

CHAPTER I

**Brief review on transition metal-
catalyzed organic reactions and eco-
friendly reaction media**

Section I.A. Transition metal–catalyzed organic reactions

I.A.1. General view of transition metal catalysts in organic reactions

Transition metals have many unusual properties that make their chemistry different from main group elements and those properties uniquely selected them towards certain specific roles. Most of them are associated with greater variability and tunability of transition metal compounds. This is almost solely because of the facts that transition metal compounds have incompletely filled and closely spaced ‘d’ orbitals. Moreover transition metal compounds can exhibit variable oxidation states, with finely controlled and tunable redox properties. It is possible because the ‘d’ orbital energies and spacing can be altered by incorporating suitable ligands. As a result of these specific properties many of the highly critical reactions in organic chemistry could be successfully achieved by employing transition metal compounds as catalyst. Transition metal catalysts display remarkable efficiency for the formation of carbon–carbon and carbon–heteroatom bonds through the reactions of suitable nucleophiles with organic electrophilic partners. Within this subset of the periodic table, palladium (Pd), copper (Cu), cobalt (Co), rhodium (Rh), ruthenium (Ru) complexes offer the broadest utility and deepest mechanistic insight into “cross–coupling reactions”. In modern synthetic chemistry cross–coupling reactions have evolved as a critical support to construct or design organic compounds.

I.A.2. Application of transition metal catalysts in organic reactions

The various transition metals such as palladium (Pd), copper (Cu), nickel (Ni), cobalt (Co), rhodium (Rh) and ruthenium (Ru) have been widely used in catalyst form to conduct diverse organic transformations. As the present research work included in this thesis belongs to Pd–catalyzed C–C coupling reaction and Cu–catalyzed cycloaddition reaction, we therefore emphasize similar type of other reactions catalyzed by these two metals. It is noteworthy that among these metals palladium is hugely explored because of its application in several important cross–coupling reactions.

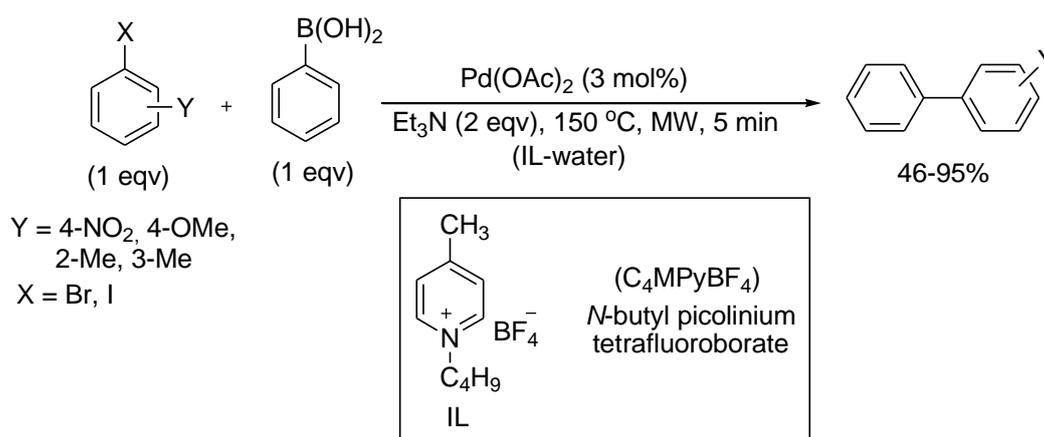
I.A.2.1. Palladium–catalyzed reactions

It is worth mentioning that among the various transition metals palladium is topmost important which can catalyze many important cross–coupling reactions.^{1,2} Due to its

impact in such a variety of fields, Akira Suzuki, along with Richard F. Heck and Ei-ichi Negishi, were awarded the Nobel Prize in Chemistry for “Palladium–catalyzed cross–couplings in organic synthesis” in September 2010. The catalytic roles of palladium–based catalysts have also been exciting in many other transformations in the field of organic chemistry. These include oxidation of alkenes,³ hydrogen transfer reaction from alcohol to C=C, C=O, C=N bonds,⁴ C–H functionalization,⁵ etc. Here we have highlighted some name reactions, mostly based on C–C cross–coupling reactions.

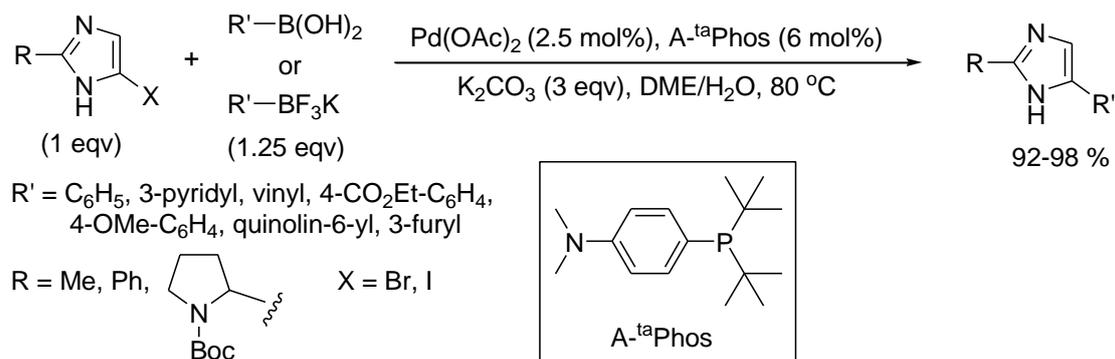
I.A.2.1.1. Suzuki–Miyaura cross–coupling reaction

Castro *et al.* reported phosphine–free Pd(II) catalyzed Suzuki–Miyaura (SM) cross–coupling reaction in picolinium based ionic liquid under microwave irradiation.⁶ This ionic liquid with water played the role of good solvent property where the reaction was clean and lead to very high conversion into the product (Scheme I.1).



Scheme I.1. Suzuki–Miyaura cross–coupling reaction in ionic liquid–water co–solvent system

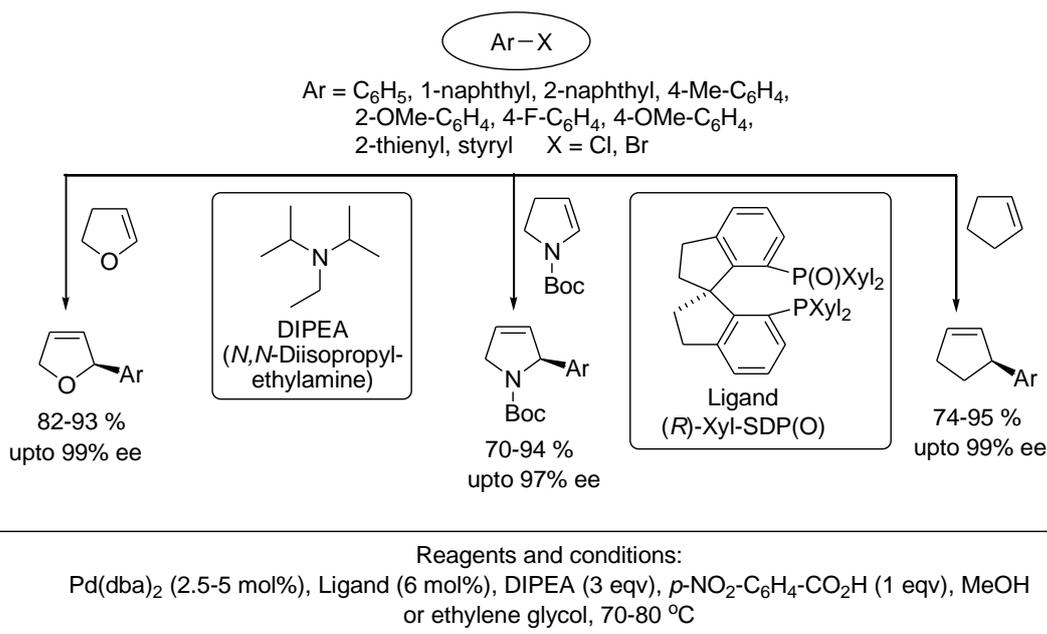
Another example of Pd(OAc)₂–catalyzed SM coupling reaction of unprotected haloimidazole is given by Yasuda *et al.*. A wide array of functionalized imidazoles were synthesized by taking different aryl and heteroaryl boronic acid (Scheme I.2).⁷



Scheme I.2. Suzuki–Miyaura coupling reaction on haloimidazoles

I.A.2.1.2. Mizoroki–Heck reaction

Asymmetric intermolecular Heck reaction was performed using $\text{Pd}(\text{dba})_2$ catalyst in presence of chiral ligand [(*R*)-Xyl-SDP(O)], a bisphosphine oxide having a spiro bisindane skeleton. In this reaction *p*-nitrobenzoic acid was used as an additive and DIPEA as a base (Scheme I.3).⁸

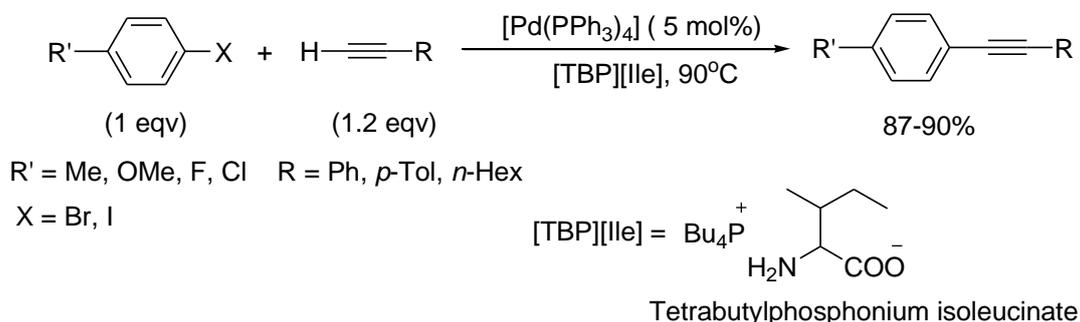


Scheme I.3. Asymmetric intermolecular Heck reaction

I.A.2.1.3. Sonogashira reaction

In 2011 Fukuyama *et al.* reported Pd-catalyzed amine-free and copper-free Sonogashira coupling reaction,⁹ in phosphonium based amino acid ionic liquids. Investigation of the reaction using $\text{Pd}(\text{PPh}_3)_4$ and $[\text{PdCl}_2(\text{PPh}_3)_2]$ as palladium catalyst and using different tetrabutylphosphonium ionic liquid (varying in amino acids such as Glycine, L-Alanine, L-Valine, L-Methionine, L-Phenyl alanine, L-Isoleucine in the anionic counterpart) revealed that the best result was obtained using $\text{Pd}(\text{PPh}_3)_4$ as

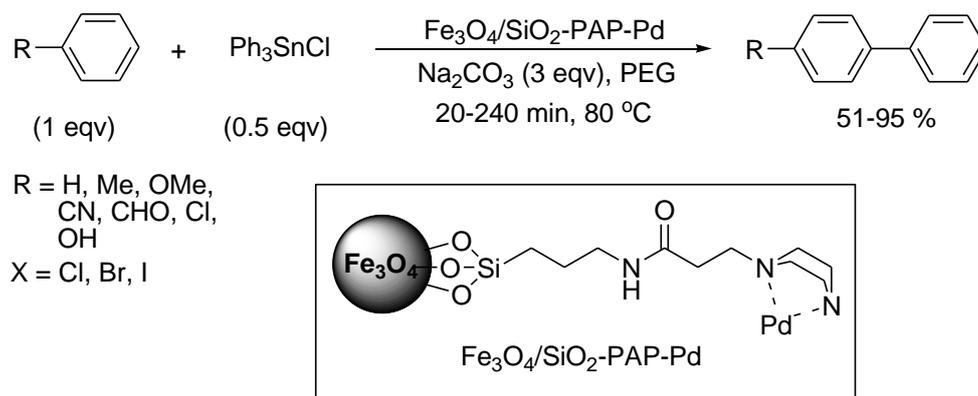
palladium source and in [TBP][Ile] i.e. tetrabutylphosphonium isoleucinate ionic liquid (Scheme I.4).



Scheme I.4. Sonogashira coupling reaction in [TBP][Ile]

I.A.2.1.4. Stille cross-coupling reaction

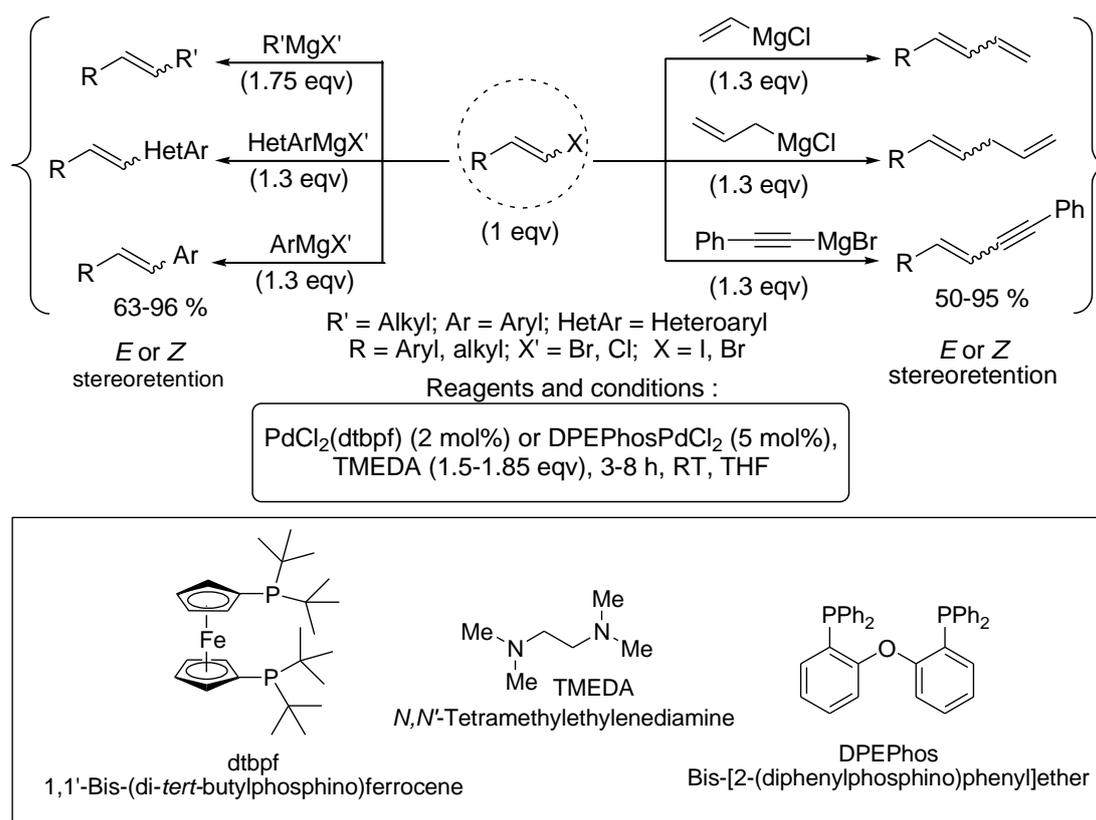
Very recently Norouzi *et al.* synthesized magnetic nanoparticle-supported palladium catalyst ($\text{Fe}_3\text{O}_4/\text{SiO}_2\text{-PAP-Pd}$) and used it for Stille cross-coupling reaction of various aryl halides (Scheme I.5).¹⁰



Scheme I.5. Stille cross-coupling reaction by magnetic nanoparticle-supported palladium catalyst

I.A.2.1.5. Negishi coupling reaction

The cross-coupling reaction between organozinc compound and organic halides or triflates is known as Negishi coupling reaction and this reaction was the pioneer work of Ei-ichi Negishi,¹¹ who was the co-recipient of 2010 Nobel prize in Chemistry. Applying this approach a library of 1,5-disubstituted-3-amino-1*H*-1,2,4-triazoles have been synthesized using Knochel's base tetramethylpiperidynyl zinc chloride lithium chloride ($\text{TMPZnCl}\cdot\text{LiCl}$) and bis(*di-tert*-butylphenyl phosphine)palladium chloride (Scheme I.6).¹²



Scheme I.10. Stereoselective Kumada–Corriu cross–coupling reaction at room temperature

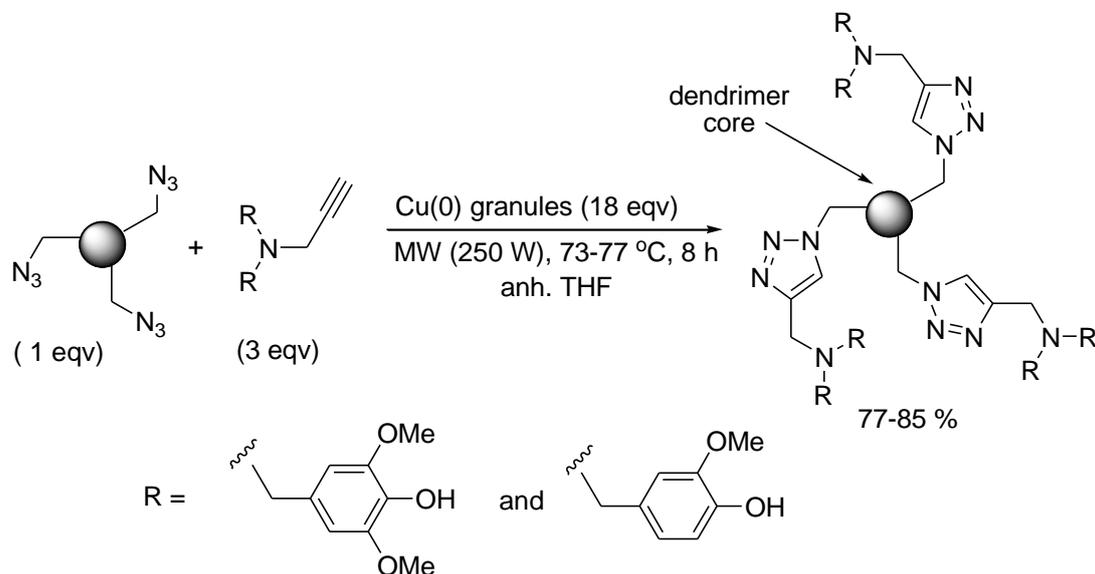
I.A.2.2. Copper–catalyzed reactions

Copper–catalyzed Glaser homo–coupling and cross–coupling reaction offer a powerful tool for the formation of symmetrical diyne molecules²⁰ and C–hetero bonds such as C–S,²¹ C–P,²² C–O,²³ C–N,²³ etc. Besides these reactions copper can also catalyze many other organic reactions such as cross–dehydrogenative–coupling,²⁴ cycloaddition reaction,²⁵ electrophilic amination reaction²⁶ etc. The indisputable advantages of Cu–catalysts over other catalysts include: low cost, ready accessibility and ability to form stable complexes by strong coordination with suitable ligands. Here we have shown a few and selective examples of Cu–catalyzed cycloaddition reactions based on the recent literature.

I.A.2.2.1. Click reaction

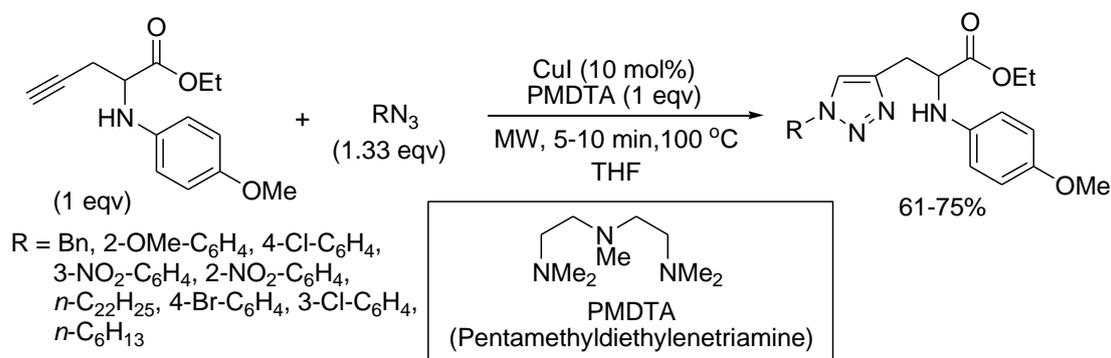
Copper (I) catalyzed azide–alkyne cycloaddition (CuAAC) reaction is commonly known as click reaction. It is a type of 1,3–dipolar cycloaddition reaction between alkyne and azide. However, the term ‘click’ given by K. B. Sharpless is not limited for this reaction only. Lee and Du prepared syringaldehyde (4–hydroxy–3,5–dimethoxybenzaldehyde) and vaniline (4–hydroxyl–3–methoxybenzaldehyde) based

dendrimer by CuAAC reaction (Scheme I.11).²⁷ The reaction was catalyzed by Cu-granules and assisted under microwave irradiation in presence of tetrahydrofuran (THF) solvent. These triazole based dendrimeric compounds act as potent antioxidant for which they have many biological applications.



Scheme I.11. Synthesis of triazole containing dendrimer catalyzed by Cu(0) granules

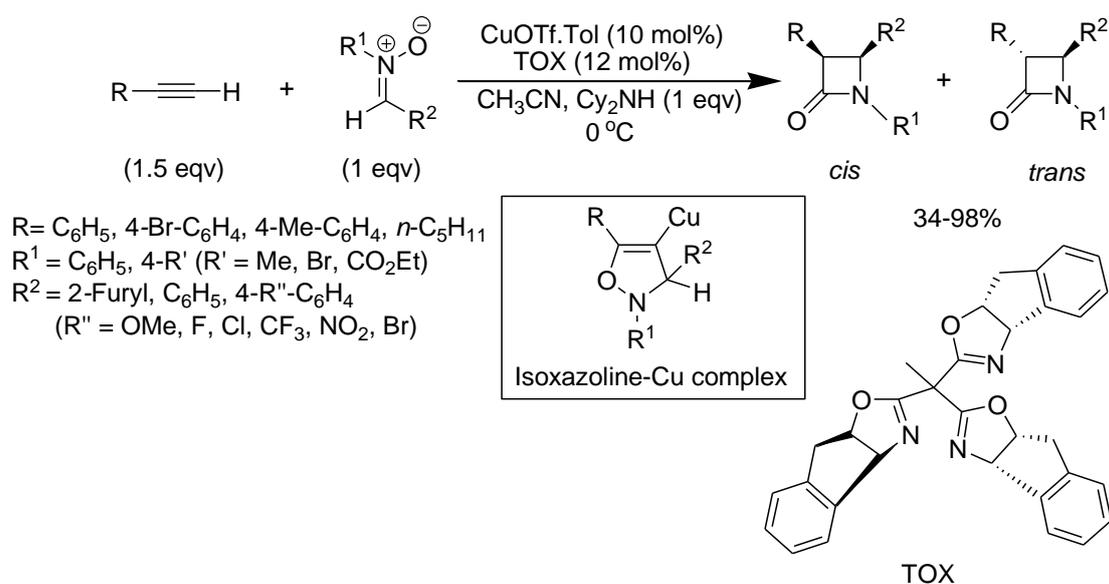
Stefani *et al.* prepared β -1,2,3-triazolyl- α -amino ester by Cu-catalyzed cycloaddition reaction of α -amino ester having propargyl group and sodium azide using microwave as non conventional energy source. The reaction was optimized both by microwave absorbing solvent methanol as well as microwave non absorbing solvent THF and also under neat condition. Comparatively better result was obtained in aprotic solvent THF (MW-non absorbing) using CuI as catalyst and PMDTA as ligand (Scheme I.12).²⁸



Scheme I.12. Synthesis of β -1,2,3-triazolyl- α -amino ester by CuAAC reaction

I.A.2.2.2. Kinugasa Reaction

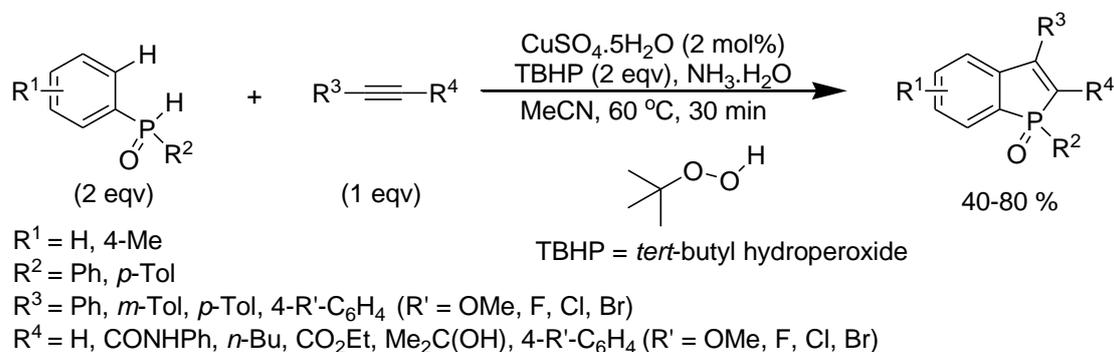
In 1972 Kinugasa and Hashimoto reported the [3+2] cycloaddition between nitrone and *in situ* generated Cu(I)-acetylide to form both *cis* and *trans* β -lactams.²⁹ Afterward various methods have been developed for asymmetric Kinugasa reaction including the work by Chen *et al.* in 2012 using tris(oxazoline) ligand (TOX) and Cu-catalyst (Scheme I. 13).³⁰ The reaction was believed to proceed *via* five-membered isoxazoline-Cu complex intermediate.



Scheme I.13. An enantioselective synthesis of β -lactams *via* Kinugasa reaction

I.A.2.2.3. Cycloaddition reaction between alkyne and phosphine oxide

In a recent report Tang and his co-workers have synthesized benzophosphole oxide by Cu-catalyzed cycloaddition reaction between secondary phosphine oxide and alkyne. The reaction is supposed to proceed *via* phosphorylation followed by cyclization step.³¹



Scheme I.14. Synthesis of benzophosphole oxide by Cu-catalyzed cycloaddition reaction

Section I.B. Eco–friendly reaction media

I.B.1. Role of reaction media in organic chemistry and requirement of green solvent

Solvents play a crucial role in chemical reactions. Most of the chemical processes during fine chemical synthesis in research laboratory or in chemical industry involve solution phase and therefore organic solvents are usually the first choice for that. Solvents are needed both in reaction as well as in separation or purification steps either by extraction or by recrystallization. They can play a crucial role in the stabilization of the reactive intermediates and also affects on the rate of any particular reaction in terms of selectivity (chemo / regio / stereo). It is therefore challenging to use these solvents owing to their toxicity, volatility and flammability nature. Therefore majority of such solvents are associated with their hazardous nature which cause several ill effects in human health and in the environment. Moreover these solvents are derived from non renewable sources like petroleum, which is in contrast to the very basic principle of “Green Chemistry”.³² It is now widely recognized that for the development of sustainable and clean synthetic methodologies there is a very basic need of scientific and potential replacement of volatile organic compounds (VOCs) as solvents and reaction media.³³ The concept of green solvents,^{34,35} or eco–friendly reaction media has come from this point of view. Green solvent must have a high boiling point, low vapour pressure, be non–toxic, can dissolve a great range of organic compounds, be inexpensive and of course is recyclable. All these things put together tend to narrow the possibilities of finding a compound or a class of compounds that can effectively be called a green solvent. The proposal of eco–friendly reaction media as alternative solvents expresses the goal to minimize the environmental impact.

I.B.2. Various directions towards eco–friendly reaction media

Fischer and his co–workers discussed the following directions for the development of eco–friendly reaction media or green solvents.³⁵ Chemists should replace hazardous solvents with ones that show better EHS (environmental, health and safety) properties.

- 1) Alternative solvents would be such that, it can increase bio–degradability or reduce ozone layer depletion

- 2) Reaction with bio-solvents which are generated from renewable sources, for example ethanol produced by fermentation of sugar compounds or cellulosic materials
- 3) Use of supercritical fluids that are environmentally harmless instead of volatile organic solvents
- 4) Use of ionic liquids (ILs) that show low vapor pressure that less emission to air.

The same research group proposes a comprehensive framework for the environmental assessment of solvents that covers major aspects of the environmental assessments. The proposed framework is demonstrated on 26 organic solvents.³⁵ Results show that simple alcohols (methanol, ethanol) or alkanes (heptanes, hexane) are environmentally preferable solvents on the other hand use of dioxane, acetonitrile, acids, formaldehyde and THF is not recommended for an environmental perspective. Use of co-solvents such as alcohol : water are environmentally more favourable than pure alcohol.

I.B.3. Brief account of various green solvents or eco-friendly reaction media

Use of non-conventional,³⁶ reaction media in organic synthesis is a pre-requisite for making the environment green. Besides water the most prevalent of these solvents systems include (not exclusively) supercritical fluids, ionic liquids and fluoruous solvent. Liquid polymer and some renewable solvents are also considered as alternative solvent. Here we have briefly discussed their green characteristics and limitation while using in a chemical reaction.

I.B.3.1. Water

Beyond doubt water is the largest green solvent and most common molecule on the planet and also cheapest one. To apply water in a reaction we must consider its general properties. It is a very polar solvent and has high dielectric constant and associated with extensive hydrogen bonding. Although water is an excellent solvent for many inorganic compounds besides it is also able to dissolve some organic molecules such as sugar, proteins and low molecular weight acids.

The green characteristics of water are: non flammable, non-toxic and renewable. Use of water is very much safe for health and environment. Its density is 1 g cc^{-1} (sufficiently different from most organic substances) for which it can be easily

removed by biphasic separation. As water is colourless and odourless it is therefore very easy to recognize whether any contaminations are associated with water or not. It is also regarded as the universal solvent in nature.

However use of water in a chemical reaction also has some limitations, such as low solubility of some compounds in water makes difficulty during reaction though the problem can be overcome by applying phase transfer catalysts in water mediated reactions.³⁷ Again moisture sensitivity of some catalyst and reagents make them deactivate while using water in a reaction.

I.B.3.2. Supercritical fluids (SCFs)

Substances enter into their supercritical phases above critical pressure (P_C) and critical temperature (T_C). The critical points of supercritical fluids represent the highest temperature and pressure at which the substance can exist as a vapour and liquid equilibrium. At triple point three phases (solid, liquid and gas) of a compound co-exist. Some substances have readily available critical points (T_C and P_C) whereas some require extreme conditions. The most useful eco-friendly solvents according to green chemists are supercritical water,³⁶ and supercritical carbon dioxide ($scCO_2$)³⁸. T_C and P_C of $scCO_2$ are 304K (31 °C) and 72.8 atm whereas that of water are 647K (374 °C) and 218 atm.

Supercritical water has been recognized as an attractive and green reaction medium due to its unique properties and environmentally favourable nature. Dielectric constant of supercritical water roughly corresponds to that of common organic solvents so organic reactions get facilitated in this medium.

$scCO_2$ is inexpensive and obtained as a side product of fermentation and combustion. The most important properties of $scCO_2$ for which it is considered as green solvent are: it is non-toxic, non flammable, renewable as well as excellent and facile ease of separation after reaction. Thus it is an important alternative solvent in green chemistry for catalyzing many reactions. Carbon dioxide in its liquid or supercritical state has prodigious potential as an environmentally benign reaction medium for sustainable chemical synthesis.³⁸ Isolation of product upto 100% dryness after reaction is achieved by simple evaporation of the solvent at atmospheric or reduced pressure. This is very much important in the final steps of pharmaceutical synthesis where even

trace amount of solvent residues are considered problematic. It also provides many chemical advantages that improve its green recommendation by reducing waste.³² For example it can't be oxidized and therefore oxidation reactions using oxygen or air can be carefully and intensively studied in this media. It is sustainable and also globally available cheaply in >99.9%. The use of CO₂ do not lead to global warming as its usage involve no net addition to the atmosphere, it is taken from atmosphere and returned there. Supercritical carbon dioxide finds application in a number of industrial processes.

Though it is poor solvent for many compounds but it can be improved by adding co-solvents (e.g. MeOH) or surfactants. scCO₂ is widely used in supercritical fluid extraction (SFE) and also in supercritical fluid chromatography (SFC).³⁹

Besides its green properties it has also many disadvantages: reaction with it requires high pressure reactor therefore it is not cost effective, heat transfer is limited which may arise problem for exothermic reactions. It has a tendency to react with good nucleophile in some cases.

I.B.3.3. Ionic liquids (ILs)

During the last decade ionic liquids (ILs) have become a focus of increasing interest for many organic transformations. ILs are salts containing cations and anions which are poorly coordinated and usually exist as fluid below 100 °C, or even at room temperature (room temperature ionic liquids; RTILs). They are non volatile as well as non flammable and hence they have very negligible vapour pressure, therefore emit no volatile organic compounds (VOCs) to the environment. Because of these attractive properties, ILs may be used as environmentally benign and green solvents. The first RTIL, ethyl ammonium nitrate [EtNH₃][NO₃], (MP 12 °C) was discovered in 1914,⁴⁰ but an enormous interest was initiated only after the development of binary ionic liquids from mixtures of aluminium (III) chloride and *N*-alkylpyridinium or 1,3-dialkylimidazolium chloride.⁴¹ ILs are also referred to as 'designer solvent',⁴² as their physio-chemical properties and the phase behaviour of the systems can be regulated and controlled by altering their structures.⁴³ The cation part of ionic liquid can be varied from imidazolium to phosphonium (Figure I.1). The anionic part may be organic or inorganic.

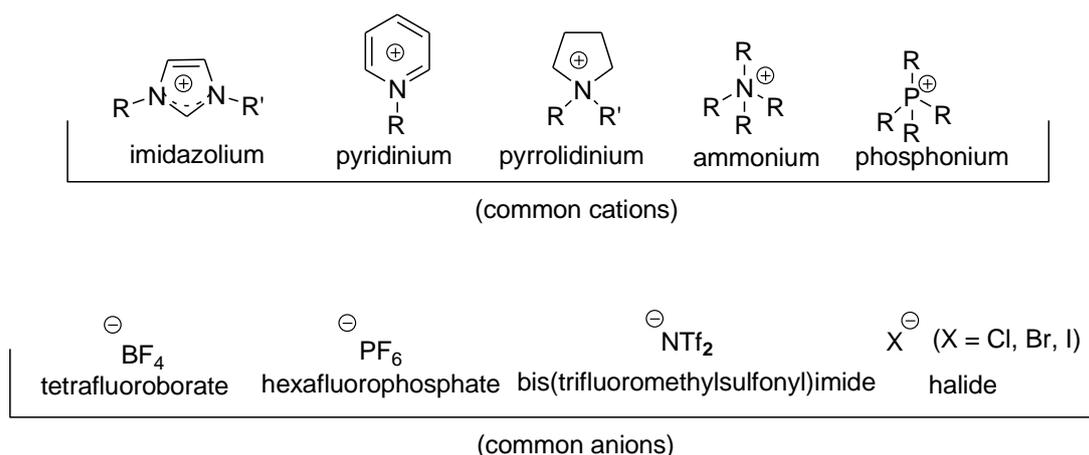
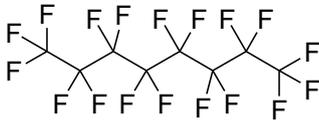
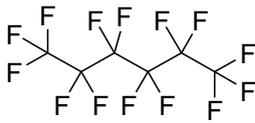
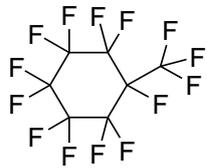
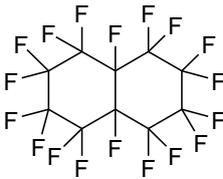
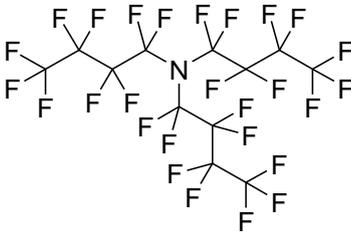
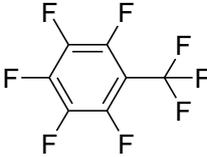


Figure I.1. A few variations in cations and anions of ILs

I.B.3.4. Fluorous solvents

The term ‘fluorous’ was first introduced by Horvath and Rabai in 1994.⁴⁴ After that Gladysz *et al.* in 2002 defined and pointed that fluorous solvents (or perfluorinated solvents) are compounds that are highly fluorinated and based on sp^3 carbon network structures.⁴⁵ Though most of the fluorous solvents are alkane but they may contain functional groups like ether or amine. Various types of perfluorinated solvents are perfluoroalkane, perfluoroalkyl ether, perfluoroalkyl amine etc. Being non-toxic (unlike freons), non flammable, thermally stable and recyclable they are used as chemically benign and environmentally friendly solvents. Perfluorinated solvents have high ability to dissolve O_2 and therefore could be used in medical technology also. Fluorous fluids are chemically inert, have high stability and high density because of the presence of strong C–F bonds. They show low solubility in water and organic solvents at room temperature but could be miscible at high temperature.

Table I.1. Examples of various fluorous solvents with their chemical formulae and structures

Common name	Chemical formula	Structure
Perfluorooctane (FC-77)	C_8F_{18}	
Perfluorohexane (FC-72)	C_6F_{14}	
Perfluoro(methyl cyclohexane) (PFMC)	$C_6F_{11}CF_3$	
Perfluorodecaline	$C_{10}F_{18}$	
Perfluorotributylamine (FC-43)	$C_{12}F_{27}N$	
α,α,α -Perfluorotoluene (Oxsol-2000)	$C_6F_5CF_3$	

Fluorous phase reactions have a slightly different approach in comparison to other alternative solvents such as ionic liquids or supercritical fluids where they are basically used as solvent replacement system. On the other hand because of the non polar character of fluorous solvents they are not suitable for most organic reactions and therefore they tend to be used in conjunction with a traditional organic solvents or

could be used taking an immiscible solvent. The combination of fluorosolvent and organic solvent produces a fluorosolvent biphasic system (FBS).

In FBS technique highly fluorosoluble reagent and catalyst reside in the fluorosolvent phase whereas the starting materials are dissolved in an immiscible solvent phase that may be organic or non organic even water. Upon heating the whole mixture is converted to one phase and produces a homogeneous system, where the reaction occurs. On cooling, the two liquid layers again separated from each other. Now the organic phase contains the product while unreacted fluorosolvent reagent or catalyst or byproducts remain in the fluorosolvent phase. After separating the product from organic phase the catalyst present in the fluorosolvent phase could be recycled. Thus without adding organic solvent FBS could be applied for biphasic product separation (Figure I.2).

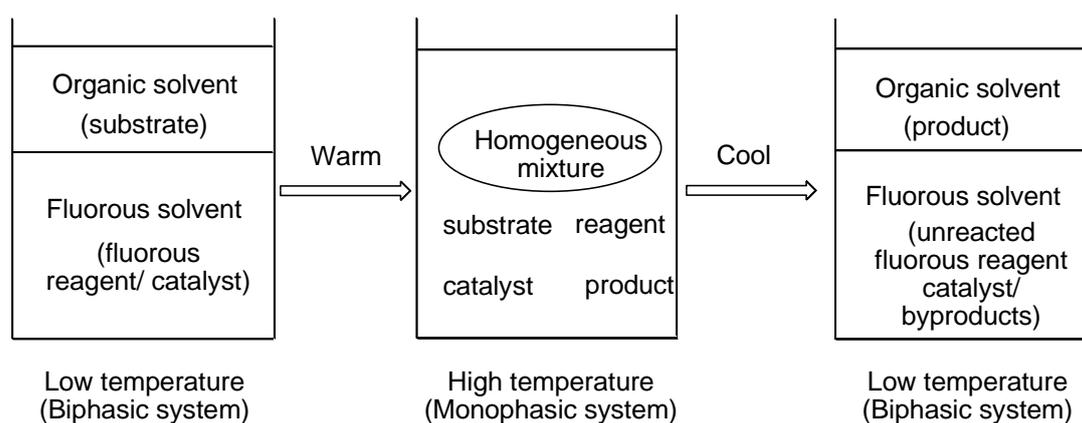


Figure I.2. Schematic representation of fluorosolvent biphasic product separation

However synthesis of fluorosolvents are difficult, generally require large amount of volatile organic solvents or toxic reagents such as HF or F₂. Due to their disadvantages like high cost, low biodegradability and global warming issues, perfluorinated solvents are nowadays replaced by hydrofluoroethers (HFEs). Commercial HFEs, such as HFE-7100, HFE-7500 and F-626 possess higher polarity than perfluorinated solvents due to the presence of an oxygen atom between a fluoroalkyl group and alkyl group (Figure I.3).³⁶

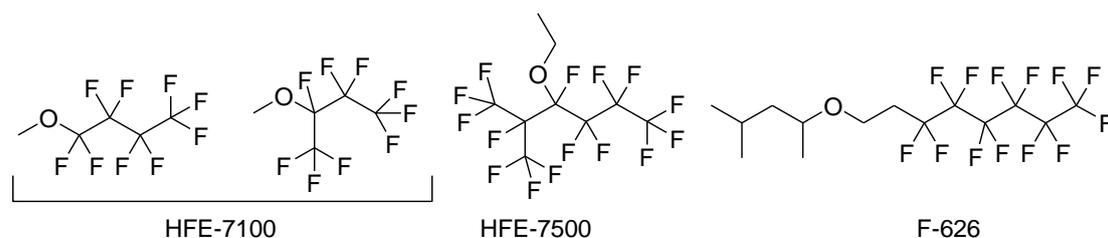


Figure I.3. Structures of hydrofluoroethers (HFEs)

I.B.3.5. Liquid polymer

Another example of eco-friendly reaction medium are low molecular weight polymers having very low glass transition temperature can be used as non volatile solvents. Especially poly (ethylene)glycols (PEGs) and poly(propylene)glycols (PPG)s (Figure I.4). As expected from green solvents PEGs has low flammability and low (to zero) vapour pressure. PEG is known to be inert, bio-degradable, bio-compatible and therefore non-toxic. It can be recovered and recycled from solutions by distillation or by extraction.

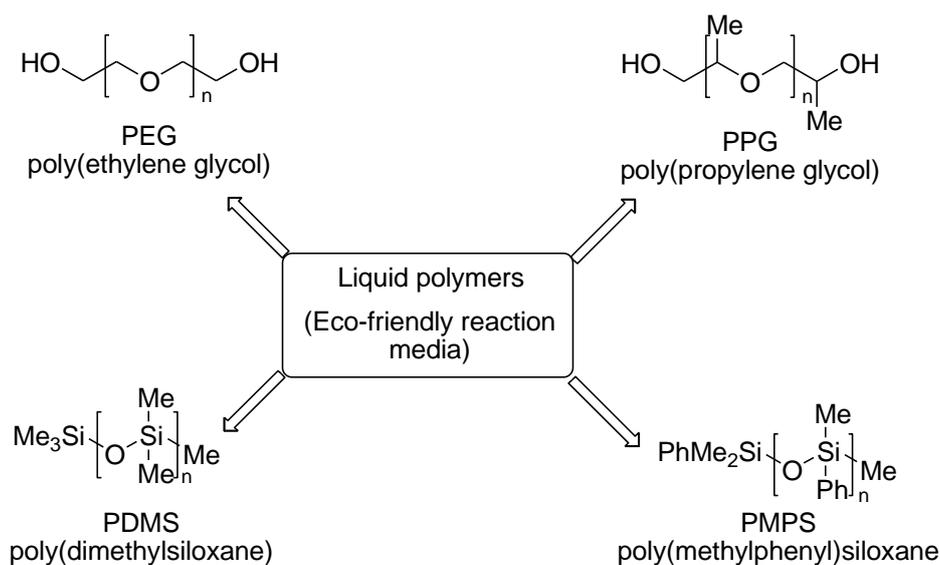


Figure I.4. Structures of different liquid polymers used as eco-friendly reaction media

It can also be used widely in aqueous biphasic system (ABS) and also as phase transfer catalyst (PTC). PEGs (molecular wt. 200–6000) can be used as alternative solvent. Poly(propylene) glycols which are generally more viscous than PEGs are also used as alternative reaction media. The non alcoholic hydrophobic liquid polymers such as poly(dimethylsiloxane) (PDMS) and poly(methylphenyl)siloxane nowadays have started to be used as eco-friendly reaction media (Figure I.4).

I.B.3.6. Renewable solvents

Alcohol

Glycerol which is a byproduct of a biodiesel, is non-toxic and has high boiling point and negligible vapour pressure and it can dissolve many organic and inorganic compounds. Ethanol and methanol are common laboratory solvents worldwide but both are volatile organic solvents with low flash point and large explosion range.

Ester

Ethyl lactate (boiling point 154 °C) can be used replacing toxic halogenated solvent. Though it has limited application as solvent due to presence of both alcoholic and ester group. But in combination with THF it has been used as solvent to prepare magnetic tapes replacing toxic methyl vinyl ketone and toluene. γ -Valerolactone (GVL) is another example bio-renewable ester which act as solvent. It has boiling point 207 °C and is biodegradable in nature and also having very low volatility and vapour pressure. It is used both as green solvent and potential fuel. It is stable towards hydrolysis in water.

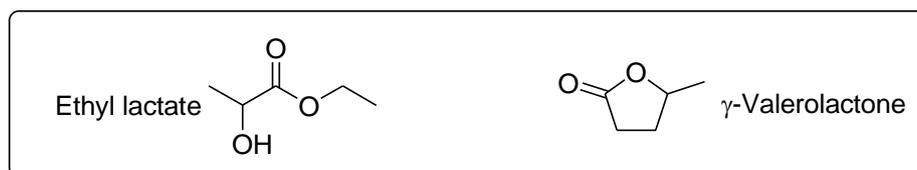


Figure I.5. Structure of ethyl lactate and GVL

Biodiesel

Biodiesel are derived from methanolysis of various plant oils and animal fat including soybean oil, rapeseed oil and even from waste vegetable oil. For example, methyl soyate biodiesel is derived from soybean oil (a triglyceride) and methanol by transesterification reaction. It can be used as an eco-friendly reaction media as it has lower toxicity than toluene and methylene chloride. Lower vapour pressure, high flash point, readily biodegradable and non-ozone depleting properties are the key features for considering it as a green solvent.

The greenest solvent in terms of reducing waste,³² is the use of no solvent that is solvent-free or solventless or 'neat' reaction condition. Although in many cases VOCs are used to extract or purify the product from reaction mixture but under solvent-free approach the amount of solvent or VOCs required for purification

dramatically decreased compared to conventional approaches using external solvent and therefore solventless or solvent-free approach is generally very green or eco-friendly.

Thus from the above discussion it is clear that there remains ample scope to develop metal-catalyzed C-C coupling reaction or metal-free new reaction methodologies using green reaction media like water, ionic liquid or supercritical fluids or under solvent-free approach.

I.C. References

References are given in BIBLIOGRAPHY under Chapter I (pp. 180–182).