

CHAPTER I

**A brief review on green chemistry, recent
developments and green initiatives in transition
metal catalysed and metal-free C-C and C-X
coupling reactions.**

INTRODUCTION

1. A. GREEN APPROACHES IN ORGANIC SYNTHESIS

Human lives in today's world are very much dependent on numerous commodities prepared in various chemical industries for meeting its everyday needs. Be it the necessities related to food and nutrition, personal hygiene and care, medicine and health services, advanced materials, polymers, oils, lubricants and many others, all are synthesized in various chemical set-ups. Increased reliance of people on these products has lead to set-up of much more such inputs in all parts of the world. These industries use various reagents, solvents, salts etc. for various purposes. Many of them are harmful for the persons involved. These industries generate huge chemical wastes in the form of both organic and inorganic residues and discharges. These result in immense pollution of our land and water resources. Harmful gases evolving in various reactions, burning of fuel and use of harmful volatile solvents also pollute the air we breathe. Till date, chemical industries are the leading sources of environmental pollution. The hazards of these chemical processes involve both physical impacts like threats to explosion, ignition, corrosion and biological hazards like chronic toxicity, carcinogenic effects and ecological contamination. It leads to a serious issue of waste management that may again involve cost issues and health threats.

With enormous increase in such problems people and scientists across the world have realised the global threats of mismanaged chemical by-products like global warming, bioaccumulation, stratospheric ozone depletion, adulteration of natural resources, chemical waste stagnation, radiation problems etc. Masses are now realising the need of sustainable growth, *i.e.* using processes that lead to prosperity of not only the current generation but also realising the well being of future generations. Processes should be designed so that the resources can be best preserved and least or no harm to the nature should be tolerated.

Thus many scientists are now intending to design chemical processes that are environmentally benign or eco-friendly. In general terms this may be called green synthesis. And the chemistry involved is called green chemistry.

1. A. 1. Concept of Green Chemistry and Sustainability

Green chemistry is the term coined by Anastas and colleagues of the US Environmental Protection Agency (EPA).¹ Green chemistry may be defined as *the invention, design and application of chemical products and procedures to reduce or to eliminate the use and generation of hazardous substances*. Green chemistry is the chemistry of sustainability. Sustainability is to allow our future generations as many options as we have today. Thus sustainable development is one that *meets the needs of present generation without compromising the abilities of coming generations to fulfil their own necessities*.

Classical methods of chemistry focused chiefly on the aim of selectivity and efficiency of reactions that was measured largely on the basis of the amount of product formed. But nowadays efficiency of a chemical process is also examined based on the extent of waste generation and nature and toxicity of materials and product formed. Henceforth, it is not only the industrial effectiveness that matters but the environmental impact of the process is also important in determining the effectiveness of any process.

Any chemical or process must have some impact on environment due to its mere existence. Hence, achieving a process that is absolutely green is not practically possible. Chemists indulged in green synthesis endeavour to develop green procedures by reducing the hazards in any form related to a process to a minimum extent. This is not feasible to attain such a situation in a single protocol. Hence, one can adopt *green approaches* using catalyst, green solvents and auxiliaries, designing atom economic and energy efficient processes *etc.* to make the procedure environmentally safe. Green methods may involve inventing new procedures that are eco-friendly or to modify the already existing methodologies to make it greener. There are twelve guiding principles for the aspirants of Green chemistry² (**figure. I. 1**) that can be pursued for Greener synthesis. These principles will be discussed in detail in the later section. Changes in the existing methods can be brought in stages by providing greener parameters in the production system to the extent possible. Scientists can therefore apply any one or more of the methods described in the Green chemistry principles to make their synthesis greener.

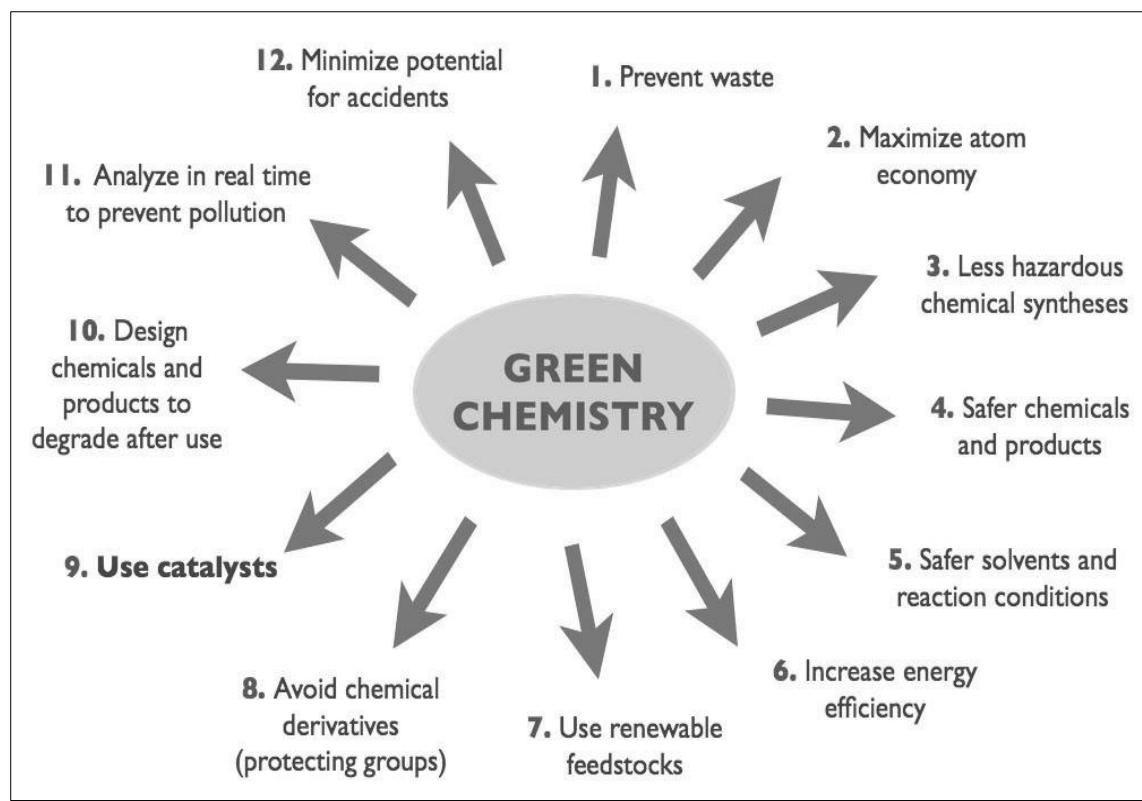


Figure I. 1. Principles of Green Chemistry

1. A. 2. Matrices of Green Chemistry

Extent of greenness of any reaction is not an absolute but a relative term. To have an idea of the relative greenness of one process with respect to another one need to have some measurable parameters. These parameters are called the matrices of green chemistry. Over the years many matrices such as atom economy, eco-footprint, Environmental (E) Factor, Effective Mass Yield, Reaction Mass Efficiency, Eco-Scale *etc.* have been formulated by various working groups.³ These are used based on the relevant field, ease of application *etc.* Here are the two most widely accepted matrices suitable for organic chemist:

1. A. 2. 1 Atom economy

Atom economy, introduced by Barry Trost⁴ is a measure of the extent to which the employed reagents are converted to the desired final products. More the reagents used get transformed into desired products less the by products formed. Hence, a reaction with greater atom economy can be considered greener. Atom economy is measured based on the stoichiometric chemical equation of the reaction and it can be calculated as:

$$\text{Atom Economy (\%)} = \frac{\text{Molecular weight of desired product}}{\text{Sum of Molecular weight of all substances produced}} \times 100$$

A reaction with 100% yield may be less green if it produces by product. Calculation of percentage yield does not consider the unwanted products generated during a reaction. However, atom economy takes into consideration all the products both desired and undesired formed during any reaction. Thus atom economy is a better tool to calculate actual efficiency of a reaction.

It is an easy to calculate and compare method but it also has some drawbacks. It does not take into account the inorganic reagents, catalysts and solvents used in the reaction. Again, it does not consider the nature of the by products generated.

1. A. 2. 2 Environmental (E) Factor:

This metric was introduced by R. Sheldon⁵ to compare the waste generated during any reaction with respect to the formation of the desired product. It can be calculated as;

$$\text{E-factor} = \frac{\text{Total weight of the waste (Kg)}}{\text{Weight of the desired Product (Kg)}}$$

It includes all reagents and solvent loss, energy input and other process aids. Water loss can be included or excluded as per convenience. Lesser the E-factor greener the process will be. This method is very easy to apply in chemical firms. It can be calculated from the total weight of raw materials purchased and the products sold. One has to subtract the desired product weight from the raw material weight and divide it by the weight of product sold. E-factor for an ideal process should be zero. Sheldon compared the E-factors of different firms and concluded that most of the wastes are generated per year by the oil refineries. However, its E-factor is equivalent to 0.1. Pharmaceutical plants produce least chemical waste per year but its E-factor is very high (25 to >100). This is because the process of drug designing is more complex. It requires multi-step reactions and the purity of the product is very crucial. Due to the ease of calculation and the range of things consider in E-factor, it is the most preferred matrices these days.

1. A. 3. Principles of Green Chemistry and their use in modern synthesis

1. A. 3. 1. PREVENT WASTE

It is better to prevent waste than to treat or clean up waste after it has been created.

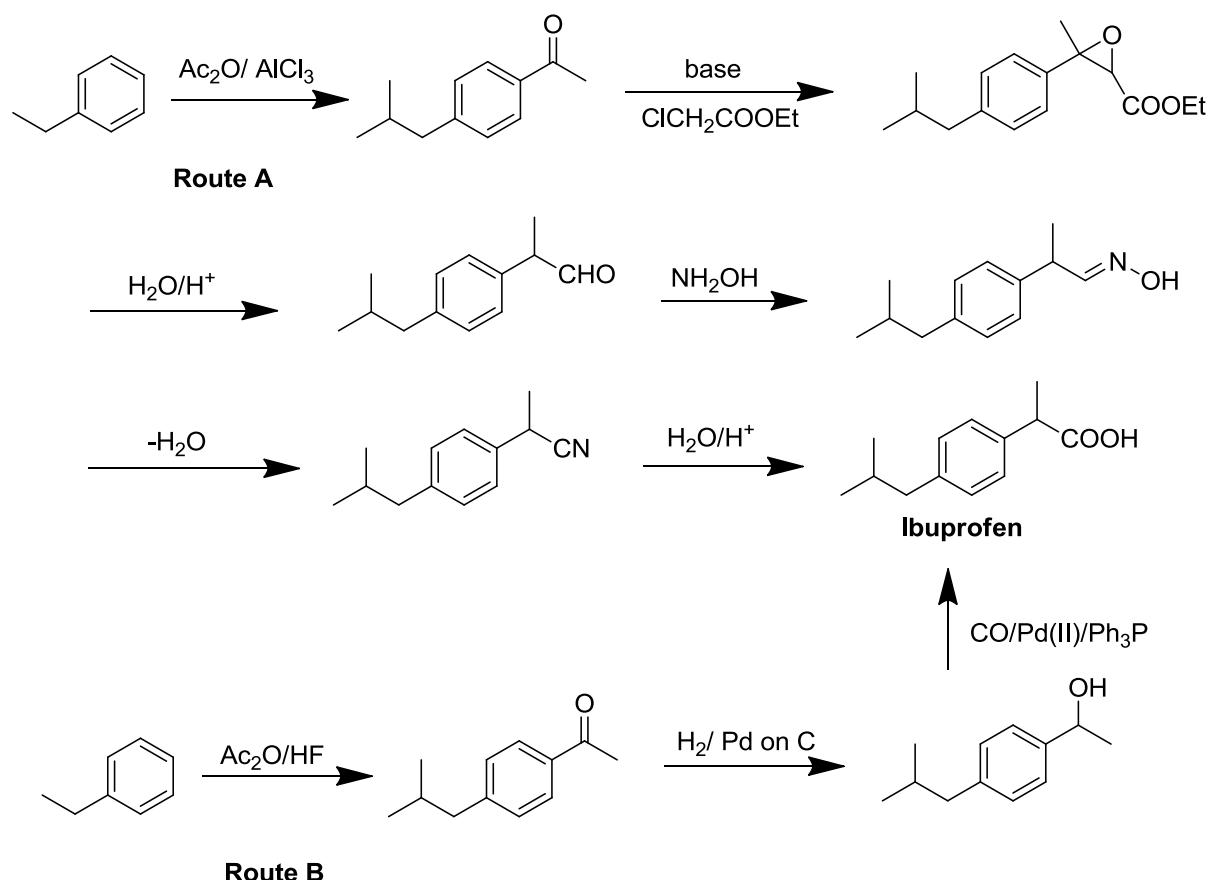
For instance, synthesis of phloroglucinol was conducted previously using 2,4,6-trinitrotoluene.⁶ Yield calculated according to classical methods was higher than 90%. However, in practice excess use of oxidants, reductants and inorganic bases in the overall process lead to a product to by-products ratio equal to 1:40 by weight. The huge by-products generated containing highly toxic chromium metal salts was alarming. The process was discouraged and it was realised that minimum waste generation should be kept as an aim during designing a chemical process. It also minimises the problem of waste management and disposal.

1. A. 3. 2. MAXIMISING ATOM ECONOMY

Synthetic methods should be designed to maximise the incorporation of materials used in the process in final products. In this term the process efficiency can be measured using the concept of atom economy.

Synthesis of ibuprofen in 1960s was performed according to (**Scheme I. 1, route A**). Only 40% of the reactant atoms were converted to products while the rest entered to the waste stream. A new procedure was developed by BHC company⁷ (**Scheme 1, route B**). In this method 77% of the reactant atoms are converted to product and this process with higher atom economy is much greener than the previous one.

Scheme I. 1: Synthesis of ibuprofen IN 1960s



1. A. 3. 3. LESS HAZARDOUS CHEMICAL SYNTHESIS

Wherever possible, synthetic method should be designed to use and generate substances that pose little or no toxicity to human health and environment.

Nature of waste produced during a chemical process in form of inorganic salts, catalysts, solvents etc. is an important factor to be noted in green synthesis. A little amount of one by product may be more hazardous than large amount of some other due to its very intrinsic toxic nature. Again, some waste materials can be easily disposed, decomposed, recycled, treated or reused while other may be very difficult and expensive to manage. Some chemists are also paying attention in designing reactions which produce by products that can be further used in other important syntheses.

Redesigning traditional methods of chemical transformations for minimising use and generation of hazardous substances is one of the major challenges for 21st century chemists.

1. A. 3. 4. DESIGN OF SAFER CHEMICALS

Chemical products should be designed to affect their function while minimising their eco-unfriendly traits.

The thing which does not exist cannot harm the nature in any way. Hence, during designing a product one should pre-think about its predetermined or possible effects on human health and environment. If the chemical proposed is potentially harmful, one should well ponder upon its actual need that whether it can be avoided in any way. Other greener alternatives to solve the desired purpose should be searched. A very good example to illustrate this is that the use of pesticides and insecticides are due to their toxic effects. But keeping in view their harmful effects on the surroundings, chemists have managed to develop pheromones based insecticides⁸ and water soluble biodegradable pesticide^{9, 10}. This has reduced the toxic effects on the surrounding while maintaining the efficacy for the desired purpose.

1. A. 3. 5. SAFER SOLVENTS AND AUXILIARIES

The use of auxiliary substances (e.g.; solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

Organic solvents are used in chemical reactions for easy mixing of reactants to facilitate the reaction and thus make it faster and efficient. These solvents do not participate in the reaction and thus released as by-products. Various auxiliaries are used for isolating the products from the reaction mixture containing unreacted substrates, inorganic salts, metals etc. Solvent waste is also associated with the purification of isolated products. Traditionally used solvents especially the chlorinated ones are very inflammable, toxic and corrosive. Recycling of solvents can be a solution to minimise this problem. However, recycling also leads to much loss in the process. One has to compromise with the purity to some extent in many cases. Thus, discharge of solvent wastages poses a huge problem towards environmental wellbeing. Various ways that are being practiced nowadays by the chemists to minimize these hazards are as follows:

a. Conducting solvent free reaction

Such reactions could be performed by

- Using a liquid substrate or base as solvent for mixing up of the reactants.

- Using solid surfaces like activated silica¹¹ or graphene oxides¹² for carrying the reaction in the pores of the surface.
- Carrying the reaction by hand mixing in a mortar with pistil or using a ball mill.¹³

b. Conducting reactions in water

Water is a solvent that is easily available and poses no harm to our environment. Water as a solvent should be the first choice of any chemist whenever possible. Both in-water and on-water reactions are reported for green organic synthesis.¹⁴ If required, phase transfer catalysts can be used to enhance substrate solubility in water.

c. Using other green solvents like ethanol, glycols, isopropanol, *t*-butanol etc.

These solvents are non-toxic and highly recommended as greener choices for conducting organic reactions.¹⁵ They are not volatile and being water soluble can be easily removed from the reaction mixture.

d. Using solid support catalyst¹⁶ or magnetically separable catalyst¹⁷ that can be easily removed from the product and reused without much washing.

e. Using other alternative solvents like supercritical CO₂, fluorous biphasic systems, ionic liquids, green microemulsion etc.

- Supercritical CO₂ can be easily generated at moderate temperature of 31 °C and pressure of 74 bar. It is non-inflammable, non-toxic and non-reactive towards many substrates. It can be easily removed from the reaction system by bringing it to room temperature and pressure. These remarkable properties make it a preferred solvent for many reactions. It dissolves hydrogen very well and thus is a very good solvent for hydrogenation¹⁸ and hydroformylation¹⁹.
- Fluorous biphasic systems are used to minimise loss of auxiliaries used during work up processes in organic synthesis. Organometallic catalysts used in the reaction are provided with fluorophilic ligands that allow dissolving of the catalyst in the fluorous phase. Fluorous solvents comprising fluorinated alkenes, ether, tertiary amine compounds get miscible with organic solvents at high temperature and become immiscible when the temperature is lowered.²⁰ Hence reaction is carried out at elevated temperature and the catalyst is separated by lowering the temperature.

- Ionic liquids that are liquid at low temperatures are encouraged to be used as solvents for greener chemical reactions.²¹ These are non-inflammable, water soluble, poses negligible vapour pressure, ionic in nature. These properties make them suitable for stabilising charged or polar intermediates and products, enhance selectivity of certain reactions, easy to separate from organic layer.

1. A. 3. 6. DESIGN FOR ENERGY EFFICIENCY

The energy requirements of chemical processes should be noted for their environmental and economic impacts and should be minimised. If possible synthetic method should be conducted at ambient temperature and pressure.

Energy is required during various stages in a reaction methodology. Be it the purpose of heating, producing cooling effect, creating vacuum or enhancing pressure, all require dissipation of energy. Energy lost in all forms should be kept in mind while designing a chemical process and attempts should be made to minimize energy requirements. Conventional methods of synthesis used burning of fossil fuels as energy sources in majority. This created large amount of air pollution. Nowadays, alternative energy sources are searched that cause reduced or no pollution. These can be called clean sources of energy. Some common alternate energy sources widely used in chemical procedures include light energy (photochemical reactions), high-frequency electric field (microwave reactors), sound energy (sonication techniques) etc. These also preserve our fossil fuels from depletion. Introduction of efficient catalyst also lowers the temperature requirements in many processes.

1. A. 3. 7. USE OF RENEWABLE FEEDSTOCKS

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practical.

Fossil fuels used as chief sources of energy in chemical firms are huge source of environmental pollution. It also leads to extinction of our valuable non-renewable resources. Use of clean and renewable sources of energy like solar, hydel, geothermal etc. is highly desirable for preserving environmental wellbeing. Carbon based fuels and chemicals can be derived from biomass. Biomass that comprise of waste plant products (weeds, crop left overs, municipal wastages etc.) has emerged as widely acceptable renewable feedstocks in past few

decades Decomposition of biomass can be carried out by fermentation or thermochemical method. It produces biogas that can be directly used for combustion (bio refineries) and bio-oil that can be used to derive various chemicals (platform molecules). These chemicals can serve as building blocks in synthesis of various vital compounds. Over 300 key platform molecules that can be obtained through biomass degradation involve glycerol, levulinic acid, succinic acid, glutamic acid, fumaric acid, malic acid, aspartic acid, sorbitol, glucaric acid, 2,5-furan dicarboxylic acid, xylitol, glycerol, 3-hydroxybutyrolactone etc.²².

1. A. 3. 8. AVOIDING DERIVATISATION

Unnecessary derivatisation (blocking group, protection/deprotection, temporary modification of physical/chemical process) should be avoided wherever possible.

Derivatisation, blocking and deblocking etc. lead to increase in number of steps in the overall synthesis. Every step is associated with its own reagents and by-products. Moreover, each time the intermediate is isolated it require use of solvents and auxiliaries. Thus one should avoid derivatisation and should search methods of direct conversions. Development of *in-situ* reagents, one-pot synthesis and tandem processes have also provided good greener alternatives in such areas.

1. A. 3. 9. CATALYSIS

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

Most organic processes require stoichiometric inorganic reagents and the later constitute major portions of waste generated during these transformations. For instance, stoichiometric reductions using Na, Mg, Zn, Fe, LiAlH₄, NaBH₄ etc. and oxidation reactions using KMnO₄, Cr₂O₃, MnO₂ etc. Recently, transition metal catalysis based on metals like Pd, Ag, Cu, Ni, Rh etc. has provided a breakthrough in organic synthesis practices.²³. Small proportions of the metal used as catalyst carry out tedious transformations effectively and atom economically. Major advantages of using catalyst in organic reactions are;

- Enhance rate of reaction
- Minimise energy requirements associated with the conversion
- Enhance selectivity of the reaction
- Enhance reaction efficiency (atom economy)

- Reduce wastages
- Chiral ligands on metal catalysts have made it possible to synthesize stereoselective products and this has brought a major breakthrough in drug industry.
- Bio catalysis eliminates use of hazardous metals keeping all other benefits of catalysis. They are extremely specific in their actions.

1. A. 3. 10. DEGRADABLE END PRODUCTS

Chemical products should be designed so that at the end of their function they do not persist in the environment and breakdown into innocuous degradation products.

Designing processes leading to degradable end products prevent the problem of persistent chemicals and bio accumulators. Biodegradability can be attained by introducing some functional groups that are susceptible to hydrolysis, photolysis or other sort of degradation. Entities developed after degradation should be non toxic and ecologically safe. Hence, production of non-degradable polymers, plastics and halogen based pesticides should be avoided and suitable alternatives should be searched.

1. A. 3. 11. MODIFYING ANALYTICAL METHODS

Analytical methodologies need to be further developed to allow for real time, in process monitoring and control prior to the formation of hazardous substances.

Analytical method should be developed to analyze and pre estimate possibility of synthesis or leakage of hazardous substances. The processes should be monitored minutely for detecting all products and by products formed and their impact on the environment. Gases escaping during a reaction should also be captured and scrutinized properly.

1. A. 3. 12. MINIMISING SCOPE FOR ACCIDENTS

Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

Processes involving volatile and flammable materials should be avoided to use high temperature. Otherwise, such reactions should be conducted at very small scales. Use of poisonous chemicals should be avoided to the extent possible. Such chemicals should be

handled with utmost care and all necessary precautions. Leakages of any sort of harmful chemical in environment must be avoided.

1. B. C-C AND C-X COUPLING REACTIONS

For the synthesis of organic molecules especially the large and complex ones, retro-synthetic approach is very useful. It involves identification of building blocks that can be joined together to form the required molecule in single or multiple stages. These substrate moieties should be easily available or can be prepared in laboratory. Joining of these fragment units is an important task. C-C and C-X (X= N, O, S etc.) coupling reactions prove to be the most useful in such cases especially when least disturbance in basic skeletons of the substrates is required. Coupling reactions are highly significant in synthesis and derivatisation of aromatic and heteroaromatic compounds as compared to the classical methods of organic synthesis.

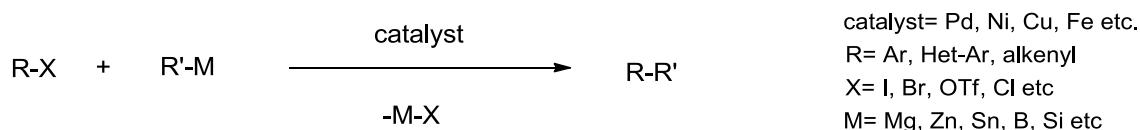
In coupling reactions two moieties, same (homocoupling) or different (heterocoupling) containing an active group react together to form bond(s) between each other with loss of active groups. Here, the groups involved in direct bonding merely undergo change while rest of the carbon skeletons remain unaffected. The process is named C-C or C-X coupling based on the type of bond newly formed during the reaction. To form C-C bond organic halide substrate (bearing electrophilic carbon) can be coupled with Grignard compounds or organoborons (bearing nucleophilic carbon). For C-X coupling reactions, compounds like alcohols, phenols, amines, thiols *etc.* are used as nucleophilic substrates.

Coupling reactions are usually carried out with the aid of transition metals (in activated forms or their salts or complexes) that act as catalysts. Pd metal has emerged as the most wonderful transition metal catalyst till today because of the versatile and broad spectrum of reactions that it can be applied to. One of the reasons for it may also be that the chemistry of this metal is most extensively studied and extensive results have been obtained. Other metals like Ni, Cu, Fe, Ru *etc.* also emerged as potential catalysts in organic synthesis. These transition metal catalysed coupling methods make it easier to deal with reaction centres containing sp^2 and sp carbons (aromatic, alkene and alkynes). Coupling reactions are classified usually based on the use of organometallic substrate and are mostly named based on the name of the pioneers in the field.

1. B. 1. C-C Coupling Reactions

A general scheme representing metal catalysed coupling reaction is represented in **eq 1**.

eq 1



Common variants of C-C Coupling reactions

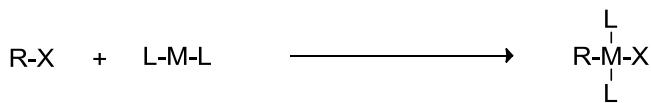
1. Suzuki-Miyaura-	Boron mediated	Pd, Ni catalysed
2. Kumada-Tamao-Corriu-	Magnesium mediated	Pd, Ni, Fe catalysed
3. Negishi-	Zinc mediated	Pd, Ni catalysed
4. Stille-Kosugi-Migita-	Tin mediated	Pd catalysed
5. Sonagashira-	Copper mediated	Pd, Pd and Cu catalysed
6. Heck Mizoroki-	Palladium mediated	Pd, Ni catalysed
7. Hiyama-	Silicon mediated	Pd catalysed

Before discussing recent trends and green perspectives of these reactions we must go through the general stages that are involved in most transition metal catalysed C-C coupling reactions.²⁴

1. Oxidative addition

Here the metal catalyst inserts itself in the R-X bond. Both coordination number and oxidation state of the metal increases by two units. Addition of a transition metal to an organic halide gives *trans*-addition product. This is so as the organic halide breaks before reaction and undergo SN_2 type addition to the metal. σ -donor ligands like triphenylphosphine *etc.* on the metal catalyst facilitates oxidative addition as they stabilise the metal in its higher oxidation state. π -acceptor ligands like carbonyl or alkenes suppress oxidative addition. This is because such a group will stabilise the metal in its lower oxidation state. In case of organic halide, an electron withdrawing substituent is good for facile oxidative addition. A general example may be given as **eq 2**.

eq 2.

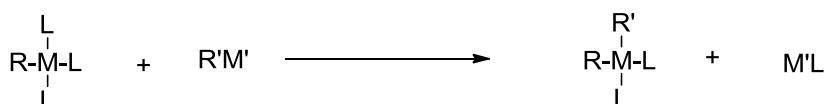


2. Transmetallation

As is evident from the name, in transmetallation a ligand (alkyl, aryl, alkynyl, allyl, halide *etc.*) relocates from one metal to another. The direction of ligand shift may be either thermodynamically or kinetically controlled depending upon the electropositivities and availability of vacant orbitals on metals concerned.

In this stage of coupling reactions organometallic reagents like organotin, organozinc *etc.* react with other organometallic agent formed through oxidative addition of organohalide to metal catalyst in stage one. It is a crucial stage in which both the organic fragments to be coupled get attached to the same metal. There is no change in oxidation state of the metal catalyst in this step. General example can be written as **eq 3.**

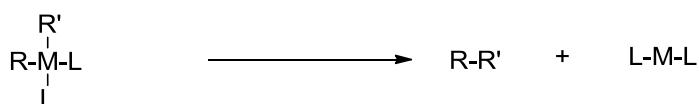
eq 3.



3. Reductive elimination

Reductive elimination is the reverse of oxidative addition. Here two alkyl/aryl ligands on the metal complex formed in above stage join together to form a σ -bond and leaves the central metal. Both oxidation state and coordination number of the metal catalyst decreases by two. In other words we can say that the final product is formed and the catalyst is regenerated in this stage. The two ligands that are eliminated must be *cis* to each other so that they can interact properly. This step is favoured by high oxidation state of the metal and presence of bulky ligands. General example can be written as **eq 4.**

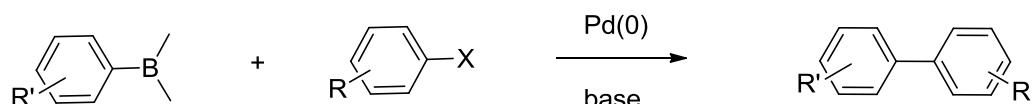
eq 4.



1.B.1.1 Suzuki-Miyaura Coupling

Reported first in 1979,²⁴ Suzuki-Miyaura coupling also popularly known as Suzuki coupling has become one of the most important methods of biaryl synthesis. Considering the importance of this methodology Suzuki was awarded Nobel Prize for his contribution in the field in 2010. The reaction chiefly involves coupling of an aryl or alkenyl halide (or pseudo halide) with organoboron reagents (boronic acid, ester, trifluoroborate salts etc.). General eq. for the reaction can be written as **eq 5:**

eq 5:

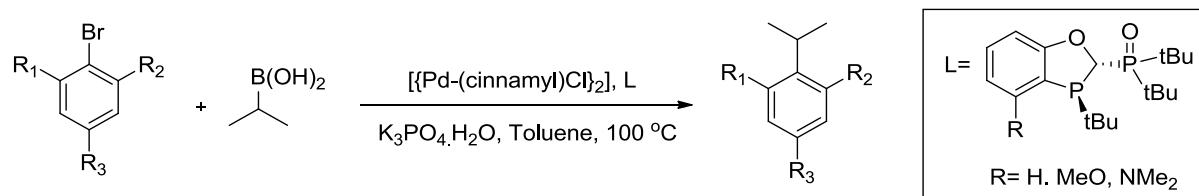


In the field of Suzuki coupling with time can be observed through the surplus reviews that are already available. The applications of this reaction are versatile and a spectrum of molecules involving lead natural compounds, polymers, semiconductors, chiral compounds, *etc.* can be synthesized using this reaction.²⁵ Very recently, Liu. Reported regioselective synthesis of important heterocycles 2,4-disubstituted 1,2,3-triazoles.²⁶ It involves direct arylation of 2-aryl-1,2,3-triazole N-oxides with arylboronic acids at room temperature (**Scheme I. 2**). Li. carried Suzuki coupling between sterically hindered *o,o'*-di substituted arylbromides and acyclic secondary alkyl boronic acids (**Scheme I. 3**). To achieve that, they have used bulky ligands (**L**) in the process. It promotes reductive elimination and at the same time inhibits side reactions like β -hydride elimination, isomerization, and reduction. The ligand structure and hence reaction outcomes may be tuned by changing substituent *R* in **L**. Using this reaction as a key step they proposed synthesis of gossypol (a male antifertility agent and PAF antagonist).²⁷

Scheme I. 2: Suzuki coupling of 2-aryl-1,2,3-triazole N-oxides with arylboronic acids



Scheme I. 3: Suzuki coupling between sterically hindered *o,o'*-di substituted arylbromides and acyclic secondary alkylboronic acids



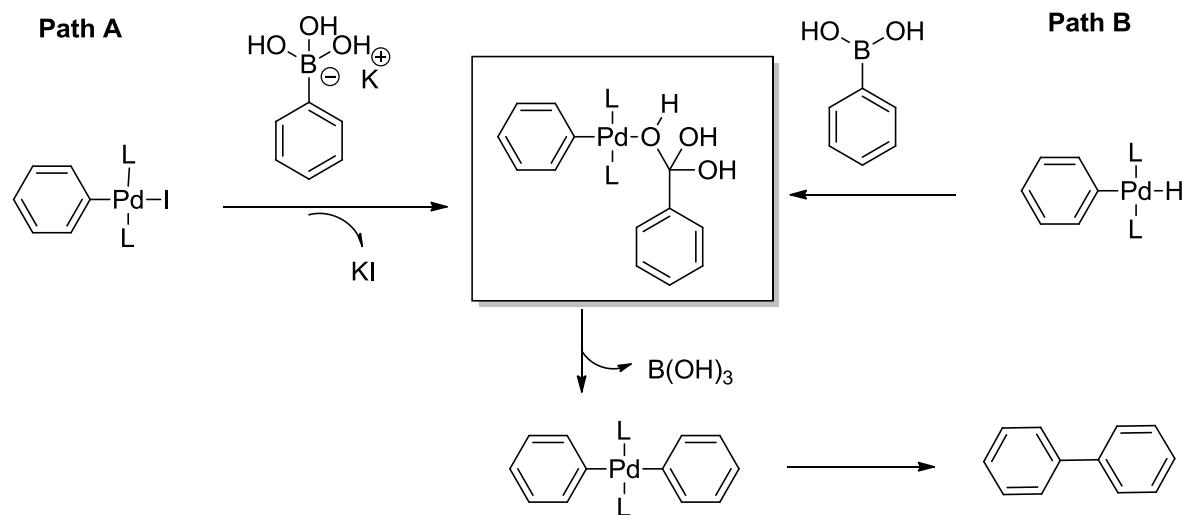
The reaction performs very well in presence of Pd(0) catalyst that dominates the studies worldwide. But Ni has also been used by various groups as an effective catalyst for the reaction. In view of abundance and cheapness Ni use is appreciated. It is found to be effective in presence of variety of substrates *viz*; aryl electrophiles such as sulfamates, carbamates, carboxylates, ethers, carbonates, phosphoramides, phosphonium salts, phosphates, common phenols and alkyl substrates including both secondary and primary alkyl iodides, bromides, and chlorides.²⁸

Use of organoboron reagents is an achievement of the process as they can be easily synthesized and stored. Their by products are less toxic and are less difficult to manage. This results in lesser environmental hazards especially when we are concerned with large scale synthesis. Again, the process involves milder reaction conditions and tolerates variety of functional group substituent on both the substrates. The reaction has been very successful in designing heterocyclic structures and is being utilised for synthesizing number of useful biological compounds. A recent review by Lennox *et. al.* describes the types of organoborane reagent that can be used depending on the reaction situations and desirable outcomes.²⁹ They discuss the methods of preparing these reagents, some of their relevant properties and type of mechanisms they follow.

Unlike other similar reactions like Stille coupling *etc.*, role of base here is very important. The transmetallation step is assisted with the base. Lima *et. al.* have proposed recently that in transmetallation step base converts the boronic acid derivative to more reactive organoborate form R-B(OH)₃⁻ that enhances the reaction outcomes. The reaction is found to be dependent on amount of base, equilibrium between the boronic acid and borate and pKa values of the components. Hence selective outcomes can be tuned by playing carefully with the type and amount of bases used.³⁰ Very recently, Thomas and Denmark in their work revealed the possible pathways (**Figure I. 2**) in transmetallation step of base catalyzed Suzuki cross

coupling using low-temperature rapid injection nuclear magnetic resonance spectroscopy and kinetic studies.³¹

Figure I. 2: Possible pathways in transmetallation stage of Suzuki cross coupling using NMR and kinetic studies



Green Initiatives

Many approaches have been adopted by various groups to reduce the discharge of harmful waste in Suzuki coupling reactions.

Use of greener solvents

These include use of greener solvents as water, ethanol, PEG, supercritical CO_2 , ionic liquid media *etc.*³² Solvent free reactions are also reported by various groups. There are many reviews separately covering the issue of Suzuki coupling in water. Both homogenous and heterogeneous reactions been developed using phase transfer catalyst, ionic liquids, water soluble ligands, NHCs, solid supports *etc.*³³.

Heterogeneous Catalysis

Use of heterogeneous catalysts that are easily recovered and recycled is another way of green modification. Solid supports like polymer (polystyrene *etc.*), silica can be modified and used for supporting palladium metal through covalent linkages. Encapsulation of metal in cavities of chelating surfaces like zeolites, silica, charcoal, clays, alumina *etc.* is also used by various groups of workers.³⁴ Pascanu *et. al.* used Pd supported on mesoporous metal organic framework (MOF) MIL-101-NH₂ and synthesised many highly functionalised biaryls in

green water-ethanol medium.³⁵ Magnetically separable Pd catalyst by means of solid support containing diaminoglyoxime (DAG)-functionalized Fe₃O₄ was synthesized by Veisi and co-workers.³⁶ This catalyst conducted efficient Suzuki coupling in solvent -free conditions. Very recently, Wang *et. al.* report a Pd catalyst supported on a double-structured amphiphilic polymer composite. The catalyst is reusable and highly efficient in water-ethanol system.³⁷

Photocatalysis

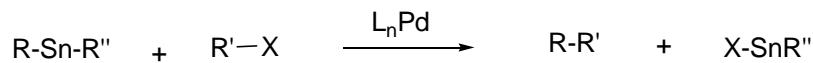
Use of photo catalysis minimize the energy requirements and enhance the reaction efficiency. A major challenge in Suzuki cross coupling was the slow rate of reaction of bulky reagents like secondary alkyl borons. This is due to slow transmetallation that need high activation energy to form classical pentacoordinate transition state. Recent studies have revealed that use of some photoactive component can lead to a rapid single electron transmetallation by shifting the reaction pathway through radical intermediates. It lowers the energy requirements and reaction can be carried out at room temperature. This reduces generation of byproducts and increases the reaction output.³⁸

1.B.1.2. Stille Coupling

Stille cross coupling reaction involves Pd catalysed coupling of organic electrophiles (generally an organohalide) with organotin reagents. This also follows the three step general mechanism discussed in previous section. Oxidative addition of organic halide to the active Pd(0) catalyst form, transmetallation with organo-tin reagent and finally the reductive elimination of product bearing the required C-C bond. Base is not required here. Beauty of the reaction lies in the tolerance of functional groups, range of coupling partners that can be used (sp, sp², sp³), easy preparation and stability of organotin reagents. Drawbacks of the process comprise the toxicity of tin compounds and their low solubility in water.

General eq. for the reaction can be written as **eq 6**

Eq 6:

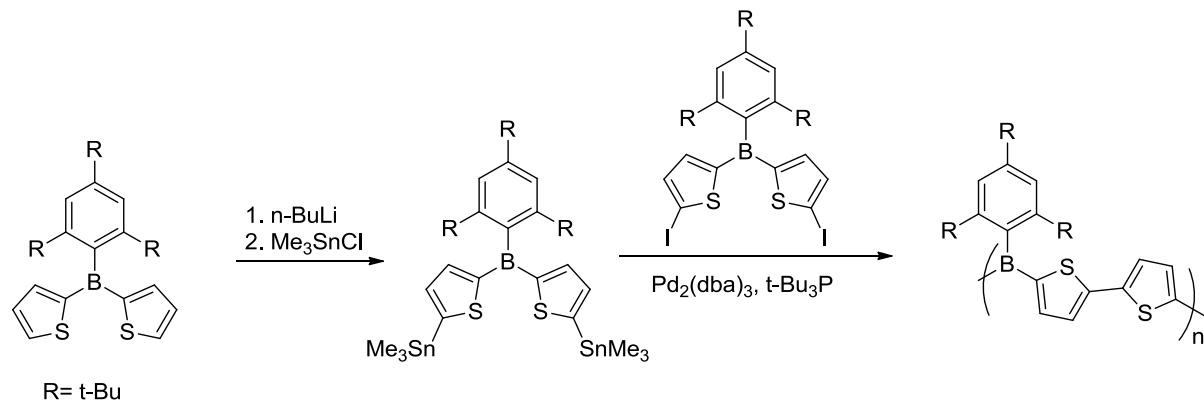


R'X = RCOCl, Ar-X, allyl-X,
benzyl-X, vinyl-X,

R= H, alkene, alkyne, aryl, allyl, benzyl, alkyl
R'' = methyl, butyl

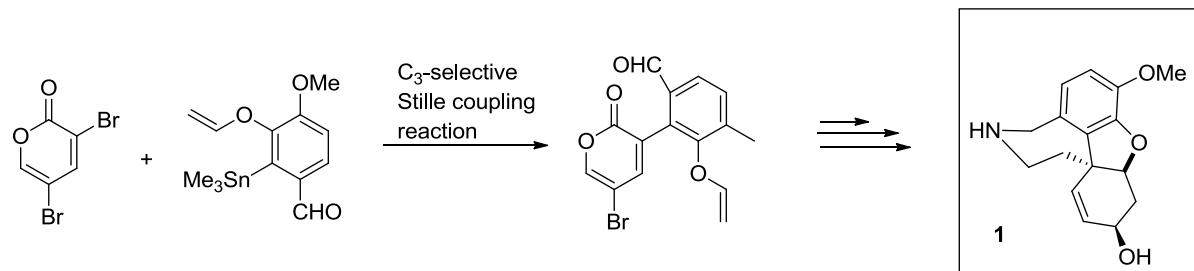
Stille coupling has valid contribution in the field of polymer chemistry,³⁹ medicinal compound synthesis and synthesis of complex organic structures.⁴⁰ Recently, Yin *et. al.* synthesised a series of highly robust, electron deficient, boron incorporated conjugated polythiophene polymers via Stille coupling of stannylated thienylborane monomers (Scheme 4).⁴¹

Scheme I. 4. Synthesis of boron incorporated conjugated polythiophene polymers *via* Stille coupling of stannylated thienylborane monomers



Total synthesis of Galanthamine **1**, a commercially available drug for the symptomatic treatment of senile dementia of Alzheimer's disease was achieved by Stille/Diels Alder cascade reaction by Chang *et. al.* (**Scheme I. 5**).⁴²

Scheme I. 5. Total synthesis of Galanthamine **1**, by Stille/Diels Alder cascade reaction



Similar approach was used by Halle and co-workers⁴³ for the synthesis of antibiotic Mycophenolic acid and its derivatives. Stille coupling of iodolactone **2** with stannane **3** yielded **4** that on hydrolysis produced Mycophenolic acid **5** (**Scheme I. 6**). Very recently, Monteiro *et. al.*⁴⁴ envisaged promising route towards synthesis of prostaglandin **6** analogues.

Alfaprotosol **7** key intermediates could be synthesized through Stille coupling of alkyne derivatives of Corey intermediates and organotin compounds (**Figure I. 3**)

Scheme I. 6. Synthesis of Mycophenolic acid *via* Stille coupling

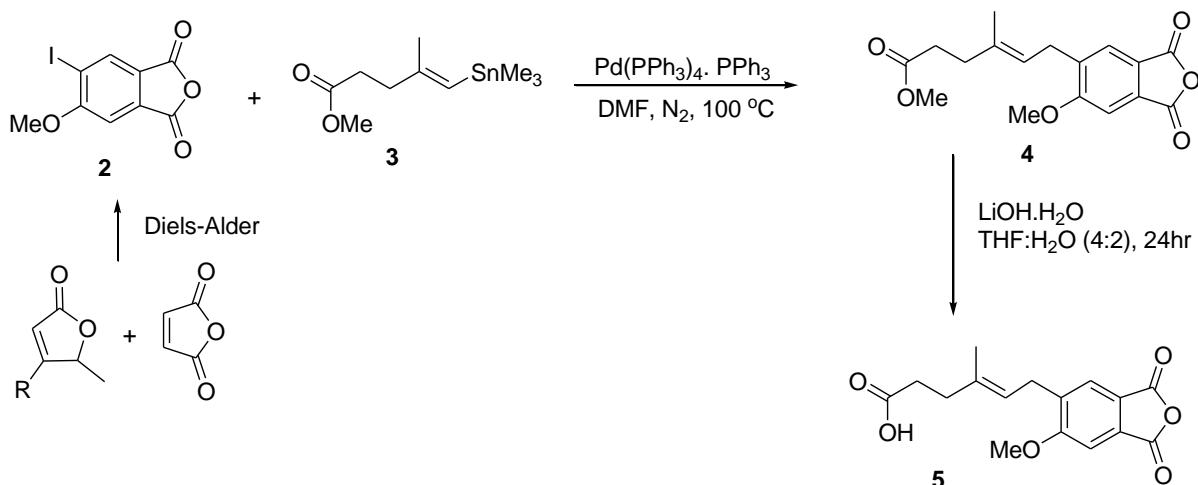
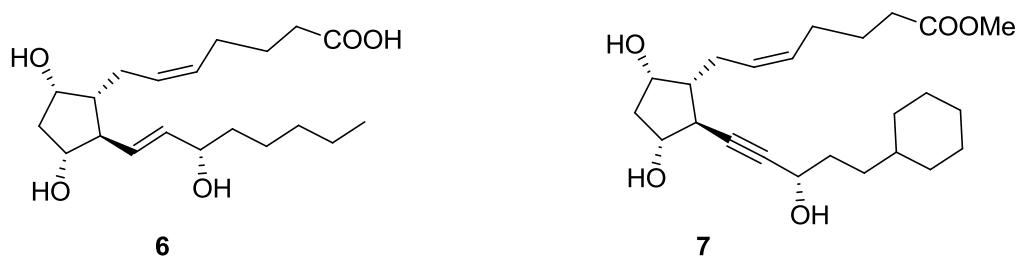
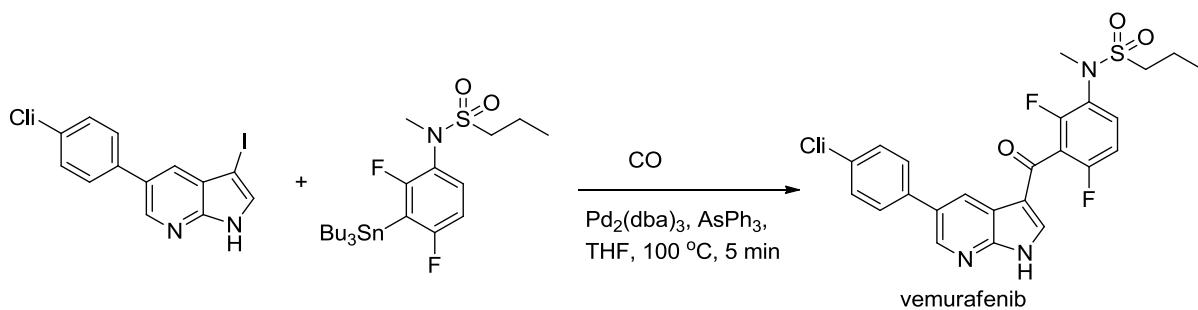


Figure I. 3 Structure of Prostaglandin and Alfaprotosol



Synthesis of Vemurafenib, a serine/threonine kinase inhibitor approved for the treatment of melanomas tumor was achieved by Slobbe and group through carbonylative Stille coupling (Scheme I. 7).⁴⁵

Scheme I. 7. Synthesis of Vemurafenib through carbonylative Stille coupling

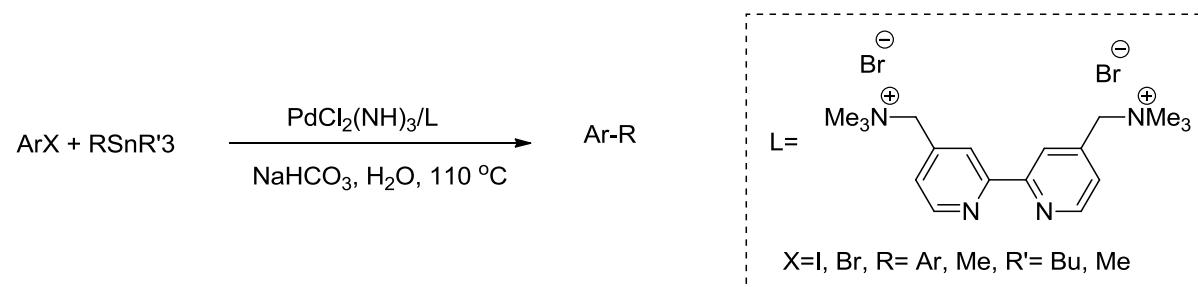


Other recent valuable applications of Stille coupling include synthesis of fully Substituted pyranones,⁴⁶ synthesis of the 1,2-seco fusicoccane diterpene skeleton,⁴⁷ modifications at C-17 of steroidal skeletons,⁴⁸ synthesis of π -helicams truncated to an *all-s-cis all-Z* oligoene chain,⁴⁹ selective construction of a trisubstituted alkene precursors of 5,6-dihydrocineromycin B.⁵⁰

Green Initiatives

Many recyclable and reusable catalysts suitable for Stille coupling reaction have been developed that can be applied to various organic synthesis schemes. Pd supported on magnetic magnetite (Fe_3O_4) nanospheres were reported to be efficient catalysts for biaryl synthesis through alkyl halides and organostannanes.⁵¹ Heterobiaryl were synthesised by Li and co-workers through Stille coupling catalysed by alumina supported Pd nanopaticals.⁵² Silica supported NHC carbene and ionic liquid units stabilising Pd(0) nanopaticles was developed by Ghasemi *et. al.* The catalyst was recyclable and can be used for biaryl synthesis through both Suzuki and Stille coupling.⁵³ Another organically modified mesoporous silica catalyst prepared from Palladium with chloropropyltriethoxysilane and 2-amino-3-hydroxypyridine immobilized on MCM-41 was developed by Nikoorasm *et. al.* This heterogeneous catalyst was used to conduct Sille coupling in green PEG solvent.⁵⁴ Wu *et. al* developed a water soluble and reusable palladium(II)/cationic 2,2'-bipyridyl catalyst. The catalyst was highly efficient for Stille coupling reaction in water at 110 °C (**Scheme I. 8**).⁵⁵

Scheme I. 8: Stille coupling via reusable palladium(II)/cationic 2,2'-bipyridyl catalyst

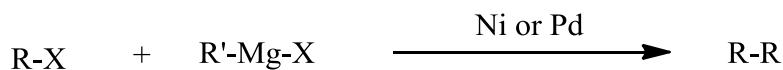


1. B.1.3. Kumada Coupling

Kumada coupling reaction involves transition metal catalysed coupling of Grignard reagent (RMgX) with alkyl, vinyl or aryl halides. Kumada and Corriu first reported it in 1972 through independent works.⁵⁶ General equation of the reaction is **eq 7**. Ni, Pd and Fe, Co catalysts⁵⁷

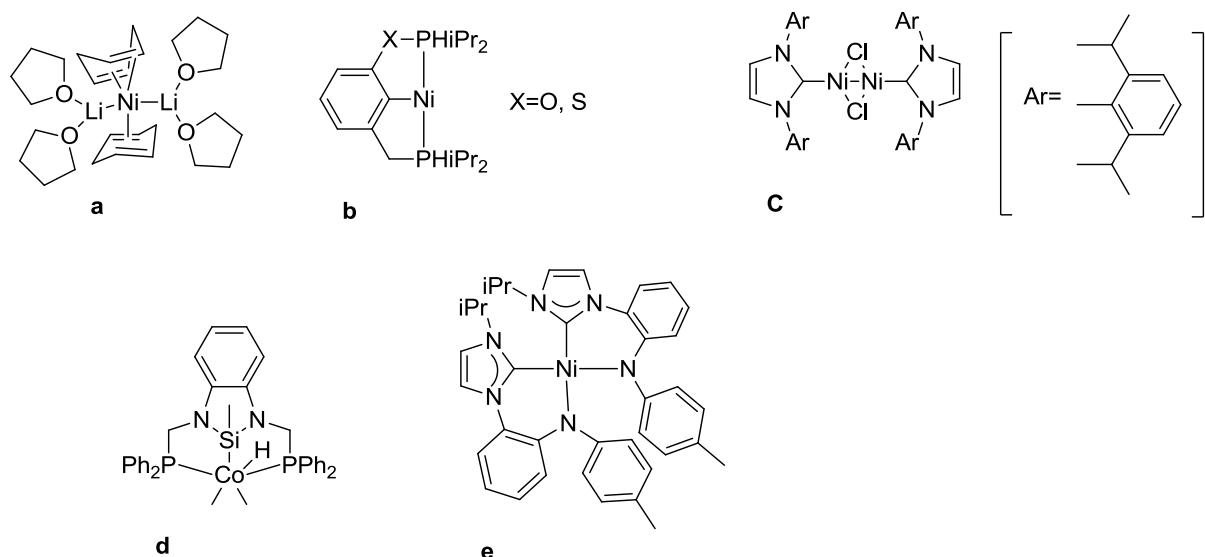
along with different ligands are used in the reaction. Heravi *et. al.* have reviewed various ligands used in the variants of this reaction.⁵⁸ Types of complex catalysts developed in some recent works that are suitable for efficient Kumada coupling are represented in **figure I. 4**.⁵⁹

eq 7:



R= alkyl, alkenyl, aryl, heteroaryl

Figure I. 4. Complex catalysts used in recent Kumada Coupling reaction

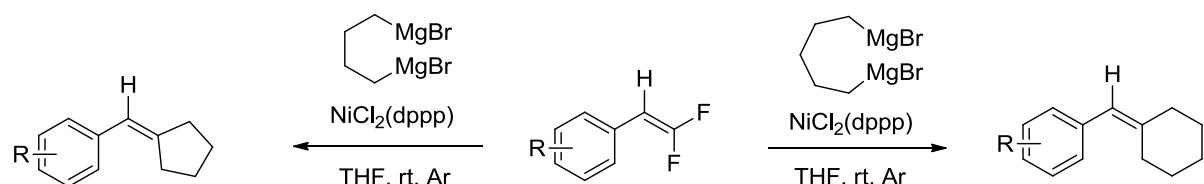


Many medicinally valuable compounds, skeletons and sub-structures have been prepared using this reaction. A highly selective adenosine A_{2A} receptor ligand antagonist ST1535, is prepared by Bartocinni *et. al.* that is a potential drug for the treatment of Parkinson's disease. They used an environmentally benign Fe catalyst in the process (Scheme I. 9).⁶⁰ Exocyclic trisubstituted alkenes (a part structure of many drugs) were prepared by Dai *et. al.* via Nickel-catalyzed Kumada type cross-coupling reaction of gem-difluoroalkenes with di-Grignard reagents (Scheme I. 10).⁶¹ Ye and co-workers manufacture 2,4 diaryl quinazolines trough Ni-catalysed coupling of quinazoline-4-tosylates and aryl Grignard reagents (Scheme I. 11).⁶² Very recently, Linghu *et. al* synthesized pyridine (**8**) a key intermediate in the assembling of ERK (Extracellular-signal-regulated) kinases inhibitor GDC-0994, (Scheme I. 12).⁶³

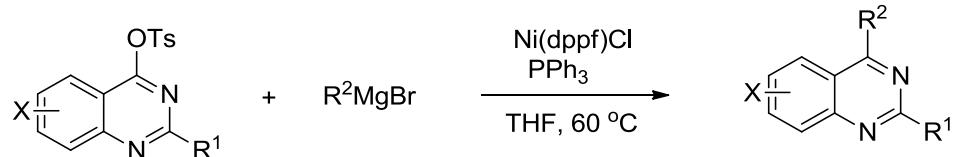
Scheme I. 9. Synthesis of highly selective adenosine A_{2A} receptor ligand antagonist ST1535 through Kumada Coupling



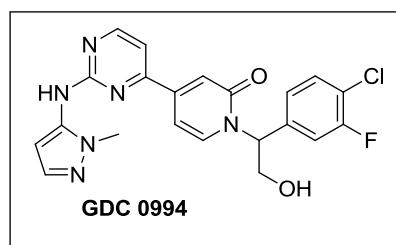
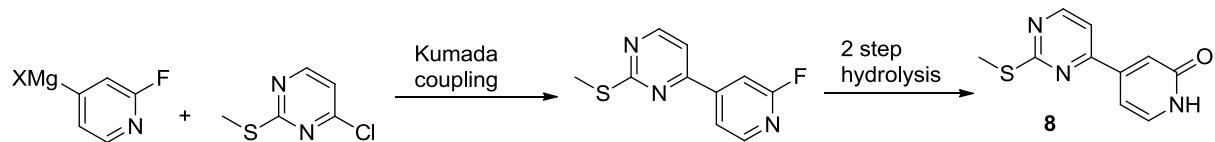
Scheme I. 10. Nickel-catalyzed Kumada type cross-coupling reaction of gem-difluoroalkenes with di-Grignard reagents



Scheme I. 11. Kumada coupling of quinazoline-4-tosylates and aryl Grignard reagents



Scheme I. 12. Synthesis of GDC-0994, a key intermediate in the assembling of ERK (Extracellular-signal-regulated) kinases inhibitor



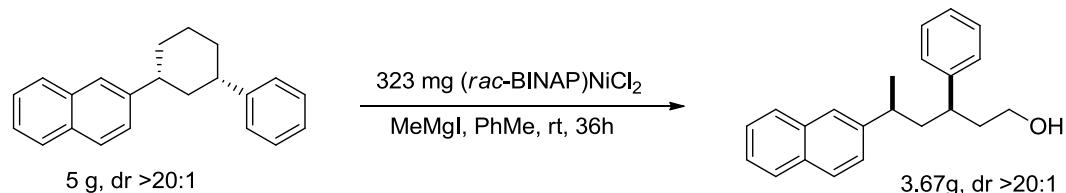
Kumada coupling has turned to be a good tool for chemoselective C-C bond formation⁶⁴ and asymmetric synthesis. Some of the important recent works in the field of asymmetric synthesis are represented through the following scheme (**Scheme I. 13**)⁶⁵⁻⁶⁸

Green initiatives

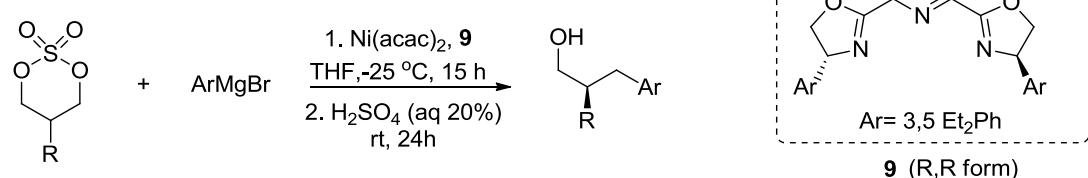
Use of Fe catalyst in place of Ni or Pd catalysts is itself a greener approach. Kumada coupling reaction on water medium was developed for the first time recently by Bhattacharjya *et. al.* It was a coupling of aryl iodides with *in-situ* generated Grignard reagents. Formaldehyde was used as an additive. Apparent homocoupling products were obtained when single aryliodide was used. Heterocoupling products along with other byproducts were obtained when two types of aryliodides were used. Latter required higher catalytic loading however (**Scheme I. 14**).⁶⁹

Scheme I. 13: Recent applications of Kumada coupling reaction in chemoselective or asymmetric synthesis (with references in parentheses)

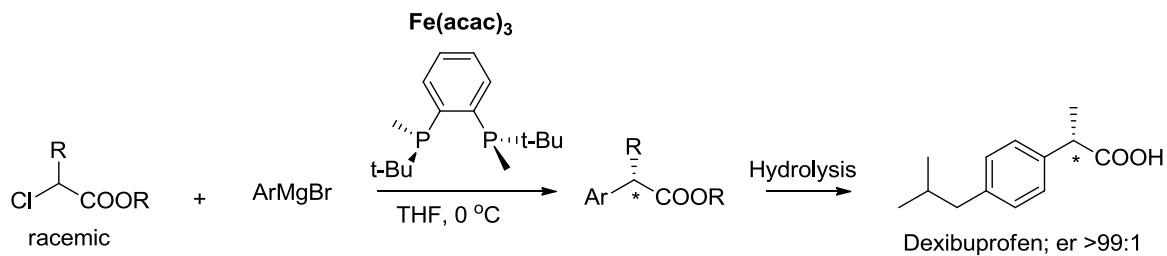
a. Coupling of tetrahydropyran derivatives with MeMgI on a 5g scale⁶⁵



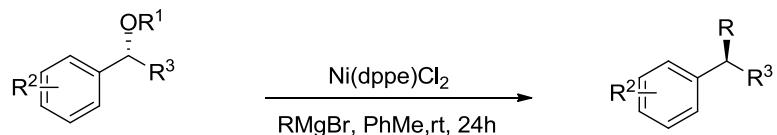
b. Enantioselective Kumada Couplings of Prochiral Cyclic Sulfates⁶⁶



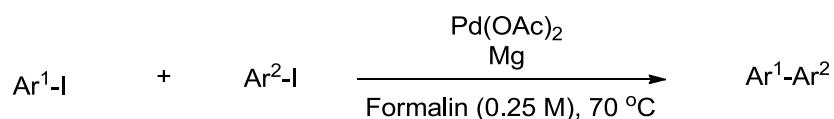
c. Enantioselective coupling of α -chloroalkonates with Grignard Reagents⁶⁷



d. Stereospecific Cross-Coupling Reactions of Benzylic Ethers and Esters⁶⁸



Scheme I. 14. Fe catalysed Kumada coupling of in-situ generated Grignard reagents using formalin as additive



Many recoverable and recyclable are being designed to reduce the use of harmful metals. A heterogeneous recyclable catalyst consisting of sulfur-modified Au-supported Ni nanoparticles (SANi) was developed by Hoshiya and group that was good for Kumada as well as Negishi coupling reaction.⁷⁰ Another recyclable SBA-15-EDTA-Pd catalyst was prepared by Rathore *et. al.* that was highly efficient Kumada, Heck and Stille coupling reactions. It comprised Pd-EDTA complex anchored over modified mesoporous surface of SBA-15.⁷¹ A magnetically recoverable Pd(0) catalyst was developed by Wu and co-workers that was good for Kumada and several other C-C coupling reaction. Despite these attempts, scopes and possibilities in the field are yet to be explored and works are in progress.⁷²

1. B. 1. 4. Negishi Coupling

This reaction was first reported in 1977 by Negishi⁷³ who won Nobel Prize for his contribution in 2010. The reaction has been proved to be highly contributing in the field of organic synthesis especially the designing of terpenoid systems. The reaction has a very high substrate scope, uses cheap and easily available reagents and can be performed in milder conditions as compared to Suzuki reaction due to the faster transmetallation step. General equation for the reaction may be given as **Eq 8**. A recent review by Haas *et. al.* discusses the synthesis of organozinc reagents, ligands and catalysts newly developed or employed in the reaction.⁷⁴ Metals other than Pd or Nickel viz; Cu, Co, Fe etc have also been used for the reaction and their chemistries are being further explored for developing the Greener aspects of the reaction.⁷⁵ In a very recent work Pell and co-workers have developed a Rh-Zn complex and tried to study the aspects of Rh catalysis In Negishi coupling.^{75b} The results however, were not that promising but further attempts maybe continued.

Eq 8:



R' = aryl, vinyl, alkynyl, acyl, allyl, benzyl, homoallyl, homobenzyl, primary alkyl

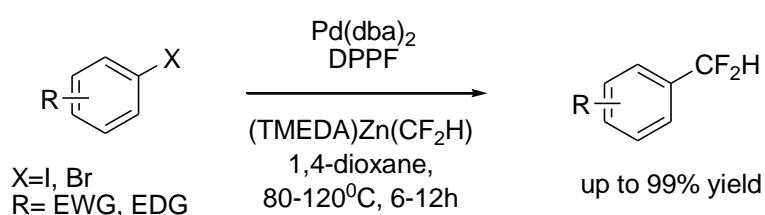
R = aryl, vinyl, alkynyl, allyl, benzyl, primary alkyl

X = I, OTf, Br, Cl (sluggish)

Biaryls, heteroaryls with varied substituents⁷⁶ including many medicinally valuable compounds can be synthesized using Negishi coupling reaction. Difluoromethylated aryl compounds can be prepared using Pd catalyzed Negishi coupling of (Difluoromethyl)zinc reagents with aryl halides (**Scheme I. 15**). Presence of a diammine ligand on the organozinc reagent is required for stability of latter in DMF solution.⁷⁷ In a multi reaction two-pot process, Negishi coupling and halogen dance tandem reactions were used by Hayashi and co-workers for synthesis of thiophene fused indoles.⁷⁸ Similar one-pot halogen dance/Negishi coupling approach was used by Okano *et. al.* for regiocontrolled synthesis of polyarylated thiophenes from 2,5-dibromothiophenes (**Scheme I. 16**).⁷⁹

Tungen and co-workers achieved total synthesis of anti-inflammatory and Pro-resolving Lipid Mediator MaR1_{n-3} DPA **10** (**Figure I. 5**) for the first time using Negishi sp³-sp³ cross-coupling reaction.⁸⁰ Flexible and functionalized benzocyclotrimers **11** (**Figure I. 5**), potential compound for designing guest molecules in supramolecular chemistry are synthesized by Martin *et. al.* by Negishi cross-coupling and intramolecular nucleophilic substitution.⁸¹ The reaction was used to develop ¹¹C-C bond by Rejc *et. al.* using ¹¹C (CH₃I). Such reactions are very crucial to develop ¹¹C-labelled active compounds for diverse applications.⁸² Stereospecific α -arylation of optically pure 2,3-epoxy-1,1,1-trifluoropropane was executed by Zhang *et. al.* Optically pure 2-CF₃-2-(hetero)aryloxiranes produced in the process can be used to synthesize CF₃ substituted chiral alcohols (**Scheme I. 17**).⁸³

Scheme I. 15. Negishi coupling of (Difluoromethyl)zinc reagents with aryl halides



Scheme I. 16. Regiocontrolled synthesis of polyarylated thiophenes

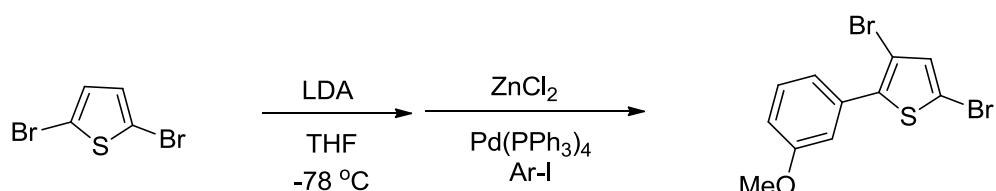
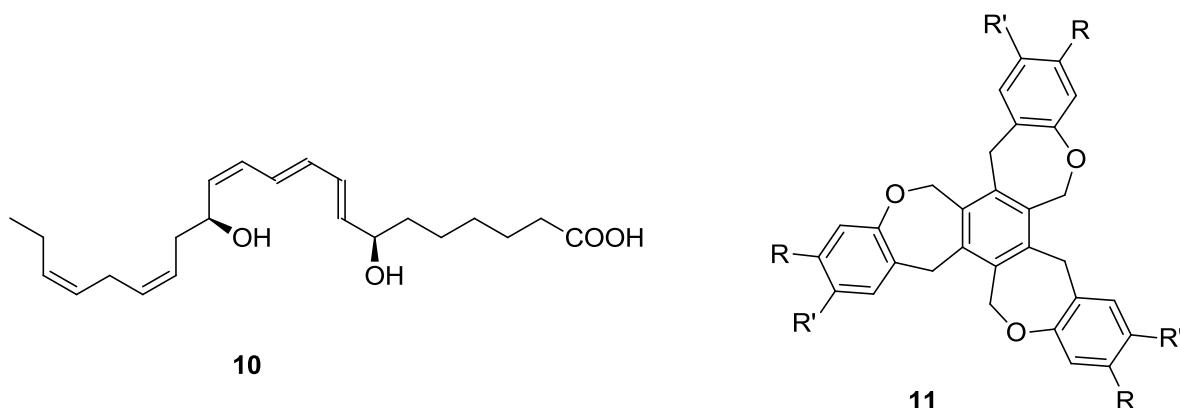
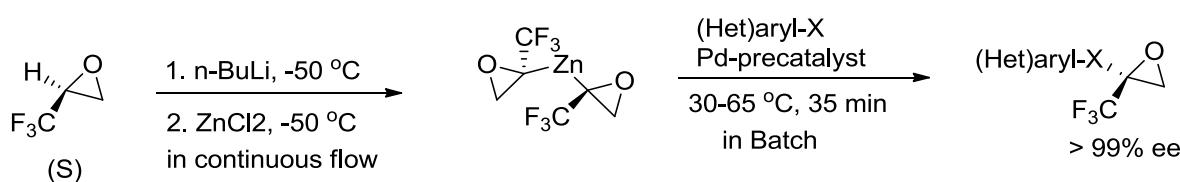


Figure I. 5. Vital compound synthesized through Negishi coupling



Scheme I. 17. Synthesis of CF_3 substituted chiral alcohols via Negishi coupling reaction



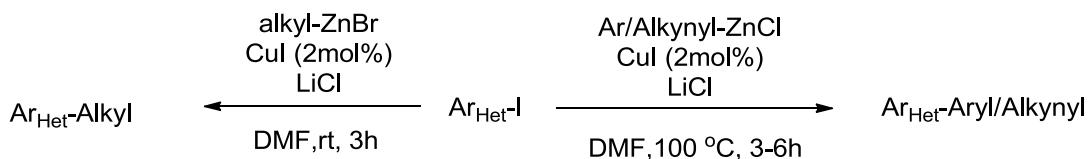
Green Initiatives

Many heterogenous recyclable catalysts are designed that can be used for Negishi cross-coupling reactions. A rapid room temperature Negishi cross coupling of hindered and electronically deactivated coupling partners was carried out by Price and co-workers using a silica-supported precatalyst, Pd-PEPPSI-IPent-SiO₂ (**Scheme I. 18**). The reaction shows high selectivity in producing non-rearranged products in the coupling of secondary alkyl zinc reagents.⁸⁴ Thapa *et. al.* developed ligand-free Negishi coupling using copper catalyst. This method was successful in conducting coupling of alkyl-, aryl-, and alkynylzinc reagents with heteroaryl iodides. Coupling of 1°, 2° and 3° alkylzinc reagents was attained at room temperature without rearrangement (**Scheme I. 19**). While higher temperatures were required for aryl- and alkynylzinc reagents.⁸⁵

Scheme I. 18. Room temperature Negishi cross coupling Pd-PEPPSI-IPent-SiO₂ precatalyst



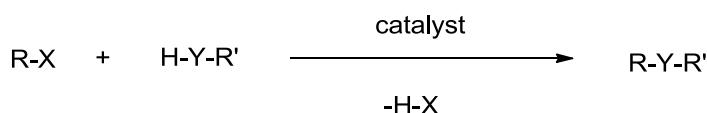
Scheme I. 19. Copper catalyzed, ligand free Negishi coupling



1. B. 2. C-X Coupling Reactions

A general scheme representing metal catalysed C-X coupling reaction is represented in **eq 9.**

eq 9.



X= Cl, Br, I, B(OH)₂ etc.

Y= N, S, O etc.

Common variants of C-X Coupling reactions

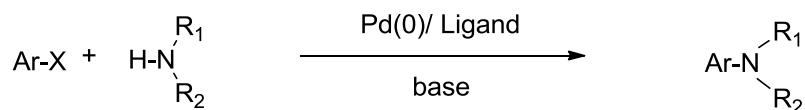
1. Buchwald-Hartwig reaction
2. Chan-Lam Coupling

1. B. 2. 1. Buchwald-Hartwig amination reaction

Attempts of C-N coupling reactions were endeavoured by various working groups earlier but reports before Buchwald and Hartwig were associated with drawbacks like sluggish transformation, poor substrate scope and functional group tolerance. The duo with their independent works between 1994 and 2000 contributed huge benefits to the field.⁸⁶ Buchwald-Hartwig reaction includes Palladium catalysed C-N bond formation reaction

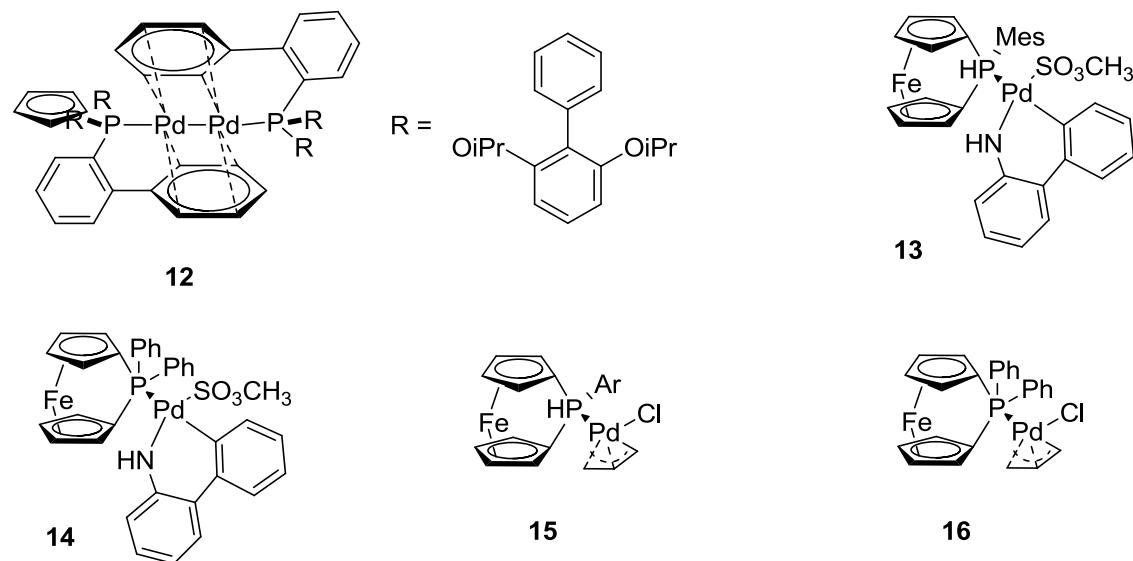
basically through the cross coupling of amines and aryl halides (or pseudohalides). A general equation for the reaction can be represented as **eq 10**.

eq 10:



Role of ligand is very important for the reaction and very limited examples of ligand free transformations are yet observed. This inspires scientists to develop and modify the ligand and complex structures to achieve better and improved results out of such reactions. Their contributions can be studied through a number of reviews related to the reaction.⁸⁷ An interesting study regarding the selection of base for different reaction mediums is reported by Sunesson *et. al.* Range of substrates that can be used mostly depends on the choice of ligands.⁸⁸ Since the advent of this reaction, contribution of phosphine ligands is evident. Very recently, Kirlikovali and co-workers utilized an air-stable Pd(I) dimeric complex **12** (**Figure I. 6**) as a suitable precatalyst for the coupling of both alkyl and aryl amines.⁸⁹

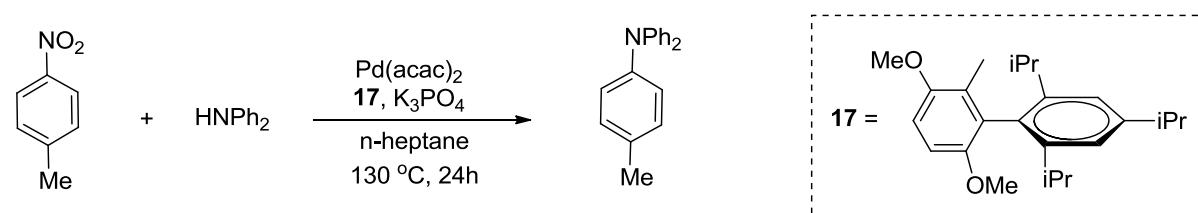
Figure I. 6. Catalysts used in recent Buchwald-Hartwig reaction



Feyrer *et. al.* synthesised various Ferrocene based phosphine ligands **13-16** (**figure I. 6**).⁹⁰ They used them as redox-switchable catalysts for Buchwald reaction. Electronic and steric factors of the ligands used influenced the rates of reaction for various complexes prepared. In

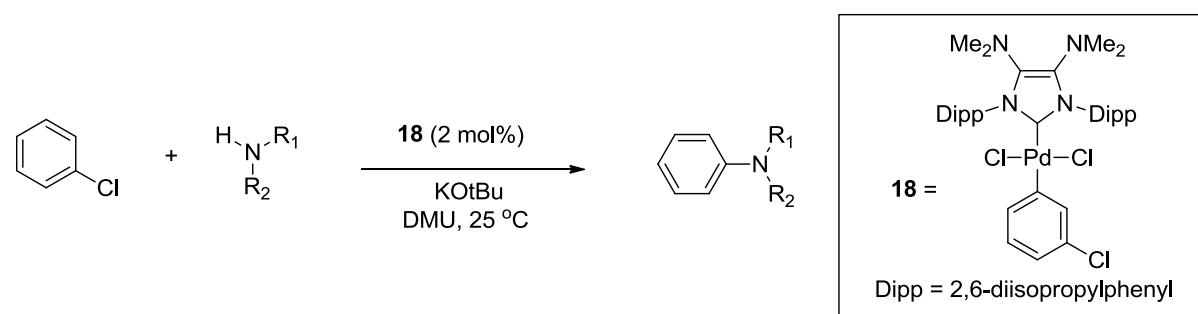
solution, addition of oxidising agent changed the nature of complex catalyst from neutral to cationic and thus resulted in enhancing or depreciating the reaction rates. Amination of nitroarenes was achieved by Inoue *et. al.* using dialkyl(biaryl)phosphine ligands **17**, (**Scheme I. 20**).⁹¹

Scheme I. 20. Amination of nitroarenes using dialkyl(biaryl)phosphine ligands

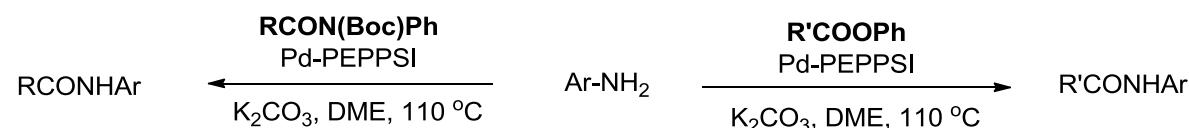


NHCs are also proved to be powerful ligands for C-N coupling. Effective use of amine substituted NHCs in Buchwald Hartwig reaction was shown by Zhang *et. Al.* (**Scheme I. 21**).⁹² They later proposed butterressing effect as the key-factor in skeletal modification of NHCs around central Pd atom for such reactions.⁹³ Pd-PEPPSI catalysts are also very effective for the reaction.⁹⁴ Buchwald–Hartwig cross-coupling of esters and amides (transamidation) using Pd-PEPPSI catalysts was conducted by Shi *et. al* recently. They thus, synthesized amides through the reaction. Interestingly, both amides and esters react in similar conditions (**Scheme I. 22**).⁹⁵ Pd nanoparticles are also utilized as active catalytic tools in the Buchwald-Hartwig reacrtion.⁹⁶

Scheme I. 21. NHC catalysed Buchwald Hartwig reaction

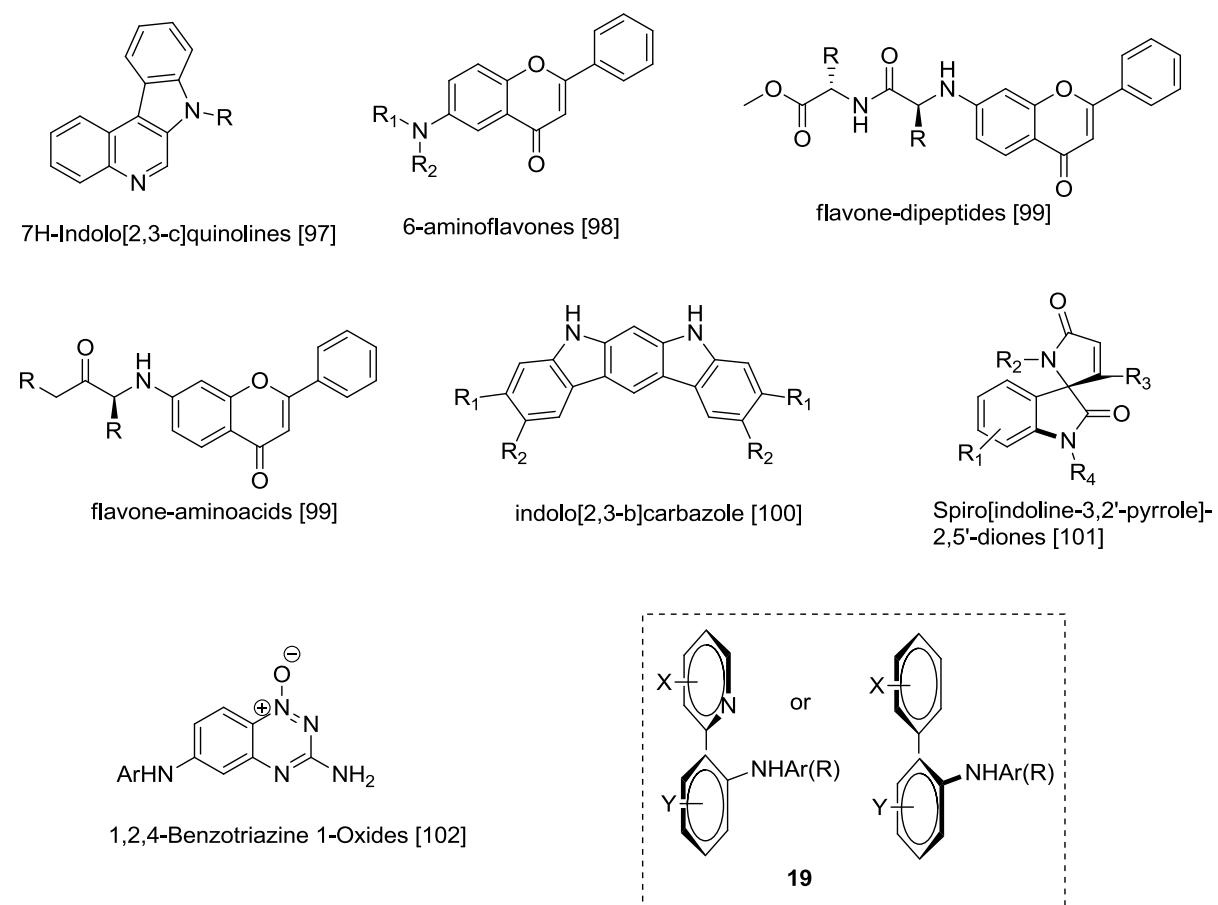


Scheme I. 22. Buchwald–Hartwig cross-coupling of esters and amides (transamidation) using Pd-PEPPSI catalysts



C-N bond is present in majority of drugs and other biologically active compounds. This fact in itself suggests the contribution of Buchwald-Hartwig process in the field of organic synthesis. Some recent noteworthy applications are worth mentioning here. Important key biological motifs that are synthesised recently are shown in (**figure I. 7**).⁹⁷⁻¹⁰³ Conjugated microporous polymer networks that is 3D polyaminoanthraquinonylamine based polymers were synthesized very recently by Liao *et. al.* for supercapacitor energy storage.¹⁰⁴ Isoquinoline-aminonaphthalene type N,N-Ligands **19** (**figure I. 7**) were synthesized via asymmetric Buchwald-Hartwig amination by Lopez and co-workers.¹⁰⁵

Figure I. 7. Vital biologically active motifs synthesised through Buchwald-Hartwig reaction

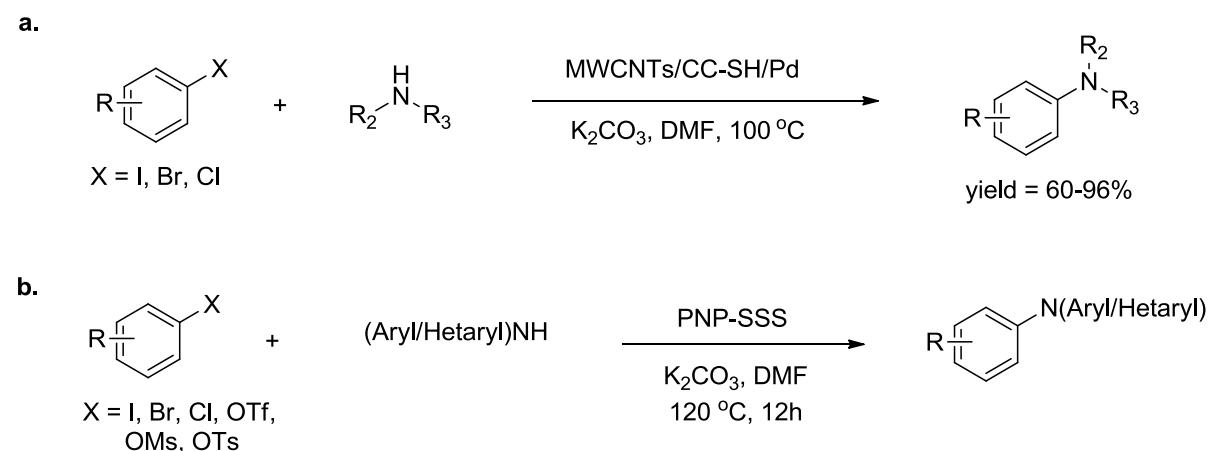


Green Initiatives:

Several attempts of designing environmentally benign Buchwald-Hartwig amination processes are reported. Synthesis of reusable catalyst is a good approach to prevent harmful discharge of Pd in the environment. Very recent works that devise methodologies using

recyclable catalysts involve anchoring of palladium nanoparticles on solid supports like thio modified-multiwalled carbon nanotubes (MWCNTs/CC-SH/Pd)¹⁰⁶ or silica starch substrate (PNP-SSS)¹⁰⁷ (**Scheme I. 23**). The catalysts were reusable for more than five runs without much loss of catalytic activity. A highly active and stable Pd-NHC catalyst [Pd(IPr*)(cin)Cl] (IPr* = 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene; cin = η³-cinnamyl) for continuous flow Buchwald-Hartwig reactions was prepared and studied by Chartoire *et. al.*¹⁰⁸ Use of magnetic iron oxide nanoparticles in the solid support make the catalyst magnetically recoverable after the reaction is over. This helps a lot in preventing solvent loss during recovery and multiple washes of the catalyst.¹⁰⁹ The catalysts are capable to provide high yields for multiple runs.

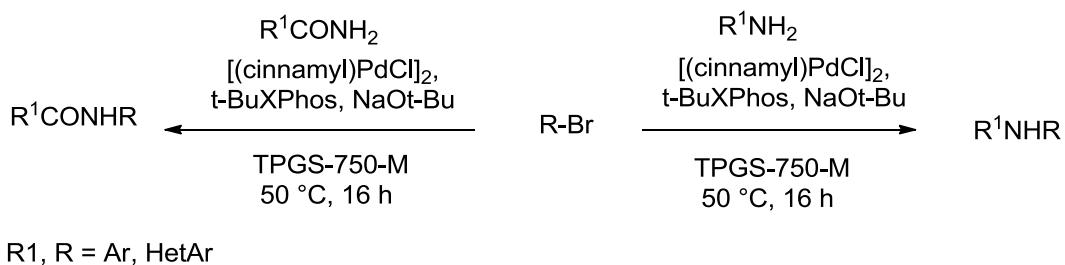
Scheme I. 23: Buchwald Hartwig reaction using palladium nanoparticles supported on (MWCNTs/CC-SH/Pd) and (PNP-SSS)



Many greener schemes have been devised that use water as a reaction medium for Buchwald-Hartwig C-N coupling reactions. In a novel approach Lipshutz showed how important cross coupling reactions like Sujuki, Heck, Buckwald, Sonagashira etc. can be carried out in water using polyoxyethanyl-α-tocopheryl succinate (TPGS-750-M), a non-ionic amphiphile surfactant.¹¹⁰ Inspired by them Wagner *et. al.* prepared an aqueous micellar medium using t-BuXPhos with $[(\text{cinnamyl})\text{PdCl}]_2$ in TPGS-750-M as the reaction medium.¹¹¹ Coupling of arylbromides or chlorides with a large set of amines, amides, ureas and carbamates was attained with excellent yields (**Scheme I. 24**). Liu *et. al.* used 2-aryl indenylphosphine ligand with $\text{Pd}(\text{dba})_2$ to conduct Buchwald-Hartwig amination of aryl chlorides in solvent-free condition (**Scheme I. 25**). Keeping all other parameters alike same reaction can be carried in aqueous medium too providing higher yields in some entries.¹¹² Solvent-free Buchwald-

Hartwig cross coupling reactions were also conducted by topchiy *et. al* using ligands like RuPhos **20** (RuPhos = 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl) and (THP-Dipp)Pd(cinn)Cl **21** (THP-Dipp = 1,3-bis(2,6-diisopropylphenyl)-3,4,5,6-tetrahydropyrimidin-2-ylidene, cinn = cinnamyl, 3-phenylallyl) (**Figure I. 8**).¹¹³

Scheme I. 24. Buchwald-Harwig reaction in aqueous micellar medium using t-BuXPhos with $[(\text{cinnamyl})\text{PdCl}]_2$ in TPGS-750-M



Scheme I. 25. Buchwald-Hartwig amination of aryl chlorides in solvent-free condition

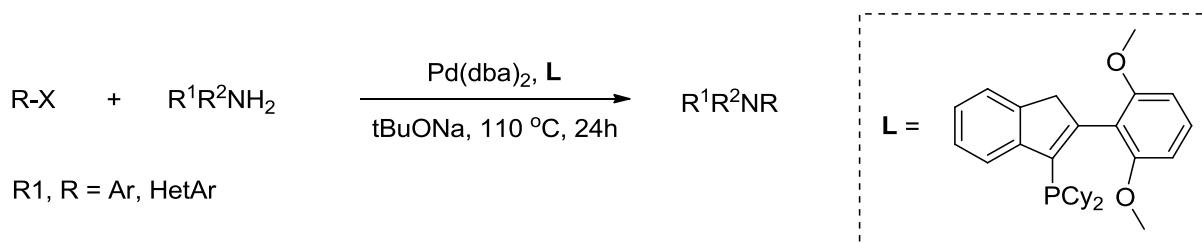
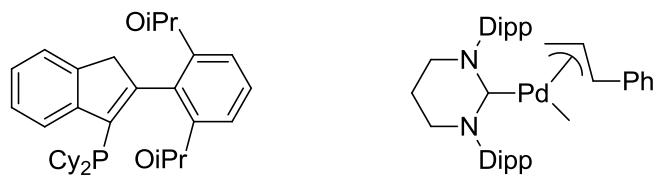
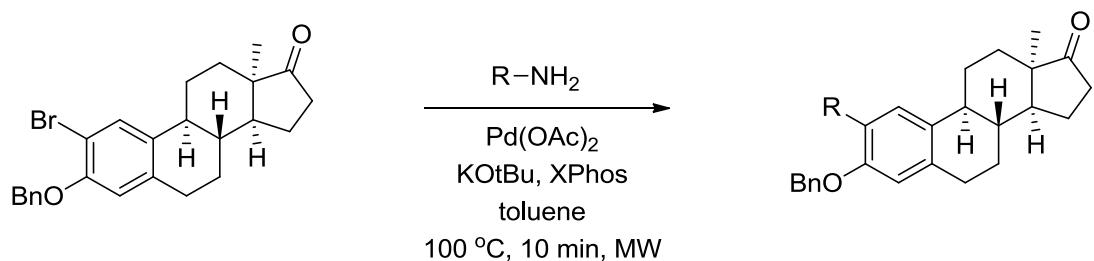


Figure I. 8. Ligands used in solvent-free Buchwald-Hartwig cross coupling reactions

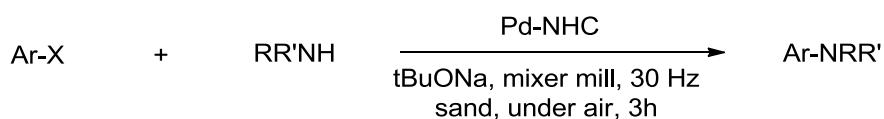


Advanced processes designed that target saving energy consumed in the processes involve use of microwave irradiation as recently by Bacsa *et. al.* (**Scheme I. 26**)¹¹⁴ and Saikia *et. al.*,¹¹⁵ use of ball-milling concept very recently by Cao *et. al.* (**Scheme I. 27**)¹¹⁶ and continuous flow process as by Fal *et. al.*¹¹⁷

Scheme I. 26. Buchwald-Harwig reaction using microwave-irradiation



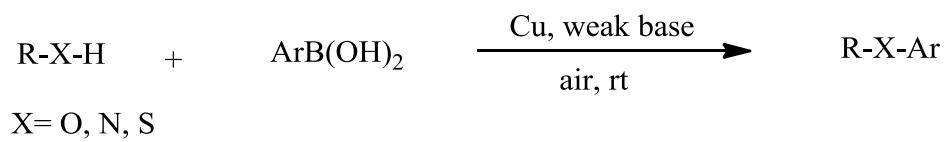
Scheme I. 27. Buchwald-Harwig reaction using Ball-milling.



1. B. 2. 1. Chan-Lam type C-X (C-O, C-S, C-N) Coupling reactions

Chan-Lam coupling reaction also known as Chan-Evans-Lam coupling reaction is a Cu catalyzed cross coupling reaction of a nucleophilic substrates like amine, alcohol or thiol with boronic acid or similar electrophilic substrates. Thus the overall change may be a C-N, C-O or C-S bond formation. General equation for the reaction may be written as equation 11.

Eq 11:



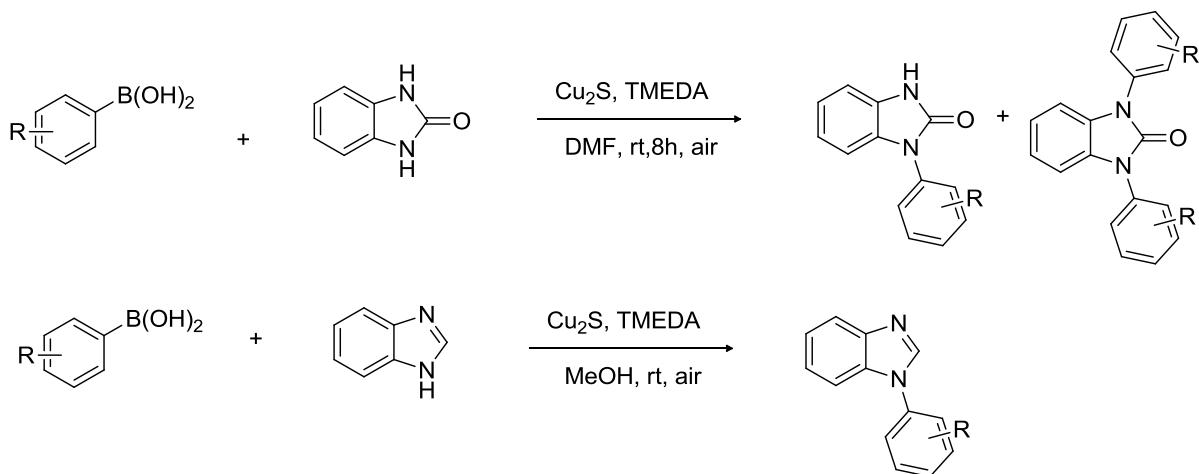
The reaction has many advantages than its complementary Suzuki type C-C cross coupling of boronic acid derivatives. Copper catalysts used are cheaper and greener as compared to Pd, mild reaction conditions (room temperature, weak base), versatility of nucleophilic coupling partners (alcohols, thiols, amines, azides, sulphonyl azides, N-arylcarbamates, nitroarenes, pyrazoles etc.) and generation of important C-S, C-O and C-N bonds that are very crucial in biological, pharmaceutical and material science applications. Due to mild reaction conditions presence of many other functional groups on the substrate are very well tolerated in the reaction. Beneath are the recent trends and applications of these reactions in a nutshell.

1. B .2. 1. A. Chan-Lam type C-N coupling:

Chan-Lam type C-N cross coupling is the most common form of this reaction. As above mentioned many active N-containing nucleophilic substrates have been explored and well utilized in the reaction. This has lead to synthesis of huge range of compounds including heterocyclic simple and complex molecules. To illustrate this, a point wise discussion of various essential biologically active compounds that can be synthesized using this reaction is presented below. The corresponding methodologies are represented in **Scheme I. 28 (a-j)**.

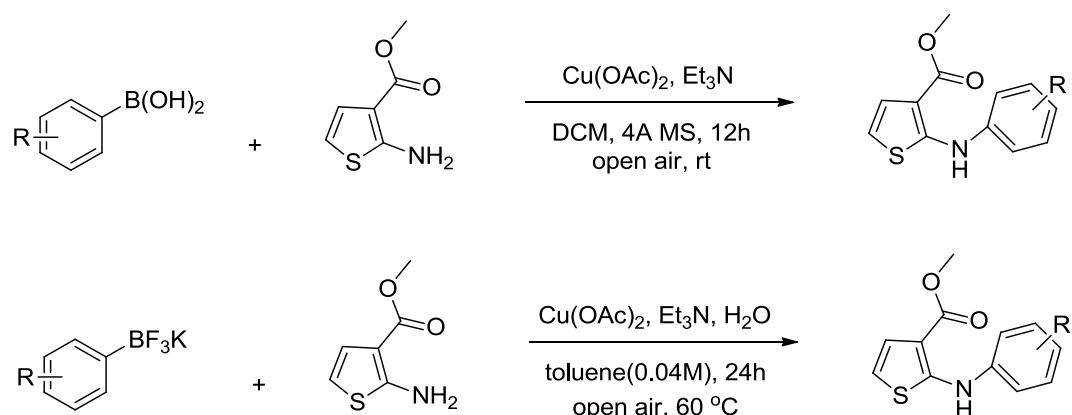
- a. Arylation of benzimidazole, benzimidazolone and imidazole derivatives at room temperature using Cu/TMEDA system was achieved by Janíkova *et. al.* Various functional groups were tolerated in the reaction including -OH and -Br.¹¹⁸

Scheme I. 28a.



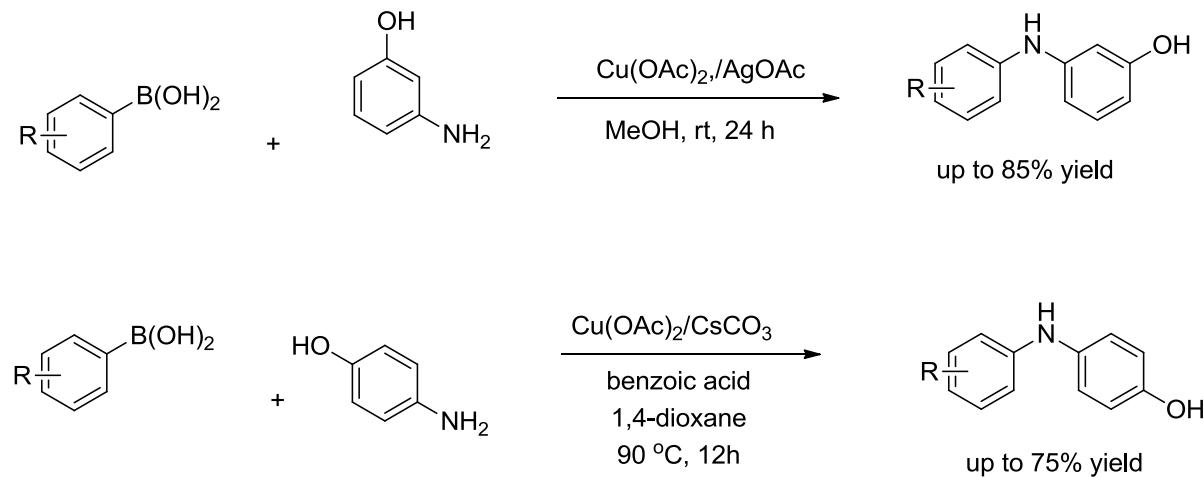
- b. N-arylation of methyl 2-aminothiophene 3-carboxylates with both arylboronic acids and potassium aryltrifluoroborate salts (Rizwan *et. al.*). Desired coupling products were obtained in moderate to good yields.¹¹⁹

Scheme I. 28b:



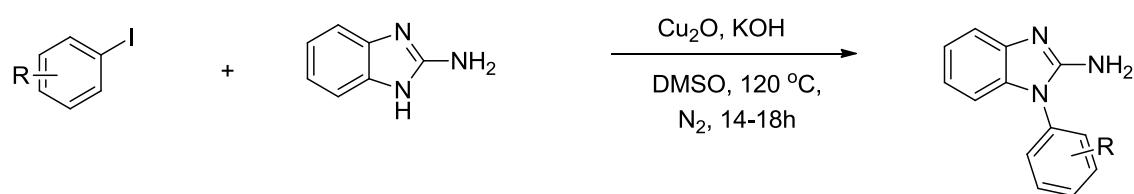
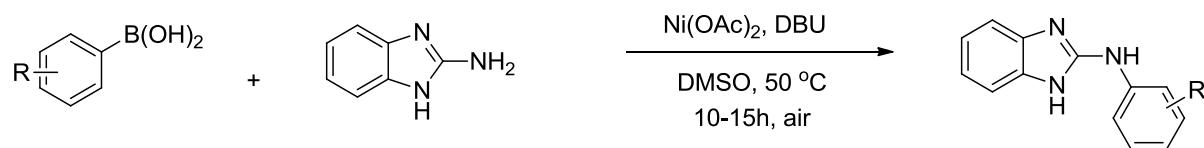
c. Chemoselective N-arylation of aminophenols developed by Reddy *et. al.* Selective N-arylation over O-Arylation was studied by DFT calculations. N-arylation was found to be more favored both kinetically and thermodynamically according to calculations based on the Free energy changes associated with each step of the reaction.¹²⁰

Scheme I. 28c.



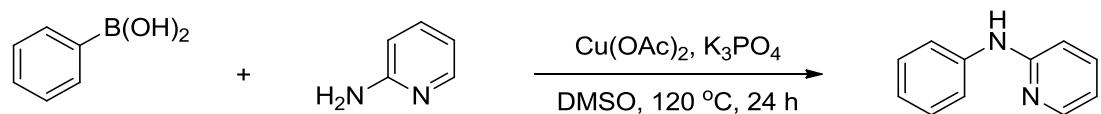
d. Very interesting chemoselective N-arylation of 2-aminobenzimidazoles is reported by Kumar *et. al.* Arylation of amino group- N took place with arylboronic acids through Ni catalysed Chan-Lam coupling while azole- N was arylated through Cu catalysed coupling of the substrates using aryl iodides.¹²¹

Scheme I. 28d.



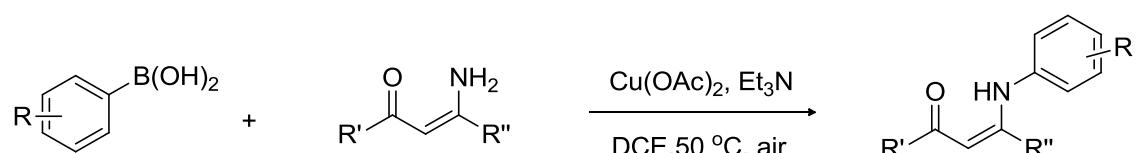
e. A convenient synthesis of *N*-arylpyridin-2-amines was performed by Chen *et. al.* through Chan-Lam coupling of 2-aminopyridines and arylboronic acids. All the products were obtained in moderate to good yields.¹²²

Scheme I. 28e.



f. Duan *et. al.* conducted easy synthesis of *N*-aryl enaminones through Chan-Lam coupling of Enaminones with arylboronic acids. These compounds can serve as important building blocks in synthesis of vital organic compounds.¹²³

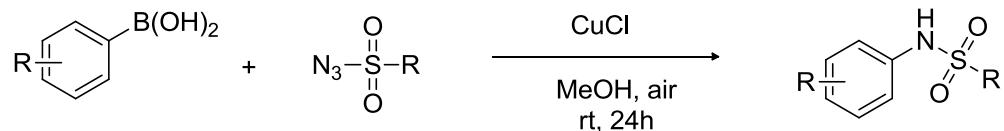
Scheme I. 28f.



g. *N*-arylsulfonamides can be synthesized through Chan-Lam coupling of sulfonyl azides and aryl(Hetaryl)boronic acids (Moon *et. al.* 2014). The reaction was compatible with arylboronic

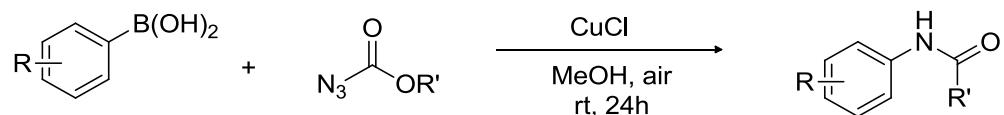
esters and aryltrifluoroborate salts. Both aryl and alkyl-sulfonamides were used in the reaction.¹²⁴

Scheme I. 28g.



h. Analogous synthesis of N-aryl carbamates through Chan-Lam coupling of azidoformates with arylboronic acids is also performed. Desired products were obtained in excellent yields in most of the case. The products were further used to synthesize urea derivatives.¹²⁵

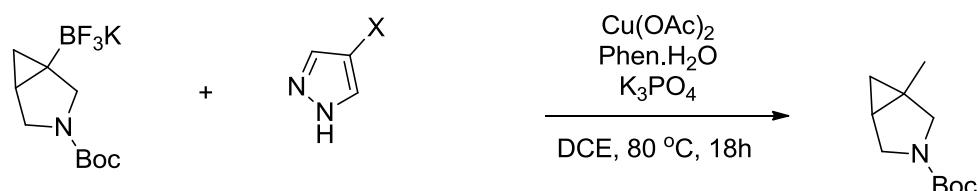
Scheme I. 28h.



R'= aryl, benzyl, alkyl

i. Synthesis of complex motifs 1-heteroaryl-3-azabicyclo[3.1.0]hexanes containing C-tertiary arylamines at the ring juncture was performed Harris *et. al.*¹²⁶

Scheme I. 28i.

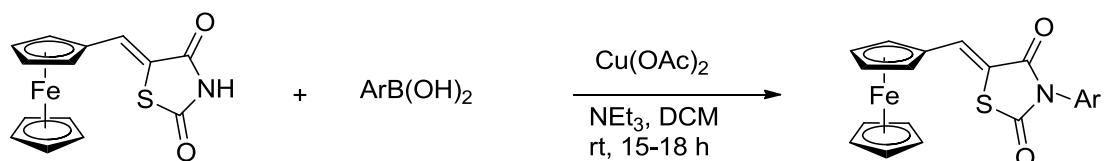


X= EDG, EWG, H, Ph

Phen = Phenanthroline

j. N-arylation of ferrocenyl 2,4-thiazolidinedione conjugates **23** with arylboronic acids by Shinde *et. al.* provided novel N-arylated products **24** that are potent to bear optoelectronic and antidiabetic properties.¹²⁷

Scheme I. 28j.

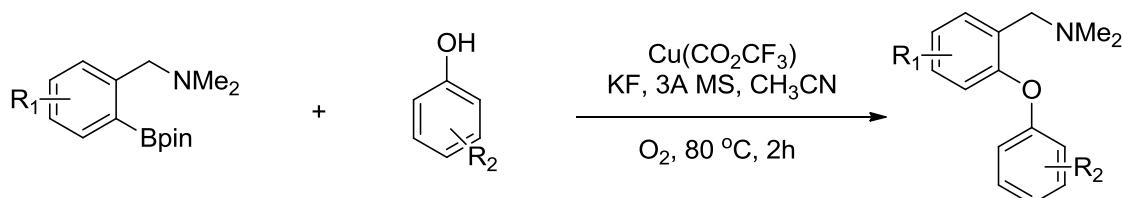


1. B. 2. 1. B. Chan-Lam type C-O coupling:

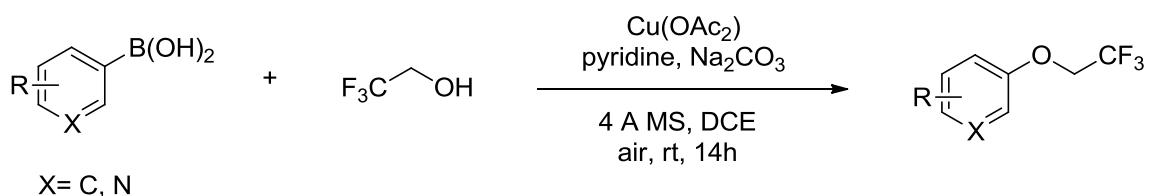
This type of Chan-Lam coupling results in formation of C-O bond through coupling of reagents like alcohols and arylboronic acid derivatives. Such reactions have found appreciable contribution in synthesis of important bioactive motifs¹²⁸, drug molecules, polymer surface modification¹²⁹ etc. Type of boronic acid derivative or active –O coupling partner can also be varied here as in the above C-N coupling reaction. Some of the recent reaction methods developed are as follows (**Scheme I. 29(a-d)**):

Scheme I. 29. Chan-Lam type C-O coupling reactions

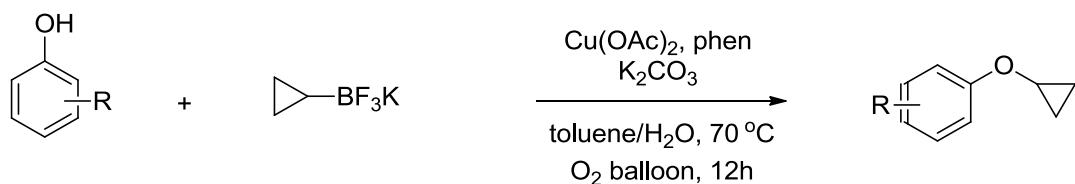
- a. etherification of ortho-borylated benzylic amines with phenols¹³⁰



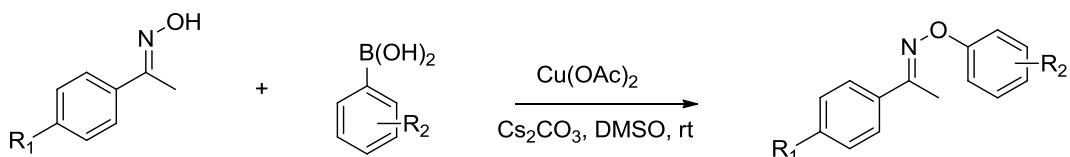
- b. Synthesis of trifluoroaryl ethers through copper-catalyzed oxidative trifluoroethoxylation of arylboronic acids with CF3CH2OH.¹³¹



- c. Chan–Lam cyclopropanylation of phenols and azaheterocycles¹³²



d. O-arylation of oximes with arylboronic acids¹³³

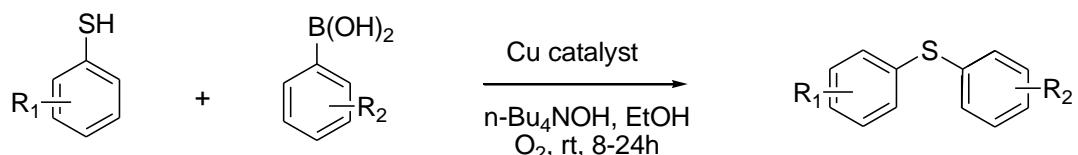


1. B. 2. 1. C. Chan-Lam type C-S coupling:

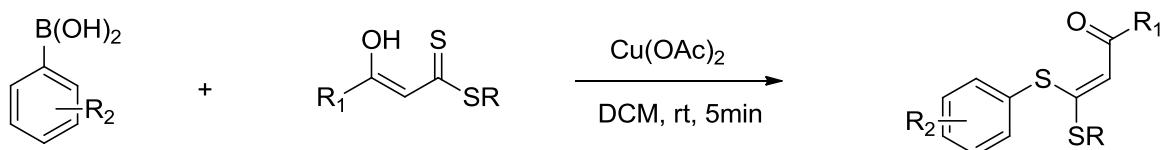
Chan-Lam type C-S coupling reaction is emerging as a promising tool in organic synthesis due to abundance of C-S linkages in crucial compounds of biological, polymer, pharmaceutical significance. This involves copper catalyzed cross coupling of thiols with arylboronic acids. Initially, copper catalyzed C-S cross coupling was not much envisaged as thiols in presence of copper dimerise to form disulfides. But eventually, it was observed that the reaction can be appropriately molded for selective or preferential thioether synthesis. In this reaction type again various derivatives of kind of derivatives of the substrates can be used. Some of the recent methodologies developed based on Chan-Lam type C-S coupling are as follows (Scheme I. 30):

Scheme I. 30. Chan-Lam type C-S coupling reactions

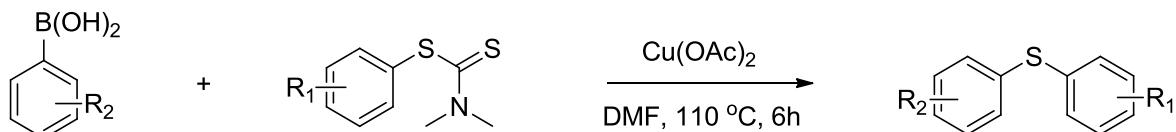
a. Cross coupling of arylboronic acids and thiols using heterogenous recyclable Cu catalyst.¹³⁴



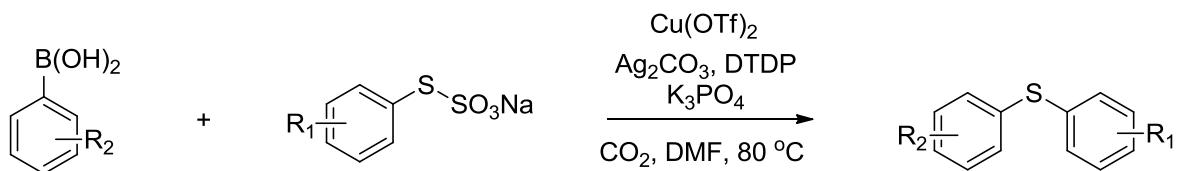
b. A rapid and mild protocol for synthesis of unsymmetrical α -oxoketene S-aryl, S-alkyl acetals via S-arylation of α -enolic dithioesters with arylboronic acids¹³⁵



c. C-S Chan- Lam coupling of phenyldithiocarbamates and thiols to form thioethers ¹³⁶



d. Chan-Lam type C-S coupling reaction between SO_3^- masked aryl/hetaryl sulfides with aryl/hetaryl boronic acids in CO_2 environment. Formation of disulfide byproducts was reduced to minimum in carbondioxide medium as compared to nitrogen or oxygen environment. It was proposed that the masking effect will prevent strong coordination between transition metal and active S, prevent dimerisation, provide relieve from foul smell of the reagent.¹³⁷



Green Initiatives

As we have observed till here Chan-Lam coupling is a very versatile tool in organic synthesis. It uses cheap, less toxic and abundantly available Cu metal catalysts. It generally requires mild reaction conditions like room temperature, oxygen or air environment. Ligand free and base free variations are developed. To make the process more environment friendly many working groups have applied recoverable and recyclable catalysts in the process.¹³⁸

Han *et. al.* synthesized a heterogeneous catalyst containing copper immobilised on covalent organic framework for coupling of anilines with arylboronic acids. The catalyst is highly stable and reusable for up to 8 cycles furnishing very high yields. The reaction was performed in green MeOH-water medium.¹³⁹ Copper-zeolite recyclable catalysts were used by

Chasseing *et. al* for base-free and ligand-free Chan-Lam type coupling of N-heterocycles and arylboronic acids in methanol medium.¹⁴⁰ Magnetically recoverable catalysts developed by using Fe₂O₃ Sharma *et. al.* very recently. The catalyst provided very good yields upto 6 cycles in water as solvent.¹⁴¹ Yoo *et. al.* developed visible light (blue LED) mediated copper catalysed cross coupling of aniline derivatives and electron deficient arylboronic acids. Nitrile-based solvents were found highly favourable for the reaction.¹⁴²

1. C. CONCLUSION

C-C and C-X coupling reactions have applications in all fields of organic synthesis. The reactions are highly versatile and are handy tools for our laboratories and industries for numerous purposes. Contribution of transition metals especially Palladium to the field is unmatched. They provide excellent efficiencies and discourage use of stoichiometric metals in the reactions as was in case of classical synthetic methods. Having Greener Approach towards designing and adopting any synthesis methodology is the need and demand of current and future generation. It is high time everyone should realize the importance of Greener methodologies. Researchers worldwide have come up with various approaches like recyclable catalyst, green solvent medium, avoiding toxic reagents and practices, avoiding organic and inorganic waste discharge, using clean and green energy sources, adopting one-pot tandem processes etc.

I. D. REFERENCES

References are given in BIBLIOGRAPHY under Chapter I (pg-210-121)