IITB-Monash Research Academy

Indian Institute of Technology Bombay | MONASH University

An Indian-Australian research partnership

Project Title:	**Designing palladium based N−heterocyclic carbene complexes for anticancer application**	
Project Number	**IMURA0719**	
Monash Main Supervisor (Name, Email Id, Phone)	Prof. Glen Deacon Glen.deacon@monash.edu	*Full name, Email*
Monash Co-supervisor(s) (Name, Email Id, Phone)	Prof. Bayden Wood Bayden.wood@monash.edu	
Monash Head of Dept/Centre (Name,Email)	Dr David Turner (grad coordinator chemistry) david.turner@monash.edu	*Full name, email*
Monash Department:	Chemistry	
Monash ADRT (Name,Email)	Prof Peter Betts Peter.betts@monash.edu	*Full name, email*
IITB Main Supervisor (Name, Email Id, Phone)	Prof. Prasenjit Ghosh pghosh@chem.iitb.ac.in	*Full name, Email*
IITB Co-supervisor(s) (Name, Email Id, Phone)		*Full name, Email*
IITB Head of Dept (Name, Email, Phone)	Prof. Krishna P. Kaliappan hod@chem.iitb.ac.in	*Full name, email*
IITB Department:	Department of Chemistry	

Research Clusters:

Highlight which of the Academy's CLUSTERS this project will address? *(Please nominate JUST **one.** For more information, see www.iitbmonash.org)*

Research Themes:

Highlight which of the Academy's Theme(s) this project will address? *(Feel free to nominate more than one. For more information, see www.iitbmonash.org)*	

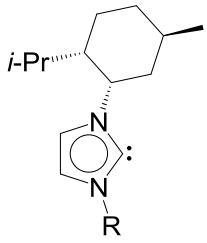
1	*Material Science/Engineering (including Nano, Metallurgy)*	***1***	*Advanced computational engineering, simulation and manufacture*
2	*Energy, Green Chem, Chemistry, Catalysis, Reaction Eng*	2	*Infrastructure Engineering*
3	*Math, CFD, Modelling, Manufacturing*		
4	*CSE, IT, Optimisation, Data, Sensors, Systems, Signal Processing, Control*	3	*Clean Energy*
5	*Earth Sciences and Civil Engineering (Geo, Water, Climate)*	4	*Water*
6	*Bio, Stem Cells, Bio Chem, Pharma, Food*	5	*Nanotechnology*
7	*Semi-Conductors, Optics, Photonics, Networks, Telecomm, Power Eng*	6	*Biotechnology and Stem Cell Research*
8	*HSS, Design, Management*		

The research problem

Define the problem

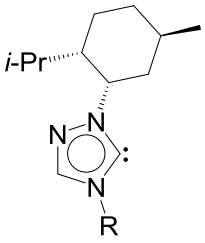
The project originates at a basic idea of looking for an alternative to platinum based anticancer metallodrugs for obvious toxicological issues associated with these complexes and thus it aims to explore the potential of palladium compounds as viable alternatives to platinum ones in cancer therapy. The project also aims to develop highly potent anticancer metallodrugs similar to that of some of the highly active organic counterparts as the metal based anticancer compounds are somewhat less potent, displaying IC_{50} values usually in μM range than the organic analogues having IC_{50} values in nM range. The project thus aims at enhancing the anticancer activity of the proposed palladium complexes through enhanced solubility in polar medium by incorporation of polar substituents on the ligand framework. The project further seeks to use N−heterocyclic carbene (NHC) as ligand platforms for stabilizing the proposed palladium complexes in light of the fact that these ligands remains unexplored for biomedical applications even though they have been immensely successful in homogeneous catalysis.

Based on our earlier observation (*J Am Chem Soc*., **2007** *129* 15042-15053) of $(NHC)_2PdCl_2$ complexes exhibiting promising anticancer activity with respect to cisplatin under *in-vitro* conditions, we propose to carry out a comprehensive variation of N−heterocyclic carbene ligand motifs in the current project. In this regard, the following six different N−heterocyclic carbene ligand motifs would be explored for the anticancer property studies (Figure 1).



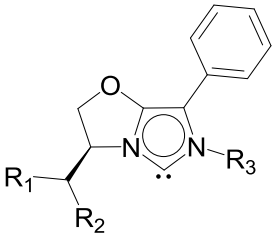
imidazole based NHC

(*i*).



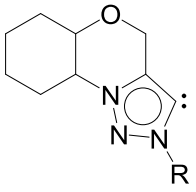
triazole based NHC

(*ii*).



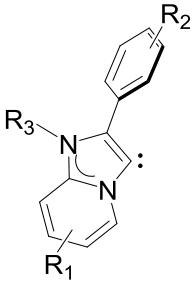
bicyclic oxazolidine fused NHC

(*iii*).



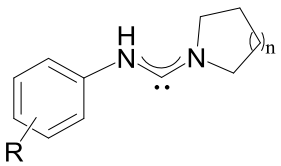
tricyclic triazolooxazine based NHC

(*iv*).



abnormal NHC (aNHC)

(*v*).



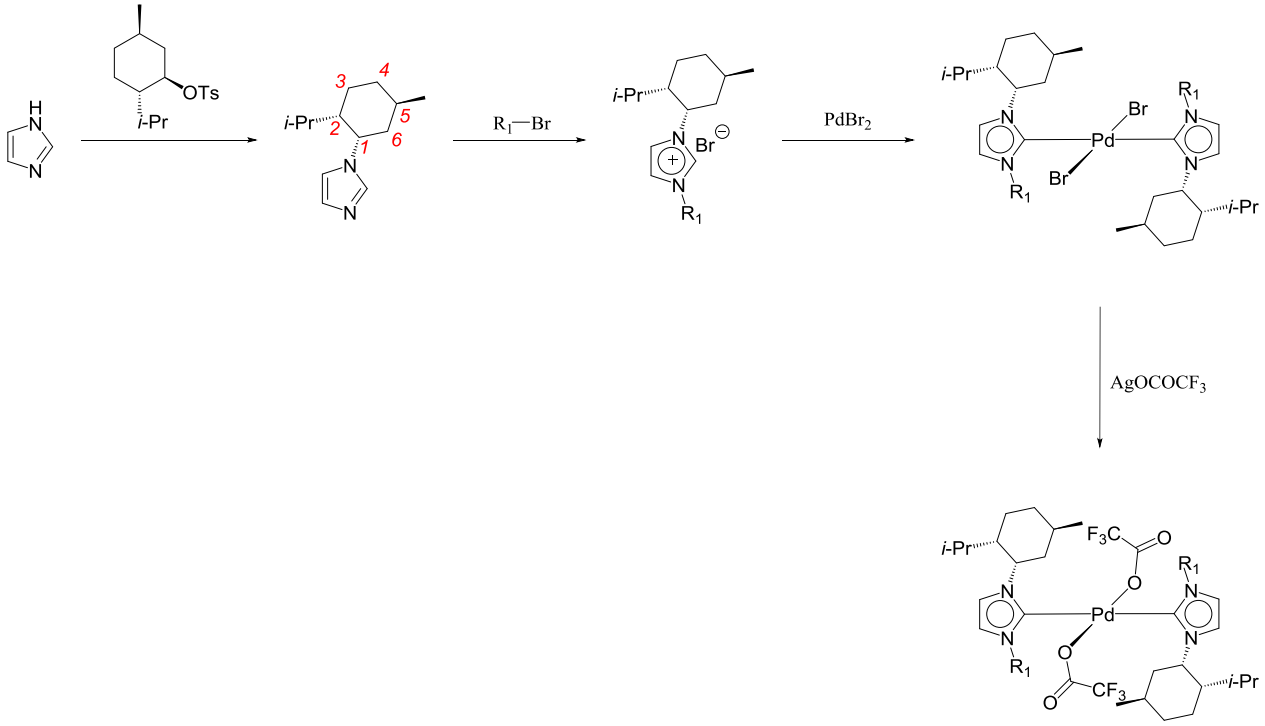
acyclic diamino carbene (ADC)

(*vi*).

Figure 1.

(*i*). Imidazole based NHC

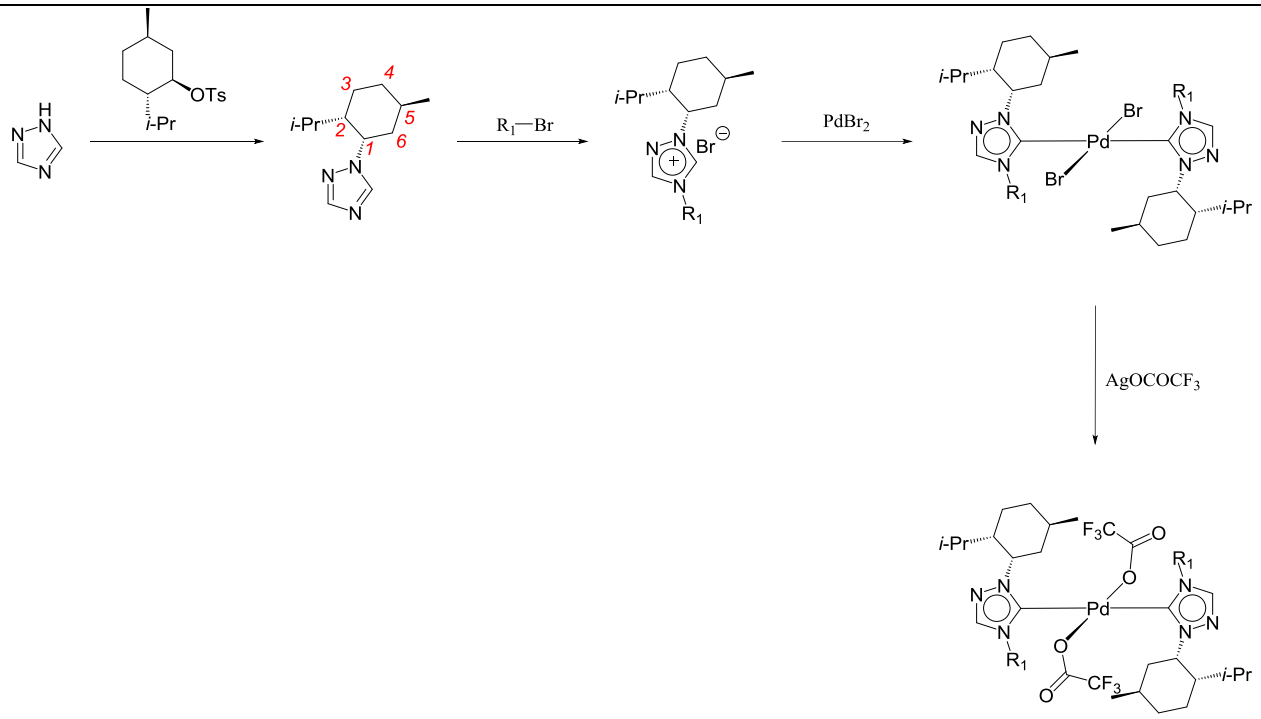
The imidazole derived N–heterocyclic carbene ligand precursors, would be prepared by the alkylation of 1-((*1S*,*2S*,*5R*)-2-i-propyl-5-methylcyclohexyl)-1H-imidazole (*Eur. J. Inorg. Chem*. **2015**, 1604–1615) with various alkyl and arylkyl halides. Subsequent reaction of the imidazole derived N–heterocyclic carbene ligand precursors, with $PdBr_2$ in the presence of Et_3N would give the imidazole derived *trans*-$(NHC)_2PdBr_2$ type complexes. Further the reaction of *trans*-$(NHC)_2PdBr_2$ type complexes with $AgOCOCF_3$ would give the imidazole derived *trans*-$(NHC)_2Pd(OCOCF_3)_2$ type complexes (Scheme 1).



Scheme 1.

(*ii*). Triazole based NHC

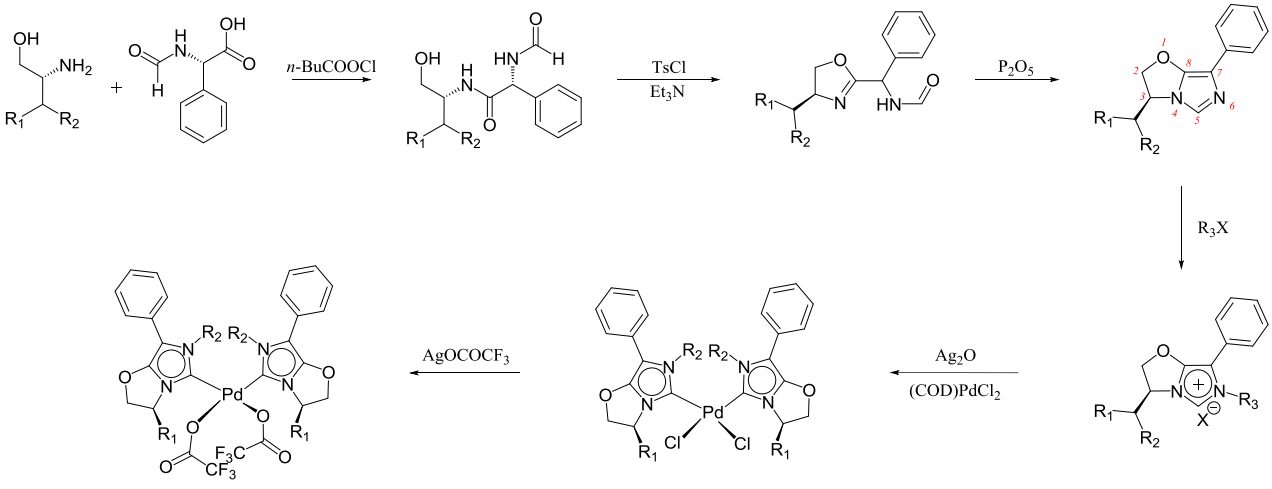
The 1,2,4-triazole derived N–heterocyclic carbene ligand precursors would be prepared by the alkylation of 1-((*1S*,*2S*,*5R*)-2-i-propyl-5-methylcyclohexyl)-1H-1,2,4-triazole with various alkyl and arylkyl halides. Subsequent reaction of the 1,2,4-triazole derived N–heterocyclic carbene ligand precursors, with $PdBr_2$ in the presence of Et_3N would give the triazole derived *trans*-$(NHC)_2PdBr_2$ type complexes (*Eur. J. Inorg. Chem*. 10.1002/ejic.201700017, In Press). Further the reaction of *trans*-$(NHC)_2PdBr_2$ type complexes with $AgOCOCF_3$ would give the triazole derived *trans*-$(NHC)_2Pd(OCOCF_3)_2$ type complexes (Scheme 2).



Scheme 2.

(*iii*). Bicyclic oxazolidine fused NHC

The bicyclic chiral oxazolidine fused imidazoles would be constructed in four steps, starting from the reaction of amino alcohols with (R)-2-formamido-2-phenylacetic acid in presence of *n*-butyl chloroformate and N-methyl morpholine as a base producing an amide intermediate. The intramolcular cyclization of the amide intermediate in presence of *p*-toluene sulphonyl chloride (TsCl) would result in the formation of the formyl oxazole derivatives. A second intramolcular cyclization leading to the chiral bicyclic oxazolidine fused imidazole compounds would be affected by the dehydration of formyl oxazole in presence of anhydrous P_2O_5. The alkylation of the oxazolidine fused imidazoles with various alkyl and arylkyl halides would give the corresponding chiral bicyclic oxazolidine fused N–heterocyclic carbene precursors. Further $(NHC)_2PdCl_2$ type complexes of chiral bicyclic oxazolidine fused N–heterocyclic carbene ligands would be synthesized by the reaction of the later with $(COD)PdCl_2$ through the transmetallation method. Subsequent reaction of $(NHC)_2PdCl_2$ type complexes with $AgOCOCF_3$ would give the chiral bicyclic oxazolidine fused N–heterocyclic carbene complexes of the type $(NHC)_2Pd(OCOCF_3)_2$ (Scheme 3).

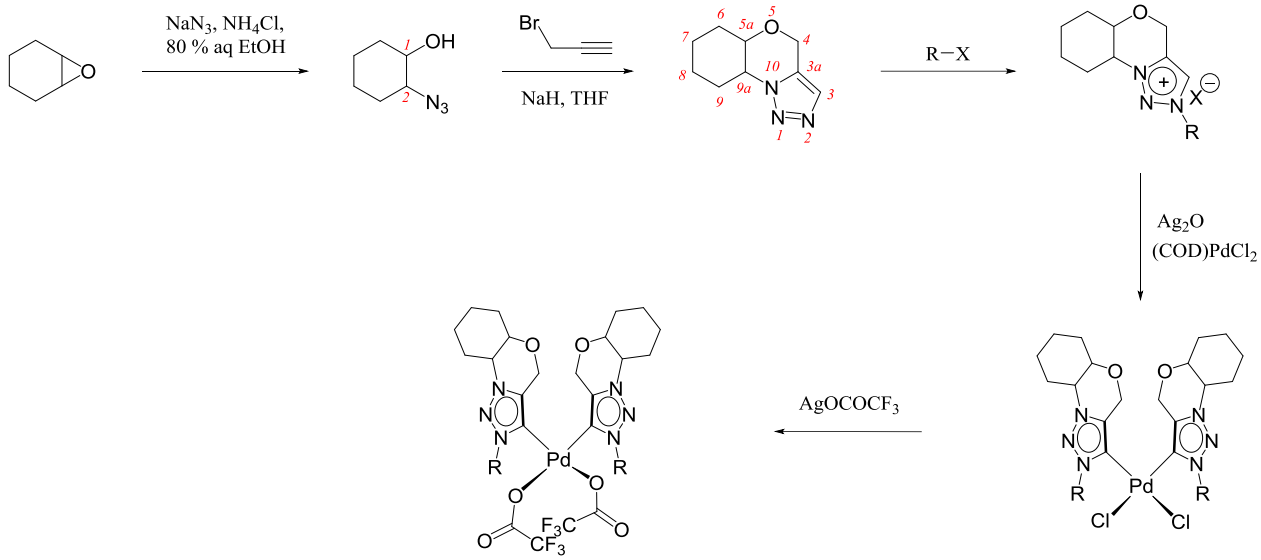


Scheme 3.

(*iv*). Tricyclic triazolooxazine based NHC

The ring opening of cyclohaxene oxide would end up in 2-azidocyclohexanol which upon reaction with propargylbromide would give the tricyclic triazolooxazine. The alkylation of the tricyclic triazolooxazine with

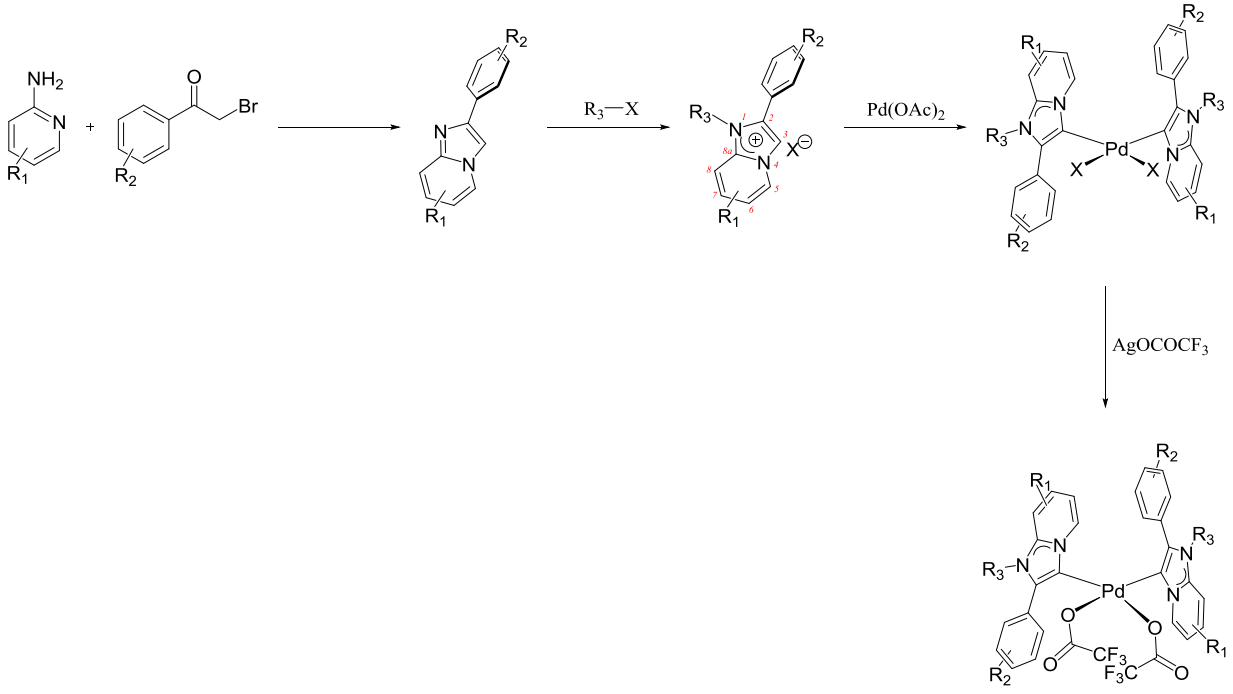
various alkyl and arylkyl halides would give the corresponding tricyclic triazolooxazine based NHC ligands. The triazolooxazinium halide salts would be converted to its *in situ* silver analogue by reaction with Ag_2O and then subsequently upon treatment with $(COD)PdCl_2$ would give the $(NHC)_2PdCl_2$ type complexes. Further reaction of $(NHC)_2PdCl_2$ type complexes with $AgOCOCF_3$ would give the tricyclic triazolooxazine based N–heterocyclic carbene complexes of the type $(NHC)_2Pd(OCOCF_3)_2$ (Scheme 4).



Scheme 4.

(*iv*). Abnormal NHC

The alkylation reaction of the 2-(R_2-phenyl)-imidazo[1,2-a]pyridines with with various alkyl and arylkyl halides would yield the abnormal N-heterocyclic carbene precursors, 1-R_3-2-(R_2-phenyl)-imidazo[1,2-a]pyridinium halide salts (*Polyhedron* **2013**, *64*, 20–29). The reation of the abnormal NHC precursors with $Pd(OAc)_2$ would produce the abnormal NHC complexes of the type $(NHC)_2PdX_2$ which upon further reaction with $AgOCOCF_3$ would give the abnormal N–heterocyclic carbene complexes of the type $(NHC)_2Pd(OCOCF_3)_2$ (Scheme 5).

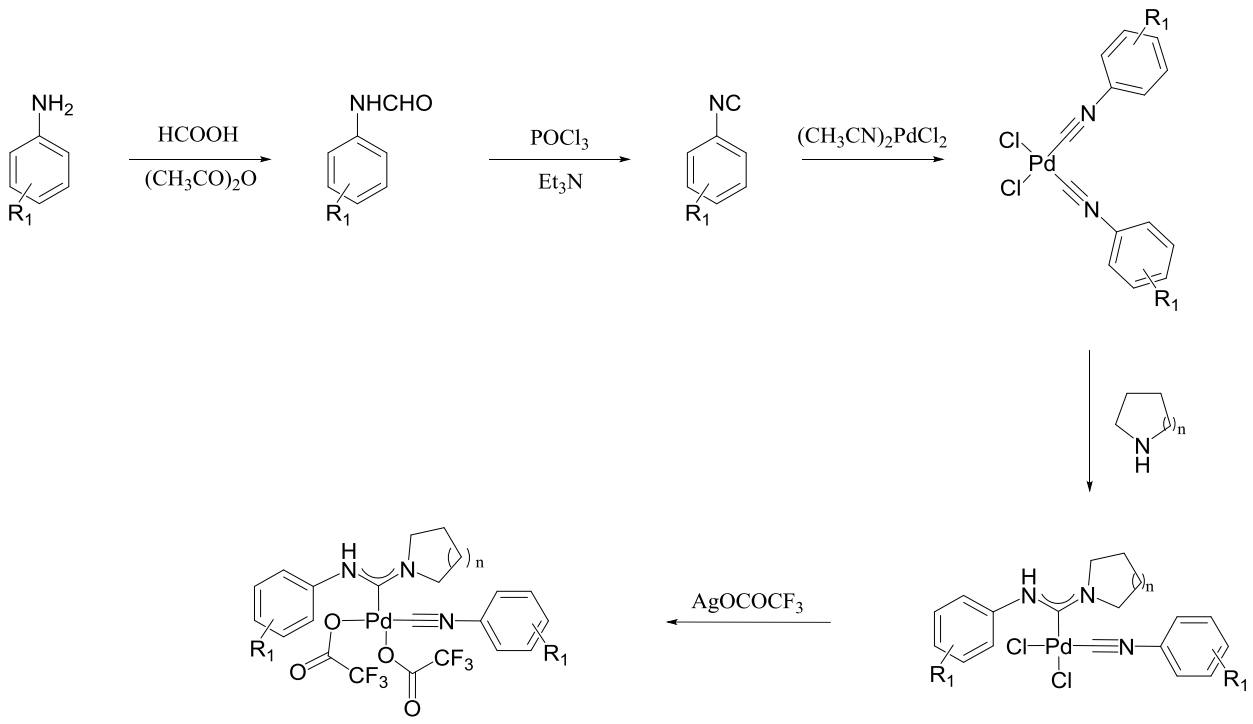


Scheme 5.

(*iv*). Acyclic diamino carbene (ADC)

By making use of the reaction of isocyanides with the palladium precursor, $(CH_3CN)_2PdCl_2$, palladium isocyanide complexes of the type $(ArNC)_2PdCl_2$ would be obtained which upon further reaction with

aliphatic cyclic nitrogen bases would give the palladium complexes of acyclic diamino carbenes. The subsequent reaction of the palladium acyclic diamino carbene complexes with $AgOCOCF_3$ would give the acyclic diamino carbene (ADC) complexes of the type $(ADC)(ArNC)Pd(OCOCF_3)_2$ (Scheme 6).



Scheme 6.

Project aims

Define the aims of the project

(*i*). To synthesize various types of N−heterocyclic carbene ligand motifs.

(*ii*). To synthesis $(NHC)_2PdX_2$ (X = halide) and $(NHC)_2Pd(OCOCF_3)_2$ type complexes of these N−heterocyclic carbene ligands.

(*iii*). To carry out anticancer studies of these palladium N−heterocyclic carbene complexes.

(*iv*). To carry out DNA binding studies of these palladium N−heterocyclic carbene complexes.

Expected outcomes

Highlight the expected outcomes of the project

(*i*). Several new N−heterocyclic carbene ligands and their palladium N−heterocyclic carbene complexes would be synthesised.

(*ii*). The utility of these palladium N−heterocyclic carbene complexes in anticancer studies would be determined.

(*iii*). The mode of action of these palladium N−heterocyclic carbene complexes would also be determined.

How will the project address the Goals of the above Themes?

Describe how the project will address the goals of one or more of the 6 Themes listed above.

The proposed project would address the goal to Biotechnology and Stem Cell Research as it may provide new palladium based N−heterocyclic carbene complexes as potential metallodrugs for the anticancer applications.

Capabilities and Degrees Required

List the ideal set of capabilities that a student should have for this project. Feel free to be as specific or as general as you like. These capabilities will be input into the online application form and students who opt for this project will be required to show that they can demonstrate these capabilities.

A PhD student having Masters degree in Biochemistry or Organic Chemistry is required to carry out the project.

Potential Collaborators

Please visit the IITB website www.iitb.ac.in OR Monash Website www.monash.edu to highlight some potential collaborators that would be best suited for the area of research you are intending to float.

Prof. Glen Deacon
A/Prof. Bayden Wood

Select up to **(4)** keywords from the Academy's approved keyword list **(available at www.iitbmonash.org)** relating to this project to make it easier for the students to apply.

Pharmacology
Biochemistry
Bioscience
Nanotechnology and Nanosceince