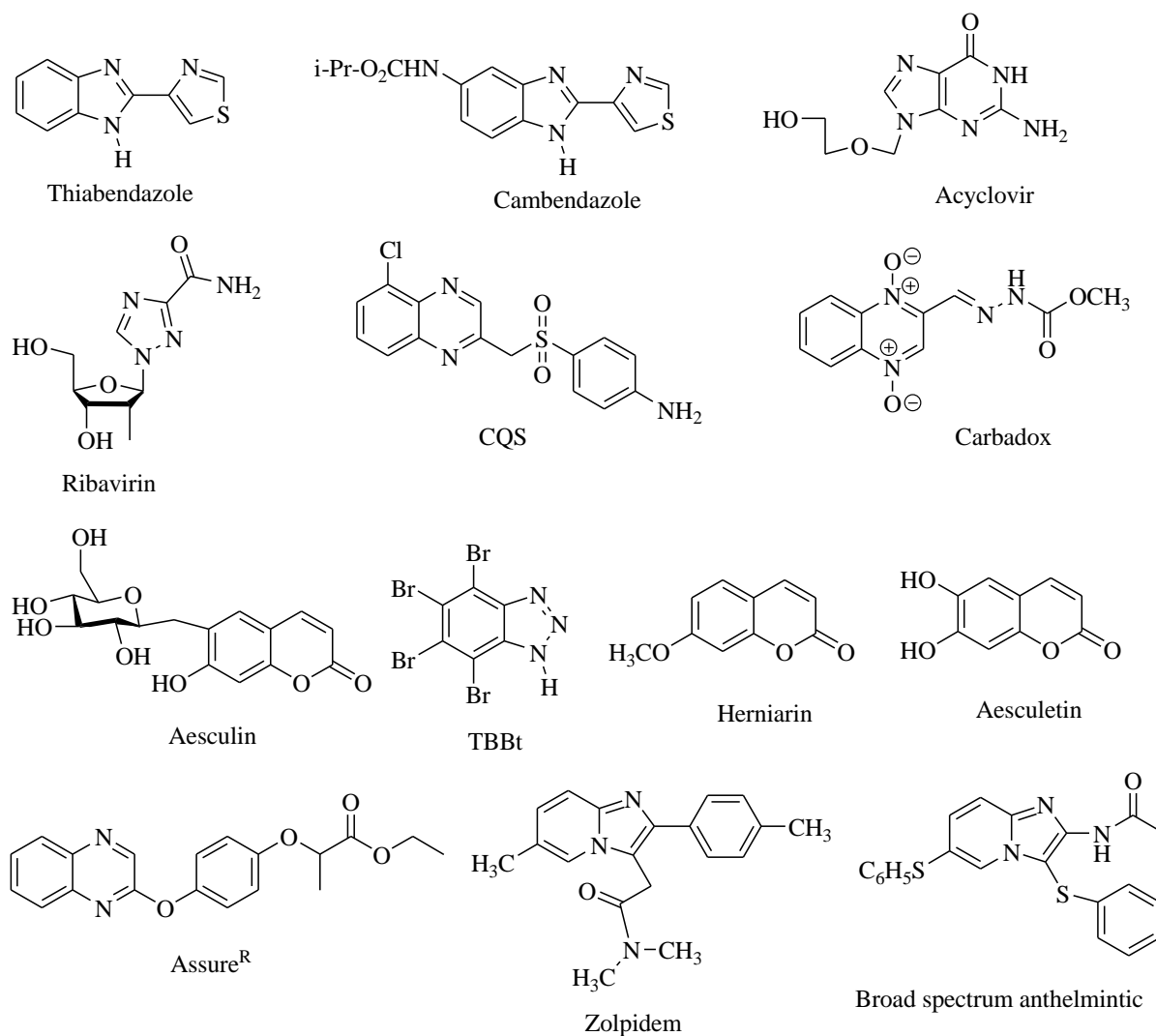


## **CHAPTER I**

**Solid-supported organic reactions with special emphasis  
on Silica and Graphene oxide (GO)**

## I.A. General Introduction

Heterocyclic compounds probably constitute the largest and most varied family of organic compounds. They are widely distributed in nature.<sup>1-3</sup> The various natural products, dyestuffs and pigments consist of heterocyclic core having wide range of application in pharmaceuticals, textiles, leather industries, bio-engineering, lubricants, paints, food and nutrition.<sup>4</sup> Besides, heterocycles are versatile building blocks in various organic syntheses. Heterocyclic moieties may be regarded as the basic of all living organisms whether that is the fundamental unit of haemoglobin or DNA or chlorophyll. Poly-functionalized heterocyclic compounds containing five or six membered heterocyclic rings of nitrogen, sulphur or oxygen are of great importance in the drug discovery process.<sup>5</sup> A few examples are shown in the Figure I.A.1.



**Figure I.A.1.** Few examples of biologically important heterocycles

Due to such huge applicability synthesis of new heterocyclic compounds and their functionalization has been a subject of great interest over the past few decades. A number of synthetic routes for heterocycles have been evaluated.<sup>6,7</sup> But synthesis on insoluble supports or by catalysis is most accepted and is growing rapidly.<sup>8-11</sup> Recently solid-phase synthesis is gaining huge popularity over toxic and hazardous organic solvent-based syntheses.<sup>12-19</sup> Since molecules in a crystal are bound tightly and regularly, solid-phase organic synthesis (SPOS) is more effective compared to the solvent based syntheses.<sup>20</sup> In addition, reduced pollution, low cost, easy handling and simplicity in process are main factors playing in favour of SPOS.<sup>21</sup>

To overcome the difficulties with heterogeneous catalysts in many cases compared to homogeneous ones, heterogenized homogeneous catalysts are gaining interest. Recently water has emerged as one of the most suitable mediums for such catalysts to carry out various organic syntheses. Catalysts heterogenized on inorganic or organic supports like silica, layered clays,<sup>22</sup> and polymers,<sup>23</sup> have been successfully employed in aqueous media.

#### **I.A.1.Traditional concept of organic reactions: Disadvantages of homogeneous synthesis**

Organic chemicals are vastly used as raw materials or reagents for various applications such as in manufacturing of polymers, pharmaceuticals, pesticides, paints, artificial fibres, food additives etc. Hence their production on a large scale compared to the laboratory scale requires a big industrial process. Such production involves the use of energy, basic chemical ingredients from the petrochemical sector, catalysts and after the end of the reaction, separation, purification, storage, packaging, distribution etc. In early days most of the organic syntheses involved homogeneous system using toxic organic solvents accompanied with number of toxic by products as waste. The reaction condition used was harsh and hazardous leading to environmental pollution. For example, the old traditional synthetic route to maleic anhydride used benzene as the starting material whereas the new method used n-butane as the starting material which has no such toxicity as benzene. Without much waste compared to the traditional one, the second method was very efficient and highly atom economic as is required in green chemistry.<sup>24</sup> Thus the disadvantages of homogeneous syntheses can be summarised as follows:

- 1. Use of volatile organic solvents**
- 2. Unsatisfactory product yields**
- 3. Critical product isolation procedures**

#### 4. Expensive and detrimental metal precursors

#### 5. Harsh reaction condition

Hence Chemical industries all over the world are competing for innovative and safer reaction pathways to match up with today's requirement a green protocol with the intension of reduction in synthetic stages, lower energy use, higher yields, minimum waste and replacement of traditional petrochemical supplies as raw materials with renewable starting chemicals.<sup>25-27</sup>

### I.A.2. Green chemistry

Talking about green chemistry we must discuss first its so-called twelve principles.

1. **Waste prevention:** Rather than cleaning up or minimizing waste, it is better to prevent their production.
2. **High atom economy:** Conversion of most of the starting materials into the final product is preferred.
3. **Less hazardous chemical syntheses:** Synthetic methods should be designed keeping in mind lesser or no generation of toxic by-products.
4. **Designing safer chemicals:** Minimizing toxic effects as far as possible the chemical products should be designed in such a way that they perform their desired functionalities only.
5. **Safer solvents and auxiliaries:** Unnecessary or much use of solvents or separation agents should be avoided. Instead if possible solvent-free syntheses may be tried.
6. **Lesser energy consumption:** All reactions should be done in ambient temperature and pressure if possible so that lesser energy consumption is counted which is better for environment.
7. **Use of renewable feed stocks:** For economic and environmental purpose as well renewable raw materials or feed stocks should be used.
8. **Reduction in unnecessary derivatization:** Protection-deprotection, modification of physical or chemical processes etc. extra steps should be minimized as far as possible.
9. **Catalysis:** Compared to stoichiometric reagents catalytic reagents are far better.
10. **Degradable chemical products:** After performing their desired functions chemical products should degrade such that no toxicity occurs in environment.

11. **Real-time analysis for pollution prevention:** Highly developed analytical methods should be applied for real-time analysis and in-process monitoring of formation of hazardous substances.
12. **Accident prevention:** A safer synthetic method with easily handled, lesser or non-toxic reagents should be employed to avoid unwanted releases, explosions or fire.

Thus these twelve principles of green chemistry are entitled to make changes in the conventional ways used for decades in organic syntheses leading towards sustainable development.<sup>8,28,29</sup> Hence today's organic chemists keep their eyes open on two factors associated with green chemistry namely E-factor and atom economy.

#### **I.A.3. E-factor for waste in chemical reactions**

Environmental factor, E is the indicator of mass of waste per unit mass of product. The value increases dramatically on going from bulk to fine chemicals due to the involvement of multi-step syntheses in the production of fine chemicals accompanied with the use of stoichiometric reagents rather than catalytic methodologies. Management of E-factor is directly linked to finding pathways with reduced or even no waste.

#### **I.A.4. Atom economy**

Atom economy or efficiency is another important factor to evaluate the amount of waste generated by alternative routes to a specific product. It can be calculated by dividing the molecular weight of the desired product by the sum total of the molecular weights of all substances produced in the stoichiometric equation for the reaction involved. It implies that more atom economy is associated with less waste and hence less E factor.

#### **I.A.5. Introduction to solid-phase**

To develop an environment friendly procedure for organic synthesis solid-phase heterogeneous catalysts have drawn much attention from 1940. After the pioneering work of Merrifield on solid-phase peptide synthesis,<sup>30</sup> this field attained vast popularity in organic syntheses and has crossed a long way till date. In compatible with the requirements of green chemistry solid-support organic synthesis has emerged as a growing area for carrying out number of well known reactions instead of traditional pathway.

### **I.A.6. Advantages of Solid-phase organic synthesis (SPOS)**

#### **1. Easy filtration**

After completion of a reaction solid-supported reagents are easily removed.

#### **2. Better purification**

Even if excess reagents are added to drive the reaction to completion no difficulty is faced during purification.

#### **3. Recyclability**

Since solid-phase heterogeneous catalysts are easily recoverable in most cases they can be used intact in further successive steps which account for an economic pathway.

#### **4. Easy to handle**

Working with flow reactor or fully automated processes where expensive or time-intensive catalysts are used it is very essential to handle the system carefully. Solid-phase catalytic systems render this easiness very well.

#### **5. High selectivity**

Solid-phase heterogeneous catalysts are highly selective in performing various organic reactions providing desired products.

#### **6. No toxicity**

Some homogeneous reagents may be toxic, explosive or noxious which may poison the reaction medium. But when contained in a solid-support there is less or even no chance of toxicity in the reaction medium.

#### **7. Fine tuning**

According to choice solid-support can easily be modified to tune up with the requirement of the particular reaction.

#### **8. Compartmentalization**

The solid-support can be used to compartmentalize library members leading to a split-pool synthesis.

Thus use of solid-supports in organic synthesis takes us to closer to the greener synthetic route.

### **I.A.7. Different polymeric materials used as solid-supports**

Based on the requirement of different reaction conditions various types of solid-support are used. They are classified mainly in three categories as (a) Inorganic supports, (b) Organic supports and (c) Inorganic-organic hybrid polymeric supports.

### **I.A.7.a. Inorganic supports:**

#### **1. Alumina**

Alumina ( $\text{Al}_2\text{O}_3 \cdot \text{H}_2\text{O}$ ) is a thermally stable solid-support having high surface area used as acid and base catalysis or as supports for other catalytic materials (eg. metal oxides, sulphides etc.). It is applicable as a drying agent, catalyst, catalyst support.

#### **2. Zeolites**

Zeolites are crystalline microporous aluminosilicates consisting of molecular-sized intracrystalline channels and cages used as highly selective adsorbents. These insoluble supports have high surface area.

#### **3. Clay minerals**

Finely grained crystalline sheet silicates form a large family of clay minerals which act as inert support for highly dispersed metals, metal complexes, enzymes etc.

#### **4. Silica**

Polymorphic forms of silica, hydrated or anhydrous  $\text{SiO}_2 \cdot x\text{H}_2\text{O}$  is most often used as catalyst-support due to high surface area and large pore volumes.

#### **5. Graphene oxide (GO)**

Recently carbocatalyst GO has been extensively used either singly or doped with metals in various organic synthesis due to large surface area, bio-compatibility, inertness, and outstanding electronic, optical, thermal & mechanical properties.

### **I.A.7.b. Organic supports:**

#### **1. Ion-exchange resins**

An ion-exchange resin or polymer is an insoluble support structure, normally in the form of small (0.5–1 mm diameter) beads, usually white or yellowish, fabricated from an organic polymer substrate. The beads are typically porous, providing a high surface area. Most typical ion-exchange resins are based on cross-linked polystyrene (PS) or partially cross-linked divinylbenzene (DVB). Ion exchange resins are widely used in water softening, water purification, production of high purity water, metal separation, catalysis, juice purification, sugar manufacturing and pharmaceuticals.

#### **2. Dendrimers**

Dendrimers are repetitively branched molecules. It is typically symmetric around the core, and often adopts a spherical three-dimensional morphology. Controllable properties of dendrimers include toxicity, crystallinity, tecto-dendrimer formation

and chirality. Applications of dendrimers typically involve conjugating other chemical species to the dendrimer surface that can function as detecting agents (such as a dye molecule), affinity ligands, targeting components, radioligands, imaging agents, or pharmaceutically active compounds and they have also application in drug delivery, gene delivery, sensor technologies, blood substitution.

### **3. Biopolymers**

Biopolymers are polymers produced by living organisms; in other words, they are polymeric biomolecules. Polynucleotides (RNA and DNA; polymers composed of nucleotide monomers), polypeptides (polymers of amino acids and polysaccharides) and cellulose are the few common examples of biopolymers. It can be sustainable, carbon neutral and are always renewable. They are biodegradable and some are also compostable.

### **4. Elastomers**

Elastomers are another class of polymer with both viscosity and elasticity. Each of the monomers is usually made of carbon, hydrogen, oxygen or silicon. Elastomers are amorphous polymers existing above their glass transition temperature, so that considerable segmental motion is possible. Their primary uses are for seals, adhesives and molded flexible parts.

#### **I.A.7.c. Inorganic-organic hybrid polymeric supports:**

Polymers containing inorganic and organic components are named as hybrid polymers. One of the best known examples is polydimethylsiloxane, commonly known as silicone rubber. It has  $-\text{[O-Si(CH}_3\text{)}_2\text{]}_n-$  repetitive unit based on silicon and oxygen. Polygermanes, polystannanes, polysilanes are some of the useful supports in this regard.

Investigations embodied in this thesis work primarily involve two different solid-supports, viz. graphene oxide (GO) and mesoporous silica with a view to promote various organic reactions, and here a summary of their diverse applications and further scopes are presented.

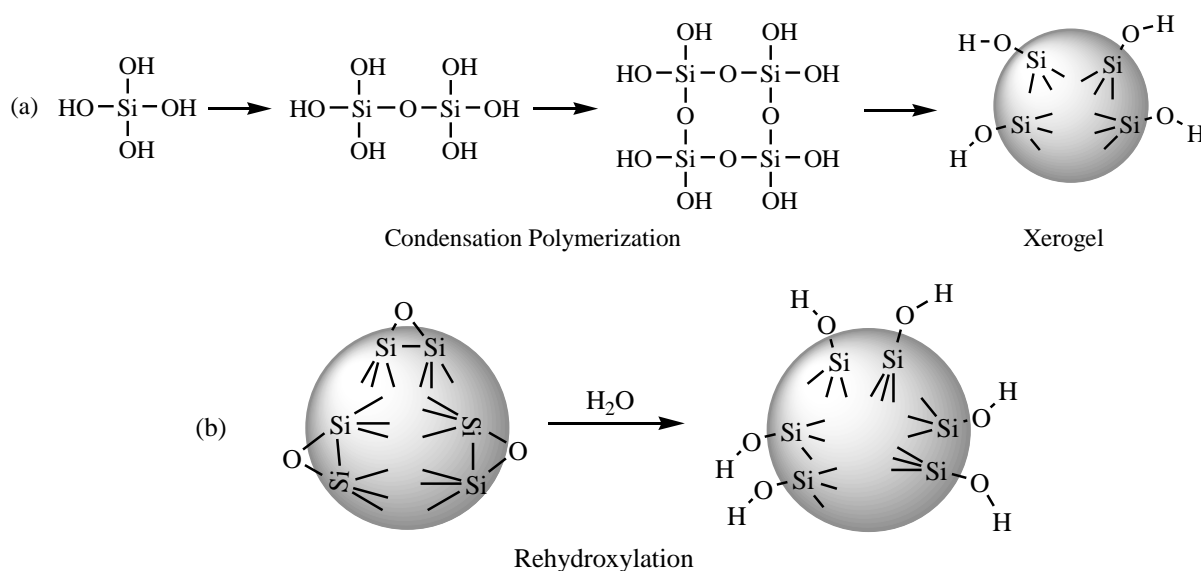


## I.B. Silica

### I.B.1. Silica: A brief introduction

Studies of the condensation processes of silicic acid carried out by Hofmann, Endell and Wilm,<sup>31</sup> Rideal,<sup>32</sup> Kiselev,<sup>33</sup> and slightly later by Carman,<sup>34</sup> showed that hydroxyl (silanol) groups are present on the surface of silicates and silicas. According to dehydroxylation mechanism,<sup>33</sup> water is evolved from the  $-OH$  groups attached chemically on silica surface during calcinations. Apart from this there is present physically adsorbed water as well. Presence of hydroxyl groups on silica surface was later proved by infrared spectroscopy by Yaroslavsky and Terenin,<sup>35-37</sup> and then confirmed by Kurbatov and Neuymin.<sup>38</sup>

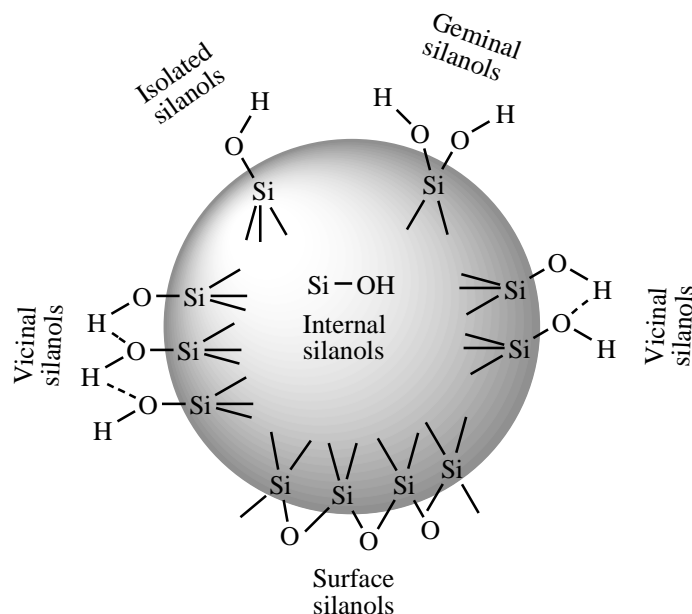
There are two processes for silanol group formation on the silica surface.<sup>39,40</sup> One such process involves the condensation polymerisation of  $Si(OH)_4$  where the supersaturated solution of this acid is converted into its polymeric form leading to the changes into spherical colloidal particles containing  $Si-OH$  groups on the surface. After drying, the hydrogel yields xerogel as the final product retaining some or all of the silanol groups on its surface (Figure I.B.1.a). According to the second process, surface  $-OH$  groups can form as a result of rehydroxylation of dehydroxylated silica when treated with water or aqueous solutions. The surface Si atom accommodates in a complete tetrahedral configuration and becomes saturated with hydroxyl groups in aqueous medium (Figure I.B.1.b).



**Figure I.B.1.** Procedure for the formation of silanol groups on the silica surface

Different types of groups present on the silica surface are subdivided as shown in (Figure I.B.2).

- (i) Single silanols, Si–OH,
- (ii) Geminal silanols or silanediols, Si(OH)<sub>2</sub>,
- (iii) Vicinal, bridged, or hydrogen bonded –OH groups,
- (iv) Siloxane groups or Si–O–Si bridges with oxygen atoms on the surface of silica,
- (v) Structurally bound water inside the silica skeleton and internal silanol groups.



**Figure I.B.2.** Different types of silanol groups, siloxane bridges and internal –OH groups present on amorphous silica surface

Presence of silanol groups may direct the properties of amorphous silica such as their sufficient concentration may make the surface hydrophilic. The –OH groups form H–bonding with adsorbates and hence their removal may lead to hydrophobic properties,<sup>39,40</sup> to the surface. The last number of decades saw a rapid growth in those fields of science and technology that deal with production and utilization of various colloid and micro-heterogeneous forms of silica with developed surfaces, such as sols, gels, and powders. The properties of pure silica, as an oxide adsorbent, are determined in the first place by:

- (i) The chemical activity of the surface, this activity depends on the concentration and the distribution of different types of –OH groups, and on the presence of siloxane bridges and
- (ii) The porous structure of the silica.

Different types of silica are widely used as efficient adsorbents and selective absorbents, active phase carriers in catalysis and so on. Of late the use of SiO<sub>2</sub> is on the rise in the manufacture of modern high-quality materials such as microelectronics, optics, fiber optics, liquid crystals, different composites including bio-composites, ordered nano-structured silica materials, mono-dispersed colloids etc.

### **I.B.2. Research motivation with silica**

Heterocyclic compounds occur widely in nature. Since, they are hugely applicable and essential to life,<sup>41,42</sup> a vast synthetic methodology of new heterocyclic compounds have been developed in the past few decades. Among them multi-component reactions (MCRs) are a promising and significant tool in organic synthesis,<sup>43</sup> due to its utilization for the synthesis of diverse highly functionalized molecules,<sup>44</sup> via the formation of carbon–carbon and carbon–heteroatom bonds in one-pot in a very fast, efficient and timesaving manner without the isolation of any intermediate. According to ‘Green Chemistry’ fundamental scientific methodologies can protect human health and the environment in an economically beneficial manner.<sup>45</sup> Therefore the development of novel MCRs is a popular area of research in current organic chemistry.<sup>46</sup>

Therefore, there has been great quest towards the development of greener chemical processes which reduce the use of traditionally employed homogenous catalysts and adopt heterogeneous catalysts.<sup>47</sup> Although heterogeneous catalysts have some advantages in terms of improved product yield and short reaction time, their high cost and need of organic solvents still offer challenge to researchers for the exploitation of catalytic activity of readily available heterogeneous materials that are compatible in aqueous media. A suitable heterogeneous system must not only minimize the production of waste but should exhibit activities and selectivities also comparable or superior to existing homogeneous routes.

Silica is one of the best inorganic heterogeneous materials. Silica/silica-based catalysts have many advantages such as they are abundant, inexpensive, easy to prepare, surface being both thermally and chemically stable during the reaction process, and insoluble in most of the organic solvents which means that they are recoverable and recyclable. Comparing with functionalized organic polymers, silica is more robust to drastic conditions and harsh reagents and therefore a variety of silica grafted reagents have been devised for solid-phase organic syntheses.<sup>48-52</sup> Mild reaction conditions, cleaner reaction medium, easily available and

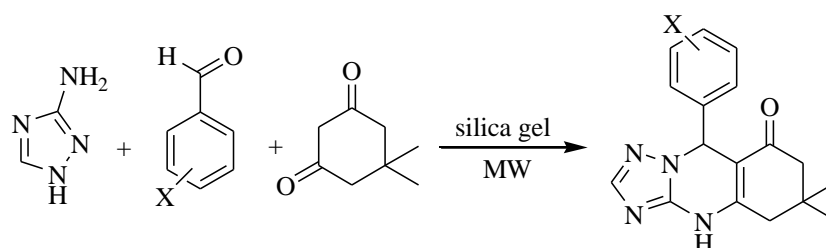
reusable catalytic system, simple isolation of the product and scalable approach all of these criteria of greener synthetic strategies,<sup>53</sup> can be achieved by using it.

### I.B.3. Reactions promoted on silica-surface

Primarily two types of silica either directly as available or functionalized, called as modified silica are known to utilize to promote various reactions, supports etc.

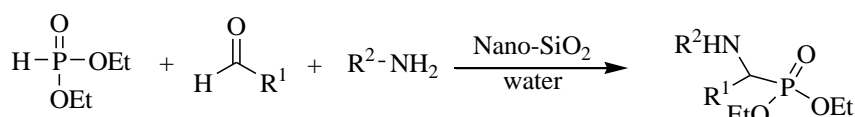
#### I.B.3.a. Unmodified silica-promoted reactions

Derivative of triazolo/benzimidazoquinazolinones via silica-promoted solvent-free method using microwave irradiation was developed by Krishnamurthy and Jagannath with an excellent yield.<sup>54</sup>



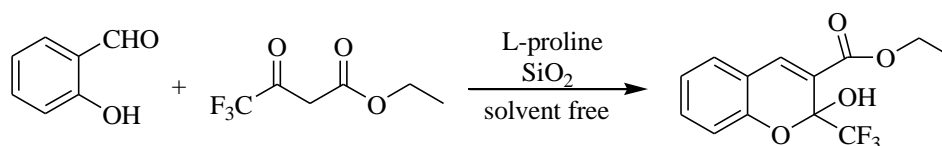
**Scheme I.B.1.** Silica-promoted synthesis of triazolo/benzimidazoquinazolinones

Nano-SiO<sub>2</sub>-catalyzed on-water synthesis of  $\alpha$ -aminophosphonates from aldehydes, amines and diethylphosphate under ultrasonication was prepared by Nasser and Sadeghzadeh from inexpensive starting materials.<sup>55</sup>



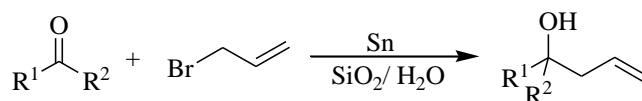
**Scheme I.B.2.** Nano-SiO<sub>2</sub> catalyzed synthesis of  $\alpha$ -aminophosphonates

A novel synthesis of 2-hydroxy-2-(trifluoromethyl)-2*H*-chromene-3-carboxylates under solvent-free condition in an oven or microwave via the Knoevenagel condensation of salicylaldehydes with ethyl trifluoroacetoacetate followed by intramolecular cyclization in the presence of silica-immobilized L-proline was studied by Xu et al.<sup>56</sup>



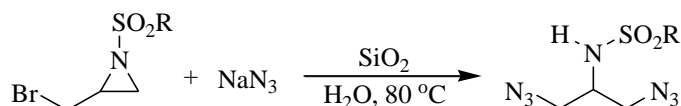
**Scheme I.B.3.** Silica-immobilized L-proline catalyzed Knoevenagel condensation

Silica as a phase-transfer catalyst (PTC) was employed for Barbier reaction in allylation of carbonyl compounds mediated by tin.<sup>57</sup>



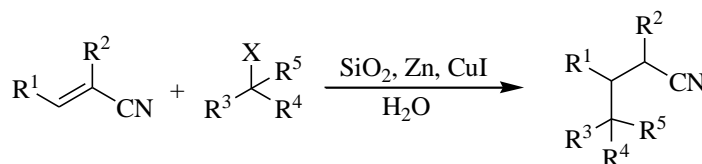
**Scheme I.B.4.** Silica gel as a phase-transfer catalyst for Barbier reaction

Kimpe et al.,<sup>58</sup> performed the ring opening of 2-(bromomethyl)aziridines using silica-water reaction media.



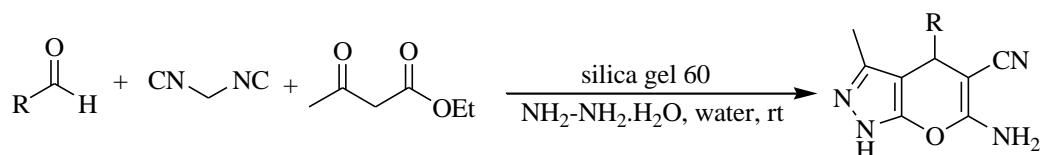
**Scheme I.B.5.** Silica-promoted ring opening of 2-(bromomethyl)aziridines

A new silica-supported zinc-copper matrix promoted the conjugate addition of alkyl iodides to alkenenitriles in water.<sup>59,60</sup>



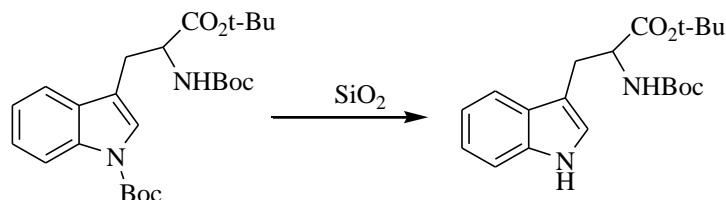
**Scheme I.B.6.** Silica-supported zinc-copper matrix used in conjugate addition

Silica-water system,<sup>61</sup> has been utilised as a potentially valuable reaction medium for the synthesis of pyrano[2,3-*c*]pyrazoles via a green multicomponent one-pot cyclocondensation of aldehydes, malononitrile, hydrazine hydrate and ethyl acetoacetate.



**Scheme I.B.7.** Silica-water system to the synthesis of pyrano[2,3-*c*]pyrazoles

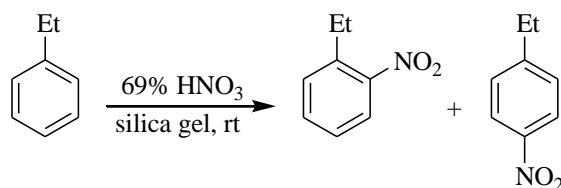
A series of deprotection procedures,<sup>62</sup> has been efficiently performed by silica. *N*-Boc deprotection of anilines, indoles and imidazoles occurred effectively in a cleaner way using silica-adsorbed reagents compared to the method without silica.



**Scheme I.B.8.** Deprotection procedures performed by silica gel

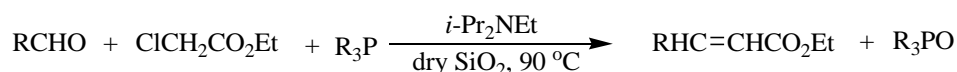
A number of other well known reactions such as the Friedel-Crafts-type nitration of arenes, Wittig-type olefination of aldehydes and Morita-Baylis-Hillman reaction of aldehydes with methyl acrylate were performed efficiently under solvent-free milder condition using

silica. In case of Friedel-Crafts-type nitration of arenes aqueous 69% nitric acid alone can do the task at room temperature when used silica.<sup>63,64</sup>



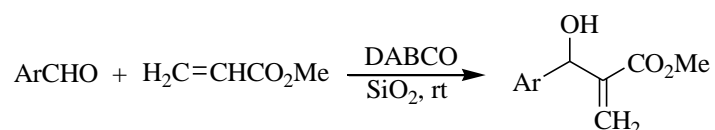
**Scheme I.B.9.** Silica-mediated Friedel-Crafts-type nitration of arenes

Silica accelerated the convenient direct one-pot Wittig type olefination of aldehydes,<sup>65</sup> with ethyl chloroacetate, phosphine and a base.



**Scheme I.B.10.** Silica used in Wittig type olefination of aldehydes with ethyl chloroacetate and phosphine

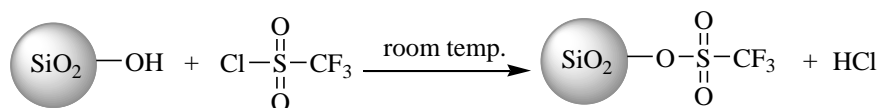
Dried silica in combination with 1,4-diazabicyclo[2.2.2]octane (DABCO) effectively promoted the Morita-Baylis-Hilman reaction,<sup>66</sup> of aldehyde and methyl acrylate at room temperature providing addition product.



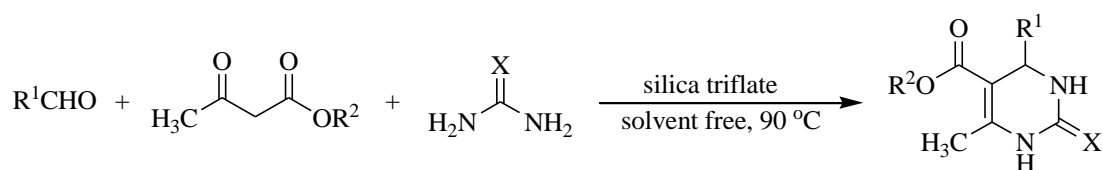
**Scheme I.B.11.** Silica-promoted Morita-Baylis-Hilman reaction

### I.B.3.b. Modified silica-mediated reactions

Shirini and Marjani et al.,<sup>67</sup> prepared silica triflate by the reaction of silica with trifluoromethylsulfonyl chloride at room temperature which efficiently catalyzed a solvent-free one-pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones and -thiones (DHPMs) having similar biological activity.

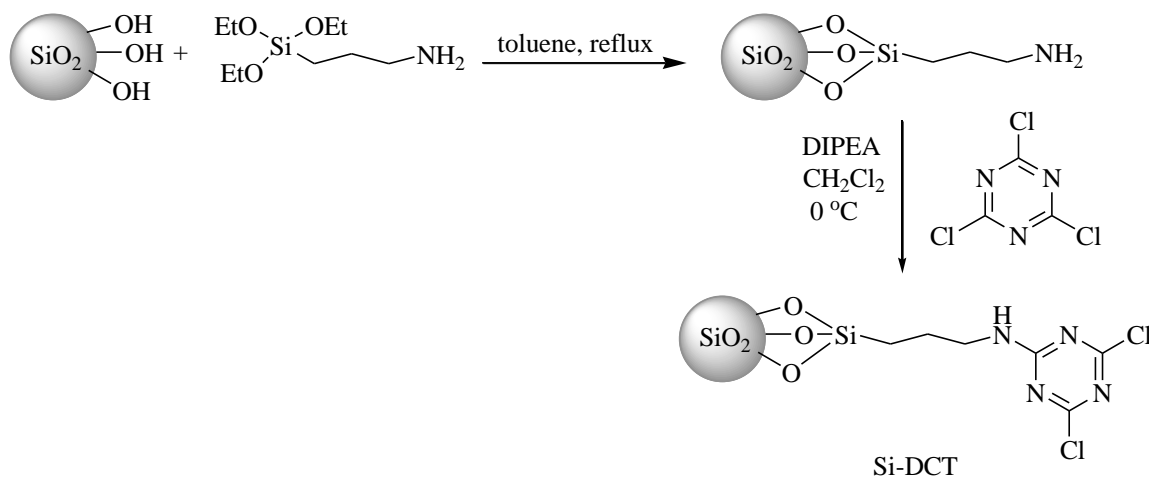


**Figure I.B.3.** Synthesis of silica triflate

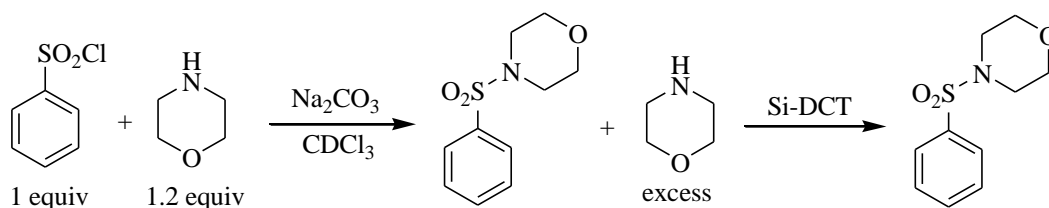


**Scheme I.B.12.** Silica triflate-mediated one-pot synthesis of DHPMs

M. Pattarawarapan et al. prepared silica-supported dichlorotriazine (Si-DCT) from silica and 3-aminopropyltrimethoxysilane followed by reaction with cyanuric chloride.<sup>68</sup> Then modified silica (Si-DCT) has been explored as solid-support scavenger of excess amine nucleophiles in the synthesis of model sulphonamide amide.

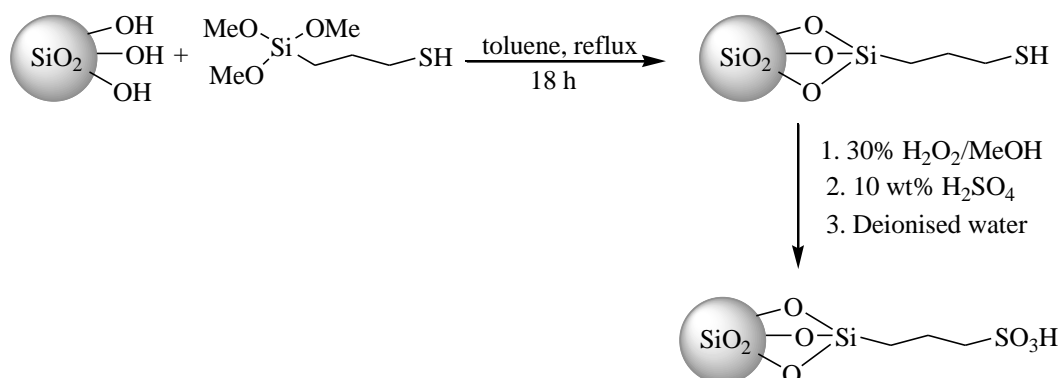


**Figure I.B.4.** Synthesis of silica-supported dichlorotriazine (Si-DCT) scavenger

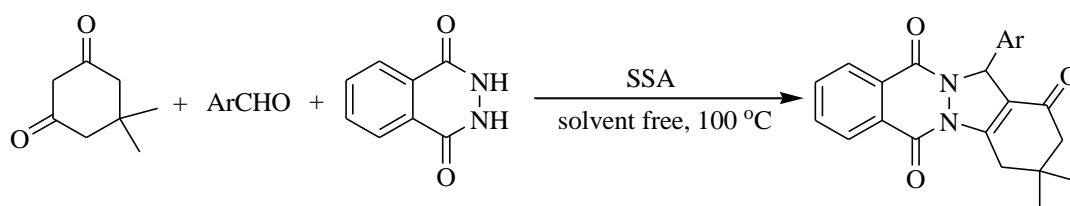


**Scheme I.B.13.** Si-DCT as a solid-support scavenger of excess amine

Recyclable solid silica-sulfonic acid (SSA)-catalyzed effective one-pot green synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives under thermal and solvent-free condition,<sup>69</sup> has been developed. The catalyst was easily prepared as shown below (Figure I.B.5) and stable up to 300 °C.

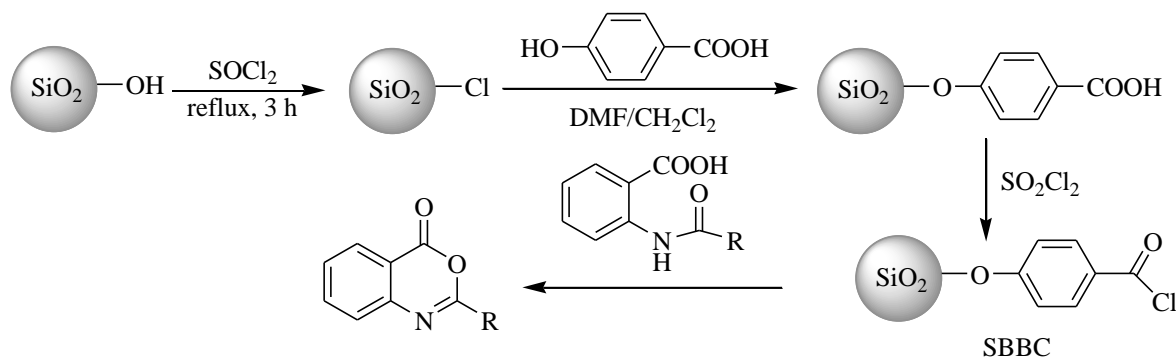


**Figure I.B.5.** Preparation of solid silica-sulfonic acid (SSA)



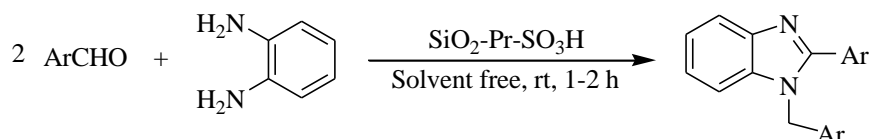
**Scheme I.B.14.** SSA-promoted one-pot green synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione

Another modification of silica, silica-bound benzoyl chloride (SBBC) has been utilized as a recoverable and reusable dehydrating agent in reaction with 2-acylamino benzoic acid providing an economically viable synthetic route to 4*H*-3,1-benzoxazin-4-ones.<sup>70</sup>



**Scheme I.B.15.** SBBC-mediated synthesis of 4*H*-3,1-benzoxazin-4-ones

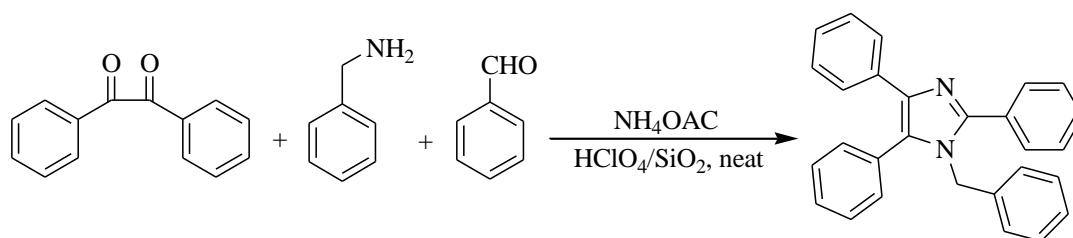
Synthesis of 2-Aryl-1-arylmethyl-1*H*-1,3-benzimidazoles has been established,<sup>71</sup> under solvent-free condition at room temperature by the reaction of *o*-phenylenediamine with different types of aromatic aldehydes in the presence of silica-sulfonic acid catalyst.



**Scheme I.B.16.** Silica-sulfonic acid catalyzed synthesis of 2-Aryl-1-arylmethyl-1*H*-1,3-benzimidazoles

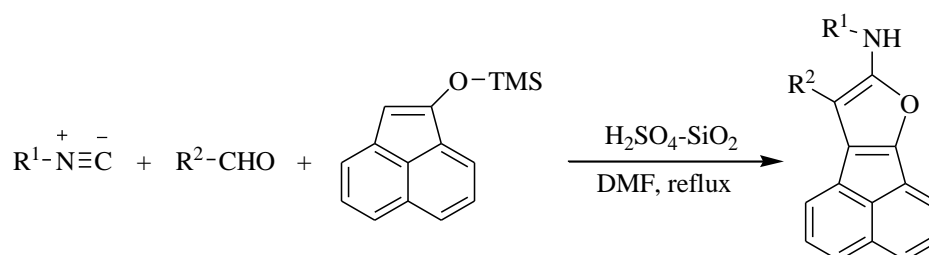
A four-component one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles via the condensation reaction of various aldehydes, benzil, aliphatic or aromatic amines and ammonium acetate has been developed by Kantevari et al. under solvent-free condition catalyzed by perchloric acid adsorbed silica ( $\text{HClO}_4\text{-SiO}_2$ ).<sup>72</sup>





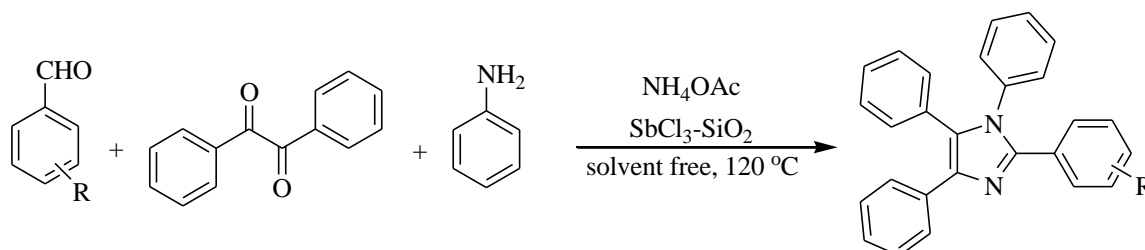
**Scheme I.B.17.** HClO<sub>4</sub>-SiO<sub>2</sub> catalyzed synthesis of 1,2,4,5-tetrasubstituted imidazoles

Sandaros et al.,<sup>73</sup> synthesized acenaphtho[1,2-*b*]furan efficiently by one-pot reaction of (acenaphthylen-1-yloxy)trimethylsilane with various aldehydes and isocyanides in the presence of silica-supported ionic liquid.



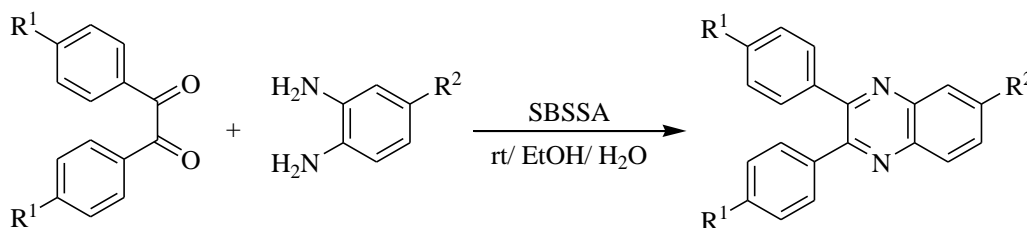
**Scheme I.B.18.** Silica-supported synthesis of acenaphtho[1,2-*b*]furan

Safari et al. developed antimony trichloride based silica (SbCl<sub>3</sub>/SiO<sub>2</sub>)-catalyzed,<sup>74</sup> the four-component cyclocondensation of 1,2-diketone, aldehyde, ammonium acetate and primary amine under solvent-free conditions to afford the corresponding tetrasubstituted imidazoles in high yields.



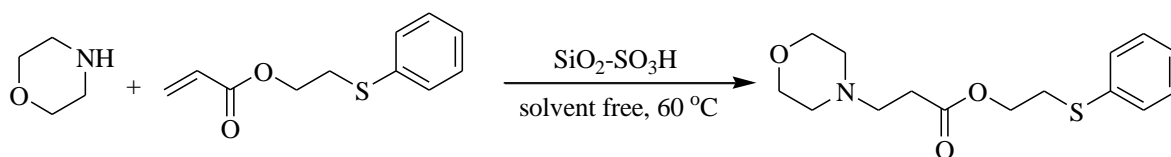
**Scheme I.B.19.** Silica-supported SbCl<sub>3</sub> catalyzed four-component condensation reaction

Silica-bonded S-sulfonic acid (SBSSA)-catalyzed room temperature synthesis of quinoxaline derivatives from 1,2-diamino compounds and 1,2-dicarbonyl compounds was studied by Niknam et al.<sup>75</sup>



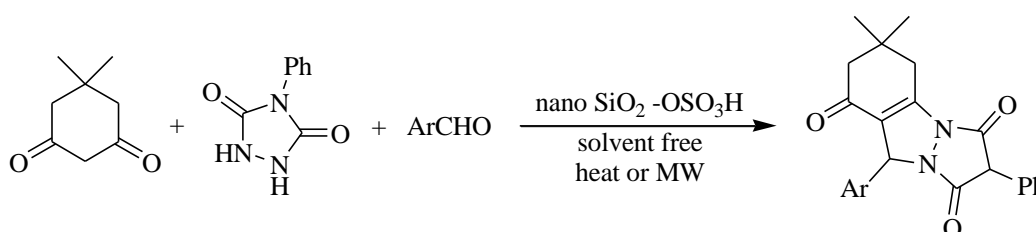
**Scheme I.B.20.** SBSSA-catalyzed synthesis of quinoxaline derivatives

Chemoselective aza-Michael addition reactions of amines to  $\alpha,\beta$ -unsaturated compounds using silica sulfuric acid (SSA or  $\text{SiO}_2\text{-SO}_3\text{H}$ ) in good to excellent yields has been developed by Wang et al.,<sup>76</sup> in a highly efficient, inexpensive, recyclable, convenient and greener way.



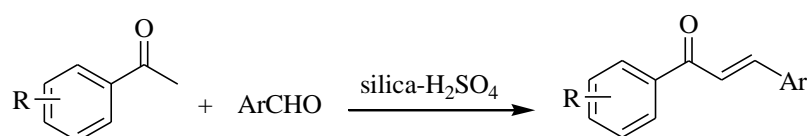
**Scheme I.B.21.** SSA-mediated chemoselective aza-Michael addition reactions

Hamidian et al. developed silica nanoparticles-catalyzed a novel synthesis of triazolo[1,2-a]indazole-1,3,8-trione derivatives by reaction of urazole, dimedone and aromatic aldehydes by conventional heating or microwave irradiation under solvent-free conditions.<sup>77</sup>



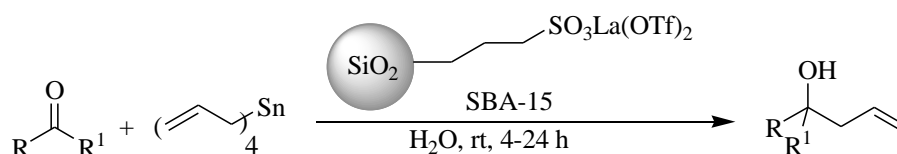
**Scheme I.B.22.** Silica nanoparticles-catalyzed synthesis of triazolo[1,2-a]indazole-1,3,8-trione derivatives

Silica-sulfuric acid-mediated an efficient synthesis of a variety of chalcones was reported by Sultan et al. in very good yield compared to base catalyzed solvent-free conditions as well as acid or base catalyzed refluxing conditions.<sup>78</sup>



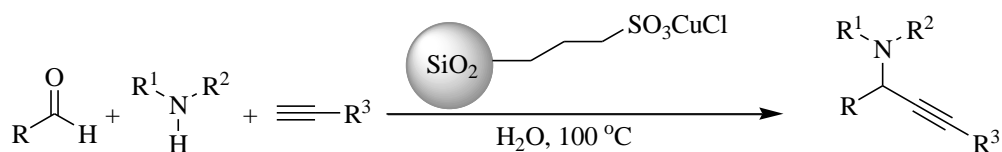
**Scheme I.B.23.** Silica-sulfuric acid-catalyzed synthesis of chalcones

A solid lewis acid catalyst, lanthanum sulfonate immobilized on mesoporous silica (SBA-15) was prepared by Kim et al.,<sup>79</sup> and used to catalyze the allylation reaction of carbonyl compounds with tetraallyltin.



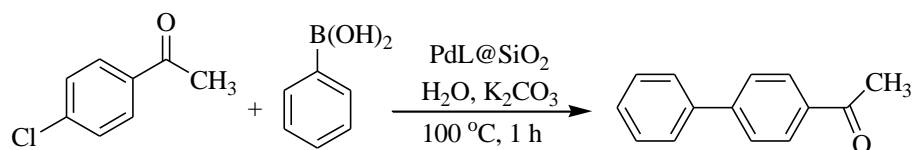
**Scheme I.B.24.** Allylation reaction of carbonyl compounds with tetraallyltin using solid lewis acid catalyst

Silica-anchored copper chloride was synthesized using 3-mercaptopropyl-trimethoxysilane as a spacer to explore its activity in three-component coupling reactions.<sup>80</sup>



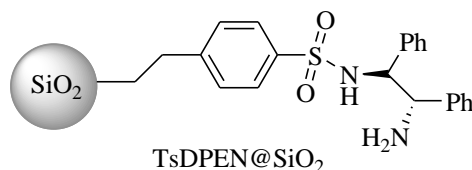
**Scheme I.B.25.** Silica-anchored CuCl used in three-component coupling reactions

An oxime-carbapalladacycle complex anchored to silica (PdL@SiO<sub>2</sub>) was synthesized and efficiently used for the Suzuki-Miyaura coupling of *p*-chloroacetophenone and phenylboronic acid in water.<sup>81</sup> No leaching occurred and the catalyst was reused eight times without significant decrease in activity.

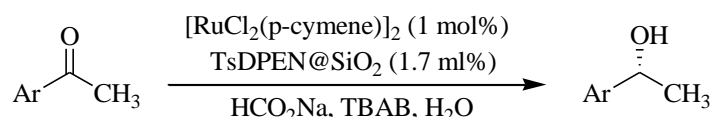


**Scheme I.B.26.** PdL@SiO<sub>2</sub>-promoted Suzuki-Miyaura coupling reaction

Silica-supported Ru-TsDPEN catalyst,<sup>82</sup> was used to catalyze on-water asymmetric transfer hydrogenation for aromatic ketones with excellent enantioselectivity (up to 99% ee) and very high reactivity (>99% yield) in 2-8 h (Scheme I.B.27).

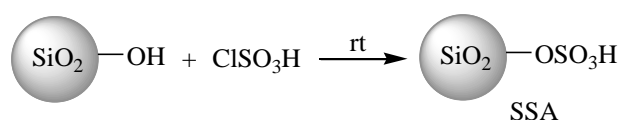


**Figure I.B.6.** Structure of TsDPEN@SiO<sub>2</sub>

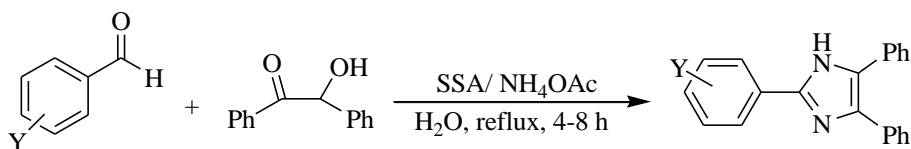


**Scheme I.B.27.** On-water asymmetric transfer hydrogenation using silica-supported chiral auxiliary

Chlorosulfonic acid reacts with silica to produce silica sulfuric acid (SSA),<sup>83</sup> a superior proton source compared to other acidic solid-supports and acidic resins, such as polystyrene sulfonic acid and Nafion-H,<sup>84</sup> examined under heterogeneous conditions. SSA can efficiently catalyze the reaction of benzaldehydes, benzoin and ammonium acetate in water to synthesise trisubstituted imidazoles.<sup>85</sup>

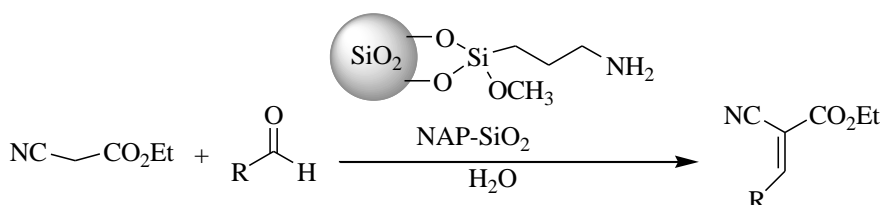


**Figure I.B.7.** Synthesis of silica sulfuric acid (SSA)



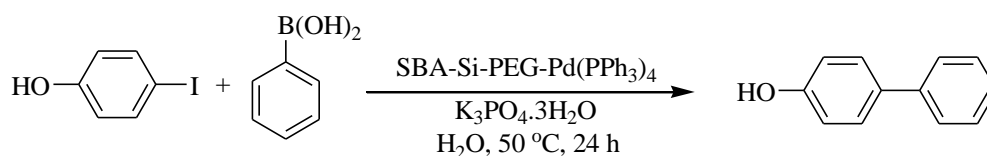
**Scheme I.B.28.** SSA-mediated synthesis of trisubstituted imidazoles

NAP-SiO<sub>2</sub> as a catalyst used in the Knoevenagel reaction between an aldehyde and ethyl cyanoacetate was achieved at ambient temperature on-water.<sup>86</sup>



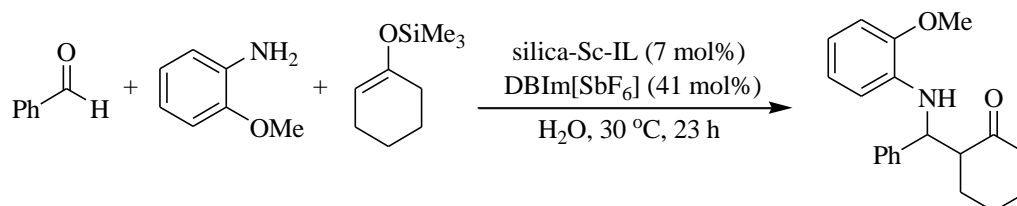
**Scheme I.B.29.** NAP-SiO<sub>2</sub> catalyzed Knoevenagel reaction

The PEG-coated mesoporous silica-supported palladium complex was synthesized from tetraethylene glycol and applied effectively in on-water Suzuki-Miyaura coupling reaction.<sup>87</sup>



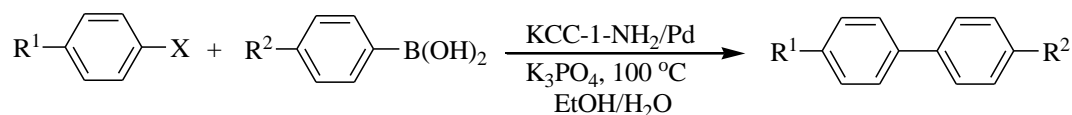
**Scheme I.B.30.** PEG-coated silica-supported palladium-catalyzed Suzuki-Miyaura coupling

Heterogeneous silica-supported scandium/ionic liquid catalyst,<sup>88</sup> was successfully applied to Mukaiyama aldol reactions, Michael reactions, Mannich reactions, allylation reactions and asymmetric hydroxymethylation.



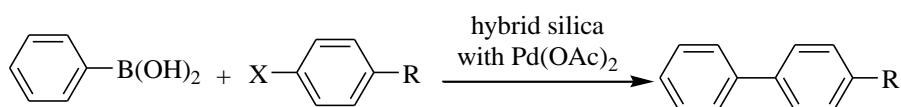
**Scheme I.B.31.** Silica-supported scandium/ionic liquid catalyst in Mukaiyama aldol reaction

KCC-1-NH<sub>2</sub>/Pd nanocatalyst was successfully employed for the Suzuki coupling of aromatic halides and even challenging substrates like aryl chlorides under sustainable ligand-free conditions.<sup>89</sup>



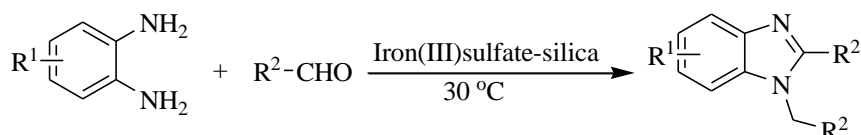
**Scheme I.B.32.** Suzuki coupling using KCC-1-NH<sub>2</sub>/Pd as nanocatalyst

Another catalytic system formed by palladium acetate [Pd(OAc)<sub>2</sub>] and hybrid silica materials has been utilised in the Suzuki-Miyaura coupling reaction even of the unreactive halides like aryl chlorides.<sup>90</sup>



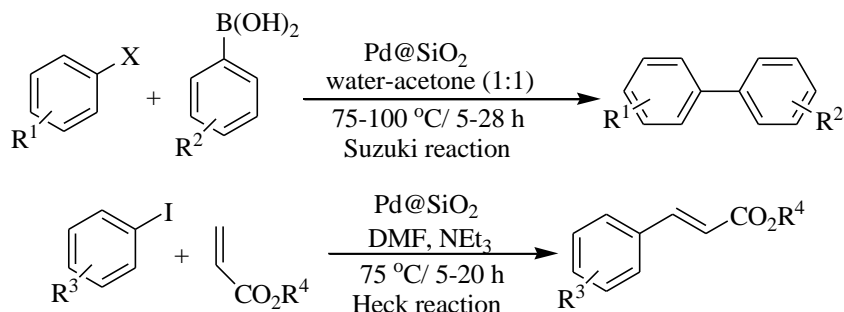
**Scheme I.B.33.** Pd(OAc)<sub>2</sub> and hybrid silica materials in Suzuki-Miyaura coupling reaction

An efficient synthesis of functionalized 1,2-benzimidazoles,<sup>91</sup> via one-step condensation–aromatization reaction of *o*-phenylenediamines with electronically divergent aldehydes has been developed in our laboratory under solvent-free conditions at ambient temperature using eco-friendly ferric sulfate soaked with silica [iron(III)sulfate–silica].



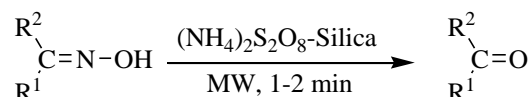
**Scheme I.B.34.** Efficient synthesis of functionalized 1,2-benzimidazoles using iron(III)sulfate–silica

Another recent work from our laboratory revealed a phosphene-free eco-friendly pathway for Suzuki-Miyaura and Heck coupling using newly synthesized mesoporous silica-supported Pd nanoparticles [SiO<sub>2</sub>@PdNP] as a sustainable heterogeneous catalyst.<sup>92</sup>



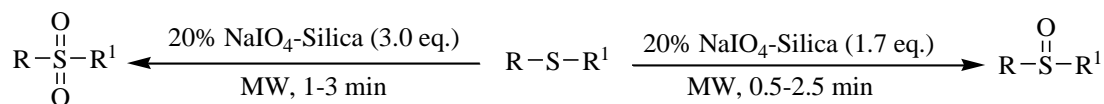
**Scheme I.B.35.** SiO<sub>2</sub>@PdNP-mediated Suzuki-Miyaura and Heck coupling reaction

The solvent-free deprotection of protected carbonyl groups such as in aldoximes or ketoximes has been successfully demonstrated using relatively benign ammonium persulfate on silica,<sup>93</sup> under microwave irradiation.



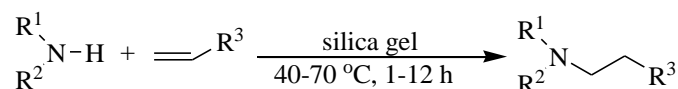
**Scheme I.B.36.** Deprotection of protected carbonyl groups using ammonium persulfate on silica

Sodium periodate on silica has also been employed selectively in the oxidation procedure,<sup>94</sup> of sulfides to sulfoxides or sulfones as desired under microwave irradiation providing a much safer and mild oxidation procedure than the traditional ones.



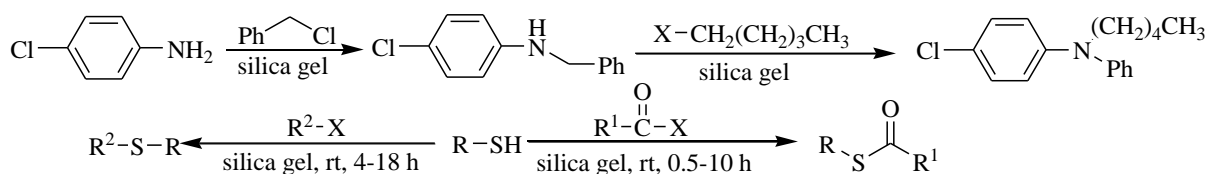
**Scheme I.B.37.** Sodium periodate on silica in oxidation of sulfides to sulfoxides or sulfones

Again silica-promoted solvent-free green synthesis of  $\beta$ -amino esters and nitriles via hetero-Michael conjugate addition of aliphatic and aromatic primary or secondary amines has been developed in our lab.<sup>95</sup>



**Scheme I.B.38.** Silica-promoted synthesis of  $\beta$ -amino esters and nitriles

Further selective N-alkylation of amines,<sup>96</sup> and S-acylation and alkylation of thiols,<sup>97</sup> have also been performed effectively by silica in our laboratory.



**Scheme I.B.39.** Selective N-alkylation of amines and S-acylation and alkylation of thiols using silica

#### I.B.4. Scope

At present, organic reactions using solid-phase approaches are gaining more importance because reactions with a loaded substrate can be manually sequenced and driven to higher yields by using excess reagents, which are subsequently removed by simple filtration.<sup>98-104</sup> Thus concept of solid-phase chemistry now covers solid-phase reagent chemistry which may operate in two ways as suggested. According to the first one the substrates are chemically bound to the surface of the solid-supported reagent and converted to the product during liberation from the solid.<sup>105</sup> As per the second concept the core structure of the library molecule resides in solution and solid-phase reagents are added to the mixture to facilitate the reaction,<sup>106</sup> after which the solid-phase reagent or its residue is removed from the heterogeneous reaction mixture by simple filtration.

Silica is widely used nontoxic, non-flammable, nonreactive and stable heterogeneous material. It has a large surface area ( $5\text{--}800 \text{ m}^2\text{g}^{-1}$ ) allowing high density of functional groups to be immobilized on its surface. It is rigid insoluble material with high mechanical and thermal stability, not swell in any organic solvent.

A number of modifications have sought its versatile application in organic syntheses. Silica in water is emerging as a new, useful and powerful benign reaction medium provoking a new era of heterogenized homogeneous catalysis.<sup>107,108</sup> Recently functionalized silica has been successfully utilized as solid-supported scavenger to facilitate purification processes in organic syntheses.<sup>109</sup> Solid silica-sulfonic acids are found to behave like organic–inorganic hybrid catalyst. This heterogeneous reusable catalyst has been efficiently employed to catalyze number of heterocyclic syntheses.<sup>110-114</sup> Various organic reactions have been promoted by silica in our laboratory, such as hetero-Michael conjugate addition,<sup>95</sup> selective N-alkylation of amines,<sup>96</sup> S-acylation,<sup>97</sup> and alkylation of thiols and selective synthesis of 1,2-disubstituted benzimidazoles,<sup>91</sup> SiO<sub>2</sub>@PdNP catalyzed phosphine-free Suzuki and Heck coupling reactions.<sup>92</sup>

A brief discussion mentioning recent applications of highly flexible and tunable silica surface in diverse organic reactions are few representative examples among the myriads and clearly establish its vast potentiality. Simple control of the surface and functionalization of the mesoporous silica could offer excellent opportunity to explore new and greener processes. The present work will demonstrate our efforts on highly regioselective reactions using silica with simple modifications, presented in Chapter IV.

## I.C. Graphene oxide (GO)

### I.C.1. Developing interest towards newly introduced polyfunctional graphene oxide (GO)

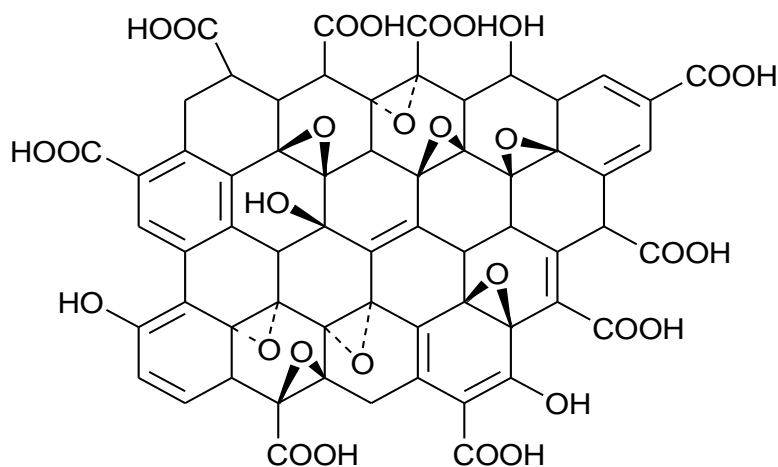
For the sake of sustainability and economic consideration, tremendous interest is growing towards metal-free catalysis, where graphene-based carbonaceous materials might play an important role. Graphene (G) is a flat and strain-free system whose plane can be attacked from both sides when dispersed in a solvent. Graphene is a two-dimensional (2D) carbon allotrope which can be viewed as both a solid and a macromolecule with molecular weights of more than  $10^6$ – $10^7$   $\text{g mol}^{-1}$ . In natural graphite, the graphene layers stick together through very pronounced  $\pi$ - $\pi$  stacking interactions. This non-covalent interlayer binding contributes significantly to the high thermodynamic stability of graphite. A solid sample of graphene can only be stabilized on a support, such as a surface. Therefore, non-supported graphene powder does not exist and partial restacking to graphite will take place. While graphene is composed of only  $\text{sp}^2$ -hybridized carbon atoms, graphene oxide (GO) has a carbon structure having both the  $\text{sp}^2$  and  $\text{sp}^3$  hybridized carbon atoms with a high degree of oxygen functional groups. Such functionalization has a profound impact on the properties, for example, graphene exhibits extraordinarily high conductivity,<sup>115</sup> but GO is an insulator. The stability of G makes partial reduction of GO going toward G relatively easy, decreasing the oxygen content. However, GO reduction is generally not complete, leaving in the material various extents of residual oxygenated functional groups. For this reason, it is very common to distinguish G obtained from GO that is generally referred as “reduced GO” (rGO). Advances in these areas have been buoyed by improvements in the methods used to synthesize and characterize GO, as well as functionalized derivatives thereof.

GO is prepared basically from oxidation of graphite. Several structural models have been proposed for GO depending on oxidation condition,<sup>116</sup> and starting graphite material during its preparation.<sup>117</sup> There are five different routes for synthesizing GO have been described including Staudenmaier,<sup>118</sup> Brodie,<sup>119</sup> Hofmann,<sup>120</sup> Hummers,<sup>121</sup> and Tour methods.<sup>122</sup> XPS, elemental analysis, NMR spectroscopy and FT-IR spectroscopy revealed the fact that a greater amount of oxygen functionality and a higher proportion of carbonyl and carboxylic acid groups have been introduced by permanganate based oxidations (Hummers and Tour methods) than compared to chlorate based oxidations (Staudenmaier, Brodie and Hofmann methods) which leads to a remarkable difference of activities of GO towards a organic reactions. Among the synthetic methods of GO, the modified Hummers method is most



acceptable due to impart a greater amount of functionalities to the synthesized GO. The prepared GO shows FT-IR spectra  $3368\text{ cm}^{-1}$  for hydroxyl (O–H),  $1718\text{ cm}^{-1}$  for carboxylic acid (–COOH) and  $1620\text{ cm}^{-1}$  for C–C double bonds.<sup>123</sup> Among various models the most widely accepted one is Lerf-Klinowski model (figure I.C.1) where hydroxyl and epoxide groups decorate the basal plane and carboxylic acid or carboxylate groups are present on the edges of the sheet. There are two types of carbon atoms present in GO such as  $\text{sp}^2$  hybridized graphene like carbon atoms and  $\text{sp}^3$  hybridized highly oxygenated ones.

Harsh oxidizing conditions used for the synthesis of GO are known to shred the graphite into smaller particles. This effect is believed to occur in a step-wise process via the progressive oxidation of epoxides, defects, or other functionality on the carbon surface, resulting in the formation of holes in the plane, smaller flake sizes, and highly oxidized species (e.g., carboxylic acids) on the periphery of the sheets. During the formation of graphite oxide, the graphene layers in graphite become intercalated by an acid to form an intercalation compound, with all layers being intercalated. Subsequent oxygenation of such intercalation compounds occurs on both sides of the basal plane and in this way graphite oxide is formed. GO consists of about 45 mass% carbon.



**Figure I.C.1.** Commonly accepted schematic representation of GO according to Lerf-Klinowski model

Various standard techniques like FT-IR spectroscopy,<sup>124</sup> X-ray photoelectron spectroscopy (XPS),<sup>125</sup> solid state NMR spectroscopy,<sup>126</sup> electrochemical methods,<sup>127</sup> have been employed to analyze the chemical functionality of GO whereas its surface functionality has been verified by number of chemical reactions.<sup>128,129</sup> Laser scattering methods,<sup>130</sup> or solid state techniques such as TEM,<sup>131,132</sup> or AFM,<sup>133</sup> have been successfully utilized to analyze its

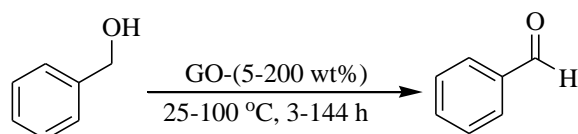
physical characteristics. GO is slightly acidic in nature (pH 4.5 at 0.1 mgmL<sup>-1</sup>).<sup>134</sup> It also possesses highly oxidizing property as well.

Due to the presence of various functional groups, the surface of GO can effectively be modified by carrying out simple organic transformations like functionalization of carboxylic acid group or hydroxyl group or ring opening of epoxide groups etc. to finely tune the material's chemical and physical properties. Methods used to derivatize GO are highly dependent on the desired application and properties such as electrical and thermal conductivity, hydrophilicity and mechanical reinforcement. In polymer composite processing, GO can be made dispersible in organic solvents via functionalization with hydrophobic groups that influence interfacial interactions with the polymer. Functionalized derivatives of GO can be reduced to obtain an electrically or thermally conductive material. The functionalization of GO can be divided into two categories- peripheral functionalization and basal plane functionalization. Modifications of the periphery of GO utilize the reactivity of the carboxylic acid groups whereas basal plane modification has traditionally harnessed the reactivity of the resident hydroxyl and epoxide groups. The procedures to functionalize GO is as follows:

- (i) Functionalization of the carboxylic acids on GO,<sup>135-139</sup> with SOCl<sub>2</sub> followed by condensation with a nucleophile like DCC, NHS, EDC, DMAP, alcohols, amines or with another carboxylic acid activator.
- (ii) Functionalization at the hydroxyl groups on GO,<sup>140,141</sup> with DDMAT, DMDA.
- (iii) Functionalization via epoxide ring opening on GO,<sup>142</sup> with sodium salt of malononitrile.
- (iv) Reactive intermediate functionalization of GO with aryl diazonium salts,<sup>143,144</sup> carbenes,<sup>145,146</sup> and nitrenes.<sup>147,148</sup>
- (v) Covalent and non-covalent approaches to GO based polymer composites with SEBS.<sup>149</sup>

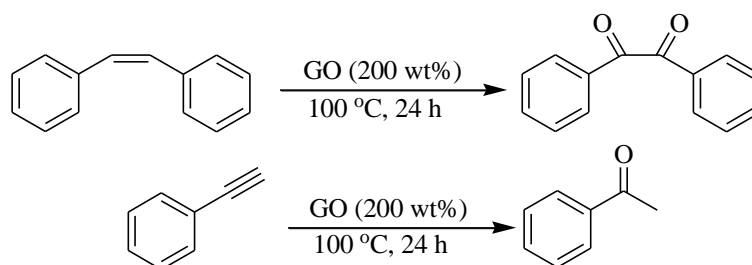
### I.C.2. Applications of GO as carbocatalyst: Brief background

Bielawski and co-workers reported the seminal work on the use of GO,<sup>150</sup> and graphite oxide,<sup>151</sup> as carbocatalysts for aerobic oxidation reactions of neat benzyl alcohol to benzaldehyde in the presence of GO with TON 10<sup>-2</sup> molg<sup>-1</sup>.



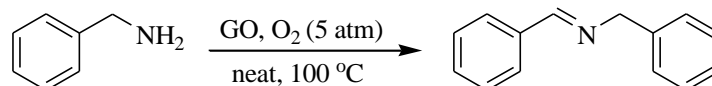
**Scheme I.C.1.** GO-promoted aerobic oxidation reactions of neat benzyl alcohol to benzaldehyde

On continuing work they also explored the ability of this catalyst to oxidize unsaturated hydrocarbons and hydration of alkynes,<sup>151</sup> with greater than 98% conversion.



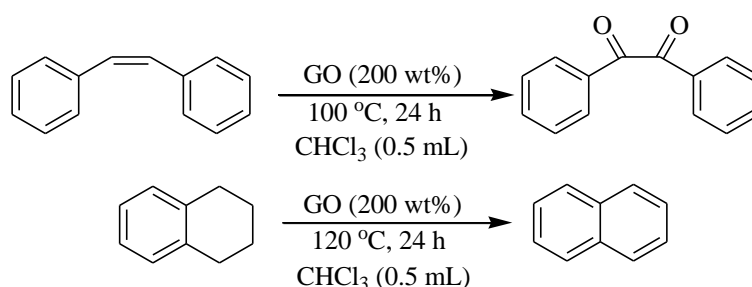
**Scheme I.C.2.** Oxidation of unsaturated hydrocarbons and hydration of alkynes using GO

Graphite oxide as an efficient and durable metal-free catalyst for aerobic oxidative coupling of amines to imines was developed by Liu and co-workers.<sup>152</sup>



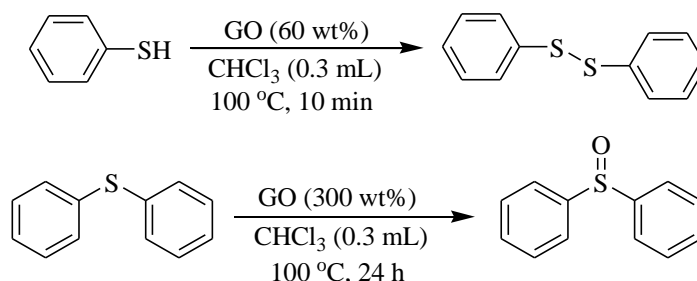
**Scheme I.C.3.** GO catalyzed aerobic oxidative coupling of amines to imines

The novel carbocatalyst graphite oxide as an effective oxidant for the oxidation of olefins to their respective diones, methyl benzenes to their respective aldehydes, diarylmethanes to their respective ketones, and various dehydrogenations was shown by Bielawski et al.<sup>151</sup>



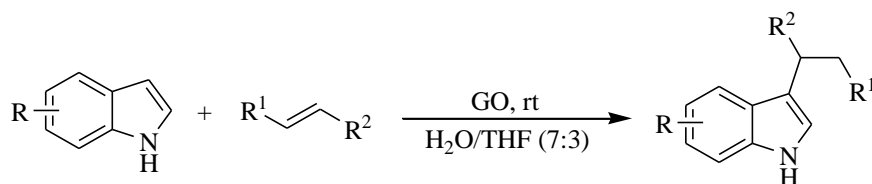
**Scheme I.C.4.** Carbocatalyst GO-promoted oxidation of olefins

Again Bielawski et al. developed,<sup>153</sup> a selective oxidation of thiols to disulfides and sulphides to sulfoxides using graphite oxide (GO).



**Scheme I.C.5.** Selective oxidation of thiols to disulfides and sulphides to sulfoxides using GO

Rao et al. studied the Friedel–Crafts addition of indoles to  $\alpha,\beta$ -unsaturated ketones with graphite oxide as a recoverable and recyclable heterogeneous catalyst.<sup>154</sup>



**Scheme I.C.6.** GO-mediated Friedel-Crafts addition reaction

Besides direct uses of graphene oxide (GO) and reduced graphene oxide (rGO) as carbocatalysts, they have been utilized as potential supports to immobilize different metal NPs and use them in diverse areas including catalysis. However, reviewing this area of research is beyond the objectives of the present work and hence not covered.

### I.C.3. Scope

Graphite oxide (GO) is one of the preferred types of graphene like materials for its use as carbocatalyst due to its easy synthesis compared to reduced graphene oxide (rGO) or graphite and the presence of oxygenated functional groups. Affordability and sustainability are among the main advantages of GO compared to other catalysts.<sup>150</sup> In addition, the high density of oxygen functionalities such as epoxide, alcohol and carboxylic acids present on GO allows an excellent dispersion of this material in aqueous suspensions and convenient reactivity for modification via covalent anchoring of catalytically active units. For these reasons, GO has been widely used as carbocatalyst to promote oxidation, coupling and acid/base reactions.

GO facilitates the Friedel–Crafts addition of  $\alpha,\beta$ -unsaturated ketones to indoles,<sup>154</sup> the conversion of polysaccharides to 5-ethoxymethylfurfural,<sup>155</sup> various dehydrative or cationic addition polymerizations,<sup>156-158</sup> alcohols to the corresponding aldehydes,<sup>151,159,160</sup> alkanes to the corresponding olefins,<sup>151,161,162</sup> thiols to the corresponding disulfides,<sup>153</sup> organic sulfides to the corresponding sulfoxides,<sup>153</sup> aqueous sulfide anions to polysulfides,<sup>163</sup> and amines to the corresponding imines.<sup>164,165</sup> Combination of GO with zeolites has been shown to be highly active in the dehydration of secondary and tertiary alcohols to their corresponding olefins.<sup>166</sup> Derivatives of GO, functionalized with basic moieties have also been shown to exhibit bifunctional acid–base behaviour,<sup>167</sup> and GO has been used as a phase-transfer catalyst (PTC) to improve the organic solubility of inorganic salts such as KOH.<sup>168</sup> In addition to its inherent reactivity, GO has also been used as a support for exogenous metal catalysts.<sup>169</sup> GOs not only have been used as a catalyst-support, a filler in polymer composites and a catalyst itself but have started to find increasing utility in various biomedical

applications also. The oxygen functionality of GO can be modified with various compounds that increases its biocompatibility and bio-functionality. Bio-molecule functionalized GO derivatives have a diverse set of applications ranging from chemical sensing to drug and gene delivery systems.<sup>170-172</sup> As homogeneous and heterogeneous catalysts are based on transition metals both noble,<sup>173-175</sup> and base,<sup>176,177</sup> there is a growing demand of sustainability which can be achieved by developing alternative catalysts based on renewable resources. The price of some precious metals based inorganic materials as catalysts is considerably higher than the feedstock carbon materials. Biomass based carbon materials are considered paradigmatic examples of sustainability.<sup>178,179</sup> In organic synthesis, there is need to develop metal-free catalytic system in order to reduce the dependency on metals as well as to avoid the toxicity of various metals.<sup>180-182</sup>

While partially reduced GO (rGO) has been amply demonstrated as an effective and electron-rich solid-support for the immobilization of various metal NPs and use them in catalysis, graphene oxide (GO) bearing several oxygenated functional groups has recently been shown as useful and renewable carbon material to catalyze organic reactions. However, this area of research is its infancy and the present thesis work demonstrate some successful catalytic applications using GO leading to the synthesis of complex and heterocyclic molecules (Chapter II and III).

## **I.D. References**

References for Chapter I are given in Bibliography section (page 125–133).