Cooperative catalysis by silica-supported organic functional groups

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Hybrid inorganic–organic materials comprising organic functional groups tethered from silica surfaces are versatile, heterogeneous catalysts. Recent advances have led to the preparation of silica materials containing multiple, different functional groups that can show cooperative catalysis; that is, these functional groups can act together to provide catalytic activity and selectivity superior to what can be obtained from either monofunctional materials or homogeneous catalysts. This *tutorial review* discusses cooperative catalysis of silica-based catalytic materials, focusing on the cooperative action of acid–base, acid–thiol, amine–urea, and imidazole–alcohol–carboxylate groups. Particular attention is given to the effect of the spatial arrangement of these organic groups and recent developments in the spatial organization of multiple groups on the silica surface.

1. Introduction

The intent of this tutorial review is to summarize some of the recent advances in a specific class of multifunctional, heterogeneous catalysis. A number of research groups have been pursuing new and creative approaches towards incorporating multiple functional groups into heterogeneous catalysts in such a way that they may act in a cooperative fashion to improve the reactivity of the catalyst. In the process of exploring such materials, many new materials have been reported and some give rise to reactivity unachievable with homogeneous catalysis. A number of different approaches have been used to prepare bifunctional heterogeneous catalysts on various support scaffolds, and in this review we present a brief summary of the literature pertaining to catalysis with multiple organic functional groups supported on silica. These materials are significant both from an academic and industrial standpoint.

A number of lessons from the basic principles of enzyme catalysis can be applied to preparing more efficient synthetic catalysts. One important way that enzymes accelerate chemicals reactions is through cooperative interactions between precisely positioned reactive groups in the active site. With functional groups (metal centers, nucleophiles, acids, bases, hydrogen bond donors, hydrogen bond accepters) positioned at fixed distances to one another in the active site, these groups are capable of interacting through electrostatic, hydrogen bonding, and covalent interactions to influence their reactivity. Through these types of interactions, enzymes are capable of significantly accelerating reactions (rate enhancement of many orders of magnitude) as well imparting dramatic effects on selectivity. In addition to the precise positioning of reactive groups at a fixed distance to one another, the relative positioning of these groups within the active site and the formation of hydrophobic/hydrophilic pockets in the active site affects the chemical environment of the reagents allowing for further rate accelerations, enhanced regioselectivity (complete regioselectivity in some cases) as well as complete enantioselectivity for a number of reactions. As an example, serine proteases are able to accelerate the cleavage of amide bonds, a reaction that is extremely slow uncatalyzed, by a factor of $\sim 10^{12}$ through cooperative interactions between neighboring nucleophilic alcohol, basic imidazole and acidic carboxylic acid groups (Fig. 1).[1] By adapting these approaches of spatially positioning functional groups and modifying the

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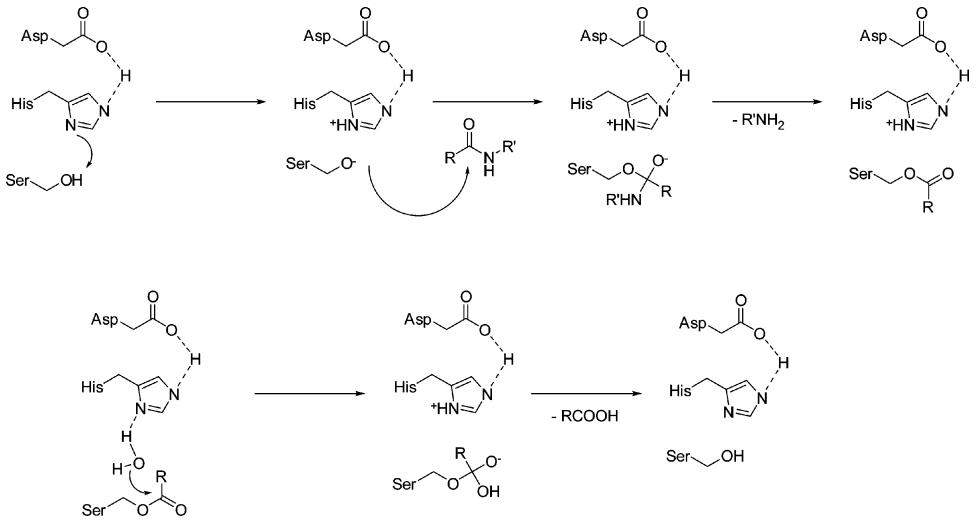


Fig. 1 Schematic of the mechanism of peptide hydrolysis by a serine protease. The enzyme activity is the result of cooperativity among adjacent serine, histidine, and aspartic acid residues.

surface of the catalyst, it may be possible to further improve upon current heterogeneous catalysts.

Silica-based materials are commonly used as heterogeneous catalysts. Organic functionalization of amorphous, mesoporous, and zeolitic silica materials leads to a vast array of catalytically active materials. Most investigators have focused on tethering a single functional group on the surface, often in order to immobilize an existing homogeneous catalyst (see for instance the review by Molnar and Rac[2]). Further refinement of this methodology has led to the creation of organized pairs or clusters of identical surface functional groups. The next step in the evolution of these materials is bifunctionalized silica catalysts where multiple different functional groups are responsible for improved catalytic activity. In this tutorial review, we discuss the progress that has been made in this field, ranging from randomly-distributed bifunctional materials to spatially-organized solids.

2. Cooperative catalysis

In the context of catalysis, the term *cooperativity* refers to a system where at least two different catalytic entities act together to increase the rate of a reaction beyond the sum of the rates achievable from the individual entities alone. Homogeneous cooperativity has been studied using multiple small molecules[3–5] or polyfunctional molecular catalysts.[6–8] Numerous examples have also been reported of inorganic cooperativity in heterogeneous catalysts by incorporating multiple different metal centers onto a support. Here, we focus exclusively on cooperativity among organic sites on the surface of a heterogeneous catalyst (with a specific focus on silica-supported organic groups).

There are several different ways in which two different surface functionalities can act cooperatively to catalyze a reaction (Fig. 2). The two groups (A and B) can each activate a different reactant; A activates a nucleophile and B activates an electrophile, for instance, increasing the reactivity of both. Or the two groups can sequentially activate one reactant; A activates reactant R1 to R1′, and B activates R1′ to R1″. On the other hand, the surface groups can act on each other: A can activate B and increase its ability to catalyze a reaction, such as when the imidazole group modifies the nucleophilicity of the adjacent alcohol in the case of a serine protease. Finally, the surface groups can act in concert to stabilize a transition state through multiple weak interactions. Any of these strategies can be used to design a synthetic catalyst that takes advantage of multifunctional cooperativity.

In this tutorial review, we will focus primarily on several examples of cooperative catalysis that have a well-established literature precedent: acid–base, amine–urea, acid–thiol (in the synthesis of bisphenol A), and imidazole–alcohol–carboxylic acid (as in the catalytic triad of protease enzymes). In each case, immobilization offers different opportunities and advantages.

2.1 Choice of silica support

The advantages of heterogeneous catalysts over homogeneous ones are numerous. Traditional heterogeneous catalysts can be recycled after a reaction or used continuously in a packed bed reactor, and the separation of the catalyst from the reaction mixture is simplified.[9] With bifunctionalized materials, other advantages arise, such as the possibility of new reactivity that is impossible in solution. For instance, mutually-destructive functionalities such as acid and base can be immobilized in the same matrix, allowing for their coexistence. Furthermore, the spatial positioning of the different catalytic groups can be modified to tune the catalyst to a particular reaction, which is impossible when the two groups are both in solution.

One of the most common supports for heterogeneous catalysts is mesoporous silica. Amorphous silica is sometimes used due to its high surface area and low cost, but the irregularity of the surface and pore structure can be detrimental in some applications. Microporous materials, such as zeolites, can be difficult to functionalize, and the small pore size limits the scope of catalytic reactions. Mesoporous silica, such as SBA-15[10] and MCM-41,[11] is easy to functionalize in either a direct synthesis or postsynthetic grafting procedure.

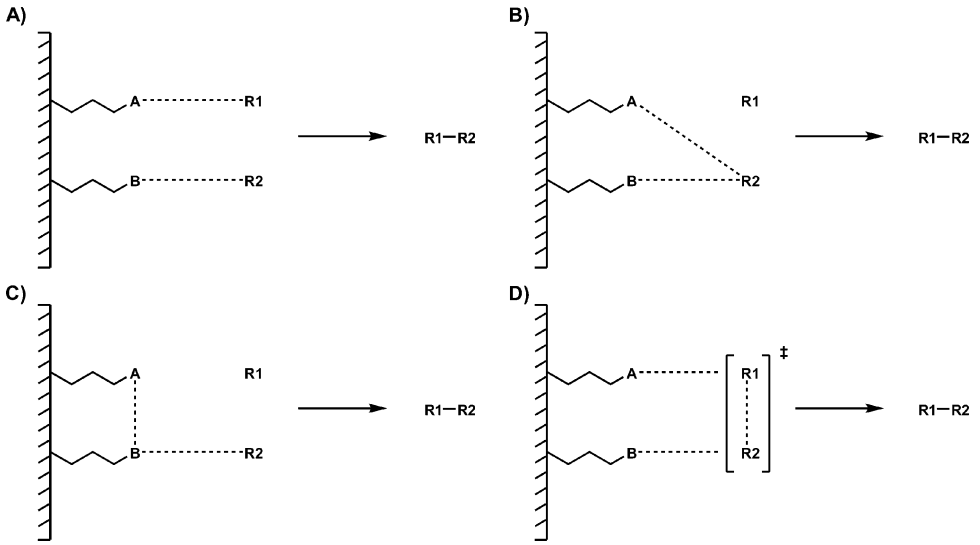


Fig. 2 Some of the modes of cooperativity between surface groups A and B in catalyzing the reaction between reactants R1 and R2. (A) Dual activation, where A activates R1 and B activates R2. (B) Sequential activation, where A activates R2 and B further activates R2. (C) Self-activation, where A activates B which then activates R2. (D) Multiple-point transition-state stabilization.

The larger pore size (~2–10 nm) reduces mass transfer limitations and allows even large reactant molecules to enter the pores. Numerous reviews of silica functionalization exist in the literature.[12–15]

In a direct synthesis (also known as a one-pot synthesis), a silica precursor is polymerized in the presence of functional organosilanes in a single step. Using this route to functionalized silica materials, higher loadings of functional groups can be achieved and those groups can be well distributed within the silica matrix. The disadvantages of the method include the necessity to extract the structure-directing agent (since calcination would destroy the organic functionality) and, in the case of ordered materials, the possibility of the functional silanes disrupting the long-range order. Mesoporous silicas typically become less well-ordered as the organic loading increases, and microporous materials often will not crystallize in the presence of large amounts of organosilanes.

Postsynthetic modification, or grafting, involves covalently attaching organosilanes to the surface silanols of a pre-made silica material. In general, a more-reactive silane will lead to higher organic loadings but do so to give less well-distributed surfaces (such as clustering at pore mouths). Trichlorosilanes (highly reactive) or trialkoxysilanes (less reactive) are often used. Since the silica is synthesized before grafting, highly-ordered silica geometries can be maintained even at moderately high organic loadings.

2.2 Cooperative catalysis *vs.* modulation of surface properties

It is helpful to consider the question of how to tell whether two functional groups on a surface are truly providing cooperative catalysis. Heterogeneous catalysis by definition involves two phases, which means reactant partitioning between the solution and solid phases can affect the kinetics of reaction. Often, the catalytic activity of a functionalized hydrophilic surface can be enhanced by adding a second (hydrophobic) functionality that increases the reactants' partitioning to the catalyst surface. This second functionality does not directly participate in the catalytic cycle, and the resulting system is not cooperative. In some cases, a bifunctional catalyst system can appear to exhibit cooperativity, but care must be taken to decide whether both groups play a direct role in the reactivity or whether they just modulate surface properties. For example, silica materials decorated with both sulfonic acid and hydrophobic alkyl groups exhibit greater activity than acid-only materials in a number of instances, such as esterification reactions.[16–18] A similar hydrophobicity effect has been shown for silylated titanium-containing SBA-15 materials.[19] In these instances, hydrophobic surface groups do not play a direct role in the catalytic mechanism, but rather tune the transport of hydrophobic reactants to the surface and water away from the surface (thus, there is not a true cooperative relationship between the acid and alkyl groups).

In the case of alkyl moieties such as methyl or octyl groups, which are more or less chemically inert, it is obvious that these groups only provide surface hydrophobicity, rather than playing a direct catalytic role. There are cases, however, where this distinction is not so obvious. For instance, Huh *et al.*[20] investigated bifunctional materials containing both 3-[2-(2-aminoethylamino)ethylamino]propyl groups and either allyl, ureidopropyl, or mercaptopropyl groups. The resulting bifunctional materials showed widely varying activity and selectivity for the Henry reaction when two competing aldehyde reactants are present, one of which contained a long hydrophobic tail. The variation in catalytic properties was likely caused by the different hydrophobicity of the olefin-, urea-, and thiol-functionalized materials. In other instances, on the other hand, urea and thiol groups provide improved activity through cooperativity with another functionality (*vide infra*).

When data suggest that a bifunctional catalyst (containing groups A and B, say) outperforms the monofunctional catalyst (containing only A), one way to distinguish between cooperative catalysis and surface hydrophobicity is to remove the B from the surface and replace it with a homogeneous analog (say, B′). If the role of B is merely to moderate transport

between the solid and liquid phases, then the activity of a heterogeneous catalyst containing only A should not be improved by addition of B′. If this improvement is seen, on the other hand, then it suggests genuine cooperativity between A and B. It should be noted, however, that the cooperative effect may be lessened by removing the catalytic group from the surface.

2.3 Cooperativity with the silica matrix

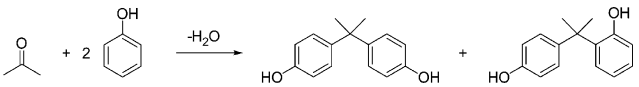
The surface of the silica support can itself play a large role in the catalytic activity of heterogeneous catalysts. The weakly-acidic silanol groups can form hydrogen bonds to reactants or transition states, leading to cooperative catalysis with surface organic groups. Cooperativity between organic functional groups and inorganic supports has been reviewed by Notestein and Katz,[21] and will not be discussed in great detail, but a few recent advances are worth noting.

The cooperative effect of silanol groups has been thought to improve the catalytic activity of mesoporous silica-supported amines in base-catalyzed reactions such as the nitroaldol (Henry) condensation,[22,23] Knoevenagel condensation[22,24,25] and Michael addition.[22] For instance, in the report by Bass *et al*.,[22] amine-functionalized silica catalysts were prepared by bulk imprinting with protected amines. Before amine deprotection, the silanols were either capped with propyl groups (leading to a non-polar aprotic surface), capped with propylnitrile groups (leading to a polar aprotic surface), or left unmodified (with a surface both polar and protic). In the Knoevenagel reaction of 3-nitrobenzaldehyde and malononitrile, the silanol-containing catalyst achieved 100% conversion in 100 minutes, while the nitrile-modified catalyst reached only ~50% conversion in the same time, and the propyl-modified catalyst only ~25%. The authors reason that both the polar and protic character of the silanols contribute to the cooperative catalytic behavior.

Because the protic nature of the weakly-acidic silanols is thought to activate the electrophilic reactants *via* hydrogen bonding, it follows that introducing stronger acid groups onto the surface could be expected to increase the cooperative effect. Motokura *et al*. demonstrated that this approach is indeed feasible.[26] They incorporated amine groups into silica–alumina, which is more acidic than silica, and showed an increase in reactivity compared to using a silica or alumina support. Primary and tertiary amine groups were introduced on to surfaces by the grafting of 3-aminopropyltriethoxysilane and 3-(diethylamino)propyltrimethoxysilane. The resulting catalysts were tested for activity in benzaldehyde cyano-ethoxycarbonylation and nitroaldol and Michael reactions. In the cyano-ethoxycarbonylation reaction, silica- or alumina-supported amines gave only 16–17% yield, whereas tertiary amines on acidic silica–alumina supports gave 95% yield. Interestingly, the primary amine on the same support showed almost no activity. In the nitroaldol reaction between benzaldehyde and nitromethane, the same acid–base cooperativity was observed, except that the primary amine gave excellent results, and the tertiary amine was almost completely inactive. The authors proposed that the first step in amine grafting involved acid–base interaction between the amine and acidic surface sites, followed by the reaction of the trialkoxysilane with nearby silanols. Thus, the immobilized amines are found near the acid sites.

3. Randomly-distributed bifunctional catalysts

A catalytic reaction where bifunctional cooperativity has been long known is the synthesis of bisphenol A from acetone and phenol (Scheme 1). This reaction can be catalyzed by strong acids alone, but the activity and selectivity can both be increased dramatically by adding a thiol (either homogeneous or heterogeneous) as a co-catalyst.[27,28]



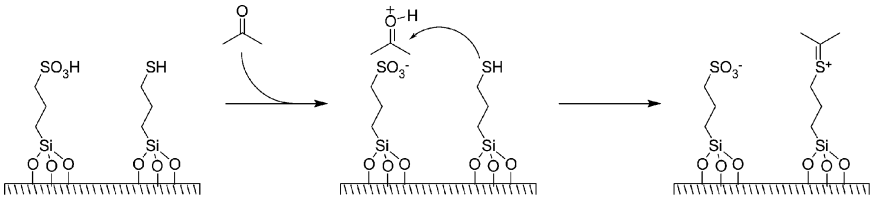
Scheme 1 The synthesis of bisphenol A from acetone and phenol. The *p*,*p*′ isomer is the desired product.

Early attempts to incorporate thiols and acids into heterogeneous catalysts involved modification of sulfonic acid-containing ion-exchange resins either through esterification with a mercaptoalcohol[29] or partial neutralization with a mercaptoamine.[30] Using heterogeneous thiols avoids the contamination of product with thiols, and also avoids the problems associated with malodorous homogeneous thiols.

Zeidan *et al*.[31] incorporated arylsulfonic acid and alkylthiol groups into mesoporous silica by a direct synthesis method, in which 2-(4-chlorosulfonylphenyl)-ethyltrimethoxysilane and 3-mercaptotrimethoxysilane were co-condensed with tetraethyl orthosilicate into a mesoporous silica (SBA-15). The resulting randomly-distributed acid–thiol catalysts exhibited far greater activity and selectivity than materials containing only the acid. Catalysts containing different acid/thiol ratios were tested (0.25, 0.5, 1.0, 2.0). A catalyst with an acid/thiol ratio of 0.5 was found to give the best yield (82 mol per mol acid site). Additionally this same material gave the highest product selectivity (>95%).

Furthermore, a physical mixture of separate acid-containing and thiol-containing silicas gave only modest results (per site yield of 19 and 75% selectivity for bisphenol A), suggesting that the acid and thiol groups must be in proximity to one another for enhanced catalytic activity. The authors hypothesized that the origin of this cooperativity is sequential activation of the acetone first by protonation, then by thiol attack, forming a highly electrophilic sulfonium intermediate (see Scheme 2). Significant improvements in reactivity and selectivity were observed with these immobilized combinations of thiols and sulfonic acids over the corresponding homogeneous combination of these same groups. This sequential activation is enhanced by immobilizing these functional groups near one another on the surface.

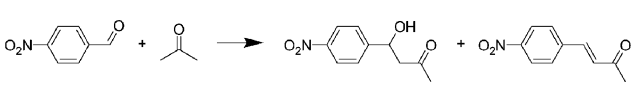
Next, we describe an example of cooperativity *via* dual nucleophilic–electrophilic activation. Huh *et al*.[32] have prepared mesoporous silica nanospheres containing both amine and urea groups. These materials were used to catalyze a variety of chemical reactions (aldol, Henry, cyanosilylation) and exhibited significantly enhanced reactivity compared to the individually functionalized catalysts. For example, the



Scheme 2 The first two steps of proposed mechanism for acid/thiol cooperativity in bisphenol A synthesis.[31] Acetone is first protonated by an acid site. An adjacent thiol then attacks to form the sulfonium intermediate, which is then attacked by phenol.

urea functionality alone gave no reaction in the aldol reaction between acetone and *p*-nitrobenzaldehyde (Scheme 3). The amine alone exhibited modest activity, but the mixed amine–urea catalyst (at a ratio of 1 : 4) gave a four-fold increase in turnover number. The authors propose a mechanism where the urea activates the electrophilic reagent through hydrogen bonding to a carbonyl, while the amine groups serve to deprotonate and further activate the nucleophilic reagent. Through independent activation of each reagent by the two organic functional groups, cooperative catalysis allowed for enhanced reactivity to be observed in this case with the two organic groups randomly dispersed on the surface.

Materials containing functionalities that are incompatible with one another in solution have been reported. In these materials, incompatible functional groups were immobilized together on a silica surface and interesting chemical reactivity was observed. Zeidan *et al.*[33] have reported materials functionalized with both acid and base groups that would be incompatible if not tethered to a surface. These materials were prepared through direct synthesis and the two incompatible functional groups were randomly distributed throughout the silica material. In this report, strongly acidic aryl sulfonic acid groups were simultaneously incorporated into SBA-15 along with primary amine groups, generating a bifunctional acid–base material that was a good catalyst in the aldol condensation reaction between acetone and *p*-nitrobenzaldehyde. In this case, the bifunctional material significantly outperformed materials functionalized individually with either group, as well as a physical mixture of the independently functionalized materials, further illustrating the cooperative effect of these groups that must be near enough to one another to be capable of interacting. This material is particularly unique since when these two groups are used together homogeneously, no reaction is observed. Furthermore, adding homogeneous acid to a catalyst containing only the heterogeneous base rendered the catalyst inactive. The same result was obtained for the case of homogeneous base and heterogeneous acid. Thus, upon immobilization, acidic and basic functional groups are capable of reactivity unachievable in solution. Also, a dramatic solvent effect was observed wherein the reactivity of the catalysts was found to vary greatly with the solvent of the reaction as protic solvents presumably promote proton transfer and neutralization of the incompatible acid and base groups.



Scheme 3 Aldol condensation between acetone and *p*-nitrobenzaldehyde.

In a follow-up to this report, Zeidan *et al.*[34] replaced the sulfonic acid groups with weaker acidic groups (phosphonic, carboxylic), again distributed on a surface with primary amines. The activity of these catalysts was found to increase as the strength of the acid component decreased. The authors attributed this trend to changes in the proton-transfer interactions between the acid and amine groups, where a weaker acid is more easily reprotonated than a stronger acid. The cooperative effect of these materials was profound: carboxylic acid alone was not strong enough to give measurable yield in the aldol reaction, and primary amine alone gave only 33% conversion. However, when both of these functionalities were present in close proximity, the reaction went to completion (see Table 1).

Through a different approach, Alauzun *et al.*[35] have prepared materials containing incompatible acid and base groups that are isolated from interacting with one another. They reported a porous silica material containing sulfonic acid sites in the framework and amine groups in the pores. This was achieved by a direct synthesis with bis(triethoxysilylpropyl) disulfide and Boc-protected aminopropyltriethoxysilane, followed by disulfide reduction and oxidation and thermolysis of the Boc groups. The accessibility of the amino groups in this material was illustrated by reaction with acrylamide. A solvent effect was observed whereby in protic solvents the reactivity of the amines was diminished, presumably due to proton transfer between the sulfonic acid and amine groups, similar to the solvent effect reported by Zeidan *et al*. No catalytic data were reported for this material, but it should be well-suited for carrying out sequential reactions in one reaction mixture, such as an acid-catalyzed reaction followed by a base-catalyzed reaction, due to the sequestration of the groups. Similarly, this type of sequential reactivity with incompatible acid and base groups would not be achievable through analogous homogeneous catalysis.

4. Functional group positioning

Cooperative surface catalysis relies on the two functional groups being close enough to each other on the surface

Table 1 Total yield of aldol products (alcohol and olefin) for reaction of acetone with *p*-nitrobenzaldehyde for various silica-supported acid and/or base catalysts[34]

Catalyst	Acid type	Base type	Total yield (%)
1	Sulfonic	Amine	62
2	Phosphonic	Amine	78
3	Carboxylic	Amine	99
4	Sulfonic	None	16
5	Phosphonic	None	0
6	Carboxylic	None	0
7	None	Amine	33

to interact with each other or with the reacting molecules. Thus, one would anticipate that the catalytic activity of such materials would depend on the distances between catalytic surface sites. However, does the activity decrease monotonically as the distance grows? Is there a minimum distance in the case of mutually-destructive functionalities? Is there an optimal distance for the cooperativity, and does it vary from reaction to reaction? The answers to these questions are vital to designing better polyfunctional catalysts, but currently these answers are also largely unknown. A few authors have sought to probe these questions by attempting to control the spatial positioning of surface functional groups and seeing what effect spatial organization has on catalysis.

4.1 Imprinting

The traditional way to position multiple functional groups in a solid involves imprinting, in which a template molecule is used to guide the organization of the relevant functionalities.[36,37] There are two variations: non-covalent and covalent imprinting. In non-covalent imprinting, the imprint molecule serves to position the forming material through hydrogen-bonding or other non-covalent interactions. In covalent imprinting, the imprint molecule is itself incorporated into the material, after which it is cleaved, leaving behind the desired functional groups.

Multiple-point covalent imprinting has been employed to form pairs or triplets of identical functional groups within a silica matrix. The catalysts reported by Katz and Davis[38] illustrate this approach. Different molecular templates were prepared incorporating carbamate-protected amine groups and triethoxysilyl groups. Using sol–gel polymerization, these templates were then imprinted into bulk, amorphous silica and in a second step the molecular template was removed. The templates were removed by reaction with trimethylsilyl iodide, and the resulting materials contained one, two or three amine functionalities spatially positioned in the pocket vacated by the imprint (Fig. 3). Several groups have used similar approaches to prepare dimeric catalytic sites with two identical functionalities. But positioning two *different* groups is more difficult, since it usually involves two different chemical steps to deprotect the two functionalities. An additional difficulty arises if one or both of the deprotection steps is highly reversible, because both functionalities must be deprotected simultaneously in order for the imprint to be fully cleaved and diffuse away.

Bass and Katz[39] circumvented this difficulty using thermolysis in order to deprotect simultaneously thiols and amines that were grouped into pairs on a mesoporous silica surface. They synthesized an imprint molecule containing both carbamate and xanthate groups, each bound to a triethoxysilyl group. After the imprint was grafted onto the surface, the carbamates and xanthate groups were cleaved by thermal treatment at 250 °C to form primary amine and thiol groups, respectively. The pairing was experimentally verified by reaction of the bifunctional surface with *o*-phthalaldehyde, which generates a fluorescent species upon reaction with an amine and a thiol. Different imprints were synthesized with two xanthate groups, leading to materials functionalized with sites containing two thiol groups and one amine group. Furthermore, the amine–thiol distance was increased by using a precursor containing a longer alkyl linker. Although no catalytic properties were reported, the versatility of amine and thiol groups allows for the possibility of further transformation to other catalytic species; for instance, selective reaction of the thiols with Ellman's reagent converts the thiol sites to aryl carboxylic acid sites paired with amines, creating a material which could be used potentially as an acid–base catalyst.

Non-covalent imprinting has been used to prepare silica functionalized with dihydroimidazole, carboxylate, and amine groups to mimic the catalytic triad of lipase enzymes. Markowitz and co-workers[40] copolymerized tetraethyl orthosilicate with organosilanes containing these three functionalities, along with imprint molecules that formed non-covalent interactions with the organosilanes. The imprints used were chiral transition state analogues for α-chymotrypsin peptide hydrolysis or known chymotrypsin inhibitors. After a microemulsion polymerization, the resulting silica particles were washed to remove the surfactant and imprint molecules (see Fig. 4).

The imprinted catalyst particles were used to hydrolyze nitroanilide peptides. The hydrolysis rate acceleration was only modest (see Table 2), but the rate was higher when imprint molecules were used, indicating the organizing effect of the imprint molecules. In the hydrolysis of benzoyl-DL-arginine-*p*-nitroanilide (DL-BAPNA), the reaction rate increases by a factor of 1.8 when randomly-distributed amine, dihydroimidazole, and carboxylate groups are present. When various imprint molecules are used, the rate increases by an additional factor of 2–4. The chirality of the imprint molecules bestowed some enantioselectivity on the silica catalyst particles. D-BAPNA was hydrolyzed nearly 15 times faster than L-BAPNA using a catalyst prepared with **Imp3**.

As an additional control experiment, silica particles were synthesized using various imprint molecules but no functional silanes (Table 2, entries 3, 5, 7). The resulting imprinted all-silica particles still exhibited increased hydrolytic activity compared to the non-imprinted particles (a two- to three-fold increase). Thus, it is difficult to ascertain how much of the increased activity of the imprinted functionalized particles is due to the functional group organization, and how much is due to the imprinting of the bulk silica, or whether residual unextracted imprint molecules are playing some role. Furthermore, no investigation was made into the individual role played by each of the three functional groups. It is possible that only one of the functionalities is responsible for the catalytic activity; to confirm that cooperative catalysis is indeed operating, it would be necessary to show that mono- and bifunctionalized silica particles have reduced hydrolytic activity compared to the trifunctional material.

4.2 Site pairing

SBA-15 materials functionalized with sulfonic acid sites grouped into pairs have been investigated by Dufaud and Davis[41] and Mbaraka and Shanks.[42] These materials were obtained by incorporating a disulfide bridging group onto the surface, followed by reduction of the disulfide to pairs of thiols

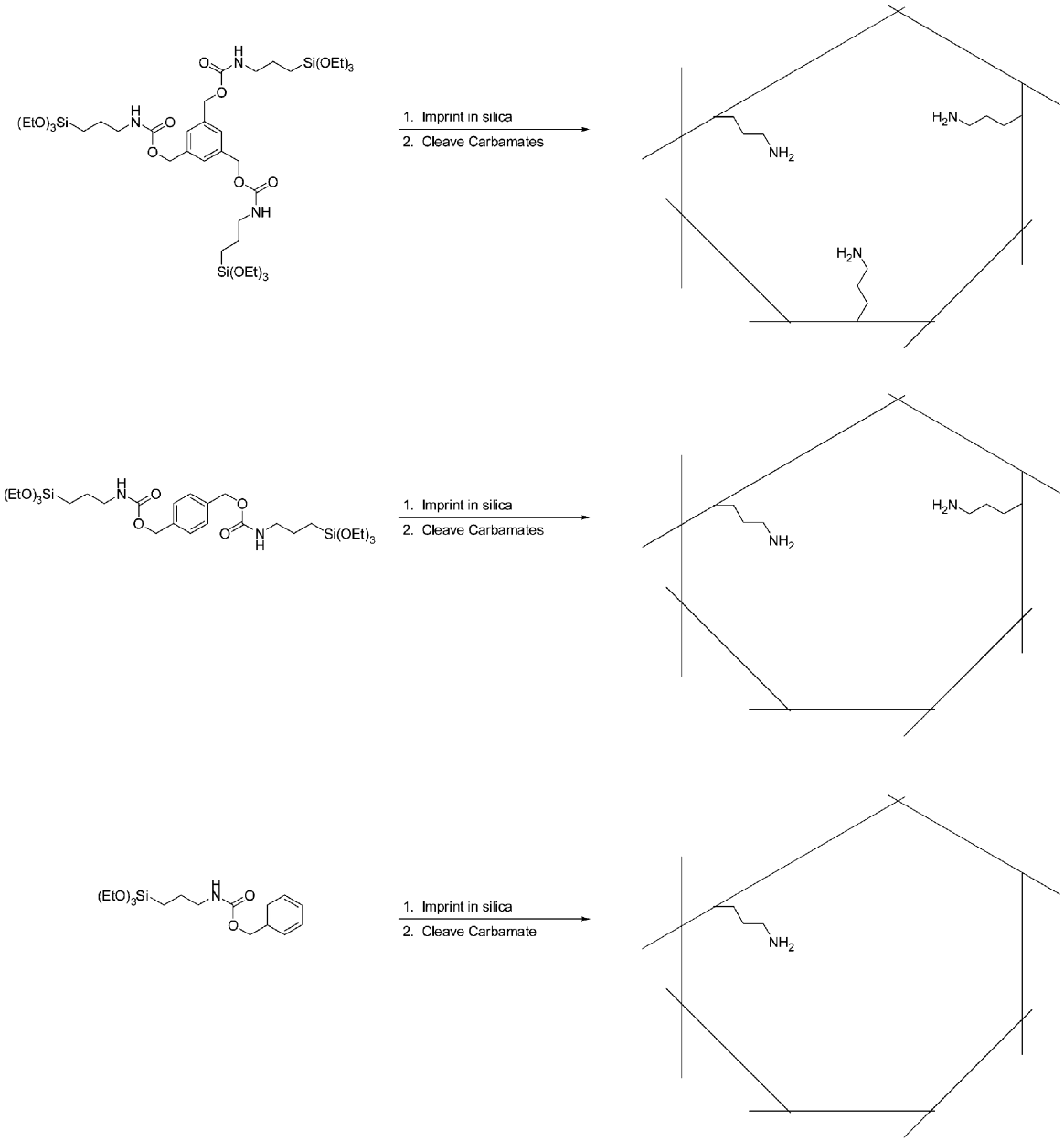


Fig. 3 Molecular imprinting technique used by Katz and Davis[38] to position primary amine groups in amorphous silica. Precursor molecules containing one, two, or three carbamate groups led to materials containing single, pairs, or triplets of amines.

and subsequent oxidation with peroxide to generate the acid pairs. Dufaud and Davis[41] reported that the activity of the acid catalysts for bisphenol A synthesis was about two-fold higher when the acids were grouped into pairs; however, this increased activity is more likely attributable to the presence of residual thiol groups or other partially-oxidized species, and not to the effect of pairing.[31]

Mbaraka and Shanks[42] studied the impact of pairing on acidity as measured by potentiometric titration. The pK_a of alkyl and aryl sulfonic acids were found to decrease slightly as the site density increased from $\sim$0.3 to 1.0 mmol g^{-1}. The paired alkylsulfonic acid groups had a pK_a nearly 0.2 units lower than the unpaired acids, with measured acidity very similar to the arylsulfonic acid groups (p$K_a \approx 1.25$). In the catalytic esterification of palmitic acid with methanol, however, the paired alkylsulfonic acid catalyst gave only a slight improvement over the unpaired catalyst, while the arylsulfonic acid material was almost twice as active. The authors conclude that other factors beyond acid strength must be responsible for the catalytic activity.

Margelefsky *et al.*[43] developed a family of catalysts where alkylsulfonic acid sites were paired with thiol groups on a silica surface and used in the bisphenol A synthesis. Sultone rings were tethered to the surface of SBA-15 and were then opened by reaction with various nucleophiles, such as hydrosulfide ion or the monoanion of a dithiol. The ring-opening reaction served both to generate the sulfonic acid group and also to tether the second functionality to the same site. In this method,

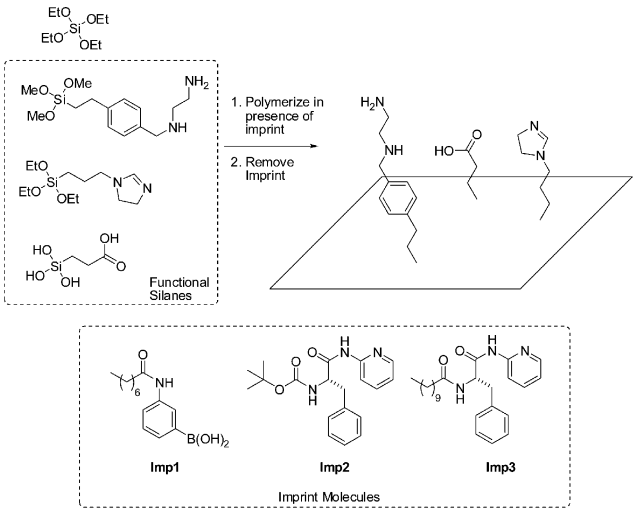


Fig. 4 Non-covalent imprinting scheme of Markowitz *et al.*[40] to prepare silica particles with similar functional groups to protease enzymes. **Imp1** is a chymotrypsin inhibitor and **Imp2** and **Imp3** are transition-state analogs for BAPNA hydrolysis.

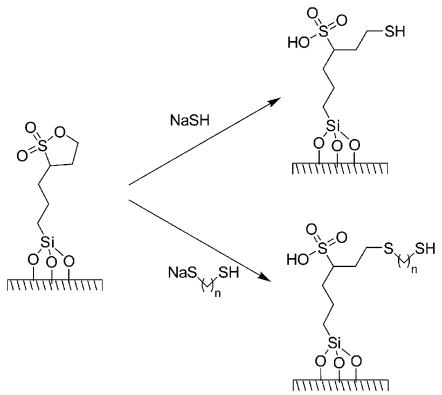
the acid/thiol ratio is fixed at 1 but the acid–thiol distance can be tuned by changing the nucleophile (Scheme 4).

The authors reported that the best activity and selectivity for bisphenol A were obtained when the acid and thiol groups were as close to each other as possible. When the acid and thiol groups were separated by three carbon atoms (Scheme 4, top), the product isomer ratio was 14 with a product yield of 83 per acid site. When the linker length was doubled using a sulfide linker (Scheme 4, bottom, $n = 3$), the selectivity dropped to 12 and the activity dropped by a factor of 2. Increasing the linker length further to $n = 4$ reduced the selectivity to 6 and again reduced the activity by a factor of 2, to a product yield of only 20 per acid site. Further increase in distance had no additional effect (the $n = 6$ catalyst performed similarly to the $n = 3$ catalyst). These data show how both the activity and selectivity of the acid–thiol catalysts are highly dependent on the distance between the two groups, and that the best catalyst is obtained when the acid and thiol groups are in very close proximity.

The activity of the acid–thiol-paired materials was compared to randomly-distributed acid–thiol catalysts, and the activity of the paired material was four-fold higher in the synthesis of bisphenol A. When the condensation was performed with cyclohexanone in place of acetone, the activity of the paired material was 14 times higher than that of the randomly-distributed catalyst. The authors suggest that, in

Table 2 Markowitz *et al.*[40] initial rate data for hydrolysis of DL-BAPNA using catalysts templated with various different imprint molecules

Entry	Imprint molecule	Functional silanes (wt%)	Relative rate
1	None	0	1.0
2	None	5	1.8
3	**Imp1**	0	2.2
4	**Imp1**	5	3.9
5	**Imp2**	0	2.8
6	**Imp2**	5	3.0
7	**Imp3**	0	2.9
8	**Imp3**	5	8.5



Scheme 4 Schematic of the synthetic route employed by Margelefsky *et al.*[43] to acid–thiol-paired silica materials. A surface sultone ring was opened with hydrosulfide (top) or a dithiol (bottom) leading to catalysts with acid and thiol groups with varying spacer lengths.

the bisphenol condensation reaction, the ketone is first protonated by the acid and then further activated by the thiol. This two-step activation is much faster when the acid and thiol groups are in close proximity.

Enantioselective catalysis has also been achieved. Zhong *et al.*[44] functionalized a surface with chiral proline-like sites containing two amine groups (see Fig. 5). Upon protonation of one of the two amine groups, the material becomes an acid–base catalyst active in the aldol reaction of acetone and *p*-nitrobenzaldehyde. Different acids were used to protonate the catalyst. The most active catalyst resulted when acetic acid was used, and the activity decreased monotonically as the strength of the acid increased. This trend is fully consistent with the conclusion of Zeidan and Davis[34] that weaker carboxylic acids led to better aldol catalysts when paired with amines.

The enantioselectivity of the amine–acetate catalysts was investigated for a number of different room-temperature aldol reactions. In the condensation of acetone and different nitrobenzaldehyde isomers, ee values ranged from 31–36%. The reaction between acetone and isobutyraldehyde provided the best enantioselectivity with 60% ee obtained. Chiral acids were also used to generate the acid–base catalysts. Interestingly, both L-tartaric and DL-tartaric acid-derived catalysts exhibited the same ee (33%) which suggests that the enantioselectivity is entirely due to the immobilized chiral acid–base site, rather than to the counterion. Although only modest enantioselectivity was achieved with this family of catalysts, the opportunities for future improvement are numerous.

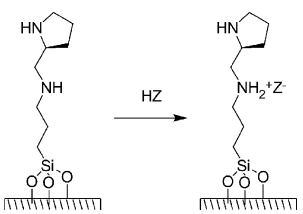


Fig. 5 Schematic of material prepared by Zhong *et al.*[44] Silica functionalized with proline-derived sites each containing two secondary amines. After partial neutralization with an acid the catalyst is active in the aldol condensation.

5. Future directions

Taken together, these examples illustrate some of the significant improvements that are achievable in heterogeneous catalysis by expanding the synthetic toolbox to include more than one functional group. A number of unique materials have been prepared that dramatically accelerate chemical reactions or allow for selectivity unachievable with homogeneous or heterogeneous catalysts functionalized with a single functional group. Whether merely trying to learn from the lessons of enzymes, or trying to replicate them synthetically, chemists have a great opportunity to extend these principles further and develop catalysts that exhibit even greater rate enhancements, specificities and enantioselectivities. In order to do so, developing a method that allows for the positioning of more than two functional groups at very precise distances to one another will be the key to synthesizing materials that are closer to enzymes. In addition to positioning the reactive groups near to one another at very carefully controlled distances and at the same distance between different sites, it will also be important to develop a method that allows for the careful positioning of these clusters of reactive groups relative to one another in such a way that there will not be interaction between neighboring groups of reactive pairs (*i.e.*, pair site isolation). Also, fine-tuning the shape of the surface these sites are positioned on as well as the hydrophobic/hydrophilic properties of the surface will be very important in advancing this area of catalysis. If one were able to finely tune the local pH on the surface near to the reactive sites to a different value than the bulk solution, very interesting reactivity could be achievable. Lastly, requisite for developing these new and exciting well-defined catalytic entities will be new methods of characterization. NMR methods for carefully determining the chemical nature of the functional groups when positioned, as well as examining the distance between the groups will be very important for characterizing the active sites. A number of other applications could be imagined for such materials, such as facilitating structure–activity relationship studies in pharmaceutical design as well as searching for inhibitors for specific active site configurations. While nature is limited to only 20 amino acids, the possible combinations for cooperative catalysis available to synthetic chemists is nearly limitless.

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