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Organic Reactions on Silica in Water

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1. Introduction

In nature, many biological processes occur in aqueous environments, and these fascinating in vivo reactions should prompt organic chemists[1] to explore the potential of water as a medium for organic reactions. In addition to scientific interest in aqueous reaction media, social pressure to find environmentally benign alternatives to current organic chemical processes has made these reactions attractive from an ecological point of view.[2] The use of aqueous media in organic reactions offers significant environmental advantages and has attracted a great deal of interest because water is a desirable solvent for the following reasons: low cost, safety, and environmental concerns. Groundbreaking studies of organic reactions in aqueous environments demonstrated that Diels−Alder reactions[3−5] and Claisen rearrangement[6] of hydrophobic reactants are accelerated in aqueous solutions. In addition to these discoveries, aqueous environments result in reactivity and selectivity that are unique from reactions in organic solvents. As a result, many versatile and efficient organic reactions have been developed.[7]

Although many organic reactions are facilitated in aqueous media, some reactions proceed very slowly because the solubility of most organic molecules in pure water is limited. Because solubility is a prerequisite for reactivity, a variety of strategies expanding the scope of water-based organic syntheses have been investigated. Most commonly, organic cosolvents, such as the lower alcohols, acetone, DMF, and acetonitrile, are used to increase the solubility of hydrophobic solutes in water.[7c,d] Some alternative means of achieving aqueous solubility are the use of phase-transfer catalysts[8] and surfactants.[9] In addition to these processes, substrate modifications, such as the addition of a positive or negative charge to an ionizable substrate[10] or the grafting of hydrophilic groups onto insoluble reactants,[11] have been investigated. However, these approaches change the chemical behavior of the substrates and tend to complicate the reactions.

Recent studies indicate that water is a promising medium for heterogenized homogeneous catalysis. Although the efficiency of heterogeneous catalysis is generally inferior to that of homogeneous systems, the advantage of immobilized catalysts include their easy recovery from reaction mixtures and their reusability. Catalysts heterogenized through covalent and non-covalent attachment to either inorganic or organic materials, such as silica, layered clays,[12] and polymers,[13] have been successfully employed in aqueous media. The chemical stability of the inorganic supports is important, especially under oxidizing conditions; the mechanical and thermal stability of inorganic supports is often excellent as well.

This review will focus on the use of silica as an inorganic support for organic reactions in water. The hydroxy group on the silica surface readily reacts with alkoxy- or chloro-substituted silyl compounds, leading to functionalized silica supports. This manipulation allows not only for the introduction of catalysts to the surface of the support but also for the control of surface hydrophobicity. The proteiform and unique character of silica surfaces have been utilized for organic reactions in aqueous media.

This review is organized into three main parts, each devoted to one form of silica that has unique effects on organic reactions in water: heterogenized catalysts on silica (immobilization by covalent binding or adsorption of catalysts on silica), hydrophobic and fluorous reverse-phase silica, and unmodified silica. The first section is subdivided into three heterogenized catalyst systems, as follows: water phase only, water−organic biphasic systems, and water−ionic liquid systems.

2. Heterogenized Catalysts on Silica

Heterogenization of homogeneous catalytic reactions allows for the facile recovery and recycling of catalysts. Two basic approaches to heterogenization have been developed. The first is immobilization of catalysts on silica supports in a water-only phase. The second strategy employs a biphasic system: the catalyst is dissolved in one phase (water or ionic liquid), and the reactant and product are dissolved in the other phase (organic solvent or water).

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Satoshi Minakata was born in 1964 in Wakayama, Japan. He received his Ph.D. in 1993 from Osaka University under the direction of Prof. Y. Ohshiro. After spending two years at the Central Research Laboratories of Dainippon Ink & Chemicals, Inc., he was appointed Assistant Professor in the Department of Applied Chemistry in Professor Komatsu's group at Osaka University. In 2002, he was promoted to Associate Professor. From 1997 to 1998, he worked with Prof. Erick. M. Carreira at the California Institute of Technology as a Visiting Associate Professor. His current research interest is the development of new methodologies for the synthesis of achiral and chiral functional molecules containing heterocyclic compounds with a view to green processes.

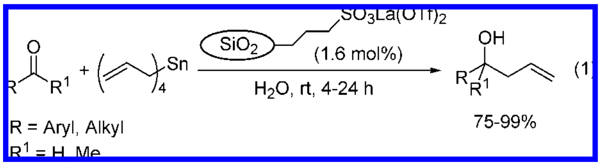
Mitsuo Komatsu was born in 1943 in Akita, Japan, and received his B.A. in 1967 and M.A. in 1969 from Osaka University. In 1974, he received his doctoral degree from Osaka University under the supervision of Prof. T. Agawa. His professional career started in 1969 when he joined the Engineering Faculty at Osaka University as an Assistant Professor. From 1975 to 1976, he worked with the late Prof. Gerrit L'bbé as a postdoctoral fellow at the Catholic University of Leuven. After being promoted to Associate Professor, he was awarded Full Professor in 1994 at Osaka University. His primary research areas are heterocyclic chemistry and heteroatom chemistry. His current interests are focused on the development of new methodologies for the synthesis of heterocyclic compounds and on their application to organic syntheses and functional materials.

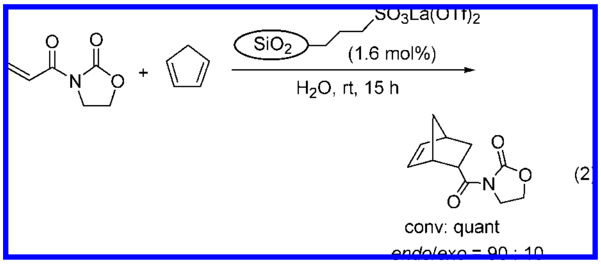
2.1. Catalysts Immobilized in a Water-Only Phase

The use of water as the sole medium for organic reactions would both significantly reduce the environmental burden of organic syntheses and facilitate the reactions. The most common applications of silica to aqueous organic reactions in water—silica-supported catalysts (metal catalysts attached to silica via ionic or coordinated ionic bond and organo catalysts, such as covalently bound acidic or basic catalysts)—have been widely explored.

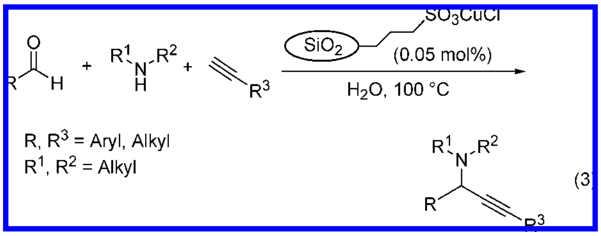
2.1.1. Simple Immobilization of Metal Catalysts on Silica

Catalytic organic reactions in water require very specific conditions to maintain catalyst stability and reactivity. Recently, Lewis acid-catalyzed organic aqueous reactions and other catalytic aqueous reactions developed by Kobayashi et al. have received considerable attention.[14−16] Kim et al.[17] developed a novel, solid Lewis acid catalyst via immobilization of a rare earth metal onto mesoporous silica. Lanthanum sulfonate immobilized on mesoporous silica (SBA-15) was prepared and used to catalyze the allylation reaction of carbonyl compounds with tetraallyltin (eq 1) and the Diels−Alder reactions of 3-acryloyl-1,3-oxazolidin-2-one with cyclopentadiene (eq 2). After the reaction was complete, the catalyst was removed by filtration and recycled more than 20 times without any loss of catalytic activity in allylation reactions employing aldehydes.

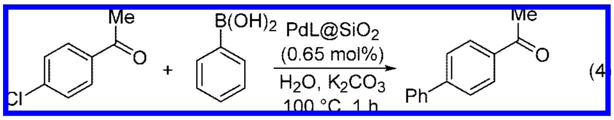




A related catalyst, silica-gel-anchored copper chloride, was synthesized using 3-mercaptopropyltrimethoxysilane as a spacer to explore its activity in three-component coupling reactions (eq 3).[18]

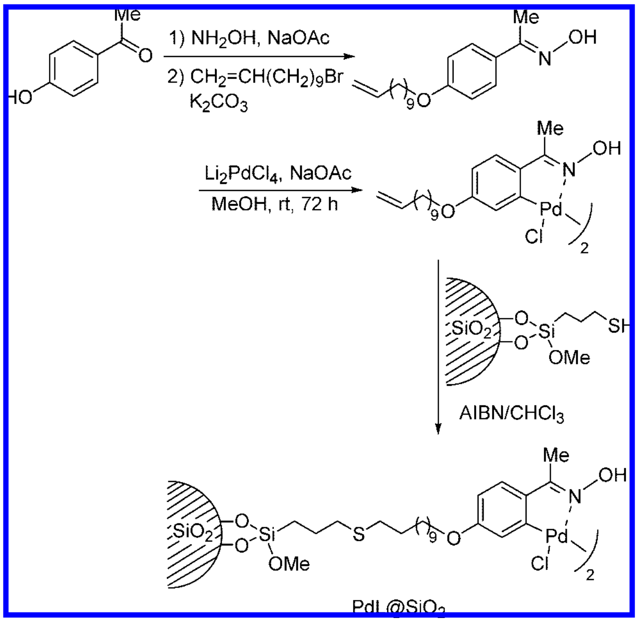


Heterogenized catalysts on silica have been employed in transition metal-catalyzed reactions in water.[19] An oxime−carbapalladacycle complex anchored to silica (pdL@SiO_2) was synthesized as shown in Scheme 1. The pdL@SiO_2 catalyst was highly efficient for the Suzuki−Miyaura coupling of *p*-chloroacetophenone and phenylboronic acid in water (eq 4); no leaching occurred, and the catalyst was reused eight times without a decrease in activity.

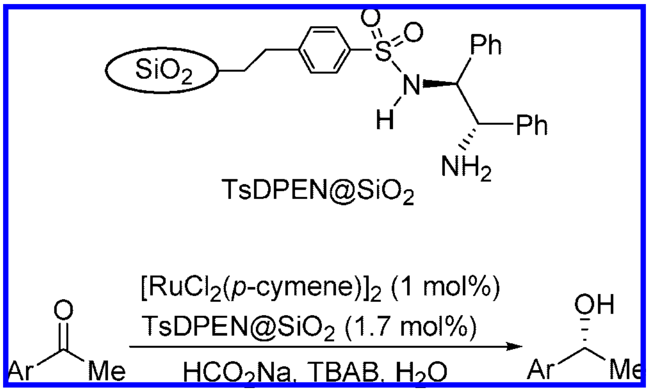


Currently, aqueous[7d] heterogeneous asymmetric catalytic reactions[20] that use the supported chiral catalysts are attracting great interest.[13a−f,21] Silica supports have also been used

Scheme 1. Preparation of Oxime−Carbapalladacycle Complex Anchored on Silica



Scheme 2. Structure of the Supported TsDPEN and Asymmetric Hydrogenation of Aromatic Ketones Using the Ru-TsDPEN@SiO2 Catalyst in Water

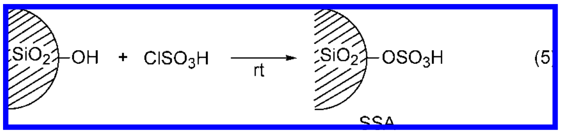


to catalyze asymmetric reactions in organic solvents.[22] The system also has been applied to aqueous reactions (Scheme 2).[23,24] The silica-gel-supported Ru-TsDPEN[25] catalyst demonstrated excellent enantioselectivity (up to 99% ee) and very high reactivity (>99% yield, 2−8 h) for aromatic ketones in asymmetric transfer hydrogenation in water. The catalyst was readily recovered and reused, while maintaining enantioselectivity and recharging Ru. A unique feature of the aqueous system was its distinct “acceleration effect” (109 TOF) in comparison with the reaction in organic solvents (10 TOF).

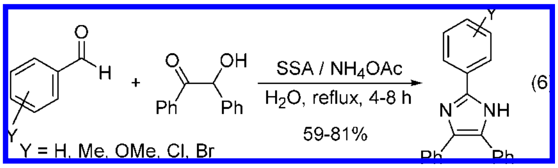
Quite recently, Li et al. developed homoallylic alcohol isomerization in water over immobilized Ru(II) organometallic catalyst with mesoporous materials.[26−28] For example, PPh_2-functionalized SBA-15 was synthesized and was used as the support to immobilize the Ru(II) organometallic catalyst (Ru-PPh_2−SBA-15). The catalyst exhibited almost the same activity and selectivity as the corresponding $RuCl_2(PPh_3)_3$ homogeneous catalyst for 1-phenyl-3-buten-1-ol isomerization.[26] Amine-functionalized SBA-15 as the ligand for Ru(II) was also applied to the isomerization and showed almost the same activity.[27] These catalysts were characterized using XRD, TEM, and N_2 adsorption−desorption isotherms, and solid state ^{29}Si MAS NMR and ^{13}C CPMAS NMR confirmed the presence of organic groups and $RuCl_2(PPh_3)_3$ complex on the silica frameworks.

2.1.2. Simple Immobilization of Acid or Base on Silica

Immobilization of an acid or base on silica via covalent bonding has many advantages over homogeneous catalysts. Heterogeneous catalysts can be recovered and reused, whereas homogeneous catalysts are less stable and contaminate reaction mixtures. A representative example of an acid supported on silica is the one developed by Zolfigol (eq 5).[29] Neat chlorosulfonic acid reacted with silica gel to afford silica sulfuric acid (SSA). The silica sulfuric acid was a superior proton source compared with all of the acidic solid supports and acidic resins, such as polystyrene sulfonic acid and Nafion-H,[30] examined under heterogeneous conditions.



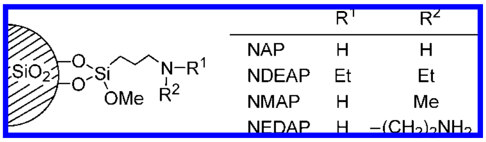
In general, the acidic sites of solid acids are inactivated by water. In fact, most acids lose their activity in aqueous solutions. However, SSA efficiently catalyzed the synthesis of trisubstituted imidazoles from benzaldehydes, benzoin, and ammonium acetate in water (eq 6).[31]



Thioacetalization of carbonyl compounds using a dithiol in the presence of a catalytic amount of silica-based sulfonic acid in water was reported by Karimi et al.[32]

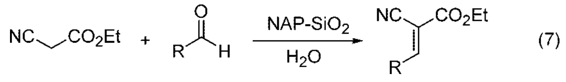
In contrast, the use of catalytic amines grafted onto silica gel for aqueous organic reactions was systematically investigated by Hagiwara et al. These investigators synthesized and employed a simple catalyst—3-aminopropylated silica gel (Scheme 3).

Scheme 3. Amines Grafted onto Silica Gel



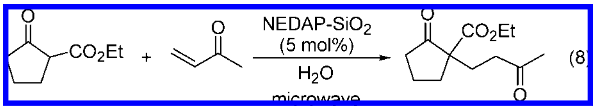
	R^1	R^2
NAP	H	H
NDEAP	Et	Et
NMAP	H	Me
NEDAP	H	$-(CH_2)_2NH_2$

The Knoevenagel reaction between an aldehyde and ethyl cyanoacetate was achieved at ambient temperature in water using NAP-SiO_2 as a catalyst (eq 7).[33] This catalyst was efficiently recycled more than five times without any pretreatment. The authors suggested that water might play a role in bringing the substrates into close proximity on the surface of the lipophilic reverse-phase silica gel.



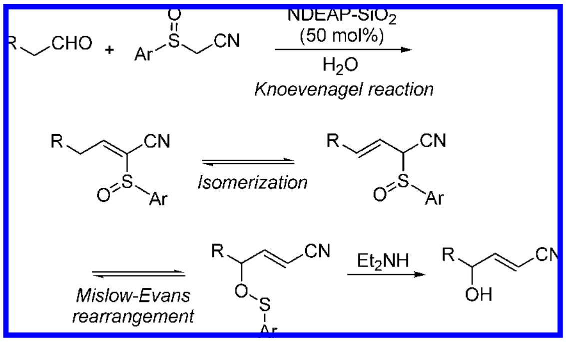
The amine catalyst supported on silica was employed in the Michael addition of 1,3-dicarbonyl compounds to α,*β*-

unsaturated carbonyl compounds in an aqueous environment with microwave heating (eq 8).[34] Although there was one published example of the 1,4-addition of nitroalkene to electron-deficient olefins catalyzed by a heterogeneous organomolecular catalyst grafted on silica gel without the use of a solvent,[35] this study was the first to demonstrate a catalytic Michael addition in water. Interestingly, among the solvents (THF, PEG, xylene, H_2O) examined, water was the best medium for the addition reaction.



Moreover, this series of catalysts was used in the aqueous catalysis of a useful reaction—sequential Knoevenagel reaction/Mislow−Evans rearrangement[36]—to yield γ-hydroxy-α,β-unsaturated nitrile (Scheme 4).[37]

Scheme 4. Sequential Knoevenagel Reaction/Mislow−Evans Rearrangement in Water Using NDEAP-SiO$_2$



2.1.3. Control of the Hydrophobicity of the Silica Surface

The metal catalyst system supported on silica described in section 2.1.1 is a simple modification of silica for the immobilization of metal catalysts. In this section, a unique system that allows for control of the hydrophobicity of the silica surface by the introduction of functional moieties is discussed.

Neumann elegantly constructed an aqueous alkene oxidation system using hydrophobic silica particles derivatized with polyoxometalates as catalysts.[38] The purpose of this strategy is the creation of multifunctionalized, insoluble, silicate-based particles, capable of effective adsorption of alkene reactants and containing centers at the particle and adsorbed substrate−water interface. Effective adsorption of the substrate was achieved by the introduction of hydrophobic silicate xerogels with covalently attached phenyl groups. To facilitate interaction with the catalytic center, an anionic polyoxometalate (POM) and quarternary ammonium cation included in the hydrophobic region were immobilized to the surface of silica. The system was used to catalyze the oxidation of alkenes to epoxides in 30% aqueous hydrogen peroxide in the absence of an organic solvent (Figure 1).

Moreover, Neumann et al. developed a new immobilization technique—supported, solvent-anchored liquid-phase catalysis.[39] Polyethers were attached covalently to silica surfaces, and the polymer acted as a solvent and/or a complexing agent for the oxidative catalyst (POM). In this system, the bound polyether catalyst phase is in contact with two immiscible liquid phases: the oxidant (30% aqueous H_2O_2) and the organic substrate (cyclooctene). The supported catalyst phase is at the interphase where the solubilized reactants come in contact and react (Figure 2).

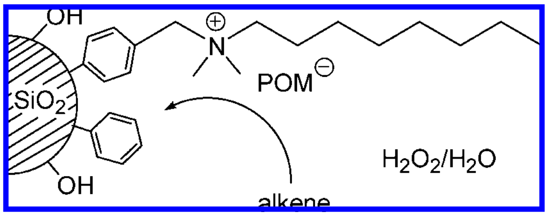


Figure 1. Simplified representation of multifunctionalized catalytic silica in hydrocarbon−water mixtures.

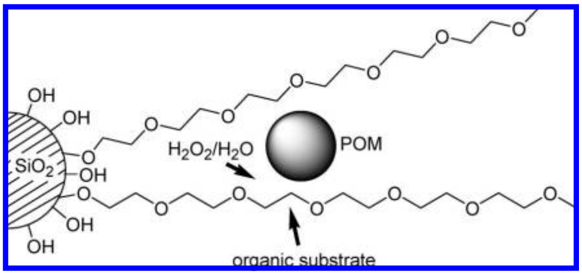
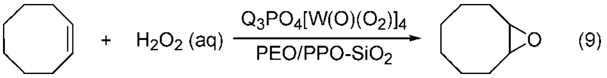


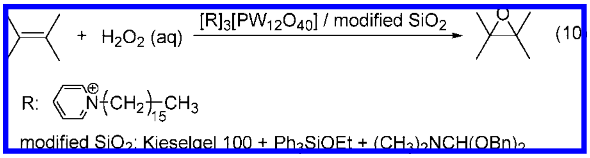
Figure 2. Illustration of the supported solvent-anchored liquid-phase catalytic system.

The utility of supported solvent-anchored liquid-phase catalysis was demonstrated by epoxidation of cyclooctene in 30% aqueous hydrogen peroxide with POM ($Q_3PO_4[W(O)(O)_2]_4$, Q = tetrahexylammonium) (eq 9).



In a related study, oxidative C−H activation of cyclohexane in water using a biomimetic methane monooxygenase enzyme precatalyst, $[Fe_2O(\eta^1\text{-}H_2O)(\eta^1\text{-}OAc)(TBA)]^{3+}$ (TBA = tris[(2-pyridyl)methyl]amine) was achieved by Newmann et al., in which an amorphous silicate modified with the combination of hydrophilic poly(ethylene oxide) and hydrophobic poly(propylene oxide) played an important role in the reaction media.[40]

Although discovery of the catalytic system described above led to the development of prototypical heterogeneous catalytic systems for olefin epoxidation in aqueous H_2O_2 without the use of organic solvents, significant problems must be overcome to demonstrate the generalizability of olefin epoxidation. An alternative surface modification of silica was investigated by Pac et al.[41] The solid catalyst was prepared by non-covalent fixing of the tungstophosphate anion on chemically modified hydrophobic mesoporous silica gel. The catalyst efficiently catalyzed the selective epoxidation of various alkenes in 15% aqueous H_2O_2 (eq 10).



Development of supported palladium catalysts that have much greater catalytic activity and are not vulnerable to leaching is highly desirable. Thus, Pd catalysts supported on not only organic materials but also on inorganic materials, such as amorphous silicate[42] and mesoporous silica, have been

Scheme 5. Synthesis of a Mesoporous Silica-Supported Catalyst

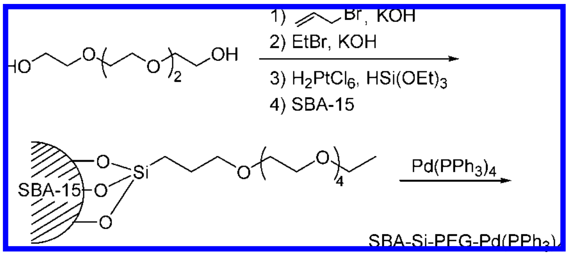
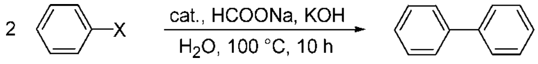


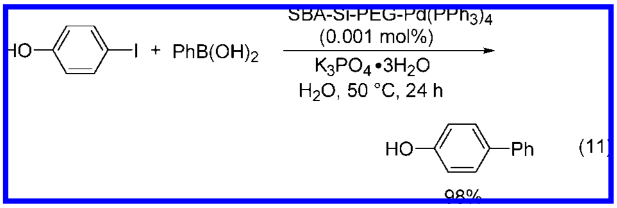
Table 1. Catalytic Performance of Palladium-Supported MCM-41, Ph-MCM-41, and Ph-PMO



	X = I		X = Br	
catalyst	conv (%)	yield (%)	conv (%)	yield (%)
Pd/MCM-41	60	34	84	0
Pd/Ph-MCM-41	75	74	84	19
Pd/Ph-PMO	95	94	93	91

developed.[43−47] To realize the Suzuki−Miyaura coupling reaction in water, a palladium catalyst supported on PEG-modified mesoporous silica was prepared.[48] The PEG-coated mesoporous silica (SBA-15)-supported palladium complex was synthesized from tetra(ethylene glycol) (Scheme 5).

Although the catalyst is 0.001 mol %, the coupling reaction proceeded efficiently (eq 11). Moreover, the catalyst remained active after exposure to air for up to 6 weeks. An aqueous suspension of the catalyst was reused several times by simple extraction of the aqueous reaction mixture, indicating that the catalyst did not leach into the organic layer.



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Although mesoporous silicas were used as supports in the two examples described above, the details of the reaction catalyzed using the silica-supported catalysts were not discussed.

Periodic mesoporous organosilicas (PMOs)—one type of mesoporous silica—were first reported in 1999.[49−54] To clarify the advantages of using PMOs in organic reactions and Ullmann coupling in water, a palladium-supported Ph-PMO catalyst was compared with the palladium catalysts, Pd/MCM-41 and Pd/Ph-MCM-41. The palladium-supported Ph-PMO catalyst exhibited good catalytic activity for the Ullman reaction of iodobenzene and bromobenzene in water, as shown in Table 1. The large difference between supported and unsupported catalysts was attributed to surface hydrophobicity, which was evaluated by the adsorption isotherms of water and toluene. Ph-PMO was found to have the most hydrophobic surface and, therefore, selectively adsorbed the halogenated aromatics from aqueous solution.[55] On the other hand, Pd/Ph-MCM-41[56] and related catalysts[57,58] showed higher activity than Pd/SiO_2 and Pd/MCM-41 for aqueous medium Ullmann reaction. Although both Ph-PMO and Ph-MCM-41 have unique character for organic reactions in aqueous media, the main difference would be attributed to not only the hydrophobicity but also the location of functional groups such as a phenyl group. In Ph-PMO catalyst, the phenyl group is in the pore wall, whereas for Ph-MCM-41, the group lay in the pore channel. The large size of the functional group in the pore channel would influence the mass transfer, leading to decreased activity. The PMO catalyst, however, remained the original pore channel after being modified with hydrophobic groups. This chemistry has been energetically developed by Li et al. and, recently, Pd(II) organometallic catalyst immobilized on the ethyl-bridged PMOs was synthesized and exhibited identical catalytic activity and selectivity with the corresponding homogeneous Pd(II) catalyst for Barbier reaction in water.[59]

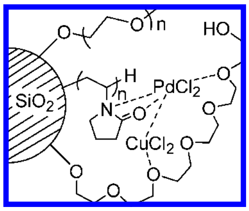


Figure 3. Schematic representation of the structure of the PNP$-$Pd$Cl_2$$-CuCl_2$/$SiO_2$$-$PEG600 catalyst.

A more complex modification of silica was performed. Namely, a combined heterogeneous catalyst, PVP$-$Pd$Cl_2$$-CuCl_2$/$SiO_2$$-$PEG600, was prepared using the reaction of silica gel functionalized with a polyethylene glycol (PEG) with an average molecular weight of 600, which functioned as a carrier system with phase transfer properties, with a polyvinylpyrrolidone (PVP)-anchored PdCl_2 and CuCl_2 complex (Figure 3). The catalyst showed good selectivity and activity for dechlorination of aromatic chlorides in water.[60]

2.2. In Water and Organic Solvent

Although this review deals with organic reactions on silica in water without the use of any organic solvents, a unique family of heterogeneous catalysts, which are called “supported aqueous-phase catalysts (SAPCs),” for water−organic interface reactions are included because this system facilitates organic reactions and leads to subsequent development of aqueous organic reactions.

Thus, significant effort has been devoted to immobilization of catalysts. In a pioneering study, Davis et al. reported a new class of heterogeneous catalysts: supported aqueous-phase (SAP) catalysis.[61] The SAPC system is designed to catalyze liquid reactants with a low-boiling-point water phase maintained on a hydrophilic support such as silica. A schematic diagram of an SAP catalyst is shown in Figure 4.

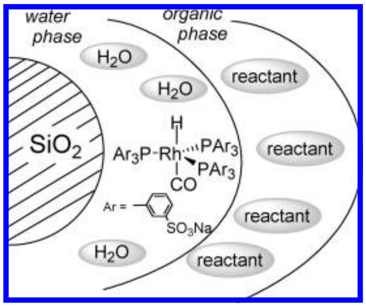


Figure 4. Schematic diagram of an SAP catalyst.

Aqueous phase impregnation results in a large area of surface contact between silica and water-soluble organome-

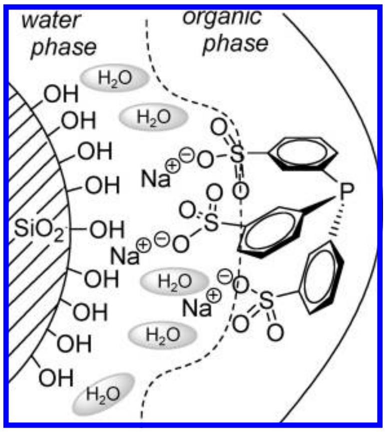
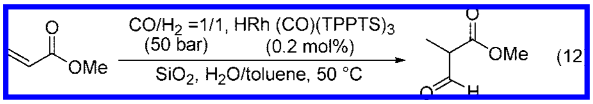


Figure 5. Proposed immobilization of water-soluble P(*m*-$C_6H_4SO_3Na)_3$ on the hydrophilic support.

tallic complexes. Reactants diffuse from the bulk organic phase into the silica and react at the water−organic interface. The resulting products diffuse back out into the organic phase. This system was applied to hydroformylation of oleyl alcohol catalyzed by HRh(CO)[P(*m*-$C_6H_4SO_3Na)_3]_3$ (HRh(CO)$(TPPTS)_3$). The reaction conditions were as follows: 0.002 g of Rh per gram of oleyl alcohol; organic phase, 25 vol % oleyl alcohol in cyclohexane; molar ratio, $CO/H_2 = 1$; pressure, 5.08 MPa; temperature, 50 °C; and reaction time, 5.5 h. The corresponding aldehydes were obtained in 96.6% yield under these conditions. The SAPCs were recyclable without loss of catalytic activity. In addition, hydroformylation occurred in the absence of SAPC when the filtrate plus additional oleyl alcohol was used; no further conversion was detected, indicating that rhodium is not leached into the organic phase.[62] SAP catalysis was applied to a phosphine-modified cobalt carbonyl, $Co_2(CO)_6$[P(*m*-$C_6H_4SO_3Na)_3]_2$, for the hydroformylation of 1-hexene,[63] and to the same reaction of alkyl esters of acrylic acid catalyzed by HRh(CO)$(TPPTS)_3$.[64]

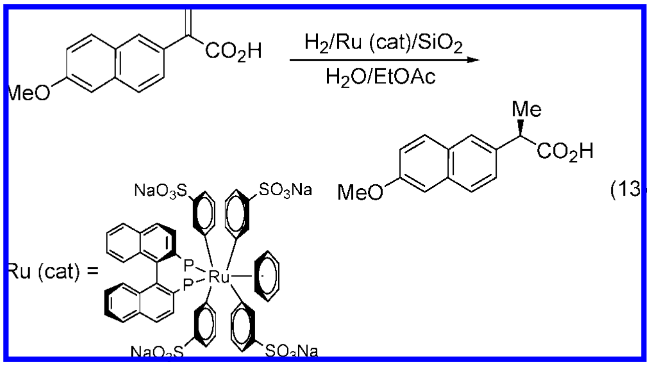
To verify that hydroformylation really occurs at the water−organic solvent interface, the relationship between the normal/iso ratio of aldehydes produced by hydroformylation and the form of some catalysts, including organic soluble catalysts, was investigated by Horváth.[65] When an aqueous solution of HRh(CO)$(TPPTS)_3$ was immobilized on a high surface area silica support, the effect of the olefin size was reduced. The immobilized catalyst on silica showed a significant water loss, but no rhodium leaching. These results suggest that the hydrophilic support retains water-soluble phosphines by hydrogen bonding of the hydrated sodium-sulfonate groups on the surface (Figure 5).

Although the "supported aqueous phase" system has several advantages, as described above, catalytic systems often suffer from poor activity and are always far slower than the analogous homogeneous reactions. Chaudhari et al. reported an acceleration effect on the hydroformylation of 1-octene catalyzed by HRh(CO)$(TPPTS)_3$ in the presence of triphenylphosphine (TPP).[66] However, under these biphasic conditions, turn-over frequencies (TOFs) were almost comparable to those obtained with homogeneous systems. Enhancement of catalytic hydroformylation of methyl acrylate by use of the SAP and biphasic system was achieved by Mortreux et al. (eq 12).[67] Methyl acrylate was hydroformylated with an exceptionally high TOF of 2370 h^{-1}. Polar interactions between methyl acrylate and silica gel and/or the water phase supported on the silica gel surface would be responsible for the TOF improvement.



(12

Other than hydroformylation of carbon−carbon double bonds, the SAP catalysis system was extended to hydrogenation of α,*β*-unsaturated aldehydes that yields allylic alcohols.[68] Asymmetric synthesis of naproxen was successfully performed by use of an SAP system with a Rh-BINAP catalyst as a chiral source. Impregnation of water from the organic phase, ethyl acetate, was used to hydrate the SAP catalyst. When water-saturated ethyl acetate was used, 100% conversion (s/c = 31.5) was achieved within 3 h with 70% ee (eq 13).[69]



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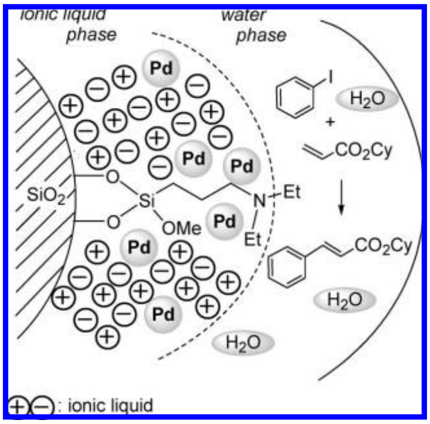
2.3. In Ionic Liquid and Water

More recently, ionic liquids have attracted much attention as an alternative reaction medium for homogeneous catalysis.[70−74] Instead of using water in an SAP catalysis system, as described in section 2.2, an ionic liquid was applied to a similar system for hydroformylation of 1-hexene.[75] In this system, an ionic liquid and an organic solvent were used, whereas the combination of an ionic liquid and water was employed in biphasic heterogeneous catalysis systems.[76−79]

Hagiwara et al. reported that palladium acetate immobilized on reversed phase silica with the aid of an ionic liquid ([bmim]PF_6) was highly efficient in catalysis of the Mizoroki−Heck reaction in water (Scheme 6). When the reaction was carried out with NDEAP-Pd (see Scheme 3, Pd loading = 0.047 mmol/g) and 2 equiv of *n*-Bu_3N in water

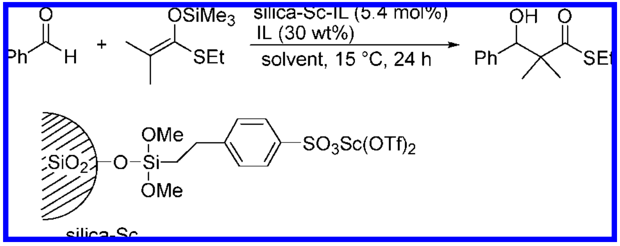
Scheme 6. Mizoroki−Heck Reaction in Water Catalyzed by Immobilized Pd Catalyst



at 100 °C, the efficiency (TON, 200,000; TOF, 20,000) was higher than that in organic solvent.[76]

Kobayashi et al. established an elegant heterogeneous silica-supported scandium/ionic liquid catalyst system for organic reactions in water.[77] The catalyst (silica-Sc-IL) was readily prepared, and it was successfully applied to Mukaiyama aldol reactions, Michael reactions, Mannich reactions, allylation reactions, and asymmetric hydroxymethylation. To show the utility of the catalyst, various reaction conditions were examined for the model Mukaiyama aldol reaction of benzaldehyde with 1-ethylthio-1-trimethylsiloxy-2-methyl-1-propene. The reaction proceeded efficiently in water (Table 2, entry 1), but sluggishly in hexane and ether and under solvent-free conditions (entries 2−4). Although the reaction also proceeded without ionic liquid (entry 5), moderate to good yields were obtained with other ionic liquids (entries 6−8). A wide range of other Mukaiyama reaction substrates were tested using the catalyst.

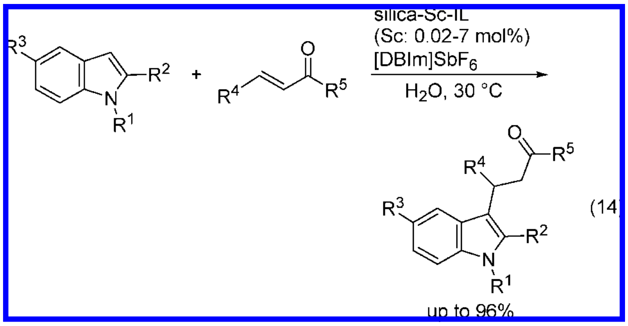
Table 2. Mukaiyama Reaction with Silica-Sc-IL



entry	solvent	IL[a]	yield (%)
1	H_2O	$[DBIm]SbF_6$	97
2	hexane	$[DBIm]SbF_6$	26
3	Et_2O	$[DBIm]SbF_6$	22
4	none	$[DBIm]SbF_6$	25
5	H_2O	none	31
6	H_2O	$[DBIm]NTf_6$	64
7	H_2O	$[DBIm]PF_6$	76
8	H_2O	$[BMIm]SbF_6$	54

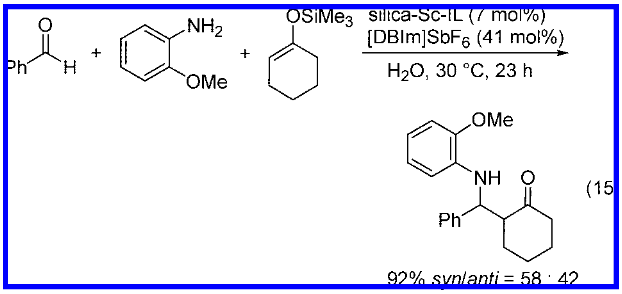
[a] [DBIm], 1-butyl-3-decylimidazolium; [BMIm], 1-butyl-3-methylimidazolium.

The catalyst was highly efficient for the Michael reaction of indole derivatives with enones in water (eq 14).



(14)

A three-component Mannich reaction between an aldehyde, amine, and silicon enolate and an allylation reaction between a ketone and tetraallyltin also gave excellent yields (eqs 15 and 16).



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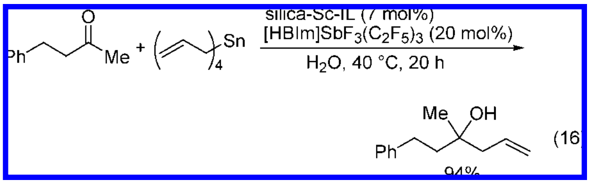
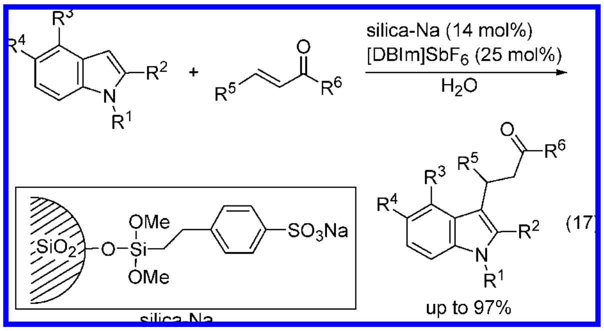


(16)

The first asymmetric version of the catalytic system was tested with silica-Sc-IL and a chiral ligand in the hydroxymethylation of aqueous formaldehyde and a silicon enolate, giving a hydroxymethylated ketone with 66% ee. This is the first example of the combination of silica-gel-supported metal catalysts and ionic liquids creating an efficient hydrophobic environment for organic reactions in water.

Moreover, an alternative neutral catalyst system derived from silica-supported sodium sulfonate with an ionic liquid for Michael reactions of indole derivatives with α,*β*-unsaturated carbonyl compounds in water was developed by Kobayashi et al. (eq 17).[78] Because the reaction proceeded under neutral conditions, acid-labile substrates were successfully employed in the aqueous Michael reaction.



(17)

An alternative aqueous silica-supported catalyst was prepared by use of a coating ionic liquid. Jérôme et al. prepared a Brønsted acid (sulfonic acid)-immobilized silica gel[79] and investigated the selectivity of the catalyst in organic reactions. The silica material and ionic liquid used in this study are shown in Figure 6.

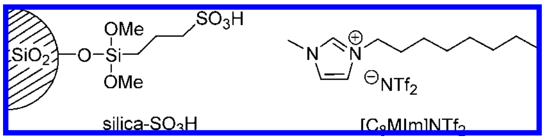
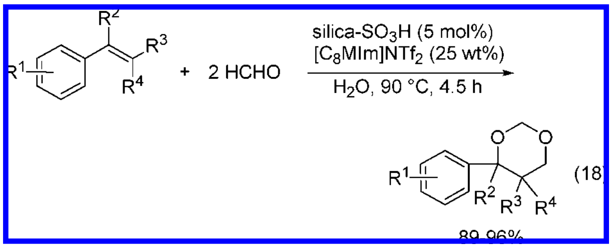


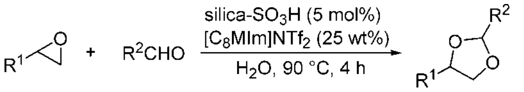
Figure 6. Silica materials and ionic liquid.

Prins cyclization (eq 18), cycloaddition (eq 19), and dehydrative etherification (eq 20) proceeded well in both formalin and pure water. When 25 wt % of $[C_8MIm]NTf_2$ was loaded onto $SiO_2{-}SO_3H$, Prins cyclization of α-methylstyrene with formaldehyde in water proceeded in 94% yield. Tandem dehydration/Prins cyclization of tertiary and secondary alcohols was achieved by use of this system.



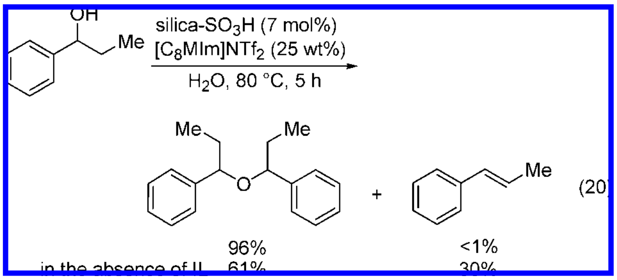
(18)

Although epoxides are unstable under aqueous acidic conditions, cycloaddition of aldehydes to epoxides occurred exclusively in the presence of silica−SO_3H−[C_8MIm]NTf_2, leading to 1,3-dioxolane derivatives.



(19)

In general, dehydrative etherifications of secondary benzyl alcohols are catalyzed by transition metals; Brønsted acid catalysts are rarely used in the reaction due to the ready dehydration of benzyl alcohols to styrene derivatives. When silica−SO_3H was used for etherification of 1-tolyl-1-ethanol, β-methylstyrene was produced in 30% yield and the desired ether was obtained in only 61% yield. In contrast, coating the silica−SO_3H with 25 wt % of [C_8MIm]NTf_2 improved the selectivity to give the desired ether in 96% yield.



(20)

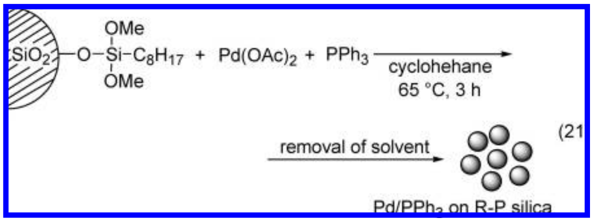
3. Hydrophobic Silica and Fluorous Reverse-Phase Silica

This section covers simply modified silica gels used for organic reactions in water, which are immobilized with alkyl chains or fluorous alkyl chains. As described thus far, the supported liquid-phase catalyst consists of a thin layer, which resides on a high surface area of hydrophilic silica. The desired reactions occur at the film−organic interface. In this section, some examples of reactions that use reverse-phase silica, which allows for the use of polar and nonpolar substrates, are presented.

3.1. Reverse-Phase Silica Supports

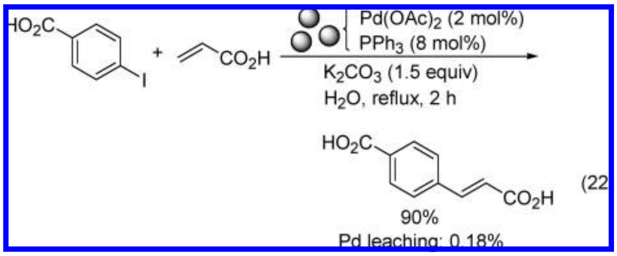
Tanaka and co-workers originally found the simplest system using reverse-phase silica for organic reactions in water. In general, biphasic reactions involving hydrophobic substrates and water-soluble reagents are slow. Such reactions are facilitated by the use of phase-transfer catalysts or surface-active agents. An alternative reaction system, rapid reaction at the phase boundary between an aqueous nucleophile (NaI, NaOAc) and an alkyl halide (n-C_8H_{17}Br or $PhCH_2Cl$), bound by hydrophobic interactions to monolayers immobilized on silica, was developed.[80] Typical nucleophilic substitution reactions that occurred at the phase boundary proceeded up to 3 orders of magnitude more rapidly than conventional liquid−liquid reactions.

Williams and co-workers reported the use of reverse-phase silica in the Heck reaction.[81] The reverse-phase catalyst was prepared by treatment of derivatized silica (reverse phase silica) with palladium acetate and triphenylphosphine in cyclohexane (eq 21).



(21)

A reverse-phase, supported catalyst was employed in the aqueous Heck reaction. Coupling between iodobenzene and acrylic acid was carried out to give the desired product in 90% yield with very little leaching of palladium into the bulk aqueous phase (eq 22). Although the system was applicable to water-insoluble nonpolar substrates, such as iodobenzene and methyl vinyl ketone, methanol is required as an organic cosolvent for the reaction to proceed.



(22)

When a nonpolar substrate was used on the reverse-phase, supported, silica-coated catalyst and water was the only solvent, the organic reaction was very inefficient. An alternative method was developed to overcome this problem. The method relies on the transport of hydrophobic substrates to an entrapped catalyst, and the transport of the resulting product from the entrapped catalyst back into the bulk phase. Specifically, a catalyst is entrapped inside a hydrophobically modified silica. In the presence of a surfactant, the hydrophobic substrate forms an emulsion in water and the powdered catalytic sol−gel material is dispersed in the emulsion. Avnir and Blum termed this process EST (emulsion-solid transport).[82] A schematic illustration of EST is shown in Figure 7.

On the basis of the concept, emulsified chalcone was hydrogenated by ethyl-derivatized silica (catalyst A) to give the saturated ketone in 84% yield. Interestingly, the employment of octyl-derivatized catalyst B afforded fully saturated 1,3-dicyclohexylpropan-1-ol in 52% yield and 1,3-dicyclohexylpropan-1-one in 36% yield (Scheme 7). A similar phenomenon was observed for the hydrogenation of *cis*-stilbene.

To develop new water-tolerant solid acids, acid catalysts comprising polyoxometalate (heteropolyacid) molecules and organografted mesoporous silica were designed by Inumaru et al.[83] They found that acidic protons in the hydrophobic environment of organomodified mesoporous silica showed high catalytic activity for ester hydrolysis in water. The concept of the nanostructured catalyst is shown in Figure 8. n-Octyl and 3-aminopropyl groups were grafted onto the pore walls of the mesoporous silica, SAB-15. The aminopropyl

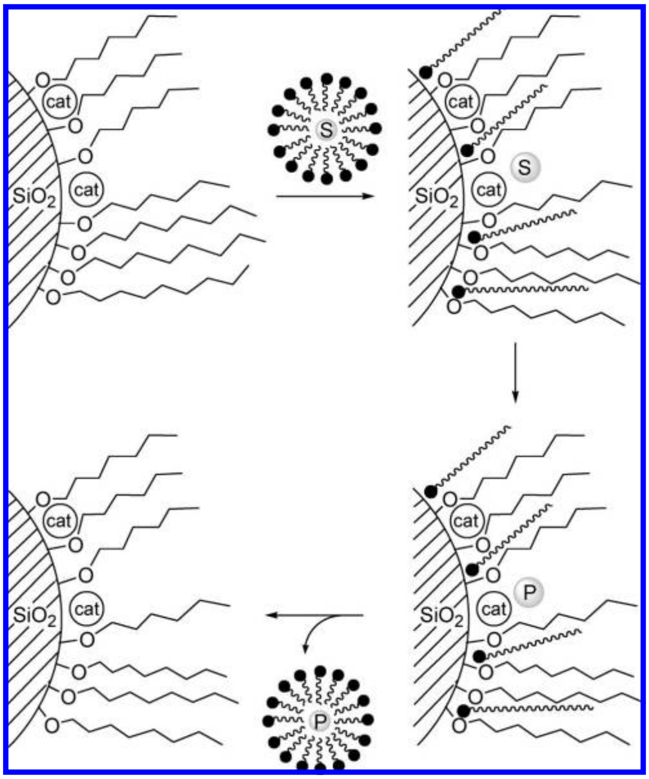


Figure 7. Illustration of the transport, reaction, and adsorption/desorption steps of the EST process.

groups immobilize the $H_3PW_{12}O_{40}$ polyoxometalate anions on the pore walls, whereas octyl groups form hydrophobic regions around the polyanions.

The catalytic activities of various acid catalysts for the hydrolysis of ethyl acetate in water are listed in Table 3. The octyl-grafted catalyst (PW/C_8–AP–SBA) showed the highest activity. Most inorganic solid acid catalysts do not work when water is used as the solvent with the following exceptions: H-ZSM-5 and $Cs_{2.5}H_{0.5}PW_{12}O_{40}$, which have hydrophobic surfaces. Some ion-exchange resins show activity in water.

3.2. Fluorous Reverse-Phase Silica

Besides normal reverse-phase silica comprising alkyl chains and porous silica, fluorous reverse-phase silica gel (FRPSG) was used as a solid support to immobilize fluorous catalysts of aqueous organic reactions. Since Horváth and Rábai introduced the concept of fluorous biphasic catalysis (FBC) in 1994,[85] much effort has been devoted to the development of fluorous chemistry.[86−93] Although FRPSG has been generally used in solid–liquid extraction to separate fluorous compounds from organic compounds as well as in HPLC,[88,94−97] Bannwarth et al. originally reported Suzuki–Miyaura and Sonogashira coupling reactions catalyzed by fluorous-tagged palladium complexes immobilized on FRPSG in 1,2-dimethoxyethane.[98] In this section, FRPSG-supported catalysts for several aqueous organic reactions are described.

Nishikido and co-workers reported that FRPSG-supported Lewis acids that have fluorous ligands act as effective catalysts of Baeyer–Villiger and Diels–Alder reactions in water.[99] The FRPSG shown in Figure 9 and fluorous Lewis acids prepared according to the literature[100] were employed in the Baeyer–Villiger reaction.

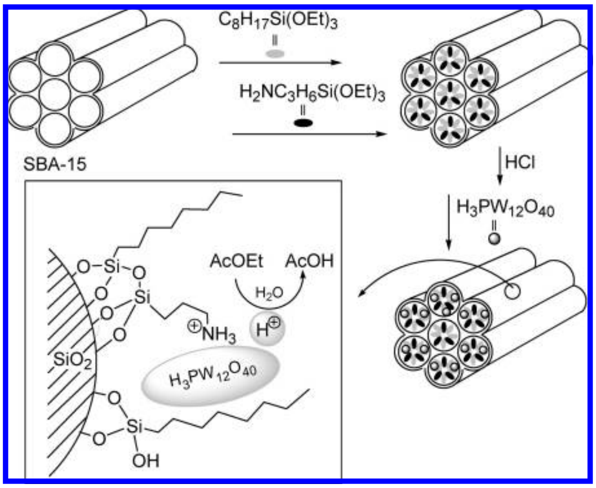
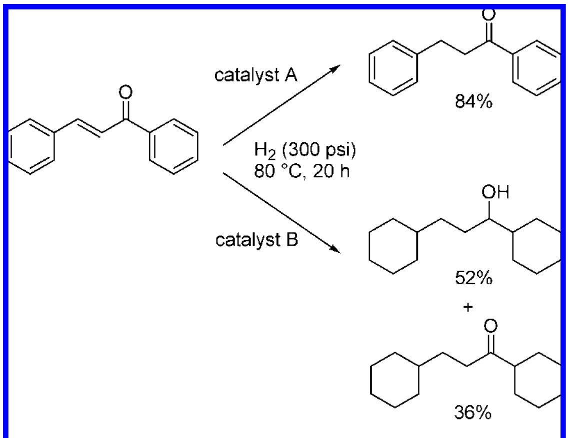


Figure 8. Schematic illustration of the preparation of the PW/C_8-AP-SBA catalyst.

Scheme 7. Hydrogenation of Chalcone with Catalysts A and B



catalyst A: ethyltriethoxyorthosilicate (ETOS)
tetramethylorthosilicate (TMOS)
methyltrioctylammonium chloride (Aliquat 336)
[ETOS]:[TMOS] = 1:20 / Aliquat 336 / $RhCl_3•3H_2O$

catalyst B: octyltrichlorosilane (OTS)
[OTS]:[TMOS] = 1:20 / Aliquat 336 / $RhCl_3•3H_2O$

The influence of the support material on reaction rate was investigated. Standard (octadecylsilylated) reverse-phase silica and normal silica gel were compared with FRPSG as support material for fluorous Lewis acids in the Baeyer–Villiger reaction of adamantanone using $Hf[N(SO_2C_8F_{17})_2]_4$ (Table 4). The reaction in 2% aqueous hydrogen peroxide (5 equiv) at 25 °C for 3 h showed distinct differences in reaction rate for the different support materials. FRPSG-supported $Hf[N(SO_2C_8F_{17})_2]_4$ gave the best result.

When $Sc[C(SO_2C_4F_9)_3]_3$ was employed in the FRPSG-supported system, the Diels–Alder reaction proceeded smoothly in water. In the presence of FRPSG-supported $Sc[C(SO_2C_4F_9)_3]_3$ (5 mol %), 2,3-dimethyl-1,3-butadiene with 1.2 equiv of methyl vinyl ketone gave the cycloadducts in high yield (Table 5). The recovered catalyst was used in the reaction three times without loss of activity. As shown in the table, immobilization of $Sc[C(SO_2C_4F_9)_3]_3$ on FRPSG efficiently accelerated the Diels–Alder reaction in water.

Bannwarth applied the FRPSG system originally developed for organic solvents[98] to aqueous media.[101] The Suzuki–Miyaura coupling reaction was examined using FRPSG and a perfluoro-tagged Pd complex. When catalyst A (0.1 mol %) on FRPSG was used to catalyze the coupling in water, the rate of conversion was nearly 100% (eq 23).

Table 3. Activity of Catalysts for Hydrolysis of Ethyl Acetate in Water

catalyst	state of catalyst[a]	activity of catalyst[b]	catalytic per cat. weight[c]	activity per cat. protons[d]
PW/C_8−AP−SBA	solid	0.091	25.1	275
$H_3PW_{12}O_{40}$	liquid	1.0	78.7	78
$Cs_{2.5}H_{0.5}PW_{12}O_{40}$[e]	solid	0.15	30.1	200
Nafion-H resin[e]	solid	0.8	161.9	202
SO_4^{2-}/ZrO_2[e]	solid	0.35	25.5	127
H-ZSM-5 zeolite[e]	solid	0.39	27.6	70
γ-Al_2O_3[e]	solid	0.47	0	0
HY zeolite[e]	solid	2.6	0	0
H_2SO_4[e]	liquid	19.8	992	46

[a] Liquid, homogeneous catalysis; solid, heterogeneous acid catalysis. [b] Acid amount (10^{-3} mol g^{-1}). [c] ln μmol $g_{cat.}^{-1}$ min^{-1}. [d] ln mmol mol_{acid}^{-1} min^{-1}. [e] Reference 84.

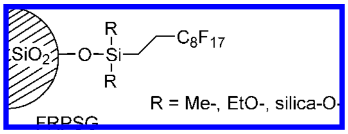
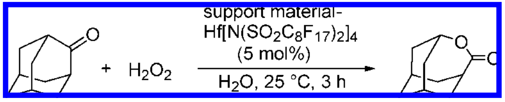


Figure 9. Fluorous reverse-phase silica gel.

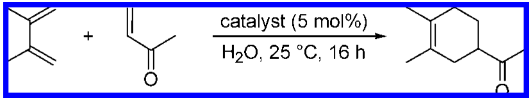
Table 4. Effect of the Support Material on the Rate of the Baeyer−Villiger Reaction



support material	yield (selectivity)[a] (%)
fluorous reverse-phase silica	64 (90)
standard reverse-phase silica	51 (94)
normal silica	33 (97)
none	37 (84)

[a] Determined by GC.

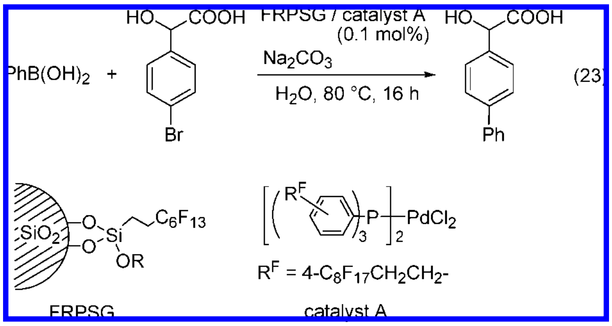
Table 5. Diels−Alder Reaction Using FRPSG-Supported $Sc[C(SO_2C_4F_9)_3]_3$ in Water



catalyst or additive	yield (selectivity)[a] (%) cycle 1	2	3	4
FRPSG−$Sc[C(SO_2C_4F_9)_3]_3$	91 (91)	91 (93)	99 (99)	95 (97)
$Sc[C(SO_2C_4F_9)_3]_3$	54 (54)			
FRPSG	23 (24)			
standard reverse-phase silica gel	5 (8)			
normal silica gel	5 (5)			
none	1 (1)			

[a] Determined by GC.

The product was easily separated by filtration, and the supported catalyst was reused five times.

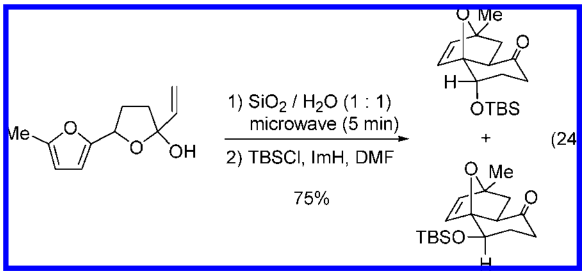


(23)

4. Silica without Modification

Silica gel without modification is generally used for separation of organic compounds as in normal-phase chromatography. Alternatively, there is considerable current interest in the use of micelles, microemulsions, surfactants, and other microheterogeneous liquids as media for organic reactions in water. All reactions performed in organized systems require a complicated procedure to separate the surfactants and phase-transfer catalysts from products. Silica can be viewed as being analogous to microheterogeneous liquids. Silica should be an effective aqueous organic reaction media because the organic substrate is adsorbed to the silica by hydrophobic interactions between the surface of the silica and the organic molecule. A significant advantage of the silica medium is that the workup procedure is extremely simple. On the basis of this concept, simple organic reactions using silica−water reaction media were developed as follows.

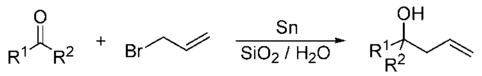
In the course of studying the construction of bicyclo[6.2.1]ring systems, Roskamp et al. reported catalysis of an intramolecular Diels−Alder reaction by use of silica gel saturated with water.[102] Initial attempts to perform a Diels−Alder reaction with the hemiacetal led to either decomposition of the starting material or poor yields of the cycloadducts. However, the hemiacetal was converted to cycloadducts during flash chromatography on silica gel. As a result, good yields of adducts could be achieved by adsorbing the hemiacetal onto silica gel and, saturating the mixture with water, followed by exposure to microwave irradiation (eq 24).



(24)

In this study, the effect of the addition of water to the silica on the reaction was explained by the following mechanism: (1) efficient generation of heat during the microwave process, (2) acceleration of the Diels−Alder reaction via a hydrophobic effect, and (3) facilitation of the hemiacetal−hydroxy ketone equilibrium.

A phase-transfer catalyst (PTC) was employed in allylation of carbonyl compounds mediated by tin (Barbier reaction), in which silica gel was used as a PTC; however, the effect of silica in water was not described (eq 25).[103]



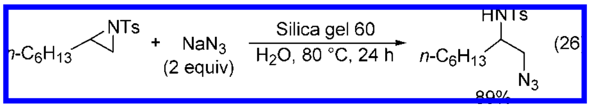
(25)

A Heck-type reaction between an arylboronic acid and styrene was achieved using water-soluble rhodium catalyst entrapped in the water-filled pores of mesoporous silica particles, in which the silica can be used as host for a Rh catalyst.[104]

The silica−water system was originally established by Minakata and Komatsu.[105,106] A new aqueous organic transformation reaction that exploited the adsorptive nature of silica was the formation and ring opening of aziridines (Figure 10).

Iodine-catalyzed formation of aziridines from olefins by use of chloramine-T (CT)[107,108] proceeded efficiently in silica−water reaction media. Comparison of the silica−water medium with normal silica gel and MCM-41 indicated that the product yield is dependent on the specific surface area of the silica gel. A variety of olefins were successfully aziridinated using the process (Table 6).

When MCM-41 was used, the efficiency of aziridination was dependent on the olefin structure. The high degree of freedom for acyclic olefins reduces surface interaction with MCM-41. The generality of the media in organic synthesis reactions was illustrated by the efficient ring opening of aziridines with water-soluble nucleophiles (Table 7 and eqs 26 and 27).



(26)

(27)

Holmberg et al. also found that mesoporous solid materials, such as silicas, could be used as medium for organic reactions in water. They studied a typical nucleophilic substitution reaction involving a lipophilic organic compound (4-*tert*-butylbenzyl bromide) and an inorganic salt (potassium iodide). The reaction occurred at the hydrophilic/lipophilic interface, and, because the interface was large, the reaction occurred at a rapid rate. After completion of the reaction, the solid was simply recovered by centrifugation.[109]

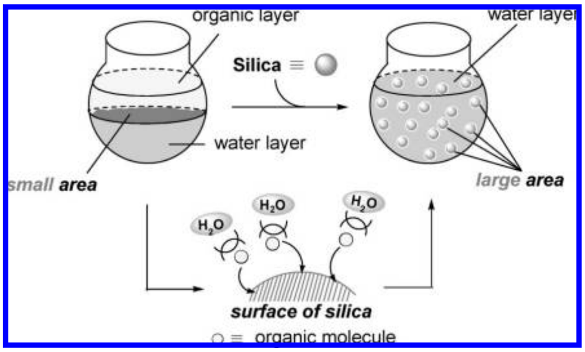
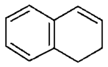
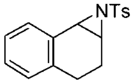
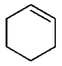
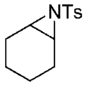
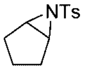
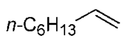
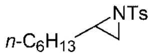
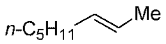
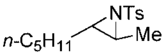
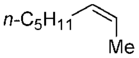
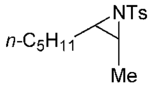
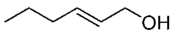
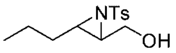
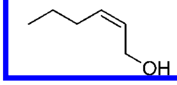
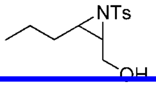


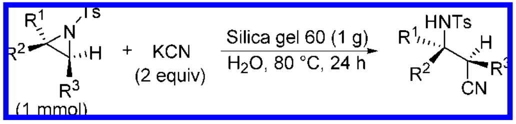
Figure 10. Schematic diagram of an organic reaction using a silica−water system.

Table 6. Silica−Water-Mediated Formation of Aziridines from Various Olefins[a]

olefin	aziridine	Yield (%)	
		MCM-41	Silica gel 60
		75	68
		75	68
		64	53
		7	26[b] 49
		4[c]	42[c]
		27[d]	70[d]
		56[c]	58[c]
		72[d]	61[b, d] 59[d]

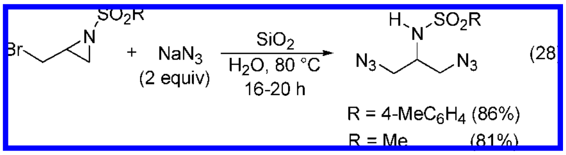
[a] Reaction conditions: olefin (1 mmol), CT (2 mmol), I_2 (20 mol %), K_2CO_3 (2 mmol), silica (MCM-41; 0.25 g or silica gel 60; 1 g), H_2O (1.5 mL), rt, 3 h. [b] Silica gel 60 (0.5 g). [c] *Trans* only. [d] *Cis* only.

Table 7. Ring Opening of Aziridines with KCN Using a Silica−Water System



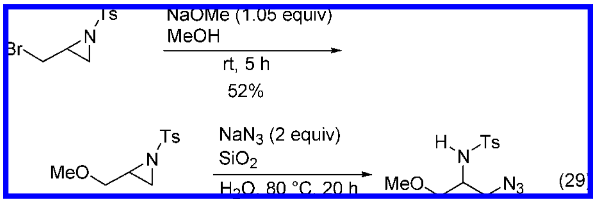
aziridine			
R^1	R^2	R^3	yield (%)
n-C_6H_{13}	H	H	69
CH_2Ph	H	H	72
sec-C_4H_9	H	H	57
Ph	H	H	24
CH_2OH	H	H	32
H	$-(CH_2)_3-$		58
H	$-(CH_2)_4-$		88

The application of a new protocol for the ring opening of 2-(bromomethyl)aziridines using silica−water reaction media was performed by De Kimpe et al.[110] The diazido compounds were obtained by treatment of the aziridines with 2 equiv of sodium azide in water in the presence of silica (eq 28).



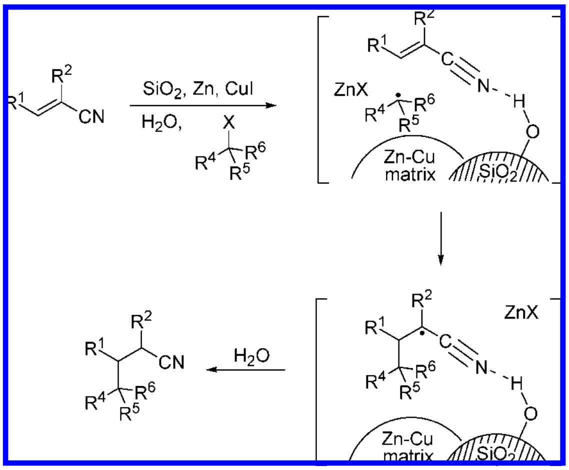
(28)

A stepwise approach based on this method enabled the synthesis of various 1,3-heteroatom-substituted 2-aminopropane derivatives. 2-(Bromomethyl)-1-tosylaziridine was converted to the corresponding 2-(methoxymethyl)-1-tosylaziridine upon reaction with 1.05 equiv of NaOMe in MeOH. Treatment of the latter aziridine with 2 equiv of sodium azide in water in the presence of silica gel gave the desired 2-aminopropane derivative (eq 29).



A new silica-supported zinc−copper matrix promoted the conjugate addition of alkyl iodides to alkenenitriles in water.[111,112] This system overcame the difficulties associated with conjugate addition to disubstituted alkenenitriles, such as cyclic nitriles with nonstabilized carbon nucleophiles. Silica gel is abrasive, and many chemists facilitate maximal surface exposure by grinding the zinc−copper matrix, which might provide a reactive metal surface in close proximity to alkenenitriles anchored in position by hydrogen bonding to nitrile nitrogens.[113] Use of water as the solvent favors localization of the two hydrophobic reagents at the metal surface (Scheme 8).[114]

Scheme 8. Silica-Supported Zn−CuI Conjugate Addition



X-ray diffraction and electron microscopy techniques suggest that the active copper species generated from elemental zinc and copper(I) iodide is finely dispersed, zerovalent copper.

Although the role of silica was not discussed, Neumann and co-workers found that a bispyrimidinylplatinum−polyoxometalate, $[\mathrm{Pt(Mebipym)Cl_2}]^+[\mathrm{H_4PV_2Mo_{10}O_{40}}]^-$, supported on silica is an active catalyst for the aerobic oxidation of methane to methanol in water under mild conditions.[115]

5. Conclusion

This review describes various organic reactions on silica in water. During the past two decades, numerous organic reactions in aqueous media have been developed in response to the demand for more environmentally benign organic syntheses. This development promotes the use of silica because of its unique properties, as described in this review. Some disadvantages of heterogeneous processes over homogeneous methods are alleviated by use of these systems. Although silica-based materials appear to be attractive for conducting organic reactions in water, reusability of silica, especially mesoporous silica, remains to be solved because of its mechanical instability. However, the flexibility of silica, that is, the facile immobilization of organic molecules to the silica surface and simple control of the framework, allows for unlimited potential of organic reactions "on" silica. When a new reaction is discovered, a devoted chemist can no longer ignore the possibility of performing the reaction using the silica−water system. Thus, the combination of silica and water is a new, useful, and powerful organic reaction medium.

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