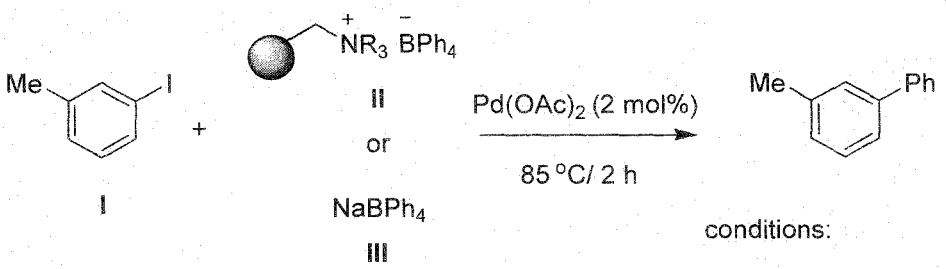
Summary

The research work embodied in this thesis entitled was initiated on December, 2005 in the Department of Chemistry, North Bengal University, Darjeeling – 734 013, under the supervision of Prof. B. Basu, Department of Chemistry, North Bengal University. The studies described in this thesis are primarily directed towards development of immobilized reagents and their manifold applications in various organic transformations. The thesis has been divided into two parts.

Part I: Section A is entitled as ***"Poly-ionic Heterogeneous Phenylating Agent for Base-Free Suzuki–Miyaura Coupling Reaction"***. This section deals with a new poly-ionic resin-bound tetraphenylborate that has been prepared and can serve as efficient phenylating agent in Pd-catalyzed Suzuki–Miyaura (SM) coupling with aryl halides in absence of any base. The conditions are mild, operationally simple and the poly-ionic resins can be recharged and reused for several runs.

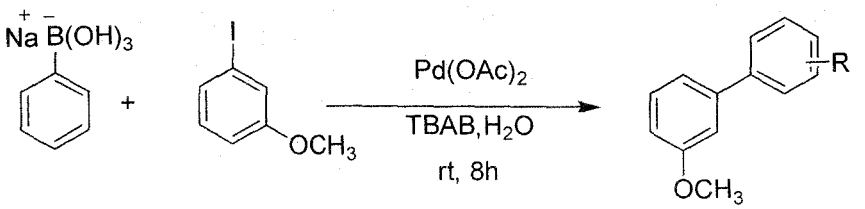


conditions:

(a) **I/II**/Na_2CO_3 = 1:1 g/mmol:1; 90%
(b) **I/III**/Na_2CO_3 = 1:1:1; 43%
(c) **I/III**/Na_2CO_3 = 1:2.5:1; 88%
(d) **I/III** = 1:2.5; 88%
(e) **I/II** = 1:1 g/mmol; 96%

A brief account of this work has been published in *Synlett*, **2008**, 255-259.

Part I: Section B is entitled as ***"Highly effective alternative aryl trihydroxyborate salts for a ligand-free, on-water Suzuki–Miyaura coupling reaction"***. We have presented here an efficient easily accessible and air-stable sodium aryl trihydroxyborates which can be effectively used as an alternative source of organoboron species in ligand free Pd-catalyzed SM cross-coupling reactions in water under an aerobic atmosphere and at room temperature. The protocol has been found to be broadly applicable to a variety of aryl halides (X = Br, I) and also to aryl chlorides bearing electron withdrawing groups.



A brief account of this work has been published in *Green Chem.*, **2010**, *12*, 1734–1738

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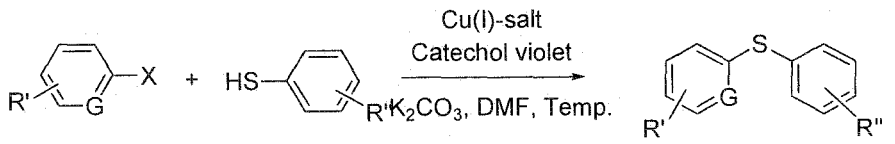
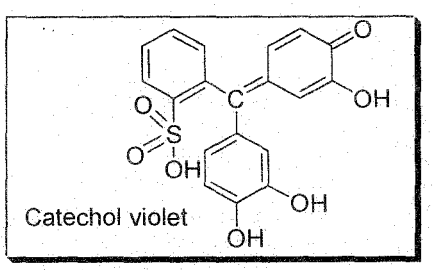
Part II: This part is entitled as ***"Catechol Violet as Novel and Efficient Ligand for Cu(I)-Catalyzed C–S Coupling Reactions"***. We have presented here an efficient copper(I) catalyzed C-S coupling reaction protocol, where a wide variety of aromatic halides such as aryl iodides, bromo-pyridines, activated aryl chlorides and vinyliodide undergo coupling with aromatic or aliphatic thiols to afford the corresponding thioether in good to excellent yields. Presence of catechol violet (CV) (only catalytic amount), which is stable in air, greatly accelerated the reaction. Wide variety of functional group tolerance has also been observed in this reaction methodology.





A brief account of this work has been published in *Tetrahedron Lett.* **2009,** *50*, 5523-5528.

Green Chemistry:

1.1. Introduction:

The term green chemistry is defined as the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances. Green chemistry, also called sustainable chemistry, is a philosophy of chemical research and engineering that encourages the design of products and processes that minimize the use and generation of hazardous substances. Whereas environmental chemistry is the chemistry of the natural environment, and of pollutant chemicals in nature, green chemistry seeks to reduce and prevent pollution at its source. As a chemical philosophy, green chemistry applies to organic chemistry, inorganic chemistry, biochemistry, analytical chemistry, and even physical chemistry. Although the focus of green chemistry is on industrial applications but it also has wide spread application in other field of chemistry. The focus is on minimizing the hazard and maximizing the efficiency of any chemical choice. It is distinct from environmental chemistry which focuses on chemical phenomena in the environment.

Another aspect of the definition of green chemistry is found in the phrase "use and generation". Rather than focusing only on those undesirable substances that might be inadvertently produced in a process, green chemistry also includes all substances that are part of the process. Therefore, green chemistry is a tool not only for minimizing the negative impact of those procedures but also aims at optimizing efficiency, although clearly both impact minimization and process optimization are legitimate and complementary objectives of the subject. Green chemistry, however, also recognizes that there are significant consequences to the use of hazardous substances, ranging from regulatory, handling and transport, and liability issues, to name a few. To limit the definition to deal with waste only would be to address only part of the problem. Green chemistry is applicable to all aspects of the product life cycle as well.

Finally, the definition of green chemistry includes the term "hazardous". It is important to note that green chemistry is a way of dealing with risk reduction and pollution prevention by addressing the intrinsic hazards of the substances rather than those circumstances and conditions of their use that might increase their risk.

1.1.1. Importance of green chemistry to adopt a hazard-based approach:

To understand this, we have to revisit the concept of risk. Risk, in its most fundamental terms, is the product of hazard and exposure: Risk = Hazard X Exposure.

A substance manifesting some quantifiable hazard, together with a quantifiable exposure to that hazard, will allow us to calculate the risk associated with that substance. Virtually all common approaches to risk reduction focus on reducing exposure to hazardous substances. Regulations often require increases in control technologies and treatment technology, and in personal

protective equipment such as respirators, gloves, etc., in order to reduce risk by restricting exposure.

The definition of green chemistry also illustrates another important point about the use of the term "hazard". This term is not restricted to physical hazards such as explosiveness, flammability, and corrodibility, but certainly also includes acute and chronic toxicity, carcinogenicity, and ecological toxicity.

1.1.2. Principles of Green Chemistry:

1. **Prevention**

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

2. **Atom Economy**

   Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. **Less Hazardous Chemical Syntheses**

   Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. **Designing Safer Chemicals**

   Chemical products should be designed to affect their desired function while minimizing their toxicity.

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.

6. **Design for Energy Efficiency**

   Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. **Use of Renewable Feed stocks**

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

8. **Reduce Derivatives**

   Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. **Catalysis**

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

10. **Design for Degradation**

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

11. **Real-time analysis for Pollution Prevention**

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

12. **Inherently Safer Chemistry for Accident Prevention**

Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires. Therefore, green chemistry applications include the use of supercritical water oxidation, on water reactions, solid supported media reactions etc. These are shortly described here.

1.2. Solid Supports in Organic Synthesis:

Homogeneous palladium catalysis has gained enormous relevance in various coupling reactions such as Heck, Stille, Suzuki, Sonogashira, and Buchwald-Hartwig reactions. Many products could be synthesized by this methodology for the first time or in a much more efficient way than before. The massive increase in use and the boardening range of applications for homogeneous catalysis has a number of drawbacks, in particular, the lack of reuse of the catalyst or at least the problem of recycling of the catalyst. This leads to a loss of expensive metal and ligands and to impurities in the products and the need to remove residual metals.[1]These problems have to be overcome in the application of homogeneous Pd-catalyzed coupling reactions in industry and are still a challenge. In order to address these problems, heterogeneous Pd catalysis is a promising option. Organic synthesis has played a vital role in changing the world and will undoubtedly continue to do so into the future. The benefits afforded by synthesis already considerably enrich our lives, from the development of drugs in the ongoing fight against disease to the more aesthetic aspects of society with preparation of perfumes and cosmetics. Furthermore, the quality and quantity of our food supply relies heavily upon synthesized products, as do almost all aspects of our modern society ranging from paints, pigments, and dyestuffs to plastic, polymers, and materials of all kinds. For the prevention of environment from hazardous chemical, chemists deserve to be regarded as trendsetters in recycling of the reagent as well as the catalyst tends to developments of ligand-free Pd catalysts have provided interesting and practically important alternatives to ligand assisted methodologies. On the other hand, homogeneous catalysis has a number of drawbacks, in particular, the lack of reuse of the catalyst or at least the problem of recycling of the catalyst. This leads to loss of expensive metal as well as ligands to impurities in the products and the need to remove residual metals. In order to overcome these problems, heterogeneous Pd

catalysis is a promising option for Suzuki coupling. Pd is fixed to a solid support, [2] such as activated carbon,[3]zeolites and molecular sieves,[4]metal oxides,[5] mainly silica or alumina, KF-Al_2O_3 but also MgO, ZnO, TiO_2, ZrO_2), clays, [6] alkali and alkaline earth salts ($CaCO_3$, $BaSO_4$, $BaCO_3$, $SrCO_3$), porous glass, [7] organic polymers or polymers embedded in porous glass. Basic supports such as basic zeolites, layered double hydroxides, KF-Al_2O_3 or sepiolites can play a similar supporting role as phosphines in homogeneous catalysis,[8] or can act as bases, [9] that is, no external bases are necessary in these cases. Due to their controlled pore size, microporous and mesoporous materials, such as zeolites, can be advantageous over simple metal oxides. Pd (0) clusters can be encapsulated in these pores. The pore size and structure of such supports can have an important impact on the reactivity and selectivity of those catalysts. Thus, cases were reported where a larger pore size of mesoporous silica allowed reaction of larger substrates as compared with microporous supports. The characterization of a heterogeneous Pd catalyst on a molecular level is still a problem, although TEM, X-ray diffractometry, and IR spectroscopy allow important insights into the structure. Often, heterogeneous catalysts are still chosen on an empirical basis without understanding why a given catalyst is superior to another one. There are also cases included where Pd is fixed to an inorganic solid support (e.g., silica or iron oxide) by the help of organic ligands, that is, as a complex. Such ligands can be part of a polymer, for example, in glass/polymer composites.[10] Supported reagents are reactive species which are associated with a support material. They transform a substrate (or substrates) to a new chemical product (or products) and the excess or spent reagent may be removed by filtration. Reuse of heterogeneous catalyst is often possible but is sometimes limited due to leaching of the Pd without redeposition (leaching up to 14% Pd from Pd/C was observed in Heck reactions, [11] changing of crystallite structure of the Pd on the support surface, [12] chemical change of Pd ligands (e.g., oxidation of phosphanes leading to high leaching of Pd) grafted to the solid support, or congesting the catalyst surface, for example, by salts formed as by-products in the coupling reaction.[13] There were cases reported where the catalytic activity dropped considerably in the second run, while marginal losses of catalytic activity were observed in the following runs. Reuse of catalytic Pd can also be achieved, when colloidal Pd is formed by leaching from the support and these colloidal particles are separated and submitted to another run. Interestingly, there are a few cases reported where the recycled catalyst exhibited higher activity than the original one.

The concept of solid-phase synthesis was first realized by Merrifield, [14] in 1963 with the preparation of large number of peptide compound via attachment of the intermediates to polymer backbone. Organic chemists Leznoff and Frechet established the validity of small-molecule solid-phase synthesis in the 1970s, [15] the focus today is on applying solid-phase

synthesis in combinatorial discovery efforts. In this regard, the majority of small molecules synthesized on solid phase have been heterocyclic in nature. The solid-phase organic synthesis of small organic molecules depends greatly on the adaptation of solution reactions to solid phase. Now these methods are revolutionizing pharmaceutical, agrochemical sectors. SPOS offers some advantages as compared to solution chemistry. Purification is facilitated by simple filtration, avoiding time-consuming separation techniques; consequently, building blocks and reagents can be added in excess to drive reactions to completion. Amenability to automate and the less favourable interference between functionalities linked to the solid support are other benefits of this chemistry. Again solid phase techniques allow the use of high-boiling solvents because their evaporation is not an issue. A wide variety of supports were investigated.[16]The importance of the correct choice of reaction solvent, the ideas of site isolation, and examples of micro environmental effects were identified, studied, and substantially understood.[17]

1.3. Synthesis of functionalized polystyrene Resin:

Several strategies have been examined for the synthesis of polystyrene resin (Figure 1): (1) using heterogeneous cross-linked polystyrene in different formats or preparing the polymer in such a way that the functional groups are concentrated toward the surface of the resin, (2) using a cross-linker other than divinylbenzene to heterogenize polystyrene in order to modulate the physical and chemical properties of the resin, (3) adding functional groups to the polystyrene backbone that provide desired properties, and (4) grafting polystyrene onto a heterogeneous support and the use of the graft as the point of substrate/reagent/catalyst attachment in order to reduce the importance of resin swelling.

Scheme 1

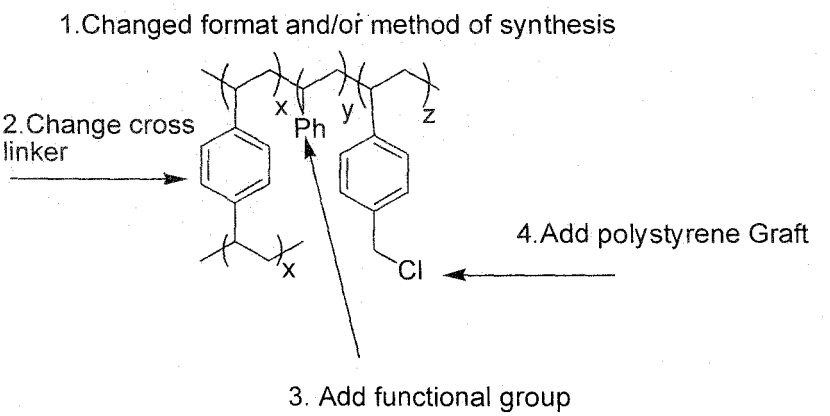
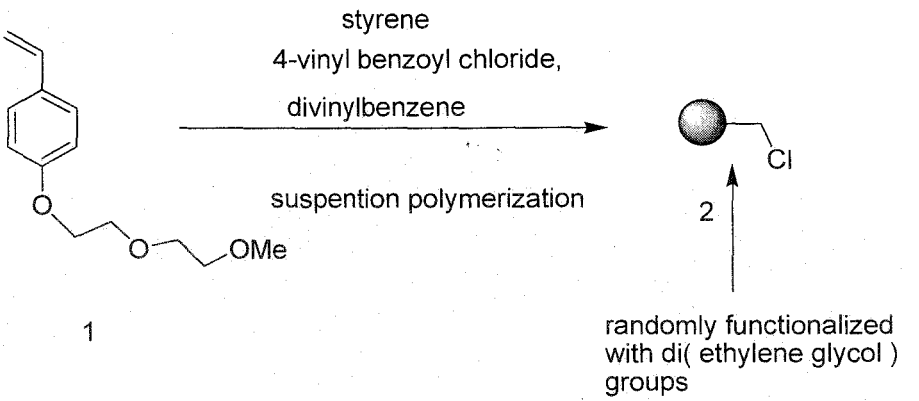


Figure 1

Use of PEG derivatives to cross-link polystyrene led to resins that performed well in solid-phase peptide synthesis, presumably due in part to their good swelling in the required solvents. This inspired Bradley to develop a complimentary strategy and add short oligo (ethylene

glycol) groups to the backbone of divinylbenzene cross-linked polystyrene to make the resin beads more compatible with polar solvents.[18] \

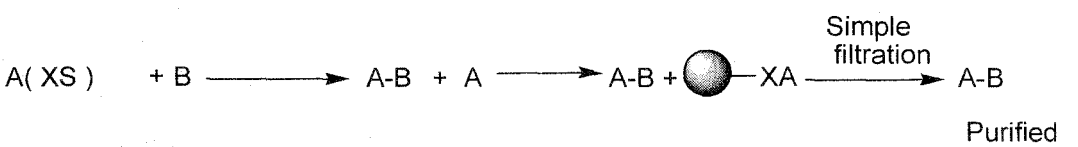
Scheme 2



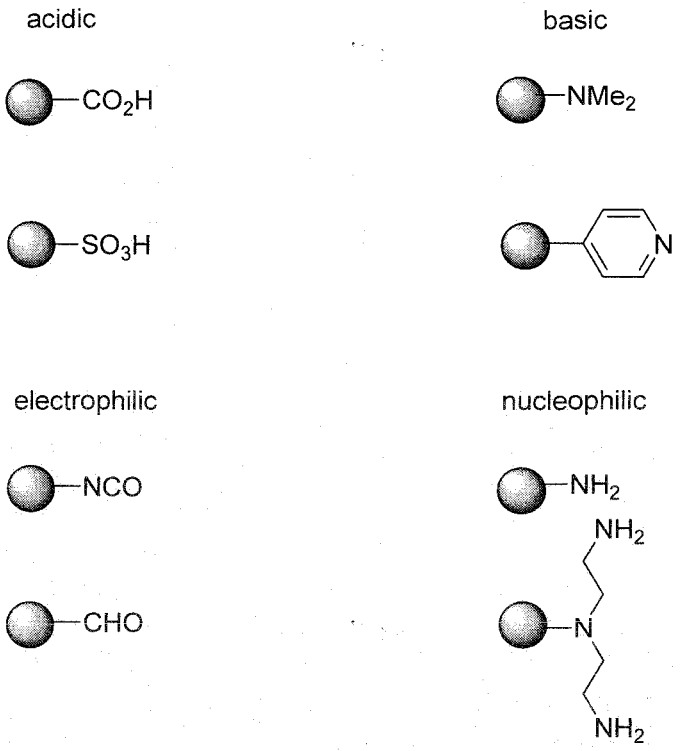
I.3.1. Reagents/Catalyst Supported onto Polymers and Applications:

Designing and synthesis (or exploring the availability) of the polymeric frameworks with suitable linkers remains the primary task of SPOS, and various techniques have been adopted for attachment of the reagents and/or catalysts. A brief status of the literature reports is therefore pertinent to delineate here. Use of solid-supported reagents, [19] a novel extension has recently been reported by several groups and its subsequent application towards more efficient solution phase combinatorial chemistry. This technique involves traditional solution phase chemical synthesis in which the reaction mixture is purified by using a solid support. These solid supported reagents can be used to remove an excess of reactants and thus give the required product in high yield and in a single operation (Scheme 3). This technique offers many of the advantages of solid supported organic synthesis in the ease of reaction workup, and product purification with the additional advantages associated with traditional solution phase synthesis. Previously this strategy has been referred to as a solid-supported scavenger (SSS), polymer-supported quench (PSQ), or complementary molecular reactivity and molecular recognition (CMR/R), [20] wherein such reagents will be referred to as polymeric scavenger reagents (PSRs). There are only two different classes of scavenger available; those that are ionic (acidic and basic reagents) in origin and those that are covalent (electrophilic and nucleophilic reagents) (Scheme 3).

Scheme 3



Schematic representation of a reaction involving a polymer scavenger



Representative examples of the four different classes of polymeric scavengers

Catalyst and reagent are immobilized onto polymer surface involving (a) covalent binding (b) entrapment where a pre-formed catalyst is enveloped within a polymer network and (c) ion-pairing, where cations or anions are bound complementary resin sites (d) adsorption method. By far, the methods (a) and (c) are most commonly used for their broad applicability, the fact that stable, active catalysts and reagents are formed and insignificant leaching. Binding is usually effected in two ways: (i) grafting the catalyst or reagent onto the pre–derivatized supports or (ii) copolymerization of the active species with styrene and divinylbenzene (DVB).Immobilization can also be affected by micro–encapsulation, where the polymers are physically enveloped by thin films of reagents or catalysts, and perhaps stabilized by the interaction between π electrons of benzene rings of the polystyrene used as a polymer backbone and vacant orbital of reagents or catalysts. The size of microcapsule achievable has been reduced from a few micrometers to nanometers only to gain the sufficient activity.[21] Since the literature is quite vast, a concise account of various kinds of attachment of few relevant reagents and catalysts followed by specific applications in different organic transformations has been presented here.

1.4. Covalent Binding of Reagents: linkers

In the solid phase synthesis requires a covalent linker group sometimes referred to as a "handle", to attach the small molecule onto the polymeric resin. Currently a wide variety of

linkers exist, many of which are based upon chemistry originally developed for oligomeric solid phase synthesis.

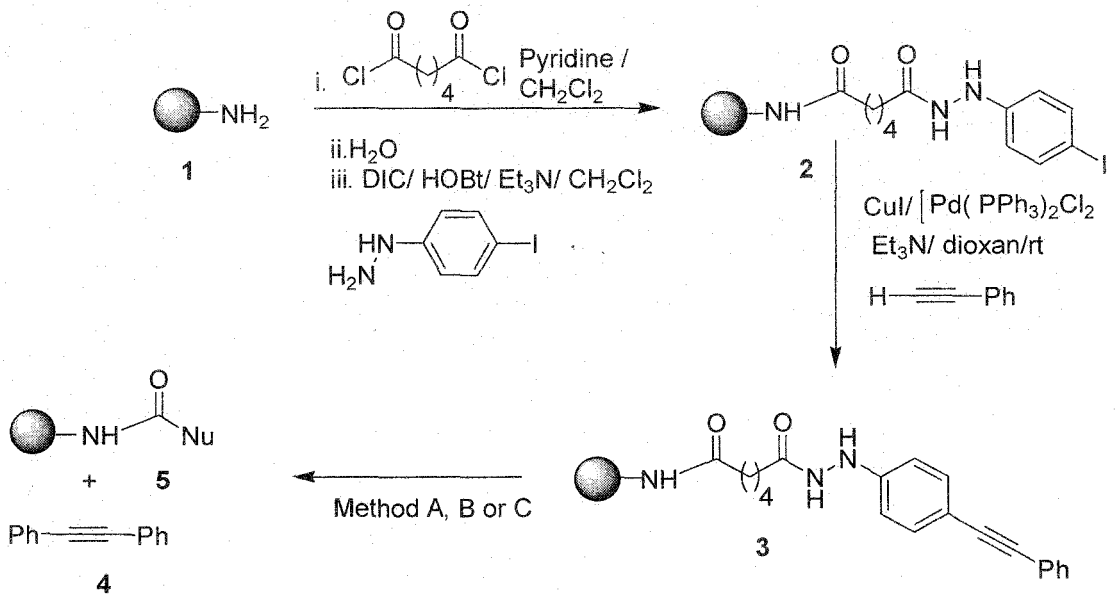
1.4.1. Traceless linkers:

Functional groups have a dramatic outcome on the potential medicinal efficiency on the final drug-like target molecules. Keeping this idea in mind chemists designed ''traceless linkers".

1.4.1. A: Nitrogen linkers

An aryl hydrazine oxidation labile traceless linker has been reported.[22] Different amino functionalized polymers **1** (polystyrene-NH_2, Tentagel-NH_2, Argopore-NH_2) were loaded with 4-iodophenylhydrazine to give **2**. This was subjected to Heck, Suzuki, Sonagashira, or Stille couplings, the example shown being the Sonagashira coupling with phenylacetylene, to give **3**. Three different cleavage methods were used (Method A, Cu $(OAc)_2$/MeOH/pyridine/RT/2 h; Method B, $Cu(OAc)_2$/*n*-propylamine/RT/2 h, Method C, NBS/ pyridine/CH_2Cl_2/RT/45 min then MeOH) to give stilbene.

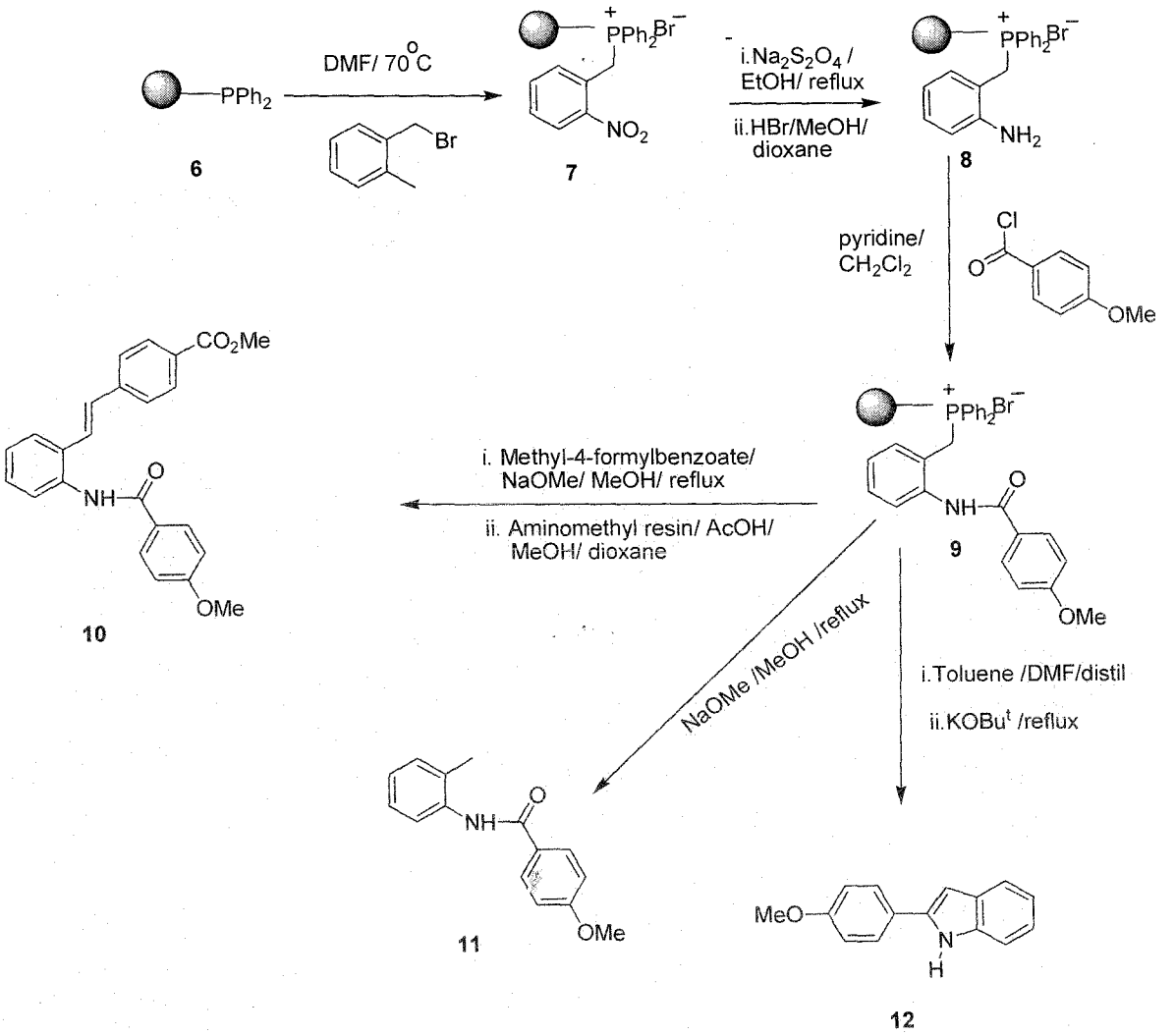
Scheme 4



1.4.1. B: Phosphorus Linker

Phosphorus as a traceless linker was employed by Hughes.[23] Commercially available polystyrene-bound phosphine **6** was loaded with 2-nitrobenzylbromide to give the resin-bound phosphonium salt **7** , which was converted to the aniline **8** then acylated giving the phosphonium resin **9**. Cleavage could then be facilitated by intermolecular Wittig reaction giving a 3:1 *E/Z* mixture of **10**. The aminomethyl resin was used as a solid-phase scavenger reagent for the excess aldehyde used. Hydrolysis of the carbon-phosphonium bond generated the 2-methylanilide **11**. Intramolecular Wittig reaction occurred upon distillation prior to adding base, giving indole **12**.

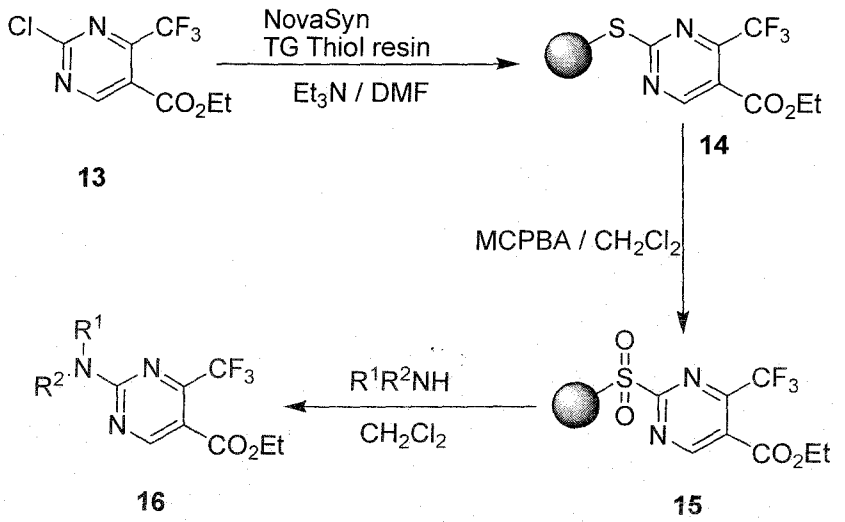
Scheme 5



1.4.1. C: Sulfur Linker:

The first example of a sulfur-based traceless linke was introduced by Suto.[24] Oxidative activation of a sulfide to a sulfone allowed nucleophilic displacement of the sulfone, incorporating further diversity into the final compound. Suto used this technique to synthesize functionalized pyrimidines **16** (Scheme 6). The 2-chloropyrimidine **13** was loaded onto Tentagel thiol resin, a PEG resin. The sulfide resin **14** is oxidized using MCBPA to the sulfone **15**, which was cleaved from the resin using primary and secondary amines to give pyrimidines **16** in 50-93% yield. The purity of the cleaved compounds were generally excellent (mainly >90%). The ester was also manipulated to synthesize amides and ethers. Using highly reactive sulphonamide linkers solid phase synthesis of carboxylic acids or amines has also been synthesized.

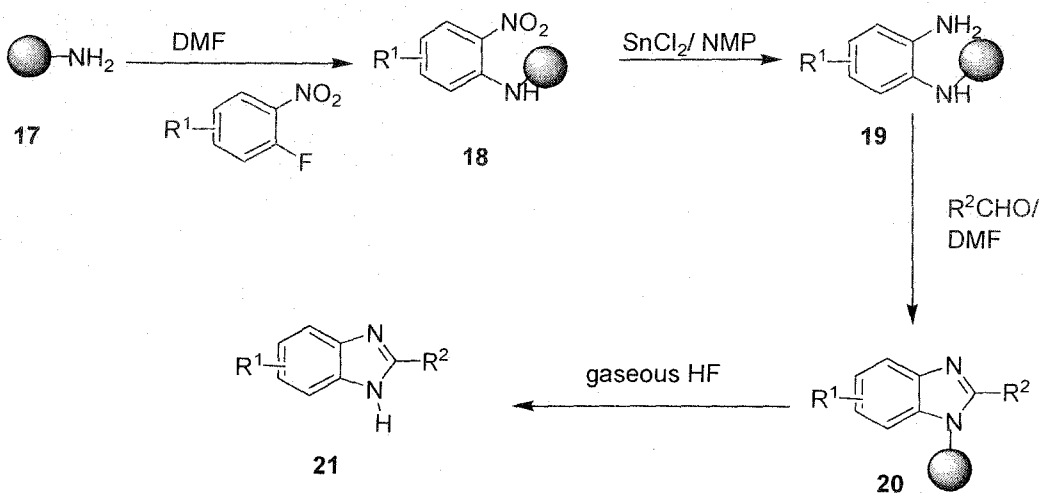
Scheme 6



1.4.1. D: Protecting-Group-Based Traceless Linkers:

The linkers were based on the chemistry of a particular element and its use in solid-phase traceless synthesis. This section will concentrate on linkers based around protecting groups, auxiliaries, or chemically specific traceless linkers. MBHA polystyrene has been used in the synthesis of benzimidazoles.[25] MBHA polystyrene **17** was loaded with 2-fluoronitrobenzene derivatives to give **18**. Reduction of the nitro group gave resin-bound aniline **19**, which was condensed with aldehydes to produce the resin bound benzimidazoles **20**. Cleavage was achieved using gaseous HF to give benzimidazoles **21**.

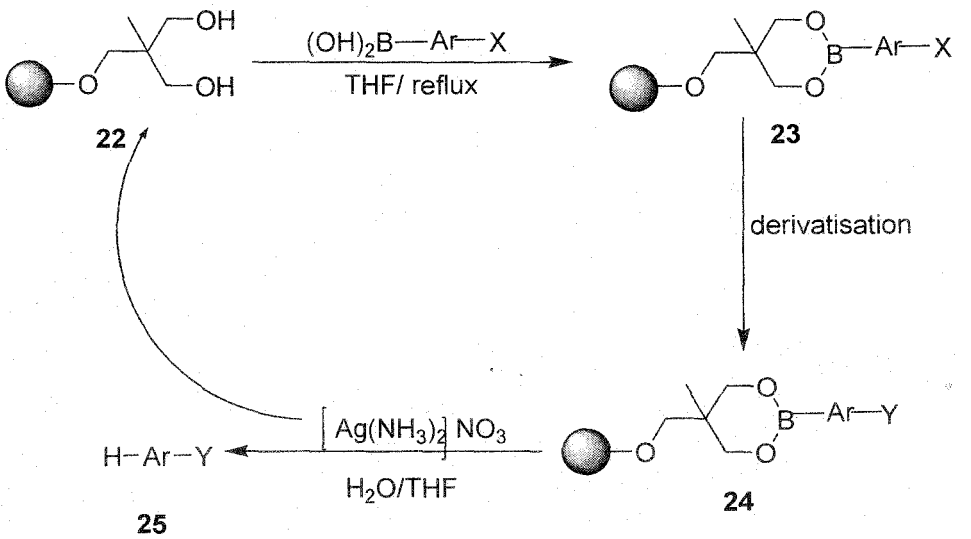
Scheme 7



1.4.1. E: Boron linker:

A novel boronate linker,[26](Scheme 8) was developed from **22**, which allows boronic acids to be attached to give **23**. A function X was then derivatized in a number of ways including ester and amide formation, reductive amination, and an Ugi four-component condensation, giving derivatized boronate **24**. A mild protodeboronation cleavage protocol was developed using silver diamine nitrate in water and THF to release the functionalized aromatic compound **25**, regenerating the initial linker **22**.

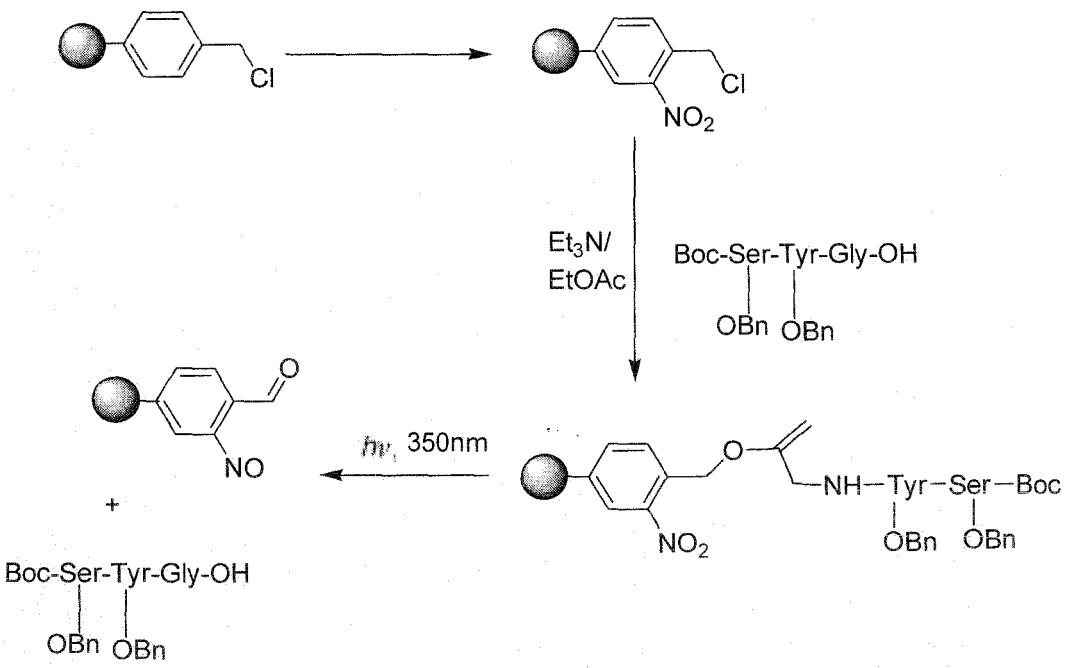
Scheme 8



1.4.1. F: Photolabile Linkers:

Photolabile linkers are very useful in the generation of combinatorial libraries as they offer compound cleavage under mild conditions directly into a solvent suitable for biological testing. The first account of a photolabile linker to bind a substrate to a solid support was published in 1973 by Rich *et al.*[27] and was based on the *o*-nitrobenzyl alcohol derivatives introduced by Patchornik.[28] Its preparation was extremely easy, and took advantage of the already present chloromethyl group on the resin aromatic framework: simple nitration of chloromethylated polystyrene beads was followed by heating the resulting benzylic chloride with an amino acid (or a peptide fragment) and a base (Scheme 9). Photolysis (350 nm) gave a tripeptide with an overall yield of 62%.

Scheme 9



1.5. Solid Supported Catalysts:

Solid-supported catalysts are complex assemblies. Their preparation is a challenging task. Minor changes of their preparation conditions can significantly influence the delicate balance of conflicting demands: high activity, high selectivity, and long lifetime. Palladium can be deposited on a solid support in different ways.[29] The preferred mode of deposition depends also on the type of support. The surface of the support can be covalently functionalized by ligands, such as phosphines, pyridines, or mercaptans, which form complexes with dissolved metal salts. This methodology is widely used in polymer,[30] and silica-supported,[31] palladium catalysts. Grafting of Pd complexes to the solid support by starting with a Pd complex bearing linker groups in the ligands is another method to prepare solid-supported Pd catalysts.[32] The support usually has an impact on the activity of the catalytic system. Particle size, surface area, pore structure, and acid-base properties are important parameters of the support. Sol-gel processes can also be used for the preparation of solid-supported Pd catalysts, mainly for silica- and alumina supported Pd catalysts. The support is generated from a monomer, such as tetraethoxysilane or aluminum isopropoxide in the presence of a soluble Pd compound, such as $PdCl_2$, Pd $(NH_3)_4Cl_2$, or Pd (acac) $_2$ (coprecipitation) and eventually a linker. In this way, usually amorphous materials are obtained, where a part of the Pd is encapsulated. Basic supports such as basic zeolites, layered double hydroxides, or sepiolites can play a similar supporting role as phosphines in homogeneous catalysis or can act as bases, that is, no external bases are necessary in these cases. Due to their controlled pore size, microporous and

mesoporous materials, such as zeolites, can be advantageous over simple metal oxides. Pd (0) clusters can be encapsulated in these pores. The pore size and structure of such supports can have an important impact on the reactivity and selectivity of those catalysts.[33] Thus, cases were reported where a larger pore size of mesoporous silica allowed reaction of larger substrates as compared with microporous supports.The characterization of a heterogeneous metal catalyst on a molecular level is still a problem, although TEM, X-ray diffractometry, and IR spectroscopy allow important insights into the structure. Often, heterogeneous catalysts are still chosen on an empirical basis without understanding why a given catalyst is superior to another one.

Poly-ionic resins have been addressed in the section ion exchange resin.

1.5.1. Covalent binding of catalyst:

Silica, a neutral oxide, is totally hydroxylated and the hydroxyl layer covered with physically absorbed water.[34] Removal of water,[35] at higher temperature results an amorphous porous,[36] silica gel having the surface area up to 1000 m^2/g. Two methods are usually followed for the preparation of silica–supported catalyst. One is impregnation and other is grafting. Pd/SiO_2, Ru/SiO_2, Pt/SiO_2 etc. catalysts were prepared by impregnation. In these cases a calculated amount of $Pd(thd)_2$, $Ru(thd)_2$ or $(CH_3)_3(CH_3C_5H_4)Pt$ [thd is 2,2,6,6–tetramethyl–3,5–heptanedionato] was introduced to silica in the presence of toluene, distilled water or ammonia solution (25%) as a solvent. In case of grafting,[37] the catalyst is prepared by building up a suitable ligand on the surface of a commercial mesoporous silica gel followed by the complexation of the metal [palladium (II)] and thorough conditioning of the catalyst including prolonged treatment with hot solvents helps to ensure catalyst stability in subsequent reactions. This supported palladium catalyst has been successfully used for Heck, Suzuki reaction and the catalyst can be reused in these reactions without noticeable loss of activity. The systematic use of immobilization of organ functional groups has increased in the past three decades, mainly on silica, because this support offers pronounced advantages over other organic/inorganic supports as listed below:

(a) Immobilization on silica results in great variety of silylating agents, allowing pendant functional groups in the inorganic framework.[38]

(b) Attachment is easier on silica surface than on organic polymeric supports, which have a high number of cross-linking bonds, requiring hours to reach equilibrium for surface activation.[39]

(c) Silica gel being the most popular substrate for surface studies because it is the first commercially available high specific surface area substrate with constant composition, enabling easy analysis and interpretation of results

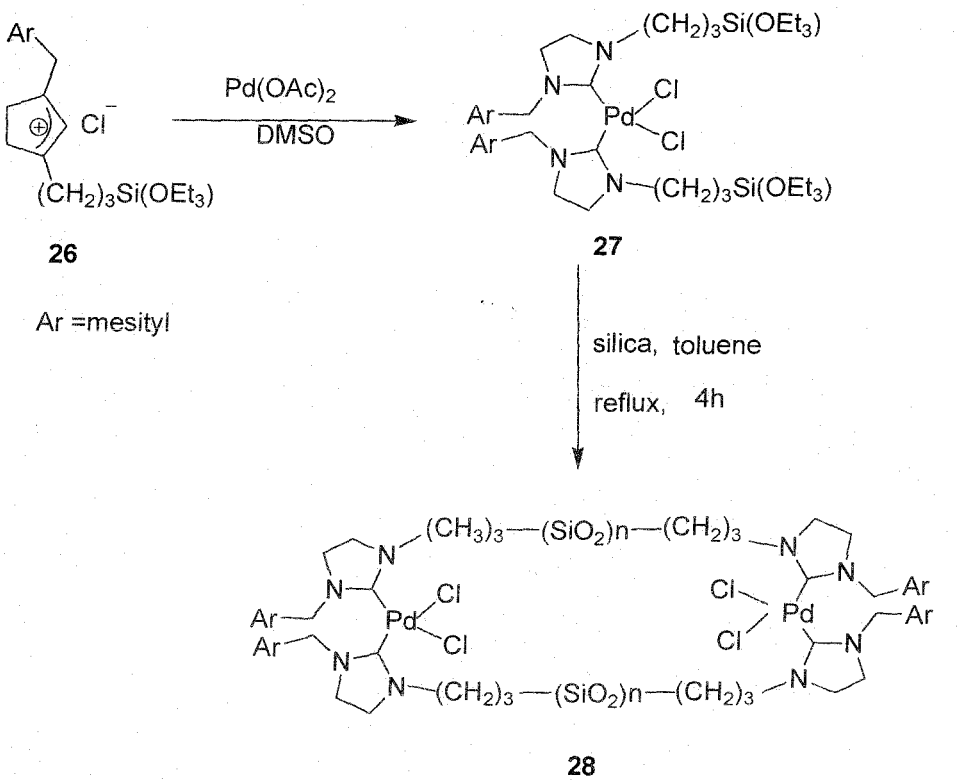
(d) Silica gel has high mass exchange characteristics and no swelling.[40]

(e) Silica support has great resistance to organic solvents

(f) Silica has very high thermal resistance.[41]

Example an electron-rich imidazolidine carbene Pd (II) complexes **27** could be grafted onto mesoporous silica via a propyltriethoxysilane linker (Scheme 10).[42] The resulting catalyst **28** exhibited excellent activity in Suzuki and Heck coupling.

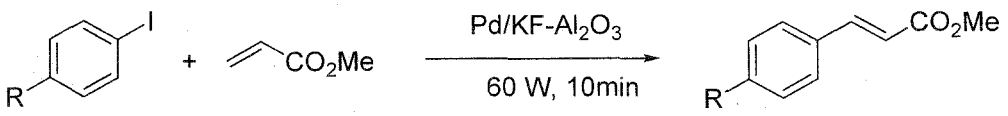
Scheme 10



1.5.2. Palladium on metal oxide other than silica:

The first report about a heterogeneous Heck reaction using Pd supported on metal oxide was published by Kaneda *et al.* in 1990.[43] Chlorobenzene was coupled with styrene in methanol at 150°C using Pd/MgO as catalyst and Na_2CO_3 as base. Later on several metal oxides (MgO, Al_2O_3, TiO_2, ZrO_2, ZnO, mixed MgLaO, etc.) have been used as supports for Pd catalysts in Heck reactions. Ar-X with X) I, Br, Cl, OTf, COCl, SO_2Cl, or N_2BF_4 were coupled with acrylates,[44] acrylonitrile,styrene,[45] vinyl alkyl ther,[46] terminal alkenes.[47] Biffis and co-workers reviewed palladium metal catalysts in Heck reactions in 2001.[48] Microwave irradiation can be applied to Heck reaction catalyzed by Pd on several metal oxides as shown in the coupling of iodobenzene with 1-decene.[49] Slightly higher yields were achieved in the microwave-mediated solvent less Heck reaction of aryl iodides with methyl acrylate in the presence of palladium on KF/alumina (Scheme11).

Scheme 11



R=H, 62% ; R= OMe, 68%

1.6. Ion Exchange resins:

Ion exchange materials are insoluble substances containing loosely held ions which are able to be exchanged with other ions in solutions which come in contact with them and normally obtained as beads of 1-2 mm diameter. These exchanges take place without any physical alteration to the ion exchange material. Ion exchangers are insoluble acids or bases which have salts which are also insoluble, and this enables them to exchange either positively charged ions (cation exchangers) or negatively charged ones (anion exchangers). Many natural substances such as proteins, cellulose, living cells and soil particles exhibit ion exchange properties which play an important role in the way they function in nature. Synthetic ion exchange materials based on coal and phenolic resins were first introduced for industrial use during the 1930s. A few years' later resins consisting of polystyrene with sulphonate groups to form cation exchangers or amine groups to form anion exchangers were developed. The most typical ion exchange resins are based on cross linked polystyrene and the required active groups can be introduced after polymerization, or substituted monomers can be used. For example, the cross linking is often achieved by adding 0.5-25% of divinylbenzene to polystyrene at the polymerization process. Non-cross linked polymers are used only rarely because they are less stable. Cross linking decreases ion- exchange capacity of the resin and prolongs the time needed to accomplish the ion exchange processes. Particle size also influences the resin parameters; smaller particles have larger outer surface, but cause larger head loss in the column processes.

Their insolubility renders them environmentally compatible since the cycle of loading/regeneration/reloading allows them to be used for many years. Ion-exchange resins have been used in water softening, removal of toxic metals from water in the environment, wastewater treatment, hydrometallurgy, sensors, chromatography, and biomolecular separations. They have also been used as catalysts, both in place of homogeneous catalysts such as sulfuric acid and to immobilize metallic catalysts.

1.6.1. Types Ion Exchange resins:

There are four types of ion exchange resins and these ares-

- Strong cation exchange resins, containing sulphonic acid group or the corresponding salts.
- Weak cation exchange resins, containing carboxylic acid groups or the corresponding salts.

- Strong anion exchange resins, containing quaternary ammonium groups.
- Weak anion exchange resins, containing primary, secondary, and/or ternary amino groups, e.g. polyethelene amine.

The affinity for a series of anions with this resin was determined to be: citrate > sulfate > oxalate > iodide > nitrate > chromate > bromide > thiocyanate > chloride > formate > hydroxyl > fluoride > acetate.[50]

1.6.2. Properties:

A. Cross linkage:

The amount of cross linking depends on the proportions of different monomers used in the polymerization step. Resins with very low cross linking tend to be watery and change dimensions markedly depending on which ions are bound. Copolymers of styrene containing low amounts of divinylbenzene (1-4%) are characterized as follows:

- Large moisture content
- Lower capacity on a wet volumes basis
- High equilibrium rates
- Reduce physical stability
- Decreased selectivity for various ions, but ability to accommodate larger ions is increased.
- Thermally stable.
- Selectivity for various ions is decreased, but ability to accommodate larger ions is increased. Copolymers of styrene containing high amounts of divinylbenzene (12-16%) exhibit characteristics in the opposite direction.

B. particle size:

The physical size of the resin particles is controlled during the polymerization step. A higher mesh number means more and finer wires per unit area and thus a smaller opening. Screens are used to sieve resins to get a fairly uniform range of sizes. The particle size affects the equilibrium and flow rate of the ion-exchange process as follows:

- Decrease in particle size shortens the time required for equilibration
- Decrease in flow rates with decreasing particle sizes.

C. Uses of Ion Exchange resins:

Ion exchange resins are widely used in different separation, purification and decontamination process examples are: Water softening, Water purification (Removal of Herbicides from Water; Sorption of Phenol, Removal of Herbicides from water, [51] Uranium recoveries from seawater, Inversion of sucrose. Sugar Cane Juice Processing and many other relatively uses.

- Recover of radioactive metal
- Sorption of Gases

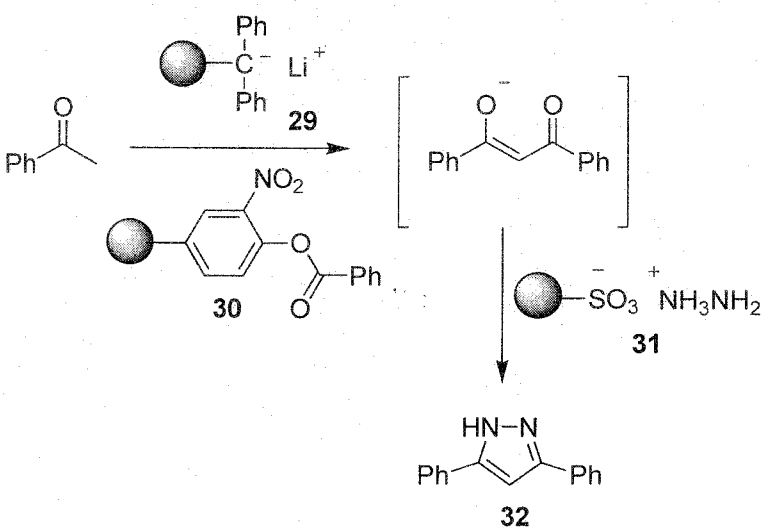
- Olefin/Paraffin Separations in industries
- Manufacture of various pharmaceuticals and also for isolating and purifying pharmaceutical product.
- In chemistry as metal scavengers and catalysts in organic reaction.

1.7. Catalytic activity of ion exchange resin in organic reactions: A few Applications are presented here.

A. **Cation Exchange Resin:**

Scheme 12 describes the "wolf and lamb" technique utilized by the Cohen group.[52] It involves the use of a polymer-bound trityllithium base **29** to remove an acidic proton from acetophenone. The anion generated then undergoes a *C*-acylation reaction with a benzoyltransfer polymer **30** and is passed without isolation into Amberlyst® A-15 resin (hydrazine form), affording 3,5- diphenylpyrazole when filtered from the spent polymer reagent.

Scheme 12

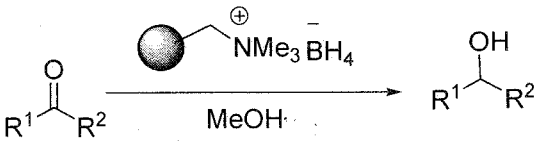


B. Anion Exchange Resin:

A. **Reduction using polymer supported reagents:**

The selective reduction of functional groups is a common need in organic synthesis. Borohydride exchange resin, [53](BER) was introduced in the 1970s and has since proven to be of considerable value in the reduction of organic compounds. This reagent reduces both ketones and aldehydes readily to corresponding alcohol (Scheme 13).

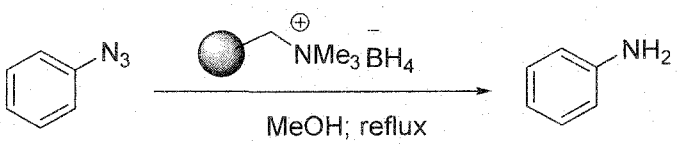
Scheme 13



R' = H or any alkyl group

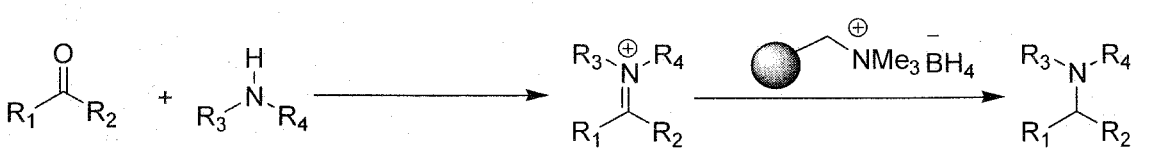
Complete reduction of benzaldehydes to the corresponding hydrocarbons can be accomplished using BER-Ni(OAc)$_2$. Less reactive aromatic aldehydes, such as those with two electron-donating groups, are reduced only to the benzyl alcohols. $CuSO_4$ has also been used as an additive to increase the reactivity of BER.[54]Alkyl and aryl halides (not chloro) can be reduced to hydrocarbons under certain conditions. Azides and nitro compounds are cleanly reduced to give amines in high yields the reduction of azides to amines is a synthetically useful process. BER in MeOH reduces aryl azides and sulfonyl azides to the corresponding aryl amines and sulfonamides, respectively.[55]

Scheme 14



Alkyl azides are either not reduced at all, or the reactions proceed in poor yield. The reactivity of $NaBH_4$ can be enhanced by combining it with certain transition metal salts. The same is true of BER, and a system employing BER-Ni(OAc)$_2$ reduces both alkyl and aryl azides in high yields.[56] Primary, secondary, and tertiary azides are all reduced under these conditions. BER can also reduce imines, and has proven to be useful as a reducing agent in the reductive amination of aldehydes and ketones[57] (scheme15). Aldehydes are reductively aminated cleanly with both primary and secondary amines. Ketones react well with less hindered aliphatic amines, and give lower yields with aromatic amines.

Scheme 15

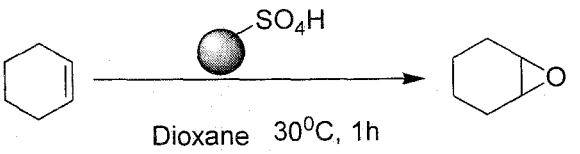


B. Oxidation using polymer-supported reagent:

Medicinal chemists often need to perform mild and selective oxidation reactions. A variety of polymer-supported oxidizing agents have been developed which offer some advantages over more traditional oxidants. Per acid type resins (PARs) prepared from polymer-bound carboxylic acids perform for epoxidation reactions (scheme 16), oxidation of sulfides or

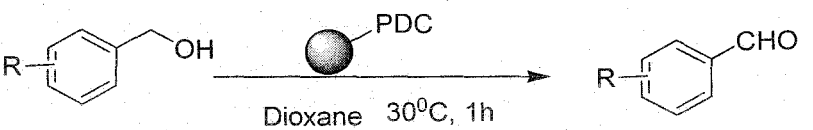
sulfoxides to sulfones, and conversion of ketones to esters.[58] The PARs are quite stable, and can be easily regenerated after each use.

Scheme 16



Frechet and colleagues developed poly (vinylpyridinium dichromate) (PVPDC) as an inexpensive, convenient to use, recyclable oxidant.[59] Oxidations of alcohols to carbonyl compounds performed with this reagent (scheme 17).

Scheme 17

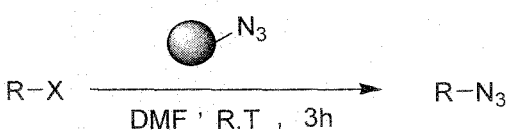


Polymer-supported periodate, can be used for the oxidation quinols to quinones, 1, 2-diols are cleaved to the corresponding carbonyl compounds, sulfides are oxidized to sulfoxides.

C. **Substitution reactions using polymer supported nucleophiles or reagents**:

Alkyl azides are useful intermediates in organic synthesis, and can be prepared using a polymeric quaternary ammonium azide. This reagent allows for the conversion of activated and nonactivated alkyl halides into azides at room temperature[60] (scheme 18). The reaction proceeds most rapidly in polar solvents such as DMF and acetonitrile, but reasonable reaction rates are also obtained in a variety of other solvents. This reagent has also been used to open epoxides of polycyclic aromatic hydrocarbons to give azidohydrins.[61]

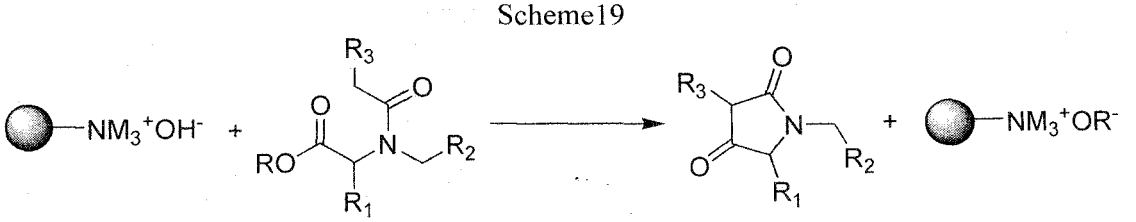
Scheme 18



D. Cyclization process using polyionic resin:

Ganesan, *et al.* are used poly ionic resin hydroxide form of Amberlyst A-26 as a catalyst for the Dieckman cyclization to give 2, 4-pyrrolidinediones (Scheme19).[62]

Scheme19



1.8. Micro-encapsulation:

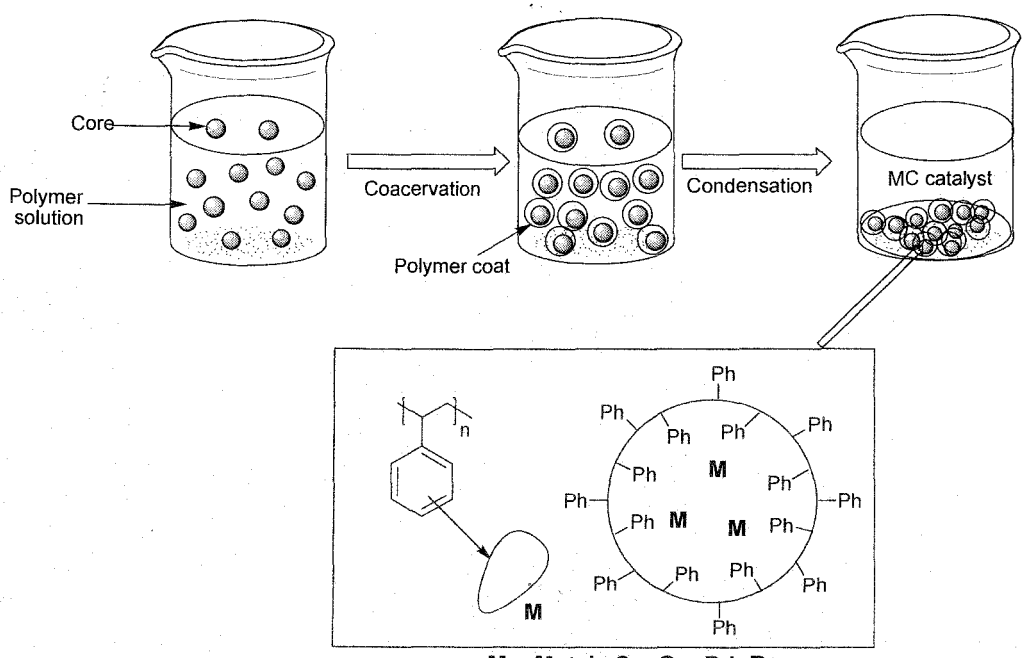
Micro-encapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules many useful properties. In a relatively simplistic form, a microcapsule is a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. Most microcapsules have diameters between a few micrometers and a few millimeters. Microencapsulation technique has found application in-

- Drug delivery systems.
- Radiation therapies
- Cell entrapment
- Controlled release technique

Recently, microencapsulation technique has been applied to the immobilization of catalysts on to polymers. Here the catalysts would be physically enveloped by thin films of polymer, and at the same time immobilized by the interaction between π- electrons of benzene rings of the polystyrene used as a polymer backbone and vacant orbitals of the catalyst. Microencapsulation is widely practiced industrially and has found use in such diverse applications as drug delivery systems,[63] radiation therapies,[64] cell entrapment,[65] and the controlled release of pesticides.[66]

1.8.1. Microencapsulated and Related Catalysts for Organic Chemistry

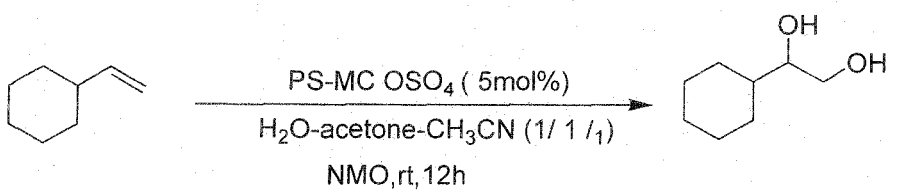
"Green Chemistry" is spreading all over the world. Green Chemistry (environment-friendly chemistry) is chemical technology for eradication of environmental pollution by changing from conventional processes to environmentally friendly processes, which do not produce or use environmental pollutants or dangerous substances, and also by replacing conventional chemical products with environmentally friendly or harmless ones. And for continuous development of human beings, realization of symbiosis in chemistry and the environment is the most important subject in this century. In this era chemist are developed a new method for immobilizing metal catalysts onto polymers, the microencapsulation method was first introduced in 1998.[67] The idea of the new method is to apply the microencapsulation technique for immobilization of catalysts onto polymers (Figure 1).That is, catalysts would be physically enveloped by thin films of polymers (polystyrene derivatives in many cases) and at the same time immobilized by interaction between π electrons of the benzene rings of the polystyrenes, which are used as a polymer backbone, and vacant orbitals of the catalysts (metal compounds). The catalysts were new types of heterogeneous catalysts and were named as "microencapsulated (MC) catalysts". Their application to medicine and pharmacy was extensively studied.



1.8.1. A: Microencapsulated OSO_4

PS-MC OsO_4 has been successfully applied to asymmetric dihydroxylation at room temperature for 6-48 hours and it is less toxic, nonvolatile and easily recovered.[68]

Scheme 20

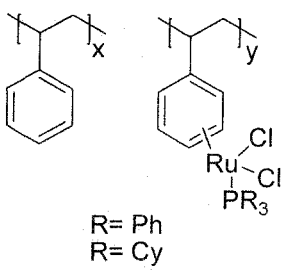


NMO = N-methylmorpholine N-Oxide

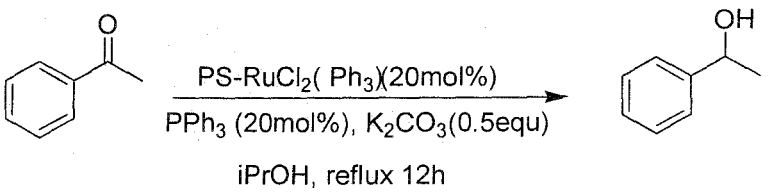
1.8.1. B: Microencapsulated Ru:

PS-$RuCl_2(PPh_3)$, this is the first example of a polymer-supported ruthenium catalyst in which the benzene rings of the polymer coordinated to the ruthenium to immobilize the catalyst onto the polymer, has been successfully used in the smooth reduction of acetophenone to the corresponding alcohol in high yield.

Scheme 21

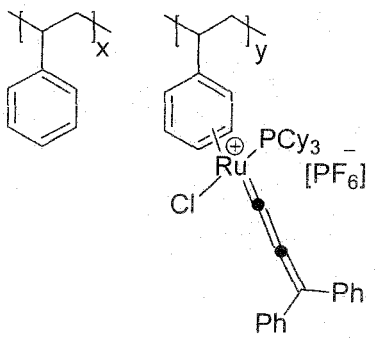


PS-$RuCl_2$(PPh_3)

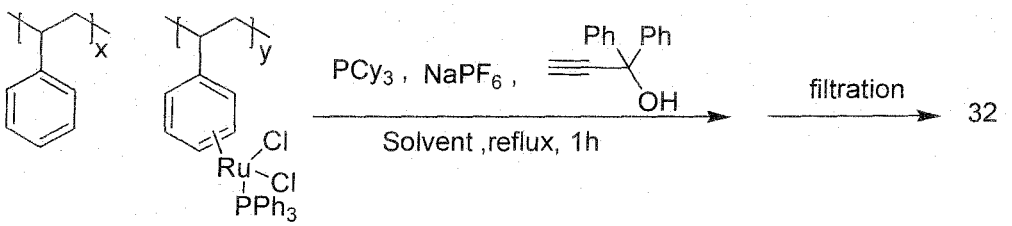


An activated polymer supported ruthenium catalyst (**33**) prepared when PS- $RuCl_2(PPh_3)$, tricyclohexylphosphine(PCy_3),1,1-diphenyl-2-propynol and sodium hexafluorophosphate ($NaPF_6$) were mixed in several solvents, and the mixture was stirred for 1 h under reflux conditions. This activated PS Ru-catalyzed ring-closing metathesis of olefins.

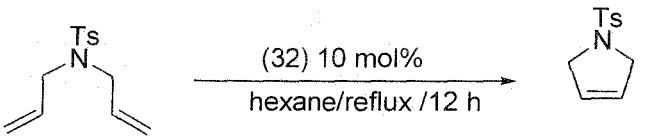
Scheme 22



(**33**)

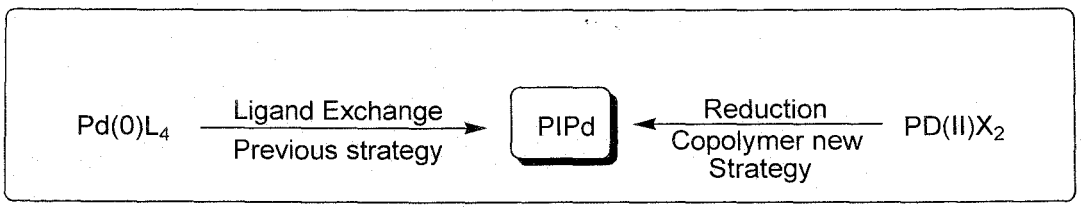


Scheme 23



1.8.1. C: Encapsulated palladium (0):

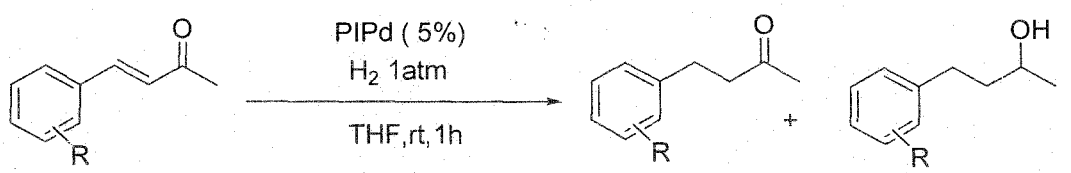
Several polymer-supported palladium catalysts have been developed for allylic substitution, oligomerization, decarboxylation, hydrogenation, isomerization, telomerization, Suzuki coupling, the Mizoroki-Heck reaction, etc. Palladium catalyst was successfully immobilized onto a polymer using the microencapsulation technique. There have two strategies for the polymer incarcerated method.



Hydrogenation:

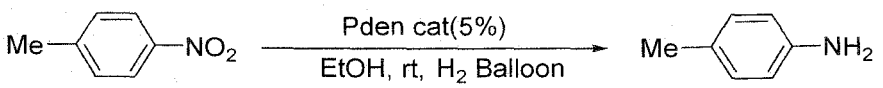
PIPd was tested in hydrogenation of benzalacetone (scheme 24).[69] The reduction was completed within 1 h in THF under ordinary pressure, the reactions proceeded smoothly to afford the desired products in high yields and it should be noted that the catalyst was recovered quantitatively by simple filtration and that the same yields were obtained even after the fifth use.

Scheme 24



Polyurea microcapsules160 another type of microencapsulated catalyst was found to be suitable by virtue of their chemical structure a backbone of urea functionality that could ligate and thus retain catalytically active metal species. Polyurea microcapsules containing palladium acetate (Pd EnCat) were also applied to hydrogenation reactions.[70] Pd-EnCat was prereduced under H_2 (50 bar) for two days, and hydrogenations were then carried out with this reduced catalyst. The reactions were performed on a 1 mmol scale (with respect to substrate) using 5 mol % of prereduced Pd EnCat under an atmosphere of H_2 maintained by an inflated balloon or under higher pressure using an autoclave. The studies carried out revealed that these Pd microcapsules are effective in the hydrogenations of alkenes, alkynes, and imine and nitro functionalities (scheme 25).

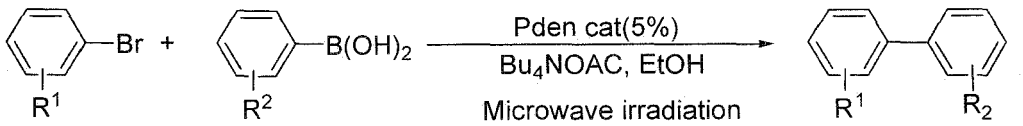
Scheme 25



Suzuki reaction:

Ley *et al.* carried out Suzuki reactions in ethanol (scheme26) where the catalyst used as Pd^0Encat. The catalyst system is highly efficient when used in conjunction with microwave heating, showing enhanced reactivity and a prolonged lifetime.[71]

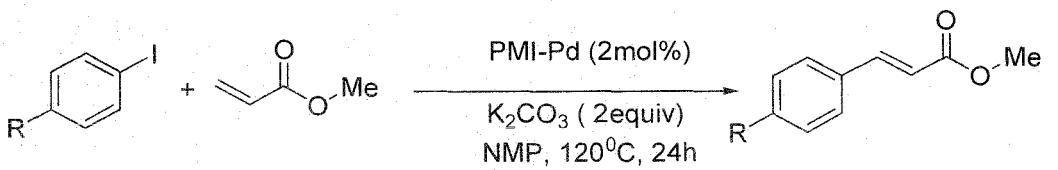
Scheme 26



Heck Reaction:

Polymer micelle incarcerated palladium are effective and stable cross-coupling catalysts.[72] Chemists have demonstrated its catalytic activity in a Heck reaction of iodobenzene with ethyl acrylate. They observed high conversions at low loading (0.5 mol %) at 100-120°C in all cases. The loading of Pd was determind by XRF analysis after decomposition.

Scheme 27



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