CHAPTER II

SOLID PHASE ORGANIC SYNTHESIS - AN OVERVIEW

II.A. INTRODUCTION

Solid phase synthesis is a methodology whereby synthetic transformations are conducted with one of the reactant molecules attached to an insoluble material referred to as the solid support. It was originally developed for peptide synthesis. Since the recent impact of combinatorial chemistry, solid phase techniques have been applied more generally to organic synthesis. One of the requirements of solid phase chemistry is a linker to attach a substrate molecule to the solid phase. As synthesis proceeds, this material is transformed to the product, which can be finally removed by cleavage of the linker.

Merrifield first used the term ‘solid phase peptide synthesis’ in 1963 to describe the synthesis of a tetrapeptide on a polymer, which remained insoluble throughout the synthesis. Although the expression ‘Solid phase synthesis’ was used by Merrifield, it is not an accurate description. The synthesis of peptides does not occur on the surface of a truly solid material, but instead within gel-like matrix of connected polymeric molecules swollen by solvent molecules. In fact, the peptide was synthesized on a highly fluid and solution like environment. The development of this strategy of solid-phase organic synthesis (SPOS) was initially spurred by the facilitated product purification; the reaction products remained bound to an insoluble resin and reagent excesses were simply removed by repeated rinsing. An insoluble resin, most often crosslinked polystyrene (PS) was functionalised with a linker moiety carrying a functional group to which the substrate was connected. A reaction or sequence of reactions was carried out to convert the supported substrate into the supported product and excess reagents were washed away after each step. Finally,
selective cleavage yielded pure product in solution and the insoluble support, which was recycled for further use. The original method of Merrifield's dipeptide synthesis on a polymer support has since been extended basically to every type of reaction in organic chemistry, including polypeptide, polysaccharide, and polynucleotide synthesis. Because supported synthesis is very amenable to automation, it has become an important synthetic method.

II.B. SOLID PHASE ORGANIC SYNTHESIS - CONCEPTUAL FEATURES

The potential exploitation of polymer supported species in chemical process has attracted considerable industrial interest and in recent years, commercialisation of a number of systems has been achieved and these species are regarded as 'high value polymers'.

A number of authoritative text books covering the detailed science of this area has already been published.41-46 Immobilization of a reactive species on a support provide a number of important advantages like 'macroscopic handle for separation and purification, retention of precious species, 'encapsulation' of corrosive, noxious or toxic species, stabilization of reactive species carrying out chemical synthesis which reduces side reactions and enhances selectivity with considerable reactivity.

The massive increase in the number of papers describing the use of polymeric supports in organic synthesis over the past decade is a vivid demonstration of its impact in the chemical community. The advantages gained by this methodology are striking with four main factors. The ease of chemistry is the main factor – reactions can be carried out in three steps: addition of reagents, filtering and washing of the resin. Second factor is elimination of purification in each step. For each step of a multi-step synthesis, the only purification needed is a resin-washing step. Only the final product of cleavage needs to be purified. The third aspect is that, in a solid phase synthesis, high concentration of the reagents can be used to drive the reaction to completion.

Solid phase synthesis of small organic molecules has received renewed attention since the first
report of the polymer supported synthesis of compounds of therapeutic interest. Solid phase synthesis is now a key component of the high-throughput synthesis and screening approach to drug discovery,\(^47\) the technique of utilizing insoluble polymeric supports for carrying out organic chemical transformation has achieved wide spread acceptance as evidenced by the appearance of a large number of research papers, reviews, monographs and books.\(^{20,21,48-60}\) Now the technique finds application in almost all areas of chemistry, including biology and medicine. The recent rapid growth in the number of organic transformations that have been successfully demonstrated on solid supports has involved both the use of the established amine, halide, hydroxyl supports developed originally for peptide synthesis, and the design and synthesis of new supports to permit the anchoring and releasing of other functional groups. Developments have been made in the relevant fields, which include polymer coated electrodes,\(^61\) field effect transistors,\(^62\) chemical sensors\(^63\) and solar energy applications\(^64\).

Recent advances in polymer-supported solid phase synthesis have opened up an entirely new strategy in the field of research, both for biological and chemical applications. The success of solid phase synthesis of polypeptides have stimulated efforts to apply this method in other biochemical and organic synthesis. The selective conversion of one functional group in a molecule having two or more functional groups by covalently binding the molecule to a polymer support is another important advantage of solid phase synthesis. Attachment of the enolisable ester to a polymer support at low loading levels allows the alkylation and acylation reaction to be performed without intermolecular condensation which otherwise happens.\(^65\)

A critical review of the existing literature that covers the various features of solid phase synthesis has been attempted to be included in this section. The aim is not to enlist all the polymer-supported organic reactions, but to consider the polymer supported reactions, which has relevance to the present study.
II.B1. Types of Supports

A large number of organic and inorganic materials have been investigated as support matrices. The prime requirement of a polymeric material to be used as a support for carrying out organic synthetic transformations is the easiness of chemical modification to incorporate specific reagent functions. The ease of chemical modification of a resin and its application as a reagent or a catalyst can depend substantially on the physical properties of the resin itself. Functionalised polymeric supports must possess a structure which permits adequate diffusion of reagents into the reactive sites which in turn is dependent on the extent of swelling or solvation, the effective pore size and pore volume and the chemical and mechanical stability of the resins under the conditions of a particular chemical reaction or reaction sequence. Polymer supports used for organic synthesis are of two types, passive and active supports. In passive supports, the macromolecular matrix acts as a carrier on which the synthesis of the desired substance is carried out and finally cleaved from the support. Active supports effects a synthetic or catalytic transformation on a soluble substrate. This group includes polymeric reagents in which the active site is consumed during the reaction and polymer supported catalysts in which the reactive site catalyses a number of chemical reactions.\textsuperscript{31,43,66,67}

The use of solid supports in organic synthesis relies on three inter connected requirements:-

i. A crosslinked, insoluble, but solvent swellable polymeric material that is inert to the conditions of synthesis.

ii. Some means of linking the substrate to this solid phase that permits selective cleavage of the product from the solid support.

iii. A successful synthetic procedure compatible with the linker and the solid phase.

The proper choice of a polymer support, which acts as a carrier for attaching functional groups, depends very much on the nature of the application. A polymeric support not only binds
the reactive species, but also plays a decisive role in determining the reactivity of attached species. Therefore, a number of factors should be considered in choosing a polymer as a support; their availability and cost, mechanical, thermal and chemical stability, porosity and compatibility with reagents and solvents etc. Usually, commercially available inexpensive polymers are preferable to more expensive polymers, which must be specially synthesized. The support polymer must be thermally and chemically inert under the conditions required for its functionalisation and subsequent use. Heterogeneous supports are more advantageous than homogeneous ones and this requires the support to possess an appreciable degree of crosslinking. Although a variety of inorganic\textsuperscript{68,69} and organic\textsuperscript{70,71} polymeric matrices have been used as supports in polymer supported chemistry, the most widely used one is polystyrene matrix.

II.B.1.a. INORGANIC SUPPORTS

Inorganic polymers such as silica\textsuperscript{72} and molecular sieves\textsuperscript{73} have been used as supports in solid phase organic synthesis. They have hydroxyl groups on the surface that can be used as the centre for attaching functional groups. Inorganic oxides, molecular sieves (zeolites) and glasses have been employed widely in large scale applications. Modified silica, unlike synthetic polymers, is rigid and not susceptible to swelling. Physical adsorption of reagents and catalysts on inorganic supports, by hydrogen bonding between oxygen functions of the support surface and polar groups on the reagent or catalysts, have been used in many heterogeneous synthetic reactions.\textsuperscript{74}

II.B.1.b. ORGANIC SUPPORTS

The Organic matrices used as supports may be natural or synthetic polymers. Among the naturally occurring polymers, cellulose finds wide application.\textsuperscript{75} Wegscheider,\textsuperscript{76} Knapp and Lieser\textsuperscript{77} have reviewed the chemistry of cellulose as a polymeric support for use in the pre-concentration of trace elements. Chitin, (N-acetyl D-glucosamine) is yet another naturally
occurring marine polymer used as a support. Its acetylated derivative, chitosan finds application in removing heavy metal ions from discharge water.

Earlier organic supports experimented were those of polysaccharides prepared from cellulose, agrarose and sepharose. Some of these supports have been functionalised and used widely in applications such as affinity chromatography, enzyme immobilization and ion exchangers. These were rejected later due to synthetic inconvenience associated with them. Synthetic polymer supports fall into two classes, condensation and addition polymers. Condensation polymers are high molecular weight structures usually formed by the combination of small polyfunctional monomers through the removal of simple molecules such as water, ammonia, alcohol, etc. Addition polymers are formed by free radical polymerisation of mixtures of olefinic and diolefinic compounds.

II.B. b(i). Polystyrene Resin

The resin bead first used by Merrifield, and still widely used today, is a gel type polymer made from crosslinked polystyrene because of its comparatively low cost, easy availability, mechanical strength, chemical inertness and ease of functionalisation. Crosslinked polystyrene beads can be obtained by polymerisation of styrene with crosslinking agent divinyl benzene in the presence of benzoyl peroxide.

During the polymerisation process, around 1% divinyl benzene is added to the styrene to link the polystyrene chains together. This degree of crosslinking is sufficient, by holding the chains together, to give mechanical strength and insolubility – the resin bead is essentially one gigantic macromolecule – but not so much crosslinking as to prevent the swelling of the bead when immersed in solvent or as the organic compounds grow on the polymer. Indeed, swelling is an essential feature of gel resins, as it reflects an internal flexibility of polymer backbone that can maximize the available functionality as well as permitting free diffusion of solvents and reagents.
into the bead. Although used for a wide range of chemistry, the polystyrene clearly has limitations if used for highly electrophilic reagents, and the thermal stability of the resin limits reaction conditions to below 130° C, Scheme II.1.

\[
\begin{align*}
\text{CH}_2=\text{CH}_2 + \text{CH}_2\equiv \text{CH} \rightarrow \text{CH} \equiv \text{CH}_2
\end{align*}
\]

\text{Scheme: II.1. Preparation of DVB crosslinked polystyrene}

b.(ii). Polyacrylamide Supports

Sheppard designed polyacrylamide polymers for peptide synthesis as it was expected that these polymers would more closely mimic the properties of the peptide chains themselves and have greatly improved solvation properties in polar, aprotic solvents.85-87 This resin swells in polar solvents, but has limited ability to swell in less polar solvents such as methylene chloride. Other polyamide-based resins have been designed using alternative backbone monomers. In particular, replacing the N,N' -dimethyl acrylamide with the more liophilic N-acryloyl pyrrolidine produces a polymer that swells in solvents such as methanol, ethanol,
2,2,2-trifluoroethanol, isopropanol, acetic acid and water. These solvents generally do not swell polystyrene sufficiently for synthesis. But in addition, it also swells well in methylene chloride. N,N'-MBA crosslinked polyacrylamide was prepared by solution polymerisation using AIBN (Azoisobutyronitrile) as the initiator, (Structure: II.1)

Structure II.1. N,N'-MBA crosslinked polyacrylamide resin

II.B.b. (iii). Poly(methyl methacrylate) support

Lightly crosslinked poly (methyl methacrylate) systems have been found to be a high quality support for studying the behaviour of polymer metal complexes. PMMA resins compared to PS systems facilitate easy metal ion uptake from aqueous solution. A low degree of crosslinking, high level of functionalisation and origin of electron charges near the polymer backbone tend to encourage the reaction condition. The poly (methyl methacrylate) resin can be prepared with different crosslinking agents like Divinyl benzene and EGDMA, (Scheme II.2 and Scheme II.3).
Scheme II.2. Synthesis of DVB crosslinked PMMA

Scheme II.3. Synthesis of EGDMA crosslinked PMMA
II.B.b. (iv). Poly(hydroxyethyl methacrylate) supports

Poly (hydroxyethyl methacrylate) [PHEMA] beads of fairly large size crosslinked with ethyleneglycol dimethacrylate (EGDMA) have some advantages over PMMA and PS supports.\(^8\) It comes under the category known as hydrogels and has attracted considerable attention because of its non-toxicity, non-irritability and biocompatibility with the living tissues. Poly (hydroxyethyl methacrylate) beads crosslinked with EGDMA were prepared by suspension polymerisation with A.I.B.N as initiator in the presence of Mg(OH)\(_2\) in water, (Scheme III.4 a & III.4 b).

Scheme II.4.a. Synthesis of DVB crosslinked PHEMA
b. (v). Grafted Polymer Supports

Another type of polymer support which produces a polar reaction condition that is closer to the solvents generally used by solution synthetic chemists is grafted polymer beads. The most pre-eminent of these is TentaGel resin, which consists of polyethylene glycol support with the
insolubility and handling characteristics of the polystyrene bead. The synthetic environment within TentaGel is closely related to ether and tetrahydrofuran solvents, and consequently has the potential for compatibility with the large range of reactions that are currently being investigated for compound library synthesis.\textsuperscript{90} The resin was originally prepared by the polymerisation of ethylene oxide on crosslinked polystyrene already derivatized with tetraethylene glycol to give polyethylene glycol chains.\textsuperscript{91}

There have been few resins designed de novo specifically for use as general platforms for SPOS in common organic solvents.\textsuperscript{92} One group of such resins utilizes bifunctional styrene derivatized PEG chains to crosslink polystyrene as a means for improving general resin performance.\textsuperscript{93-96} Improved swelling and mechanical properties have been observed with these resins. However, the choice of PEG-based crosslinkers can interfere with the use of strong bases and organometallic reagents, and imparts hydrophilic properties not always desirable for organic synthesis. To circumvent the inherent problems associated with PEG, an alternative flexible polytetrahydrofuran (PTHF) crosslinker could be used to prepare a new class of resins. These resins have outstanding swelling properties in all solvents where swelling was observed and the amount of swelling decreases as the level of crosslinking increases.\textsuperscript{97}

b. (vi). Magnetic Beads

The various beads described above are usually handled by manual methods, but in the search for improved procedures for distributing resins, new procedures have been proposed. One method frequently employed is the production of a suspension, where the pipetting of slurries is improved by ensuring that the resin and solvents have similar densities. One other approach to the manipulation of resin beads is the development of the magnetic polymer bead. Poly (divinyl benzene) was nitrated and the nitro groups reduced with ferrous sulphate hexahydrate. This reduction produces ferrous and ferric ions within the bead that could be converted into magnetic
crystals by the addition of concentrated ammonium hydroxide solution followed by gentle heating. After thorough washing, the beads contained 24-32% iron by weight and were easily manipulable by a hand-held bar magnet.98

b. (vii). Other Supports

Other polymer supports used in organic synthesis are polyacrylic acid, poly(glycidyl methacrylate) and polymaleimide co-polymers. Some other attractive supports include polymers of 2-vinyl thiophene,99 3-(1,2-dibromoethyl) styrene (3-DBS)100 and quinolines. Another class of highly rigid support was made by the polymerisation of acenaphthylene with styrene and DVB.101,102 Polyacenaphthylene–DVB103 and Polyacenaphthylene–1,4–B D M A104 copolymers have been introduced as supports to prepare recyclable solid phase oxidizing reagents in organic synthesis. t-Butyl chromate and t-butyl hydroperoxide reagents derived from Polyacenaphthylene resins were found to be more reactive than those derived from polystyrene resins. Hydrophilic polymers of N-vinyl pyrrolidine,105 vinyl alcohol,106 ethylene glycol,107 vinylchloride,108 ethyleneimine,109 2- and 4-vinylpyridine,110 benzimidazole,111 ethylene-maleic anhydride112 etc., have also been prepared and functionalised to serve as polymeric supports in organic synthesis. Poly(ether ether ketone) (PEEK), and poly(ether ether sulphone) (PEES) polymers are attractive on account of their high thermal stability.113 The design of synthetic polar polymer supports like polyamides85,114-117 and poly (acryloyl pyrrolidine)s118,119 could overcome many of the difficulties associated with polystyrene supports. These supports are compatible with polar reagents and solvents. A number of reagents have been developed based on these supports, as many of them were found to be much superior to those based on polystyrene due to the better hydrophilic / hydrophobic balance they could provide.120 Based on their reactivity and stability, relative to other types of synthetic
polymers, poly(methyl methacrylate)s$^{121}$ and poly(acenaphthylene)s $^{122}$ have been prepared and chemically modified for utilization as supports for reagents and catalysts.

b. (viii) **Dendrimer Supports**

Dendrimers are a class of perfectly branched, tree-like polymers concentrically built up around a central core unit.$^{123-127}$ In contrast to regular polymers, these globular cascade molecules possess a highly ordered and well-defined structure, which provides them with special chemical and physical properties. The number of reactive groups on a bead can be increased via the attachment of dendritic fragments (dendrons) that bear similar reactive groups at their periphery. In this strategy, the dendron can be regarded as a linker, as well as a reactive group scaffold, which in addition gives the supported molecules more soluble-like properties due to its large size. A resin-bound lysine dendrimer has been reported for multiple-antigenic peptide synthesis.$^{128}$ PAMAM dendrons were synthesized onto an insoluble polystyrene-polyethylene glycol resin.$^{129}$ The primary amine groups at the dendron periphery were functionalized with a super acid-sensitive linker, 4-(4'-hydroxymethyl-3'-methoxy) henoxybutyric acid (HMPB) and loaded with protected glycine (Gly) to synthesize the peptide. The full advantage of this high-loading approach was shown in the synthesis of a library of tri- and hexa-peptides using split and- mix library applications on related PS-PEG-PAMAM supports of generation 2.0.$^{130,131}$ Chan and co-workers have developed an alternative, yet related system using a tri-amino ester building block for the construction of dendronized PS-beads.$^{132}$ By means of a protection-deprotection repeated synthesis, two generations of triple-branched dendrons were attached to aminomethylpolystyrene. These resins seem comparable to the triple-branched PAMAM resins in terms of loading capacity and swelling behavior, but can have the advantage of reactive group differentiation.
b. (ix). New Supports

There are recent reports of novel solid phase supports for the synthesis of number of organic compounds, which are either new one or modified form of supports that are in common use. Using (ArgoGel-Rink-NH-Fmoc) resin, S-palmitoylated peptides were synthesized.\textsuperscript{131} Solid phase synthetic strategy toward succinyl hydroxamate peptide using biotylated photoactivable hydroxamate building block,\textsuperscript{134} a multifunctional Ceremide type tether for the chromo enzymatic synthesis of GM\textsubscript{3} and GM\textsubscript{2} Gangliosides,\textsuperscript{135} a facile solid phase synthesis of C-terminal peptide aldehydes and hydroxamate using Back bone Amide Linker- Polyethylene glycol- Polystyrene support\textsuperscript{136} (BAL-PEG-PS-) were reported. A series of 10-acyl and 7,10 diacyl paclitaxel analogues were prepared on polystyrene functionalised with butyl diethyl Silane linker\textsuperscript{137} (PS-DES), solid phase oligosaccharide synthesis of glycans\textsuperscript{138} on a hydroxymethyl benzyl benzoate spacer linker which was connected to 1\% crosslinked Merrifield resin, solid phase synthesis of aldehydes using a novel polymer supported phenyl selenomethyl trimethyl silane,\textsuperscript{139} bioactive molecule synthesis over peptidomimetic building blocks made of sugar amino acids are recently reported.\textsuperscript{140} A new strategy for solid phase synthesis of 2,5-disubstituted 1,3,4-oxadiazoles have been developed from resin bound acylhydrazines in several steps providing 78-88\% over all yield and excellent purity.\textsuperscript{141} Magnetic nanoparticles as an orthogonal support of polymer resins found application to solid phase Suzuki cross coupling reaction.\textsuperscript{142} Chem matrix resin\textsuperscript{143} is a new, totally poly (ethylene glycol) based resin, made exclusively from primary ether bonds and are therefore highly chemically stable. Large uniform sized polymer beads for use as solid supports were prepared using styrene and divinylbenzene by free radical polymerisation\textsuperscript{144} in an ascension process through a heated column. Beads with diameter in excess of 1mm have been prepared and the size of the bead was adjusted by the diameter of the injection needle and injection speed. Mechanically robust tablet consisting of neat functionalised polystyrene beads
were generated by the pre-treatment of polystyrene beads with non-polar organic solvents and this novel dosing methodology provided high speed in solid phase synthesis. Combinatorial and highly parallel synthetic strategies have stimulated the development of new polymer support materials with compositions and properties that allow a broader spectrum of organic transformations. Generation of texaphyrin solid supports and derivatives in which a polymeric or solid matrix was covalently modified by the addition of one or more texaphyrin or texaphyrin derivatives has been reported. The use of controlled pore glass in solid phase oligosaccharide synthesis, use of polyethylene glycol-grafted polystyrene supports in solid phase synthesis of peptides, oligo nucleotides and small organic molecules and design of reactive porous polymer supports such as poly (2-vinyl-4,4-dimethylazlactone-co-acrylamide-co-ethylenedimethacrylate) monoliths for high throughput bioreactors are some of the recent investigations made in the field of polymer supported organic synthesis.

II. B.2. Linear and Crosslinked Polymer Supports

Both linear and crosslinked organic macromolecular species have found wide applications as supports, the latter in particular being experimentally very attractive due to the possibility of easy reaction workup. The advantages associated with the use of linear polymers include the possibility of all reactions being carried out in solution in a homogeneous medium with only limited diffusion problem and with equal accessibility to all the functional groups. High conversions will be possible by using linear polymer, but separation from low molecular weight contaminants will be difficult. The advantages of using linear polymer supports were demonstrated by the use of N-chloronylons. Some polymers have branched chains arising as a result of side reactions. Crosslinked or network structures are formed as in the case of monomers containing more than two reactive groups in stepwise polymerization.
Crosslinked polymer supports are used widely as it being insoluble in all solvents, can be prepared in the form of spherical beads, which do not coalesce when placed in a suspending solvent and can be separated from low molecular weight contaminants by simple filtration and washing with various solvents. Macroreticular resins result in the formation of tiny, highly crosslinked solid particles surrounded by solvent droplets containing some dissolved monomer and the crosslinking agent. Crosslinked popcorn polymer can be prepared from a mixture of vinyl monomer and a small amount of divinyl species and warming gently in the absence of any polymerisation initiators and solvents. Polymerisation occurs, producing opaque, granular material referred as popcorn or cauliflower polymer. The main advantage of using macroporous resins is their large interior surface area within large pores, which allow easy access of the reagents and solvents. This large surface area is essential for high reactivity, as highly crosslinked beads do not swell. Disadvantages of using macroporous resins are lower reactivity, lower capacity and poor mechanical stability of the beads, which tend to break-up when handled repeatedly.

II. B.3. FUNCTIONALISATION OF POLYMER SUPPORTS

Polymers, which act as carriers or supports for a reactive species or functional group, are called functional polymers or reactive polymers. Functional polymers are macromolecules, where the polymer chains function as a carrier matrix for a reactive species or functional group. The bound reactive species may be the part of the polymer backbone or attached to the side chain as a pendant group. The incorporation of the active species could be achieved either by physical adsorption or chemical bonding. The influence due to steric constraints induced by the polymer backbone and the local environment created within the polymer around the reactive species can modify its activity.

In solid phase organic synthesis, a polymer substrate has an attached molecule on which some transformation can be carried out using small molecular reagents. A polymer catalyst
contains a group that performs a catalytic function in certain reactions, usually reactions between small molecules. The introduction of complexing groups into the polymeric matrix gives the ability to interact with the metals by way of coordination bonds, there are numerous chelating macromolecular ligands with various chemically active groups fixed on different supports.\textsuperscript{162}

In general, there are two approaches for the functionalisation of polymer supports. In the first approach, the required chemical group, which performs the particular function, is attached to the already available polymer by a suitable reaction. The attachment is usually through a covalent bond, but ionic bonding can also be used. This is called 'chemical modification route'. Alternatively the required functionality can be introduced into a polymerisable monomer and then this functional monomer can be used as one component of the polymerising mixture during resin synthesis. This is called the 'functional monomer' route. Combination of these approaches is also possible. The functional monomer route allows the structure of the functional group to be clearly defined and offers more control over the number and distribution of groups and the chemistry is better defined. Coupled with lower cost, chemical modification route is the one, which has been most widely employed. In principle, any chemical transformation, which has been carried out on small molecules in solution, can be achieved on analogous macromolecular structures. For polystyrene based resins, electrophilic substitutions can be achieved quite readily and various functionalised polymers are produced, (Scheme II.5). Amination of the chloromethylated species using trimethyl amine yields anion exchange resins.\textsuperscript{163} This is an example of attack by nucleophile and is the second important group of reactions used for introducing functionality into polystyrene resins, (Scheme II.6).
Scheme: II.5. Electrophilic substitution reactions of polystyrene

Scheme: II.6. Nucleophilic substitution reactions of chloromethyl polystyrene
II. B4. Solvation Characteristics of Polymer Supports

The reactivity of a polymeric reagent is governed by the extent of solvation of the polymer support. The solvation properties are not so important in the case of soluble polymers, which can form a homogeneous solution. The polymer chain exists as random coils, which can be highly expanded or tightly contracted depending on the nature of the solvent.

Crosslinked polymers, which are macroscopically insoluble in almost all solvents, absorbs considerable amount of the solvent, expanding the crosslinked polymer network, forming a pseudo-gel. This expansion or swelling of the polymer chains depends on factors like the thermodynamics of the polymer-solvent interaction, the size of the solvent molecule and the porous structure of the network.

The lightly crosslinked resins resemble a homogeneous solution such that the gel network is largely that of a solvent with only a small fraction of the total mass being polymer backbone. While in highly crosslinked resins, the polymer backbone becomes more rigid and the polymer chains cannot expand appreciably by interacting with the solvent. In this case, the mass transport of reagents and solvent into the resin is diffusion controlled. Considerable chain entanglement occurs, which reduces the extent of swelling in the presence of good solvents. Polymers with large pores, macroporous and macroparticulate, also absorb reasonable amounts of solvents.

The main advantage of using macroporous resins is their large interior surface area within large pores, which allow easy access of the reagents and solvents. This large surface area is essential for high reactivity as the highly crosslinked beads do not swell appreciably and reactions are carried out on what essentially amounts to a monolayer. Since the reactivity of macroporous resins is not a function of swelling, reactions can often be carried out in a variety of solvents with
out appreciable change in reaction rate. The ability of the resin to swell in both organic and aqueous media is especially important in solid phase organic synthesis. Polymethylacrylamide fulfils this requirements and this resin was originally used for evaluation of technology feasibility.\textsuperscript{167} Sheppard and his coworkers were the first to recognize and point out the dichotomy of using highly non-polar polystyrene based support on which highly polar oligopeptide was to be constructed. The solvents that expand the polystyrene backbone will tend to collapse the peptide chains and similarly solvents, which expand the peptide, will tend to collapse the support backbone. An ideal situation might be one in which both support and peptide are expanded and this led Sheppard to develop a new resin, based on N,N- dimethylacrylamide.\textsuperscript{85}

Copolymer of HEMA, and ethylene dimethacrylate has high degree of porosity and large internal surface which ensures a rapid attainment of equilibrium during solvation and sorption.\textsuperscript{88}

II. B5. Effect of degree of crosslinking

Crosslinked or network structures are formed in the case of monomers containing more than two reactive groups in step-wise polymerisation. Branching represents controlled extension of the linear chain by branching in which increasing the molecular weight by branching does not produce a rapid transition from a soluble gel to an insoluble one. Free rotation of the branched chain around the primary chain may be the factor, which favours the increased solubility of this type of branched polymers. At a higher concentration of the bifunctional compound, diffusional restriction comes into play.

Crosslinked polymer supports are used widely compared to linear supports. Crosslinked polymers as if being insoluble in all solvents, can be prepared in the form of spherical beads, which do not coalesce when placed in a suspending solvent and can be separated from low molecular weight contaminants by simple filtration and washing with various solvents. Crosslinked polymers exhibit considerable differences in properties depending on the degree of
crosslinking and the method of synthesis. The two types of crosslinked polymer beads which are most frequently encountered are gel and macroporous resins. Suspension polymerisation is the usual method employed for the synthesis of crosslinked polymers.\textsuperscript{164} The size of the polymer beads obtained by this method is dependent on several factors like the speed of stirring, the shape of the reaction vessel and stirrer, the droplet density, the volume fraction of the dispersed phase, etc. Gel polymers are prepared by using a vinyl monomer suspended in water in the presence of small amounts of a crosslinking agent. They are usually found to be slightly less reactive as the reactions will be limited by diffusion of the reagent within the resin pores. If the crosslink density is very low, the gels will become difficult to handle and may, under some conditions be degraded to produce soluble linear fragments. Saldadze et al have reported the change in colouration of complex from blue to deep green when increasing the extent of crosslinking from four to sixteen.\textsuperscript{169}

II.C. SYNTHESIS OF ORGANIC MOLECULES ON FUNCTIONALISED POLYMERS

The massive increase in the number of papers describing the use of polymeric supports in organic synthesis over the past decade is a vivid demonstration of its impact in the chemical community. The various small molecule synthesis can be classified into different groups depending on the nature of the bond formation.

II.C.1. Carbon-Carbon Bond Forming Reactions

The development of efficient and reliable methods of forming carbon–carbon bonds remains an important goal in solid-phase synthesis. Chiral N-acyloxazolidinones function as chiral auxiliaries as well as linkers in two reported solid-phase variants of the widely used Evans asymmetric alkylation of imide enolates.\textsuperscript{170,171} During the course of the alkylation study using the above linker, Merrifield resin, Wang resin and TentaGel resins were examined and it was
concluded that Wang resin gave superior performance in terms of yield and diastereo selectivity. \(\alpha,\beta\) Unsaturated ester attached to the solid supports was used to synthesise 3-hydroxy propionamides. A technique termed “unnatural peptide synthesis (UPS)” has been extended to allow \(\alpha,\alpha\)-disubstituted amino acids and peptides to be prepared. Supported silyl enol ethers readily participate in Mannich type three-component condensation reactions, affording amino alcohols after reductive release from the resin. Zargosa reported solid-phase synthesis of substituted thiophenes from an isothiocyanate, an active methylene compound and an \(\alpha\)-halocarbonyl compound.

II. C. 2. Pericyclic Reactions

A number of bicyclic adducts were prepared by Diels–Alder cycloaddition of an immobilised diene with an activated dienophile. Isoxazolines have been prepared using solid-phase synthesis by way of dipolar [3+2] cycloaddition reactions. Dipolar [3+2] cycloaddition reactions have also been investigated using the technique known as fluorous-phase synthesis, where the solid-support is replaced by a fluorocarbon.

Armstrong and Tempest have examined the thermolysis of cyclobutenone derivatives on the solid-phase, presenting the electrocyclic ring-opening–ring-closure sequence as a potential method for the synthesis of “multiple core structure libraries”. A modified Fischer indole reaction was used to synthesise spiroindoline containing structures. The Fischer synthesis of indoles has also been carried out with one of the components immobilised on a dendrimer, and the dendrimer-bound products were isolated by size exclusion chromatography. An advantage of the dendrimer based approach is the facile reaction monitoring by NMR spectroscopy.

II. C. 3. Electrophilic Aromatic Substitution

The reactivity of polystyrene towards electrophilic aromatic substitution is well recognized and provides convenient access to functionalized polystyrene based resins. Thus
electrophilic aromatic substitution of substrates immobilised on polystyrene resin is complicated by the reactivity of this support. Tetrahydroisoquinoline derivatives were prepared using an eight-step route involving intramolecular electrophilic aromatic substitution to form the bicyclic core. The synthesis of the indazole involved intramolecular electrophilic aromatic substitution reaction.

II.C.4. Organometallic Chemistry

Among the most exploited category of carbon-carbon bond formation is the resin bound electrophiles with organometallic reagents. The simplest example is polystyryllithium, usually prepared by direct metallation of polystyrene. The reaction of resin-bound electrophiles with organolithium and -magnesium reagents should be more straightforward in most cases and many examples have been published. Grignard reagents proved superior to organolithium reagents with isolated yields ranging from 13 to 68%. An important group of carbon-carbon bond forming solid-phase reaction is the palladium-catalysed couplings, recently described examples include: Stille, Suzuki, Sonogashira, and Heck couplings. Two groups have synthesised indoles using the palladium-catalysed coupling of alkynes with resin-bound aryl iodides. The development of robust and selective ruthenium and molybdenum catalysts has revolutionised the alkene metathesis in organic synthesis. Ring closing alkene metathesis has been used to prepare cyclic peptide analogues. Bolton et al have published a full paper describing their work on the synthesis of bicyclic amino acid derivatives using a solid-phase reaction. Organocuprate chemistry was also used in the synthesis of prostaglandin analogues on an organic solvent soluble, non-crosslinked polystyrene matrix.

II.C.5. Radical Reactions

Examples of solid supported radical chemistry is scarce and only few reports of this category are available. An intramolecular samarium diiodide-mediated radical reaction of aryl
iodides followed by TFA-induced cleavage from the resin provided cyclic ethers in respectable yields. Reactions worked well on polystyrene or PEG-grafted resins, although removal of Sm\(^{3+}\) by-products was easier when PEG-grafted resins were employed. By this method bromoalkene was cyclised to the dihydro benzofuran which proceeded catalytically when a polyethylene glycol grafted resin was used.

II. C.6. Multicomponent Condensation (MCC) Reactions

Many research groups have noted the attraction of forming a number of covalent bonds as well as introducing several elements of diversity in one synthetic operation. The Ugi four-component condensation is one of the most widely used Multiple Component Condensation (MCC) reactions, having been applied to the solid-phase synthesis of several acyclic structures including C-glycoside peptides, and amino glycoside antibiotic mimetics. A multicomponent condensation approach based on the Doebner reaction was used to synthesise 2-arylquinoline-4-carboxylic acid derivatives. Immobilising the pyruvic amide on the solid-phase proved advantageous, avoiding the pyruvic acid polymerisation which can occur in the analogous reaction in the solution-phase. I,4-benzodiazepines, 1,4- benzodiazepine-2,5-diones, perhydro-1,4-diazepine-2,5-iones, diketopiperazines, and diketomorpholines, quinazoline -2, 4-diones, hydantoins have been synthesised using the solid phase strategy.

II. C.7. Nucleophilic Aromatic Substitution

Nucleophilic aromatic substitution is an attractive approach to the functionalisation of electron deficient aromatic rings, with the introduction of a wide range of readily accessible heteroatomic nucleophiles. Reported examples include the formation of substituted anilines, substituted purines and ethers. Initially the macrocyclic biaryl ether bond present in cyclic peptide derivatives were formed using a two-step procedure from silyl ether.
II. C.8. Carbon –Heteroatom Bond Formation

Wide range of heteroatomic nucleophiles were introduced into the electron deficient aromatic ring which include Carbon-Nitrogen, Carbon-Oxygen and Carbon-Sulphur bond formation.

II. C.8.a. Carbon-Nitrogen Bond Formation

The synthesis of sterically demanding tertiary amines by reductive alkylation of secondary amines with aldehydes may proceed slowly and several cycles of reductive amination may be required to achieve good conservation. Chemists have reported double or sequential reductive alkylation of resin –bound primary amines to provide tertiary amines where one or both of the alkyl groups introduced were methyl. Resin-bound imines and iminium salts have also been reported to undergo attack by a variety of nucleophilic reagents including Grignard reagents, organolithium reagents and alkynes. Classes of compounds which have been shown to undergo N-alkylation using this approach include: peptides; sulfonamides; indoles; benzodiazepines; quinazoline-2,4-diones; and xanthines.

II. C.8.b. Carbon-Oxygen Bond Formation

The traditional Williamson method for the synthesis of ethers, using a heterogeneous base such as sodium hydride, is not straight forward when the alcohol component is bound to an insoluble polymer. Successful alkylation of secondary alcohol has been achieved using sodium hydride as the base in the presence of small quantity of crown ether.

II. C.8.c. Carbon-Sulphur Bond Formation

Thioethers have been formed by 1,4-addition of thiolate anions to resin-bound Michael acceptors.

II. D. LINKERS AND CLEAVAGE STRATEGIES

The attachment point of the linker to the solid support or spacer should be chemically stable during the synthesis and cleavage, and as for any solution phase protecting group, yields for its
phase synthesis. A great number of linkers have been developed in the last few years in order to allow many multistep organic syntheses to be performed and the use of a broad range of reagents allowing cleavages in a very selective manner. Although a linker should ideally enable a selective cleavage to take place under a defined set of conditions, these conditions are in reality not only dependent on the linker but also on the compound attached to the linker, the spacer, and importantly on the resin type, its loading and bead size. Thus, smaller beads have a much greater efficiency of cleavage under photolytic conditions. Reduced crosslinking dramatically enhances the rate of cleavage from solid supports under acidic conditions.

II. D. 1. Linkers

The clear distinction made between resins and linkers is that resins will be considered as an inert matrix, passive to chemistry, while linkers will be considered simply as immobilised protecting groups and will be classified into two types: (i) Integral linkers in which part of the solid support core forms part or all of the linker and (ii) Non-integral or grafted linkers in which the linker is attached to the resin core.

Best example for integral linker is chloromethylated polystyrene or Merrifield resin (Structure II.2). Linkers such as the o-nitro-(α methyl) bromobenzyl linker prepared by Pillai et al\textsuperscript{237} is a classic example of an integral linker. Its synthesis was realized by functionalising polystyrene/DVB resin with acetyl chloride/AlCl\textsubscript{3}, reducing the resulting ketone and bromination of the resulting alcohol. The nitro group was then incorporated by nitration of the resin (Scheme II.7).

Also included in this list are the benzhydrylamine (BHA) linker prepared by Friedel-Craft acylation of polystyrene with benzoyl chloride.\textsuperscript{238} Another light-cleavable bromine linker
Structure II.2 Chloromethylated polystyrene

Scheme II.7. Preparation of o-nitro (α-methyl) bromobenzyl linker

was obtained by functionalisation of 2% polystyrene/DVB with 2-bromopropionyl chloride/AlCl₃ under Friedel-Crafts conditions²³⁹ (Structure II.3). Majority of linkers used in solid phase synthesis are non-integral type. A light-cleavable linker, o-nitrobenzyl (ONB) linker was prepared²⁴⁰ by coupling 3-nitro-4-bromomethylbenzoic acid onto aminomethyl polystyrene resin, in clear contrast to the integral linkers (Structure II.4). The p-alkoxybenzyl alcohol Wang linker was initially prepared by reacting 4-hydroxybenzyl alcohol with Merrifield resin in the presence of sodium methoxide²⁴¹ (Structure II.5).

Structure: II.3. 2-bromopropionyl polystyrene resin

Structure: II.4. Polystyrene supported 3-nitro-4-bromomethyl benzyl amide linker
II.5. WANG Resin

II. D1.a. Classification of Linkers

It is difficult to classify the linkers into different groups as many can be applied readily to the linking of different functionality with minor modification. The different classes of linkers are: acid labile linker, base labile linker, nucleophilically cleavable linker, photocleavable linker, metal-assisted cleavage, safety catch linkers and miscellaneous linkers.

II. D1.b Acid Labile Linker

The two main modes of electrophilic cleavage are using protons and halogens. Solid phase method of synthesis of peptides involved the anchoring of the free carboxylic end of the N-protected amino acids on to nitrated chloromethylated polystyrene resins and the release of the peptide was done with HBr in glacial acetic acid. (Structure II.6a). Amination of 3nitro-4-chloromethyl polystyrene gave 3-nitro4-aminomethyl polystyrene (Mitchell resin, Structure II.6.b). When a carbamate linker was attached to Merrifield resin, product release occurred with the liberation of carbon dioxide by using acid. The presence of acid labile phenyl acetamide methyl (PAM) linker was shown to increase the stability of the peptide 100 fold (Structure II.7).

Structure: II.6.a. 3-nitro-4-chloromethyl polystyrene  
Structure: II.6.b. 3-nitro-4-aminomethyl
Structure: II.7. Phenyl acetamide (PAM) linker

Marshall designed a Benzhydrylamine linker (BHA)\textsuperscript{244} (Structure II.8) which was acid labile and gave selective N-C cleavage. HF and other strong acidolytic cleavage procedures suffer from a common draw back that they are extremely hazardous and not generally applicable to multiple parallel synthesis. Addition of more donating groups decreases the acid strength needed to cleave the linker. Wang described the p-alkoxy benzyl alcohol linker\textsuperscript{245} which allowed the cleavage of peptide using mild acid. Rink linkers contain extra methoxy or alkoxy groups. Addition of extra phenyl groups give rise to Rink and Trityl derivatives.(Structure II-9 & Structure II.10)

Structure: II.8. Benzhydrylamine linker

Structure: II.9. Rink Linker

Scheme: II.10. Trityl linker.
Hydroxymethyl phenoxy acetic acid (HMPA) and hydroxymethyl phenoxy propionic acid (HMPP) display similar acid labilities as Wang linker\textsuperscript{246}. (Structure II-11 & Structure II-12). The SASRIN (Super Acid Sensitive Resin) linker has the same structure as the Wang linker but with the addition of a methoxy group. Wang and SASRIN resins have been used for the generation of sulfonamides.\textsuperscript{247} SASRIN linked to solid support through an ether bond was first described by Mergler\textsuperscript{248} (Structure II.13). PAL (Peptide amide unloaded linker) described by Albericio\textsuperscript{249} contains 2-methoxy group in the ortho position of Wang linker.

Introduction of alkoxy groups onto benzhydryl system gives another mild acid sensitive Rink linker.\textsuperscript{250} In 1991 Lebel reported the synthesis of SCAL (Safety catch acid sensitive linker).\textsuperscript{251} Trityl linkers were developed initially by Leznoff\textsuperscript{252} and Frechet\textsuperscript{253,254} which were also mild acid cleavable linkers and they avoided recemisation problems. A hydroxyl linker based on the tetrahydropyranyl (THP) protecting group has been developed by Thomson and Ellman.\textsuperscript{255} The methylbenzhydrylamine linker (MBHA) on polystyrene was first developed for the improved synthesis of peptide amides made on polystyrene using the Boc-protection strategy. The Rink linker is now the preferred method for the generation of primary carboxamides on solid phase.\textsuperscript{256}

![Structure II.11. Hydroxymethyl phenoxy acetic acid linker (HMPA)](image)

![Structure II.12. Hydroxymethyl phenoxy propionic acid linker (HMPP)](image)
II. D1.c. Base Labile Linkers

Benzyl esters are easily cleaved by dinitrate alkali and even milder conditions like, $K_2CO_3$ in methanol, or tetrabutyl ammonium hydroxide in T.H.F are enough for cleavage.\textsuperscript{257} Electron withdrawing groups considerably increase the cleavage rate. The glycolamidic ester linkage, which is stable towards acids, can be cleaved with NaOH.\textsuperscript{258} Merrifield\textsuperscript{259} cleaved the phenacyl linker using the 18-crown-6 complex of KCN. The REM linker is suitable for solid phase synthesis of tertiary amines, which are base labile. REM resin comprises hydroxymethyl resin derivatized as the acrylate ester, which upon Michael addition of a secondary amine gives resin-bound tertiary amine. Quaternisation of tertiary amine with an alkyl halide activated the linker for cleavage by a Hoffman elimination.\textsuperscript{260} Recyclable benzyl and aryl salflone analogues of the REM system have also been devised.\textsuperscript{247}

II. D1. d. Nucleophilic Cleavage

Thiol linkers are suitable for the formation of activated carboxylic acid derivatives. The corresponding thioesters can undergo nucleophilic cleavage from the support liberating esters, amides, aldehydes, ketones, alcohols or intramolecular fashion.\textsuperscript{226} The hydroquinone-O$_2$O'-diacetic acid (QDA) linker has been suggested as a faster-cleaving alternative to the succinyl linker, usually employed in solid-phase oligonucleotide synthesis.\textsuperscript{261,262} Malonic acid derived linker has been used to prepare oligonucleotide 3-monophosphates.\textsuperscript{263} The synthesis of secondary
II.D1. e. Cyclative Cleavage

An insoluble crosslinked poly-(4-hydroxy-3-nitrostyrene) resin on treatment with protected peptides gave an insoluble polymer containing an activated ester group as the linker. Deprotection of the amine end of the peptide incurred intramolecular cyclisation to afford cyclic peptides in high yield and purity. Amino acids were attached via their N-terminal to activated hydroxymethyl polystyrene resin using a carbonate linker in hydantoin synthesis.

II.D1. f. Photocleavable Linker

Photolysis offers a mild and potentially orthogonal method of cleavage that take place under neutral conditions. Photocleavable protecting groups have been used widely in carbohydrate chemistry, nucleotide and peptide synthesis. Their application and generalization toward nonoligomeric syntheses has been limited by the fact that many small organics absorb light or are sensitive to the radiation needed to cleave the linker. A number of photocleavable linkers have evolved from the o-nitrobenzyl protecting group. Rich and Guruwara first synthesized the analogous resin in 1973 for the synthesis of protected peptides; the photosensitive protecting group providing an orthogonal cleavage mechanism to acid-and base-labile groups. Their synthesis involved nitration of 1% chloromethylated polystyrene and thus resulted in nitration of excess phenyl rings. The nitro groups, being charged, thus increased the polarity of the resin and inhibited its swelling properties in organic solvents. Synthesis of a new nitro resin, containing only the nitro group essential for photochemical reaction, was thus undertaken and resulted in the widely used 3-nitro-4-bromomethylbenzoylamide resin. Another was linker made from 4-bromomethyl-3-nitrobenzoic acid attached to a BHA linker for the anchoring and release of peptide acid. Kenner applied a safety catch protecting group in solid phase synthesis of peptide by using an acylsulphonamide linker. Resins derivatized with the benzylloxycarbonyl protective group are suitable for the immobilization of primary amines.
There have been many reports on the use of some other photolabile linkers in solid-phase synthesis. Several groups have also described modifications to known linkers\textsuperscript{272} which has led to improved cleavage characteristics or allowed the immobilisation of different classes of compounds. Resin derivatized with Rich's linker has been converted to an active carbonate suitable for the tethering of alcohols to the solid-phase.\textsuperscript{273} An activated carbonate was also used for the solid-phase synthesis of amidines.\textsuperscript{274} The veratryl-based linkers showed faster rates of photolysis than the Rich linker.\textsuperscript{275} (Structure II.14 & Structure II.15)

Coupling of a resin bound glycosyl donor attached to 3-amino-3-(2-nitrophenyl) propionyl linker resulted in the conversion of benzyl glucoside.\textsuperscript{276} The o-nitrobenzyl linker has been employed as the site of ligand attachment in the synthesis of an encoded library of 4-thiazolidinones. In the area of solid-phase oligosaccharide synthesis, the use of o-nitrobenzyl based linkers has also been reported.

\textbf{Structure II.14 & Structure II.15. Veratryl-based linkers}

Attempted coupling of a resin-bound glycosyl donor, attached to the resin through the 3-amino-3-(2-nitrophenyl) propionyl linker, with a large excess of benzyl alcohol resulted in poor conversion to the benzyl glycoside.\textsuperscript{277} By using Rich's photolabile linker and reversing the
modality of the coupling (i.e. glycosyl donor in solution, acceptor on the solid support) a polymer-bound fully deprotected trisaccharide was prepared. A new o-nitrobenzyl linker is suitable for the automated synthesis of base-sensitive oligonucleotides. A photolabile linker which incorporates a safety catch activation mechanism has been reported. Deprotection of the dithiane group unmasks the photolabile acylated benzoin, allowing cleavage by irradiation at 350 nm. The potential of solid-phase organic synthesis as a method for the assembly of complex non-oligomeric natural products has been demonstrated by the synthesis of the epothilone.

An o-nitrobenzyl linker has the additional advantage that it is biocompatible and can be cleaved within aqueous buffer. Other examples of biocompatible linkers are the internal imidazole catalysed cleavable handle of Frank, and one, which employs an enzyme in its cleavage protocol.

Adaptations to the o-nitro benzyl protecting group have appeared in the literature by incorporating two additional alkoxy groups onto the benzene ring. One such example is vanillin based handles used to bond the linker to the solid phase. These linkers exhibit improved cleavage properties. Zehavi attached 6-nitrovanilin to a 2% crosslinked Merrifield resin through an ether bond and performed oligosaccharide synthesis after reduction of the aldehyde group. (Structure II.16) o-nitroveratryl models were found to be superior to the ONB analogue. Good results were seen with the α-methyl-o-nitroveratryl alcohol based linker and introduction of the additional benzylic methyl group increased the rate of cleavage.

Structure: II.16. 6-nitroveratryl alcohol linker based polystyrene
II.D1. g. Metal-Assisted Cleavage

A recyclable silyl chloride linker has been prepared by hydrosilylation of vinyl polystyrene.\textsuperscript{285} Alcohols react with the immobilised silyl chloride under the usual conditions with the expected selectivity, primary>secondary>tertiary. The germanium-containing linker proved sufficiently robust to survive the sequence of reactions used to synthesise benzodiazepines on the silicon linker. Cross metathesis of allylsilane resin provides a mild method for the immobilisation of alkenes containing a range of functionalities including acetal, ester, amide, ether and urea.\textsuperscript{286} Cyclocondensation of a resin-bound thiouronium salt with acetylenic ketones provided a novel method for the synthesis of pyrimidines linked to the solid support through an alkylthio linkage at the 2-position.\textsuperscript{287,288}

II.D1. h. Traceless Linkers

The first and foremost widely explored of these traceless linkers is the silyl linker. Ellman has investigated traceless linkers containing germanium. A sulphide linker has been used to tether pyrimidines to TentaGel resin.\textsuperscript{289} The most widely exploited class of traceless linkers are those based on silicon chemistry. In 1995, the first two linkers of this variety were developed independently by Plunket and Ellman\textsuperscript{290} and Chenera et al.\textsuperscript{291} A more general method for the direct loading of aromatic compounds onto a silyl substituted resin was described.\textsuperscript{292,293} A silane, obtained by generation of (4-methoxyphenyl) lithium followed by addition to allyldimethylsilyl chloride, was affixed via Suzuki coupling to bromophenyl substituted resin.

II.D1. i. Miscellaneous Linkers and Cleavage Strategies

Significantly better results were obtained for alkylations performed on the more rigid Argo-X polystyrene support than on conventional 1% crosslinked polystyrene. Application of solid-phase synthesis to the assembly of phenylacetylene oligomers has proved highly rewarding, providing gram quantities of the desired products more quickly and in comparable or higher yields than the
corresponding solution chemistry. Polymer-bound triphenylphosphine provides a “traceless” linker for the synthesis of olefins and toluene derivatives. Janda et al have documented the development of traceless linkers for use with soluble-polymer supports.

The development of functionalised polymers as supported reagents, supported catalysts, supported ligands, immobilized chiral auxiliaries and chiral catalysts have been reviewed in detail. The uses of functionalized polymers in combinatorial chemistry have not been included in the present discussion. Almost all types of linkers and cleavage strategies were also reviewed with special emphasis on photocleavable linkers.