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# Silica-Based Materials as Catalysts or Supports in Solvent-Free Organic Reactions

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The fine chemical and pharmaceutical industries generate huge amounts of organic solvents every year. The design of solvent-free synthetic methods has become increasingly important for modern green chemistry [1]. Several options have been proposed, including the development of neat reactions that require intensified energy windows (e.g. microwave irradiation, sonication, mechanochemistry) and the use of surfactants and ionic liquids under organic solvent-free conditions [2–8]. In this context, silica-based materials are gaining relevance as they can be utilized as effective catalysts, reaction media, and supports for synthesis of small molecules [9, 10]. These materials are heterogeneous, hence easy to separate from the product mixture after reaction. This chapter, thus, focuses on the synthesis and successful use of silica solids in organic synthesis.

## 5.1 Solvent-Free Reactions Over Silica Gel

Silica gel, formally $(SiO_2)_n$, is the commonly used term for colloidal silica, an amorphous and porous polymer of silicon dioxide (Figure 5.1). The material is produced by acidifying a sodium silicate solution. A colloidal suspension is obtained, whose degree of polymerization depends on the physicochemical conditions maintained during the process. The solid is then washed and dried, leading to transparent or white, granular, porous, and amorphous solids, with variable particle sizes from a few millimeters to a few microns. Silica gel is widely used in chemistry labs as a desiccant and adsorbent. The other function of silica gel is as a catalyst carrier because of its low cost, facile scalability, and ability to immobilize organometallic compounds and other reactive groups. In addition, given its characteristic large surface area and porous structure, silica gel has also shown high catalytic activity in various reactions.

Different organic synthesis and catalysis were reported using silica gel and additives to produce added value chemicals. Among the major classes of reactions
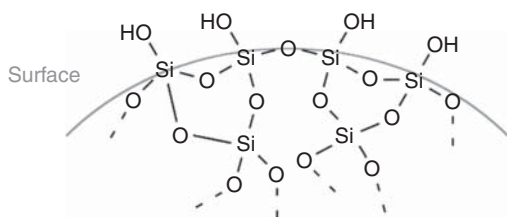
**Figure 5.1** Schematic structure of the surface of silica gel.

in organic chemistry, oxidation, reduction, C—C bond formation, and multicomponent reactions are undoubtedly the most important and have been exploited very widely in recent years.
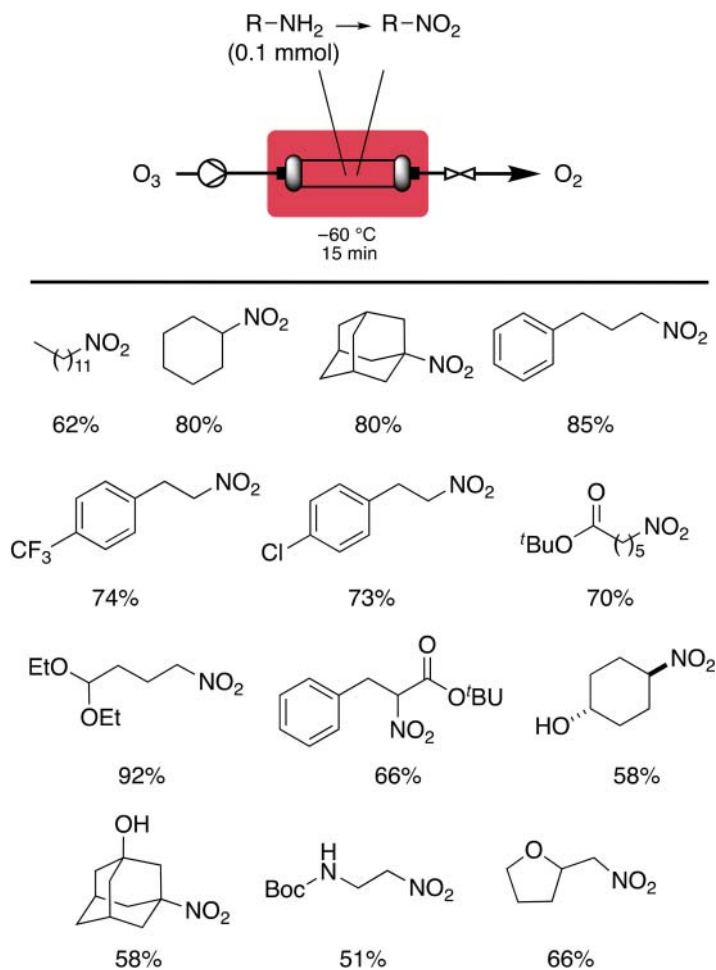
For example, nitration is a class of chemical processes in which one or more nitro ($-NO_2$) groups are introduced into an organic compound. Examples of nitration include the conversion of glycerol into nitroglycerin and the introduction of a nitro group into benzene to give nitrobenzene [11]. Typically, the reaction requires catalytic amounts of strong acids (i.e. a mixture of concentrated $HNO_3$ and concentrated $H_2SO_4$). In fact, $H_2SO_4$ provides the acid environment necessary to generate the nitronium ion ($NO_2^+$) that protonates the organic reactant [11]. Developing greener and more practical routes for this reaction and avoiding the use of such strong acids has been long desired. In this regard, Onitsuka et al. reported the function of silica gel as a solid reaction medium for the solvent-free aromatic nitration at room temperature (Scheme 5.1) [12]. Although $HNO_3$ is necessary to complete the reaction and obtain the desired product, the reaction can proceed smoothly at room temperature and is accelerated by the presence of silica gel. On the other hand, the effect of the silica gel particle size (from 63 μm to 0.5 mm) is less important for this transformation.



| Neat | 47% (8 : 25 : 67) | 6% |
| With silica gel | 75% (13 : 23 : 64) | 6% |
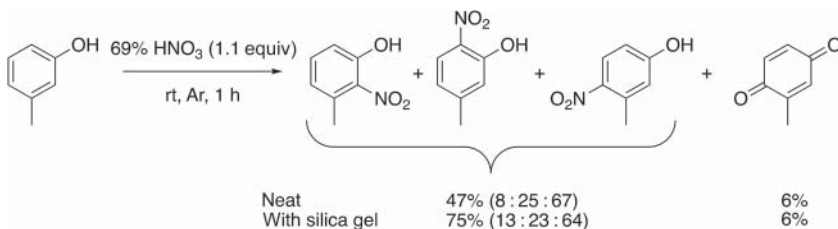
**Scheme 5.1** The nitration of *m*-cresol using 69% nitric acid in the presence of silica gel. Source: Onitsuka et al. [12]/MDPI/CC BY.

Recently, Skrotzki et al. reported the ozone-mediated primary amine and pyridine oxidations, CH hydroxylation, and arene oxidation in continuous flow process. In order to limit the overoxidation of substrates and solvent, primary amines were absorbed onto silica gel and then ozone was flowed to the system at −60 °C for a residence time of 15 minutes. Application of this method afforded the target nitro compounds in good yields (Scheme 5.2) [13].

The same group reported the continuous flow synthesis of N-oxides at −60 °C for 15 minutes, quaternary alcohols at −20 °C for 60 minutes, and carboxylic acid at −20 °C for 60 minutes (Figure 5.2).

$$R-NH_2 \longrightarrow R-NO_2$$
(0.1 mmol)

$O_3$ ——————— $O_2$

−60 °C
15 min

62% 80% 80% 85%

74% 73% 70%

92% 66% 58%

58% 51% 66%

**Scheme 5.2** Ozone-mediated amine oxidation in continuous flow. Source: Skrotzki et al. [13]/American Chemical Society.
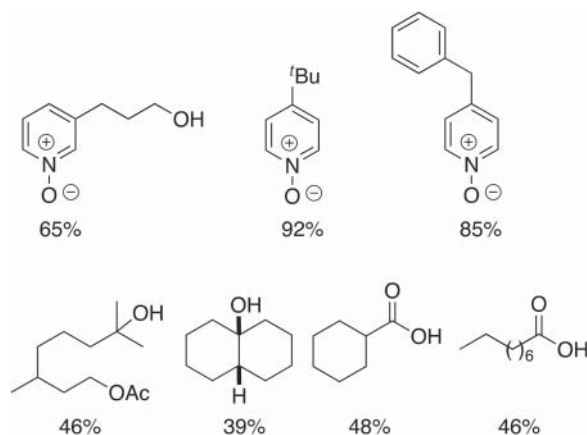
65% 92% 85%

46% 39% 48% 46%

**Figure 5.2** Scope of the continuous ozone-mediated reactions. Source: Skrotzki et al. [13]/American Chemical Society.

C—C bond formation using $SiO_2$ was reported by different groups via Wittig-type reaction, Michael reaction, aryne formation, and multicomponent reaction. The Wittig reaction is another reaction widely used in organic synthesis to replace a carbonyl group with an alkenyl group. This reaction, which is one of the most powerful tools to selectively generate carbon–carbon double bonds, was discovered by the German chemist Georg Wittig in 1954 and earned him the Nobel Prize in 1979. Solvent-free conditions have been developed for this reaction, and these involve enantioselective reaction in chiral solid media [14], microwave irradiation [15], and reaction photoacceleration by solvent fast-evaporation [16]. However, these methodologies require equipment (e.g. microwave, photoreactor, and ball milling) that is costly and not available in every lab, and this can be a challenge for their implementation. In this direction, Patil and Mävers have demonstrated a convenient method for accessing the Wittig-type olefination of aldehydes using ethyl chloroacetate, a phosphine, and a base (Table 5.1) [17]. Also, in this case, silica gel accelerates the reaction in the absence of any organic solvent. Using an equimolar mixture of benzaldehyde, triphenylphosphine, and ethyl chloroacetate,

**Table 5.1** One-pot Wittig-type olefination of benzaldehyde in the presence (and absence) of silica gel.



92% (E/Z = 92:8)

| Medium | Base | Yield (%) | E/Z |
|---|---|---|---|
| Silica gel | None | 18 | 95/5 |
| Silica gel | $Ph_3P$ | 32 | 95/5 |
| Silica gel | $Na_2CO_3$ | 29 | 92/8 |
| Silica gel | KOH | 42 | 91/9 |
| Silica gel | $Et_3N$ | 86 | 91/9 |
| Silica gel | DBU | 25 | 89/11 |
| Silica gel | Phosphazene | 20 | 93/7 |
| Silica gel | $i$-$Pr_2NEt$ | 99 | 93/7 |
| None | $i$-$Pr_2NEt$ | 67 | 94/6 |
| Toluene | $i$-$Pr_2NEt$ | 43 | 94/6 |
| PTFE | $i$-$Pr_2NEt$ | 56 | 93/7 |
| PSDVB | $i$-$Pr_2NEt$ | 58 | 92/8 |
| Alumina (acidic) | $i$-$Pr_2NEt$ | 40 | 93/7 |
| Alumina (neutral) | $i$-$Pr_2NEt$ | 36 | 92/8 |
| Alumina (basic) | $i$-$Pr_2NEt$ | 41 | 94/6 |

Source: Adapted from Patil and Mävers [17].

the authors studied the effects of the reaction medium at a fixed temperature of 90 °C. Among the reaction media tested, silica gel was found to outperform reactions conducted in the presence of a solvent (toluene), other solids (organic polymer or alumina), as well as neat conditions.

The Michael addition, which is a useful method not only for the formation of C—C but also C—S and C—N bonds in mild conditions, refers to the nucleophilic addition of an anion to a α,β-unsaturated carbonyl compound. Tanemura and Rohand described the solvent-free Michael addition of methyl 2-oxocyclopen-tane-1-carboxylate to the highly toxic methyl vinyl ketone (MVK) to produce methyl ketone derivatives in 99% yield (Figure 5.3) [18]. The scope of the reaction was developed by starting from various 1,3-dicarbonyl compounds and MVK and ethylvinylketone with yields higher than 92%. Silica gel could be recycled five times without a decrease in yields.

Katrun et al. developed an electrophilic substitution reaction of indoles with benzaldehydes promoted by hydrochloric acid supported on silica gel to produce bis(indolyl)methanes (BIMs) in a rapid, simple, and efficient manner [19]. In this
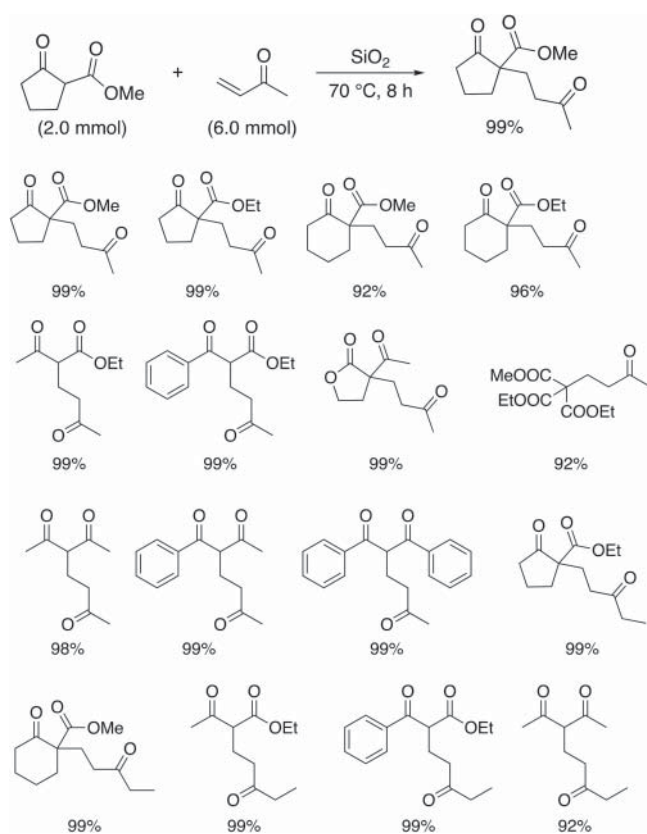


**Figure 5.3** Michael addition mediated by silica gel, and scope of the Michael addition mediated by silica gel. Source: Adapted from Tanemura and Rohand [18].

work, HCl as an inexpensive catalyst and silica gel as the support were used and developed to furnish with a short reaction time the target chemicals in high yields. Furthermore, using of this method allowed to obtain bioactive trisindoline alkaloid in 77% yield at room temperature for 30 minutes (Scheme 5.3).
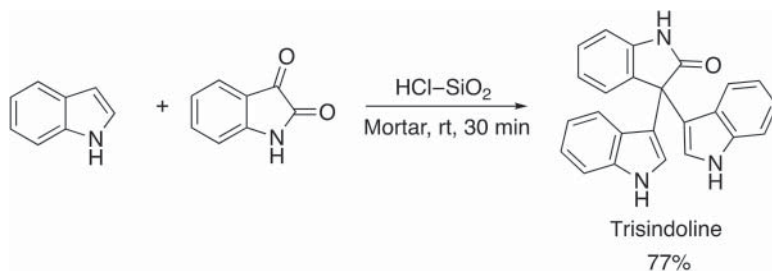


**Scheme 5.3** Synthesis of trisindoline using silica gel and HCl loading. Source: Katrun et al. [19]/CC BY.

Karimi et al. discovered an efficient and user-friendly process for the synthesis of various substituted imidazoles using silica gel-supported sodium bisulfate ($NaHSO_4$–$(SiO_2)_n$), a four-component condensation reaction between amines, aldehydes, benzyl/benzoin, and ammonium acetate, and solvent-free microwave irradiation conditions (Scheme 5.4) [20]. When compared with conventional methods in organic synthesis, the route offers attractive features such as reduced reaction time and higher yield, as well as the possibility to recover and reuse the catalyst, which makes the process green and sustainable.
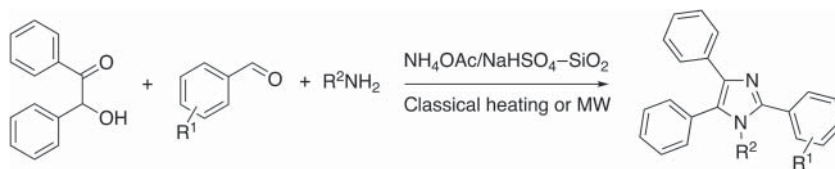


**Scheme 5.4** Solvent-free microwave (MW) synthesis of substituted imidazoles on silica gel/$NaHSO_4$ support. Source: Karimi et al. [20]/with permission from Elsevier.

## 5.2 Silica Nanoparticles and its Applications

Silica nanoparticles used as such or mixed with other metal oxides have also been shown to have promising catalytic performance in several organic transformations such as, oxidations [21], dehydrogenations [22], epoxidations [23], and photocatalytic degradation [24]. This is because of their eco-friendliness, high thermal stability, wide surface area, facile synthesis, and good catalyst recovery ability. In this context, silica can be either used as an active phase or as support.

Nanoparticles of silica mixed oxides are typically prepared via a hydrothermal method (Figure 5.4). For example, Borhade et al. have reported the role of nanocrystalline $SiO_2$:$SnO_2$ in the solvent-free synthesis of imidazole derivatives [26].
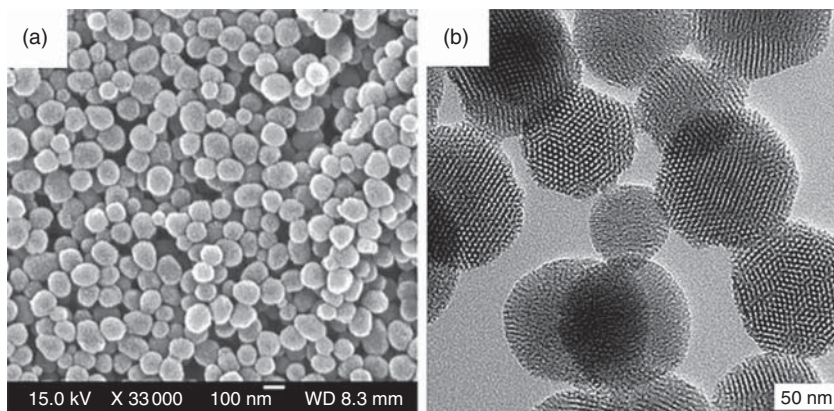
**Figure 5.4** Scanning (a) and transmission (b) electron microscopy image of mesoporous silica nanoparticles. Source: Reproduced with permission from Li [25]/Royal Society of Chemistry.

The material is prepared via a hydrothermal route. In particular, the precursors of the two oxides, namely $SiCl_4$ and $SnCl_2 \cdot 2H_2O$, are mixed in water. Then, NaOH is used to basify the solution. The mixture is transferred to a Teflon-lined stainless-steel autoclave and placed in the oven at 120 °C for 48 hours. The obtained solids are filtered at room temperature, washed, and dried. The reaction is performed by simply bringing together, at 80 °C for 30 minutes the aromatic aldehyde, a primary amine, the base (ammonium acetate), and $SiO_2$:$SnO_2$. The $SiO_2$:$SnO_2$ catalyst exhibits excellent condensation activity, enhancing the reaction rate at mild conditions.

Catalysis with silica-functionalized $SO_3H$ [27–29], silica coated with ionic liquids with or without metal [30], silica-coated CaO nanoparticles [31], silica-coated magnetic nanoparticles [32–35], and modified mesoporous silica [36] were reported recently. Shashni et al. prepared a series of mesoporous silica gel-immobilized Bronsted acid ionic liquid (SG@BAIL) nanocatalysts for the acetalization of glycerol with benzaldehyde [28]. The immobilized heterogeneous catalysts have the synergetic advantages of both ionic liquid acidic sites and solid silica gel as a support. The optimized conditions allowed for the production of the acetals at 90 °C for 75 minutes, resulting in the 94% conversion of benzaldehyde from a mixture of benzaldehyde–glycerol (1 : 1, mol/mol) in the presence of SG-$[C_3ImC_3SO_3H][OTf]$ (0.03 wt%). In these conditions, two regioisomers were obtained and the catalyst reusability showed that after 10 cycles, the conversion dropped slowly from 94% to 87% (Scheme 5.5).

Acylations of alcohol, thiol, and amine under solvent-free conditions were obtained in the presence of a magnetically recyclable silica-coated ferrite magnetite-K10 montmorillonite nanocatalyst [34]. An excess of acetic anhydride (1.5 mmol) and aniline (1 mmol) in the presence of the magnetic catalyst (15 mol%) at room temperature for 10 minutes furnished the corresponding acetate in a 96% yield. Starting with aromatic amines, aromatic alcohols, and aromatic thiols, the scope of the reaction was realized in 86–99% for 10–40 minutes (Figure 5.5).
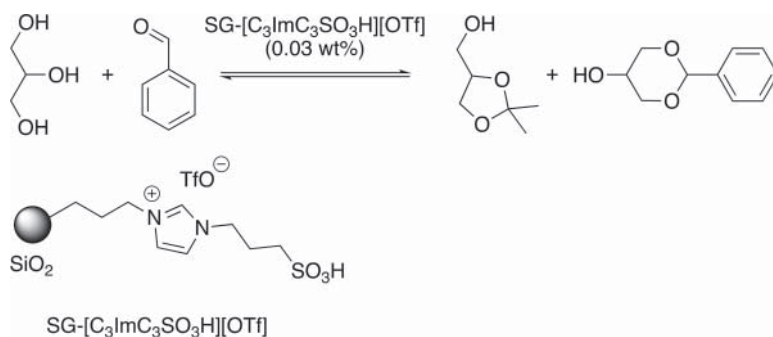
**Scheme 5.5** Acetalization of glycerol with benzaldehyde using SG-[C$_3$ImC$_3$SO$_3$H][OTf]. Source: Shashni et al. [28]/Royal Society of Chemistry.
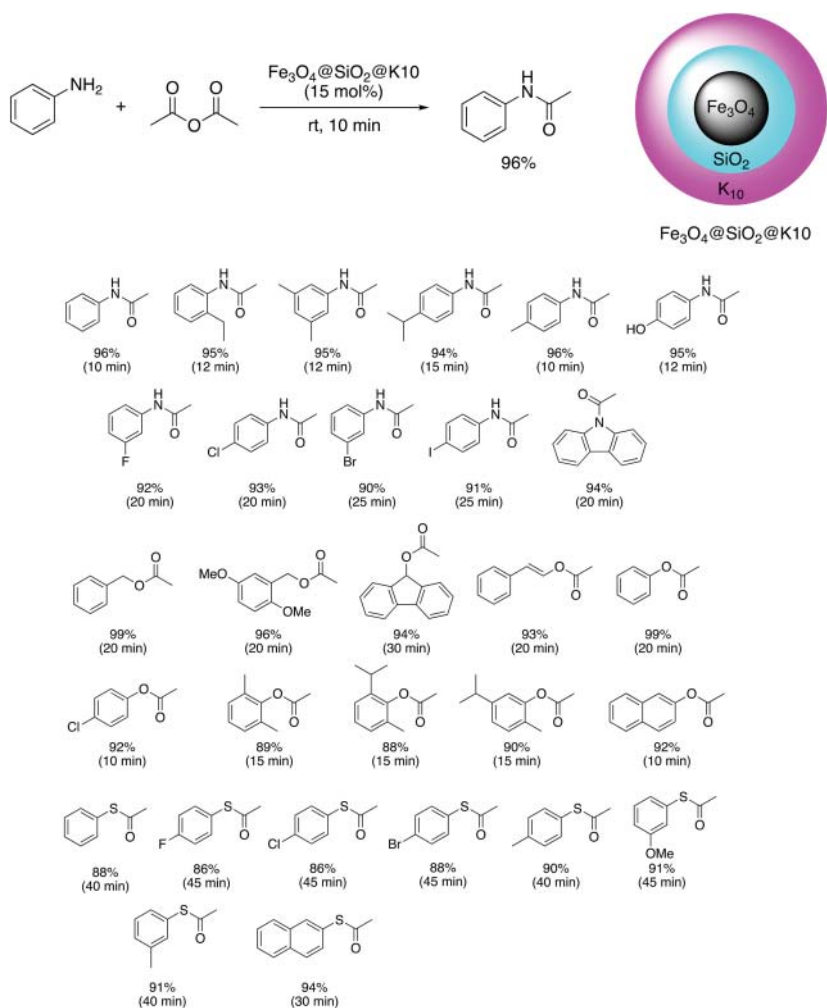


**Figure 5.5** Acylation of aromatic amine, alcohols, and thiols with Ac$_2$O under solvent-free condition using Fe$_3$O$_4$@SiO$_2$@K10 nanocatalyst. Source: Adapted from Tandon et al. [34].

A solvent-free deoximation has been demonstrated, using ammonium persulfate on silica (Scheme 5.6) [38]. Here, the oxime reagents are mixed with silica solids, and the suspension is irradiated in a microwave oven to generate aldehydes or ketones. A similar oxidation protocol using manganese dioxide impregnated on silica for the selective oxidation of benzyl alcohols to carbonyls, with high yield and under microwave conditions has been reported [37].
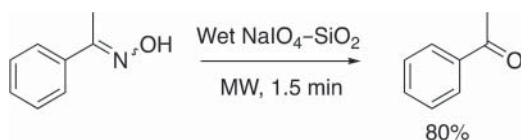


**Scheme 5.6** Solvent-free deoximation on ammonium persulfate on silica. Source: Adapted from Varma et al. [37].

Silica is often used in its most natural form as a nanopowder derived from clay. However, mesoporous silica is attracting great interest today because of its structural particularity. In fact, it is a nanomaterial with an organized network of channels of variable pore size (typically, between 2 and 30 nm), which gives them a particularly large active surface area, maximizing the "space" available for catalysis. The classical synthesis method is a cooperative self-assembly mechanism by which an inorganic precursor of the $SiO_4^{2-}$ polycondensates around micelles of surfactants. The concentration of the surfactants is chosen to reach a critical micellar concentration so that the surfactants can organize into a hexagonal network of cylindrical micelles around which the silica polymer forms. The elimination of the surfactants after the formation of the silica structure makes it possible to obtain mesoporous silica. This method produces mesoporous silica with tunable (and regular) pore size. The choice of surfactant is critical to designing the structure of the mesoporous material. Mesoporous silica has also found application in solvent-free synthetic chemistry. For example, Eidi et al. reported a protocol for the transamidation of amides in the presence of mesoporous silica under solvent-free conditions (Scheme 5.7) [39]. They have obtained a wide range of aromatic, aliphatic, and cyclic/acyclic amides with yields ranging between 60% and 100%. The material was also characterized by a series of methods to prove the stability of the nanostructure during and after catalysis and the recyclability of the catalyst.
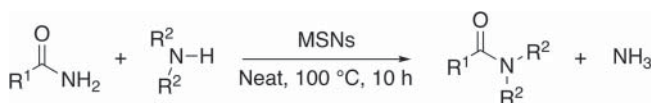


**Scheme 5.7** Transamidation of amides in the presence of mesoporous silica under solvent-free conditions. Source: Eidi et al. [39]/Springer Nature.

## 5.3 Zeolites and Hierarchical Zeolite Structures

Zeolites are aluminosilicates with a crystalline open structure and interconnected channels (Figure 5.6). They can be conceived as a set of $SiO_4$ and $AlO_4$ tetrahedra that bind together according to simple geometric shapes, forming complex cages
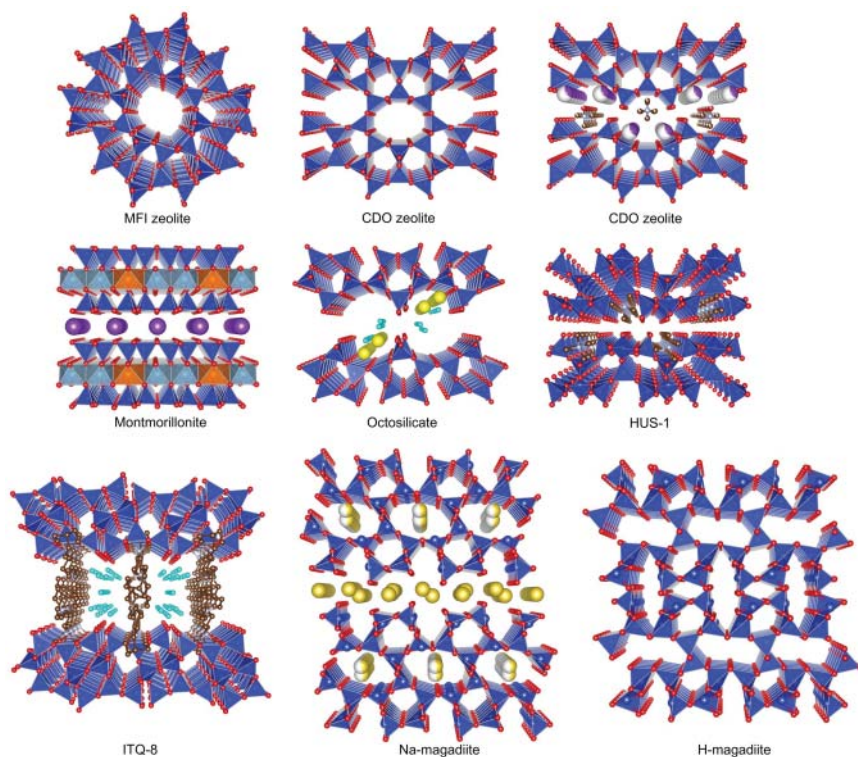
**Figure 5.6** Structures of selected zeolites. Color coding: green = Zn, red = O, brown = C, blue = Si, gray = Ti, purple = K, pale blue = Al, orange = Mg, yellow = Na, pale purple = N, light blue = O of $H_2O$. Source: Doustkhah and Ide [40]/Royal Society of Chemistry.

of low potential energy. As they have very regular geometric crystalline structures, zeolites are often used as catalysts. In particular, in a reaction, they are selective to the reagents (that is, only some reagents can access the zeolite pores and are catalyzed by the zeolites as some molecules are sterically prevented from accessing the active site) and selective to the products (i.e. when a reaction occurs, very often only one enantiomer of the product is formed, which makes these materials very useful in the pharmaceutical sector and for the production of enantiomerically active molecules). These structures tend to be acidic, and they can be made even more acidic by substituting some atomic groups with halogens (i.e. F, Cl, and Br, in general). The size of the zeolite pore is very important, as the catalytic action is linked to this: the molecules enter these pores selectively and undergo cracking and isomerization reactions. Furthermore, the type of cation present within the zeolite structure influences the ion-exchange kinetics.

There are several types of silica structures and zeolites (including mesoporous zeolite, functionalized zeolite, and metal-substituted zeolite) that have been used as catalysts or carrier materials for solvent-free synthesis [40–50].

The Knoevenagel condensation is an important C–C-forming reaction and is widely used in the synthesis of intermediates for agrochemicals, pharmaceuticals,

and polymers. The reaction is typically catalyzed by bases, acids, or catalysts containing acid–base sites. Bases such as ammonia, primary amine, secondary amine, and acids such as $CuCl_2$ and $ZnCl_2$ have been employed in the literature [51]. Saravanamurugan et al. have carried out a solvent-free liquid-phase Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate over zeolite β, zeolite Y, thermally dealuminated or zinc-exchanged zeolite β and Y (Scheme 5.8) [52]. The reaction parameters, such as time, temperature, and catalyst-loading, were varied. On the basis of their study, the authors reported high yield over Zn-β zeolite under solvent-free conditions.
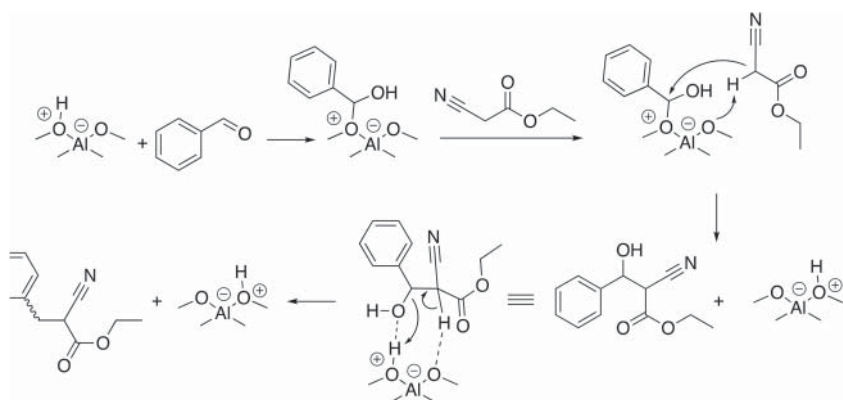


**Scheme 5.8** Mechanism for the solvent-free liquid-phase Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate over zeolites [52].

On the other hand, Sharma et al. [51] have evaluated the aldol condensation activities of a series of ion-exchanged zeolites, alumina, alkali-treated alumina, and hydrotalcite having a varied Mg/Al molar ratio under solvent-free conditions [52]. At 100 °C and 10 hours, activated hydrotalcite of Mg/Al molar ratio of 3.5 is used as a catalyst to achieve a maximum propanal conversion (c. 100%) with full 2-methylpentenal selectivity. However, the ion-exchanged zeolite is also highly active, reaching 100% selectivity at 40% conversion at the same condition. The catalyst has been recycled six times without any significant loss in catalytic performance. An atom-economical, multicomponent condensation of naphthols, aldehydes, and cyclic 1,3-dicarbonyl compounds catalyzed by HY zeolites under solvent-free conditions has been reported [53]. This ecofriendly protocol offers several advantages, such as a green and cost-effective procedure with excellent yield; shorter reaction time; simpler workup; recovery; and reusability of metal-free solid acid heterogeneous catalyst; as well as tolerance of a wide range of functional groups. Sarma et al. have reported a novel nitrogen-rich amorphous porous organic polymer synthesized using a microwave-assisted process in the presence of zeolite Y and under solvent-free conditions [54]. Its high chemical stability, reusability, and poor solubility enable the use of the porous polymer as a metal-free heterogeneous catalyst for C—C bond formation. These examples from the literature demonstrate that zeolites can be cheap and highly stable materials for the promotion of synthetic reactions under environmentally benign conditions.

Recently, a continuous acetalization of glycerol with acetone in the presence of HZSM-5 films in a capillary microreactor was reported [55]. The catalytic performance of this acidic HZSM-5 capillary film microreactor afforded the corresponding solketal in a 62% yield, and no deactivation was observed after 100 hours (Scheme 5.9).
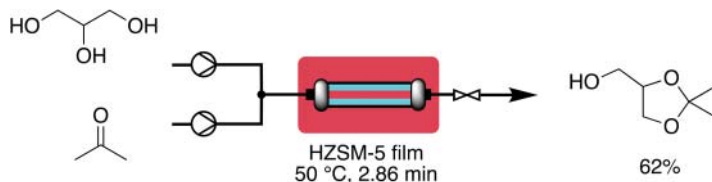


**Scheme 5.9** Continuous-flow catalytic acetalization of glycerol using a HZSM-5 film capillary microreactor. Source: Adapted from Cho et al. [55].

In terms of silica structures, Sharma and Gupta prepared silica-supported sulphonic acid catalysts and coated the material with different types of ionic liquid layers (see also Figure 5.7), evaluating the sample in the one-pot synthesis of 1,4-dihydropyridines [56]. The authors found silica sulphonic acid coated with [BMIM][PF6] to be the most active and stable catalyst. Similarly, using solvent-free conditions, and employing solid catalyst TS-1, organic reagents in neat conditions and catalytic $H_2O_2$, a significant enhancement in the benzene oxidation reaction rate (by c.15–25 times) compared with that obtained under conventional biphasic system was observed in Bhaumik et al. [57]. The authors also conducted kinetic studies that indicated that while in the presence of a cosolvent (like acetone, acetonitrile, or methanol), a long induction period is observed, and benzene competes favorably for diffusion inside the TS-1 channels; in solvent-free conditions, the induction period is almost absent. In addition, there is a strong competition between benzene and the organic solvents for diffusion inside relatively hydrophobic TS-1 channels, resulting in low conversion. Thus, the solvent-free method offers the distinct advantages of being easier to workup and being environmentally safer because of the absence of organic solvents.

Silica materials can also be modified by the introduction of metal nanoparticles to maximize the catalytic performance of the composite in the absence of solvent.
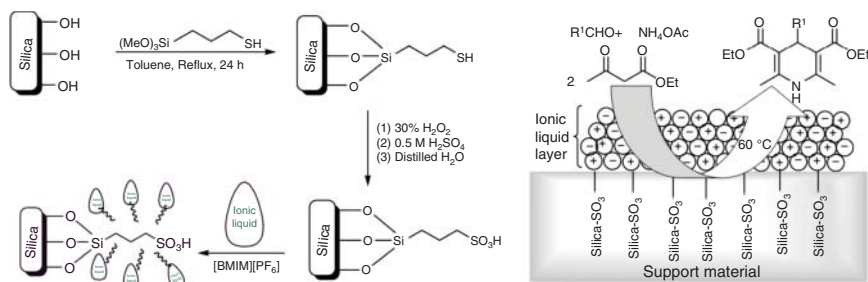


**Figure 5.7** Preparation of silica-supported sulphonic acid catalysts coated with ionic liquid layer. Source: Sharma and Gupta [56]/Royal Society of Chemistry.

For example, the preparation of bifunctional metal nanoparticles on silica-based acid catalysts has been reported by Zhu et al. [45]. In particular, the *in situ* reduction of $Au^{3+}$ with HS-functionalized mesoporous organosilicas (PMOs) created Au nanoparticles with a uniform, narrow size distribution around 1–2 nm and concomitantly sulfonic acid moieties strongly bonded to PMOs. The Au nanoparticles were mainly attached to the pore surface rather than onto the outer surface with ordered mesoporous channels, allowing for maximal exposure to reaction substrates while minimizing Au nanoparticle leaching. This unique amphiphilic compartment of the Au-HS/$SO_3$H-PMO(Et) nanostructures enabled organic reactions to proceed efficiently without using any organic solvents and even in the absence of water. These features render the silica-based catalyst particularly attractive in the practice of environmentally friendly organic synthesis.

## 5.4  Conclusion

This chapter has discussed solvent-free synthetic methods in the presence of silica-based materials. The possibility to avoid the use of a solvent opens numerous possibilities for conducting selective organic transformations in an efficient and expeditious manner using a variety of silica-based reagents and supports. The enhancement of the reaction rate over silica, as well as the high chemo-, regio-, and stereoselectivity attained, may soon bring the translation of these "curious" experiments to large-scale chemical operation, which will harness the true potential of this clean technology.

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