Part I

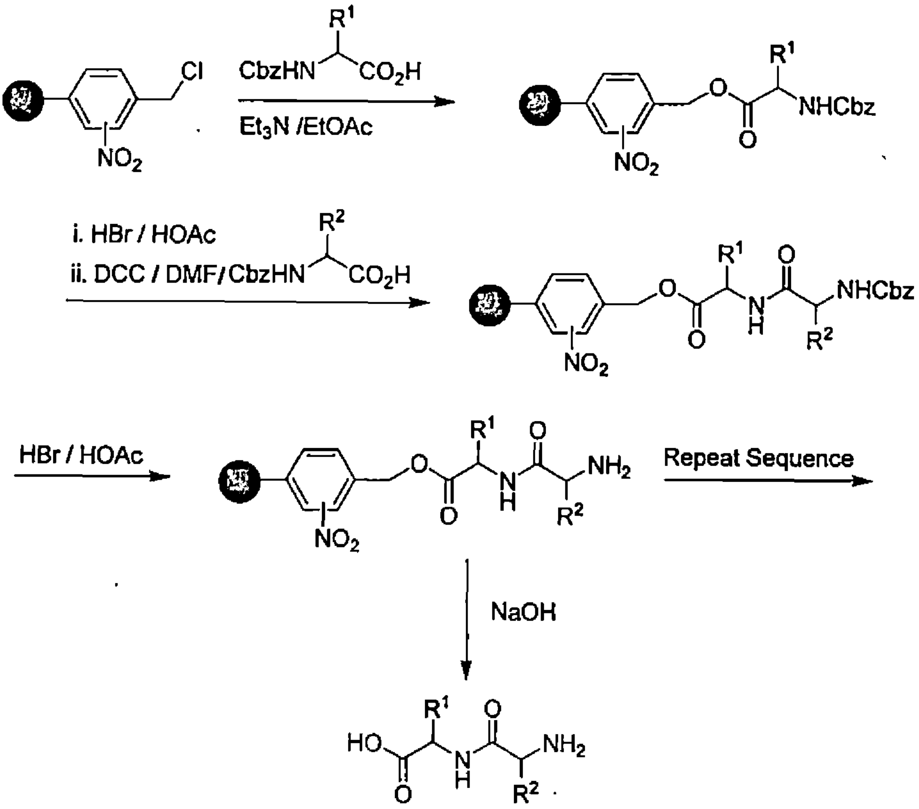
Solid Phase Organic Synthesis (SPOS)

I.1: Solid Phase Organic Synthesis (SPOS): A Brief Introduction

The creativity and art of organic synthesis has reached an interesting stage in its development. Although we now have some excellent methods to effect the construction of target molecules, with an ever increasing level of complexity, there is a need to find new, strategically important processes which are environmentally cleaner, more efficient and which lead to greater structural variation in a shorter period of time. The demand of modern society for new, functional chemical entities has driven the development of novel technologies which have begun to produce compounds at greater rate than ever before thought possible. These methods are revolutionizing the way we think, plan and optimize chemical processes and have far reaching consequences, particularly in the pharmaceutical and agrochemical sectors. In the future the impact will be even greater influencing both materials and catalyst design.

Merrifield[1] & Letsinger[2] introduced the solid phase technique for the preparation of large number of compounds in a multi parallel fashion. Merrifield first synthesized L–leucyl–L–lanylglycyl–L–valine via attachment of the intermediates to a polymeric backbone (Scheme 1). He used chloromethylated polystyrene resin as supporting materials. This was soon to revolutionize in organic synthesis due to the speed and simplicity of the technique. Actually this involves using a polymeric resin or other solid materials to support a substrate, which can then be elaborated using an excess of reagents and coupling components to drive reactions to completions. The desired molecule is then detached from the solid support and isolated following simple filtration. The interesting point of such solid phase synthesis is designing the covalent linker group, some time referred to as a ‘handle’ to attach the reagents/catalysts or substrates on to the polymeric backbone. The suitable linkers[3] can be synthesized from conventional linkers by simple coupling or substitution reactions (Merrifield, Wang, and Rink resins[4]).

Scheme 1



This general process has become the backbone of modern combinatorial chemistry and is now a widely used technique.[5] Medicinal chemists are increasingly challenged with the demand for large amounts of high purity compounds and ever–growing structural complexity of target molecules. Producing a variety of complex organic compounds in high purity and with restricted time requirements remains the major challenge. Each synthesized compound requires purification from all other components present in the reaction mixture, such as excess reagents, catalysts, by–products and solvents. In many cases the isolation and purification steps account for the majority of the time and cost of the organic synthesis. Polymer–assisted solution phase synthesis that comprises mainly polymer–supported reagents, catalyst and scavengers, offers significant advantages compare to the conventional fine chemicals synthesis.

Despite the impressive success and advantages of this type of solid phase organic synthesis, there are also severe limitations to this approach, which are worth noting. Firstly, the reactions can be slow relative to their solution phase counterparts and it can be difficult to monitor the progress of the reaction. Although several new techniques have been developed in recent years to monitor the progress of the solid phase reactions[6] (*e. g.* use of FT–IR, MALDI–MS, Gel phase and MAS NMR etc.), these techniques still do not provide same quality of analyses as compared to conventional solution phase techniques (*e. g.* TLC, GC–MS, LC–MS, SFC–MS, NMR *etc.*) A second fundamental feature of this approach is that additional steps are required to attach the substrate and detach the product from the resins: often a vestigial part of the linker unit is found in the final product and linker compatibility with reagents used can be a source of problems or limitations.

Solid supported reagents[7] and scavengers[8] have been used in organic synthesis programs since 1946.[9] In recent years however, many new and several improved solid–supported reagents/catalyst have been developed, an ever increasing number which are commercially available. The increased level of interest has largely been due to the need to generate large numbers of new compounds in a cleaner, faster and more efficient manner, and the potentials of these reagents to achieve this.

Solid–supported reagents/catalysts are attractive because one of the key advantages is that it is possible to use excess reagent to drive reactions to completion and as work–up is made by simple filtration to separate products, the chemistry is clean. Filtration also results in isolation of the solid–supported species, which is a crucial feature in cases either where the reagent acts as a catalyst, or where the spent material can be regenerated and recycled.[10] Another attractive aspect is that toxic, noxious or hazardous reagents and their by–products can be immobilized and therefore not released into solution and thereby improving their acceptability, utility and safety profile. More than one reagent can be used simultaneously and due to site isolation reagents, even species that are incompatible in solution may be used together to achieve one–pot transformation that are not possible in homogeneous solution. Furthermore, if the reaction proceeds poorly or generates by–products and impurities, scavengers or catch and release techniques can lead to isolation of pure products in a simple fashion without need for conventional work–up and purification procedures. The fact that only simple work–up operations are necessary, involving filtration and solvent removal or exchange, is a crucial feature in the libraries generation as the chemistry should then be viable for automation using robotic devices.

I.2: 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.

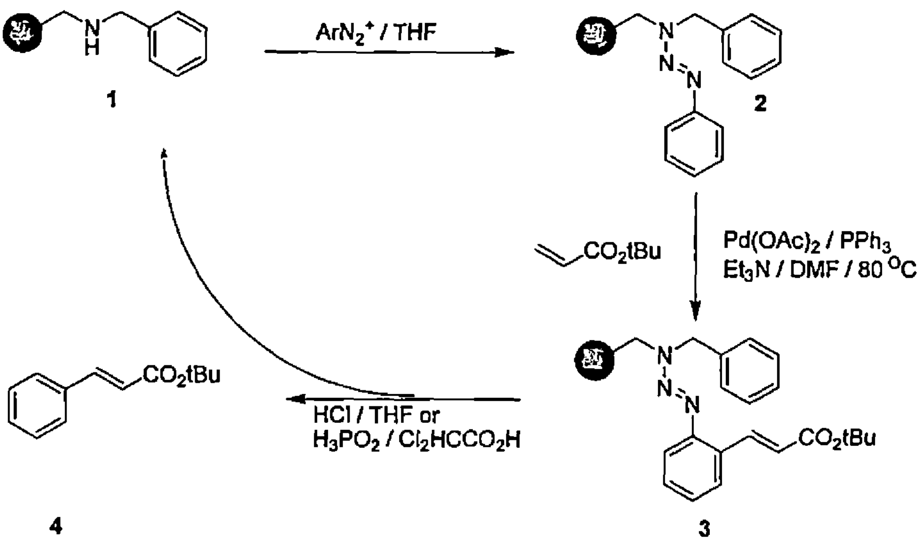
Generally, reagents and catalysts are immobilized onto polymer surface involving (a) covalent binding (b) entrapment, where a pre–formed catalyst is enveloped within a polymer network, and (c) ion–pairing, where cations or anions are bound to complementary resin sites. By far methods (a) and (c) are 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). In micro–encapsulation 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.[11] 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.

I.2.1. Covalent Binding of Reagents

I.2.1.A.1: Nitrogen as a linker: Heck Coupling

The benzylamine resin **1** was synthesized in one step from Merrifield resin. Diazonium salts were coupled to the resin to give the triazine **2**, which was used in a Heck coupling reaction[12] to give **3**. The cleavage was facilitated with either HCl in THF or reductive deamination using H_3PO_2 in dichloroacetic acid to give the Heck coupling product **4** in 81% yields (Scheme 2). Other reactions were performed after the Heck reaction on different substrates, including Sharpless dihydroxylation and Diels–Alder, in good yields. After the reaction the benzylamine resin can be reused with only slight loss of activity. Gordon *et al.*[13] recently reported that polystyrene supported amine act as base for Heck coupling reaction in $scCO_2$.

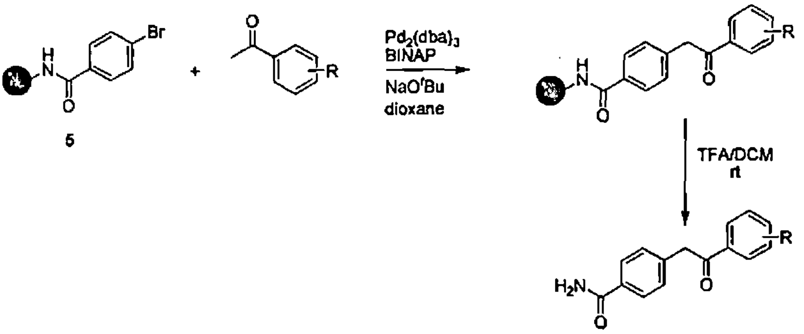
Scheme 2



I.2.1.A.2: α-Arylation of Ketones

Griebenow *et al.*[14] recently reported the α–arylation of ketones with the aid of solid phase synthesis by adapting the standard protocol of α–arylation reported by Buchwald & Hartwig.[15] In this case they initially prepared immobilized 4–bromobenzamide **5** by the reaction between polystyrene Rink amide resin and 4–bromobenzoic acid chloride. The supported 4–bromobenzamide **5** was reacted with ketone in presence of $Pd_2(dba)_3$ and finally treatment with trifluro acetic acid (TFA) yielded the desired product (Scheme 3). Both aromatic and aliphatic methyl ketone undergoes this reaction with similar efficiency.

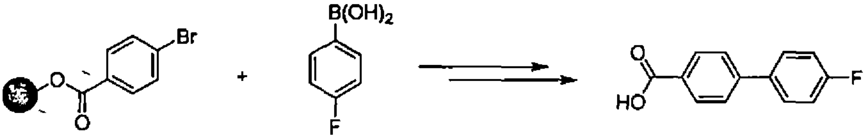
Scheme 3



I.2.1.B: Suzuki-Miyaura Coupling Reaction

Recently Suzuki–Miyaura (SM) coupling is one of the most important tools for C–C bond forming reaction. The solid phase SM cross coupling[16] strategy has been largely developed by reacting the resinbound aryl halides **6** with solution–phase boronic acids followed by the consecutive treatment with 1 N sodium hydroxide and 12 N hydrochloric acid (Scheme 4).[16k] Recently, methods have been developed for attaching boronic acids to macroporous polymer supports and these supported boronic acids[16f] have been successfully used in the SM cross–coupling reaction.

Scheme 4



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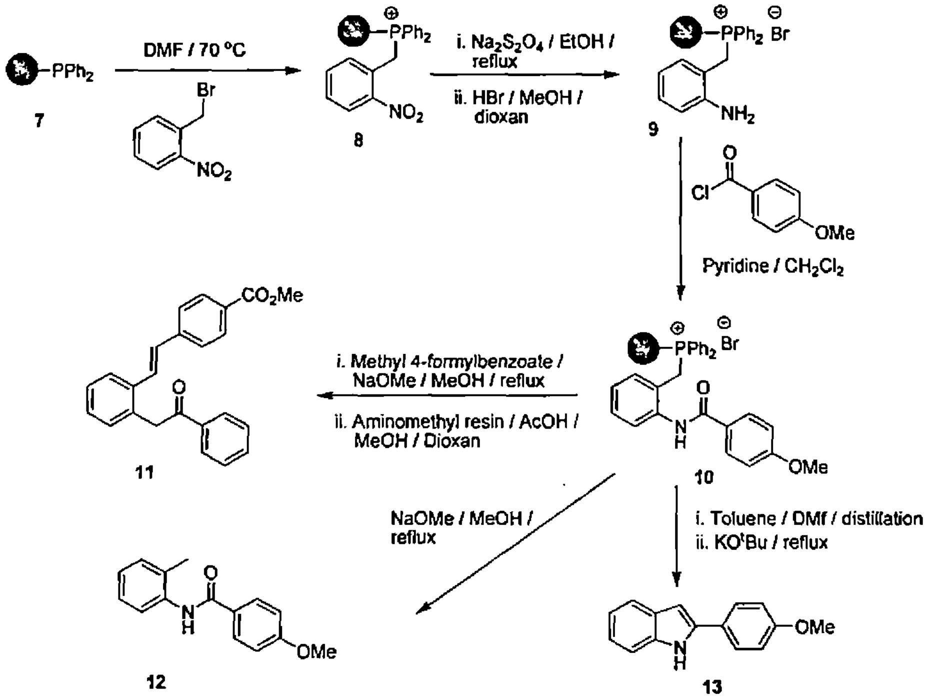
I.2.1.C: Polymer–Supported Triphenylphosphine Linker

Functionalized polymer–bound phosphonium salt has also been utilized to synthesize three different types of molecules, depending on the reaction conditions. Commercially available polystyrene–bound phosphine **7** was loaded with 2–nitrobenzylbromide to give the resin–bound phosphonium salt **8**, which was converted to aniline **9**, then acylated giving the phosphonium resin **10**. Cleavage could then be facilitated by intramolecular Wittig reaction giving a 3:1 (*E/Z*) mixture of **11**, in 82% overall yield (Scheme 5). The aminomethyl resin was used as a solid–phase scavenger reagent for the excess aldehyde used. Hydrolysis of carbon–phosphonium bond generated the 2–methylanilide **12** in 81% overall yield. Intramolecular Wittig reaction occurred upon distillation prior to adding base, giving indole **13** in 78% yields. DMF was a necessary co–solvent in the intramolecular Witting reaction.[17]

Scheme 5

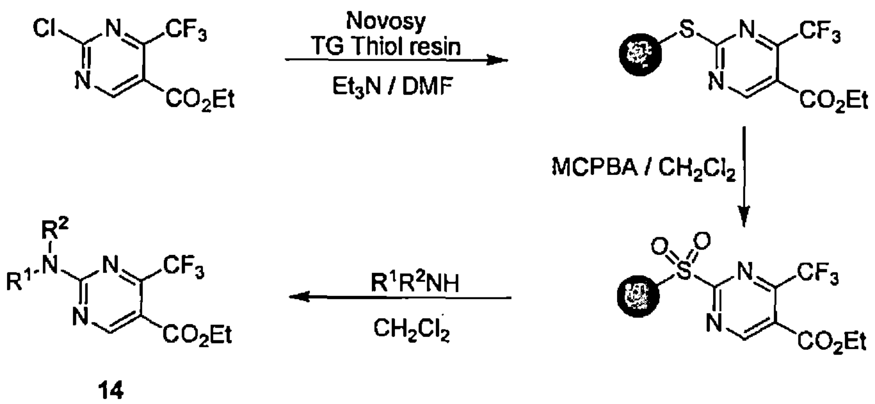


Similar to triphenylphosphine, triphenylarsine[18] is also a versatile reagent for organic synthesis, but the reports regarding supported triphenylarsine are few.[19] Supported triphenyl arsine used as a ligand for metal catalyzed coupling reactions.[20]

I.2.1.D: Polymer–Supported Sulfur Linker

Suto *et al.*[21] first introduced the sulfur–based linker for solid–phase synthesis. Oxidative activation of a sulfide to a sulfone allowed nucleophilic displacement of the sulfone, incorporating further diversity into the final compound. They used this technique to synthesize functionalized pyrimidines **14**, as outlined in scheme 6.

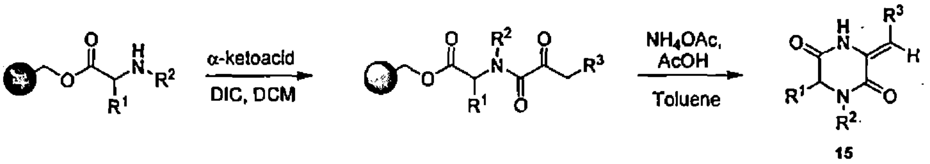
Scheme 6



I.2.1.E: *Synthesis of Heterocycles*

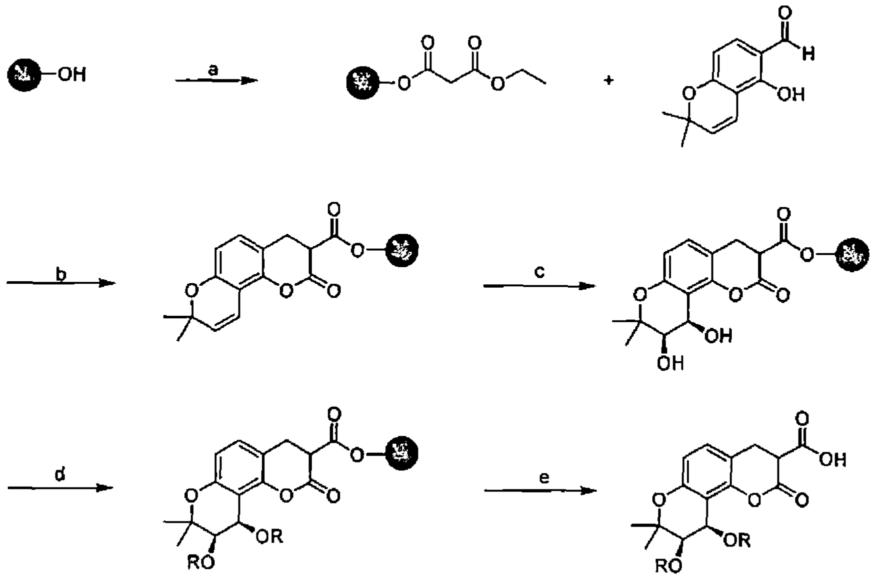
Smith *et al.*[22] developed a solid phase synthesis of piperazine–2,5–diones on Kaiser oxime resin.[23] Diazepinediones were prepared the same way. For the preparation of histidine containing piperazine–2,5–diones, Sabatino *et al.*[24] linked the histidine via the side chain to the trityl resin. When a polymer supported N–alkylated amino acid was acylated by a α–keto acid, cyclative cleavage in the presence of ammonium acetate yielded 3–alkylidene–piperazine–2,5–dione **15**, predominantly as the *Z* isomer, as outlined in scheme 7.[25]

Scheme 7



(3′*R*, 4′*R*)–di–*O*–(–)–camphanoyl–(+)–*cis*–khellactone (DCK) displayed extremely potent inhibitory activity against HIV–1 replication.[26] Therefore, (3′*R*, 4′*R*)–di–*O*–*cis*–substituted khellactones have proven to be crucial drug leads and have elicited considerable pharmaceutical interest. Thus, a general method of rapidly preparing analogues of khellactones would be advantageous and merits investigation for drug discovery. Xia *et* al.[27] developed a novel, straightforward, easily automated solid–phase procedure for the synthesis of (3′*R*,4′*R*)–di–*O*–*cis*–acyl–3–carboxyl khellactone **16**. The procedure is particularly useful because of its efficiency and ease of operation (Scheme 8).

Scheme 8



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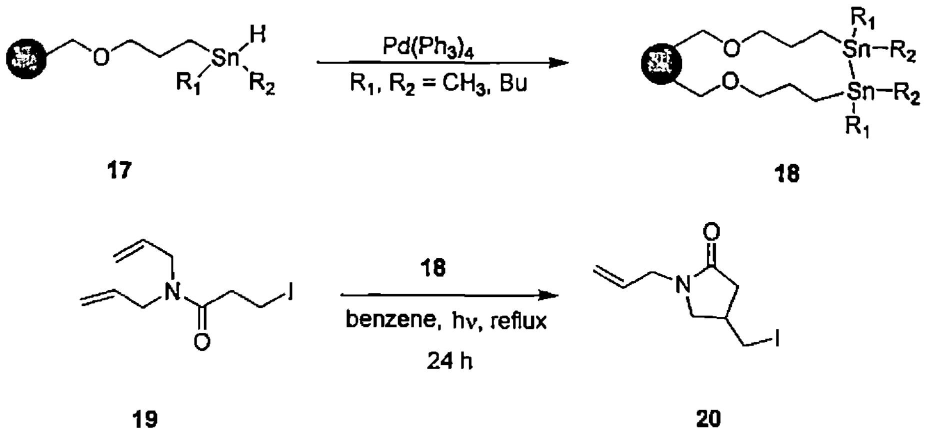
a) ethyl potassium malonate, rt;
b) pyridine, piperidine, rt;
c) $K_3[Fe(CN)_6]$, OsO_4, K_2CO_3, $(DHQ)_2$-PHAL, t-BuOH/H_2O, rt;
d) (1) R2COOH, 1 equiv DIC; (2) DIEA, DMAP;
e) 50% TFA/CH_2Cl_2

The strategy they used is to attach a polystyrene resin to the khellactone ring skeleton through a C–3 carboxylate group. The linker group of the Wang resin could serve as a carboxyl protecting group, because a free carboxyl is not compatible with the asymmetric dihydroxylation (AD) or acylation reaction conditions.

I.2.1.F: Free Radical Cyclization Reactions

Hernán and Kilburn described the synthesis of a polymer–supported distannane reagent **18** comprising cross–linking a polystyrene–bound tin hydride[28] **17**. Reagent **18** was successfully applied in free radical cyclization reactions involving the transfer of iodine atom. For example, the diallyl amide **19** underwent efficient cyclization to compound **20** using the distannane reagent **18** (Scheme 9).

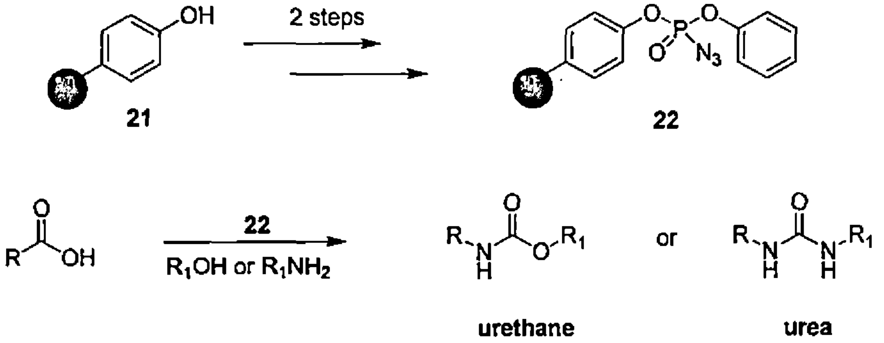
Scheme 9



I.2.1.G: Polymer–Supported Phosphoryl Azide

The preparation of a polymer–bound diphenylphosphoryl azide **22** in two steps from a phenol resin **21** (Scheme 10) was reported by Lu and Taylor.[29] The synthetic utility of reagent **22** was demonstrated in the conversion of various carboxylic acids to urethanes and urea derivatives via Curtius rearrangement. Reagent **22** was moisture–tolerant and the toxic phosphoryl azide group remains resin bound.

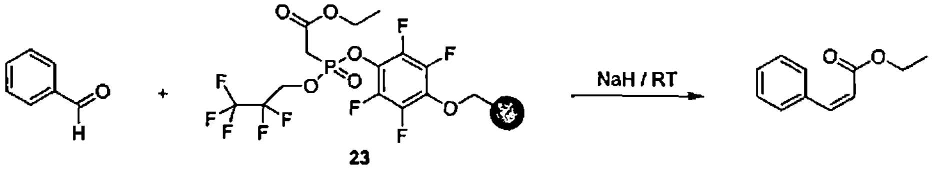
Scheme 10



I.2.1.H: Polymer–Supported Phosphonate Reagents

Martina and Talyor described the synthesis of phosphonate resins and evaluated their potential for the selective preparation of Z–isomer of α, β–unsaturated esters from aldehydes.[30] The polymer supported fluorinated phosphonate **23** was the most effective reagent in the synthesis (Scheme 11). The products were isolated by filtration of the resin without the need for chromatographic separation.

Scheme 11



I.2.2: Ionic Binding of Reagents: Ion Exchange Resins

An ion exchange resin is a polymer with electrically charged sites at which one ion may replace another. Natural soils contain solids with charged sites that exchange ions, and certain minerals called zeolites are quite good exchangers. Ion exchange also takes place in living materials because cell walls, cell membranes, and other structures have charges. In natural waters and in waste waters, there are often undesirable ions and some of them may be worth recovering. For example, cadmium ion is dangerous to health but is not present usually at concentrations that would justify recovery.

Most synthetic resins are based on styrene co–polymerized with DVB. Conventional ion–exchange resins include a range of anion (chloromethylated, aminated etc.) and cation resins (sulfonated). Styrene/DVB structures are the preferred matrices for ion–exchange resins because they offer significant capacity and stability over other resin structures.

The amount of cross–linking depends on the proportions of different monomers used in the polymerization step. Practical ranges are 4–16%. Resins with very low cross–linking tend to be watery and change dimensions markedly depending on which ions are bound. Properties that are interrelated with cross–linking are: moisture content, capacity, equilibration rate etc.

Copolymers of styrene containing low amounts of divinylbenzene (1–4%) possess following characteristics:

- High degree of permeability.
- Large moisture content

- Lower capacities on wet volume basis.
- High equilibrium rates.
- Reduced physical stability.
- Selectivity of various ions is decreased, but ability to accommodate larger ions is increased.

Copolymers of styrene containing high amounts of divinylbenzene (12–16%) exhibit characteristic in the opposite direction.

Synthetic ion–exchange resins are usually cast as porous beads with considerable external and pore surface where ions can attach. If a substance is adsorbed to an ion exchange resin, no ion is liberated. Testing for ions in the effluent will distinguish between removal by adsorption and removal by ion exchange. Of course, both mechanisms may be significant in certain cases, and mass balances comparing moles removed with moles of ions liberated will quantify the amounts of adsorption and ion exchange.

The total capacity of an ion–exchange resin is defined as the total number of chemical equivalents available for exchange per some unit weight or unit volume of resin. The capacity may be expressed in terms of milli–equivalents per gram of dry resin or in terms of milli–equivalents per gram of resin or in terms of milli–equivalents per milliliter of wet resin.[31]

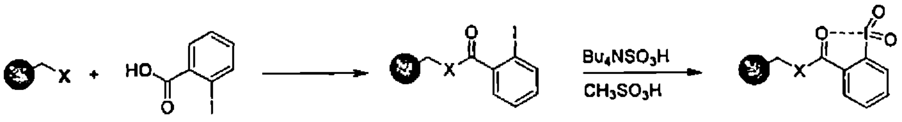
The more highly cross–linked a resin, the more difficult it becomes to introduce additional functional groups. Sulfonation is carried out after the cross–linking has been completed and the sulfonic acid groups are introduced inside the resin particle as well as over its surface. Likewise, the quaternary ammonium groups are introduced after the polymerization has been completed and they too are introduced both inside the particle as well as on its surface. Fewer functional groups can be introduced inside the particles when they are highly cross–linked and hence the total capacity on a dry basis drops slightly.

Recent examples of use of ionic resin especially for oxidation, reduction and related reactions are mentioned below highlighting the scope for using ionic resin as commercially cheap, stable and environmentally benign solid polymeric framework.

I.2.2.A: Oxidation Reactions

The selective oxidation of primary and secondary alcohols to the corresponding carbonyl compounds has found wide application in organic synthesis. This process provides the synthesis of structurally diverse carbonyl compounds, which are useful for subsequent reactions. Lee *et al.* designed polymer–supported 2–iodoxybenzoic acid (IBX) esters and amides **24** (Scheme 12) which can be employed for high–yielding oxidation of a range of primary and secondary benzylic alcohols to the corresponding carbonyl compounds. The spent polymeric reagents can easily be removed by filtration.

Scheme 12

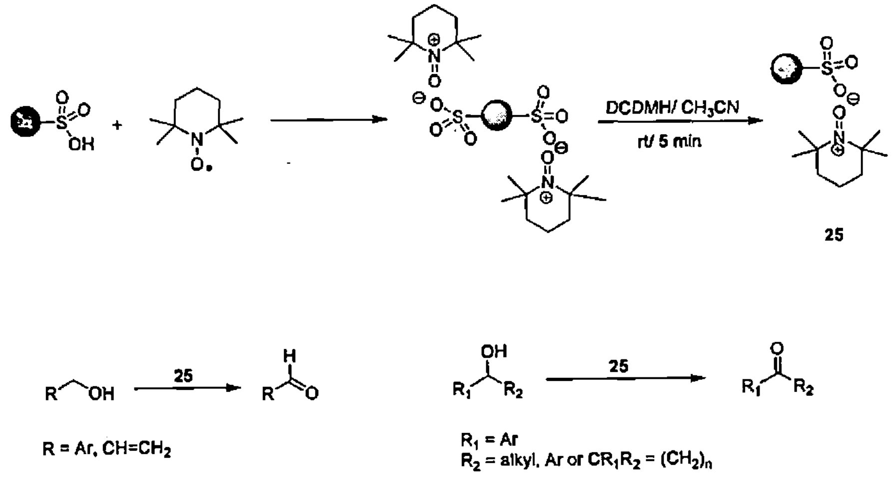


24

X = N, O

Bhattarcharyya et al. reported the synthesis and application of a novel polymer–supported oxidizing agent MP–TsO–TEMPO **25**, based on an oxo–ammonium salt of TEMPO (Scheme 13).[32]

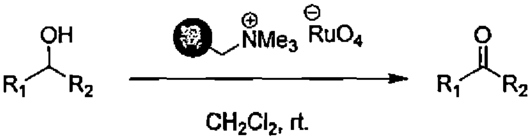
Scheme 13



The reagent **25** was prepared from MP–TsOH, a commercially available polymer–supported sulfonic acid, and can be activated to its full capacity using 1,3–

dichloro–5,5–dimethylhydantoin (DCDMH). The reagent MP–TsO–TEMPO has primary applications in selective oxidation of activated primary and secondary alcohol such as benzylic, allylic, acetylenic andalicyclic alcohols. The resulting aldehydes or ketones could be isolated in high yields by filtration of the resin and evaporation of solvents. Oxidation of alcohols to ketones and aldehydes can be achieved on the solid phase using standard reagents such as the SO_3.pyridine complex,[33] DMSO–oxalyl chloride–Et_3N, or tetra–*n*–propylammonium perruthenate complex.[34] Recently, Hinzen and Ley reported a polymer–supported perruthenate, a new oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones respectively (Scheme 14).[35]

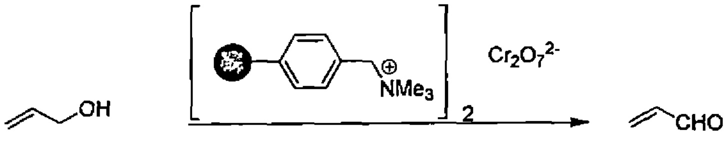
Scheme 14



R_1 = alkyl, aryl; R_2 = alkyl, H.

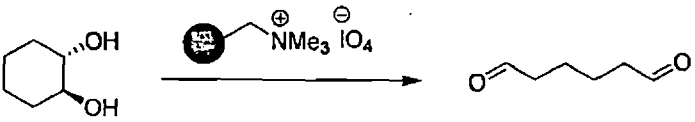
Polymer–supported quaternary ammonium perchromate (counter anion) converts allylic alcohols to α,β–unsaturated aldehydes, whereas saturated alcohols remain unaffected under the similar conditions (Scheme 15).[36]

Scheme 15



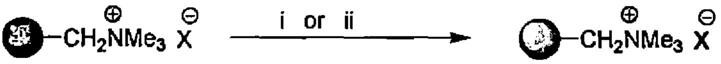
Periodates oxidize various functional groups, but due to solubility limitations, these salts are typically only utilized in hydroxylic media. Polymer–supported periodate, however, can be used in a variety of solvents, and in many cases, filtering off the resin and evaporating the solvent gives clean oxidized product. Quinols are converted to quinones, 1,2–diols are cleaved to the corresponding carbonyl compounds, sulfides are oxidized to sulfoxides, and triphenylphosphine is converted to triphenylphosphine oxide (Scheme 16).[37]

Scheme 16



The preparations of the periodate forms **28** of the macroporous ion–exchange resins Amberlyst 26 and Amberlite IRA 904 from their corresponding chloride forms **26** and of the iodate analogues **29** from the hydroxide version of those matrices **27**, as shown in scheme 17, were first described by Harrison and Hodge.[37]

Scheme 17



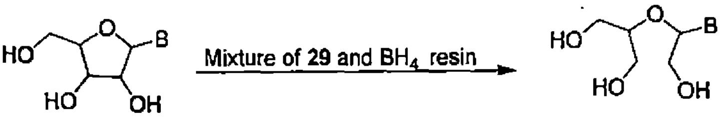
26 X = Cl
27 X = OH

28 X = IO_4
29 X = IO_3

Reagents and conditions: i $NaIO_4$ (aq); ii HIO_3 (aq)

The reagents **28** & **29** have been used for the oxidation of dihydroxybenzene to corresponding quinone. The cleavage of 1,2–diols, to corresponding carbonyl species, could easily be achieved with the reagent **28**. An interesting application of periodate resin **28**, in conjunction with resin–bound borohydride, was the conversion of nucleosides **30** to the corresponding trihydroxynucleosides **31**, as described by Bessodes and Antonakis.[38] Simply filtering a solution of the nucleoside through a column containing a well–mixed bed of a 1+1 mixture of the two resins facilitated the reaction (Scheme 18).

Scheme 18



30

31

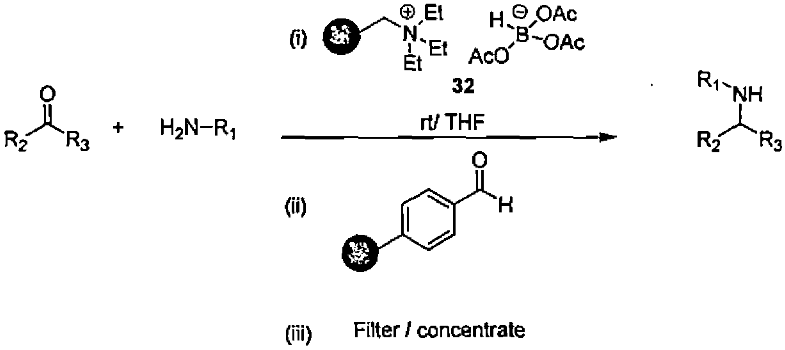
B = Adenine, Cytosine, Guanine, uracil

The process described was therefore extremely clean, and has the advantage that due to the fact that no reaction takes place between the resin bound materials, the intermediate dialdehyde need not be isolated. Periodate–containing resins have also been successfully employed in the high–yielding and remarkably clean oxidations of α–haloketones[39] into carboxylic acids, and in the rapid conversion of a range of sulfides to sulfoxides.[40]

I.2.2.B: Reduction and Reductive Amination

Amines and their derivatives are the most abundant structural moieties present in the CMC (comprehensive medicinal chemistry) database.[41] The reductive amination of carbonyl compounds provides expedient access to structurally diverse amines and has wide application in organic and medicinal chemistry. Bhattarcharyya *et. al.* have reported a novel polymer–supported triacetoxyborohydride reagent **32** (Scheme 19) for the reductive amination of aldehydes and ketones.[42] The bound triacetoxy–borohydride reagent **32** is stable and provides a broad scope and reactivity in reductive amination reactions, using primary amines, secondary amines and their salts under mild conditions. These reactions can be conveniently carried out in solvents, such as THF, DMF or NMP.

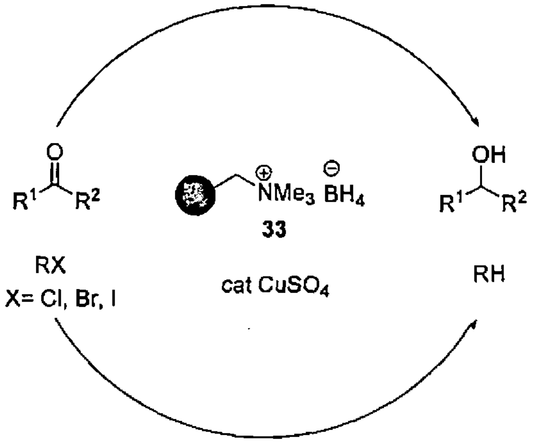
Scheme 19



Immobilized reducing agents have been used as the source of hydrogen or hydrides in reduction of different functional groups in organic molecules.[43] The chemical modification of quaternary ammonium type resins, such as Amberlyst® A–26, with $NaBH_4$[44] and $NaCNBH_3$ gives highly efficient and chemoselective reducing agents.[45] The cross–linked polymer–supported $Zn(BH_4)_2$ [46] has been employed in reduction of aldehyde in presence of ketones and that of $Zr(BH_4)_4$ [47] could reduce ketones also, while conjugated double bonds remained unreacted. Formic acid anchored with Amberlite Resins (anion exchange) has been used as hydrogen donor in catalytic transfer hydrogenation (CTH).[48]

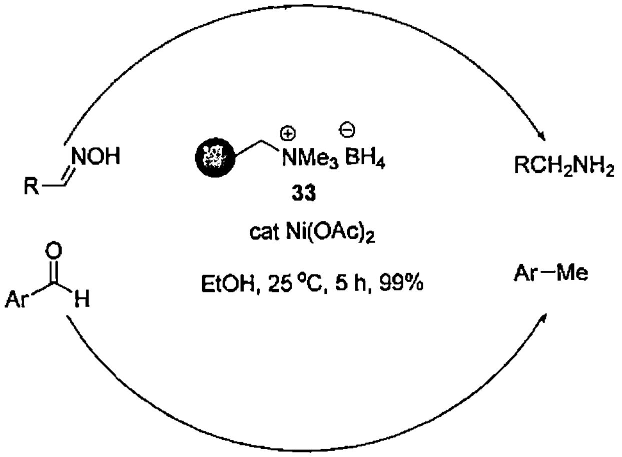
When borohydride is attached to Amberlite® IRA 400 and treated with a catalytic amount of $CuSO_4$, a functionalized polymer **33** is obtained, which can act as an efficient reductant towards different functional groups like aryl halide, azides, aldehydes, and ketones.[49] (Scheme 20) Borohydride exchange resin (BER) is useful for conversion of thioacetates to thiols by palladium–catalyzed methanolysis,[50] and selenium to dialkyl selenides.[51]

Scheme 20



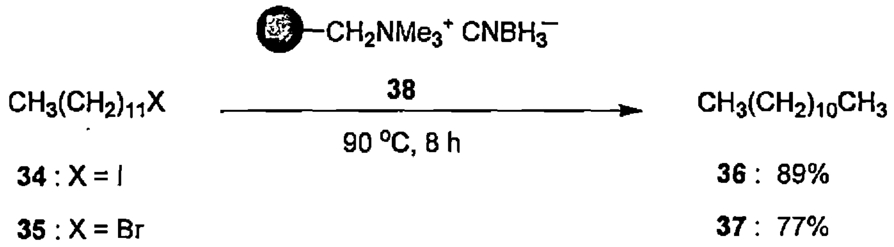
The addition of a catalytic amount of nickel (II) acetate affords a very powerful and highly chemoselective[52] functionalized polymer **33**, which allows reduction of nitro[53] and azido[54] groups as well as of aryloximes[55] to the corresponding primary amines. Alkyl and aryl halides[56] tosylates,[56a] and benzaldehydes[57] are remarkably converted into alkanes in moderate to excellent yields (Scheme 21).

Scheme 21



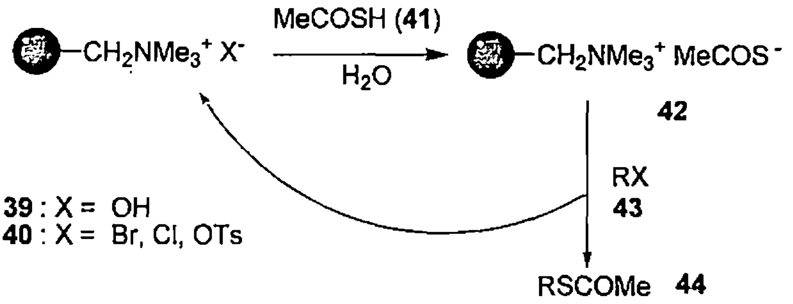
These results compare favourably with those obtained by Hutchins *et al.* when using supported cyanoborohydride (**38**).[45a] The material, which was prepared on Amberlyst A–26, was also employed to effect the conversion of pyridinium bromides into tetrahydropyridine derivatives, dimethylation of amines, reduction of ketones, and dehalogenations of **34** and **35** to alkane **36** & **37** in good yields (Scheme 22). The time taken to achieve the desired conversions was reported to be greater than that required with standard solution phase cyanoborohydride, presumably due to less efficient substrate/polymer contact, but the reactions were extremely clean. The toxic cyanide residues associated with free sodium cyanoborohydride are retained on the Amberlyst resin, and not extracted into either aqueous or organic media. The resin can be regenerated by a simple washing procedure, as in the case of borohydride resin **33**.

Scheme 22



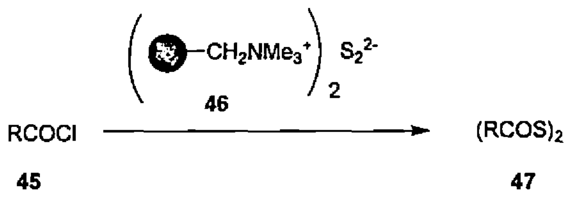
The immobilization of thioacetic acid **41** on Amberlyst A26 (hydroxy form) **39** has proved useful for the clean conversion of alkyl halides **43** into thioacetates **44** (Scheme 23).[58] The reactions were performed under a variety of conditions dependent upon the nature of the substrate, but always with a slight excess of resin **42**. The reaction conditions are relatively mild; with alkyl bromides reacting readily at room temperature, whilst chlorides and tosylates require slightly more vigorous treatment. Secondary alkyl bromides require the application of elevated temperatures, but the reaction is clean, with no elimination products being observed. The spent resin **42**, containing halide or tosylate groups, can be efficiently recycled simply by washing with dilute sodium hydroxide solution and treatment with thioacetic acid.

Scheme 23



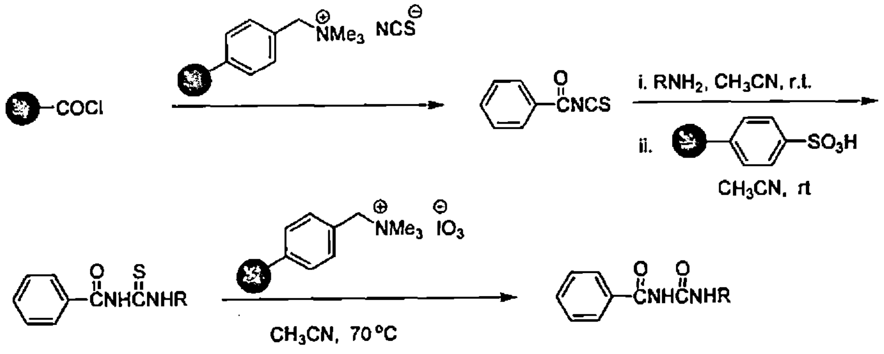
Tamami and Kiasat reported the synthesis of acyl disulfides **47**, using sulfur supported on Amberlyst A26.[59] Reagent **46** was readily prepared from elemental sulfur and the ion–exchanger, and are postulated to contain sulfur as S_2^{2-} units. This material rapidly, and cleanly, converts acid chlorides **45** to the corresponding diacyl disulfides, with no trace of the acyl sulfides being found, shown in scheme 24.

Scheme 24



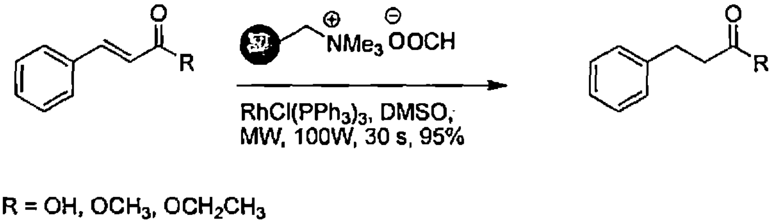
The substituted ureas have drawn considerable attention in a number of investigations due to their biological activity and wide variety of applications.[60] Most syntheses of ureas have been reported using conventional solution methods and solid–phase synthesis.[61] Recently Yang *et al.*[62] reported a simple, fast and flexible method for synthesis of ureas using polymer–supported reagents as shown in scheme 25. They carried out the synthesis of thioureas by reaction of poly(ethyl glycol) bound benzoyl chloride with amines.[63]

Scheme 25



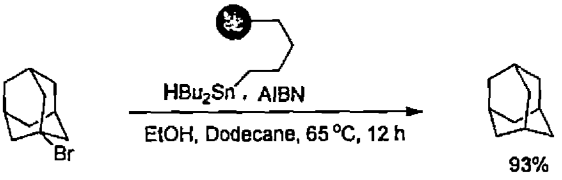
Danks *et al.* reported a facile reduction of cinnamic acid and its alkyl esters using a mixture of Amberlite® IRA 938 resin–supported formate and Wilkinson's catalyst in a minimum quantity of DMSO under microwave irradiations (Scheme 26).[64]

Scheme 26



Other important groups of functionalized polymers with reductive properties include polymer–supported organotin reagents, especially tin hydrides.[65] These types of polymer–supported tin hydrides have been employed for the reduction of sulfonic esters, xanthates, or alkyl halides[66] including tertiary bromides like adamantyl bromide.[67]

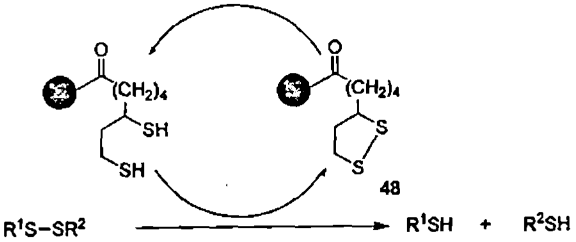
Scheme 27



Polymeric backbone is Amberlite XE 305

Polymer bound dithiol, a biomimetic tool for the reduction of disulfides, was developed by Gorecki and Potchornik.[66] The polymer bound dithiol was prepared by the treatment of disulfide **48** with NaBH₄ (Scheme 28).

Scheme 28



I.3: Solid Supported Catalysts

I.3.1: Introduction

In an era, when the world has been increasingly aware of the limits of its natural resources and the problems relating to environmental impact of disposing of waste materials, the chemical industries are under considerable pressure to discover, develop and to utilize more efficient, cleaner and "green" manufacturing protocols. The areas, which have seen the most change in recent years, have been the pharmaceutical and agrochemical sectors. These communities are constantly seeking new ways to meet the demands for new, diverse and structurally interesting molecules. 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 need to remove the residual metals.[69] The heavy metal contamination with the product is undesirable and must be limited to ppm or even lower levels in large–scale pharmaceutical processes.[70]

The heterogeneous catalysis is a most promising option to over come those problems. 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. Depending on the matrix used, the immobilized complexes can be isolated from reaction mixture via either filtration or judicious selection of a second solvent for the selective precipitation of matrices out of the reaction mixtures or extraction of the scaffolds into an orthogonal liquid phase. Thereby, immobilization of a soluble catalyst on a support allows the facile recovery and reuse of expensive and toxic catalytic heavy metal species, which cut costs and provide environmental protection benefits in industrials processes. Several approaches have been explored utilizing various immobilization techniques on solid or colloidal supports, and aiming towards efficient recovery and reuse of the active catalysts. The major thrust to achieve success in designing and developing polymer–supported metal catalysts broadly include: improved stability within the polymer matrix, increased selectivity for reactions, enhanced regio–selectivity, reusability for several runs and superior asymmetric induction due to site–specific chiral catalysts. In this brief literature review the various types of immobilized palladium catalyst onto the different heterogeneous surface and their application in various coupling reactions have been highlighted.

Among the various catalytic processes, transition metal–catalyzed organic reactions constitute the central part of contemporary organic synthesis. Transition metal catalyzed carbon–carbon and carbon–heteroatom bond forming reactions are of the most important fundamental transformations in synthetic chemistry.[71] Homogeneous palladium catalysis has gained enormous relevance in various coupling reactions such as Heck, Stille, Suzuki, Sonogashira, and Buchwald–Hartwig reactions.[72] This type of catalysis provides high reaction rate and high TON (turnover number) and often affords high selectivities and yields. The properties of such palladium catalysts can be tuned by ligands, such as phosphines, amines, carbenes, dibenzylideneacetone (dba), etc. Proper ligand design has led to catalysts, that tolerate weak leaving groups such as chloride, exhibit higher TON and reaction rates, have improved lifetimes, and are suitably stable to run the reactions without the exclusion of water or air and at lower temperatures. The structure of the catalytic species is often known, and structure–activity relations could be established. Recent developments of ligand–free palladium catalysts have provided interesting and practically important alternatives to ligand assisted methodologies.

Generally palladium is fixed to a solid support,[73] such as activated carbon,[74] zeolites and molecular sieves,[73a,75] metal oxides[73a,76] (mainly silica or alumina but also MgO, ZnO, TiO_2, ZrO_2), clays,[77] alkali and alkaline earth salts ($CaCO_3$, $BaSO_4$, $BaCO_3$, $SrCO_3$), porous glass,[78] organic polymers,[73a] or polymers embedded in porous glass.[79] On the other hand, palladium can also be fixed to a solid support as a complex; that is, the ligands are covalently bound to the support. Both techniques allow one to separate the heterogeneous catalyst after the reaction or to reuse it as long as it is not too deactivated.[80] Alternatively such catalysts can also be used in continuous–flow systems[79a] or in flow injection microreactors.[81] Normally, supported palladium catalysts require more drastic reaction conditions than homogeneous catalysts, but this does not cause problems as far as the stability of the catalysts is concerned, because they often are relatively stable. In this way, somewhat lower activities can be compensated to some extent by using higher temperatures and catalyst loadings. Djakovitch *et al.* reported a comparative study of homogeneous versus heterogeneous catalysis of palladium catalyst in Heck reactions.[82] Palladium immobilized onto zeolites showed higher activity than free $Pd(OAc)_2$ or $[Pd(C_3H_5)Cl]_2$, probably because of the stabilization of the active palladium species by the zeolite framework.[75d] The comparatively high stability of palladium on solid supports sometimes allows running the reaction even under normal ambient conditions, that is, without the exclusion of air.[83] Solid supported palladium catalysts often show higher activities than homogeneous catalysts, probably because of their higher stability.[84] The application of supported palladium was introduced into palladium–catalyzed coupling reactions relatively late (early 1970s) but has been increasingly used up to now.[85] Palladium can be deposited on a solid support in different ways.[78b,86] The preferred mode of deposition however depends also on the type of support.

An excellent review article[87] covering various types of heterogeneous palladium catalysts and their applications in different carbon–carbon coupling reactions has been published in 2007. A short account of pertinent approaches is therefore discussed here.

I.3.2: *Covalent Binding of Catalyst*

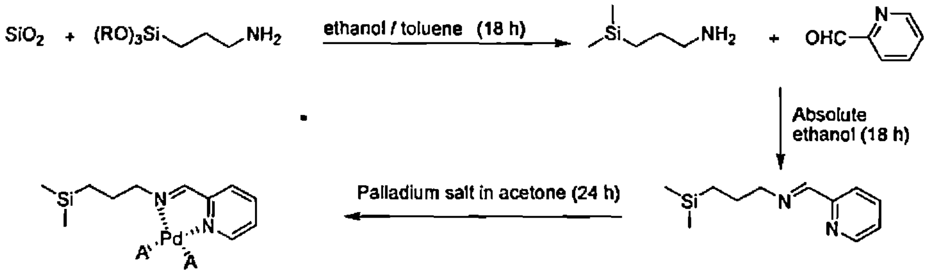
I.3.2.A: *Silica as a Support*

Silica, a neutral oxide, is totally hydroxylated and the hydroxyl layer covered with physically absorbed water.[88] Removal of water[89] at higher temperature results an amorphous porous[90] 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[91] 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)] (Scheme 29). 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 reaction and the catalyst can be reused in these reactions without noticeable loss of activity. Aminopropyltriethoxysilane modified silica were loaded with Pd nanoparticles by treating with $Pd(OAc)_2$ (Scheme 29). These catalysts worked well in Suzuki reaction of aryl bromides with arylboronic acids (K_3PO_4, toluene, 100 °C) when chelating diamines and triamines were used as organic modifiers.[91d] An optimal catalyst could be reused four times without a significant loss of activity, but the activity decreased in further runs. Suzuki coupling of less reactive aryl chlorides and bromides could be achieved with a Pd catalyst on mercaptopropyl-modified mesoporous silica (SBA-15-SH-Pd).[76g] It could be reused four times without any loss of catalytic activity.

Scheme 29



A = Aceate or chloride

Transition metal complex catalysis can be activated for the hydrogenation by tethering them to a silica-supported metal heterogeneous catalyst.[92] The combined homogeneous-heterogeneous catalyst consisting of tethered complex on a supported metal, TCSM (tetrahedral complex and supported metal), not only has the advantages of a conventional SiO_2-tethered complex catalyst but also functions by synergetic action of the two catalyst components (TCSM) in the catalytic reactions. For example rhodium isocyanide complex $RhCl[CN(CH_2)_3Si(OC_2H_5)_3]_3$ (Rh-CNR_3), when tethered on silica-supported palladium (Pd-SiO_2), gives the TCSM catalyst Rh-CNR_3/Pd-SiO_2, which is much more active for hydrogenation of arenes than the separate homogeneous Rh-CR_3 complex catalyst, the separate heterogeneous supported palladium catalyst, or the Rh-CNR_3 complex catalyst tethered on just SiO_2.[92a-b] A possible explanation for the high activities of the TCSM catalysts involves considering Pd-SiO_2 as the site where H_2 is dissociated and spills over onto the SiO_2. Silica is also the site of tethered complex which may bind and activate the arene substrate for reaction with the "spillover" hydrogen. It should be emphasized, however, that the mechanism for arene hydrogenation is not known and the other mechanisms[92c] must also be considered. Yang *et al.* [93] designed a TCSM catalyst, with the choice of two catalyst components, and employed it in reduction reaction. The rhodium complexes BF_4 (Rh(N-P)) and BF_4 (Rh(N-N)) were tethered on silica-supported palladium (Pd-SiO_2) to give the TCSM catalysts Rh(N-P)/Pd-SiO_2 and

$Rh(N\text{-}N)/Pd\text{-}SiO_2$. They used bipyridyl and pyridylphosphine chelating ligands that bind strongly to the metal ion, which significantly reduce leaching of metal.

I.3.2.B: Dendrimer as a Support

The word 'dendrimer' derive from the Greek word dendra, which refers to a tree. To put it in simpler terms, a dendrimer is polymer that branches. It is an artificially manufactured or synthesized molecule built up from branched units called monomers. Dendrimers are a novel class of three–dimensional nanoscale, core–shell structures having a variety of repeated units such as amides, amines, carbosilanes, siloxanes, esters, ethers, phenyl–acetylenes, various organometallics, amino acids that can be precisely synthesized for a wide range of applications. Several unique properties of DENs[94] make them attractive for catalytic applications.

- Solubility can be controlled principally by the chemical composition of the dendrimer periphery.[94b] This provides a means for carrying out reactions in green solvents such as water and supercritical CO_2.[94a–b]
- Particles are encapsulated within the dendrimer,[94] no additional ligands are required for stabilization.
- Small size of dendrimer means that they have a high surface–area–to–volume ratio, which is important for high efficiency.
- Catalytic groups placed at the core of a dendrimer allow controlling the microenvironment.

In addition, catalytic groups can be incorporated at the surface of a dendrimer. Catalytic groups at the surface are readily available for reaction, especially in larger dendrimers, which adopt a globular conformation with most terminal groups located at the surface. The loading on these systems is extremely high due to the inherent nature of dendrimer structures. The monometallic palladium DENs can be used as catalysts for hydrogenations,[95] Heck coupling,[96] Suzuki coupling[97] and Stille reaction.[65] These reactions are characterized by the coupling of an organostannane[98] derivative with a carbon electrophile in the presence of palladium(0).

There are many examples[99] of the use of peripherally fictionalized dendrimers in catalysis of reactions including the Kharash addition, hydrolysis, decarboxylation, Heck couplings, polyurethane formation, oxidation, (bromides and thiophenes), allylic alkylation, Stille couplings, Knoevenagel condensations, Michael–addition, nucleophilic addition, asymmetric hydrogenation, and so on.

I.3.2.C: Cyclodextrine as a Support

The catalysis of metal nanoparticles with diameters smaller than 5 nm is very attractive because of the large fraction of metal atoms that reside on their surfaces, thus affording very efficient use of the metal. However, to exhibit catalytic activity, metal surface sites must remain accessible to the substrate molecules. The surface modification of gold,[100] platinum,[101] and palladium[101] nanoparticles with cyclodextrin (CD) receptors,[102] (fig 1) which remain capable of binding appropriate solution guests. CD–capped platinum and palladium nanoparticles (diameter: 13–16 nm) were water soluble and exhibited catalytic activity for the hydrogenation of allylamine.[101] The water soluble palladium nanoparticles that covalently attach with CD behave as an active catalysts for the hydrogenation of alkenes in aqueous media.

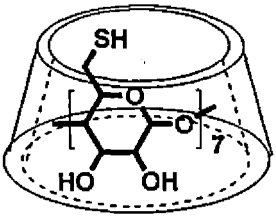
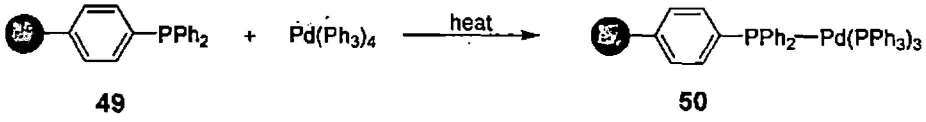


Figure 1: HS–β–CD

I.3.2.D: Polymer (Triphenylphosphine) as a Support

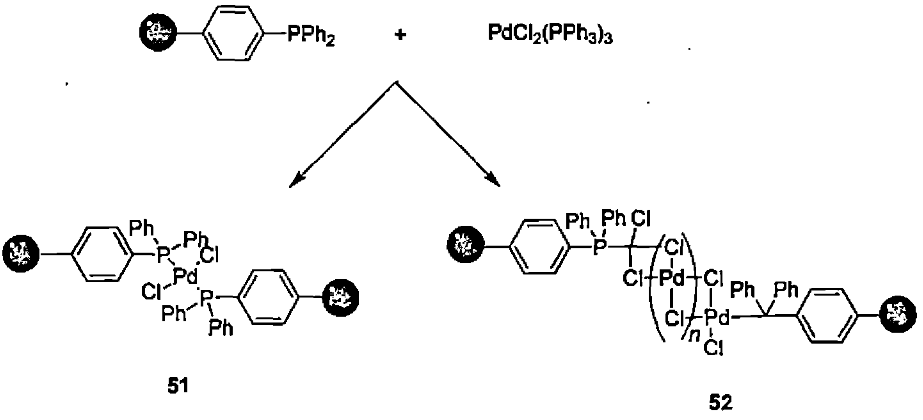
Triphenylphosphine, a common organophosphorus compound, is widely used in organic synthesis. Triphenylphosphine is a good coordinating ligand,[103] it binds well to most transition metals, especially those in the middle and late transition metal group 7 to 10. Polymer–supported triphenylphosphine **49** (PS–PPh_2; PS is polystyrene) has attracted much attention as a ligand for immobilization of metal complexes[7a,104] as it is the supported analogue of the ubiquitous simple tertiary phosphine ligand PPh_3. In 1976 Pittman *et al.*[105] first reported the preparation (Scheme 30) and use of the supported analogue **50** of the well–known palladium complex $Pd(PPh_3)_4$.

Scheme 30

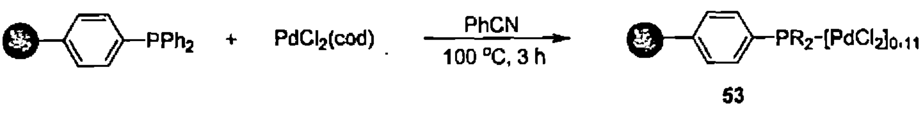


Hallberg and co-workers[106] have prepared supported analogues of $PdCl_2(PPh_3)_2$ from PS–PPh_2 and $PdCl_2$–$(PhCN)_2$ again by simple mixing of the two components (Scheme 31). They prepared supported complexes with Pd:P ratios of 1:1, 1:2, 1:3, and 1:4 and found that the bonding of the metal to the support changes with metal loading, complex **51** being formed at low metal loading and **52** at higher metal loading. Similar methodology was used by Miyaura and Inada[107] for the preparation of **53** (Scheme 32), this complex being shown to be highly active in cross–coupling reactions involving chloropyridines and activated aryl chlorides.

Scheme 31

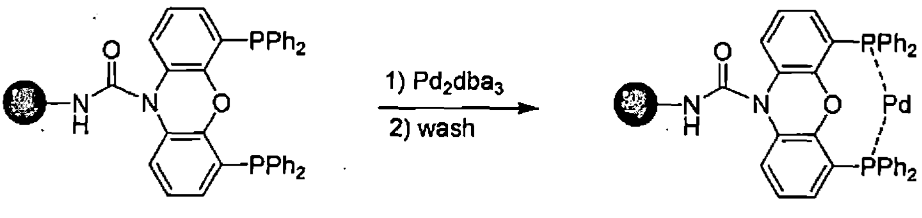


Scheme 32



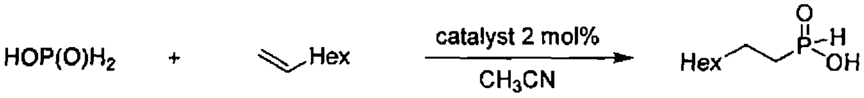
Deprêle *et al.*[108] designed a reusable polymer supported palladium catalyst for the preparation of H–phosphinic acids. The active catalyst, obtained by treating polymer supported nixantphos with Pd_2dba_3 and washing, (Scheme 33) was air–stable and did not require particular handling precautions. Water has a great role in hydrophosphinylation reaction because high amount of water suppress the reaction rate. As expected the P–C bond–forming reaction does not take place in the absence of ligand, and transfer hydrogenation occurs instead. But the supported catalyst **54** uniformly furnishes good yield and appears significantly more water–tolerant than its homogeneous counterpart (Scheme 34).

Scheme 33



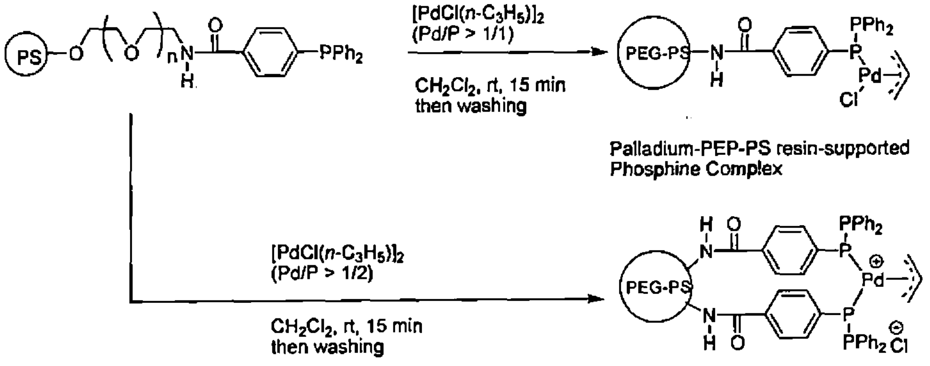
54

Scheme 34



Uozumi *et al.*[109] reported preparation of amphiphillic resin–supported triarylphosphine–palladium complexes bound to a poly(ethylene glycol)–polystyrene (PEG–PS) graft copolymers, which exhibit the high catalytic activity in allylic substitution reactions of allyl acetates with various neucleophiles in aqueous media under mild reaction conditions.[110] The PEG–PS resin–supported palladium–monophosphine complex Pd–PEP can be prepared by treatment of resin–supported phosphine[110a] with an excess amount of di(μ–chloro)*bis*(η^3–allyl)dipalladium(II) ([PdCl(η^3–C_3H_5)]$_2$) (Pd/P > 1/1) followed by the removal of unimmobilized ([PdCl(η^3–C_3H_5)]$_2$) by washing with chloroform (Scheme 35).

Scheme 35

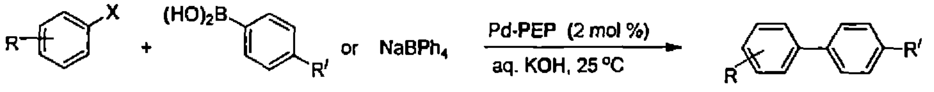


Palladium-PEP-PS resin-supported Phosphine Complex

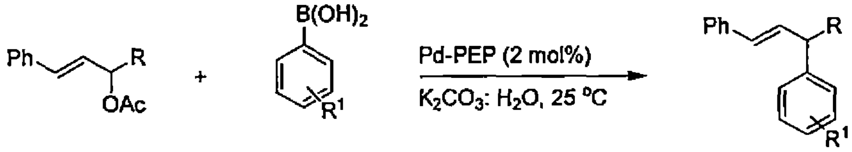
Pd-(PEP)$_2$

Resin–supported palladium–*bis*(triarylphosphine) complex[110a] [Pd–(PEP)$_2$] catalyzed the Suzuki coupling reaction with high yield of corresponding biphenyl product in water (Scheme 36). The cross coupling using water–soluble phosphine ligand, triphenylphosphinesulfonate sodium salt (TPPTS) showed lower catalytic activity.[111] Palladium–triphenylphosphine complex did not catalyze the reactions in water owing to its insolubility. The catalyst Pd–PEP is also active for the allylic arylation of cinnamyl acetate with phenyl boronic acid in aqueous medium (Scheme 37). The supported catalyst Pd–PEP showed much lower catalytic activity in organic solvent than in water.[109]

Scheme 36

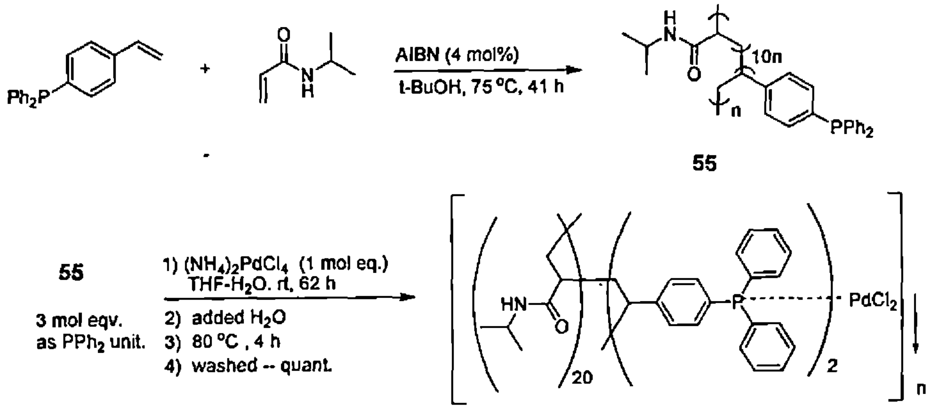


Scheme 37



Yamada *et al.*[112] introduced the self assembled process between non–cross–linked amphiphilic copolymer ligands and an inorganic species for the preparation of highly active, insoluble catalyst.[113] For example, a tungsten catalyst was formed from phosphotungstic acid and poly (N–isopropylacrylamide) with an ammonium salt.[113a] This catalyst used in ppm molar equivalent, brought about an efficient epoxidation of allylic alcohols. Since this self–assembled catalyst exhibits great potential Yamada *et al.* applied similar technique for the preparation of self–assembled palladium catalyst (Scheme 38).[112b]

Scheme 38

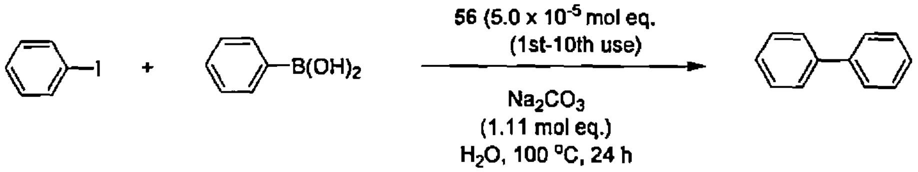


55

56

The complex **56** was so active that only (5×10^{-5}) mol equiv was sufficient to catalyze the Suzuki–Miyaura coupling between iodobenzene and phenylboronic acid under the organic solvent free conditions (Scheme 39). The reaction proceeded efficiently to give biphenyl up to 95%. The catalyst was recovered after reaction and reused up to 10 times without loss of its activity.

Scheme 39

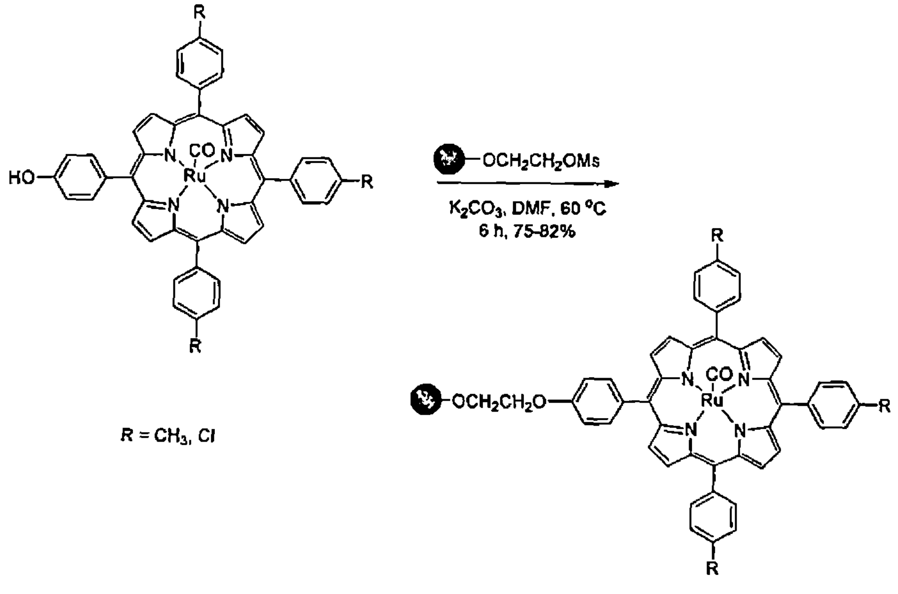


Entry	catalyst	yield
1	1st use	95%
2	10 th use	93%
3	1st-10th consecutive use	av: 95%

I.3.2.E: Supported Ruthenium Catalyst

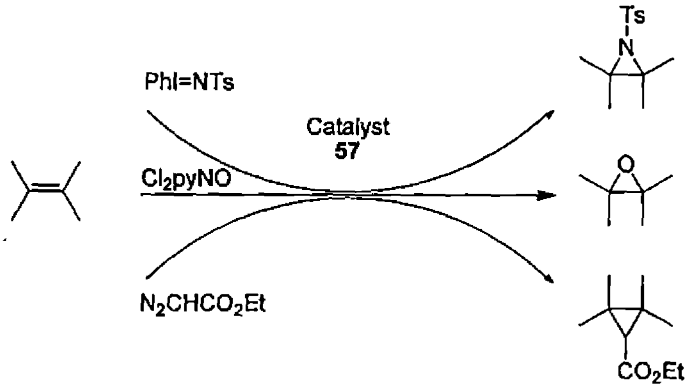
There is a growing interest in developing ruthenium porphyrin catalysts for carbon–oxygen,[114] carbon–nitrogen,[115] and carbon–carbon[116] bond–forming reactions. Extensive studies have demonstrated that ruthenium porphyrins exhibit high stability and remarkable selectivity in catalyzing organic oxidations by 2,6–dichloropyridine N–oxide and cyclopropanation of alkenes by diazo compounds. However, the catalytic reactions proceed in homogeneous media, rendering recycling of the ruthenium catalyst. Ruthenium complexes anchored with insoluble polymer supports[117] results heterogeneous catalyst that suffers from limited mobility. Zhang *et al.*[118] prepared soluble polymer–supported ruthenium porphyrin catalysts by treatment of ruthenium porphyrins with methoxypoly(ethylene glycol) (Scheme 40). Catalyst **57** exhibits high reactivity, selectivity, and stability in epoxidation and cyclopropanation of alkenes (Scheme 41).

Scheme 40



57

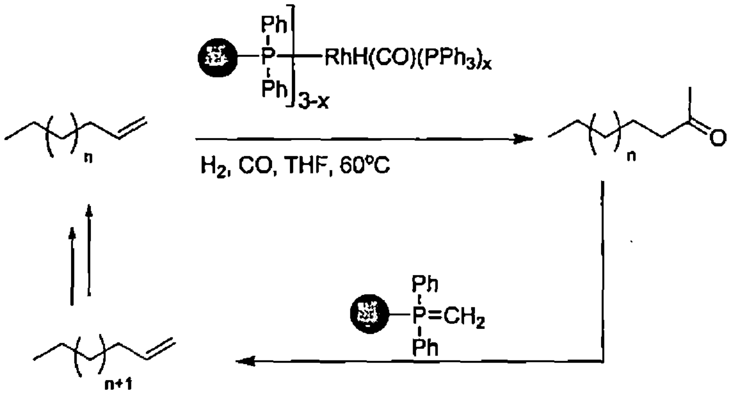
Scheme 41



I.3.2.F.1: Supported Rhodium Catalyst: Homologation of Alkenes

Regen *et al.*[119] reported a chain homologation of alkenes with polymer–supported rhodium catalyst (Scheme 42). In this strategy, a polystyrene supported rhodium catalyst effects a hydroformylation of the alkene with synthesis gas to generate aliphatic aldehydes. These then react with a polystyrene–supported Witting reagent to produce two carbon homologated alkenes which can then re–enter the reaction cycle. Advantages of this strategy include milder reaction conditions and less complex mixture than traditional alkene homologation methods.

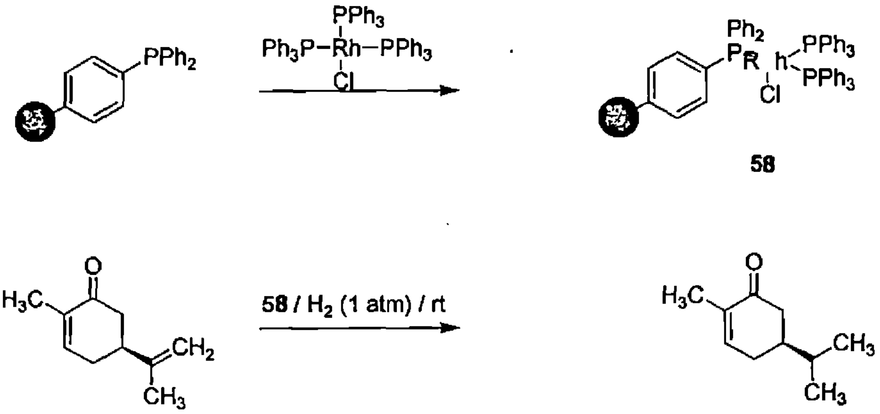
Scheme 42



I.3.2.F.2: Hydrogenation of Terminal Alkenes or Alkynes

Polymer–supported rhodium catalyst[120] on ROMPgel was developed by Barrett *et al.*[121] The ROMPgel–supported triphenylphosphine rhodium(I) chloride catalyst **58** was prepared from a triphenylphosphine ligand supported on ROMPgel (Scheme 43). The immobilized catalyst **58** has been successfully employed for selective hydrogenation of a range of terminal alkenes and alkynes in the presence of more hindered alkenes (Scheme 43). The hydrogenated products were isolated in their pure forms by filtration of the supported catalyst.

Scheme 43



I.3.3: Microencapsulation of Catalyst

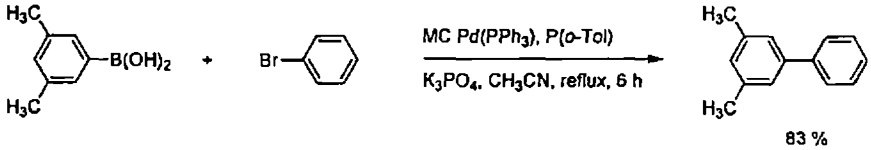
Microencapsulation is a process for entrapping materials within a shell or coating, which is typically polymeric in nature. Microcapsules of polymer-coated catalyst are formed upon cooling a homogeneous solution of the catalyst and a polymer or copolymer. This technique was exploited in the preparation of polystyrene-coacervated OsO_4,[122] $Pd(Ph_3)_4$,[123] and $Sc(OTf)_3$.[124] More recently, Kobayashi and co-workers have further developed this technique by building reactive oxirane functionality into the copolymer.[125] In this case, following coacervation of the homogeneous catalyst, the copolymer can be cross-linked thermally to form more chemically resistant cross-linked microcapsules. This technique has been exploited to form so-called "polymer-incarcerated" homogeneous $Pd(Ph_3)_4$ catalysts.[125] Various other methods and materials have been described in the literature for entrapping homogeneous metal complexes and metal nanoclusters including sol-gel materials,[126] dendrimers,[96a] and polyoxyalkylene resins.[127] The permeability and size of the microcapsules, and the coordinating properties of the matrix can be tuned by selecting the type of wall-forming oligomer or monomer, type and quantity of porogenic (i.e., organic) solvent, agitation conditions, chain extenders, and other additives. The polyurea matrix was selected, because of its ability to ligate transition-metal salts, which was considered important for both efficient microencapsulation and subsequent retainment of the metal within the matrix when used as a catalyst.[11b] It was also considered that the polyurea matrix would be relatively inert to chemical modification and give a physically robust material. Microencapsulation is widely practiced industrially and has found use in such diverse applications as drug delivery systems,[128] radiation therapies,[129] cell entrapment,[130] and the controlled release of pesticides.[131]

I.3.3.A: *Microencapsulated Palladium*

I.3.3.A.1: *Suzuki Coupling*

Kobayashi *et al.*[123] have reported the use of microencapsulated (MC) $Pd(PPh_3)_4$ for catalysis of both Suzuki coupling reaction (Scheme 44). The catalyst was prepared by the addition of $Pd(PPh_3)_4$ to a cyclohexane solution of linear PS (Mw ca. 280 000) at 40 °C followed by cooling to 0 °C. After addition of hexane to harden the polymer capsule the MC catalyst was collected by filtration. Best results were achieved using 20 mol% of catalyst and 20 mol% of PPh_3 as an external ligand.

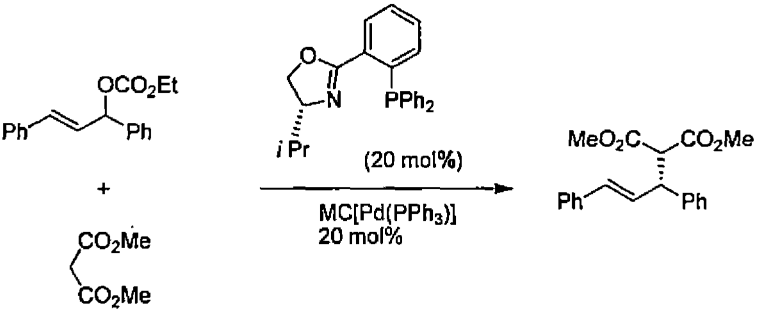
Scheme 44



I.3.3.A.2: Asymmetric Allylation Reaction

Asymmetric allylation was also carried out using MC Pd (prepared from $Pd(PPh_3)_4$) and a soluble chiral ligand (Scheme 45).[123] The reaction was found to proceed in good yield with an *ee* (83%).

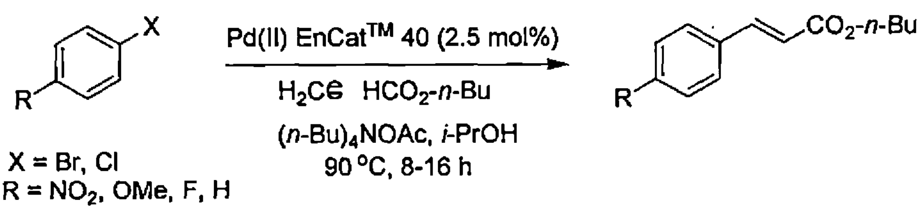
Scheme 45



I.3.3.A.3: The Heck Coupling

Pd(II) EnCat™ [132] has been effectively utilized in a series of Heck couplings in conventional organic solvents and in $scCO_2$ (Scheme 46).[133] With $(n\text{-Bu})_4NOAc$, a series of unsaturated esters were produced in high yields (with the exception of the reaction with 4-bromoanisole) without the addition of phosphine ligands. It was noted that the yields were generally higher in $scCO_2$ even at a lower catalyst loading.

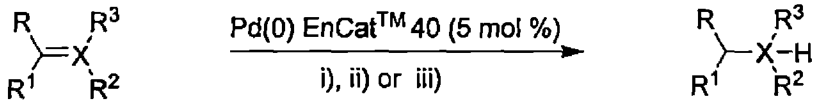
Scheme 46



I.3.3.A.4: Hydrogenation

The reduction of Pd(II) EnCat™ 40 with hydrogen produces Pd(0) EnCat™ 40, which is an effective catalyst for the selective hydrogenation of unsaturated bonds in alkenes, alkynes, imines, and nitro groups (Scheme 47).[132] Recovery of the catalyst is simple compared to that of palladium-on-carbon, levels of metal contamination in the crude products are extremely low, and the catalyst can be readily recycled. All of the initial hydrogenations reported were carried out with Pd(0) EnCat™ 40 pre-reduced under hydrogen (50 bar) for two days. It was found that this prereduction of Pd(II) EnCat™ 40 was necessary for high activity and reduced reaction times. The hydrogenations were carried out under a hydrogen atmosphere either in an autoclave or maintained by a hydrogen-filled balloon.

Scheme 47



conversion ~ 100%

R, R^1, R^2, R^3 = H, alkyl, aryl,
X = C, N

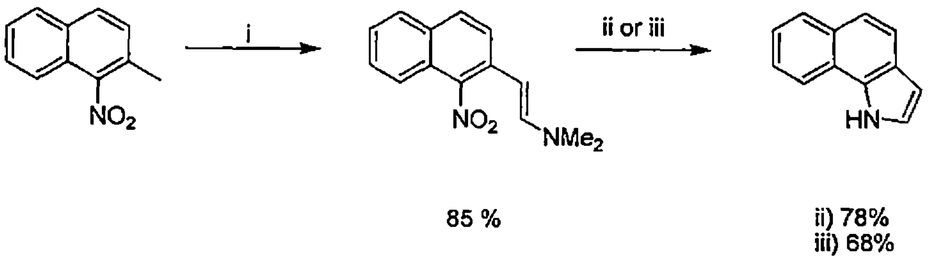
i) H_2 (balloon), EtOH, rt, 2-60 h
ii) H_2 (balloon), EtOH-MeCN (1:1), 60 °C, 3-5 h
iii) H_2 (50 bar), EtOH, rt, 18 h

I.3.3.A.5: Catalytic Transfer Hydrogenation (CTH)

I.3.3.A.5.1: Reduction of the Aryl Nitro Group

Pd(0) EnCat™ 40NP has been employed in the reductive cyclization of various Leimgruber–Batcho-derived enamines to form the corresponding indoles (Scheme 48).[134] Hydrogenation of the aryl nitro group was carried out under transfer-hydrogenation conditions to give the indole in high yield. The catalyst was recycled without noticeable loss in activity, and the reaction was accelerated by microwave irradiation at 120 °C. Thus, the combination of microwave-accelerated enamine formation and the use of a recyclable, easily removed catalyst for the reductive cyclization in the Leimgruber–Batcho reaction provide an industrially attractive route to indoles.

Scheme 48

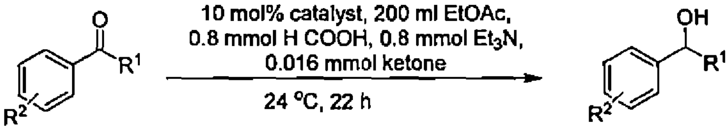


i) CuI or Yb(OTf)$_3$, DMF, µw, 180 °C, 4.5 h
ii) Pd(0) EnCat^{TM} 40NP (6 mol%), EtOAc, HCO_2H, Et_3N, 24 °C, 24 h
iii) Pd(0) EnCat^{TM} 40NP (6 mol%), EtOAc, HCO_2H, Et_3N, µw, 120 °C, 2 h

I.3.3.A.5.2: Reduction of *Aryl* Ketones

Palladium (II) acetate, microencapsulated in polyurea [PdEn–Cat™], acts as an efficient recyclable catalyst for a number of key transformations.[11b,135] Polyurea–encapsulated Pd(0) [Pd^{0}EnCat] in combination with formic acid is highly active for CTH of aryl ketones and nitro groups.[136] The [Pd^{0}EnCat] not only exhibits high reactivity but also resists leaching of palladium. At the same time, the catalyst has been proven to be highly chemoselective in the reduction of carbonyl and nitro groups. The catalyst can be recyclable up to five times without loss of its activity.

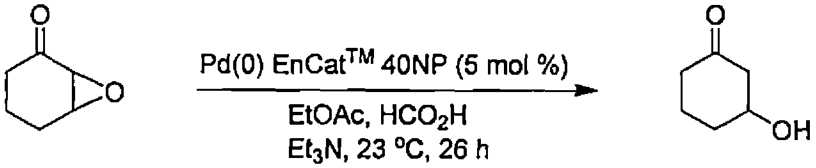
Scheme 49



I.3.3.A.5.3: Reductive Ring Opening of Epoxides

The reductive ring opening of epoxides by hydrogenolysis in the presence of Pd(0) EnCat™ 40NP has been investigated.[137] For example, the hydrogenolysis of *trans*-stilbene oxide gave the alcohol in 99% isolated yield after 5 h. Over-reduction of the alcoholic C–O bond was not observed at a detectable level even after prolonged reaction times. This illustrates the clear advantage of Pd(0) EnCat™ 40NP over Pd/C in terms of chemoselectivity. Under identical conditions, 10% Pd/C gave the desired secondary alcohol in 80% yield from *trans*-stilbene oxide and in only 48% yield from methylstyrene oxide.[138] In these Pd(0) EnCat™ 40NP reductions, the catalyst was recovered by simple filtration and reused without loss of activity. In the case of *trans*-stilbene oxide, the catalyst was recycled through 10 successive hydrogenolysis reactions and, in each case, gave high isolated yields (96–99%) of the corresponding benzylic alcohol. Moreover, the level of palladium in the reaction medium following filtration of the catalyst was below the detection limit (5 ppm) of ICP analysis.[137]

Scheme 50

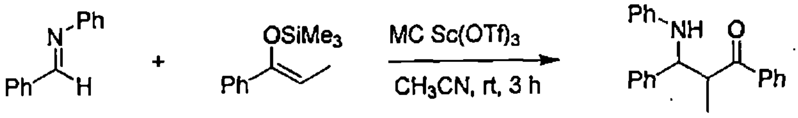


I.3.3.B: *Microencapsulated Sc(OTf)₃*

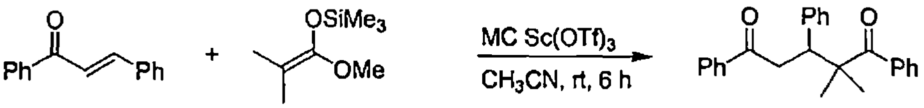
Lewis acid catalyzed reactions are of great current interest because of the unique reactivities and selectivities that can be achieved as well as for the mild conditions used.[139] Kobayashi developed polymer–supported scandium Lewis acids based on Nafion[140] and a polyacryronitrile derivative;[141] however, their reactivity was lower than for the monomeric Lewis acids. To overcome that problem they planned to utilize the polymer–supported Lewis acid, (microencapsulated Lewis acid), which is readily prepared, having higher activity than the monomeric Lewis acid, is recoverable and reusable, for many synthetic reactions. They have used MC $Sc(OTf)_3$ in several fundamental and important Lewis acid–catalyzed carbon–carbon bond–forming reactions. It was found that MC $Sc(OTf)_3$ effectively activated aldimines. Imino aldol[142] (Scheme 46) aza Diels–Alder,[142,143] cyanation,[144] and allylation[145] reactions of aldimines proceeded smoothly using MC $Sc(OTf)_3$ to afford respectively the synthetically useful *β*–amino ester, tetrahydro–quinoline, α–aminonitrile, and homoallylic amine derivatives in high yields. At the same time MC $Sc(OTf)_3$ also effectively catalyzed the Aldol and Friedel-Crafts acylation reaction (Scheme 51).[142b]

Scheme 51

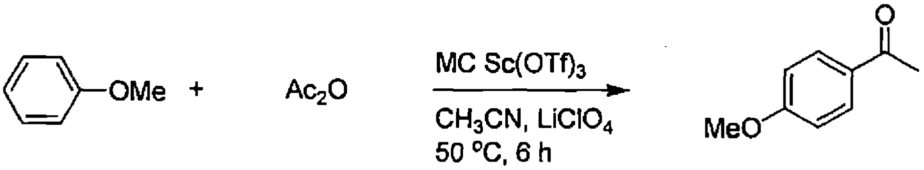
Imino Aldol Reaction



Aldol Reaction



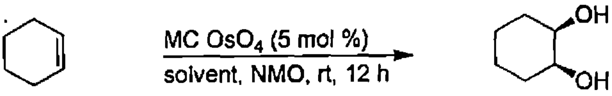
Friedel-Crafts Acylation



I.3.3.C: *Microencapsulated Osmium Tetraoxide*

Osmium tetraoxide (OsO_4) is the most reliable reagent for the dihydroxylation of olefins to give the corresponding diols.[146] The reaction proceeds in the presence of catalytic amount of OsO_4 using a co–oxidant such as hydrogen peroxide, *tert*–butylhydroperoxide, N–methylmorpholine N–oxide (NMO). Although a number of processes have gained wide acceptance in this dihydroxylation, few fruitful industrial applications have been accomplished, probably because OsO_4 is highly toxic, expensive, and volatile and can not be recovered. Kobayashi *et al.*[147] reported microencapsulated osmium tetraoxide, on polystyrene resin, that can be recovered and reused and that is effective in dihydroxylation of olefins (Scheme 52). The osmium tetraoxide immobilized onto a polymer on the basis of physical envelopment by the polymer and on electron interactions between the π electrons of the benzene rings of the polystyrene–based polymer and a vacant orbital of the Lewis acid.

Scheme 52



I.3.4: Ionic Binding of Catalyst

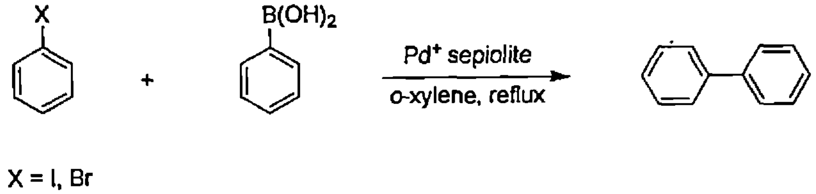
Various ways are known for ionic binding between a solid phase and a metal (either as metal or in its cationic form), a brief account of which is delineated below.

I.3.4.A: Sepiolite as a Support

Sepiolite is an abundant fibrous talc–like mineral of $Si_{12}Mg_8\,(OH)_4O_{30}.8H_2O$ formula whose structure is formed by an array of parallel channels, consisting of a double layer of SiO_4 tetrahedra sandwiching an internal octahedral sheet of MgO_6 layer.[148] Sepiolites have typically a surface area around 200 m^2/g that together with the availability of this mineral at robustness of its structure makes them suitable materials as supports in heterogeneous catalysis.[149] The Mg^{2+} ion, located at the edges, can easily be replaced with Na^+ ion on treatment with sodium hydroxide. To the neutral or alkali–exchanged sepiolites, $PdCl_2$ was added following the incipient wetness procedure. This Pd^{2+} exchanged sepiolites are highly efficient and reusable catalyst for Suzuki reaction[150] upon addition of external base. The alkali metal exchange sepiolites behave as solid bases having similar strength as acetate or carbonate. Corma *et al.*[151] designed a bi–functional catalyst where the sepiolite not only plays a passive role as support, but also an active role providing the basic sites necessary in the catalysis of both Suzuki and Heck reaction (Scheme 53 & 54). The activity of alkali sepiolite decreases significantly going from $PdCl_2$–NaSep to $PdCl_2$–Ksep or $PdCl_2$–CsSep. The activity of this sepiolite decreases on recycling due to the deactivation of the novel metal or due to the consumption of the basic sites. The most likely rationalization of the loss of activity would be a depletion of the sepiolite basic framework by the HX acid formed during reaction. The sepiolite can reactivate in part by flowing water steam to assist desroption of halogen acid. $PdCl_2$ supported on neutral sepiolites exhibit excellent balance for the Heck and Suzuki reaction but it cannot be reactivated.

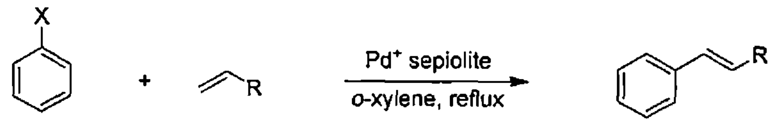
Scheme53

Suzuki Coupling



Scheme 54

Heck Coupling



X = I, Br

I.3.4.B: **Zeolites as a Support**

Zeolites are microporous crystalline solids with well–defined structures. Generally, they contain silicon, aluminium and oxygen in their framework, cations, water and/or other molecules within their pores. Zeolites have the ability to act as catalysts for chemical reactions that take place within the internal cavities. Zeolites are often known as a shape–selective catalyst due to their unique micro porous nature, where the shape and size of a particular pore system exerts a steric influence on the reaction, controlling the access of reactants and products.

As zeolites have ion–exchange properties, different metal ion can easily be introduced into it. The heterogeneous palladium catalyst can be prepared by introducing palladium into zeloites. Djakovitch *et al.*[75d] have prepared several "palladium" exchanged zeolites by immobilization of different palladium species: palladium particles [Pd(0)], ionic species ([Pd(II)] and $[Pd(NH_3)_4]^{2+}$) and the neutral complexes $[(Pd(OAc)_2]$ and $[Pd(C_3H_5)Cl]_2)$. The catalysts loaded with [Pd(0)], [Pd(II)],and $[Pd(NH_3)_4]^{2+}$ were prepared by ion exchange of Na–Y zeolites. Michalik *et al.*[152] used Na–Y zeolites for loading the palladium. Firstly they exchanged with $CaCl_2$ and prepared Ca–Y zeolites. After that palladium was introduced into the zeolites as $[Pd(NH_3)_4]^{2+}$ by ion exchange with two different amounts of 0.01 M palladium tetra amine chloride solution at room temperature. After a period of 24 h, $[Pd(NH_3)_4]^{2+}$–NaY was obtained. These immobilized palladium catalyst was successfully used for Heck coupling reaction in the presence of extrinsic base and after reaction the catalyst was recovered and reused for several run without significant loss of activity. Leaching of palladium catalyst depends on the nature of solvent. No palladium leaching[153] is observed when toluene is used as a solvent. However the use of extrinsic base could be avoided, by introducing basicity in the zeolite framework through alkali metal ion exchange.[154] Corma *et al.*[155] have prepared three different basic zeolites containing palladium. This bi–functional catalyst, containing noble metal and basic sites, are active for Heck coupling[156] and Suzuki coupling[157] reaction. The solid catalyst reused after washing with water and a minor decrease in the catalytic activity was observed. Pd(II)–NaY zeolite or Pd(0)–NaY zeolite performed very well in Suzuki reactions of aryl bromides without the addition of a ligand.[158] The catalysts exhibited excellent activity with K_2CO_3 or Na_2CO_3 as base at room temperature allowing high yields to be achieved after short reaction times. As a further way to solid–supported palladium catalysts, the complexes $PdCl_2[Ph_2P(CH_2)_4SO_3Na]$ or K were directly loaded to alkylsulfonated mesoporous supports. The resulting heterogeneous catalyst, was applied to the Suzuki coupling of 4–iodoanisole with phenylboronic acid, also showed an enhanced activity on recycling.[159]

I.3.4.C: Hydrotalcite as a Support

Hydrotalcite (HT) is a synthetic aluminium–magnesium–hydroxycarbonate. It just likes anionic clays[160] having the general formula $[M^{(II)}\ (1–x),\ M^{(III)}\ x(OH)_2]^{x+}\ [(A^{n–})x/n\ yH_2O]^{x–}$ where $x = 0.1–0.33$, $M^{(II)}$ = Mg, Cu, Ni, Co and Mn; $M^{(III)}$ = Al, Fe, Cr, and Ga; $A^{n–}$ is an interlayer anion such as $CO_3^{2–}$, $NO_3^–$ and $SO_4^{2–}$. Hydrotalcite can also be used for the preparation of supported catalyst.[160a,161] Palladium(II) supported hydrotalcite[160c] and related Ni–Al hydrotalcite[160d] have been used in the oxidation of alcohols using molecular oxygen. Bennur *et al.*[162] synthesized palladium containing Mg–Al hydrotalcites[163] from soluble salts of the metals (palladium acetate) in the required atomic ratios by co–precipitation in a solution containing a slight excess of Na_2CO_3 along with NaOH at pH 10.[164] After precipitation the precipitate was washed repeatedly with water till the filtrate was neutral to litmus then dried and directly used for Heck coupling reaction.

I.3.4.D: Metal hydroxide

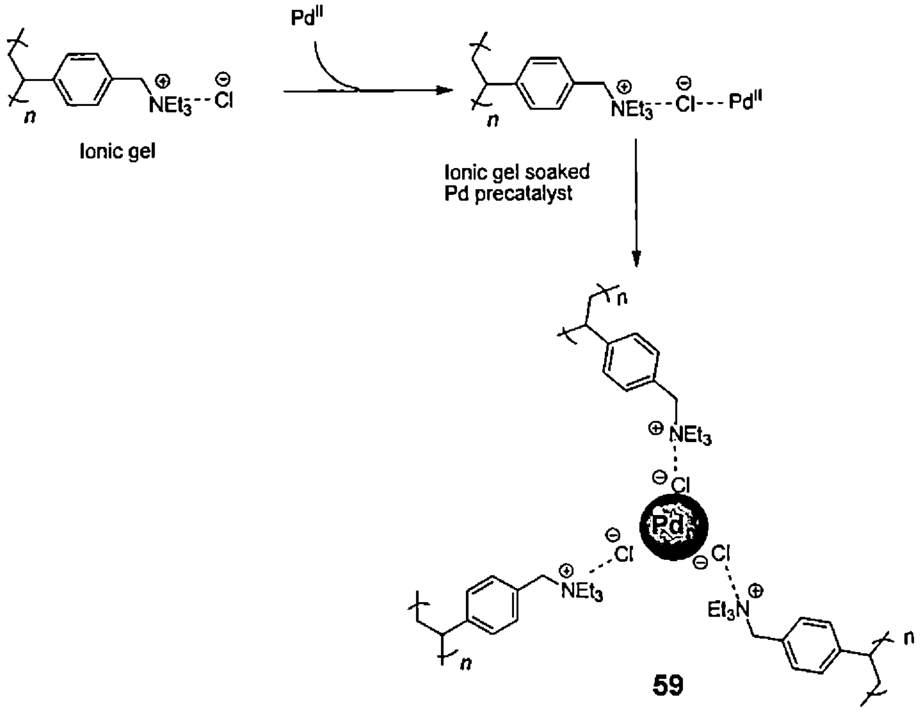
The development of phosphine free new recyclable heterogeneous catalyst is highly desirable catalytic system to dispense the use of expensive and air–sensitive basic phosphines for palladium catalyzed coupling reactions. Choudary *et al.*[165] reported, Mg–Al layered double hydroxides (LDH) and the Merrifiled resin as a surface to anchor the nano palladium(0) catalyst. It not only stabilized the nano palladium particles but also provided the adequate electron density to the anchored palladium(0) species to facilitate the oxidative addition.

LDHs have recently received much attention in view of their potential usefulness as materials,[166] anion exchangers, and more importantly as catalyst. [160d-e,167] The LDHs consist of alternating cationic $M(II)_{1-x}$ $M(III)_x(OH)_2^{x+}$and anionic A^{n-} zH_2O layers.[168] The positively charged layers contain edge–shared metal (II) and metal (III) hydroxide octahedral, with charges neutralized by anions located in the interlayer spacing or at the edges of the lamellae. Tetrachloropalladate $(PdCl_4)^{2-}$ was exchanged onto chloride saturated LDH [composition $Mg(1-x)Alx(OH)_2$ $(Cl)_x.zH_2O$] to obtain a dark brown colored LDH–Pd(II). The supported palladium salts were then reduced with hydrazine hydrate, giving an air stable black powder of nano palladium catalyst which catalyzed various coupling reactions such as Heck, Suzuki, Sonogashira and Stille affording excellent yields.

I.3.4.E: Polyionic Gel as a Support

Ionic liquids attracted great attention as alternative reaction media in organic synthesis because it is highly polar which often increase the reaction rate and the product selectivity.[169] To benefit such reactivity advantages offered by the polar ionic environments without suffering from the drawbacks, Thiot *et al.*[86d] investigated the insoluble polyionic gel beads, which constitute a highly polar microenvironment, suitable for both efficient metal scavenging and active heterogeneous catalyst preparation. Palladium and rhodium metals are efficiently soaked onto the polar microenvironment of polyionic gel beads due to strong non–covalent interactions between metal and ions within the polyionic gel (Scheme 55).[86d] The resulting palladium soaked polyionic gel **59** act as an efficient heterogeneous recyclable catalyst for Suzuki coupling (Scheme 56).[86d]

Scheme 55



Ionic gel stabilized Pd nanoparticle

Scheme 56