

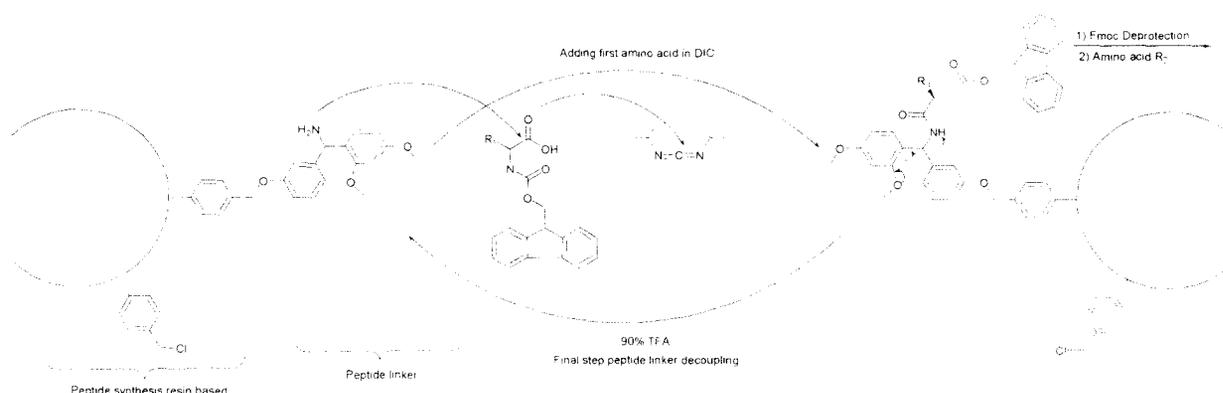
*Part I*

*An Introduction to Solid Phase Chemistry*

## I.1 Introduction

Chemical reactions do not occur in isolation, but within an environment that is dictated by the surrounding molecules or atoms or ions. This environment can be called medium and may consist of the other molecules in the gas phase, or neighbours within a crystal lattice. In many cases a solvent of some kind is used as the reaction medium. Solid-Phase Synthesis focuses on chemical reactions of substrates attached to solid supports (polystyrene, polyethylene glycol, cellulose, controlled-pore glass etc.), including methods for attachment and detachment from the supports. It is of particular interest in the field of combinatorial and parallel synthesis.

### Scheme 1



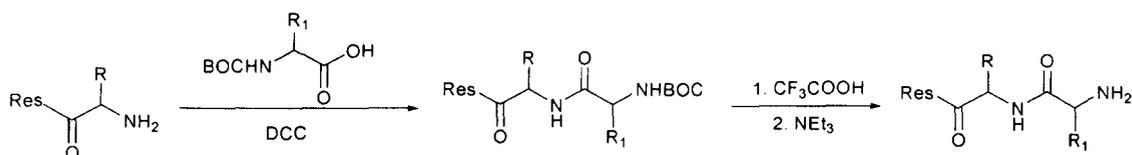
Heterogeneous organic reactions have proven useful to chemists in the laboratory as well as in the industrial context. These reactions have advantages over the conventional solution phase reactions because of the good dispersion of active reagent sites, associated selectivity and easier work-up (Scheme 1). The recyclability of some of these solid supports renders these processes into truly eco-friendly green protocols. Although the first description of surface-mediated chemistry dates back to 1924, it was not until the late 1970s that the technique received genuine attention with the appearance of two reviews followed by a series of books and account articles.<sup>1</sup>

#### I.1.1 Solid-phase peptide synthesis

The revolutionary principle behind solid phase peptide synthesis (SPPS) as conceived by Merrifield in 1959 is that if the peptide is bound to an insoluble support then any unreacted reagents left at the end of any synthetic step can be removed by a simple wash procedure, greatly decreasing the time required for synthesis (Scheme 2). What is more, the arrangement is amenable to automation. Merrifield synthetic methodology is

characterized by the use of *tert*-butyl based temporary  $\alpha$ -amino protection and benzyl, or substituted benzyl, groups for permanent side chain protection.

## Scheme 2



The fundamental differences between the Fmoc polyamide strategy when compared to the Merrifield approach are that the reactions are carried out under continuous flow and that the conditions for  $\alpha$ -amino deprotection and cleavage from the resin are far more mild. This arises from the adoption of the base labile Fmoc protecting group for  $\alpha$ -amino protection.

### 1.1.2 Need for alternative reaction media

Chemistry in alternative reaction media explores why solvents are used and the problems associated with them. Supercritical fluids, biphasic reactions, ionic and fluoruous liquids, and aqueous chemistry, which explain how they may be used to increase reaction efficiency, improve separation and catalyst recovery, and reduce emissions to the environment. Green, sustainable chemistry involves the designing of chemical processes with a view of reducing or even eliminating the use and production of hazardous materials. The use of organic solvents and their emissions has been at the centre of major environmental concern in recent years, and there is currently a great deal of interest in finding alternatives to halogenated and volatile organic solvents for synthesis.

The waste minimisation approaches are largely developed by the Environmental Protection Agency (EPA). The term *cleaner production* embraces principles and goals that fall comfortably within the waste prevention-minimisation range.

There is no widely accepted definition of clean synthesis but there is reasonable international agreement that the cleaner synthesis of chemicals, *i.e.* that involving a reduction in the toxicity and quantity of emissions and waste through changes to the process, is likely to be achieved through:<sup>2</sup>

- Better use of catalysis,
- Alternative synthesis routes that avoid the need to use toxic solvents and feed stocks,
- Reduction in the number of synthetic steps,

- Elimination of the need to store or transport toxic intermediates or reagent, and
- Novel energy-efficient methods.

It could be mentioned that catalysis features very highly on any list of preferred/relevant technologies to help achieve a reduction in waste from chemical processes through the use of cleaner synthetic methods.

### **I.1.2.1 Dry media reactions**

A dry media reaction or a solventless reaction is a chemical reaction in which solvents are not used. In a normal reaction, the reacting agents, also called the reactants, are placed in a solvent before the reaction can take place. After the reaction is completed, the new products are removed from the solvent. Dry media reactions are cost-effective because the elimination of solvents means that products will be of low cost. This, in turn, will make those products cheaply available.

### **I.1.3 Catalysts and catalysis**

Catalysts are capable of directing and accelerating thermodynamically feasible reactions while remaining unaltered at the end of the reaction. They cannot change the thermodynamic equilibrium of reactions.<sup>3</sup> The *catalytic activity* is a way of indicating the effect the catalyst has on the rate of reaction and can be expressed in terms of the rate of the catalytic reaction. *Stability* is an important catalyst property since catalysts can be expected to lose activity and selectivity with prolonged use. This then opens the way to *regenerability* which is a measure of the catalyst's ability to have its activity and/or selectivity restored through some regeneration process.

*Catalytic processes* are the application of catalysts in chemical reactions. Catalysis is described as *homogeneous* when the catalyst is soluble in the reaction medium and *heterogeneous* when the catalyst exists in a phase distinctly different from the reaction phase of the reaction medium. Corrosion of reaction vessels by catalyst solutions, and difficult and expensive separation processes are common problems. More recently there have been significant scientific and technological innovations through the use of organometallic catalysts. Normally, heterogeneous catalysis involves a solid catalyst that is brought into contact with a gaseous phase or liquid phase reactant medium in which it is insoluble. This has led to the expression *contact catalysis* sometimes used as an alternative designation for heterogeneous catalysis.

### 1.1.3.1 Heterogeneous catalysts

Most of the large-scale catalytic processes take place with gaseous substrates contacting solid catalysts due to the engineering advantages of these processes compared to homogeneous processes such as:

- Solid catalysts are rarely corrosive.
- A very wide range of temperatures and pressures can be applied to suit the process and the plant strongly exothermic and endothermic reactions are routinely carried out using solid catalysts.
- Separation of substrates and products from catalysts is easy and inexpensive.

Many solid catalysts are based on porous inorganic solids. The important physical properties of these materials are surface area (often very large and measured in hundreds of square metres per gram), pore volume, pore size distribution (which can be very narrow or very broad), the size and shape of the particles and their strength. The solid catalyst provides a surface, usually largely internal, for the substrates to adsorb and reaction.

Metal oxides are widely used as catalyst supports but can also be catalytically active. Very many mixed metal oxide catalysts are now used in commercial processes. Zeolites offer the particular advantage of shape selectivity resulting from their narrow microporous pore structure. Some of the major industrial processes to be catalysed by inorganic solids are shown in Table 1. Heterogeneous catalysis is playing an increasingly important role in smaller scale chemical manufacturing, often with the result of a major reduction in waste.

**Table 1 Some large-scale processes catalysed by inorganic solids**

Mixed iron and molybdenum oxides	$\text{CH}_3\text{OH} + \text{O}_2$ (HCHO)
Solid acids (e.g. zeolites)	Paraffin cracking and isomerisation; alkylation; olefin polymerisation
Mixed metal oxides	$\text{CH}_3\text{CH}=\text{CH}_2$ (acrolein)
Alumina	ROH (olefin + $\text{H}_2\text{O}$ )
Supported metals	$\text{H}_2 + \text{N}_2$ ( $\text{NH}_3$ )
Supported tungsten or rhenium	Olefin metathesis
Metals (Ni, Pd, Pt) and supported metals	C=C bond hydrogenation
Metals (Cu, Ni, Pt)	C=O bond hydrogenation

### I.1.3.2 Heterogeneous catalysis

The catalytic mechanism of reaction on solids can be broken down into five consecutive steps:

- Substrate diffusion
- Substrate adsorption
- Surface reaction
- Product desorption
- Product diffusion

Substrate molecules must diffuse through the network of pores to reach the internal region and the product molecules must diffuse out of the pore network. Smaller pores provide the advantage of large surface areas and high particle mechanical strengths but lead to problems with slow molecular diffusion. Internal diffusion of substrate molecules is a complex process determined not only by the resistance to flow due to the medium but also by the constraints imposed by the pore structure. All industrial adsorbents and the majority of industrial heterogeneous catalysts have large surface areas of  $> 100 \text{ m}^2 \text{ g}^{-1}$  based on porous solids and/or highly particulate materials.<sup>4</sup> In the simplest case for spherical particles of density  $\rho$  and all of diameter  $d$ , the specific surface area  $S$  can be defined as:

$$s = 6/\rho d$$

The size of the pores in porous solids can be classified as micro, meso or macro based on their width. Adsorption is brought about by the interactions between the solid and the molecules in the fluid phase. The forces involved are classified as chemisorptions (chemical bonding) or physisorption (non-chemical bonding).

### I.1.3.3 Heterogenization

Apart from the use mesoporous solids as catalysts, there is also a growing interest in the related area of heterogenization. Here, an active compound or complex is immobilised through binding to an insoluble solid. The solid is commonly a mesoporous solid so that the useful properties of the solid support (high surface area, high concentrations of active sites within pores) can be combined with the activity of the compound or complex. Alternatively, the catalyst can be an insoluble cross-linked polymer.<sup>5</sup> The principal motive for heterogenization is to facilitate separation, recovery and reuse, easier handling and lower toxicity. Non-catalytic materials such as  $\text{KMnO}_4$ -silica,  $\text{NaSCN}$ -alumina (*i.e.* those where the reagent was spent on use and could only be

reused after a separate regeneration stage) and catalytic materials such as ZnCl<sub>2</sub>-montmorillonite (*i.e.* those where the reagent is not chemically changed on use and could possibly be reused after a reactivation stage) relied on physisorption to keep the support and active species together.<sup>1e,6</sup> Some examples of well established supported reagents are given in Table 2.

**Table 2 Some well established supported reagents and applications**

KF-Alumina and other supported fluorides	Various base-catalysed reactions
KF-CaF <sub>2</sub>	Nucleophilic fluorinations
KMnO <sub>4</sub> -Silica, <i>etc.</i>	Oxidations, including RCH <sub>2</sub> OH – RCO <sub>2</sub> H
KCN-Alumina, <i>etc.</i>	Nucleophilic cyanations
KSCN-Alumina, <i>etc.</i>	Nucleophilic thiocyanations
ZnCl <sub>2</sub> -Clay (K10)	Friedel-Crafts alkylations
Fe(NO <sub>3</sub> ) <sub>3</sub> -Clay (K10)	Nitrations and oxidations
KOH-Alumina various	Base-catalysed reactions
<i>t</i> -BuOCl-Zeolite	<i>p</i> -Selective aromatic monochlorinations
K <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub> -Alumina	Various oxidations
NaBH <sub>4</sub> -Silica	Various reductions

Thus a pre-formed support can be chemically modified in a single, or more often, multi-step procedure. Alternatively, the reactive group can be introduced during resin preparation by using a conventional comonomer already carrying the reactive group required.

#### **1.1.4 Introduction to supported reagent chemistry**

The term *supported reagent* has been used to describe a wide range of materials involving an inorganic or organic support onto which a *reagent* species has been chemically or physically adsorbed. Some of the key advantages of supported reagents compared to the unsupported reagent are:

- Good dispersion of active sites and the concentration of sites within small pores can lead to significant improvements in activity
- The presence of molecular dimension pores and the adsorption of reactant molecules on the material surface can lead to improvements in reactions electivity

- Easier and safer handling

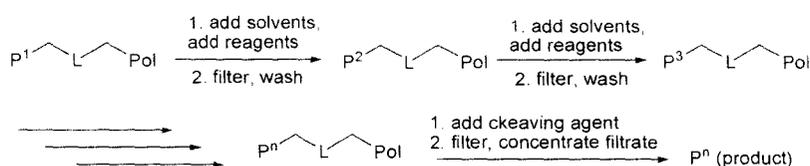
These, coupled with the normal advantages of solid catalysts of easier recovery and reuse, make supported reagent type catalysts attractive materials to organic and industrial chemists.

#### 1.1.4.1 Types of supported reagents

Whereas the motivation behind Fetizon's original work and much of the early research on supported reagents was directed towards stoichiometric reagents such as silver carbonate (so that at best only the support could be recovered unchanged), much of the more recent published work has dealt with genuinely catalytic materials whereby the entire supported reagent can, at least in principle, be recovered unchanged from the reaction.

One sub-classification of supported reagents is that between organic and inorganic supports. The organic supports are mainly polymeric, such as cross-linked polystyrenes, and are numerous, covering ion-exchange resins through to those based on quite complex surface architectures. The polymer may be a linear soluble species of various molecular weights, a cross-linked network, a membrane or even a macroscopic polymeric object.<sup>5</sup> The majority of studies on polymer-supported reactions have been performed using cross-linked polymers which are effectively insoluble in most solvents (Scheme 3).

**Scheme 3:** Schematic representation of a synthesis on solid phase; Pol: support, L: linker, P: synthetic intermediate.



Other forms of insoluble support include sheets,<sup>7</sup> crown-shaped 'pins',<sup>8</sup> or small discs.<sup>9</sup> Soluble polymers, such as non-cross-linked polystyrene or poly(ethylene glycol), can also be used as supports for organic synthesis.<sup>10</sup>

#### 1.1.4.2 Inorganic supports

There are numerous inorganic supports that are potentially suitable for conversion into supported reagents. These include silicas, aluminas, carbons (notably charcoals), montmorillonites, zeolites, and other aluminosilicates, as well as more complex materials such as partially substituted aluminosilicates (*e.g.* aluminophosphates or ALPOs) and more complex materials such as heteropolyacids. All of these materials can exist in high

surface area forms ( $100-1000 \text{ m}^2 \text{ g}^{-1}$ ) and are normally porous, with average pore diameters ranging from the microporous zeolites (from 0.3 nm) to some macroporous silicas (up to 100 nm at least). The range of suitable materials available has been greatly enhanced through the discovery of the hexagonal mesoporous silicas (HMSs),<sup>11</sup> notably the MCM materials developed by Mobil.<sup>12</sup> Several important and commonly used inorganic support materials are summarised in Table 3.

**Table 3 Commonly used inorganic support materials**

Support	Comments
Silica gels (commercial)	Widely available and inexpensive; high surface area, mesoporous and normally broad pore size distribution; surfaces are heavily hydroxylated and easily functionalised (halogenation, silylation)
Structured silicas (synthetic)	MCMs and HMS materials are mesoporous; prepared using sol-gel methods using onium or amine templates, very high surface areas ( $> 1000 \text{ m}^2 \text{ g}^{-1}$ ) and narrow pore size distribution but little long-range order; often less hydrophilic than normal silicas.
Montmorillonites (natural and synthetic)	Natural clays can have swelling structure giving microporosity; pillared clays have larger pores; acid-treated clays are partially mesoporous (and may change with ageing).
Aluminas	Moderate surface areas; available in acidic, basic and neutral forms.
Zeolites	Microporous and with tight pore size distribution; high surface areas; highly structured; small pores can give high degree of shape selectivity but may cause diffusional problems, especially in liquid-phase systems.
Other materials	Charcoals can have very high surface areas ( $> 1000 \text{ m}^2 \text{ g}^{-1}$ ) but complex surface functionalities; minerals such as calcium fluoride have low surface areas but can be useful as highly inert surfaces.

Commercial support materials such as silica gels have very broad pore size distributions. The actual chemical nature of the support material may be and often is of direct importance to its usefulness as a support material.<sup>13</sup> Silicas can react with small nucleophiles such as  $\text{F}^-$ ,  $\text{OH}^-$  and  $\text{CN}^-$ . Silica-supported fluorides are inactive, both as nucleophilic fluorinating agents and as bases. Similarly, silicas are not effective support materials for cyanides due to the formation of strong Si-CN bonds. For many chemisorbed supported reagent catalysts, silicas are preferred since they give relatively strong surface bonds. However, Si-O-C bonds are hydrolytically vulnerable and direct Si-C bonds are preferred.<sup>14</sup>

High surface areas are generally preferred since this should maximise the number of active sites and increase substrate adsorption, as well as increase the contribution from heterogeneous chemistry in cases where both homogeneous and heterogeneous reactions can occur.<sup>13</sup> Approximately, 80% of the surface area of most support materials is inside the pores. On

filling the pores with a polar reagent, the experimental surface areas are generally reduced. Removal of the reagent can fully restore the apparent surface. Overloaded supported reagents can have excess reagent physically blocking the entrance to pores. There are numerous methods for preparing supported reagents and they are summarised in Table 4.

**Table-4 Methods of preparing supported reagents**

Method	Comment
Sol-gel synthesis	Direct method; can use to introduce functional group, e.g. via (MeO) <sub>2</sub> Si-R; resulting materials can have high surface areas; may be difficult to control; becoming more popular.
Post-modification of support material	Most commonly using silane, but may be less stable than analogous sol-gel materials due to only partial surface reaction; alternative methods include via chlorination (e.g. Si-Cl (Si-R)).
Impregnation (pore filling followed by evaporation of solvent)	Requires a suitable solvent; enables good control over dispersion and loading; likely to give physisorbed reagent only.
Ion exchange	Simple and effective where appropriate.
Precipitation/ co-precipitation	Useful for poorly soluble reagents but may be difficult to control
Adsorption from solution	Easy to carry out but loading may be low.
Mixing/grinding	Easy and avoids other chemicals, but unlikely to give good dispersion.

The stability of any catalyst is ultimately of considerable importance, since it will affect its lifetime and its regenerability and it may affect process work-up and product purification. Of immediate concern in many applications, and particularly with catalysts containing immobilised metals, is leaching. Not only can this lead to a competing homogeneous contribution in the reaction, but it will also lead to added impurities in the product mixture and will reduce catalyst lifetime. Catalyst poisoning is a common problem. With porous solids, this can take the form of pore blockage, which effectively prevents access to the majority of active sites, ultimately restricting the chemistry to the external surface. The most common example of a polar adsorbate poison is water. Supported reagents which are based on porous polar hydrophilic materials such as silica and clays will efficiently remove water from most organic environments.

Pre-drying of both the catalyst and the substrates are sensible pre-treatments, although there will be cases where an aqueous environment might be beneficial to reaction, for example by helping to wash away polar products from the catalyst. Of course, thermal clean up must take place below the decomposition temperature of the

catalyst itself. Fortunately, many supported reagent-type catalysts, and even those with organic functions built on their surface, are stable to quite high temperatures (650 K or higher). It is commonly stated that solid catalysts are more easily separated from liquid reaction mixtures than homogeneous catalysts. A popular option is to use non-particulate forms of the catalysts or in the form of a membrane, for example.<sup>15</sup>

#### I.1.4.3. Methods of studying supported reagents

There are numerous analytical techniques available for the study of supported reagents. Among the more commonly available are Fourier transform infrared spectroscopy (FTIR), especially *via* diffuse reflectance techniques (DRIFTS), titration methods, thermal analysis - notably thermogravimetric analysis (TG) and differential scanning calorimetry (DSC) - or differential thermal analysis (DTA), and surface area analysis and porosity. More specialist techniques include high resolution solid state nuclear magnetic resonance spectrometry, using magic angle spinning techniques (MAS NMR), X-ray diffraction (XRD), scanning and transmission electron microscopies (SEM and TEM), and photoelectron spectroscopies (PES). These techniques and the key properties of supported reagents that they can reveal are summarised in Table 5.

**Table-5 Techniques for studying supported reagents**

Technique	Information obtained
Surface area/porosity	Total surface area; pore volume; pore size distribution; pore shape.
Infrared spectroscopy [especially diffuse reflectance IR (DRIFTS)]	Identification of surface species; level of hydration.
Ultraviolet-visible spectroscopy (especially DRUVS)	Identification of surface species; measurement of surface polarity <i>via</i> dye adsorption.
Titration methods (including spectroscopic titration)	Measurement of acid, base, oxidation and reduction sites.
Thermal analysis (including evolved gas analysis and temperature programmed desorption)	Thermal stability; dehydration/drying temperature programmed temperature; phase changes; heats of adsorption; identity of adsorbed species.
Electron microscopy (SEM and TEM)	Surface morphology; presence of microclusters; crystallinity; presence of channels/pore structure.
X-Ray diffraction	Reagent dispersion; bulk structure (regular solids).

#### **I.1.4.4 Silica**

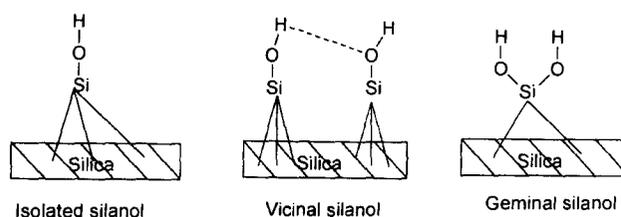
Silica is a polymer of silicic acid, consisting of inter-linked  $\text{SiO}_4$  in tetrahedral fashion, which has the stoichiometry  $\text{SiO}_2$ . Silica gel is a porous, granular form of silica, synthetically manufactured from sodium silicate or silicon tetrachloride or substituted chlorosilane/orthosilicate solution. Silica gel synthesis from sodium silicate solution is well documented by Iler,<sup>16</sup> Unger<sup>17</sup> and Barby.<sup>18</sup> Stöber et al.<sup>19</sup> have reported synthesis of spherical silica particles from tetraethoxysilane (**I**) using  $\text{NH}_3$  as catalyst. Sol–gel route is a versatile method for silica synthesis.<sup>20,21</sup> In a sol–gel process hydrolysis of sodium silicate or alkoxysilane in presence of acid or base produces  $\text{Si}(\text{OH})_4$  entities, which on controlled condensation result in a sol. As the polymeric network extends throughout the entire volume, the sol thickens to a gel.<sup>16</sup> Peptization<sup>22</sup> and precipitation methods are also used for silica synthesis from silicic acid solution. In precipitation reaction, the silica preparation conditions are to prevent the gel formation and stimulate the precipitation. Flame synthesis methods are used for vapor phase synthesis of silica particles. Internal structure of each small silica gel granule is composed of a vast network of inter-connecting microscopic pores, which attract and hold moisture by physical adsorption and capillary condensation.

##### **I.1.4.4.1 Silica surface**

The only method involving direct measurement (imaging) of outer surface of silica or modified silica is atomic force microscopy (AFM). At the surface, the structure terminates in either siloxane group ( $\equiv\text{Si}-\text{O}-\text{Si}\equiv$ ) with the oxygen atom on the surface, or one of the several forms of silanol groups ( $\equiv\text{Si}-\text{OH}$ ).

The silanol groups could be isolated (free silanol groups), where the surface silicon atom has three bonds into the bulk structure and the fourth to OH group and the vicinal or bridged silanols, where two isolated silanol groups attached to two different silicon atoms are bridged by H-bond. A third type of silanols called geminal silanols consists of two hydroxyl groups attached to one silicon atom (Fig. 1).<sup>23</sup> The pioneering work by Ong et al. has shown the presence of two types of silanol at the silica/water interface with  $\text{pK}_a$  values 4.9 and 8.5 with surface population of 19 and 81%, respectively.<sup>24</sup> The silanol groups with lower  $\text{pK}_a$  value (4.9) are believed to be isolated silanol groups with no hydrogen bonding with its neighbour. Other type of silanols with higher  $\text{pK}_a$  value (8.5) is believed to be those connected to each other through H-bonding

directly or via the bridging water molecule. Both kinds of silanols can be linked through hydrogen bonding<sup>25</sup> depending upon their local structures.



**Fig. 1**

In silica, using infrared spectroscopy, Van Cauwelaert et al.<sup>26</sup> identified the 3745  $\text{cm}^{-1}$  band to be due to both isolated and geminal silanols. McFarlan and Morrow<sup>27</sup> reported the same band at 3743  $\text{cm}^{-1}$  for precipitated silica and aerosil to be due to a pair of vicinal isolated silanols. However, Hoffmann and Knözinger<sup>28</sup> assigned the band to geminal silanols. Use of  $^1\text{H-NMR}$  could not make it possible to distinguish between the isolated and geminal silanols.<sup>29</sup> However,  $^{29}\text{Si-NMR}$  spectra show the presence of geminal hydroxyl groups at  $-92$  ppm and isolated or vicinal hydroxyl groups at  $-100$  ppm.<sup>30</sup>

Silanol groups are weakly acidic and silanol concentration on the silica gel surface after activation at 423K was found to be 4.5–8.0 groups  $\text{nm}^{-2}$  depending on the type of silica.<sup>31</sup> It is now accepted that the estimated number of OH groups accessible on the porous silica surface is between 4 and 5 OH groups  $\text{nm}^{-2}$  16,17,32,33 with an average surface area of 20.4–21.7 $\text{\AA}^2$  per silanol group. However, the local density of silanol varies from place to place and silanol number varies as a function of temperature. Physiosorbed water molecules are removed by heating the silica sample up to 440 K and at 1023 K, only isolated silanols remain on silica surface.<sup>33g</sup>

For quantification of surface silanol groups many attempts have been made with a wide varieties of new techniques such as  $^{29}\text{Si}$  cross polarization magic-angle spinning nuclear magnetic resonance,<sup>34</sup> combined rotation and multiple pulse spectroscopy<sup>34</sup> and luminescence spectroscopy.<sup>35</sup> Using  $^{29}\text{Si}$  CP MAS NMR, surface silanol concentration of  $4.8 \pm 0.4$   $\text{nm}^{-2}$  was obtained by Sindrof and Maciel on eight different hexamethyldisilazane (HMDS) modified silica.<sup>36</sup> Substituting the hydroxyl hydrogen of surface silanol by dimethylsilyl group, Yoshinaga et al. determined the surface silanol number by monitoring the Si–H stretching vibration.<sup>37</sup>

A method was developed by de Farias and Airoidi for determining silanol density by using thermogravimetric analysis.<sup>38</sup> By excluding the physically adsorbed water on silica surface they found the number of silanol groups to range from 4.3 to 6.7 OH nm<sup>-2</sup> for a series of silica. Chemical methods based on reaction of surface silanol groups with a selectively reacting compound to form a covalently bonded surface species of well-known composition have been studied extensively. Diborane,<sup>39</sup> BCl<sub>3</sub>,<sup>40</sup> diazomethane,<sup>41</sup> organosilanes,<sup>30,42</sup> and organometallic compounds<sup>43</sup> were used for such purpose, where number of hydroxyl groups per nm is derived from amount of chemisorbed species.

#### **I.1.4.4.3 Surface modification of silica gel**

Silica gel surface can be modified by two distinct processes: organofunctionalization, where the modifying agent is an organic group, and inorganofunctionalization, in which the group anchored on the surface can be an organometallic composite or a metallic oxide. Surface can be modified either by physical treatment (thermal or hydrothermal) that leads to change in ratio of silanol and siloxane concentration of the silica surface or by chemical treatment that leads to change in chemical characteristics of silica surface. Chemisorption of chelating molecules on silica surface provides immobility, mechanical stability and water insolubility, thereby increases the efficiency, sensitivity and selectivity of the analytical application.<sup>44</sup>

Different forms of silicon dioxide have been used as supports for solid-phase organic synthesis. Silica gel is a rigid, insoluble material, which does not swell in organic solvents. Commercially available silica gel differs in particle size, pore size (typically 2-10 nm), and surface area (typically 200-800 m<sup>2</sup>/g). Silica gel enables efficient and rapid transfer of solvents and reagents to its entire surface. Because the synthetic intermediates are only located on the surface of the support, enzyme-mediated reactions can be realized on silica.<sup>45</sup> Silica gel is particularly well suited for continuous-flow synthesis because its volume stays constant and diffusion rates are high.

Among the different adsorbents, silica gel especially immobilized with various organic compounds with metal chelating ability has received great attention.<sup>46</sup> The systematic use of immobilization of organofunctional groups has increased in the past three decades, mainly on silica, because this support offers pronounced advantages over other organic/inorganic supports as listed below:

- ~ Immobilization on silica results in great variety of silylating agents, allowing pendant functional groups in the inorganic framework.<sup>47</sup>

- Attachment is easier on silica surface than on organic polymeric supports, which have a high number of cross-linking bonds, requiring hours to reach equilibrium for surface activation.<sup>47c</sup>
- Silica gel being the most popular substrate for surface studies because it is the first commercially available high specific surface area substrate with constant composition, enabling easy analysis and interpretation of results.<sup>47c</sup>
- Silica gel has high mass exchange characteristics and no swelling.<sup>48</sup>
- Silica support has great resistance to organic solvents.<sup>49</sup>
- Silica has very high thermal resistance.<sup>50</sup>

However, irreversible binding of metal ions and lack of selectivity are the main disadvantages of silica bound ligands in their repeated cyclic use and elution process.<sup>51</sup> Besides the extractive concentration of metal ions, surface modification of silica gel has explored many other possibilities of application in catalytic or ion-exchange reactions.<sup>52</sup> Biochemically modified silica surface with biomolecules like enzymes, proteins, DNA and antibodies has explored the use in biotechnology as biosensors to interfacial interaction studies and drug delivery.<sup>53</sup>

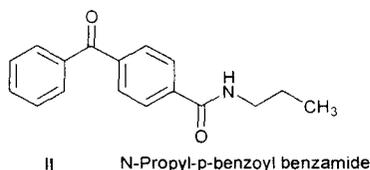
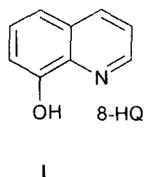
#### **1.1.4.4.4 Modification through impregnation**

Impregnation deals with physical interactions between the modifier and solid support by either inclusion in the pores of the support material or adhesion process or electrostatic interaction.<sup>54</sup> 8-Hydroxyquinoline (8-HQ; **I**) was immobilized onto silica gel for extractive concentration of metal ions by simply stirring [**I**] with the activated silica.<sup>46b, 55</sup>

Modification of silica gel with eriochrome black T (ECB-T) was reported by stirring a mixture of ethanolic solution of ECB-T and silica gel for 30 min.<sup>56</sup> Mahmoud used silica gel immobilized with the indicator ECB-T as a solid phase extractor for Zn(II), Mg(II) and Ca(II) ions.<sup>57</sup> Boric acid impregnated on silica gel was reported for chromatographic separation of substances containing vicinal *cis*-hydroxyl groups.<sup>58</sup>

Mono and diethanolamine were impregnated on silica gel for sorption studies of gaseous compounds like hydrogen sulfide (H<sub>2</sub>S), carbon disulfide (CS<sub>2</sub>), methanethiol (CH<sub>3</sub>SH) and sulfur dioxide (SO<sub>2</sub>).<sup>59</sup>

A chelating molecule *N*-propyl-*p*-benzoylbenzamide (**II**) was adsorbed onto silica surface by stirring a suspension of silica gel in ligand solution for its use in the photoisomerization of *trans*-stilbene.<sup>60</sup>

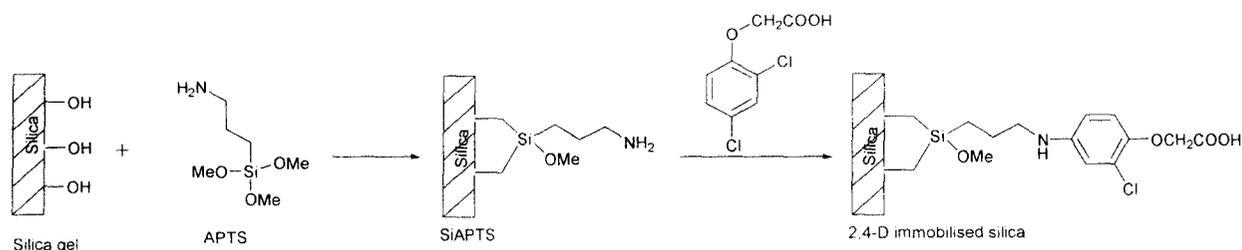


#### I.1.4.4.5 Immobilization of silane reagent

Ion-chelating organic molecules are usually bound to silica surface via silanization procedure<sup>61</sup> that involves covalent grafting. In covalent grafting, the active H atoms of the surface silanol groups dispersed on silica gel surface react with organosilyl groups to give some organic nature to the inorganic matrix of silica gel.<sup>62</sup> The advantages of the immobilization of a desired organic compound onto the silica gel are the great versatility arising from the various functionalities of the bonded groups, which should be resistant to remove from the surface by organic solvent or water.<sup>63</sup>

Silica gel preactivated at 420K and  $10^{-3}$  Torr was made to react with 3-chloropropyltrimethoxysilane in dry xylene in nitrogen atmosphere. Chloropropylsilica thus obtained was further stirred with benzimidazole in pure dimethylformamide solvent to give benzimidazole-modified silica.<sup>64</sup> Preheated silica gel when treated with the silylating agent, 3-(trimethoxysilyl) propylamine (APTS), in an inert medium produced corresponding organofunctionalized silica, which was further treated with 2,4-dichlorophenoxyacetic acid (2,4-D) to yield modified silica with acidic surface (Scheme 4).<sup>47h,64c</sup>

#### Scheme 4

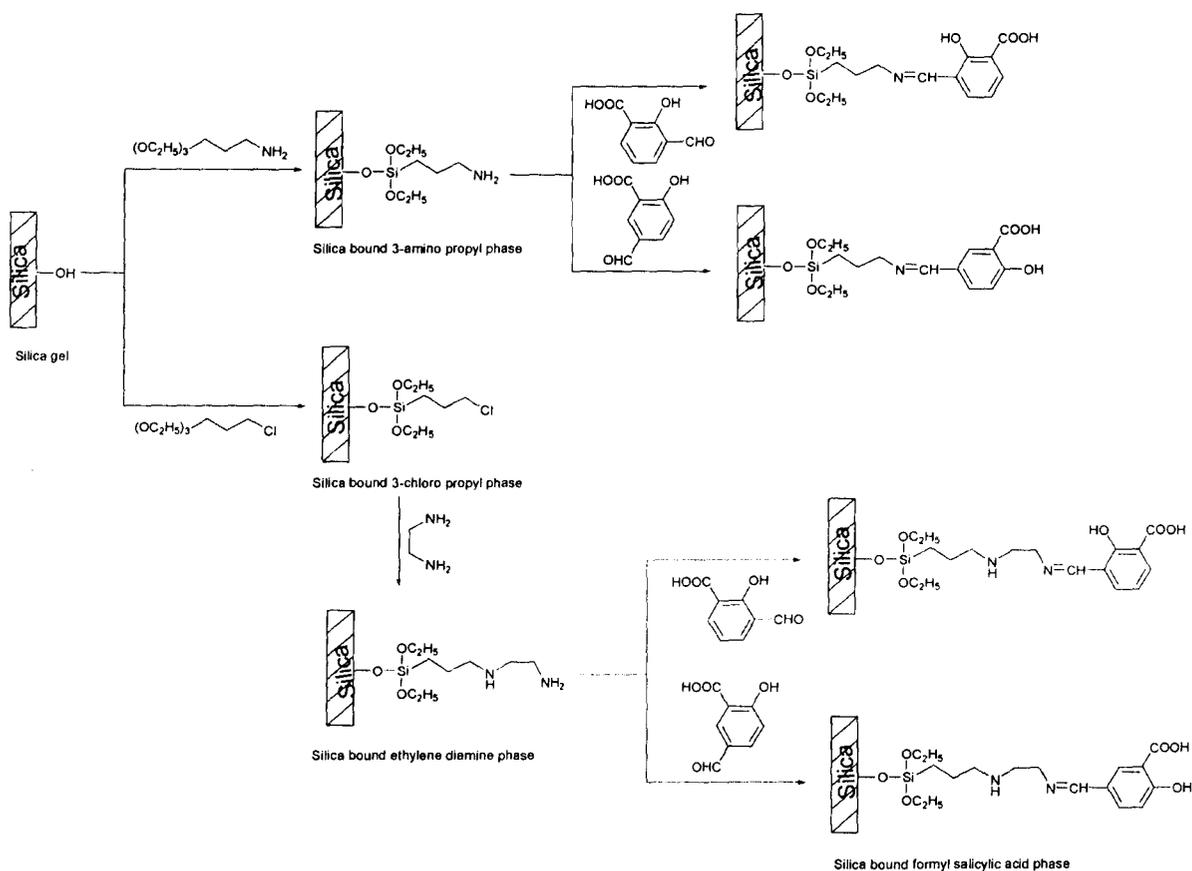


#### I.1.4.4.6 Sol-gel route of surface modification

A method for the preparation of surface-modified silica particle is described as hydrolyzing a tetraalkoxy silane compound in a medium of an alcohol containing 2.5–6.0 moles of water and 0.1–3 moles of an alkaline compound as a catalyst, each per mole of the tetraalkoxy silane compound, to form an alcocol of silica particles having alkoxy groups and hydroxy groups bonded to the silicon atoms on (Scheme 5) the surface; and then admixing the alcocol of silica particles with an organosilicon compound.<sup>65</sup> Using

sol-gel process synthesis of an inorganic-organic hybrid material is reported<sup>66</sup> where an amino-silica intermediate was obtained on stirring a mixture of tetraethoxysilane and 3-trimethoxysilylpropylethylenediamine in presence of HCl in an ice bath for 10 min followed by addition of ethanol and 5% NaHCO<sub>3</sub> solution. The silica particles thus obtained after drying were treated with 1.5% glutaraldehyde solution. Subsequently, glutaraldehyde modified silica when treated with ethylenediamine and NaBH<sub>4</sub> resulted in the desired modified silica.<sup>67</sup>

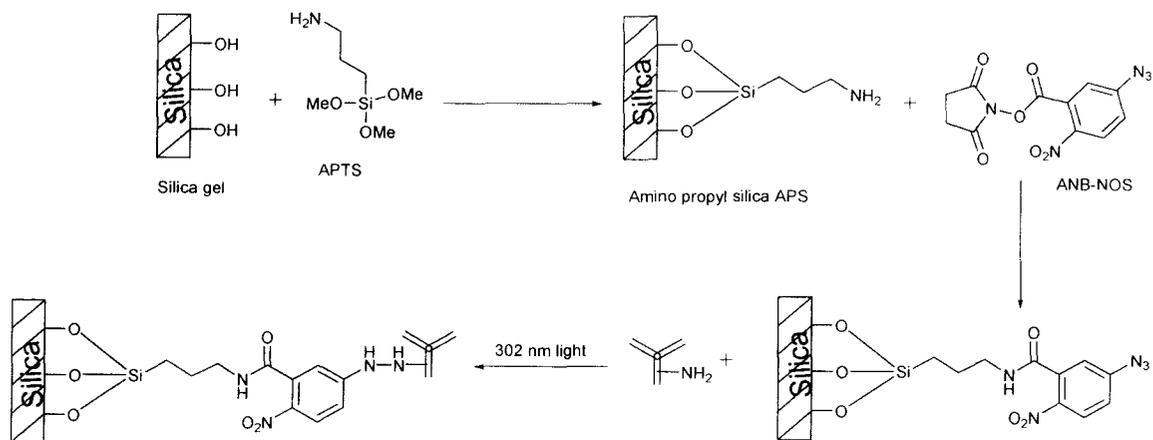
### Scheme 5



#### I.1.4.4.7 Other routes of surface modification

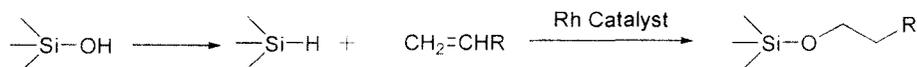
Besides the covalent grafting of silane reagent or sol-gel process, few other methods are also reported as potential routes for modification of silica surface. Preparation of alkyl bonded silica phase includes halogenation of silanol group by reaction of the surface hydroxyl groups of the silica with (Scheme 6) a halogenating agent in anhydrous aprotic solvent followed by reaction with Grignard reagent or organolithium compound.

## Scheme 6



Conversion of surface silanol to surface hydride followed by coupling of terminal olefins in presence of metal catalyst has also modified the silica surface (Scheme 7). Success of synthesis of such a modified surface depends on successful conversion of surface silanol to surface hydride, which can be achieved through either chlorination of surface silanol by  $\text{SOCl}_2$  followed by reduction with  $\text{LiAlH}_4$ <sup>68</sup> or controlled chemisorption of silanetriol,  $\text{HSi}(\text{OH})_3$ , in which the silanetriol is covalently attached to silica surface as well as adjacent silanol via formation of siloxane linkage.<sup>69</sup> Other methods reported for surface modification of silica gel to have a hydride functional group include reaction of silica with either trichlorosilane<sup>70</sup> or methylchlorosilane.<sup>71</sup>

## Scheme 7



### I.1.4.4.8 Some applications of impregnated and modified silica in organic synthesis

Perchloric acid adsorbed on silica gel ( $\text{HClO}_4/\text{SiO}_2$ ) has been found to be a highly efficient and versatile catalyst for the Michael addition of thiols to a wide variety of conjugated alkenes such as  $\alpha$ ,  $\beta$ -unsaturated ketones, carboxylic esters, nitriles, amides and chalcones in dichloromethane or methanol at room temperature (Scheme 8).  $\text{HClO}_4/\text{SiO}_2$  was prepared according to the literature procedure.<sup>72</sup>

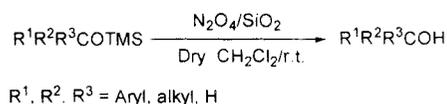
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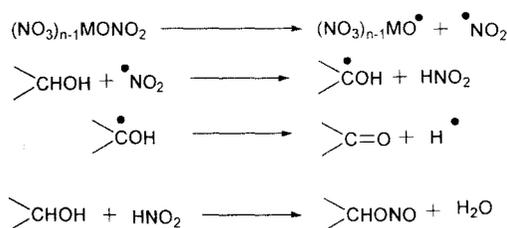


## Scheme 11



Several metallic nitrates supported on silica gel efficiently oxidized secondary alcohols and primary benzyl and allyl alcohols to the corresponding ketones and aldehydes under mild conditions (Scheme 12). Especially,  $\text{Cu}(\text{NO}_3)_2$ ,  $\text{Zn}(\text{NO}_3)_2$  are suitable for practical use. Silica gel was essential for the efficient oxidation in any case. Over oxidation of the formed aldehydes was not observed. Some mechanistic studies suggest that the key step of the process involves the formation of radical species.<sup>76</sup>

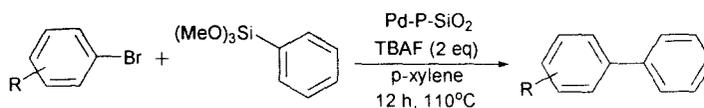
## Scheme 12



Palladium-catalyzed C-C bond formation reactions have been intensively studied and widely used in organic synthesis. In particular, palladium-catalyzed biaryl cross-coupling reactions have been performed with a number of organometallics and a wide range of aryl halides.<sup>77</sup> Although, the cross-coupling reaction has mostly been carried out in homogeneous catalytic systems, these catalysts suffer some drawbacks such as difficult catalyst recovery and separation problems. To address these problems, the immobilization of Pd catalysts on inorganic solid supports<sup>78</sup> or organic polymers<sup>79</sup> has been studied.

Silica-bonded phosphine and palladium catalyst was successfully applied to the stationary phase for the Hiyama coupling reaction in a continuous flow reactor (Scheme 13).<sup>80</sup> The amount of palladium in the silica gel was determined to be 5.92 wt % by ICP-MS method. The potential recyclability of the silica-bonded phosphine/palladium complex ( $\text{Pd-P-SiO}_2$ ) as the catalyst was explored in the model cross-coupling of 4-bromotoluene and trimethoxysilyl benzene.

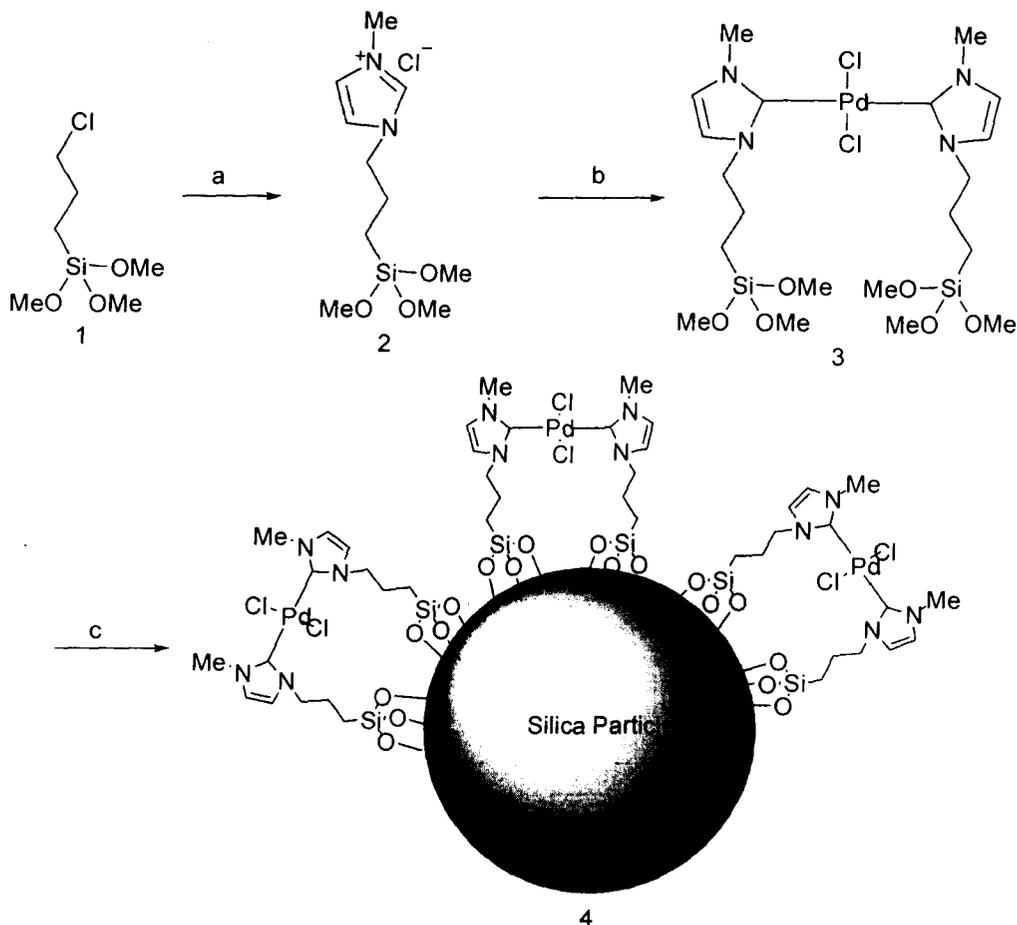
## Scheme 13



1-Methyl-3-(3-trimethoxysilylpropyl)imidazolium chloride,  $[\text{TMSPIM}][\text{Cl}^-]$ , was synthesized as a precursor of N-heterocyclic carbene (NHC), which can be coordinated

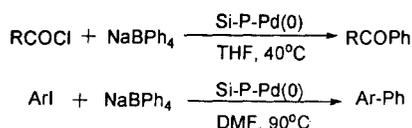
with palladium to give an organosilane-based bidentic NHC-Pd complex. NHC-Pd/silica (Scheme 14) exhibited excellent performance in the Suzuki reaction of various aryl halide derivatives (except for aryl chloride derivatives) with phenylboronic acid under mild conditions (room temperature and short reaction time). The catalyst was recycled several times without any significant loss of catalytic activity in the Suzuki reaction.<sup>81</sup>

#### Scheme 14



In the presence of a catalytic amount of silica - supported phosphine palladium (0) complex, sodium tetraphenylborate ( $\text{NaBPh}_4$ ) reacts with acid chlorides under mild conditions to give the corresponding phenyl ketones in 57 - 80% yields (Scheme 15); it also reacts with aryl iodides to afford the corresponding biaryls in 75-84% yields.

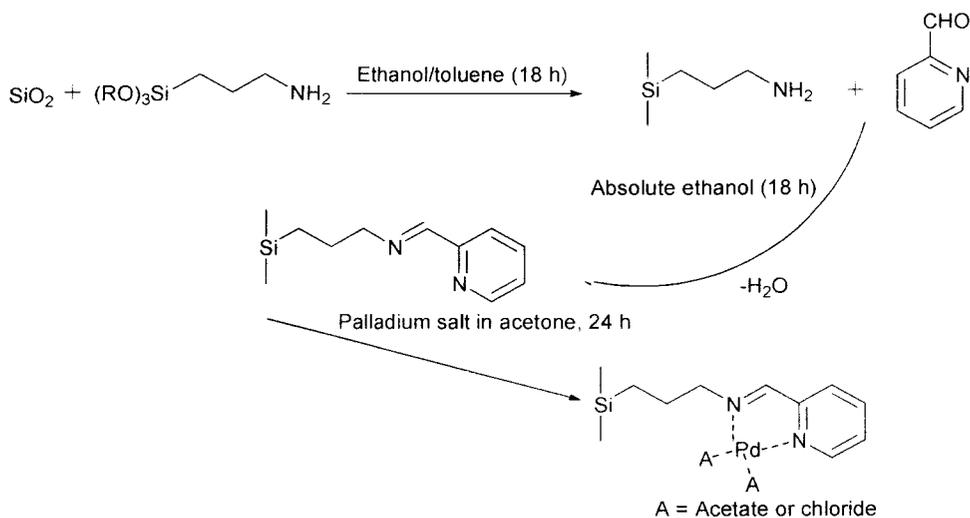
#### Scheme 15



A novel palladium catalyst supported on a chemically modified mesoporous silica gel has been prepared and exhibits high activity and stability in the Heck reaction of aryl

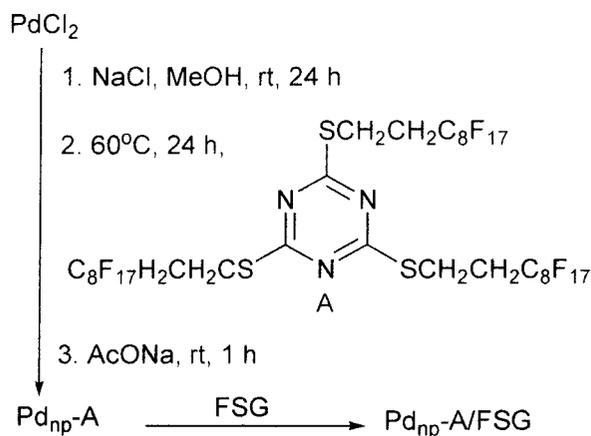
iodides with olefins (Scheme 16). The catalysts has been reused several times in reactions without significant loss of activity and selectivity.<sup>82</sup>

### Scheme 16



The utilization of perfluoro-tagged palladium nanoparticles immobilized on fluorosilica gel through fluorosilica-fluorosilica interactions (Pd<sub>np</sub>-A/FSG) (Scheme 17) in the alkylation of aryl halides, in the Suzuki–Miyaura cross-coupling, as well as in the Heck reaction between methyl acrylate and aryl iodides is described.<sup>83</sup> The catalysts are easily recovered and reused several times without significant loss of activity.

### Scheme 17



Both mesoporous (MCM-41) and spherical silica supported palladium-based diimine catalysts were prepared and their behaviors on ethylene polymerization were studied.<sup>84</sup> Ethylene polymerization with palladium-based catalysts in mesoporous silicas (MCM-41) gave polymers with less branched chains than those obtained with the corresponding homogeneous catalyst.

### I.1.4.5 Zeolitic materials

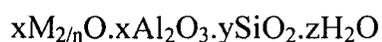
The term zeolite was coined in 1756 by the Swedish mineralogist Cronstedt.<sup>85</sup> Zeolites have a crystal structure which is constructed from  $TO_4$  tetrahedra, where T is either Si or Al. In addition to the relatively small number of naturally occurring zeolite there is a wide range of synthetic materials.<sup>86</sup> Each structure type is given a unique framework code as shown in Table 6. The size of the aperture which controls entry into the internal pore volume is determined by the number of T atoms and oxygens in the ring.

**Table-6 Zeolite codes and ring sizes**

Zeolite	Framework Code	Number of tetrahedral in ring
Sodalite	SOD	4
Zeolite-A	LTA	8
Erionite-A	ERI	8
ZSM-5	MFI	10
Fauzasite	FAU	12
Mordenite	MOR	12 and 8
Zeolite-L	LTL	12

It is possible to tune the pore-opening of a zeolite to allow the adsorption of specific molecules. For example, when  $Na^+$  ions are replaced by  $Ca^{2+}$  ions in zeolite A, the effective aperture increases. The other method used for tuning the pore openings is to change the Si/Al ratio. An increase in the ratio of Si to Al will (i) slightly decrease the unit cell size, (ii) decrease the number of exchangeable cations, thus freeing the channels, and (iii) make the zeolite more hydrophobic in character.

The general formula for aluminosilicate zeolites is:



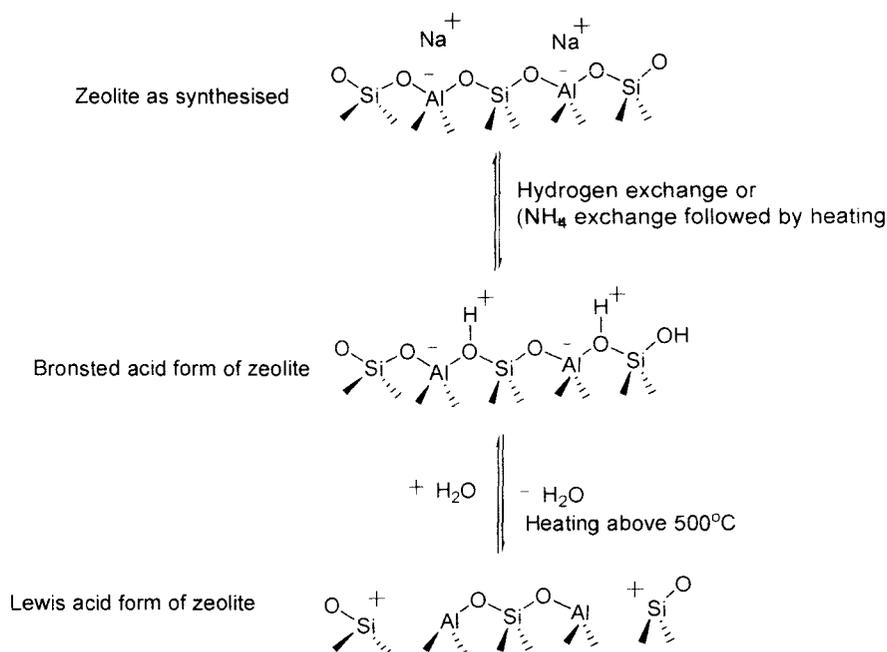
The framework carries a net negative charge equal to the number of tetrahedral aluminium ions. The negative charge is balanced by a corresponding number of non-framework cations, M. The non-framework cations are usually sited in, or have access to, the pores and can be readily exchanged for other ions by treatment with a suitable salt solution. The last component is the aqueous sorbed phase, which can be removed from the sample, without any change to the aluminosilicate framework, by heat treatment. These three components; the framework, the non-framework cations and the sorbed

phase, can each play an important role in determining the catalytic properties of zeolites.<sup>87</sup>

The sites of zeolites are normally protons attached to bridging framework oxygen atoms and are introduced into the zeolite *via* ion exchange. For example, exchange of sodium zeolite Y with ammonium ions gives the  $\text{NH}_4^+$  form, which on heating loses  $\text{NH}_3$  to leave the proton exchanged zeolite (Reaction 1).



Further heating removes water from the Bronsted acid site, exposing a three fold coordinated Al ion which has Lewis acid character. A reaction scheme for the formation of these sites is shown in Fig.2. The surfaces of zeolites can thus display either Bronsted or Lewis acid sites or a combination of the two depending on how the zeolite is prepared. Zeolites with a high Si:Al ratio have the strongest acid sites.<sup>88</sup>



**Fig.2**

#### **I.1.4.5.1 Mesoporous molecular sieves**

The relatively recent synthesis of a family of silica based molecular sieve materials (designated M41S) has attracted considerable interest because of the potential of these materials for use as larger pore catalysts. There have been several reports describing the synthesis of this materials.<sup>89</sup> In the case of MCM-41, active sites are generated by the introduction of heteroatoms into the structure. In particular, Bronsted acid sites are introduced by isomorphous substitution of Al for Si which is achieved by

hydrothermal synthesis in which charged quaternary ammonium micelles are used as the template for charged aluminosilicate inorganic precursors.

#### I.1.4.5.2. Catalytic applications of zeolites and related materials

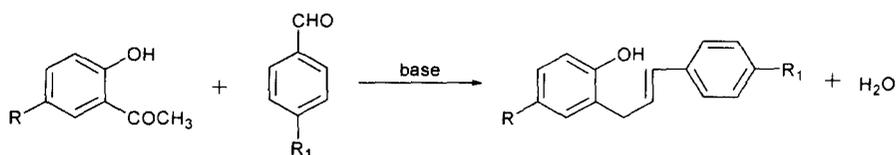
Zeolitic materials are most notably used in catalysis for shape-selective reactions. Aromatic alkylation is a good example of a reaction where the shape selectivity of the zeolite plays an important role in controlling the distribution of products. One of the most important industrial alkylations is the production of 1,4-xylene from toluene and methanol (Scheme 18). ZSM-5, in the proton exchanged form, is used as the catalyst because of its enhanced selectivity for para substituted products. The selectivity of the reaction over HZSM-5 occurs because of the difference in the rates of diffusion of the different isomers through the channels.<sup>90</sup>

#### Scheme 18



It has been reported that zeolites can be used as base catalysts when exchanged with alkali metal ions. The Cs<sup>+</sup>-exchanged zeolites, which are the most basic, have been shown to catalyse the Claisen Schmidt condensation between substituted 2-hydroxyacetophenones and substituted benzaldehyde to give the 2'-hydroxychalcone structure (Scheme 19).<sup>91</sup>

#### Scheme 19



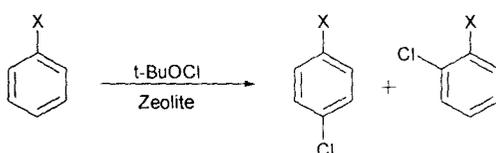
Other base catalysts such as magnesium *t*-butoxide and barium hydroxides have been used to perform the synthesis.<sup>92</sup> However, the Cs<sup>+</sup>-exchanged zeolites offer a more environmentally friendly alternative route. Cs<sup>+</sup>- and Na<sup>+</sup>-exchanged MCM-41 type materials also have basic character and have been found to be active towards the base catalysed Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate (Scheme 20).<sup>93</sup>

## Scheme 20



*t*-Butyl hypochlorite/HNa faujasite in acetonitrile represents an efficient and highly regioselective system of mono-chlorination of a wide range of mono- and disubstituted aromatic substrates in mild conditions (Scheme 21).<sup>94</sup> Partially protonated faujasite X is far superior to amorphous silicas and to other zeolites in terms of efficiency and regioselectivity (Table 7).

## Scheme 21



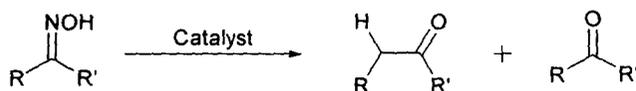
**Table 7 Influence of the Catalyst on the Chlorination of Toluene**

Catalyst	Conversion of toluene (%)	Products
HCaA	0	No Product
NaZSM-5	7	52% <i>p</i> -chlorotoluene 48% dichlorotoluenes
HNaZSM-5	20	47% <i>p</i> -chlorotoluene 53% <i>o</i> -chlorotoluene
HNaMordenite	15	40% <i>p</i> -chloro toluene 60% <i>o</i> -chlorotoluene
KL	0	No Product
NaX	11	65% <i>p</i> -chlorotoluene 35% <i>o</i> -chlorotoluene
HNaX	90	65% <i>p</i> -chlorotoluene 35% <i>o</i> -chlorotoluene
Kieselgel 60 (Silica)	80	40% <i>p</i> -chlorotoluene 60% <i>o</i> -chlorotoluene

The Beckmann rearrangement has been extensively studied for many years. The classical large-scale rearrangement of cyclohexanone oxime is carried out in the liquid phase using concentrated sulfuric acid. In the case of  $\beta$ -zeolite without silanol groups but with framework Al, conversion and selectivity are high. During the Beckmann

rearrangements studied, both the amide and the parent ketone can be observed as products (Scheme 22). The results for different zeolites are shown in Table 8.

### Scheme 22

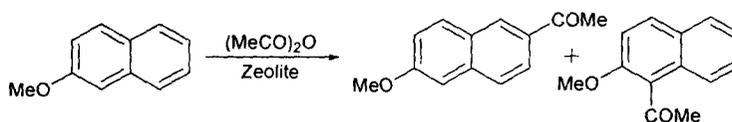


**Table 8 Beckmann rearrangement of cyclohexanone oxime over zeolites**

Zeolite	Conversion	Proportion of product
Aerosil	5	98% ketone
H-ZSM5 (high Al, High silanol)	67	95% amide
Amorphous silica	0.1	72% amide
$\beta$ -D (low Al, high silanol)	38	98% amide
$\beta$ -ND1 (low Al)	0	No product
H- $\beta$ -D (high Al, low silanol)	54	98% amide
H- $\beta$ -D (high Al, High silanol)	68	98% amide

The Fries rearrangement provides another important route to ketones. The rearrangement of phenyl acetate to hydroxyacetophenones can be used on route to *p*-hydroxyacetanilide, which is an important painkiller (paracetamol) (Scheme 23).

### Scheme 23

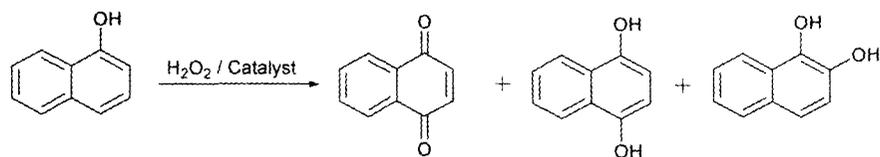


Zeolite	Conversion	Selectivity
HBEA (Untreated)	30	19:81
HBEA (Calcined)	39	53:47
HBEA (Acid treated)	54	10:90

Zeolite catalysed acylation of 2-methoxy naphthalene

Stannosilicates that can catalyse various oxidation reactions under mild conditions.<sup>95</sup> Whereas, the tin-free analogues are inactive as catalysts in the hydroxylation of phenol and 1-naphthol, the tin materials give reasonable turnover numbers in the reactions (Scheme 24). Interestingly, the impregnated versions showed poor activity presumably because of the need for highly active Sn<sup>4+</sup> centres, which are incorporated into the framework of the Sn-MCM as opposed to the impregnated materials.

## Scheme 24

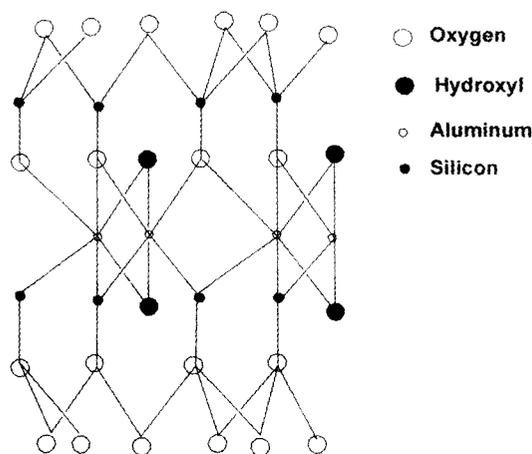


Catalyst	Conversion	Product distribution
Sn-MCM-41	19	82:13:5
Sn-impregnated MCM-41	1	50:50:0
SnO <sub>2</sub>	0.5	60:20:20

Hydroxylation of naphthalene using Sn-mesoporous materials

### I.1.4.6. Clay materials

Clays are naturally occurring layered silicates. They are essentially crystalline materials of very fine particle size, nominally  $< 2 \mu\text{m}$  in diameter. The crystal structure of clay minerals was first proposed by Pauling<sup>96</sup> and the validity of his model was confirmed by the powder X-ray diffraction technique.<sup>97</sup> According to Pauling's model the structure can be described as shown in Fig.3. SiO<sub>4</sub> tetrahedra are linked in two dimensions to form repeated hexagonal patterns of basal oxygens, *i.e.* tetrahedral sheets. AlO<sub>4</sub>(OH)<sub>2</sub> octahedra are also linked to form octahedral sheets. The octahedral sheet is further divided into two types: the dioctahedral type where two thirds of octahedral cation sites are occupied by trivalent cations (Al<sup>3+</sup>, Fe<sup>3+</sup>, *etc.*) and the trioctahedral type where all the sites are fully occupied by divalent cations (Mg<sup>2+</sup>, *etc.*): when one octahedral sheet and two tetrahedral sheets are joined together the 2:1 triple layer is formed.<sup>97</sup>



Structure of a 2:1 type clay

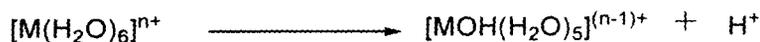
**Fig.3**

The silicate layer is an electrically neutral structure. If part of tetrahedral Si<sup>4+</sup> or octahedral Al<sup>3+</sup> is isomorphously substituted by lower valency cations the sheet becomes negative. In this case the clay will have exchangeable cations between every layer to

compensate for the negative charge of the layers. The cation exchange capacity (CEC) of clay is equivalent to the layer charge and is dependent on the degree of isomorphous substitution.

The primary classification is based on layer charge and has four groups: pyrophyllite, smectites, vermiculites and micas. Montmorillonite, which is the most commonly used clay for catalysing organic reactions, is smectite clay in which the unit layer is composed of one octahedral sheet containing aluminium and magnesium ions sandwiched between two sheets of silica oxygen tetrahedra. In between the layers are hydrated metal ions, usually  $\text{Na}^+$  or  $\text{Ca}^{2+}$  in the natural materials. The thickness of one layer is about 0.96 nm but the interlayer spacing can vary according to the extent of hydration.<sup>98</sup> When smectites are immersed in water, both intercalation of water molecules and swelling occurs. The suspended clay can also freely exchange its interlayer cations for other cations in solution. Interlayer water molecules are dissociated producing protons and exhibit Bronsted acidity (Scheme 25).<sup>99</sup>

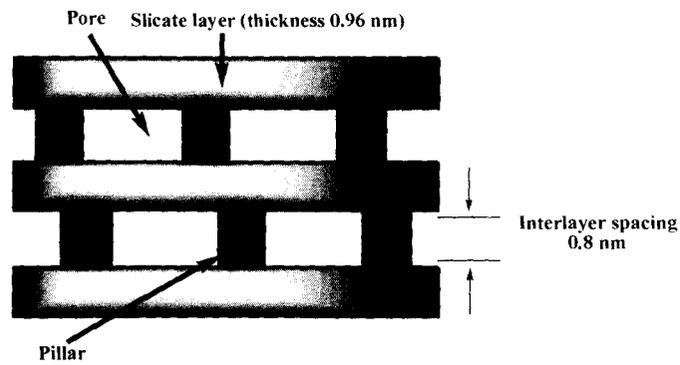
#### Scheme 25



The higher the electronegativity of the interlayer metal cation  $\text{M}^{n+}$  the stronger the acid sites. When montmorillonite is ion-exchanged with  $\text{Al}^{3+}$  ions, it displays a very high activity towards several Bronsted acid catalysed reactions, comparable to that of 98%  $\text{H}_2\text{SO}_4$ .<sup>100</sup>

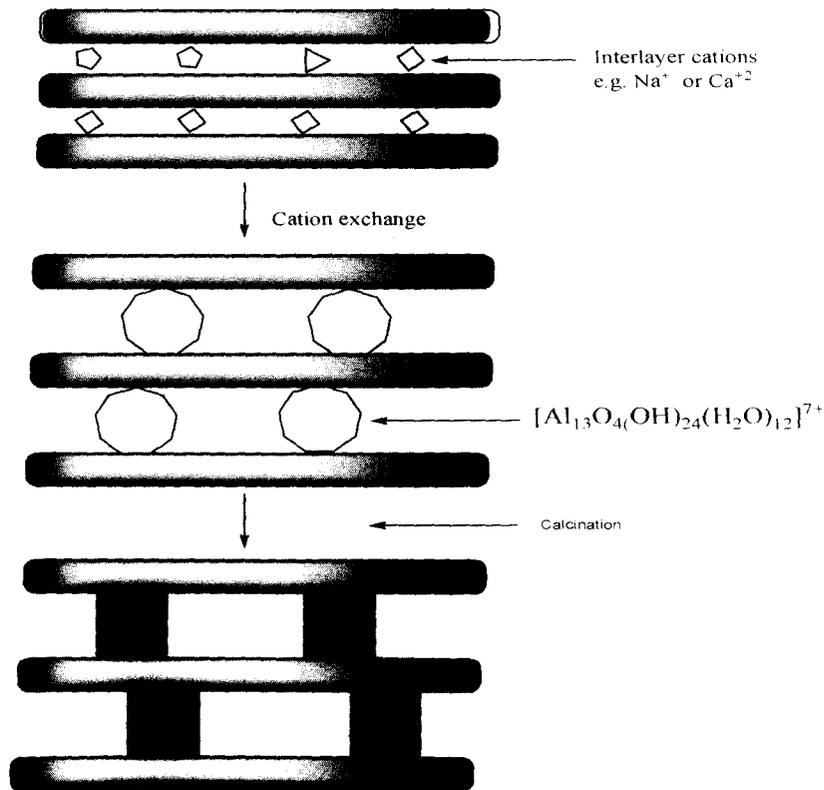
#### 1.1.4.6.2 Pillared clays

Many heterogeneous catalytic reactions are carried out at high temperatures of over 200°C. Natural clay minerals suffer from the disadvantage of interlayer collapse at temperatures greater than approximately 2000°C with consequent loss of catalytic activity.<sup>101</sup> Clays pillared with robust and large inorganic hydroxyl cations overcame the problem of thermal stability and attracted attention as potential catalysts.<sup>102</sup> Fig.4 is a schematic representation of pillared clay. Oxide pillars are inserted between the silicate layers, producing a heat-stable porous material.



**Fig.4**

The method for preparing alumina-pillared clay is shown in Fig.5. Interlayer  $\text{Na}^+$  ions in the original clay are exchanged with aluminium hydroxyl cluster cations. When this material is calcined at between 300 and 500 °C, the cations become oxide pillars and release protons into the structure. An acidic and porous clay with a surface area of 200-500  $\text{m}^2 \text{g}^{-1}$  is thus formed. The pillaring procedure makes good use of the intercalation ability of smectite clays and the resulting microporous solid retains a large exposed surface area even up to 600°C.<sup>103</sup>



**Fig.5**

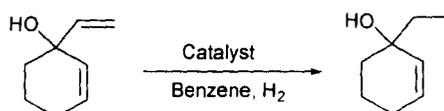
### 1.1.4.6.3 Clay catalysed reactions

The high surface area of clays also makes them particularly attractive as catalyst and reagent supports. The smectite clays do, however, have some important features which make them particularly attractive as catalyst supports. In addition to their high intrinsic surface area, their laminar structure may confer size and shape selectivity to the resultant catalysts. Another important feature is the negative charge on the silicate layers which may be able to polarise reactant molecules and enhance catalytic activity.

Most applications for clays as catalysts have been in acid catalysed reactions<sup>99,104</sup> but as an understanding of clays has developed, they have been used as the basis for a large number of more varied catalysts.<sup>2d</sup>

Palladium (II) ions have been shown to be effective hydrogenation catalysts when exchanged into a clay matrix. The rates of hydrogenation over a montmorillonite exchanged with diphenylphosphine palladium chloride decrease in the order cyclohexene > cyclopentene » cycloheptene. The same catalyst also shows a high selectivity towards the hydrogenation of non-hindered double bonds (Scheme 26).<sup>105</sup>

**Scheme 26**



The acid-treated clay Engelhard F-24 was found to be a very effective catalyst for the alkylation of diphenylamine with  $\alpha$ -methylstyrene (Scheme 27).<sup>106</sup>

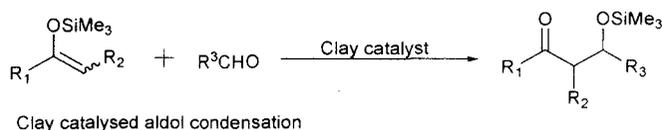
**Scheme 27**



There has been a quite limited number of reports of clay-catalysed aldol condensations. One of the more interesting of these is the aluminium-exchanged montmorillonite (Al<sup>3+</sup>-mont) catalysed cross-aldol reaction of silyl enol ethers with aldehydes (Scheme 28).<sup>107</sup> The diastereoselectivity of the reaction was independent of the catalyst but was affected by the nature of the solvent. The *threo* isomer was preferentially formed in toluene, while the *erythro* isomer was formed in 1,2-dimethoxyethane. The proton-exchanged montmorillonite (H<sup>+</sup>-mont) showed similar activity and diastereoselectivity to Al<sup>3+</sup>-mont. This fact suggests that the exchangeable Al<sup>3+</sup> cations in

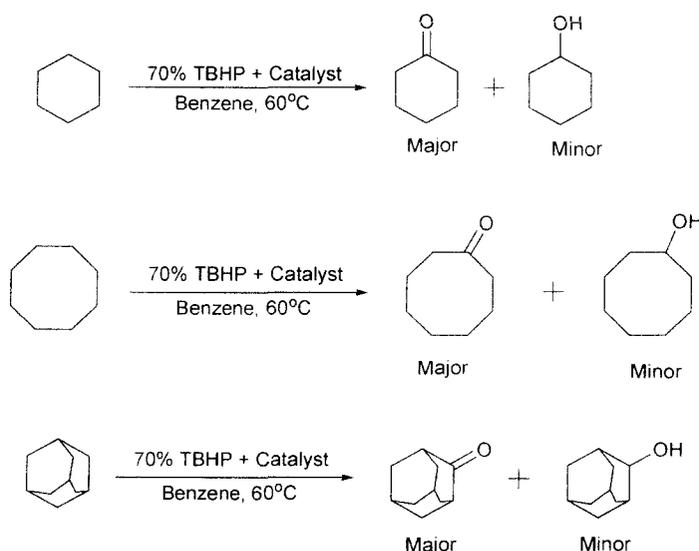
the montmorillonite do not function as Lewis acid sites and it is the Bronsted acid sites that are essential for catalysis of the aldol reaction.

### Scheme 28



Tateiwa *et al.* prepared a  $Mn^{2+}$ -exchanged clay catalyst.<sup>108</sup>  $Mn^{2+}$ -exchanged montmorillonite has been found to be an effective catalyst for the oxidation of alkanes such as cyclohexane, cyclooctane and adamantane to give the corresponding ketones (Scheme 29). Other ion-exchanged montmorillonites such as  $Al^{3+}$ -,  $Fe^{3+}$ -,  $H^+$ - and  $Na^+$ -exchanged montmorillonite showed only very low catalytic activity towards the oxidation.

### Scheme 29



#### I.1.4.7 Organic reactions on alumina and modified alumina

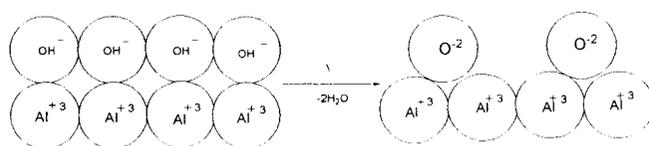
Of the metal oxides, alumina is particularly interesting. It has been used industrially as filler, adsorbent, drying agent, catalyst, catalytic support, precursor to aluminium metal, and as a reagent in the synthesis of the other aluminium-containing compound such as aluminium sulphate and fluoride.<sup>109</sup> What is especially interesting to the organic chemist is that alumina can be used as catalyst, support and reagent. Because the surface of alumina can be modified in a variety of ways, the number of potential environments available for organic reactions is very large.

#### 1.1.4.7.1 Nature of alumina and modified alumina

The term alumina refers to a series of ionic solids which have ionic formula,  $\text{Al}_2\text{O}_3 \cdot (\text{H}_2\text{O})_n$  where  $n = 0$  to  $3$ , although none of them contains  $\text{H}_2\text{O}$ . They are derived by heating naturally occurring or synthetic, crystalline, and amorphous  $\text{Al}(\text{OH})_3$ ,  $[\text{Al}_2\text{O}_3(\text{H}_2\text{O})_3]$  and  $\text{AlO}(\text{OH})$  and  $[\text{Al}_2\text{O}_3(\text{H}_2\text{O})]$ . The endpoint in the synthesis, which occurs by heating the materials above  $1100^\circ\text{C}$  is corundum, one of the hardest substance known, and the thermodynamically most stable form of  $\text{Al}_2\text{O}_3$ . This material is not widely used in organic synthesis. At temperature below  $1100^\circ\text{C}$ , a series of transition aluminas can be generated whose structures are dependent on the precursor, final temperature and mode of heating. During the course of thermolysis, hydroxyl groups combine to generate  $\text{H}_2\text{O}$  which is driven from the solids. Heating to  $600^\circ\text{C}$ , for example yields the  $\gamma$  series of aluminas which contain  $\rho$ ,  $\chi$ ,  $\eta$  and  $\gamma$  types; these materials, have the formula  $\text{Al}_2\text{O}_3 \cdot (\text{H}_2\text{O})_n$ , with  $n < 0.6$ . Higher temperatures,  $800$ - $1000^\circ\text{C}$ , yield the  $\delta$  series of aluminas which contain very few OH groups ( $n=0$ ) and include  $\kappa$ ,  $\theta$ , and  $\delta$  varieties, all of which are more crystalline than the  $\gamma$  varieties. Although outwardly these transition aluminas are much alike, they possess different physical properties including densities, surface areas, pore volumes and diameters.

When exposed to water, the surfaces of the transition aluminas are hydrated, yielding a surface layer of hydroxyl groups.<sup>110</sup> According to peri,<sup>110</sup> the ideal surface of hydrated  $\gamma$ -alumina from the side is terminated by hydroxyl groups, each of which is directly above an aluminium ion in the next layer of the crystallite. Since, there are  $12.5$  hydroxyl groups on the surface per  $100 \text{ \AA}^2$ , this corresponds to  $3.2 \text{ mmol}$  of hydroxyl groups per gram of solid for an alumina with a surface area of  $155 \text{ m}^2/\text{g}$ . Water may also be hydrogen bonded to the surface hydroxyl groups. When the solid is heated, physisorbed  $\text{H}_2\text{O}$  is lost initially and the adjacent hydroxyl groups react with one another by proton transfer to generate oxide ( $\text{O}^{2-}$ ) and  $\text{H}_2\text{O}$ , which is driven from the surface. Higher activation temperatures result in the production of greater quantities of water. At  $400^\circ\text{C}$ , for example, about  $50\%$  of the hydroxyl groups are lost; at  $600^\circ\text{C}$ ,  $80\%$  are lost, at  $800^\circ\text{C}$ , close to  $100\%$  are removed. Furthermore, when  $\text{H}_2\text{O}$  is driven from the surface, one  $\text{Al}^{+3}$  ion is exposed for every  $\text{O}^{2-}$  that is generated (Scheme 30).

### Scheme 30



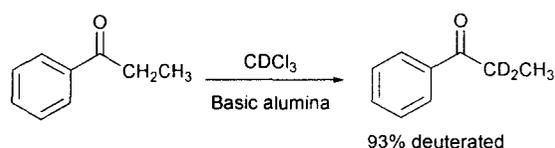
Thus, there are three species on the surface,  $\text{OH}^-$ ,  $\text{O}^{2-}$ , and  $\text{Al}^{+3}$ , whose concentrations are independent and controlled by the activation temperature. Based on this model, the surface can exhibit a variety of properties;  $\text{OH}^-$  will act as a very weak Bronstead acid<sup>111</sup> as well as a base and possibly a nucleophile,  $\text{O}^{2-}$  should be a strong base and nucleophile, and  $\text{Al}^{+3}$  is a Lewis acid. Because the ions are immobile at the temperatures used to carry out organic reactions, an activated solid will have strongly basic and acidic sites adjacent to each other which is not possible to achieve in any solution.

Unactivated  $\gamma$ -alumina is basic.<sup>112</sup> When contacted with water, for example, it yields a basic solution. Basic, neutral, and acidic aluminas, available commercially from several sources, are the types most commonly used in organic synthesis. Alumina is also amphoteric. When the solid is brought into contact with a sufficiently basic solution (pH greater than the solid's isoelectric point which normally occurs at pH = 7.2-9), the surface hydroxyl groups are deprotonated and cations are placed onto the alumina surface under reversible conditions.

#### I.1.4.7.2 Alumina catalysed reactions

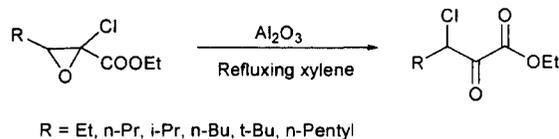
It is clear that the surface of alumina provides a polar environment,<sup>113</sup> favourable to many ionic and heterolytic reactions.  $\text{D}/\text{Al}_2\text{O}_3$  has been used to deuterate a variety of hydrocarbons and ketones.<sup>114</sup> Kunick and Messinger developed an alternative method of deuteration<sup>115</sup> in which basic alumina is used to catalyze the exchange and  $\text{CDCl}_3$ , an acidic molecule, is the source of deuterium (Scheme 31).

#### Scheme 31



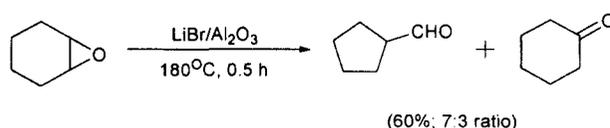
Chloroepoxystyrenes, formed in the Darzens condensation, isomerize in high yield to single products on alumina in refluxing xylene (Scheme 32).<sup>116</sup> No reaction occurs in the absence of alumina.

### Scheme 32



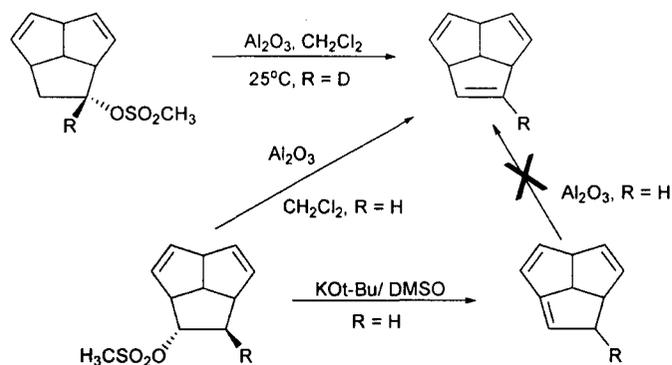
The supported reagent, LiBr adsorbed on  $\text{Al}_2\text{O}_3$  ( $\text{LiBr}/\text{Al}_2\text{O}_3$ ), also catalyzes the isomerisation of epoxides to aldehydes and ketones, either in refluxing toluene or in the gas phase at  $180^\circ\text{C}$  (Scheme 33).<sup>117</sup>  $\text{LiCl}/\text{Al}_2\text{O}_3$ ,  $\text{MgBr}_2/\text{Al}_2\text{O}_3$  and  $\text{LiBr}/\text{SiO}_2$  were less effective catalysts for these reactions. A mixture of LiBr and  $\text{Al}_2\text{O}_3$  also was not effective. Clearly, the Lewis acidic cation, its concentration, and the support influence these reactions.

### Scheme 33



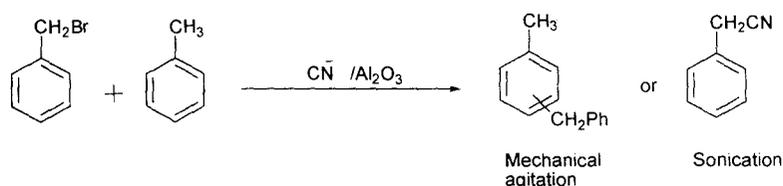
Because activated alumina is polar, contains potentially catalytic acid and base sites on its surface, and is itself dehydrated, it is not surprising that elimination and dehydration reactions occur readily on alumina.<sup>118</sup> Posner was the first to study surface catalyzed elimination reactions from a synthetic perspective.<sup>119</sup> Paquette prepared triquinacene<sup>120</sup> and optically active deuterotriquinacene<sup>121</sup> by elimination of  $\text{CH}_3\text{SO}_3\text{H}$  from the corresponding mesylates using alumina (Scheme 34).

### Scheme 34



Several Friedel-Crafts alkylation reactions on alumina are known.<sup>122</sup> In an attempt to convert an alkyl bromide into a nitrile, benzylbromide was treated with  $\text{CN}^-$  on  $\text{Al}_2\text{O}_3$  in aromatic solvent. Inexplicably, mechanical agitation of the mixture afforded the Friedel-Crafts products, whereas sonication of the mixture yielded the expected benzyl nitrile (Scheme 35).<sup>122, 123</sup>

### Scheme 35

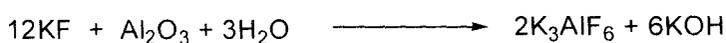


#### I.1.4.7.3 KF-Alumina

Evaporation of KF in water onto alumina yields a widely used, very basic solid containing no free  $\text{F}^-$ .<sup>28</sup> The areas in which alumina and modified aluminas, particularly  $\text{KF}/\text{Al}_2\text{O}_3$ , have found their greatest use in organic synthesis are the base catalyzed and base induced condensation reactions, conjugate additions and ylide reactions.

Fluoride is a weak base in water where it is highly solvated. On the other hand in aprotic dipolar solvents, where anions are poorly solvated,  $\text{F}^-$  is a strong base.<sup>124</sup> Several investigators have reported the characterization of  $\text{KF}/\text{Al}_2\text{O}_3$  using a variety of spectroscopic and physical organic methods.<sup>125</sup> It is clear from these studies that KF reacts with  $\text{Al}_2\text{O}_3$  to generate base: (Scheme 36)

#### Scheme 36

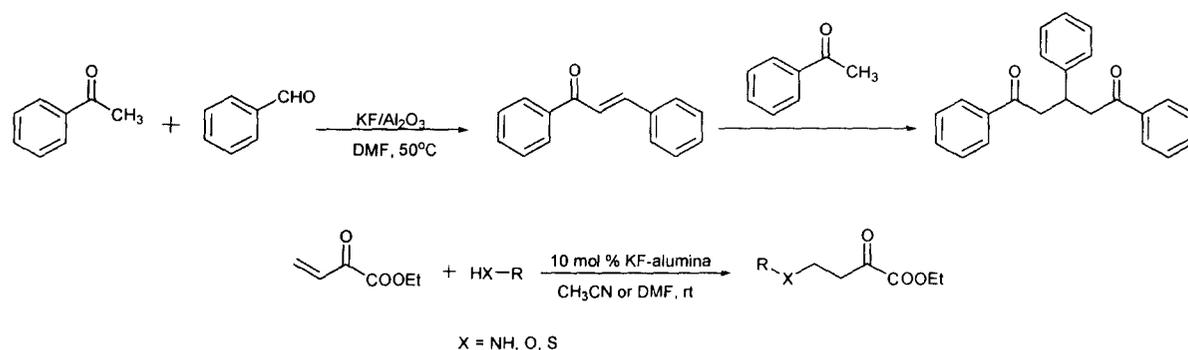


However, the activity of  $\text{KF}/\text{Al}_2\text{O}_3$  is not entirely due to the KOH generated because catalytic activity is greater than one can ascribe to KOH alone. Co-ordinately unsaturated  $\text{F}^-$ , i.e. unsolvated and the cooperative interaction of  $\text{F}^-$  with the hydrated surface may also contribute to the basicity.<sup>125</sup> The nature and causes of the basicity of this surface is however debatable in literature. While the basicity of the surface has been explained in the light of a very hard anion ( $\text{F}^-$  anion), the presence of hydroxide anion ( $\text{OH}^-$  anion), derived from the reaction of KF and alumina, can not be ruled out. The  $^{19}\text{F}$  MASNMR and IR spectroscopic measurements have also shown that  $\text{F}^-$  species on  $\text{KF}/\text{alumina}$  is more electron rich than  $\text{F}^-$  ions in solid potassium fluoride. Therefore it has been presumed that the combination of active fluoride anion as well as the hydroxide anion is accountable for the basicity of the solid surface.

The conditions of activation and the loading of KF on alumina seem to be critical to its properties. On several occasions, use of  $\text{KF}/\text{alumina}$  has been compared with other solid basic surfaces and the former has been found to be more basic, more active and more selective in respect of reaction behaviour, mildness, yield and reusability.

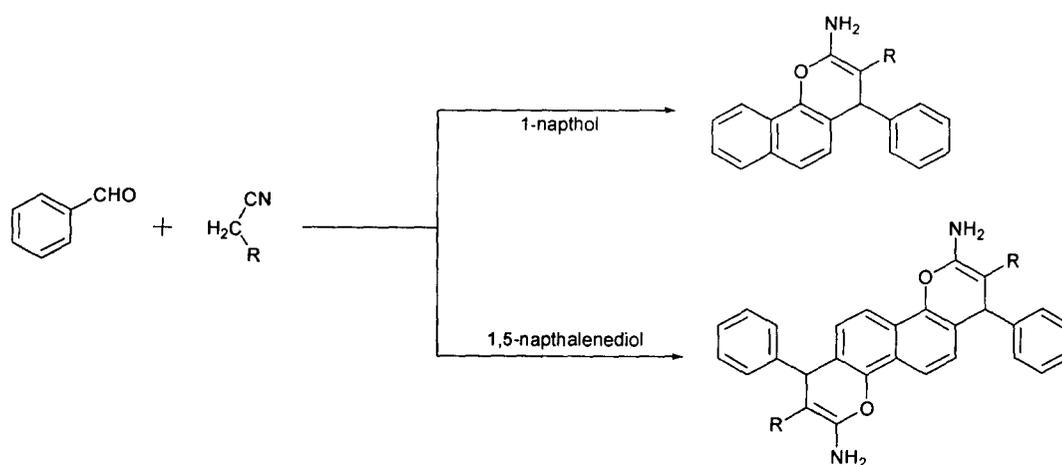
Alumina impregnated with potassium fluoride has been extensively used as solid basic surface in vast range of organic transformations since it was introduced by T. Ando and J. H. Clark.<sup>126</sup> Aldol and related condensations, Knoevenagel condensations, Michael and heteromichael condensation has been achieved on this surface very successfully (Scheme 37).

### Scheme 37



KF/alumina could catalyze Knoevenagel condensation of ethylcyanoacetate with aromatic aldehyde in ethanol under ultrasound irradiation.<sup>127</sup> Initial Knoevenagel condensation of aryl aldehydes with active methylene compounds followed by adduct with 1-naphthol or 1,5-naphthalenediol<sup>128</sup> can be efficiently performed in a one pot reaction on KF/alumina surface leading to the formation of tri- and tetracyclic compounds (Scheme 38).

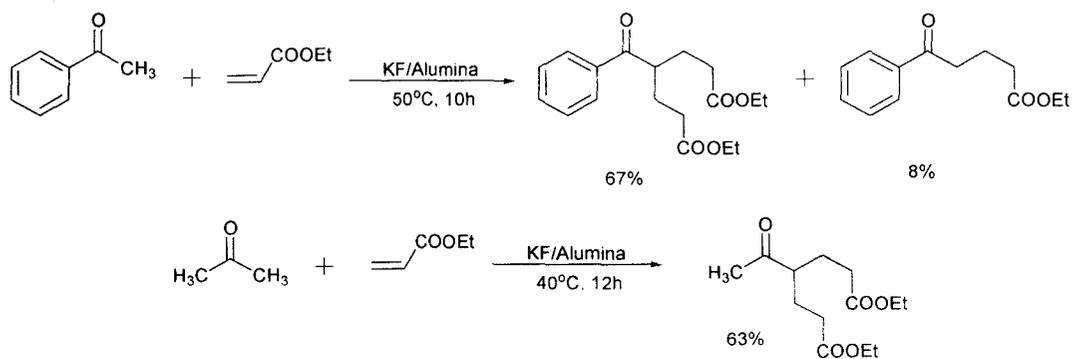
### Scheme 38



Michael condensation of nitro alkanes with electron deficient alkenes catalyzed by KF/alumina has been well documented.<sup>129</sup> A novel and expedient method for the selective double Michael additions of aromatic and aliphatic methyl ketones to activated olefins

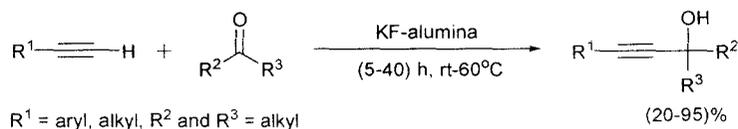
mediated by KF/alumina has been developed by Basu et al. (Scheme 39) that provides rapid access to a host of heptanedioic acid derivatives of high synthetic utility.<sup>130</sup>

### Scheme 39

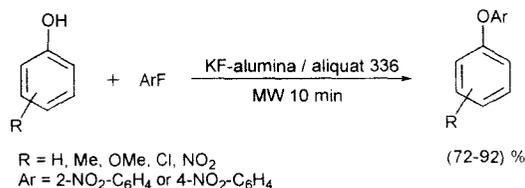


There are so many examples of KF/alumina mediated solvent free C-alkynylation of ketones (Scheme 40),<sup>131</sup> O-arylation of phenols (Scheme 41).<sup>132</sup>

### Scheme 40



### Scheme 41



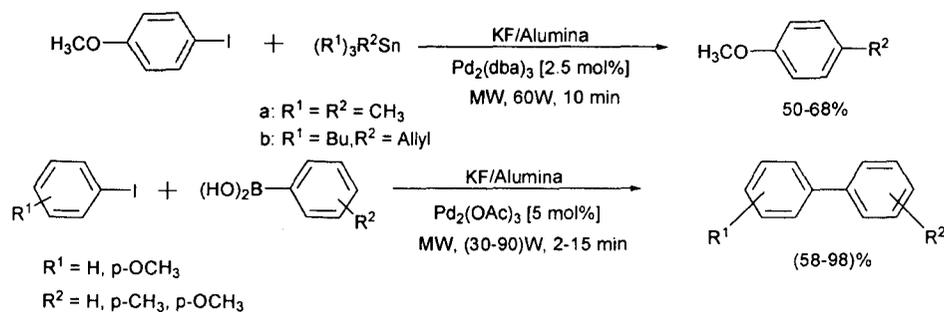
Although alumina and KF/alumina is not oxidizing agent, they can provide appropriate for heterogeneous oxidation process in combination with suitable oxidizing agents. Villemin et al. the oxidation of various substrates on solid basic surface of KF/alumina.<sup>133</sup> They have shown that several active methylene compounds can be oxidised with thiosulfonic esters,<sup>133a</sup> iodine<sup>133b</sup> or molecular oxygen.<sup>133c</sup>

Epoxydation of  $\alpha,\beta$ -unsaturated ketones was performed by using a combination of KF/alumina as a base and tertiarybutylhydroperoxide as oxidant.<sup>2h</sup> The higher activity of KF/alumina with TBHP in contrast with that of heterogeneous base hydrotalcite has been explained by the differences in surface area and basicity. Several reducing agent supported on alumina and KF/alumina have been employed as potential reductants.<sup>134</sup> Catalytic transfer hydrogenation with the aid of a stable hydrogen donor is a useful

alternative method to catalytic hydrogenation by molecular hydrogen.<sup>135</sup> Figueras and co-workers studied hydrogen transfer reduction of 4-tertiarybutylcyclohexanone by propan-2-ol as the hydrogen source on a solid basic surface. Several solid bases were employed to catalyze the transfer hydrogenation and they reported that the stronger base KF/alumina had shown low activity for hydrogen transfer.<sup>136</sup>

Transition metal catalysed C-C or C-N coupling reactions are important organic transformations to prepare diverse array of organic molecules. In many reactions, a base is required to trap the liberated acids and while carrying out similar reactions on heterogeneous basic surface, KF/alumina have been employed successfully as potential base (Scheme 42).<sup>137</sup>

### Scheme 42



Suzuki coupling reactions between aryl halide aryl boronic acids

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