by Crabtree in 2001[23] (**scheme2)**.



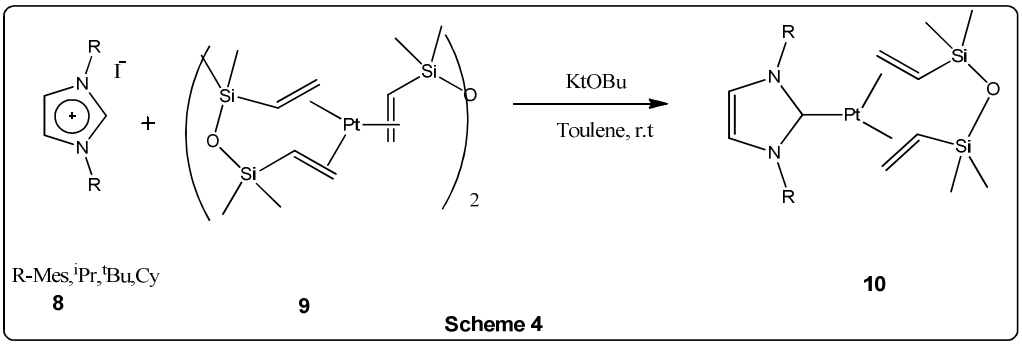
Abnormal binding mode of 1,2,3-triazole ligand at C-5 carbon atom was reported by Albrecht in 2008[24] (**scheme 3).**



Scheme 3

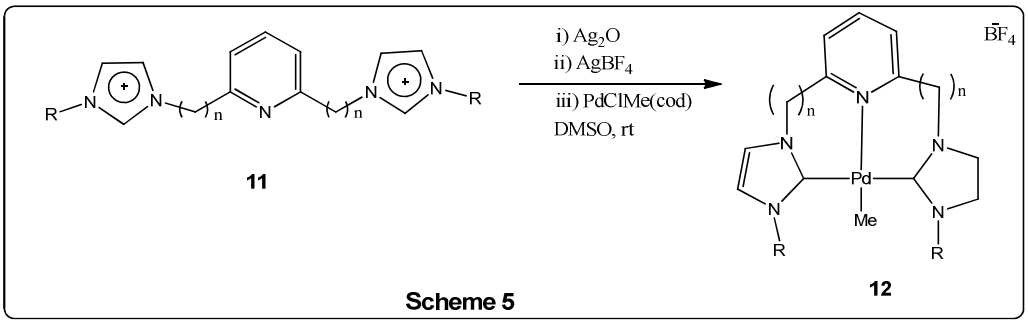
There are various methods for the synthesis of NHC-metal complexes.

A) Proton abstraction: Carbene generated by the deprotonation using a strong base (**Scheme 4**)



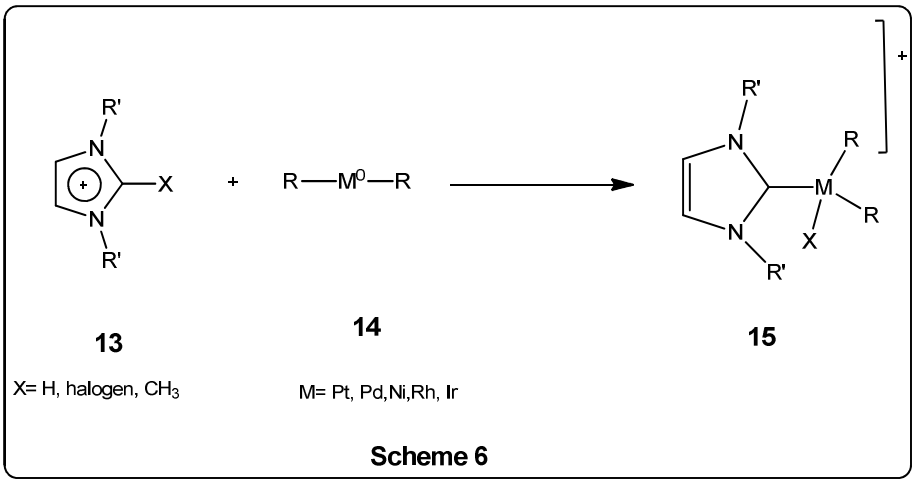
Scheme 4

B) Transmetallation from silver: Firstly, a silver complex was prepared using Ag_2O and then NHC transferred from the silver atom to another transition metal atom (**Scheme 5**)



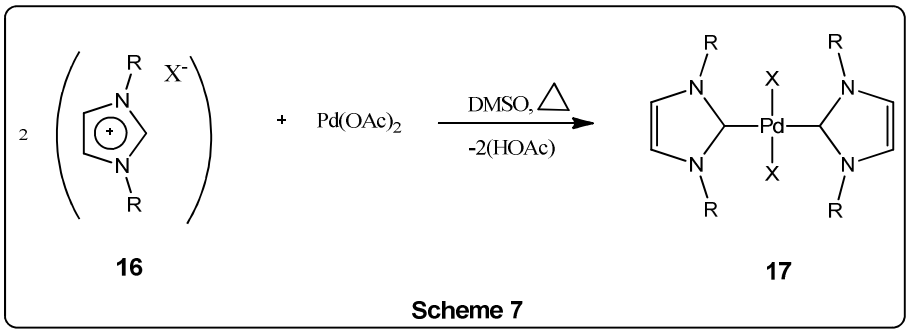
Scheme 5

C) Oxidative addition: Oxidative insertion of low valent metal precursor into a C-X bond. (**Scheme 6**)



Scheme 6

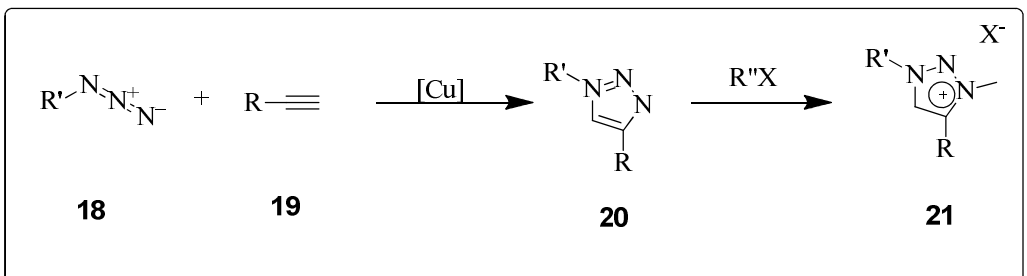
D) Direct metallation: Metallation of ligand using basic ligand of metal precursor such as $Pd(OAc)_2$ or $[Ir(COD)(OEt)]_2$ (**Scheme 7**)



Scheme 7

5.2.1 Synthesis of palladium N-heterocyclic carbene complexes

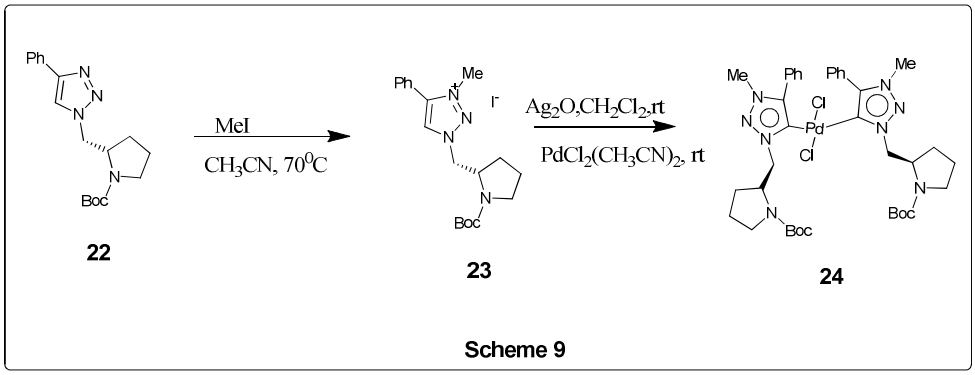
Synthesis of triazole by copper (I) catalyzed azide and alkyne click chemistry[25] followed by alkylation with suitable alkylating agent leads to 1,3,4-substituted triazolium salt (**Scheme 8**).



Scheme 8

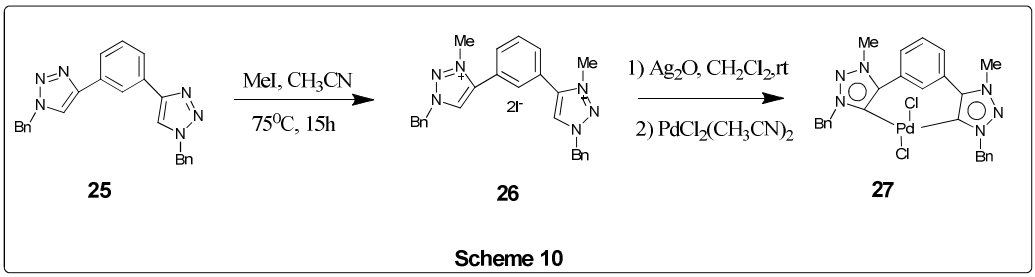
Bertrand and coworkers synthesized 1,2,3-triazol-5-ylidenes and studied its decomposition pathway.[26] Triazole ligand was synthesized from 2,6-diisopropylphenyl azide and phenylacetylene by CuAAC followed by the alkylation using methyl or isopropyl trifluoromethylsulfonate to afford the corresponding triazolium salt. Deprotonation by potassium bases affords the product in moderate yield and the deprotonation is confirmed by the disappearance of triazolium C-H in its ^{1}H NMR spectrum. They found that the triazolium salt was stable at -30°C for several days. But upon heating in benzene solution at 50°C lead to decomposition into other heterocyclic products. They concluded that the decomposition mainly took place by N3-alkyl bond cleavage.

In 2009 Sankararaman reported abnormal 1,2,3- triazolium palladium complexes and its application in Suzuki coupling reaction.[27] They synthesized the first chiral palladium complex by quarternising the chiral triazole ligand with methyl iodide. Transmetallation reaction of the initially formed silver complex was used to synthesize the palladium NHC complex (**scheme 9**).



Scheme 9

They also synthesized achiral pincer type carbene complex **27** by transmetallation from silver carbene complex using $PdCl_2(CH_3CN)_2$ (**Scheme 10**)

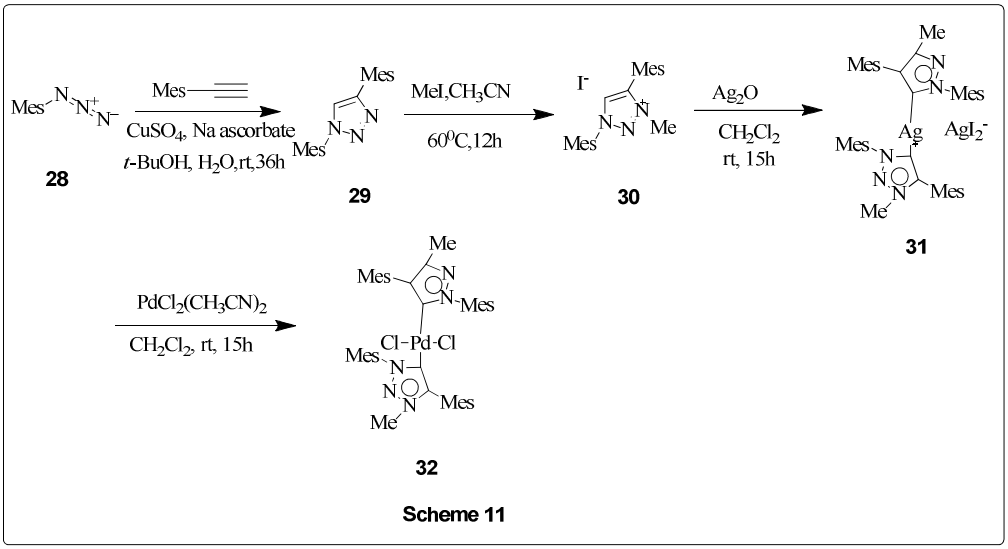


Scheme 10

The catalytic activity of **24** was first studied in Suzuki reactions. Substituted aryl bromides were treated with phenylboronic acid or 4-methoxy phenylboronic acid in

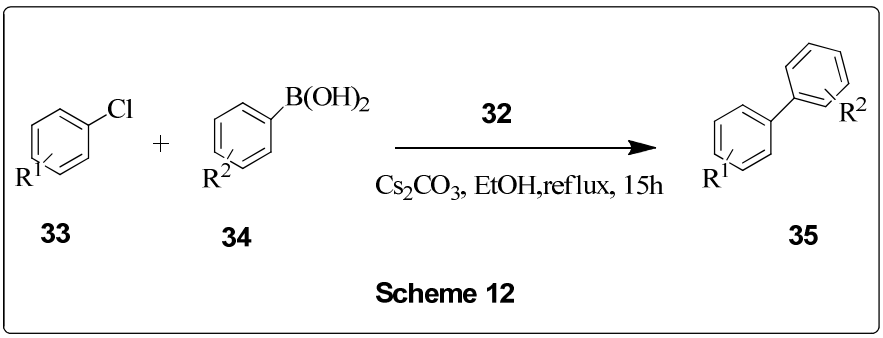
THF using different catalyst loading. Depending upon the catalyst loading, time duration and choice of substrates they got moderate to good yield of products. Next, they carried out asymmetric Suzuki coupling reaction to synthesize chiral binaphthalene derivatives. Using the pincer type carbene complex **27**, they failed to conduct the asymmetric Suzuki coupling.

Fukuzawa synthesized triazole NHC Pd complex **32**,[28] starting from CuAAC reaction of mesityl azide and mesitylacetylene in presence of $CuSO_4$ and sodium ascorbate. Triazolium ion was synthesized by alkylating triazole with methyl iodide. On reaction with Ag_2O afforded the silver carbene complex **31**. Its formation was confirmed by the disappearance of triazolium proton and this on transmetallation using $PdCl_2(MeCN)_2$ in dichloromethane at room temperature afforded dichlorobis(1,2,3-triazol-5-ylidene)palladium complex **32** (**Scheme 11**).



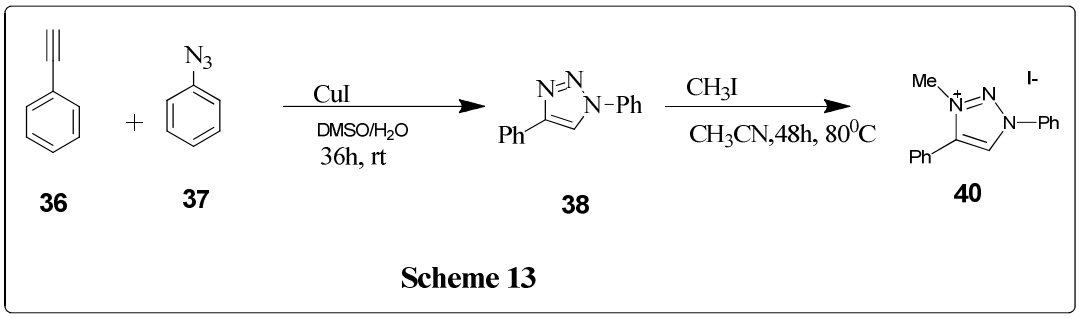
Scheme 11

The Suzuki cross coupling reaction of *p*-chloroanisole with phenylboronic acid using 1mol% of **32** in ethanol solution for 15 h in the presence of Cs_2CO_3 as base gave the desired product in quantitative yield. Efficiency of the catalyst was studied by conducting the coupling reaction in a variety of aryl chlorides with phenylboronic acid or *o*- substituted phenylboronic acid and the product was obtained in good yield (**Scheme 12**). The catalytic activity of **32** towards Mizoroki-Heck and Sonogashira coupling was also investigated.[29]

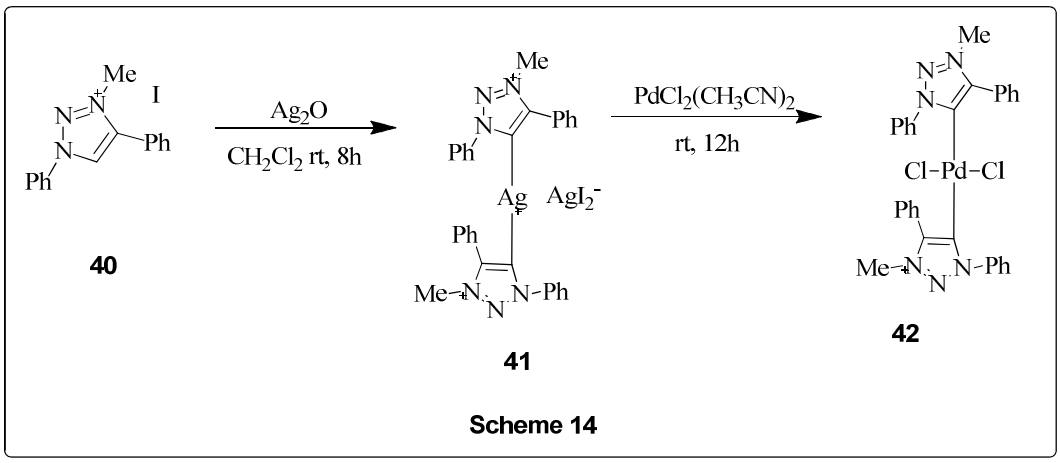


Scheme 12

Sankararaman *et.al* synthesized 1,4-diphenyl-3-methyl-1,2,3-triazol-5-ylidene palladium complexes **42**.[30] 1,4-diphenyl-1,2,3-triazole **38** was prepared from phenylacetylene and phenyl azide through click reaction which on methylation yielded 1,4-diphenyl-3-methyl-1,2,3-triazolium iodide **40** (**Scheme 13**). Palladium complexes were synthesized from **40** by transmetallation method (**Scheme 14**).

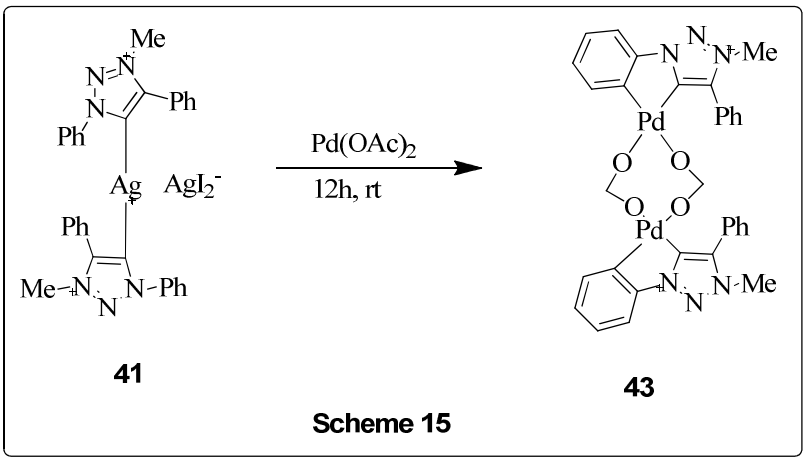


Scheme 13



Scheme 14

From the silver carbene complex **41**, palladium acetate complex **43** was synthesized using $Pd(OAc)_2$ in CH_2Cl_2 and stirring for 12h at room temperature for 12 h (**Scheme 15**).

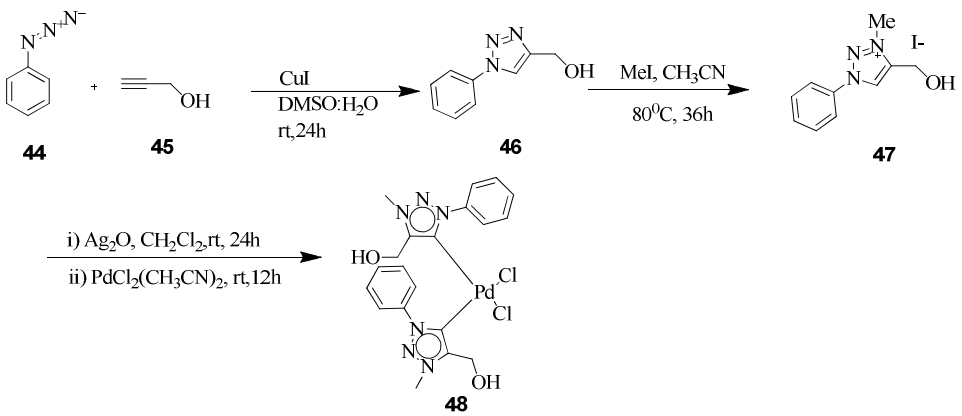


41 43

Scheme 15

Catalytic efficiency of **43** towards hydroarylation in trifluoroacetic acid at room tempearture was investigated and found to be moderate.

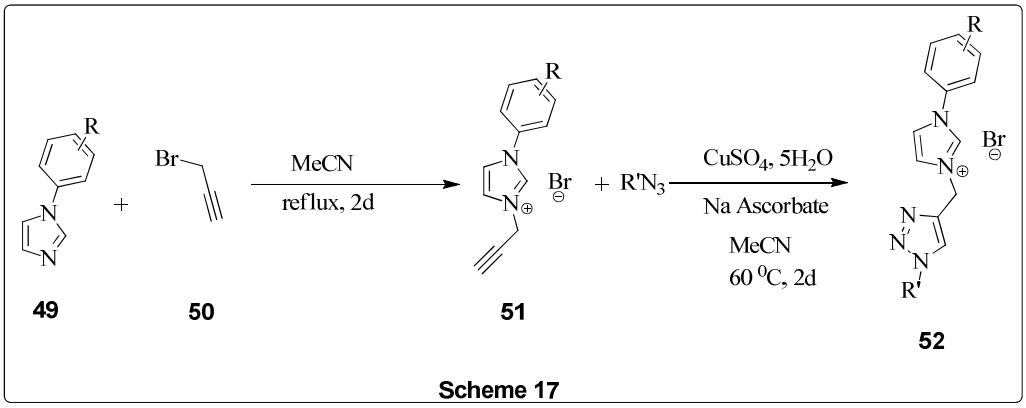
In 2013 Sankararaman and his group reported the synthesis and characterization of palladium complexes of 1,2,3-triazol-5-ylidene ligand.[31] The starting triazole **46** was prepared by CuAAC reaction between phenyl azide and propargyl alcohol in DMSO using CuI as catalyst at room temperature for 24h followed by the methylation using methyl iodide in acetonitrile at 80 °C for 36 h (**scheme 16**). Complex **48** were obtained by transmetallation using Ag_2O. The reaction was performed at room temperature for 24 h in the absence of light. *In situ* reaction of the generated silver carbene with $PdCl_2(CH_3CN)_2$ for 12h stirring afforded **48**. The complex was characterized spectroscopically and by single crystal XRD data. The XRD data reveals that the 1,2,3-triazoli-5-ylidene adopt *cis* orientation with respect to the palladium metal.



44 45 46 47 48

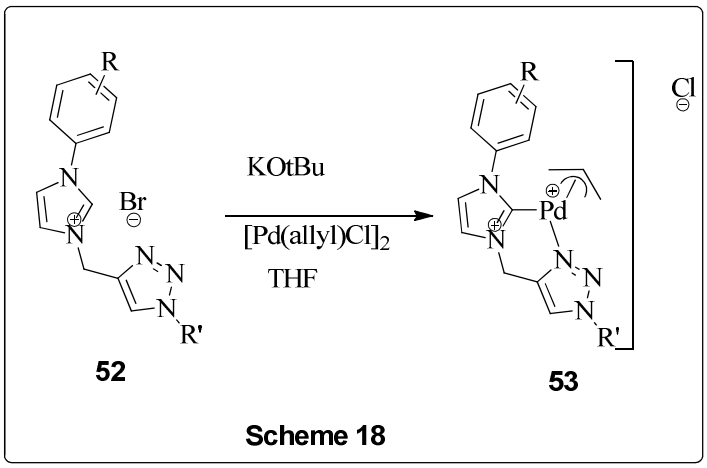
Scheme 16

Synthesis of NHC-triazolyl ligand precursors and their palladium complexes were carried out by Chen.[32] Initially they synthesized N-(Prop-2-ynyl)imidazolium salts **51** by refluxing *N*- aryl imidazole[33] and propargyl bromide in acetonitrile (**Scheme 17**). The product was obtained in quantitative yield either by precipitation or by concentration. The propargyl imidazolium salt was then treated with various azides[34] in presence of catalytic amounts of copper(II) sulfate and sodium ascorbate.



Scheme 17

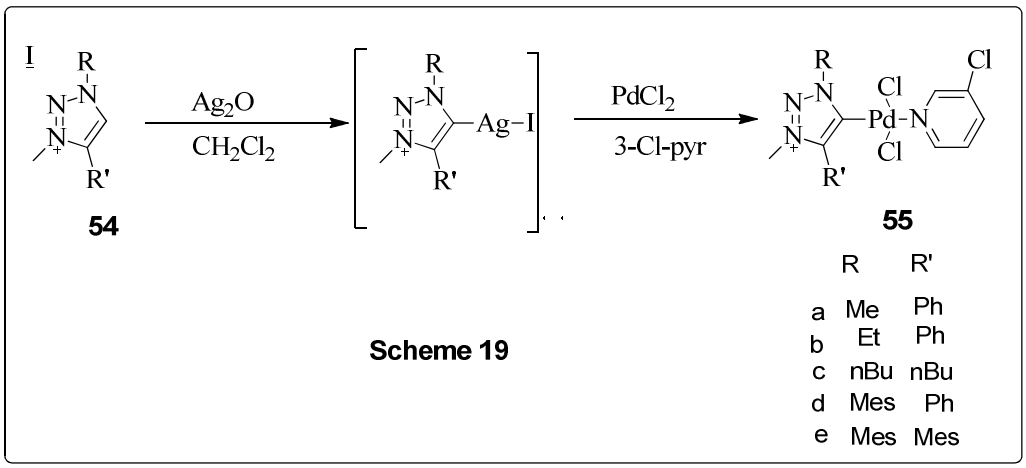
Palladium complex **53** was synthesized by the metalation with η^3-allyl palladium chloride dimer (**Scheme 18**).



Scheme 18

Transfer hydrogenation of alkynes to Z-alkenes was carried out in presence of **53**. The catalyst was found to exhibit high Z-selectivity with full conversion. Presence of bulky substituent provides 85% conversion.

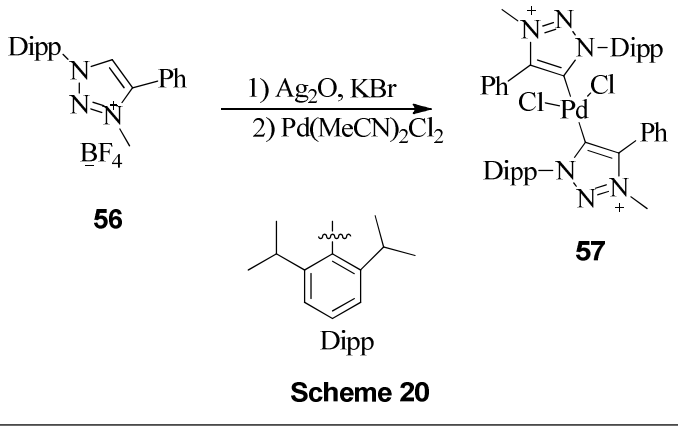
1,2,3-triazolylidene palladium complexes with 3-chloropyridine ligand was synthesized by Albrecht.[35] Metalation of triazolium salt **54** with Ag_2O followed by transmetallation with $PdCl_2$ afforded **55** (**Scheme 19**).



Scheme 19

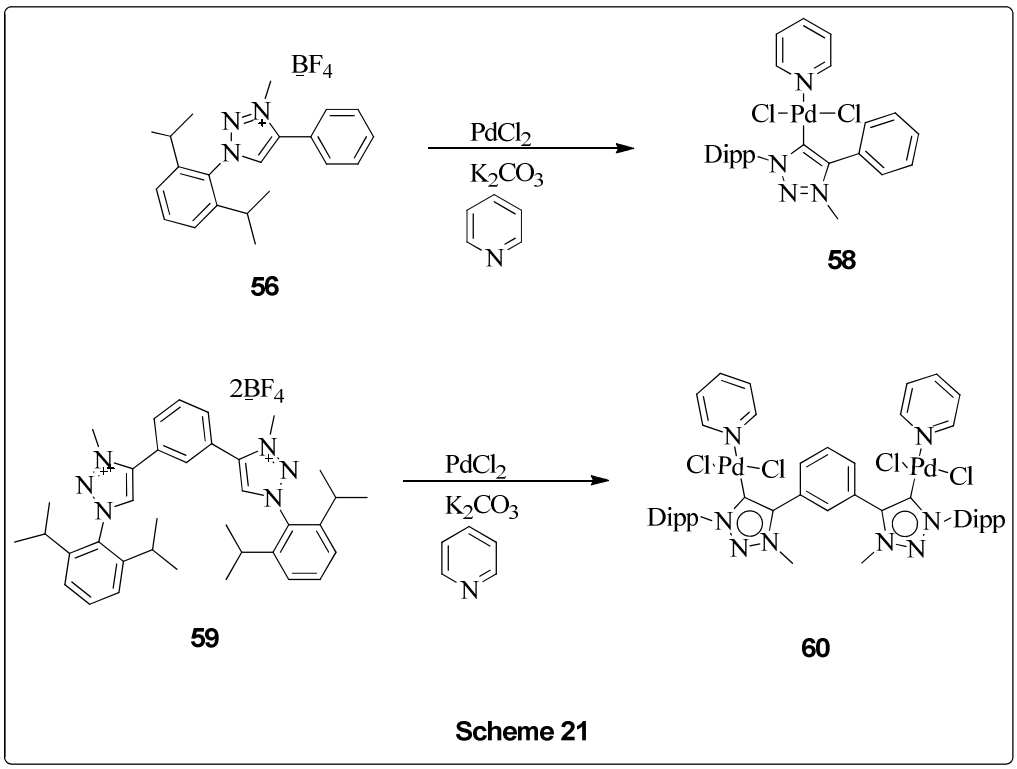
Catalytic activity of **55** was investigated for Suzuki coupling reaction and the complex was found to be heterogeneous in nature which produces palladium nanoparticle in the resting state.

Crudden and coll reported the synthesis of mono- and bimetallic PEPPSI type complexes containing triazole mesoionic carbene ligand.[17] Synthesis of palladium complex **57** was carried out via transmetallation from Ag-MIC (**Scheme 20**)



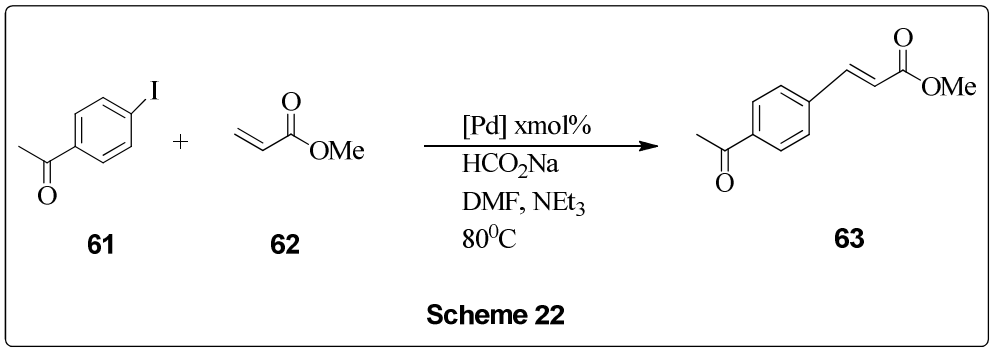
Scheme 20

Without transmetallation they synthesized two palladium complexes **51** and **53** from mesoionic carbene **56** and **59** using $PdCl_2$ in pyridine and K_2CO_3 as the base (**Scheme 21**).



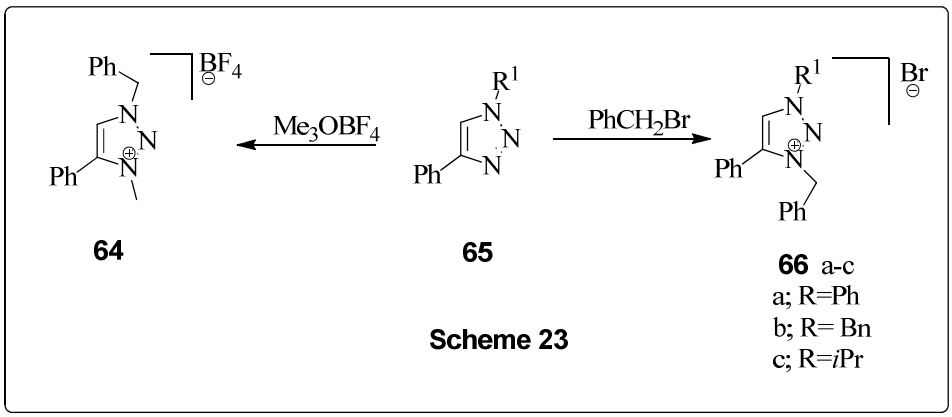
Scheme 21

Mizoroki- Heck reaction was studied using **58** and **60** as catalyst for the coupling between *p*-iodo acetophenone and methyl acrylate in presence of sodium formate as reducing agent. Using 2 mol% of catalyst, both complexes provides 99% conversion.



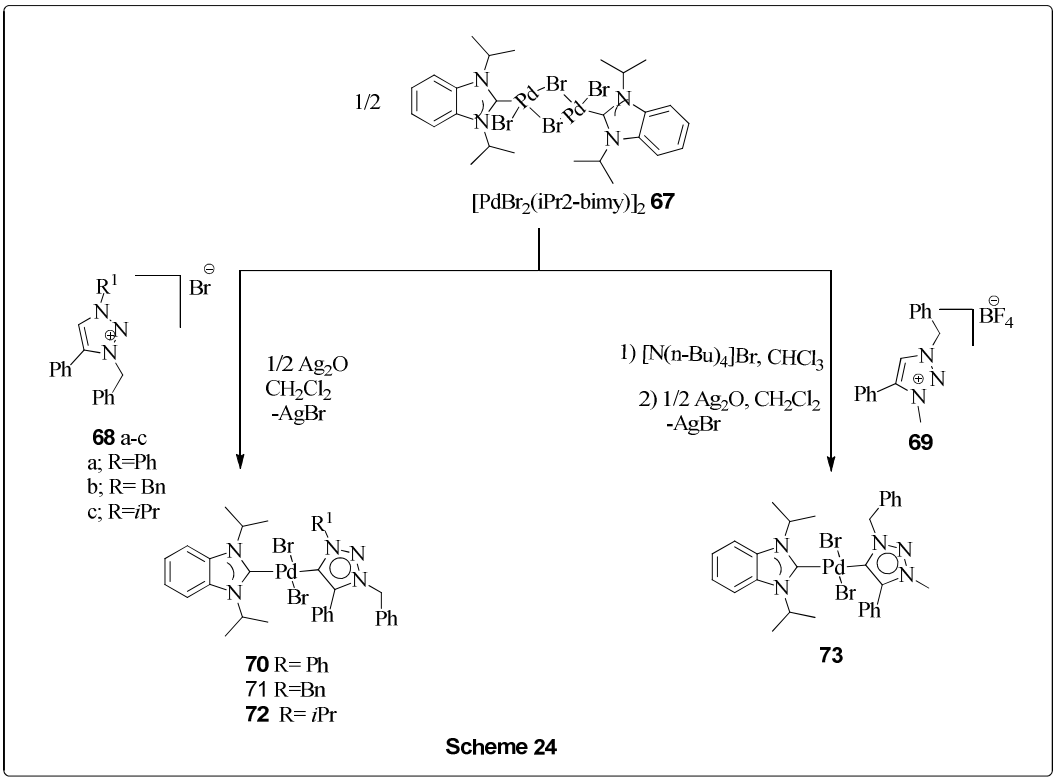
Scheme 22

Huynh reported the synthesis of palladium complexes of the type trans-[$PdBr_2$($^{i}Pr_2$-bimy)(trz)].[36] Triazole synthesized via click reaction followed by the alkylation using benzyl bromide or Meerwin salt[37] provided the triazolium salt **66** (**Scheme 23**).



Scheme 23

The palladium complexes **70, 71 & 72** were synthesized by a one-pot bridge cleaving reactions of dimeric $[PdBr_2(^{i}Pr2\text{-bimy})]_2$ **67** with 2 equiv. of ligand precursors **68(a-c)** and 1/2equiv of Ag_2O in dichloromethane. Because of the presence of BF_4^- counter ion, the complex **73** from ligand **69** was prepared via reacting tribromido complex generated *in situ* using the reaction of $[N(n\text{-}Bu)_4]Br$ to $[PdBr_2(^{i}Pr2\text{-bimy})]_2$ **67**.

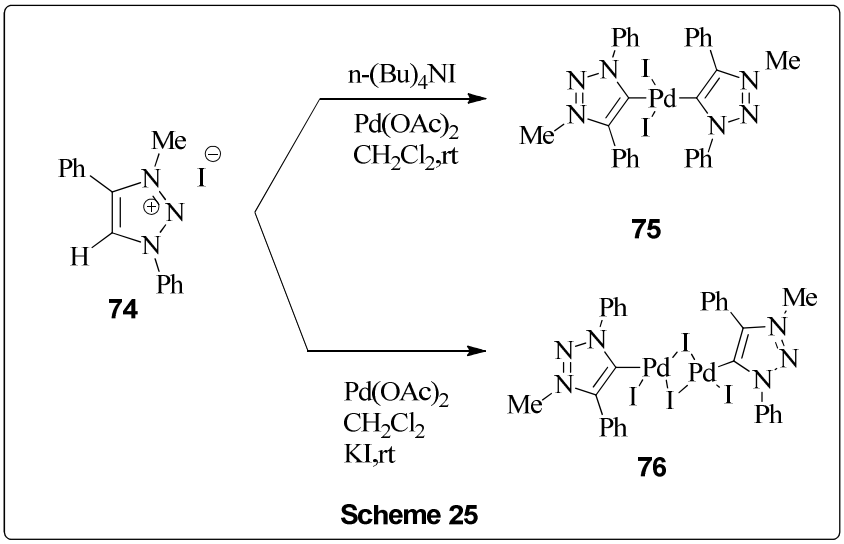


Scheme 24

Using 0.5mol% of complexes **70** and **71** each they carried out the arylation of pentafluorobenzene with 4-bromotoluene in the presence of K_2CO_3 in DMF at 120° and 140 °C. At 120 °C catalyst **70** provides better yield compared to **71**. But when

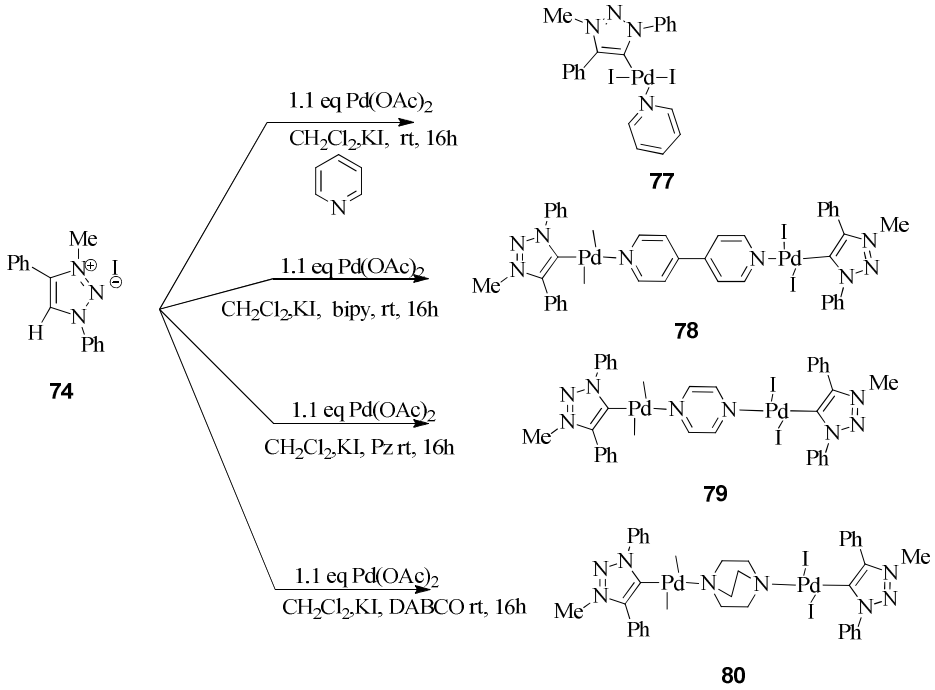
temperature was raised to 140 °C formation of Pd black was observed resulting in reduced yield.

Sankararaman reported the synthesis of mononuclear PEPPSI type complexes and bridged binuclear complexes using 1,4-diphenyl-3-methyl-1,2,3-triazol-5-ylidene.[38] Mononuclear palladium complex **75** was synthesized from triazolium iodide **74**, n-$(Bu)_4NI$ and 0.6eq $Pd(OAc)_2$ in dichloromethane at room temperature and bridged binuclear **76** complex was obtained by treating the triazolium **74** salt with $Pd(OAc)_2$ and excess KI (**Scheme 25**).



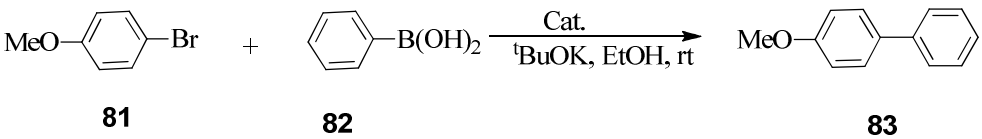
Scheme 25

Treating **74** with 2eq pyridine or its derivatives like 4,4'-bipyridine (bipy), pyrazine (Pz) and 1,4-diazabicyclooctane (DABCO) yielded linearly bridged binuclear complexes **77-80** by one pot procedure (**Scheme 26**).



Scheme 26

Suzuki coupling of aryl bromides with phenyl boronic acid was studied using **75, 76, 77** and **79**. Coupling of 4-bromoanisole with phenyl boronic acid was taken as a model reaction. PEPPSI type complex **77** was found to be catalytically more active than **75** and **76.** Complexes other than **77** requires more time to complete the coupling of aryl bromides whereas under similar conditions complex **77** failed to catalyze the coupling of aryl chlorides.



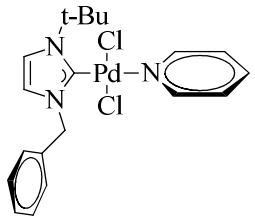
Scheme 27

5.2.2 Biological activities of palladium N-heterocyclic carbene complexes

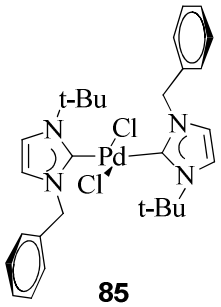
Cisplatin, carboplatin and oxaliplatin are widely used drug for anticancer treatment.[39,40] Owing to the side effects arising from the covalent interaction between platinum and DNA,[41–44] high toxicity, limited activity due to lesser aqueous solubility and multidrug resistance of tumor cells, there is a need to develop new drug. Due to

chemical and structural similarities of palladium and platinum, scientists are now considering palladium based drugs as a substitute to platinum. Cell viability and cytotoxicity assay are related to electronic and structural parameters associated with the drugs.

Panda in 2007 designed palladium NHC complexes like (NHC)Pd(pyridine)Cl_2 **84** and $(NHC)_2PdCl_2$ **85** with anticancer activity.[45]



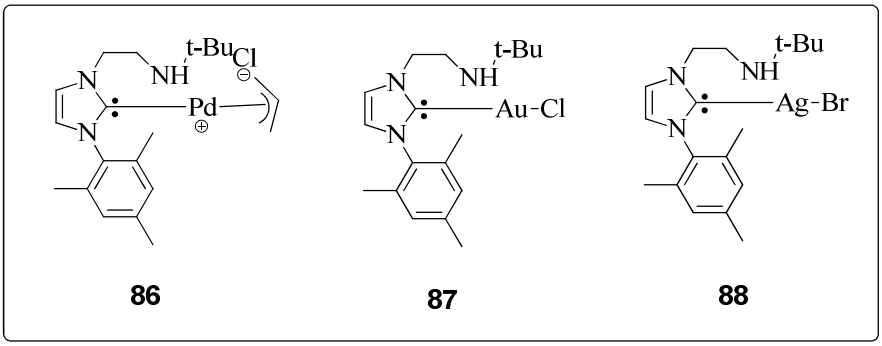
84



85

Compared to cisplatin, **85** exhibits significant cytotoxic activity towards three human tumor cells namely cervical cancer (HeLa), breast cancer (MCF-7), and colon adenocarcinoma (HCT 116). The cells were incubated with different concentrations of **85** and cisplatin to find out the inhibition of cell proliferation using sulforhodamine B assay as standard. Halfmaximal inhibitory concentration (IC_{50}) values were low at micromolar concentration of **85.**

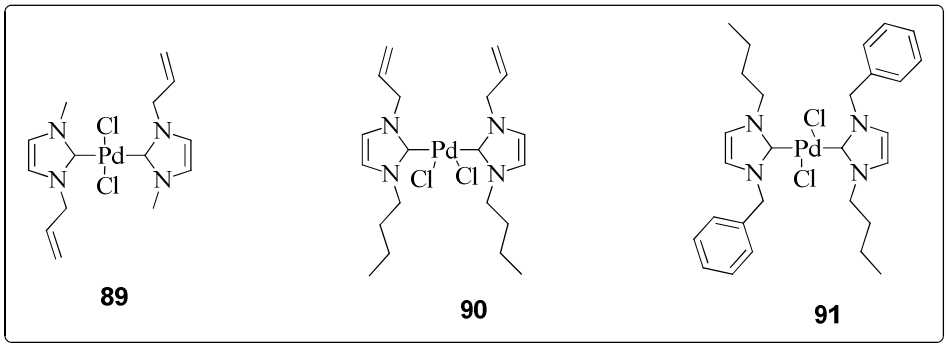
Cytotoxic activity of amino-NHC complex **86, 87**and **88** was investigated by Li in 2011.[46] The growth inhibition assays were carried out in three different human cancer cells like breast adenocarcinoma (MCF 7 and MDA-MB-231) and glioblastoma (U-87 MG) using cisplatin as reference drug.



86 **87** **88**

From the results they concluded that compared to silver NHC, palladium and gold NHC complexes exhibit remarkable ant proliferative activities.

Haque *et.al* reported the antimicrobial and anticancer activity of unsymmetrically substituted bis NHC Pd(II) complexes (**89, 90, 91**) derived from imidazol-2-yildenes, having general formula $[PdCl_2(NHC)_2]$.[47] These were synthesized by transmetallation from corresponding silver NHC complexes. Among these, **89** and **91** adopt *trans-anti* arrangement of ligands whereas **90** adopt *cis-syn* arrangement.



5.3.1 Reagents and Materials

Phenyl acetylene, palladium (II) acetate, bisacetonitriledichloropalladium(II), boronic acids from Sigma Aldrich

Sodium sulphate anhydrous, sodium ascorbate, 1,2-dibromoethane, potassium carbonate, dimethyl formamide, acetonitrile, tetrahydrofuran were purchased from Merck

Sodium azide from Nice Chemicals, Kochi

Organic halides from Spectrochem, Mumbai

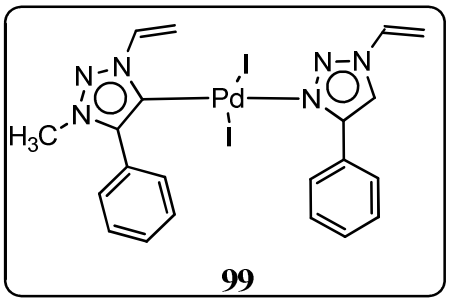
Silica Gel for Thin Layer and Column Chromatography -Merck

5.3.2 Instruments

- NMR – Bruker Avance III, 400MHz
- GC-MS –Thermo Fisher Scientific
- Single Crystal X-ray Diffractometer
- C-H-N analyzer- Elementar Vario EL III

5.4 Results and Discussion

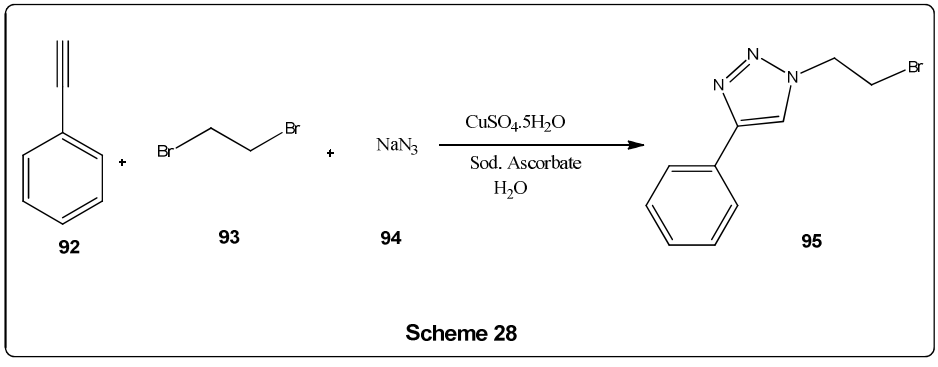
In order to effectively utilize the strong donor capacity of triazolylidene ligand and to incorporate the hydrophilicity of the palladium complex, we have designed a novel C_{tzl}-Pd-N_{tzl} complex **99.** Similar molecules using imidazoles were recently reported by Lu *et.al* and proved to be effective in catalyzing the Suzuki-Miyaura coupling between benzyl chlorides and aryl boronic acids in water[19].



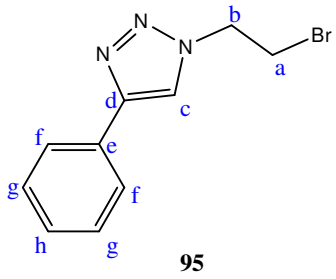
99

5.4.1 Synthesis of compounds 95, 96 & 97

Click reaction between phenyl acetylene and an *in situ* generated monoazide from 1,2-dibromoethane afforded 1,2,3-triazole **95**. Using threefold excess of 1,2-dibromoethane, monoazide formation takes place and 1-(2-bromoethyl)-4-phenyl triazole **95** was obtained as the sole product in good yields (**Scheme 28**). In this new protocol, although the dibromide was used in excess, it could be recovered during work up and be reused after distillation. The structure of the triazole **95** was confirmed from spectral data. Similar triazoles were recently reported by Das *et.al* using copper supported polymer.[48]



Scheme 28 Synthesis of Compounds **95**



95

Protons of carbon atom (**a**) that is directly attached to bromine gives triplet at 3.73 ppm, **b** protons which is directly attached to triazole ring system shows peak at 4.74 ppm which is downfield compared to **a**. One proton singlet at 7.84 ppm corresponds to the CH proton of triazole ring system (**c**). Phenylic ortho protons (**f**) appear as doublet at 7.78 ppm, meta protons (**g**) as multiplet at 7.36 ppm and para protons (**h**) 7.28 ppm.

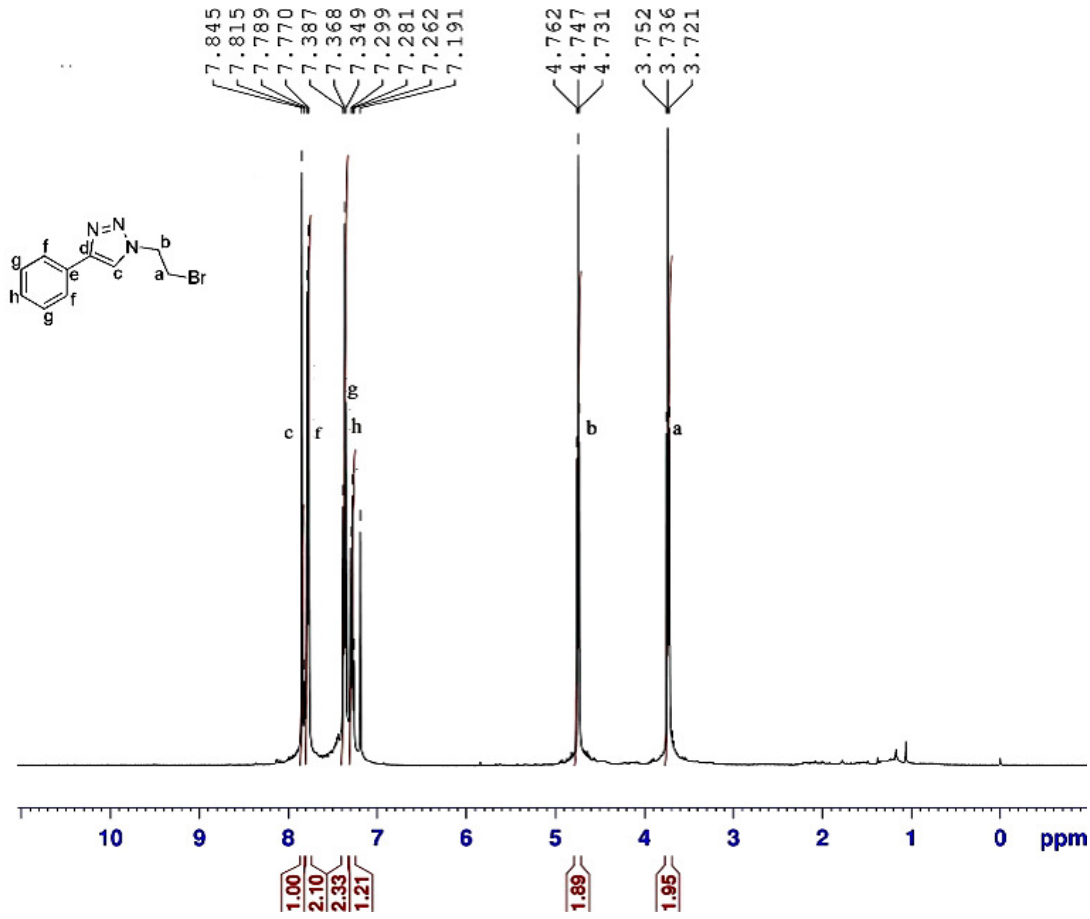


Fig 7.1 ^{1}H NMR of compound **95**

The peak at 29.3 ppm corresponds to carbon atom (**a**) which is directly attached to bromine and carbon attached to triazole ring system (**b**) shows a peak at 51.7 ppm. Triazole carbon atoms which is directly bonded to hydrogen (**c**) provide a peak at

120.5 ppm and the one which attached to phenyl ring system shows peak at 147.6 ppm. Peaks at 125.8, 128.4, 128.9 and 130.1 ppm corresponds to phenyl carbon atoms (**f, h, g** & **e**).

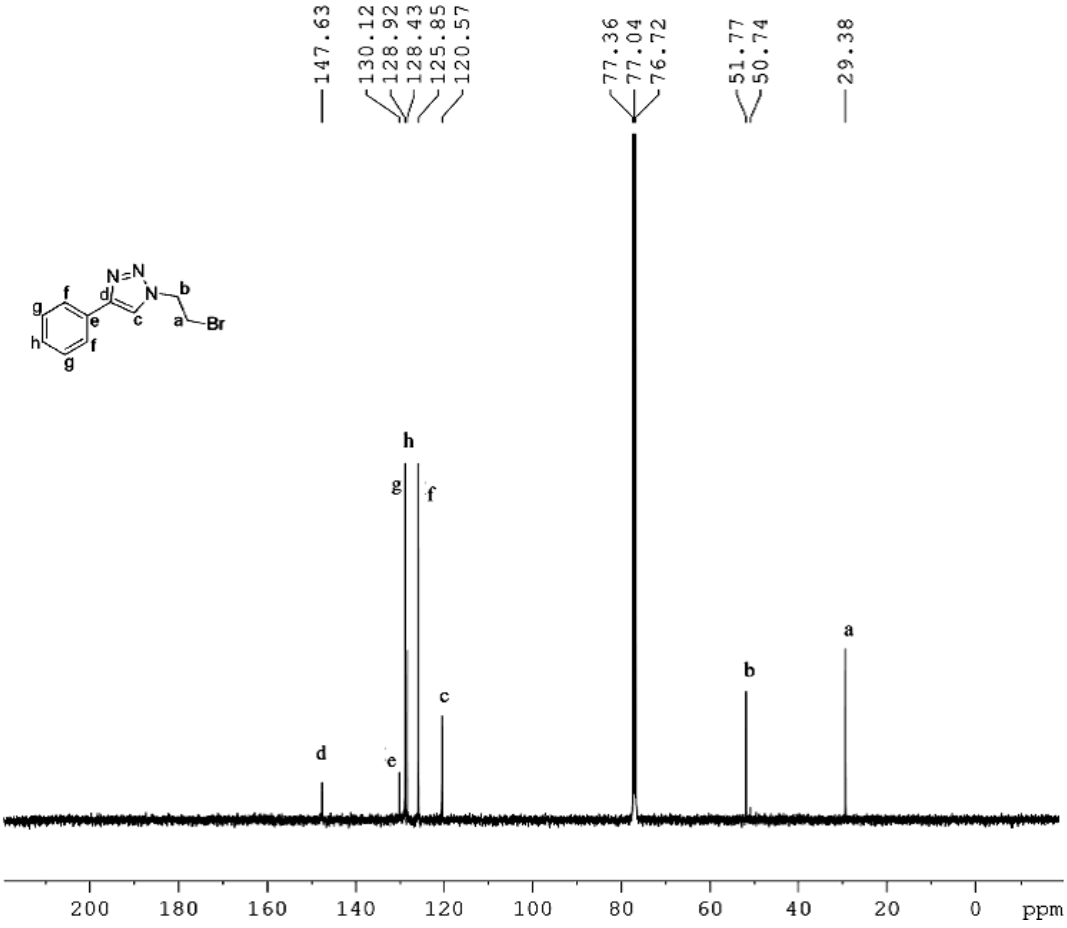
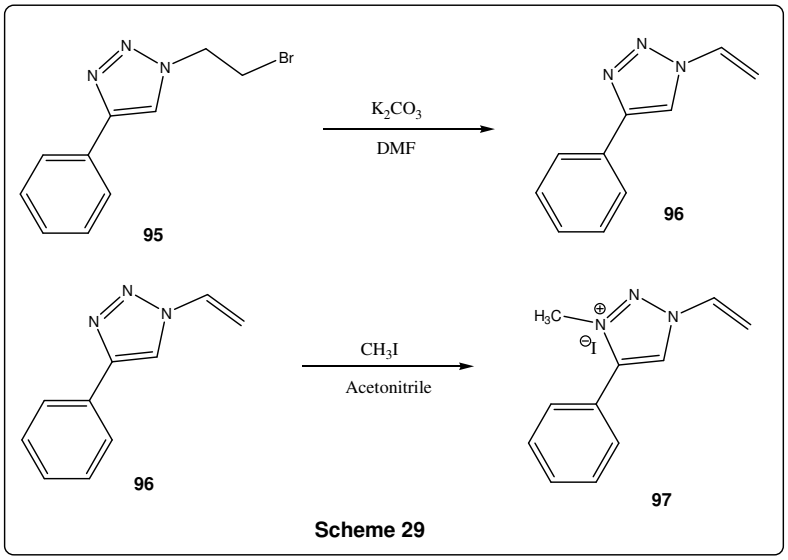
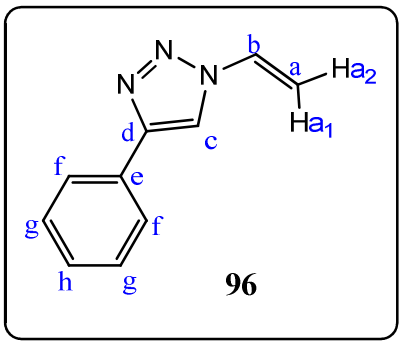


Fig 7.2 ^{13}C NMR of compound **95**



Scheme 29

Dehydrobromination of the triazole **95** using K_2CO_3 in DMF afforded the vinyl triazole **96** in 87% yields. Methylation of the vinyl triazole using methyl iodide in acetonitrile as solvent afforded the triazolium salt **3** in quantitative yield and this triazolium salt was used for palladation (**Scheme 29**).



The formation of vinyl triazole obtained by the dehydrohalogenation was confirmed by ^{1}H NMR and ^{13}C NMR analysis. Vinylic protons (**a_1** and **a_2**) appear as doublet of doublet at 5.1 and 5.64 ppm respectively while muliplet at 7.2 ppm corresponds to both meta (**g**), para (**h**) and vinyl (**b**) protons.Peak at 7.79 ppm corresponds to ortho protons of phenyl ring system. Triazole CH proton provide peak at 7.93 ppm

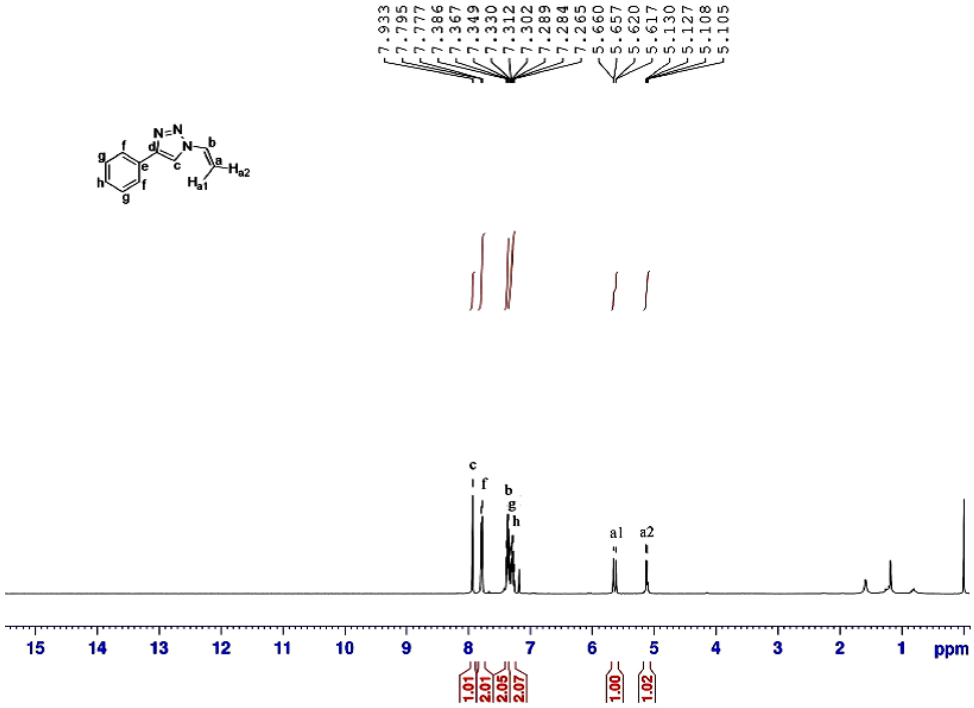


Fig 8.1 ^{1}H NMR of compound **96**

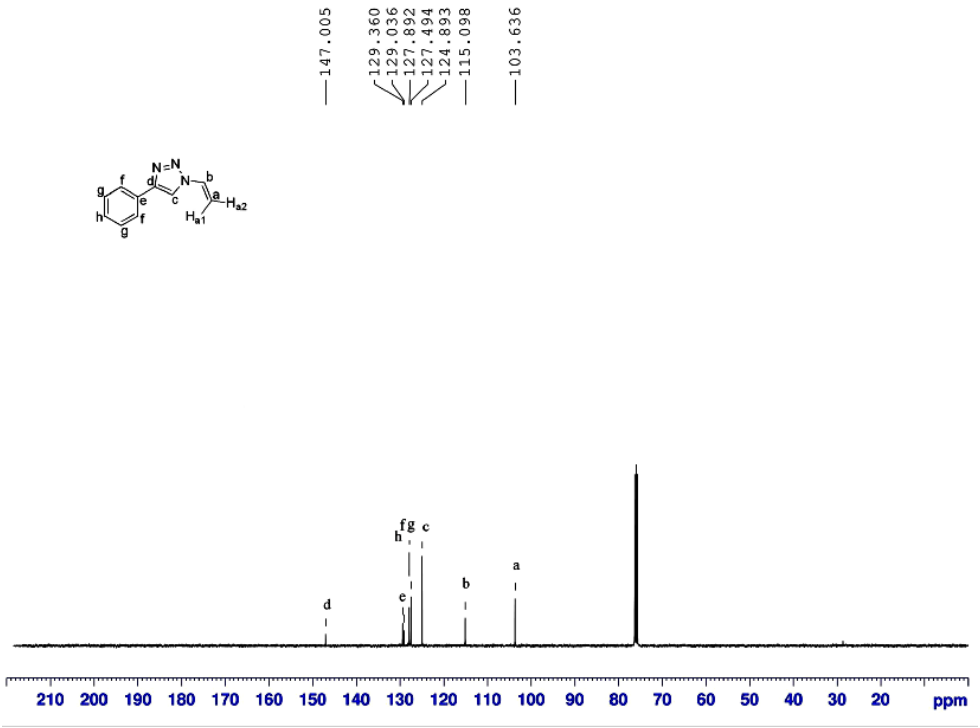
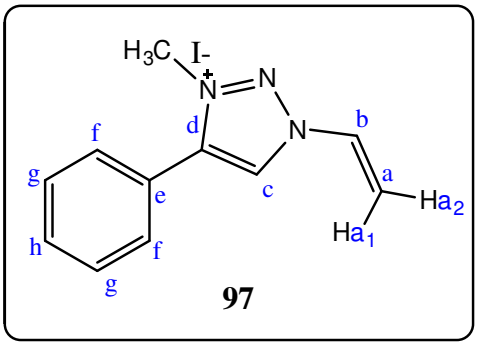


Fig. 8.2 ^{13}C NMR of compound **96**

.^{13}C NMR provides peak at 103.6 ppm corresponds to CH_2 (**a**) and NCH carbon (**b**) was observed at 115 ppm. Triazole CH peak (**c**) observed at 124.8 ppm and triazole carbon connected to phenyl ring (**d**) appeared at 147 ppm. Phenyl carbon peaks were observed at 127.4, 127.8, 129.0 and 129.3 ppm respectively.



97

The peak at 4.38 ppm corresponds to CH_3 protons. The vinylic protons (**a_1**, **a_2 & b**) appear at 5.19, 5.70-5.72 and 6.56 ppm. Triazole hydrogen (**c**) shifted to highly aromatic region after alkylation and observed at 9.74 ppm. The phenyl proton appeared at 7.44, 7.64-770 and 7.79-7.87 ppm.

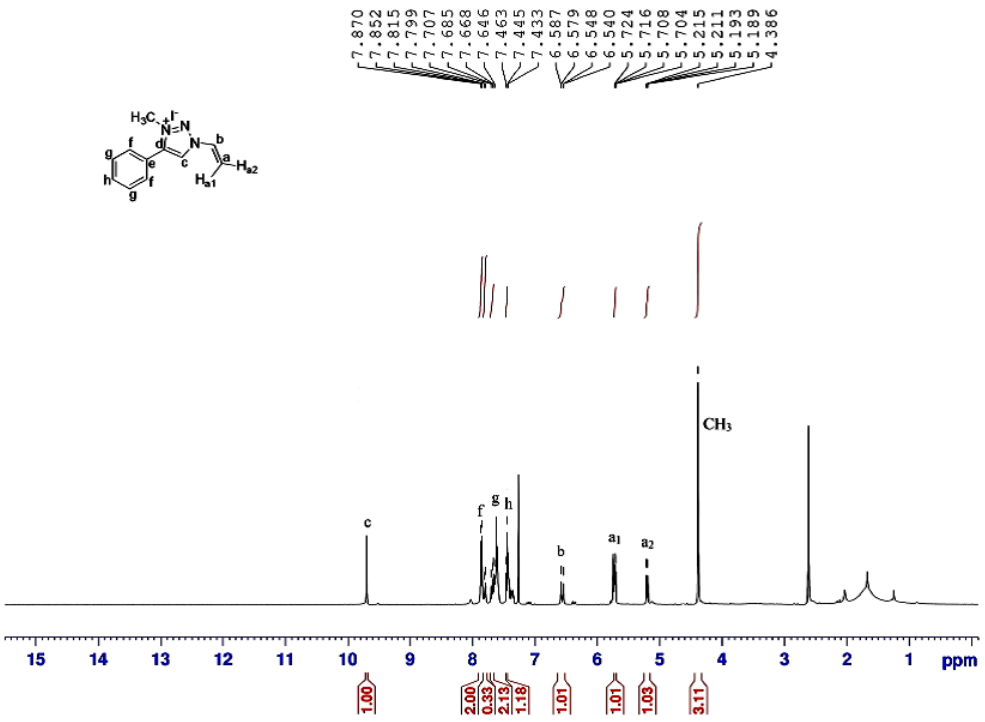


Fig. 9.1 ^{1}H NMR of compound **97**

Peak at 39.68 ppm corresponds to methyl carbon. Vinylic carbons (**a**& **b**) peaks appear at 104.7 and 116.4 ppm. Triazole carbons **c** & **d** appeared at 132.3 and 159.6 ppm. Phenyl carbons observed at 129.8 (**e**), 128.9 (**f**), 127.3 (**h**) and 125.9 (**g**) ppm.

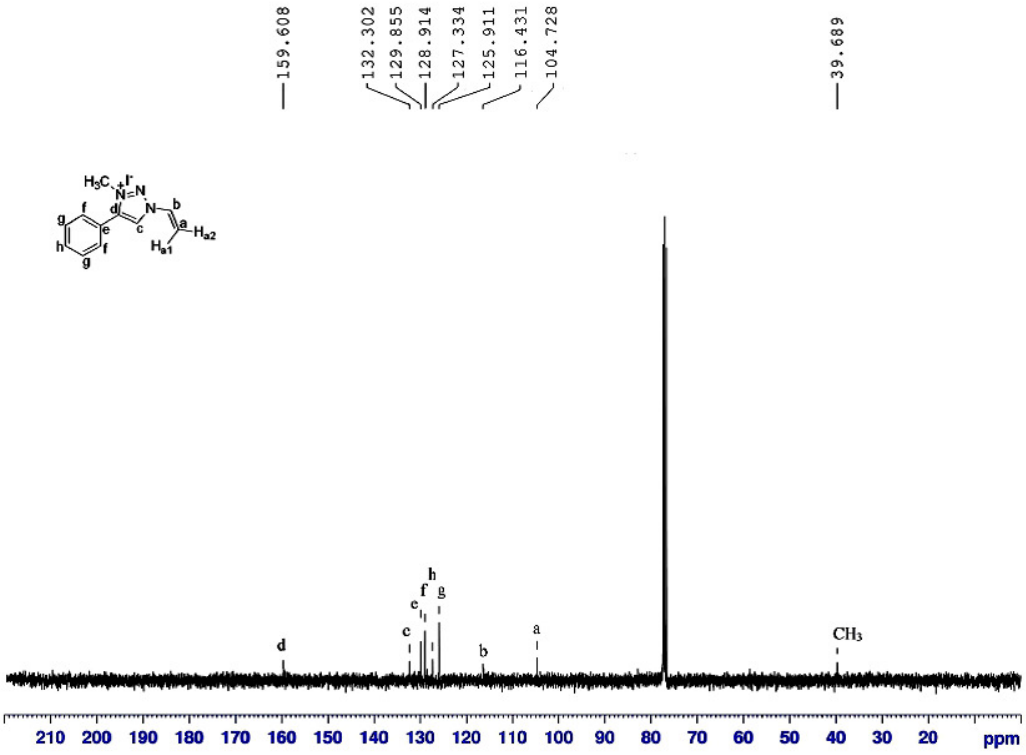
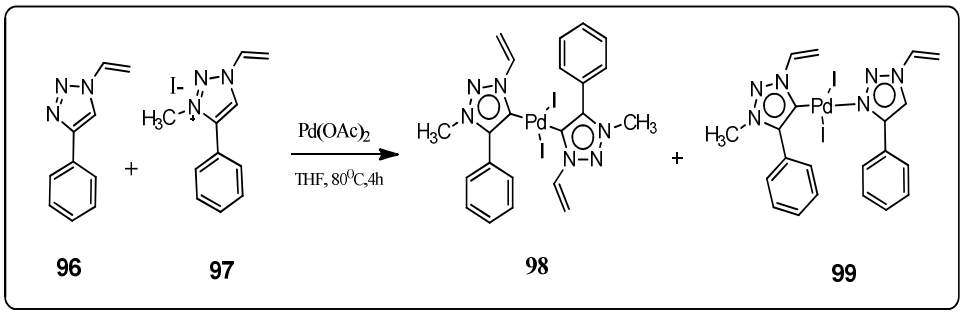


Fig 9.2 ^{13}C NMR of compound **97**

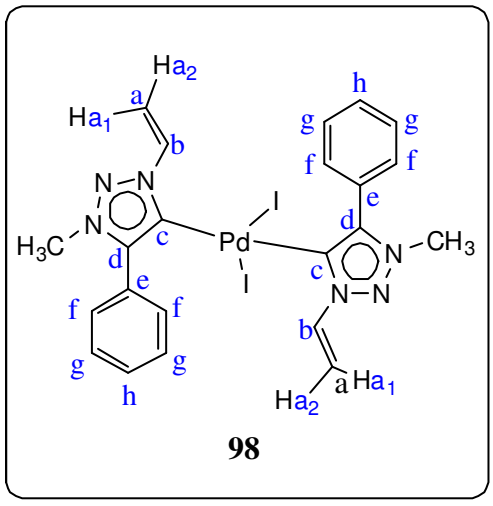
Synthesis of mixed palladium complexes

In order to synthesize the palladium triazole **99** with labile triazole moiety, equimolar quantities of triazolium salt **97** was mixed with vinyl triazole **96** and palladium acetate in tetrahydrofuran (THF) followed by heating at 80 °C for 4 h. The solvent was removed under reduced pressure to afford a red solid. Thin layer chromatography showed the presence of mixture of products. After column chromatography the complexes **98** and **99** were isolated in 22% and 15% yield respectively (**Scheme 30**).



Scheme 30 Synthesis of mixed palladium complexes

When two equivalents of the triazolium salt **97** were treated with palladium acetate in THF, the C_{tzl} -Pd-C_{tzl} complex **98** was obtained as the sole product with 62% yield. The structure of the palladium complex was confirmed by ^{1}H NMR, ^{13}C NMR and elemental analysis.



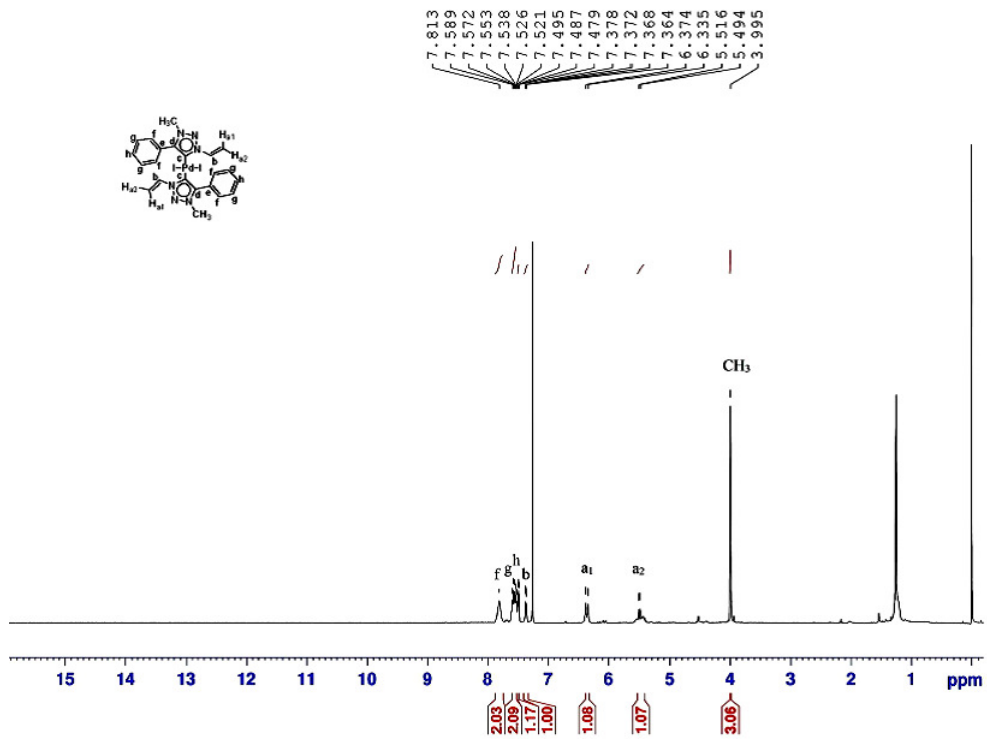


Fig 10.1 ^{1}H NMR of compound **98**

Methyl protons appeared at 3.99 ppm, vinyl protons were observed at 5.50, 6.35 and 7.37 (**a_1, a_2** & **b**). Phenyl proton (**h**) appear as triplet at 7.48 ppm, multiplet of meta protons (**g**) at 7.52-7.58 ppm and ortho proton at 7.81 ppm. Methyl carbon was observed at 37.9 ppm. Peaks of vinyl carbons (**a_1** & **a_2**) observed at 110.1 and 128.8 ppm. Aromatic carbons of phenyl ring were observed at 128.8, 129.1, 129.2, 130.1 whereas triazole carbon (**d**) connected to phenyl ring was observed at 144.8 ppm. Carbon connected to palladium (**c**) shows peak at 130.4 ppm.

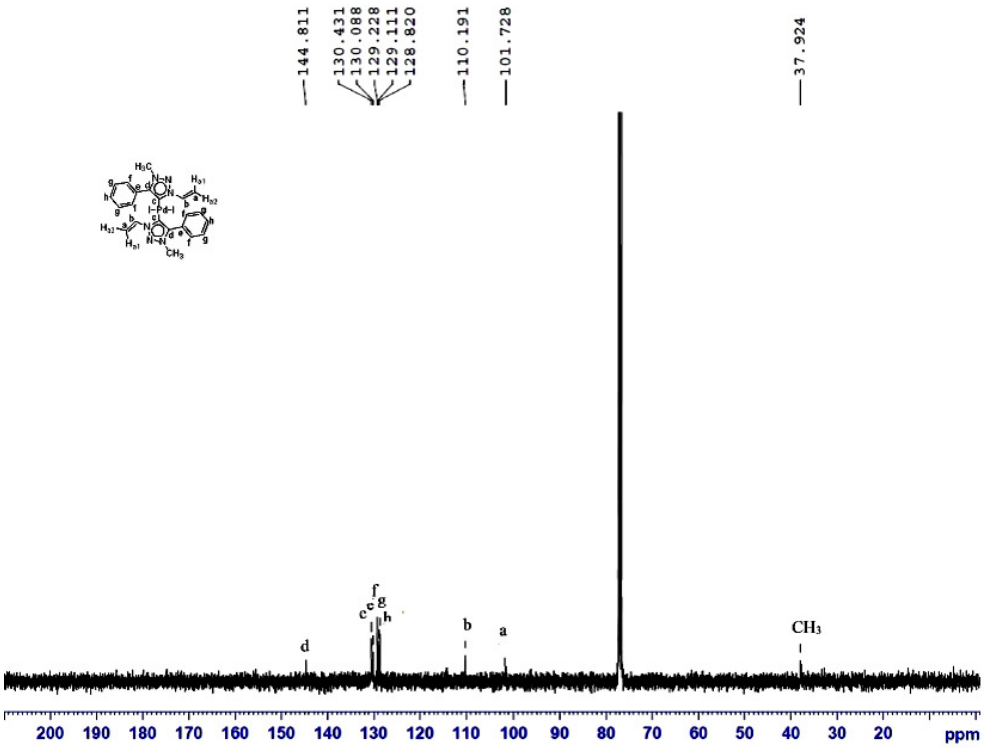
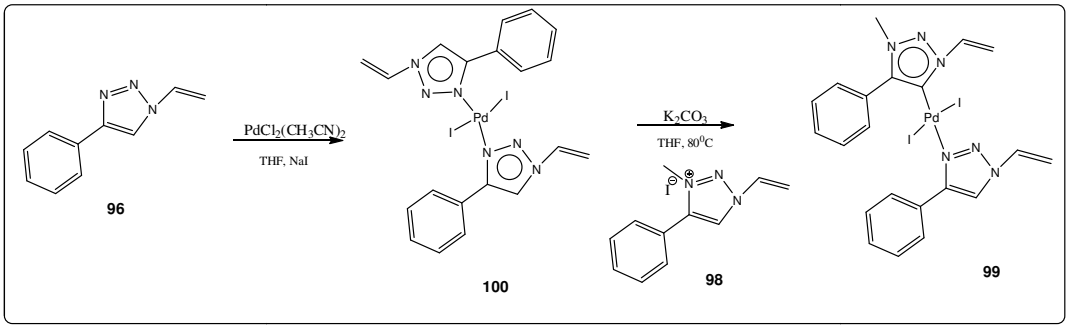


Fig 10.2 ^{13}C NMR of compound **98**

Single palladation of the vinyl triazole **96** using bisacetonitrile dichloropalladium (II) afforded the N-Pd-N complex **100**. Ligand substitution reaction of the complex **100** was then carried out for the synthesis of complex **99**. Complex **100** was allowed to react with the triazolium iodide **97** followed by heating at 80 °C in THF in the presence of base K_2CO_3 afforded the air and moisture stable orange colored palladium complex **99** in 70% yield (**Scheme 31**). Here the reaction takes place by substitution of one of the 1,2,3-triazole ligands by an *in situ* generated triazolylidene. It is noteworthy that such a synthetic strategy has not been reported so far for the synthesis of mixed N-heterocyclic carbene complexes.



Scheme 31 Synthesis of complex **99** and **100**

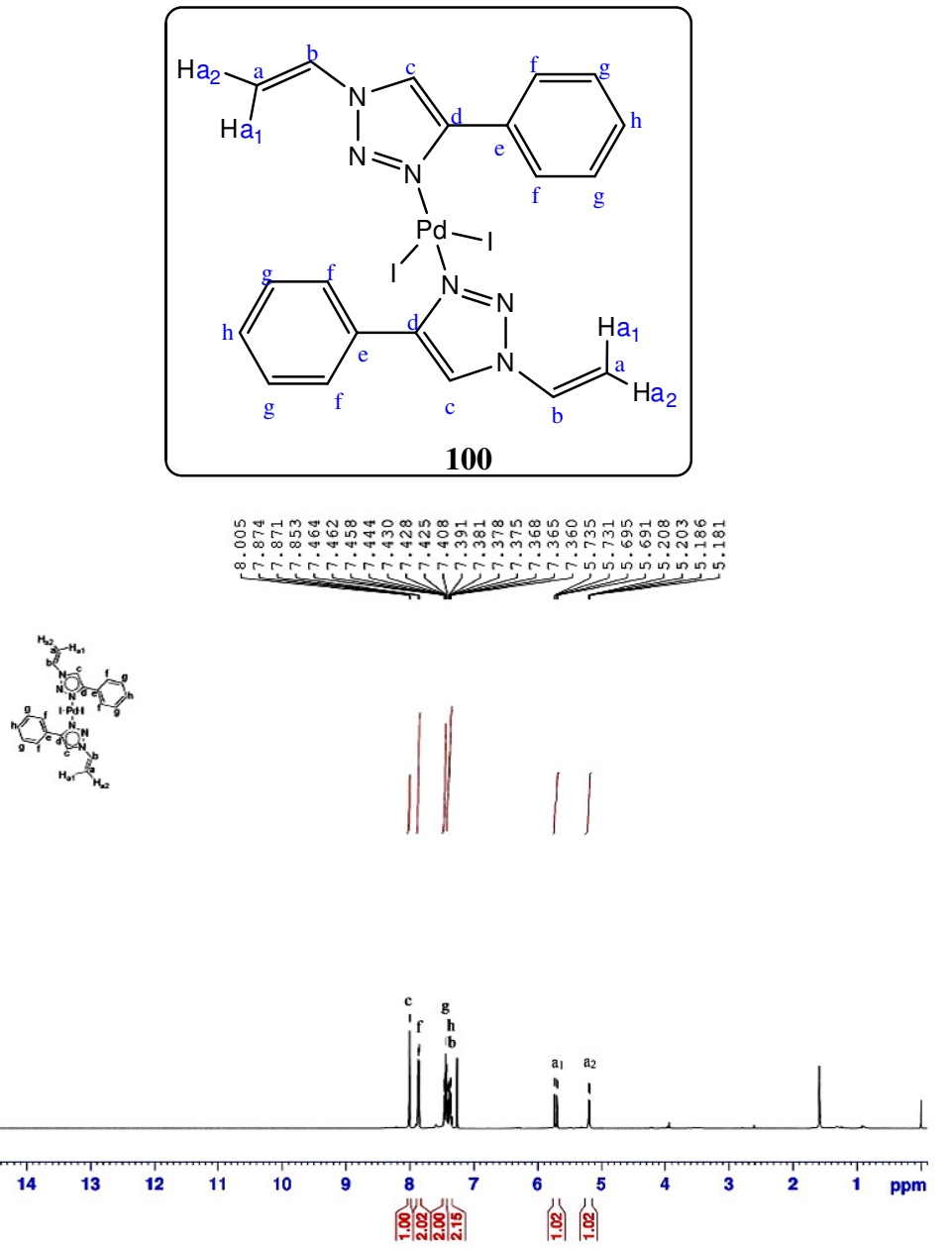


Fig 11.1 ^{1}H NMR of compound **100**

Protons of vinylic carbons (**a_1** & **a_2**) observed at 5.19 and 5.71 ppm. Mulitplet at 7.39 ppm corresponds to both vinyl and phenyl para protons (**b** & **h**)**.** Another multiplet at 7.46 ppm for meta protons of phenyl ring. Peak observed at 7.87 ppm corresponds to ortho protons (**f**) and singlet at 8 ppm corresponds to proton of triazole carbon(**c**). In ^{13}C NMR, vinyl carbons observed at 104.6 and 116.1 ppm while triazole carbon peak was detected at 125.9 ppm. Aromatic carbons were identified at 128.5, 1289, 130, 130.4 and 148 ppm.

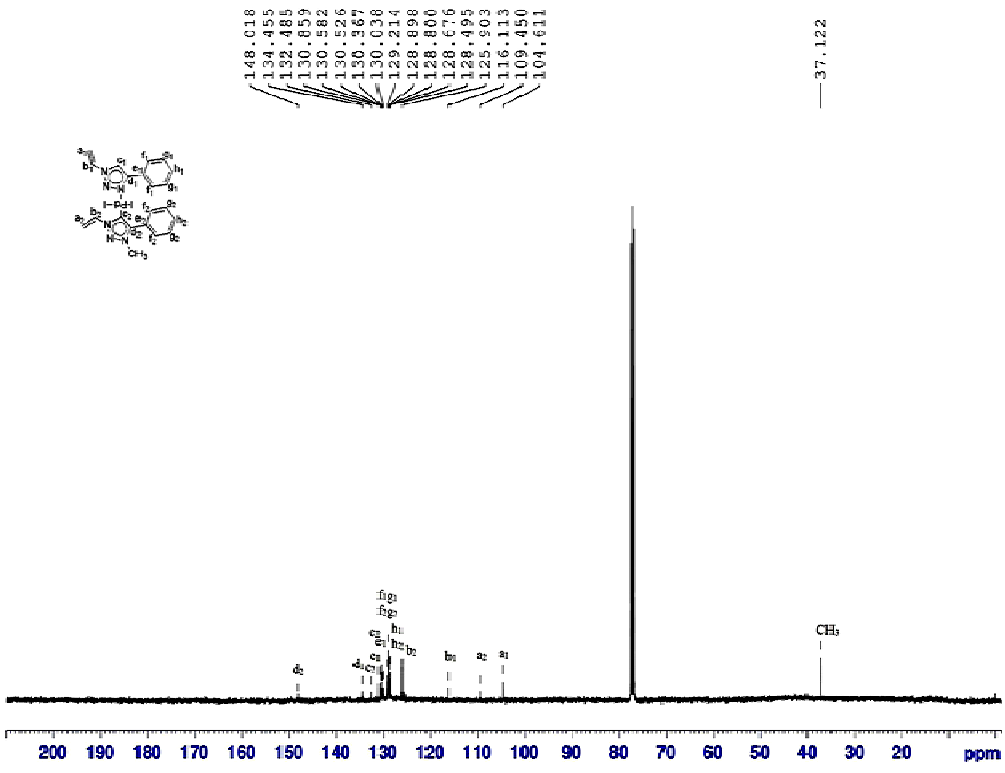
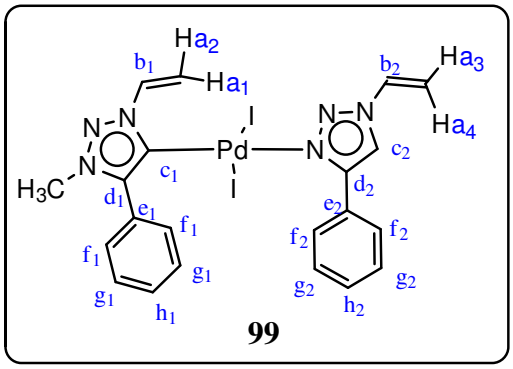


Fig 11.2 ^{13}C NMR of compound **100**



99

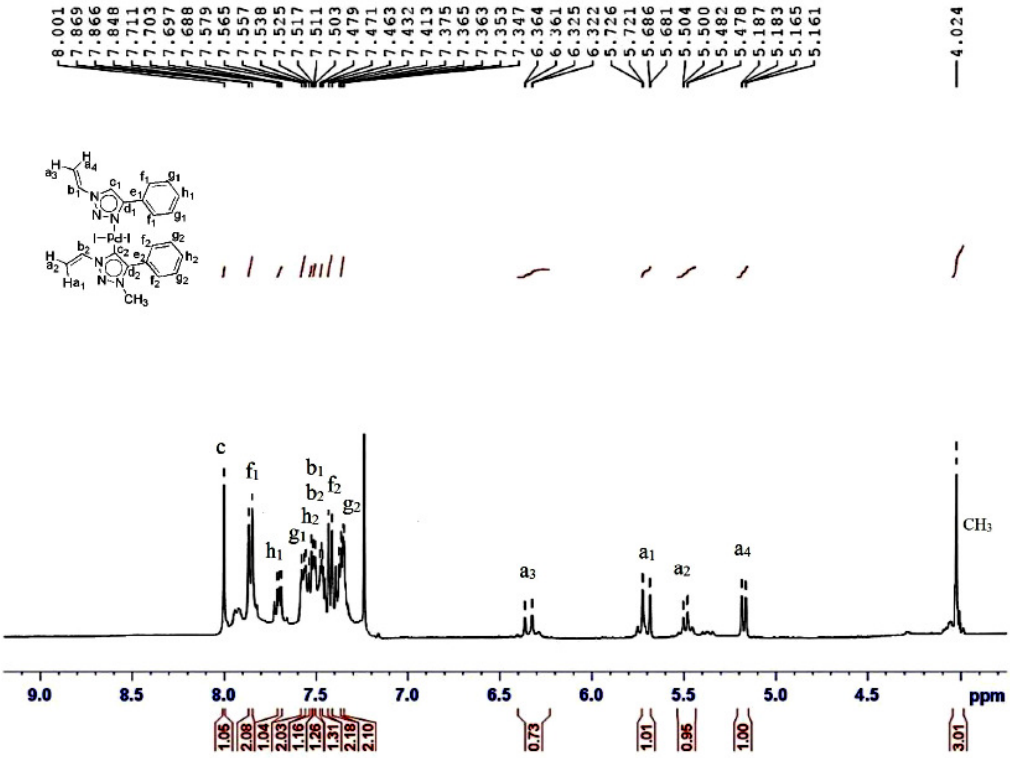


Fig 12.1 ^{1}H NMR of compound **99**

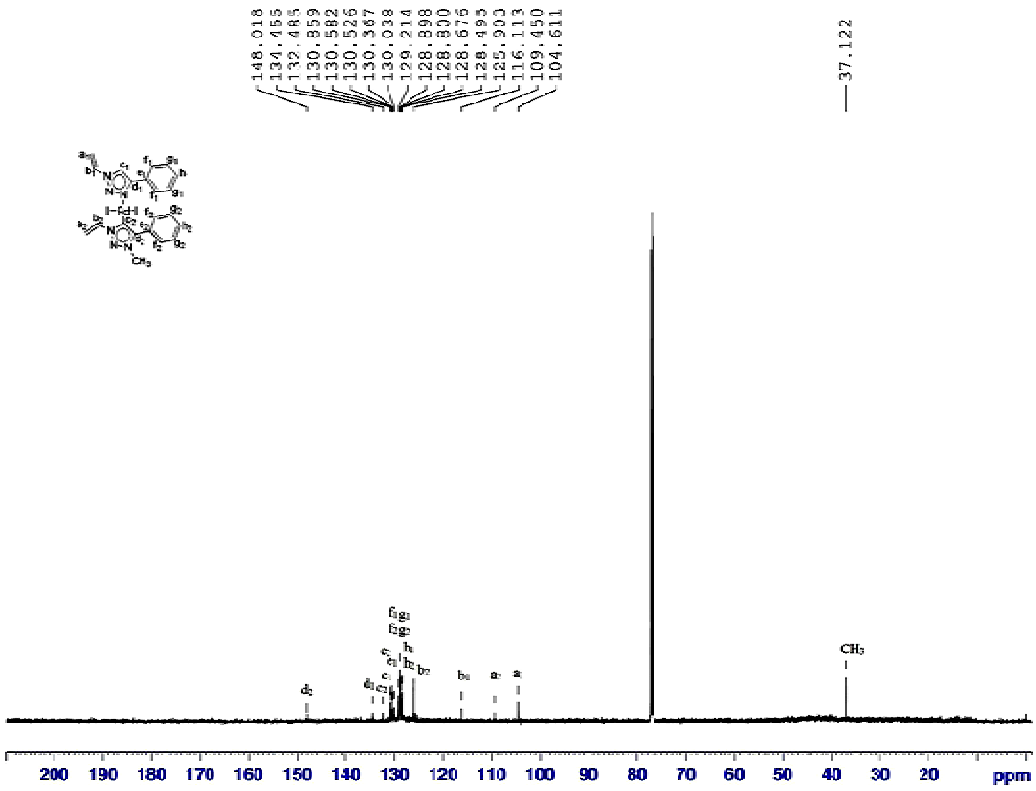
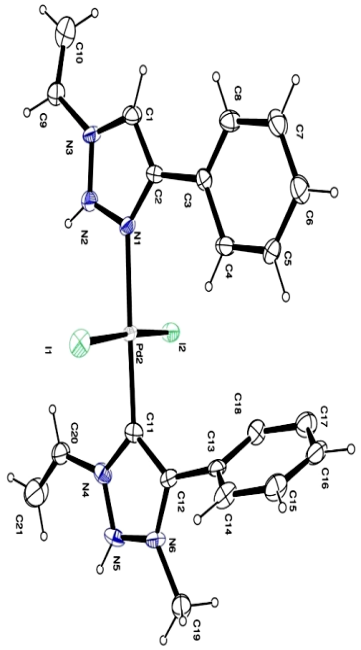


Fig 12.2 ^{13}C NMR of compound **99**

^{1}H NMR spectrum of **99** clearly indicates the presence of both N-bound triazole and C-bound triazolylidene ligands. Methyl group of the triazolylidene moiety appeared as singlet at 4.02 ppm similar to the bistriazolylidene complex **98**. Vinylic protons appeared as doublets at 5.1,5.5, 5.7,and 6.3 ppm, while the NCH protons of both ligands are shifted downfield to the aromatic region. One proton singlet at 8.0 ppm corresponds to the CH proton of the triazole ring which is consistent with the N-bound bistriazole palladium complex **100**. The ^{13}C NMR resonance peak also indicates the presence of N and C bound triazole ligands. The peak at 37.1 corresponds to CH_3 carbon. Total number of N-vinyl and aromatic carbons also account for the presence of N-bound triazole and C-bound triazolylidene ligands in the palladium complex.

Table 1 Crystallographic data of compound **99**



Parameters	
Formula	$C_{12}H_{20}I_2N_6Pd$
Formula weight	716.63
Crystal system	Triclinic
Space group	P-1
a (Å)	9.0794 (5)
b (Å)	12.1285 (7)
c (Å)	13.4377 (8)
α°	94.072(3)
β°	104.798(2)
γ°	93.927(2)
V (A^3)	1421.29(14)
T (K)	296(2)
Z	2
Reflections/unique	14906 / 3819
R_{int}	0.0317
μ mm^{-1}	2.841
***F*(000)**	680
θ range	1.57 to 23.25
Goodness-of-fit on F^2	1.100
Final *R* indices	$R_1 = 0.0681$
	w$R_2 = 0.1817$
***R* indices**	$R_1 = 0.0841$
	w$R_2 = 0.1953$

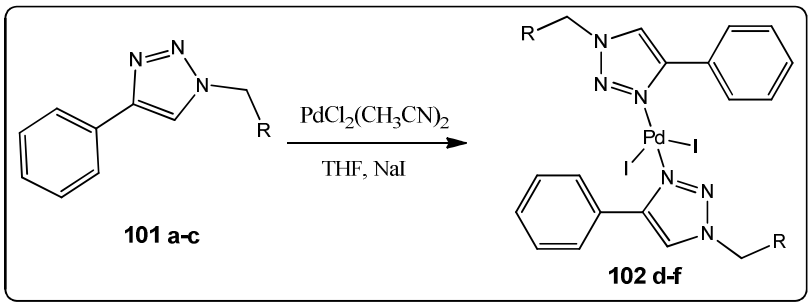
Fig. 13 ORTEP diagram of the palladium complex **99**

Pure crystals of **99** were obtained by slow diffusion of pentane into a solution of **99** in dichloromethane at room temperature. The palladium complex was characterized by single crystal X-ray diffraction (XRD) data (**Fig.13**). Single crystal XRD shows that the complex **99** adopts a distorted square planar geometry around the palladium centre. In complex **99** the two C,N ligands and the iodide ions respectively adopt *trans* geometry. The phenyl groups are oriented *cis* to each other with respect to C2-axis passing between the triazolylidene ligands, bisecting the N1-Pd-C11 angle. The Pd-C11 and Pd-N1 distances are 1.962 Å and 2.122 Å respectively. The bond lengths are similar to those related Pd $C_{carbene}$ complexes derived from triazolylidene and PEPPSI ligands[15] or imidazolylidene stabilized with N-donor ligands such as imidazole,[48] piperazine and DABCO,[49] bezoxazole,[50] dihydrooxazole,[51]

isoquinoline,[52] ethylamine[53] or PEPPSI.[20] Abnormal carbene NHC ligands are considered better σ donors than their normal analogues and this strong *trans* influence of 1,2,3-triazolylidene ligand is reflected in longer Pd-N1 bond length, favoring the "throw away" effect. Bond angle of N1-Pd-C11 was found to be 178.65 Å.

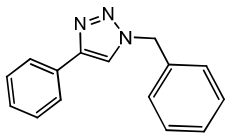
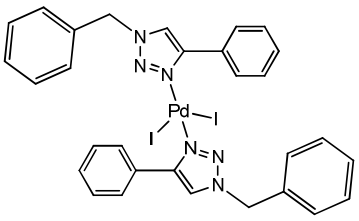
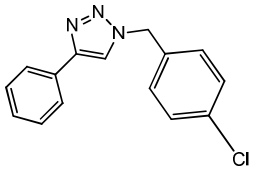
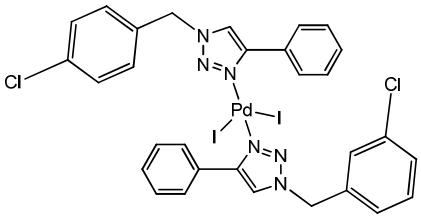
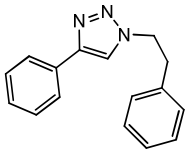
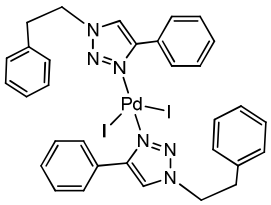
Synthesis of N-Pd-N complexes (102 d-f)

Reaction of three different 1,4-disubstituted-1,2,3-triazole (**101 a-c**) with bis(acetonitrile)dichloropalladium (II) in THF and in the presence of NaI at room temperature afforded an yellow colored solids having N-Pd-N bonding pattern (**102 d-f**).

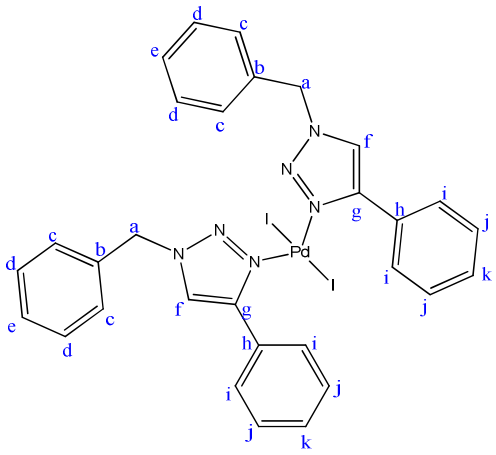


Scheme 31 General scheme for the synthesis of complexes having N-Pd-N bonding pattern

Table 2 N-Pd-N complexes

Reactant	Product
 1-benzyl-4-phenyl-1H-1,2,3-triazole **101a**	 $N_{benztzl}$-Pd-$N_{benztzl}$ **102d**
 1-(4-chlorobenzyl)-4-phenyl-1H-1,2,3-triazole **101b**	 $N_{Clbenztzl}$-Pd-$N_{Clbenztzl}$ **102e**
 1-phenethyl- 4-phenyl-1H-1,2,3-triazole **101c**	 $N_{phenethtzl}$-Pd-$N_{phenethtzl}$ **102f**

For the general discussion, compound **102d** was taken as representative molecule.



102d

^{1}H NMR of compound **102d is** given (**Fig 14.1**). Singlet observed at 5.61 ppm corresponds to benzylic protons (**a**), multiplet at 7.30-7.38 corresponds to ortho and para protons at **c** and **e**. protons at positions **d** and **k** provide multiplet at 7.40-7.48 ppm. 7.49-7.67 ppm corresponds to protons at **j** and peak detected at 7.8 ppm corresponds to proton at **i**. The triazole proton shows singlet at 8.33 ppm.

The ^{13}C NMR (**Fig. 14.2**) spectrum is in agreement with ^{1}H NMR spectral data. The downfield peak at δ149.6 ppm is due to the carbon at the position **g** and the characteristic peak of triazole carbon **f** observed at 119.5 ppm. The benzylic carbon **a** gives peak at 55.8 ppm and the values at 136.2, 128, 128.9 and 129.1 ppm corresponds to **b, c, d** & **e** carbons of pneyl ring. Peaks at 125.7, 128.1 and 128.8 belong to phenyl carbons attached to triazole carbon.

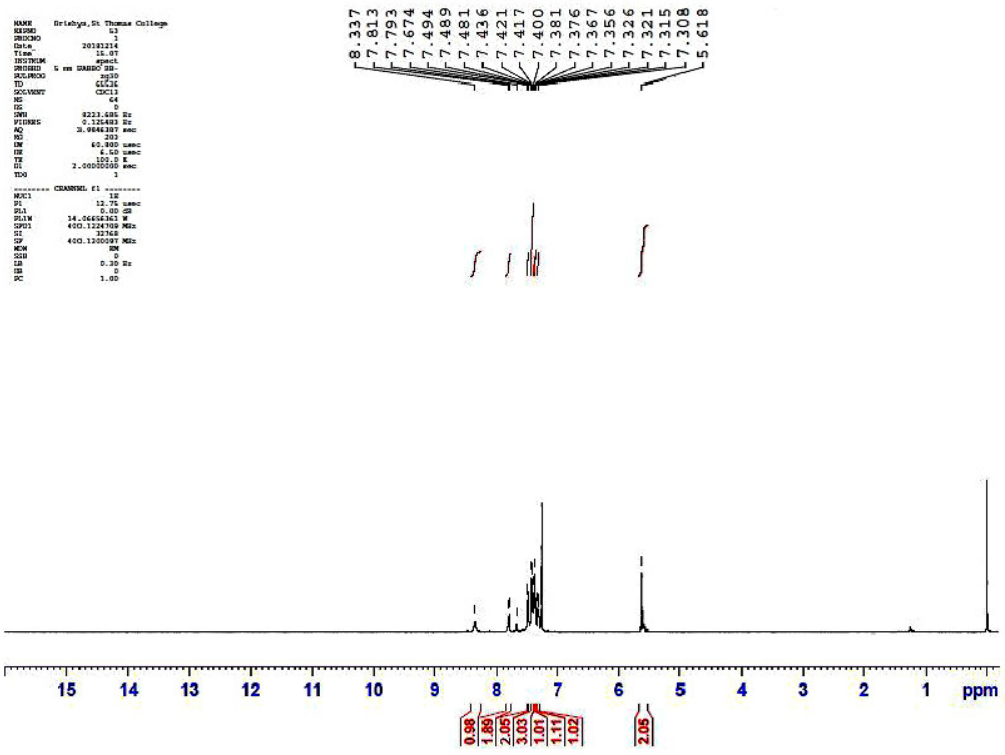


Fig 14.1 ^{1}H NMR of compound **102d**

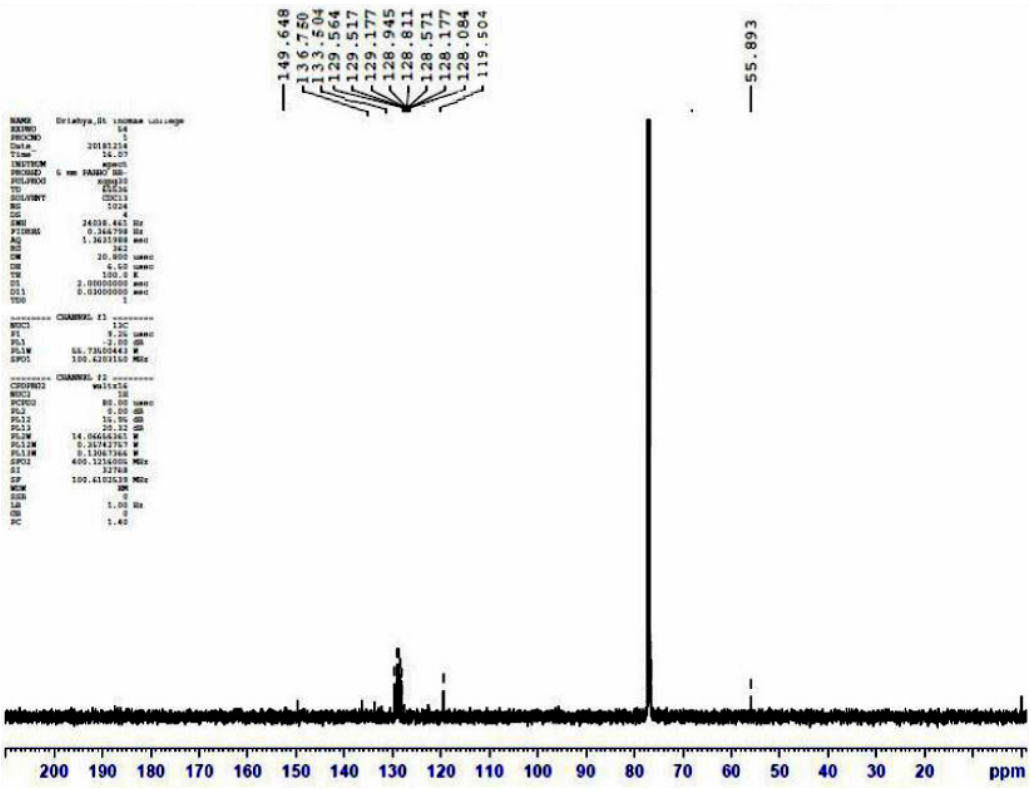
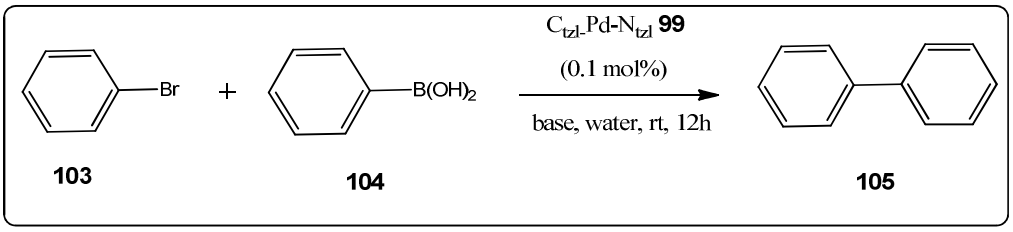


Fig 14.2 ^{13}C NMR of compound **102d**

5.4.2 Catalytic Studies of C_{tzl}-Pd- N_{tzl} complex (99)

The palladium complex **99** was screened as catalyst for Suzuki-Miyaura coupling of aryl halides with aryl boronic acids. Bromobenzene and phenyl boronic acid were selected as model substrates and the reaction was carried out under mild conditions using different bases (**Scheme 32 & Table 3**). Among the bases used, potassium *tert*-butoxide (KO^tBu) was found to be the most suitable one under our reaction conditions and gives the product biphenyls in excellent yield. KOH, K_2CO_3 and Cs_2CO_3etc resulted in slightly lower yields. The aryl halide, phenyl boronic acid, palladium catalyst and KO^tBu were taken in RB flask containing water and stirred at room temperature for 12 h. The reaction was carried out with very low catalyst loading (0.1 mol%). The better yield was obtained in the case of KO^tBu compared to KOH probably due to the difference in the dissociation constants (pKa, KOH= 15.7 and pKa, KO^tBu=17). Optimum concentration of the hydroxide is important in the formation of hydroxypalladium complex, transmetallation process and to prevent the formation of $ArB(OH)_3$.[54–56] Kolmgorov-Smirnov test was used to verify the normality of yields of KO^tBu and KOH. *t*-Test was performed to examine whether there is significant difference between the yields obtained using KO^tBu and KOH. Since the obtained p value (0.025) is less than 0.05 and there is a significant difference in the yields obtained using KO^tBu and KOH (5% level of significance)



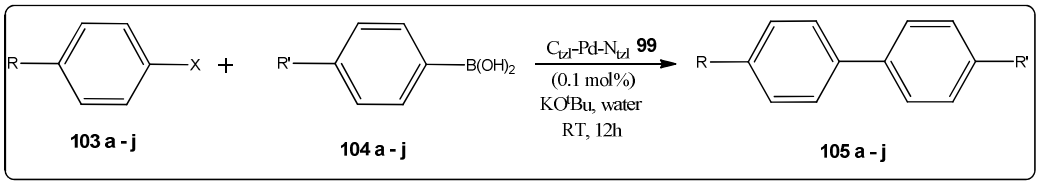
Scheme 32

Table 3 Optimization of base used for the C_{tzl}-Pd(II)-N_{tzl} complex **99** catalyzed coupling of bromobenzene **101** with phenyl boronic acid **102**

Entry[a]	Base	Yield[b] (%)
1	K_2CO_3	91
2	Na_2CO_3	86
3	Cs_2CO_3	85
4	HCOONa	45
5	$NaHCO_3$	72
6	NaOH	83
7	KOH	87
8	KO^tBu	94
9	NaO^tBu	89

[a]All reactions were carried out using **101** (1.0mmol), **102** (1.0mmol), **99**(0.1 mol%), base(2 equiv.) H_2O (5ml) at room temperature for 12h. [b] Isolated yield.

Efficiency of other palladium complexes **98** and **100** towards this coupling reaction were also investigated. However they were found to be less reactive than the C_{tzl}-Pd-N_{tzl} complex **99.** similarly, this catalyst as found to be equally good or even better than other water soluble palladium non-carbene systems.[57–60] The catalyst **99** was very effective in coupling aryl chlorides, bromides or iodides with aryl boronic acids (**Scheme 33**). It was observed that the presence of electron donating or electron withdrawing groups had very little effect on the overall yield of the product (**Table 4**).



Scheme 33

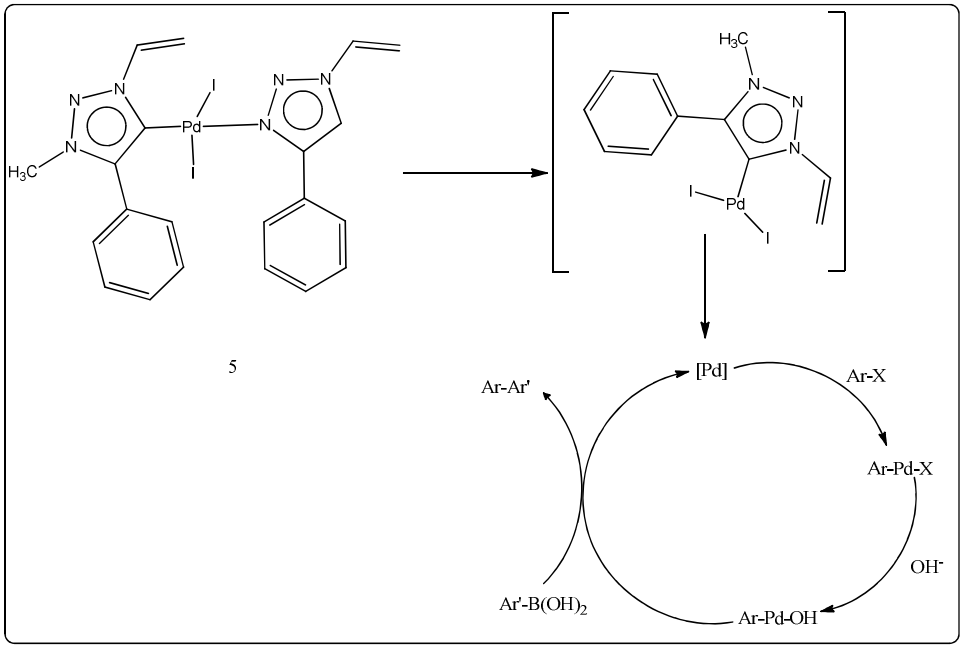
Table 4 Suzuki-Miyaura coupling reaction of aryl halides and boronic acids at room temperature

Entry[a]	R (103 a-j)	R' (104 a-j)	X	Yield[b] (%) (105 a-j)
1	H	H	I	94
2	H	OMe	I	92
3	CH_3	OMe	I	88
4	CH_3	H	I	90

5	H	2-furyl $B(OH)_2$	I	92
6	CH_3	2-furyl $B(OH)_2$	I	90
7	H	H	Br	92
8	$COCH_3$	H	Br	94
9	H	H	Cl	92
10	$COCH_3$	H	Cl	95

[a]Reactions Conditions: Aryl halide(1mmol), aryl boronic acid (1.1mmol), catalyst **99** (0.1mol%), base (KO^tBu, 2mmol), and 5ml water. [b]Isolated yield.

Reusability of the catalyst is of utmost significance with respect to economical and green chemistry perspectives. We have investigated the reusability of the catalyst by performing several catalytic runs in the same reaction vessel. Four catalytic runs were carried out by taking 0.1mol% of the catalyst. After an interval of 12h each, the product formed was extracted using diethyl ether and fresh batch of substrate and base was added into the reaction vessel without adding the catalyst. The substrate consumption was monitored by gas chromatography-mass spectrometry (GC-MS) and even after four successive runs it was observed that the overall yield was about 90%. This indicates that there is no loss of catalytic activity. The catalytic cycle herein involves heterogenization of the pre-catalyst into palladium nanoparticles which are stabilized by the triazolylidene or triazole present in the system. Imidazolium and ammonium salts are known to stabilize palladium nanoparticles generated from palladium NHC complexes.[61,62] Mercury poisoning test was used to study the involvement of palladium nanoparticles. Addition of one drop of Hg(0) to the reaction mixture reduced or decreased the yield of the reaction from 94% to 20% (**Table 10**, **entry 1**) clearly indicating the heterogenous nature of the catalyst.

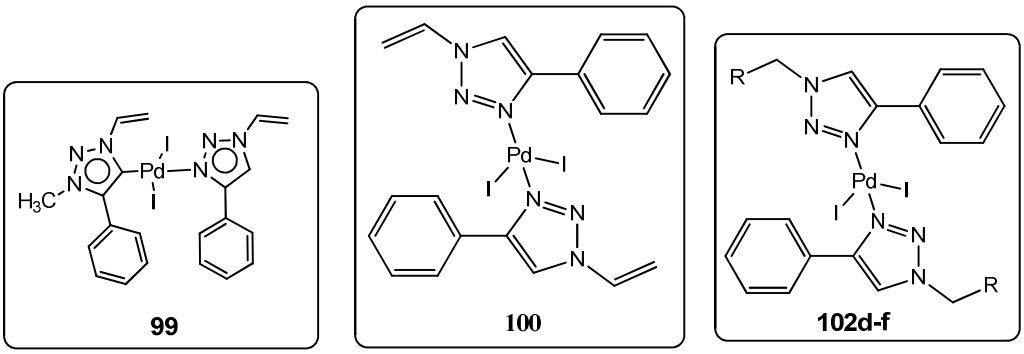


Scheme 34 Plausible mechanism for Suzuki-Miyaura coupling reaction in water

5.4.3 Cytotoxicity studies of complexes

The *in vitro* cytotoxic activity of complexes having different bonding pattern (**99**,**100** and **102 d-f**) were studied using Daltons Lymphoma Ascites (DLA) and Ehrlichs Ascites Carcinoma (EAC) cell lines. Reference drug cyclophosphmaide was used for the study.

Surprisingly, all palladium complexes show excellent *in vitro* cytotoxic activity compared to cyclophsphamide against both DLA and EAC cell lines. In DLA cell line with 200 µg of complex **99** produced 70% of cytotoxicity while 100 µg of the same drug produces 55% cell death. At lower concentrations such as 50 µg, 20 µg and 10 µg cytotoxicity was found to be decreased to 40%, 36% and 26% respectively. Complex **99** provides much more cytotoxicity towards DLA cell lines compared to complexes with N-Pd-N bonding pattern. Complex **100,** at 200 µg concentration produces 80% activity. As the concentration decreased to 100 µg, 50 µg, 20 µg and 10 µg the cytotoxicity decreases to 65%, 58% 46% and 35% respectively.



Similar results were obtained with EAC cell line using both complex **100** and **99**. Using 200 µg of complex **100** produce 68% cytotoxicity whereas 85% cytotoxicity was observed in complex **99** with same concentration. 100 µg of both complexes **100** and **99** exhibit 52% and 70% respectively. At lower concentrations like 50 µg, 20 µg and 10 µg complex **100** produce 35%, 30% and 28% respectively whereas complex **99** exhibit 56% 50% and 41% cytotoxicity.

Like complex **99**, complexes **102d-f** produces similar results which indicate that complexes with similar bonding pattern will have similar activity against both DLA and EAC cell lines (**Table 5 &6, Fig 15**). For DLA cell line the IC_{50} value of the complex **99** is 29 µg and for complex **100** it is about 84 µg. For EAC cell lines IC_{50} value of the same complexes is about 20 µg and 94 µg respectively. For DLA cell line

IC_{50} value observed at 120 µg 80 µg and126 µg for complex **102d, 102e** and **102f** respectively and that for EAC observed at 100 µg, 92 µg and 95 µg for the complexes **102d, 102e** and **102f** respectively.

We can conclude that low concentration of complex **99** is enough to produce high cell death compared to other complexes. These results pointed out that complex **99** with C-Pd-N bonding pattern shows better activity at low concentration when compared to complexes with N-Pd-N bonding pattern**.** Even though both NHC-Pd(II) complexes produce cytotoxicity towards Dalton's lymphoma ascites cell and Ehrlich's ascites carcinoma cell and the cytotoxicity was found to be concentration dependent.

Table 5 Cytoxicity results of complexes **99** & **100**

Conc(µg)	**Complexes**			
	99		**100**	
	DLA	**EAC**	**DLA**	**EAC**
200µg	80	85	70	68
100 µg	65	70	55	52
50 µg	58	56	40	35
20 µg	46	50	36	30
10 µg	35	40	26	28

Table 6 Cytoxicity results of complexes **102d-f**

Conc(µg)	102d		102e		102f	
	DLA	**EAC**	**DLA**	**EAC**	**DLA**	**EAC**
200µg	58	56	62	58	56	62
100 µg	48	50	55	52	48	51
50 µg	44	39	42	36	29	32
20 µg	35	23	36	29	23	26
10 µg	23	19	30	25	17	19

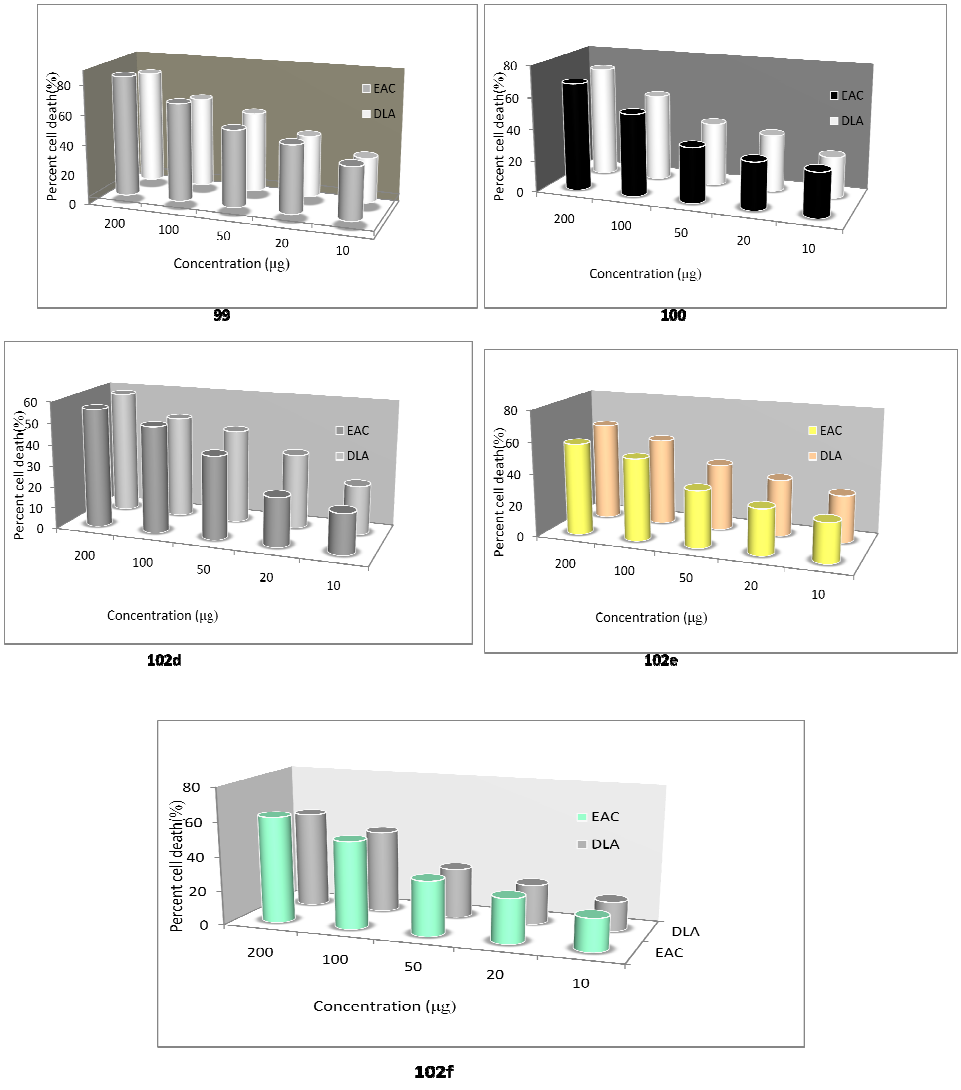
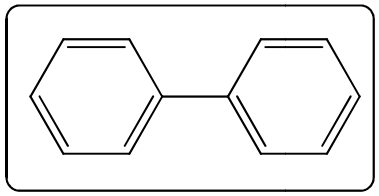


Fig 15. Cytotoxicity activities of complexes **99**, **100, 102 d-f**

5.5 Spectral data of compounds

1. 1,1'-biphenyl



^{1}H NMR (400 MHz, $CDCl_3$): δ7.59 (d, J = 7.2 Hz, 4H, C_6H_5), 7.44 (t, J = 7.4 Hz, 4H, C_6H_5), 7.01 (t, J = 6.4 Hz, 2H,). ^{13}C NMR (100.6 MHz, $CDCl_3$): 137.5, 128.7, 126.7, 126.6

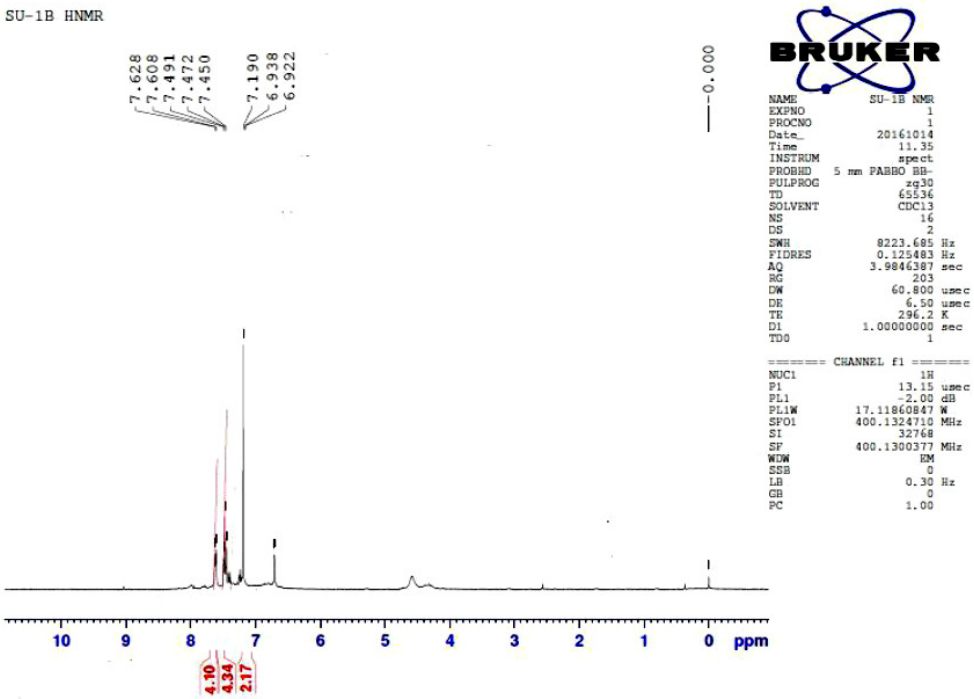


Fig 16.1 ^{1}H NMR of biphenyl

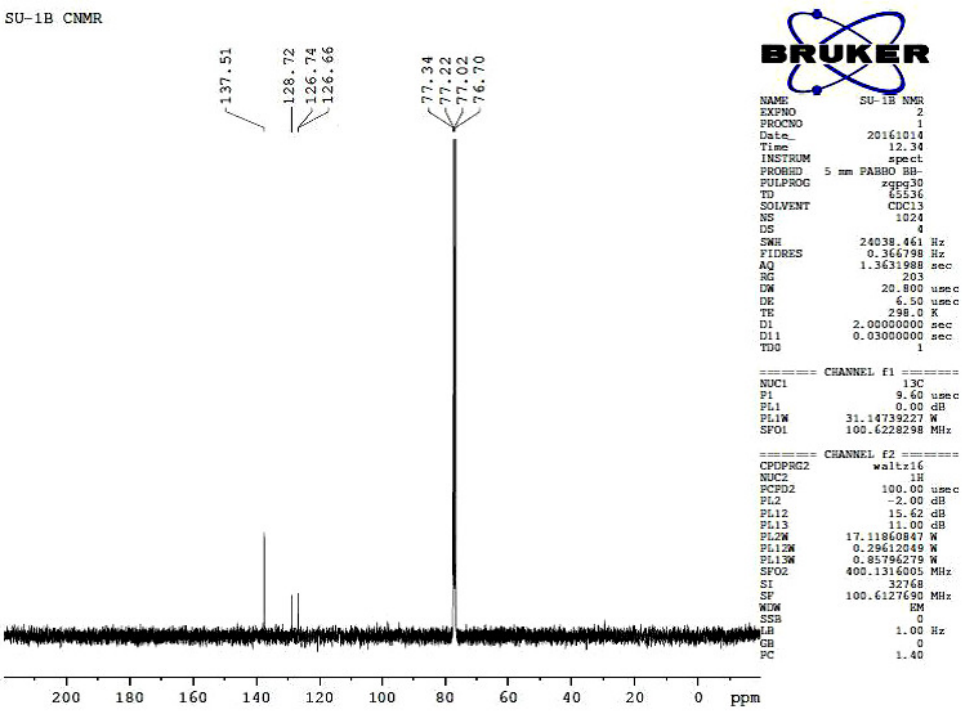
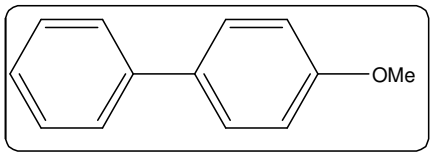


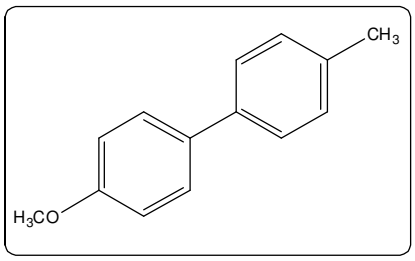
Fig 16.2 ^{13}C NMR of biphenyl

2. 4-methoxy-1,1'-biphenyl



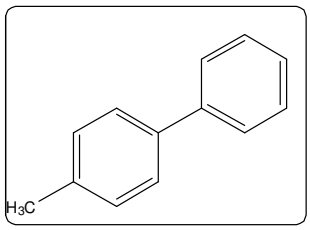
^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.60 (d, J = 1.6 Hz, 1H) ; 7.57 (d, J = 2.0 Hz, 2H) ; 7.55 (t, J = 3.2 Hz, 1H); 7.44 (m, 2H); 7.33 (t, J = 7.2 Hz, 1H); 7.01 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) : 159.21, 140.88, 132.28, 128.76, 128.19, 126.78, 115.78, 114.27, 55.38.

3. 4-methoxy-4'-methyl-1,1'-biphenyl



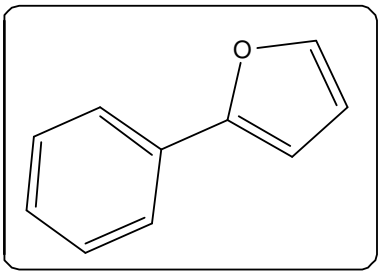
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.25 (m, 6H), 7.23-6.97 (m 2H), 3.87 (m, 3H), 2.31-2.44 (3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.12, 158.56, 141.59, 138.30, 135.51, 134.42, 130.33, 130.28, 129.94, 129.48, 128.67, 128.19, 127.98, 127.60, 127.45, 127.01, 126.62, 125.79, 123.89, 116.40, 114.18, 113.53, 55.36, 55.30, 21.59, 20.57.

4. 4-methyl-1,1'-biphenyl



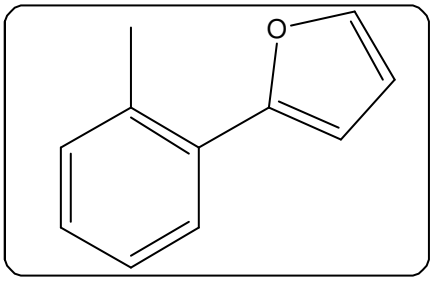
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.51 (m, 4H), 7.46–7.40 (m, 2H), 7.35-7.25 (m, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.47, 138.36, 136.88, 128.81, 128.21, 126.85, 21.32.

5. 2-Phenylfuran



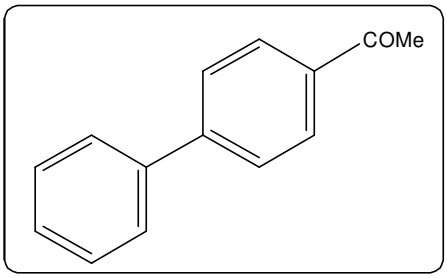
^{1}H NMR (400 MHz, CDCl3) δ 7.9 (dd, 1H) 7.75 (m, 2H, J = 7.7), 7.52 (m, 2H), 7.29-7.19 (m, 1H), 6.55 (d, 1H, J = 3.3 Hz), 6.51 (dd, 1H, J = 1.8, 3.3 Hz). ^{13}C NMR (100 MHz, CDCl3) δ 153.8, 141.8, 131.3, 127.6, 127.3, 124.1, 111.4, 108.6

6. 2-(*o*-tolyl)furan



^{1}H NMR (400 MHz, CDCl3) δ 7.6 (dd, 1H), 7.5(d, 1H), 7.3(m,1H), 7.29 (m, 2H), 6.49 (dd, 1H, J = 3.3 Hz), 6.26 (dd, 1H, J = 1.8, 3.3 Hz), 2.3(s, 3H) ^{13}C NMR (100 MHz, CDCl3) δ 148.5, 141.8, 136.1, 132.8, 131.3, 130.1, 128.9, 127.6, 127.3, 122.1, 111.4, 109.8, 20.3

7. 1-([1,1'-biphenyl]-4-yl)ethanone

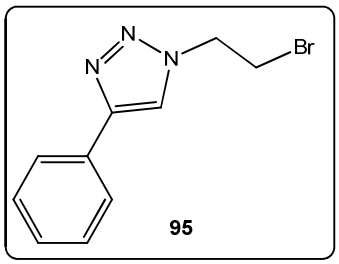


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.2 Hz, 2H, C_6H_4), 7.70 (d, J = 8.2 Hz, 2H, C_6H_4), 7.63 (d, J = 7.4 Hz, 2H, C_6H_5), 7.45-7.50 (t, J = 7.4 Hz, 2H, C_6H_5), 7.37-7.42 (m, 1H, C_6H_5), 2.64 (s, 3H, CH3). ^{13}C NMR (100 MHz, $CDCl_3$): 197.65, 145.75, 135.90, 132.68, 128.95, 128.90, 128.23, 127.26, 127.20, 26.60

5.6 Experimental details

5.6.1 Synthesis of 1-(2-bromoethyl)-4-phenyl-1,2,3-triazole(95)

1,2-dibromoethane (5.65 g, 30 mmol), sodium azide (0.65 g, 10 mmol), phenyl acetylene (0.1g, 10mmol), copper acetate monohydrate (0.03g, 0.15 mmol) and sodium ascorbate (0.03 g, 0.15 mmol) were taken in an RB flask containing 20 ml *tert*-butyl alcohol and 10 ml of distilled water. The mixture was then heated at 65 °C for 18 h. It was then cooled to room temperature. Water (50 ml) was again added to it and extracted with ethyl acetate and dried using anhydrous sodium sulphate. The solvent and excess dibromoethane were removed using rotavapor. The product was then purified by passing through a silica gel column using a mixture of hexane and ethyl acetate (3:1) as eluent. The product was obtained as pale yellow needles.

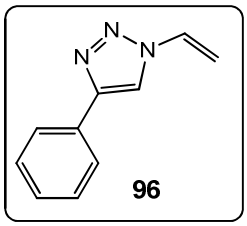


95

Yield- 2.0g (80%) Mp= 70°C, ^{1}H NMR ($CDCl_3$, 400MHz): δ 3.73 (t, *J* = 6 Hz, 2H, CH_2Br), 4.74 (t, *J* = 6 Hz, 2H, NCH_2), 7.28 (m, 1H, H_{Ar}), 7.36 (m, 2H, H_{Ar}), 7.78 (d, 2H, *J* = 7.6 Hz, H_{Ar}), 7.84 (s, 1H, H_{trz}) ppm. ^{13}C NMR ($CDCl_3$ 400 MHz): δ 29.3(CH_2Br), 51.7 (NCH_2), 120.5 (CH_{tzl}), 125.8 (C_{Ar}), 128.4 (C_{Ar}), 128.9 (C_{Ar}), 130.1 (C_{Ar}), 147.6 (C_{tzl}) ppm. EI-MS [M^+]: 251 (100%). Anal. found: C. 47.59; H, 4.05; Br, 31.65; N, 16. 75. Calc. for $C_{10}H_{10}BrN_3$: C, 47.64; H, 4.00; Br, 31.69; N,16.67.

5.6.2 Synthesis of 1-ethenyl-4-phenyl-1,2,3-triazole(96)

To a solution of 1-(2-bromoethyl)-4-phenyl-1,2,3-triazole **95** (1.0g, 4 mmol) in DMF (10 ml) and K_2CO_3 (2.8 g, 20 mmol) was added and stirred at 110 °C for 3 h. It was then cooled to room temperature. Water was added and extracted using ethyl acetate, dried over anhydrous sodium sulphate and concentrated. The product was purified by silica gel column using hexane and ethyl acetate (3:1) as eluent to afford pale yellow crystals.

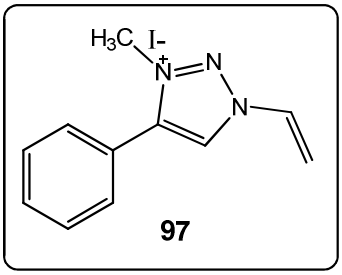


96

Yield 0.60g (87%). m.p. 85-86 °C. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.12 (dd, J = 1.2, 10 Hz, 1H, HCH_2), 5.64 (dd,J = 1.2, 17.2 Hz, 1H, HCH_2) 7.2 (m, 2H, H_{Ar}+ H_{NCH}), 7.3 (t, J = 7.6 Hz, 2H, H_{Ar}), 7.7 (d, J =7.2 Hz, 2H, H_{Ar}), 7.93 (s 1H, H_{tzl}) ^{13}C NMR: (100 MHz, $CDCl_3$) δ 103.6 (CH_2), 115 (NCH),124. 8 (CH_{tzl}), 127.4 (CH_{Ar}), 127.8 (CH_{Ar}), 129.0 (CH_{Ar}), 129.3 (C_{Ar}), 147.0 (C_{tzl}) ppm. EI-MS[M^+]: 171 (100%). Anal. found: C. 70.42; H, 5.25; N, 24. 84. Calc. for $C_{10}H_{10}BrN_3$: C, 70.16; H, 5.30; N, 24.54.

5.6.3 Synthesis of 1-ethenyl-3-methyl-4-phenyl-1,2,3-triazolium iodide (97)

1-Ethenyl-4-phenyl-1,2,3-triazole (**96**) (0.31 g, 1 mmol) was taken in acetonitrile(10 ml) to which iodomethane (2.84 g, 2 mmol) was added and heated at 60 °C overnight. After complete consumption of the starting material, the solvent was evaporated under reduced pressure. The solid obtained was washed with dichlorometane: hexane mixture (1:3). The product was obtained as off-white solid.



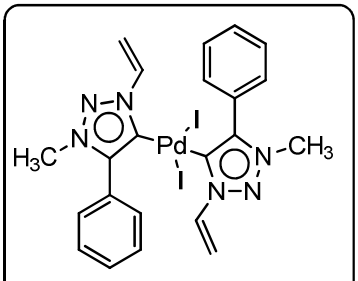
97

Yield 0.30 g(96%). m.p. 90 °C. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.38 (s, 3H, CH_3), 5.19 (dd, J = 1.6, 10.4 Hz, 1H, H_{CH2}), 5.70–5.72 (m, 1H,H_{CH2}), 6.56 (dd, J = 3.2, 18 Hz, 1H, NCH), 7.44 (t, J = 7.2 Hz, 1H, H_{Ar}), 7.64–7.70 (m, 2H, H_{Ar}), 7.79–7.87 (m, 2H, H_{Ar}), 9.74 (s, 1H, H_{tzl}). 13C NMR: (100 MHz, $CDCl_3$) δ 39.6 (CH3), 104.7 (=CH_2), 116.4 (NCH), 125.9 (CH_{Ar}), 127.3 (CH_{Ar}), 128.9 (CH_{Ar}), 129.8 (C_{Ar}), 132.3(CH_{tzl}), 159.6 (C_{tzl}). Anal. Calc. for $C_{11}H_{11}N_3$: C, 42.33; H, 3.55; I, 40.66; N, 13.46. Found:C. 42.52; H, 3.42; I, 40.36; N, 13.63.

5.6.4 Synthesis of C_{tzl}-Pd-C_{tzl} complex (98)

To an oven dried Schlenk flask, 10 ml of dried THF was added followed by 1-ethenyl-3-methyl-4-phenyl-1,2,3-triazolium iodide (**97**) (0.20 g, 0.63 mmol). Nitrogen

gas was passed through the solution for 10 min and palladium acetate (0.07 g, 0.32 mmol) was added. The reaction mixture was stirred at 80 °C for 4 h. It was then cooled to room temperature and poured into ice water, extracted using ethyl acetate, dried over anhydrous sodium sulphate and concentrated. The product was purified by column chromatography (hexane: ethyl acetate (4:1) over silica gel to get an orange solid.

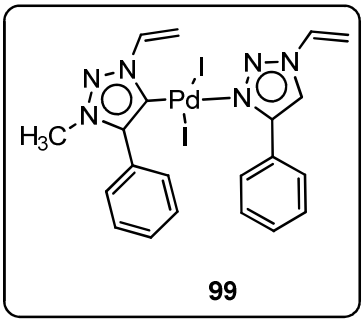


98

62% yield (0.14g). m.p. 120°C, 1H NMR: (400MHz, $CDCl_3$) δ 3.99 (s, 3H, CH_3), 5.50 (d, J = 8.8 Hz, 1H, HCH_2), 6.35 (d, J = 15.6 Hz, 1H, HCH_2), 7.37 (q, J = 1.6 Hz, 1H, NCH), 7.48 (t, J = 6.4 Hz, 1H, H_{Ar}), 7.52–7.58 (m, 2H, H_{Ar}), 7.81 (s, 2H, H_{Ar}). ^{13}C NMR: (100 MHz, $CDCl^3$) δ 37.9 (CH_3), 101.7 (=CH_2), 110.1 (NCH), 128.8 (CHAr), 129.1 (CH_{Ar}), 129.2 (HC_{Ar}), 130.1 (C_{Ar}), 130.4 (C_{tzl}–Pd), 144.8 (C_{tzl}–Ph). Anal. Calc. for $C_{22}H_{22}I_2N_6Pd$: C, 36.16; H, 3.03; I, 34.74; N, 11.50. Found: C. 36.46; H, 3.07; I, 34.92; N, 11. 42.

5.6.5 Synthesis of C_{tzl}-Pd-N_{tzl} complex (99)

1-Ethenyl-3-methyl-4-phenyl-1,2,3-triazolium iodide (**97**) (0.20 g, 0.64 mmol) was taken in a Schlenk flask containing 10 ml dry THF. Nitrogen gas was purged through the solution for 10min. Bis triazole palladium complex (**100**) (0.45 g, 0.64 mmol) was added to the solution followed by the addition of K_2CO_3 (0.70 g, 5 mmol). The reaction mixture was then heated at 80 °C for 12 h. It was then cooled to room temperature and solvent removed in vacuum. The residue obtained was filtered through silica column using dichloromethane to afford the product **99** as orange solid. Single crystal was formed by slow diffusion of pentane into dichloromethane.

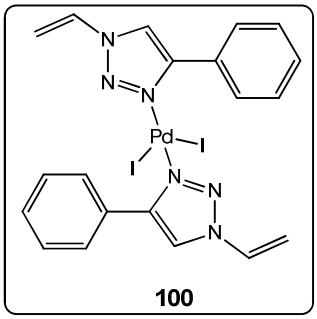


99

m.p. 160°C (decomposes). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.02 (s, 3H, CH_3), 5.17 (dd, J = 1.6, 10.4 Hz, 1H, HCH_2), 5.59 (dd, J = 1.6, 10.4 Hz, 1H, HCH_2), 5.77 (dd, J = 2, 18 Hz, 1H, HCH_2), 6.34 (dd, J = 1.2, 16.8 Hz,1H, HCH_2), 7.37 (m, 2H, H_{Ar}), 7.43 (d, 2H, J =7.6 Hz, H_{Ar}), 7.47 (m, 1H, NCH), 7.51 (m, 1H, NCH), 7.55 (m, 1H, J = 5.2 Hz, H_{Ar}) 7.68 (m, 2H, J = 5.6 Hz, H_{Ar}), 7.70 (m, 1H, H_{Ar}), 7.86 (m, 2H, H_{Ar}), 8.00 (s, 1H, H_{tzl}). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 37.1 (CH_3), 104.6 (=CH_2), 109.4 (=CH_2), 116.1 (NCH), 125.9 (NCH), 128.4 (C_{Ar}), 128.6 (C_{Ar}), 128.8 (C_{Ar}), 129.2 (C_{Ar}), 130.0 (C_{Ar}), 130.3, 130.5 (C_{Ar}), 130.6 (C_{Ar}), 130.8 (C_{tzl}), 132.4 (C_{tzl}–Pd), 134.4 (C_{tzl}–Ar), 148.0 (C_{tzl}–Ar). HRMS: Calc. 588.9829, Found; 588.9819 Anal. found: C. 35.12; H, 2.74; I, 35.57; N, 11. 63. Calc. for $C_{21}H_{20}I_2N_6Pd$: C, 35.19; H, 2.81; I, 35.42; N, 11.73; Pd, 14.85.

5.6.6 Synthesis of N_{tzl}-Pd-N_{tzl} complex (100)

To a solution of 1-ethenyl-4-phenyl-1,2,3-triazole **96** (0.170 g, 1 mmol) in THF, (bisacetonitrile) dichloropalladium (0.130 g, 0.5 mmol) and NaI (0.15 g, 1 mmol)were added. The solution was stirred at room temperature for overnight. Yellow solid obtained was filtered and washed with pentane to afford pure product **100**.



100

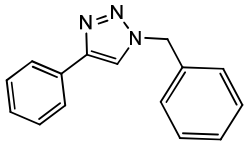
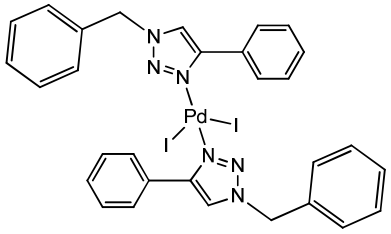
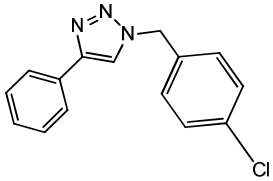
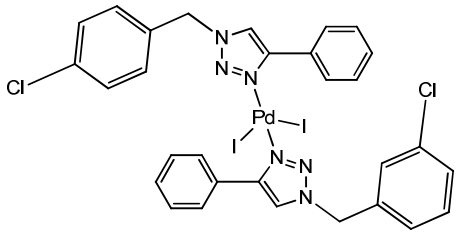
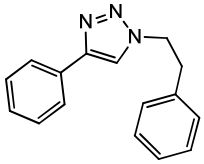
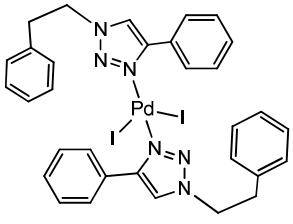
Yield: 0.31g, (90%). m.p. 70 °C, ^{1}H NMR: (400 MHz,$CDCl_3$) δ 5.19 (dd, J = 2, 10.8 Hz, 1H, HCH_2), 5.71 (dd, J = 1.6, 17.6 Hz, 1H, HCH_2), 7.39 (m,2H, H_{NCH}+HAr), 7.46 (m, 2H, H_{Ar}), 7.87 (t, 2H, J = 8.4 Hz, H_{Ar}), 8.0 (s, 1H, H_{tzl}) ^{13}C NMR: (100 MHz,

$CDCl_3$) δ 104.6 (C_{CH2}), 116.1(NCH), 125.9 (CH_{tzl}), 128.5 (CH_{Ar}), 128.9 (CH_{Ar}), 130.0 (CH_{Ar}) , 130.4 (C_{Ar}), 148.0 (C_{tzl}–Ph). Anal. found: C. 34.32; H, 2.42; I, 34.18; N, 11.75. Calc. for $C_{20}H_{18}I_2N_6Pd$: C, 34.19; H, 2.58; I, 36.12; N, 11.96.

5.6.7 Synthesis of complexes having N-Pd-N bonding pattern (102d-f)

To a solution of 1,4-disubstituted-1,2,3-triazole **(101 a-c)** (1 mmol) in THF, (bisacetonitrile) dichloropalladium (0.130 g, 0.5 mmol) and NaI (0.15 g, 1 mmol)were added. The solution was stirred at room temperature for overnight. Yellow solid obtained was filtered and washed with pentane to afford pure product (**102 d-f**) (**Table 2**).

Table 2 N-Pd-N complexes

Reactant	Product
 1-benzyl-4-phenyl-1H-1,2,3-triazole **101a**	 $N_{benztzl}$-Pd-$N_{benztzl}$ **102d**
 1-(4-chlorobenzyl)-4-phenyl-1H-1,2,3-triazole **101b**	 $N_{Clbenztzl}$-Pd-$N_{Clbenztzl}$ **102e**
 1-phenethyl- 4-phenyl-1H-1,2,3-triazole **101c**	 $N_{phenethtzl}$-Pd-$N_{phenethtzl}$ **102f**

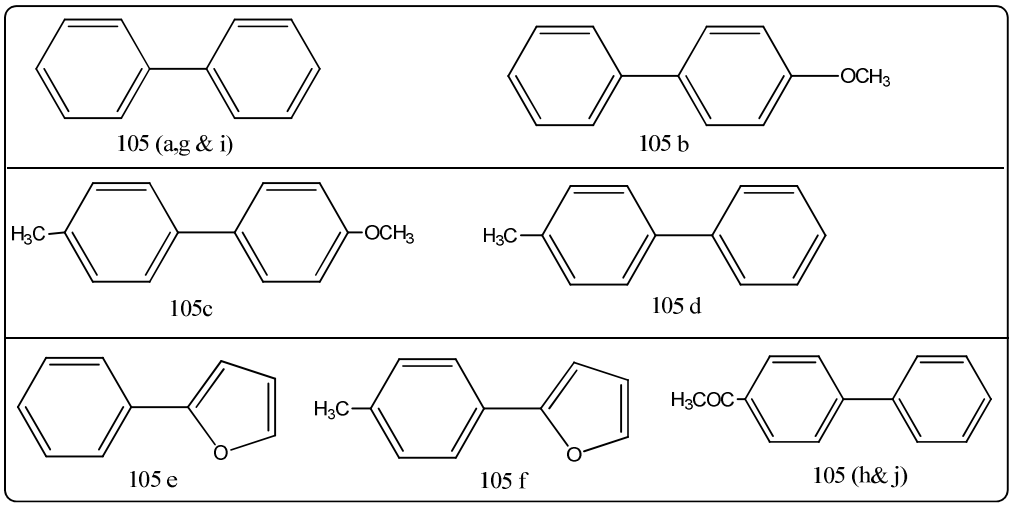
102d- Yield: 0.3 g (90%) m.p- 180 °C ^{1}H NMR: (400 MHz,$CDCl_3$) δ 5.61 (s,2H), 7.30-7.38 (m, 3H), 7.40-7.43(m, 3H), 7.48(t,2H, *J*= 2, 3.2), 7.81(m,2H), 8.33(s, 1H). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 55.89, 119.5, 125.7, 128.0, 128.1, 128.8, 128.9, 129.1, 133.5, 136.2, 149.6. Anal. Calc. for $C_{30}H_{26}I_2N_6Pd$: C, 43.37; H, 3.15; I, 30.55; N, 10.12; Pd, 12.81. Anal. Found: C, 43.32; H, 3.07; I, 30.52, N, 10.02.

102e- Yield: 0.35 g (92%) m.p- decomposes at 220 °C ^{1}H NMR: (400 MHz,$CDCl_3$) δ 5.55(s, 3H). 7.24 (dd, 2H,*J*= 1.5, 10.8 Hz). 7.32 (t, *J*= 7.2 Hz, 1H), 7.37-7.42(m, 5H), 7.49 (s, 1H), 7.79(dd, *J*=1.3, 10.2Hz, 2H) ^{13}C NMR: (100 MHz, $CDCl_3$) δ 52.3, 116.9, 127.05, 127.5, 127.85, 128.7, 129.38, 134.59, 136.83, 138.0, 149.51. Anal. Calc. for $C_{30}H_{24}Cl_2I_2N_6Pd$: C, 40.05; H, 2.69; Cl, 7.88; I, 28.21; N, 9.34; Pd, 11.83. Anal. Found: C, 40.10; H, 2.64; I, 28.18, N, 9.30.

102f-- Yield: 0.32 g (90%) m.p- decomposes at 230 °C ^{1}H NMR: (400 MHz,$CDCl_3$) δ 4.64(t, 2H, *J*=7.2, 8.4Hz). 3.30(t, *J*=7.2Hz, 2H) 7.14(dd, , *J*= 6.4, 7.8,1.3 Hz,2H) 7.27-7.33 (m, 3H),7.38-7.46(m,3H), 7.49 (dd, *J*= 7.7, 1.5 Hz, 2H) 7.77(s, 1H) ^{13}C NMR: (100 MHz, $CDCl_3$) δ 36.8, 51.9, 118.9, 125.7, 128.5, 128.7, 128.8, 128.8, 128.9, 129.0,137.8,147.9. Anal. Calc. for $C_{32}H_{30}I_2N_6Pd$: C, 44.75; H, 3.52; I, 29.55; N, 9.79; Pd, 12.39. Anal. Found: C, 44.69; H, 3.62; I, 29.50, N, 9.89.

5.6.7 General procedure for the Suzuki-Miyaura coupling reaction between aryl halide and aryl boronic acid

Nitrogen gas was purged through 5ml water taken in a Schlenk reaction tube for 10 min. Aryl boronic acid (1 mmol), aryl halide (1 mmol), KO^tBu (1.5 mmol) and the catalyst **99** (0.1 mol%) were successively added to it. The mixture was then stirred at room temperature for 12 h. It was then extracted with diethyl ether and dried over anhydrous sodium sulphate. The solvent was evaporated and the product obtained was purified by filtering through a silica gel column using hexane.



5.6.8 Cytotoxic studies of palladium N-heterocyclic carbene Complexes

Both DLA and EAC tumor cells were aspirated from the peritoneal cavity of tumor bearing mice, which was washed three times with phosphate buffered saline. The cell viability was determined using Trypan blue exclusion method. The viable cell suspension was treated with different concentration of complexes **99** and **100**. Total volume of the solution was made up to 1ml using buffer solution followed by incubation for 3h at 37°C. To the above suspension 0.1 ml of 1% trypan blue was added and kept for 2-3 minutes, and loaded to haemocytometer. Cytotoxicity was found out by counting the number of dead cell which in turn was observed by absorbing the blue color of trypan blue.

$$\% \text{ Cytotoxicity} = \frac{\text{No.of dead cells}}{No.of\ live\ cells + No.of\ dead\ cells} \times 100$$

5.7 Conclusion

Palladium complexes with different bonding pattern were synthesized. A new palladium complex with C_{tzl}-Pd-N_{tzl} was characterized by Single XRD. Newly synthesized palladium complex was found to be catalytically active for Suzuki-Miyaura coupling reaction in aqueous medium at room temperature. Coupling reaction performed with very low catalyst loading. Cytotoxicity studies of all synthesized complexes were studied and C_{tzl}-Pd-N_{tzl} complex shows higher cytotoxicity compared to other complexes.

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