inactive
homogeneous catalyst

active
heterogeneous catalyst

heterogeneous: zwitterion form

tunable surface
interactions

homogeneous:
neutral form

bulky
ligands

unsaturated
systems

bulky
ligand

M

catalytically **inactive**

bulky
ligand

M

unstable with small OR

bulky
ligand

bulky
ligand

M

M

catalytically **active**

RO

OH

RO

M

OH

OH

M

OH

stable with small OR

homogeneous dimer

unselective

heterogeneous monomer

selective binol catalyst

inactive

active hydrogenation catalyst

tunable surface acidity

Enhancing Heterogeneous Catalysis through Cooperative Hybrid Organic–Inorganic Interfaces

Justin M. Notestein and Alexander Katz*[a]

Abstract: Active-site/surface cooperativity can enhance heterogeneous organic and organometallic catalysis. We review the powerful role of the solid surface in this context for generating local acidity and, as an inner-sphere ligand, for stabilizing immobilized supramolecular assemblies and unsaturated organometallic complexes that are often unstable in solution.

Keywords: cooperativity · enantioselectivity · heterogeneous catalysis · organic–inorganic hybrid composites · surface chemistry

Introduction

Biological catalysts are thought to achieve high degrees of catalytic activity and selectivity, including enantioselectivity, by the precise organization of chemical functionality in the inner and outer spheres surrounding an active site. It remains an open question whether, and to what degree of complexity, the same can be performed generally with synthetic heterogeneous catalysts consisting of organic and inorganic active sites working cooperatively. In this Concept article, we highlight previous work addressing this question, using perspectives in which a catalyst surface is an inner-sphere ligand, as in surface organometallic systems, or an outer-sphere ligand, as in heterogeneous organic catalysis. For the former class of catalysts, enantioselective metalloenzymes such as vanadium bromoperoxidase (VBrPO) serve as both inspiration and relevant precedent,[1] because the active site consists of an isolated vanadate surrounded by an organized inner sphere, which has been characterized

by means of single-crystal X-ray diffraction.[2] For the latter class, organic catalysis in enzymes often exploits lysines as nucleophiles, and catalytic antibodies such as 38C2 are highly proficient and enantioselective catalysts, the active site of which contains an essential lysine (primary amine) residue surrounded by a chiral outer sphere.[3]

Our central theme throughout this Concept article is that the solid surface in heterogeneous hybrid organic–inorganic catalysts participates actively in the reaction mechanism. We believe a promising future direction for active site optimization of synthetic heterogeneous catalysts is to synthesize arrangements in which the surface acts synergistically with other organic ligands to stabilize specific catalyst structures or a given transition state, rather than viewing the support as an inert spectator intended only for improved recovery and handling. Such synergy in heterogeneous catalysts consisting of hybrid organic–inorganic interfaces creates features that are uncommon in most homogeneous or biological catalysis. Two of these features that are specifically addressed here are: 1) the role of the surface in providing a continuum of outer-sphere acid strength and acid–base distances, which can facilitate extraordinarily versatile acid–base bifunctional catalysis when used in conjunction with a basic active site, and 2) the increased ease of forming supramolecular assemblies on the surface through weak interactions between immobilized species, that is, assemblies that are often absent in homogeneous solution due to competition with translational entropy. A recent comprehensive review describes many of the possible roles of the surface in hybrid organic–inorganic catalysts, including additional discussion of steric protection of unstable catalysts, specific adsorption of reagents, and the use of normally incompatible catalyst combinations or solvents.[4]

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Acid–Base Bifunctional Heterogeneous Catalysis

Acid–base bifunctional cooperativity is invoked often in biological catalysis.[5] In a synthetic system, the principles of bifunctional cooperativity are demonstrated in the elegant

work of Hine et al. on Schiff base formation using primary amines.[6] They observed that the rate constant of the second-order reaction between acetone and a primary amine increases as the primary ammonium pK_a increases (Figure 1) due to higher amine nucleophilicity. In contrast,
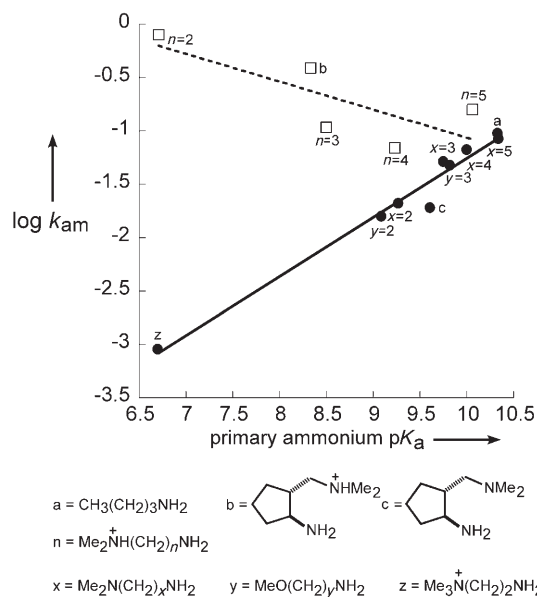

Figure 1. Linear free-energy relationships of the logarithm of the rate constant for formation of imines from acetone and various primary amines (k_{am}) versus amine pK_a. Water, 308 K, ionic strength = 0.3 N. Adapted from reference [6]. Linear regression for the bifunctional (dashed) and general base (solid) catalysts are shown.

the observed rate constants for acidic, monoprotonated diamines are dramatically larger than the unprotonated amines at any given primary ammonium pK_a, and the rate constants slightly *increase* with *decreasing* primary ammonium pK_a. This change in trend indicates a fundamentally different linear free-energy relationship for acid and non-acidic diamines, and highlights the importance of organizing acid and base components of a bifunctional catalyst in a manner that avoids forming energetically unfavorable ring structures in the former. The critical role of acidity on the imine formation rate is most apparent in the 800-fold higher activity of acidic, monoprotonated 2-dimethylaminoethylamine (**2**) relative to that found for non-acidic 2-trimethylaminoethylamine (**1**), even though both **1** and **2** are charged and have a primary ammonium pK_a of ~6.7.

Building on the results of Hine et al. that imine formation is favored under bifunctional conditions, Bass et al. have demonstrated the importance of acid–base bifunctional cooperativity in heterogeneous primary amine catalysts for aldol-related condensation reactions.[7] Bifunctional catalysis involving cooperativity between Brønsted acid sites on SiO_2 and primary amines has been postulated previously for reac-

tions such as Knoevenagel[8] and aldol condensations;[9] however, unequivocal proof for heterogeneous acid–base bifunctional catalysis has remained elusive due to the difficulty of selectively removing either the acidic or basic component of the catalyst, without altering other important catalyst properties. To rigorously demonstrate the existence and importance of acid–base cooperativity in catalysis, Bass et al. used bulk silica imprinting as a materials synthesis tool for systematically changing the outer sphere surrounding primary amine active sites, without altering other catalyst characteristics such as primary amine active-site density and network porosity. This method was used to synthesize materials **3** and **4** according to the scheme shown in Figure 2. Copolymerization of a carbamate imprint and tetraethyl orthosilicate immobilizes the carbamate within a hybrid organic–inorganic sol–gel material. This material is a silanol-rich polar/acidic network that is the direct result of sol–gel synthesis conditions. Material **4** is synthesized from this parent material by first reacting free silanols with trimethylsilylchloride to create a hydrophobic outer-sphere environment, followed by carbamate deprotection via thermolysis. Material **3** is synthesized directly by thermolytic deprotection of the parent material without additional surface modification. Importantly, materials **3** and **4** are derived from the same immobilized carbamate parent material; as a result, they are identical in most every respect except in their outer-sphere environments surrounding the primary amine active sites.

Using the fluorescence emission spectra of covalently bound pyrene aldehydes,[10] the researchers also demonstrated that imprinted materials **3** and **4** possess isolated primary amines, whereas amines cluster on a more conventional material **5** consisting of primary amines grafted at high surface density to SiO_2. Thus, bulk silica imprinting serves two synthetic purposes in this study: 1) facilitating isolation of primary amines on silica and 2) permitting changes to the outer-sphere environment, while keeping the active site in a protected form that minimizes potential side reactions between surface capping agents and primary amines.
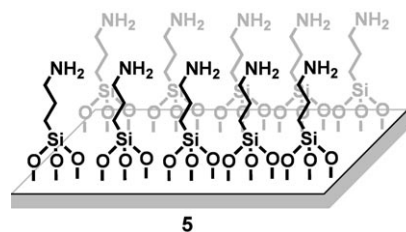
Reaction with salicylaldehyde followed by solid-state UV/Vis spectroscopy demonstrates the differences in the amine active sites when surrounded by an acidic outer sphere in **3** as opposed to a hydrophobic, non-acidic outer sphere in **4**. Primary amines in **3** form iminium cations (zwitterionic tautomer **6**), whereas the reaction of **4** with salicylaldehyde produces more of the neutral tautomer **7** (Figure 2).[7]
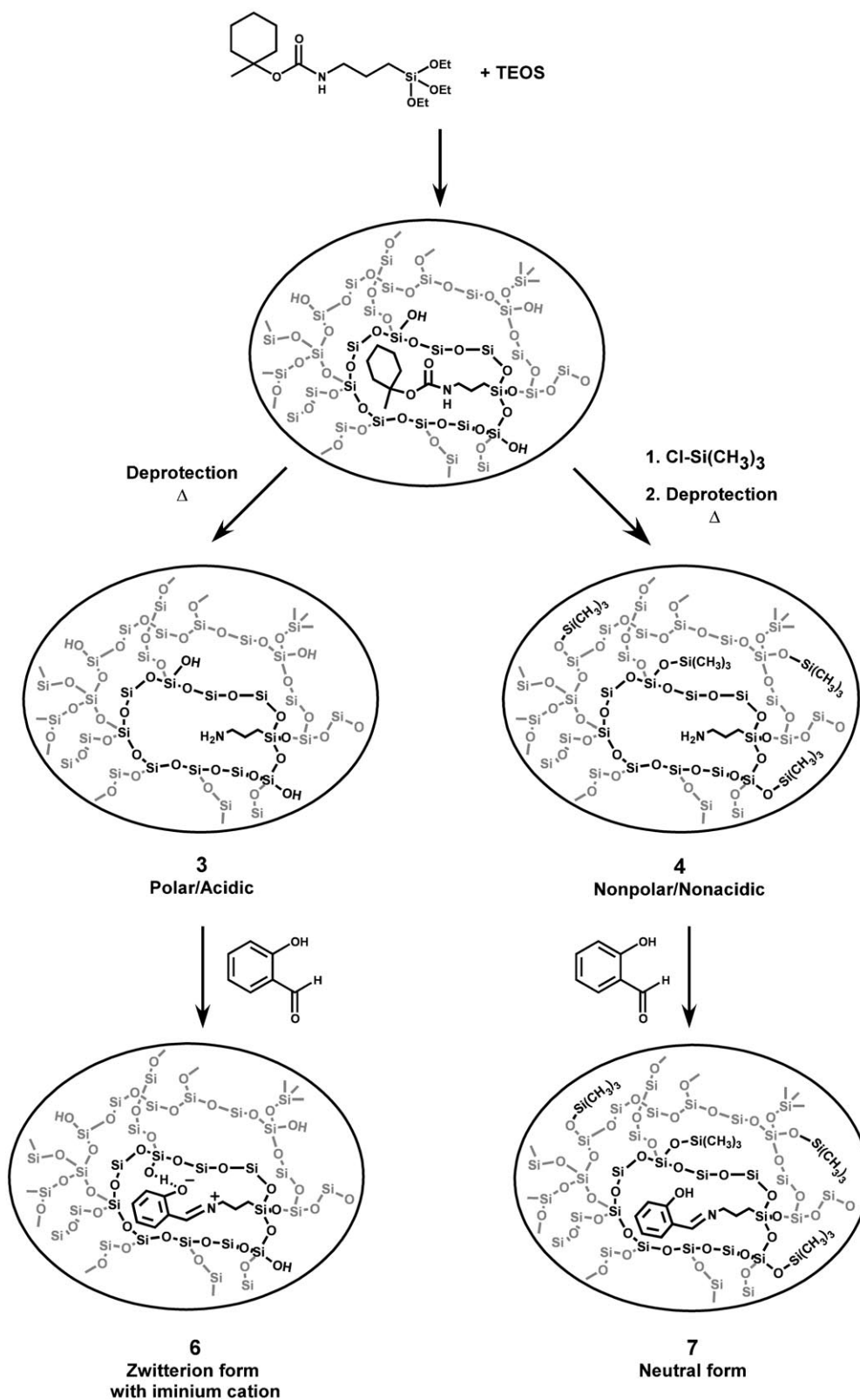
Figure 2. Scheme for the synthesis of catalytic amines on silica in a polar/acidic framework **3** and in a nonpolar/nonacidic framework **4** from the same precursor material, and their reaction with an aldehyde to form an iminium cation and an imine, respectively.

Bass et al. used materials **3**, **4**, and **5** as catalysts for the Knoevenagel condensation reaction between isophthalaldehyde and ethyl cyanoacetate, and demonstrated a 25-fold

enhancement in turnover rate (per amine) for bifunctional catalyst **3** over its hydrophobic outer-sphere analogue **4**, and a 90-fold enhancement in turnover rate over the convention-

al primary amine on silica catalyst **5** under identical reaction conditions. These authors rationalize that acidic silanols in **3** function cooperatively with primary amines to form highly electrophilic iminium cations, which can be quasi-equilibrated and energetically favored under bifunctional conditions, as occurred preferentially on **3** during salicylaldehyde binding. Parallels can be drawn with the approach used by pyridoxal phosphate-dependent enzymes, which also convert moderately electrophilic carbonyl compounds into highly electrophilic iminium cation intermediates, thereby increasing reaction rate.[11] These observations by Bass et al. prove that bifunctional mechanisms can exist in catalysts consisting of hybrid organic–inorganic materials. The results also indicate that maximizing the surface density of the amines, as in the conventional catalyst **5**, does not optimize the catalyst rate on a per site or per gram basis, since surface crowding prevents the very large rate enhancements possible from bifunctional cooperativity.

An interesting aspect of catalyst **3** demonstrated by Bass et al. is that acid–base cooperativity is observed for carbamate thermolysis within the active site, salicylaldehyde binding, and Knoevenagel condensation, and each reaction has its own acid–base distance requirements for observing cooperativity. An important question is how the solid surface is able to maintain such promiscuity in acid–base bifunctional catalysis. Many homogeneous and enzymatic bifunctional catalysts have tight restrictions on the distance between acid and base functional groups in order to maintain bifunctional catalysis. This sensitivity to acid–base separation distance is suggested by the results of Figure 1 in which the imine formation rate constant for the bifunctional n series generally decreases as n becomes larger and the catalysts behave more like the monofunctional amines. Such sensitivity to acid–base organization has been observed even for the earliest examples of synthetic bifunctional catalysts, consisting of pyridone catalysts for glucose mutarotation.[12] Hine et al. proposed that solid polymers may be more versatile bifunctional catalysts than small molecules by offering a broad distribution of acid–base separation distances.[13] The acidic silica surface in **3** also allows the catalytic system to choose the optimum acid–base separation distance for each reaction from a continuum of such distances offered by the hydrogen-bonded silanol network on the solid surface. It is this length-scale continuum that should potentially enable heterogeneous organic–inorganic hybrid catalysts to be far more versatile than any single molecular organocatalyst.

Immobilized Organometallic Catalysts as Hybrid Organic–Inorganic Materials

In our discussions below of heterogeneous organometallic catalysts, we focus on materials in which a catalytic metal is simultaneously ligated by an oxide surface and an organic molecule. Such an approach places metals within a well-defined oxide ligand field, which is useful for understanding local structure–property relationships within the context of

catalyst activity and selectivity. The examples below highlight structural control for the synthesis of hybrid organic–inorganic catalytic materials, with the ultimate and as of yet unrealized general goal of creating designable synergy between molecular and surface ligands for high organometallic catalyst activity and selectivity. These examples have been chosen for their careful study of surface interactions or because their use of novel strategies and structures for the design of hybrid organic–inorganic catalysts, with less emphasis on their activity or robustness as expressed through total turnovers. We present three routes for synthesizing defined, covalent interactions between a small molecule ligand, a metal, and a support surface as ligand. These three methods can be described generally by the sequence of immobilization, consisting of: 1) ligand then metal, 2) metal then ligand, and 3) deposition of an intact metal–ligand complex. We will discuss several systems representative of these synthesis methods. Within each example, the support oxide surface can play several roles. First, the support oxide as ligand often has electronic properties distinct from the precursor ligands, which will alter the catalytic activity of many supported complexes, even though these electronic effects can, in principle, be replicated by using appropriately chosen small molecule ligands. Secondly, the nominally planar geometry and near-continuum of oxide ligands on a surface (vide supra) allows supported complexes to form dimers and cycles that are entropically prohibitive in solution. This phenomenon can lead to new surface structures and reactivity, but also to undesired clustering and energetic heterogeneity of active sites to create less accessible or active catalysts. Finally, in cases in which ligand design excludes lateral interactions between supported metal complexes, the support can enforce coordinative unsaturation at the metal. Importantly, these surface complexes follow the strict definition of coordinative unsaturation,[14] since they will coordinate additional small molecule ligands if introduced, as opposed to many homogeneous "unsaturated" complexes that are simply too bulky to coordinate additional ligands. Of the three synthetic methods, the first route is increasingly common through the so-called "heterogenization" of preexisting homogeneous catalysts, often with the goal of facilitating catalyst recovery as has been reviewed elsewhere.[15] A common feature of many of these systems is that outer-sphere acidity can influence catalyst activity, both desirably and undesirably, even without covalent interactions between the catalytic metal and the support.

In some instances, solid acidity can have a beneficial role on heterogeneous organometallic catalyst performance. Raythatha and Pinnavaia, for example, demonstrated in 1983 that hectorite clay surface acidity serves to increase the selectivity of Rh phosphine catalysts for 1-hexene hydrogenation over isomerization.[16] Under reaction conditions, the Rh phosphine active site is susceptible to the equilibrium shown in Figure 3 between the selective dihydridorhodium complex and the unselective monohydride form.

Surface acidity in the clay shifts this equilibrium to the dihydridorhodium form, making the catalyst more selective
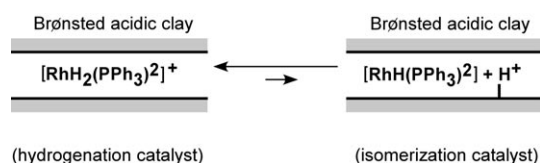
Figure 3. Solid-acid-mediated equilibrium between reactive intermediates during hydrogenation on immobilized Rh phosphines.

towards hydrogenation rather than isomerization. In a more recent example,[17] Gonzalez-Arellano et al. started with the observation of Pugin and co-workers that Ir–diphosphine complexes catalyzed imine hydrogenation at a faster rate in acetic acid.[18] Gonzalez-Arellano et al. subsequently built this positive acid effect into the solid surface by decreasing the Si/Al ratio of the supports, thus avoiding the use of acetic acid as a solvent and the associated handling problem. The heterogeneous organometallic active site **8** was assembled by a ligand-then-metal approach on aluminosilicates of varying Si/Al ratio. The measured imine hydrogenation rates increased with increasing solid acidity by as much as fivefold when compared to the Al-free materials. In both Pugin's and Gonzalez-Arellano's systems, rate increases were proposed to arise from transition-state stabilization by H^+.

8, M = Pd or Ni
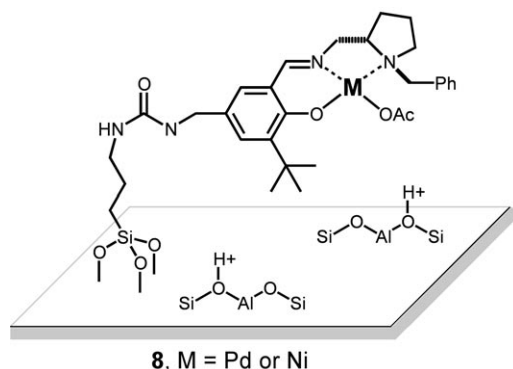
The importance of non-specific interactions between the active site and solid surface is convincingly demonstrated in the results of Baleizão et al.[19] Vanadyl salen complexes were tethered to the surface of silica to synthesize catalyst **9** for the enantioselective addition of trimethylsilyl cyanide to aldehydes. Because interactions with acidic defect sites were previously known to have a detrimental effect on the enantioselectivity of this reaction, the silica surface was capped by using trimethylethoxysilane prior to the attachment of the metal complex. FT-IR spectroscopic measurements demonstrate, however, that some residual silanols remain on the silica surface after capping, and conversion and product enantioselectivity accordingly decrease with increasing silanol content. Increasing the tether length increases its conformational entropy and should decrease the fraction of the time that the salen spends in close proximity to the surface

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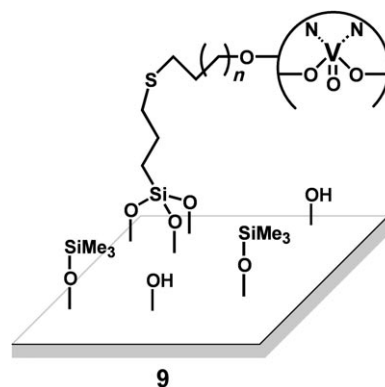
silanols. Thus, as chain length (n) increases, enantiomeric excess (*ee*) increases from 52% ($n=3$) to 63% ($n=11$) and under optimized conditions to 85% ($n=11$), which compares favorably with the homogeneous catalyst at 90% *ee* under the same conditions. This example clearly demonstrates that even in catalysts in which the support has been exhaustively silylated, metal–support interactions can affect catalysis.

In the systems discussed previously, interactions between a metal complex are present to varying degrees and with varied effects, due to the use of long tethers for immobilization. In contrast to the use of flexible chains, Goettmann et al.[20] recently designed a tethered system for intentionally facilitating metal–ligand–support interactions by creating silica-immobilized complex **10C** (Figure 4). In homogeneous solution, complex **10D** is suggested to possess both Rh−P and Rh−O interactions; this complex has been characterized by using ^{31}P NMR and low-temperature ^{1}H NMR spectroscopy. Thus, when triethoxysilane **10A** is reacted with a surface to form **10B**, a two-point attachment results, leaving the third ethoxy group free to interact with Rh^I and mimic the solution structure. The solid-state ^{31}P NMR resonance shifts of heterogeneous **10C** resemble those of the solution analogue **10D**, suggesting that Rh^I is coordinated to the phosphine ligand. Counteranion IR or NMR signals are lost, further suggesting that the silica surface is now coordinated to the metal center as an anionic $\equiv Si−O^-$ ligand. The authors propose a five-membered ring as the coordination geometry at the metal center in the heterogeneous material, analogous to the solution complexes **10D** and **10E**. Regardless of the precise geometric details at the Rh^I center, the dramatic change observed in the catalytic properties of these complexes when grafted demonstrates that the phosphine and the surface act synergistically as a bidentate LX-type ligand. Silica and homogeneous complex **10D** are completely inactive for the hydrogenation of 1-hexene in methanol, whereas the complex grafted onto the silica surface is reported to be capable of a large number of catalytic turnovers for hydrogenation of alkenes and imines. Partial activity in the homogeneous phase is recovered by using complex **10E**, which possesses the same connectivity proposed to exist in the anchored complex. Since the increase in activity
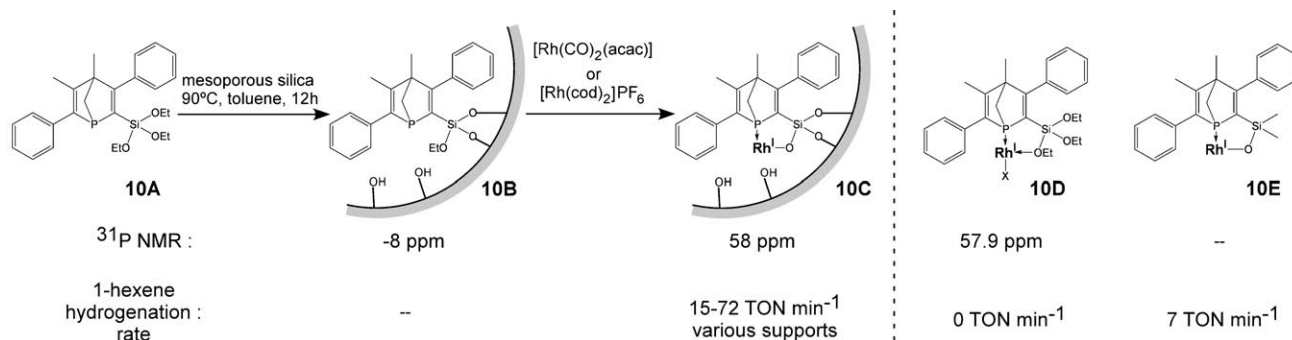
Figure 4. Silica-immobilized and homogeneous Rh^{I} phosphine complexes for hydrogenation. Hydrogenation rate is given in moles of 1-hexene consumed per Rh per minute. Carbonyl or cod ligands on Rh^{I} are omitted for clarity.

is impossible to rationalize by steric effects of the surface, it can be concluded that deliberate placement of the Rh^{I} center in covalent contact with the surface introduces strong electronic effects that can work in concert with the organic ligand for enhancing catalytic activity at the metal center.

In the second route to heterogeneous, ligand-modified catalysts, a supported metal complex is first constructed, preferably in a well-defined manner amenable to detailed structural characterization, and is modified by the functional ligand in a subsequent step. Several routes to well-defined metal oxides have been developed, all generally characterized by precursors that react predominantly with the surface and minimally with other supported complexes. As compared with incorporation into bulk oxides, these methods offer better active-site accessibility and the ability for tuning the support and metal complex independently. Metal–alkyl[21] or Cp–metal–alkyls species[22] react irreversibly with the support oxide either at surface defect sites or by direct insertion, liberating alkanes or producing surface alkyls. In these methods, surface density and acidity often control the resulting geometry and podality of the supported metal complex.[23] Alternately, sterically bulky precursors such as [TiCl$_2$(Cp)$_2$],[24] [Ti(OSiPh$_3$)$_4$],[25] or [M^{n+}{OSi(OR$_3$)}$_n$][26] may be employed for physically isolating metal centers. Metal precursors with small alkoxide or halide ligands have a propensity for forming agglomerated surface species, which may be facilitated by the loss of translational entropy upon immobilization, but these too can be successfully employed if conditions are sufficiently controlled.[27] In the cases in which oxide precursor ligands are utilized, the evolved and grafted products must be monitored or later quantitatively exchanged for determining the average grafting podality on the surface. Quite commonly, the ligands chosen to give optimal support geometries are not desired for the catalytic system, and are thus removed by calcinations or exchange.[24,28]

After deposition of the metal precursor, subsequent introduction of functional ligands must be conducted in a rational way. One frequent target for heterogenization is the Sharpless–Katsuki enantioselective epoxidation of allylic alcohols using tartrate ligands on Ti. Successful catalysts have arisen from tethering approaches[29] or from incorporation of

the ligand into a polymer,[30] but there is no unambiguous evidence for highly enantioselective catalysis arising from Ti simultaneously coordinated by the surface and the tartrate. Meunier et al. have suggested[28] that Ti is perhaps not the best metal for use in supported, Sharpless–Katsuki type enantioselective epoxidation, since chelating coordination of the tartrate, the allylic alcohol, and the peroxide is required for the selective epoxidation mechanism. This leaves no vacancy on the metal for a fifth coordination to the surface when using Ti (**11A**), which is required for immobilization.
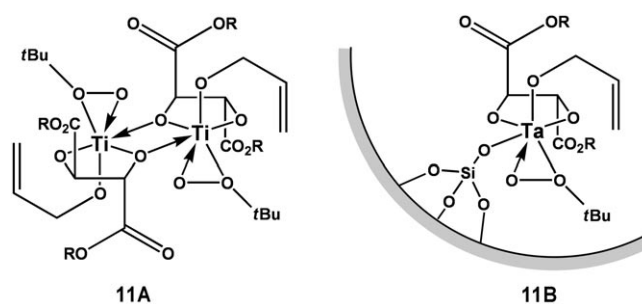
Simultaneous coordination of all of these entities exceeds the valence of Ti, but can be accommodated by supported Ta complexes (**11B**). As predicted, immobilized, isolated Ta alkyls, subsequently modified by diisopropyl tartrate, are capable of selective catalytic turnover for the epoxidation of propenol or hexenol[31] with organic hydroperoxides. Catalytically active Ta is not leached from the surface by the tartrate ligand in CH$_2$Cl$_2$, and no Ta is found in solution after reaction, providing evidence that the reaction is occurring heterogeneously.

This work also clearly demonstrates the surface's critical role in stabilizing the coordinatively unsaturated resting state of the catalytic species. The soluble Ta alkoxide precatalysts are not active, although Ti alkoxides are viable, presumably due to more extensive agglomeration of the former metal centers. The combination of sterically bulky Ta precursors and the bulk and rigidity of the surface as macroscopic ligand prevents Ta from forming electronically saturated clusters when the alkyl ligands are exchanged for

alkoxides. The highly dispersed nature of the centers allows reactant coordination to the metal and thereby initiates the catalytic cycle.

The role of a macroscopic oxide surface in enforcing unsaturation of a complex is distinctly different from the use of bulky homogeneous ligands, and is more akin to metal unsaturation within the core of enzymes.[32] As illustrated in Figure 5, extremely bulky ligands may prevent a metal
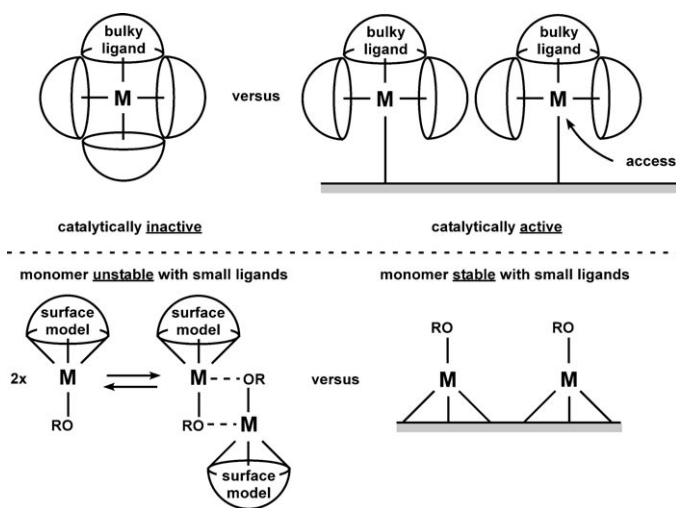

Figure 5. Bulky complexes that are inaccessible to reactants in solution can become active when one ligand is replaced by a silica surface. Complexes of surface models such as calixarenes and silsesquioxanes are susceptible to dimerization, whereas, with identical podality, the surface is not.

center from coordinating as many species as it would with smaller ligands; however, without the ability to coordinate smaller ligands (reactants), these materials are neither unsaturated by the definition of Strauss[14] nor are they catalytically active. This is illustrated by the total inactivity towards olefin epoxidation with organic hydroperoxides for soluble [Ti(OSiPh$_3$)$_4$][25] and [Ti(OSiMe$_3$)$_4$].[33] A surface, by virtue of being a rigid, macroscopic entity, is uniquely suited for maintaining coordinative unsaturation and facile reactant access at the same time. Thus, by using the example of Attfield et al.,[25] replacing one bulky -OSiPh$_3$ ligand with a silica surface allows coordination of other small ligands, but prevents active site agglomeration. To act in this way, the surface must be an actual macroscopic surface, as opposed to surface models such as silsesquioxanes[34] or calixarenes,[35] because although sterically protected on one hemisphere (Figure 5), these are still mobile entities that will dimerize on their unprotected hemispheres.[34,36] As shown in Figure 5, only when restricted to the material surface can catalyst sites be accessible from the "top" or "bottom" yet still be prevented from agglomeration.

In this manner, surface-immobilized metal centers are useful for synthesis of isolated metal centers bearing small ligands that would otherwise change their nuclearity in order to increase electron density on the unsaturated metal

center.[37] Characterization of these small ligands is very useful for spectroscopy and determination of the kinetic rate parameters of elementary steps on what may otherwise be short-lived transient species. For example, Thieuleux et al.[38] found that when supported on silica, the species ≡ZrH is isolable and inserts methane significantly slower than similarly supported =ZrH$_2$ species. Both of these species exist in solution as unstable catalytic intermediates in alkane transformations and presumably exist on more traditional supported zirconium species, for example, in olefin polymerization catalysts, but were not previously amenable to direct characterization.

Ligand modification of surface immobilized species presents a route to tune the properties of a catalyst and to study ligand effects without changes to the saturation at the metal. However, when considering reactions under conditions of turnover, the ligand to be studied must also be stable against ligand exchange. Thus, except in conditions strongly favoring cleavage of one of the tripodal bonds in the surface connection, the monodentate OR ligand in Figure 5 will likely be exchanged after several turnovers for reactions requiring coordinating species. Fraile et al.[39] recognized the need for modifying the surface titanium with chelating species in order to see more persistent ligand effects in the epoxidation of alkenes with hydrogen peroxide. In an elegant paper,[40] the LUMO energy was calculated by DFT for silica-supported Ti complexes subsequently modified by a diol (OO), an amino alcohol (ON), and a diamine (NN) and was found to correlate very closely with the observed rate
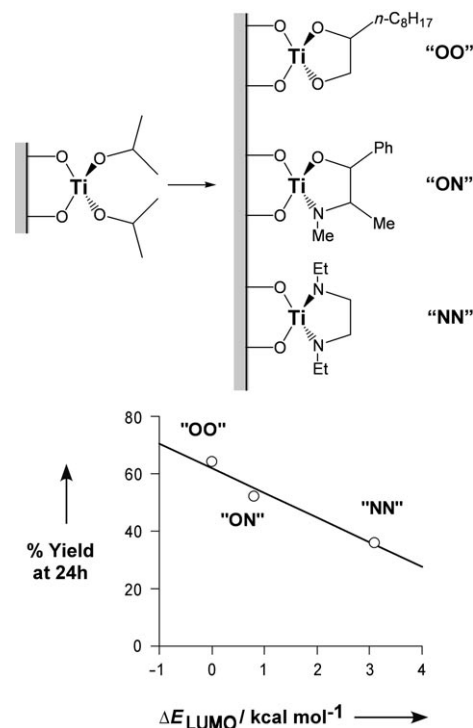

Figure 6. Modification of surface grafted Ti active sites with chelating alcohols and amines decreases the yield of cyclohexene epoxide proportional to the change in the LUMO energy.

and selectivity of cyclohexene epoxidation (Figure 6) and with the calorimetrically determined heat of ammonia adsorption on the Lewis acid sites. The ability to correlate the influence of ligands on the electronic structure to the catalytic activity of the metal is known in homogeneous catalysis[41] and is beginning to occur for supported metal oxides,[42] but, to our knowledge, has not been demonstrated previously for tuning a heterogeneous Lewis acid oxide with organic ligands. Fraile et al. noted that in their system ligand exchange is incomplete (50–80%), and thus a distribution of sites is present on the catalyst surface.[40] Since, in this case, ligand exchange reduces catalytic activity, complete inactivation of a fraction of sites rather than smaller changes to the entire site population is a possible interpretation of the observed data. It would be necessary to perform ligand variation on single-site materials for rigorously demonstrating that measured catalytic effects are ascribable only to an altered LUMO, but such a study has yet to be completed.
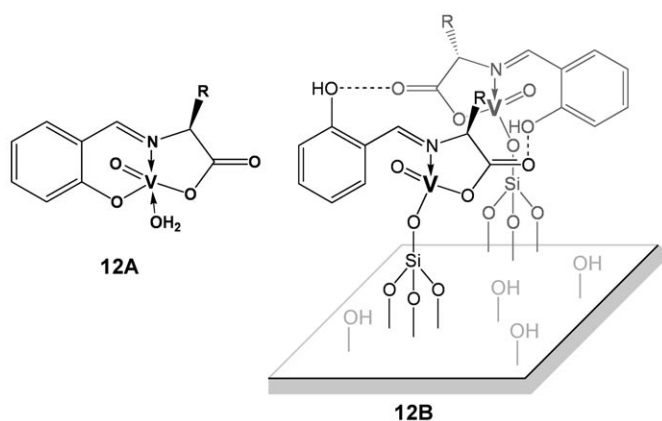
The two routes (ligand then metal; metal then ligand) presented above account for the vast majority of grafted catalysts. Although functional catalysts are accessible through these routes, they can be somewhat difficult to characterize, particularly as the complexity of the ligands increases and their symmetry drops. Solid-state NMR techniques and X-ray absorption spectroscopy have proven invaluable for structural characterization, but are not universally useful for all nuclei and cannot always provide sufficient resolution for unambiguous structural determination.

An alternative route is to construct well-defined complexes amenable to solution characterization and crystallography, and then to immobilize these complexes with minimal, or easily discernable, perturbations to the coordination environment. Tada et al.[43] recently immobilized the vanadium Schiff base complex **12A** onto SiO$_2$. Through IR spec-

12A

12B

troscopy and EXAFS, it is evident that immobilization removes weakly coordinated water, and the defects on the SiO$_2$ surface substitute for the phenolate ligand in the inner sphere, thereby reducing the V−O(N) coordination from four to three. DFT simulation of the immobilized complex suggests that the lowest energy conformation of the complex

places the phenol in coordination with V, in conflict with EXAFS results, implying that the phenol is engaged in hydrogen bonding with adjacent groups. ESR indicates the presence of another d^1 metal center at a distance of 0.4 nm, particularly in the presence of O$_2$, which corroborates the authors' DFT simulations predicting hydrogen-bonded V complex dimers (**12B**) by means of surface association. Surface association also can enforce stereochemistry at the metal center. The homogeneous complex is stated to consist of rapidly interconverting Δ and Λ stereoisomers, but the formation of dimers could stabilize $\Delta\Delta$ or $\Lambda\Lambda$ diasteriomers, similar to capsule systems developed in the team of Raymond[44] with diasteriomeric excess enforced, in this case, by ligand chirality. That dimers do not form in solution for this system indicates that the weak enthalpy of association is more than offset by a large unfavorable entropy change. On the surface, this association entropy penalty is dramatically reduced, since all complexes have already lost their translational entropy. It must be noted that chirality at the metal center has not been directly demonstrated for this system, but is an interesting possible consequence of the surface association.

These catalysts were reported to be the only known heterogeneous catalysts for the oxidative coupling of 2-naphthol to form binol and were able to catalyze this reaction with nearly 100% selectivity for binol, and, in some cases, high (90%) enantioselectivity. Particularly notable is that the homogeneous precursor is completely inactive except in the presence of acidic promoters, and, only then, possesses moderate activity and selectivity for binol, with negligible enantioselectivity. TiO$_2$- or Al$_2$O$_3$-supported catalysts exhibit absent or reduced activity, which may indicate that complex **12A** does not change coordination number upon immobilization on these supports, and provides another example of the utility of SiO$_2$ as an excellent support for stabilizing an unsaturated metal center.

As seen in Table 1, rate and enantioselectivity dramatically increase with surface density of V, reaching up to 93% conversion and 90% ee for a 3.4 wt% V loading, corresponding to the geometrical maximum surface density. Because the monomeric form of the catalyst (in solution) reacts slowly and is generally unselective, a simple explanation of the catalytic behavior with increasing V loading is an increase in the relative population of active, selective dimers (structure **12B**) as the V loading increases. Such dimers possess overall C_2 symmetry, which is a common structural motif in many successful enantioselective catalysts.[45] As

Table 1. Oxidative coupling of 2-naphthol using surface C_2 dimers of **12B** as a function of wt% V.

cat **12B** [wt% V]	time [h]	TON [binol V^{-1}]	% ee (R)
0.3	120	1	32
0.8	120	3	39
1.6	120	4	48
3.4	264	8	90

with the formation of catalytically active heterogeneous **10 C** as compared to the inactive homogeneous complex **10 D** discussed previously, this study is a good example of surface-mediated construction of a new catalytic entity. Simply by changing the coordination around the V and, importantly, geometrically restricting the complex to the plane of the support, catalytically active and selective dimers are able to form.

In the paper by Tada et al.,[43] the coordination sphere at the metal is significantly changed upon immobilization and interaction with other surface species. As a result, the outer-sphere geometry and therefore the catalytic behavior of the material is a strong function of the surface density of the metallic complex. As we proposed previously, the loss of translational entropy upon grafting results in active-site clustering even under the influence of attractive interactions that may be extremely weak in solution. This is a general phenomenon resulting in surface dimers[27] or metal oxide clusters that increase in size as metal surface density increases.[46,47] Notestein et al.[48] have instead utilized a precursor molecule that predefines the coordination at the metal and incorporates all of the desired functionality in the grafting moiety, while being sufficiently bulky to prevent agglomeration of active sites. The Ti-calixarene precursor **13 A** is a stable monomer in solution that has been characterized by single-crystal X-ray diffraction[49] and is known to react in the presence of alcohols and other ligands cleanly and selectively with loss of chloride.[36] Evidence of intact deposition of the metal–ligand complex for forming material **13 B** by means of the synthesis illustrated in Figure 7 is provided by solid-state UV/Vis and NMR spectroscopy and a strict correspondence between Ti and C elemental analysis. The surface-immobilized organometallic complex is stable under reaction conditions due to the multidentate, strongly coordinating ligand, and the HOMO–LUMO transition, reflecting the intrinsic activity of the catalytic complex, was further measured to be independent of surface density of Ti or time-on-stream.

The precursor molecule **13 A** has limited activity and selectivity for epoxidation of unfunctionalized olefins in solution, likely due in part to dimerization of the alkoxides[36] that are a product of catalytic turnover, as illustrated in Figure 5; however, the catalytic activity of **13 B** is comparable to the fastest known Ti epoxidation catalysts. In this system, the authors proposed that π donation into the calixarene ring withdraws electron density from the Ti center, which replicates the electron-withdrawing character of a prototypical silica framework **13 C**, while maintaining the accessibility to reactants of a supported complex. In contrast to a framework-substituted material, the Ti atoms in **13 B** are all displayed at the surface and are accessible even to bulky reactants, such as cyclooctene or *cis*-stilbene.[48] The calixarene macrocycle thus plays roles in 1) withdrawing electron density from the Ti atom, 2) providing lateral steric bulk to prevent Ti clustering on the surface, while 3) allowing access to the metal center by the comparatively smaller alkene and hydroperoxide reactants. The role of the surface
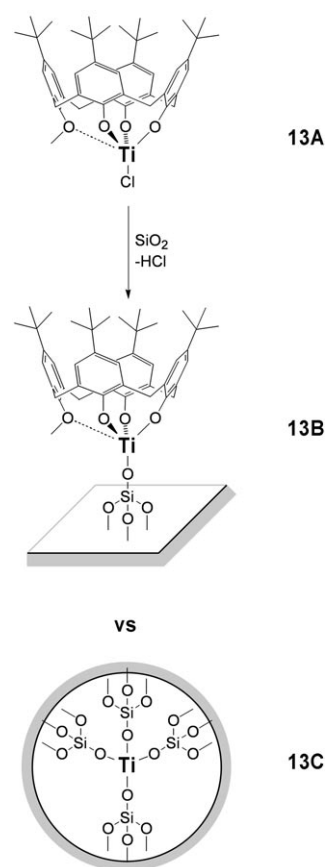

Figure 7. Grafting of calixarene–TiCl **13 A** to form single site alkene epoxidation catalyst **13 B** with better accessibility, but conceivably similar electronic structure as prototypical in-framework material **13 C**.

is to provide a fourth electron-withdrawing ligand and to stabilize the metal complex against dimerization without creating an undue steric restriction for small molecule reactants.

A precise kinetic analysis of the epoxidation of cyclohexene with organic hydroperoxides yields further information about the role of the calixarene and silica ligands. The epoxidation reaction was shown to strictly obey the proposed first-order rate law, indicating the catalyst maintained an identical coordination environment through ~100% conversion. Importantly, the catalyst was shown to have the same activity, on a per Ti basis, regardless of the synthesized surface density of Ti, justifying the authors' claim of a single-site material. To the authors' knowledge, this represents the only example of a proven single-site oxide catalyst formed from covalent grafting. Indeed, in an elegant paper, Nicholas, Ahn, and Marks[22] showed that when zirconocenium species are deposited on strongly Brønsted acidic surfaces to yield "cationlike" species electrostatically coordinated to the surface, nearly 100% of the metal centers are active, but when they are covalently bound to the surface as on silica, a far smaller percentage is active. Many Lewis acid and redox supported oxide catalysts, even those prepared from bulky precursors, also show a dependence of activity with either

catalyst site density[26, 42, 47] or with time on stream[24] due to eventual interactions with neighboring sites or alcohol poisons, both of which increase the electron density at the metal and decrease the activity. Tethered catalysts are also often not single site, and materials syntheses to physically isolate sites, such as those introduced by McKittrick, et al.[50] are a requirement for single-site-type behavior.

An important aspect of the large calixarene is that it is macrocyclic and multidentate, and therefore it is not lost during catalytic turnover and able to maintain coordinative unsaturation throughout the lifetime of the catalyst. It has been shown that these catalysts act as individual molecular entities reliant on both the ligand and the surface for their activity. Their straightforward method of synthesis should allow researchers to exploit the large diversity of molecular ligands of this type[51] and existing knowledge about the influence of the support in order to create optimized heterogeneous catalysts. One possible direction here is the synthesis of different electron-withdrawing environments on the calixarene in order to rigorously demonstrate that changing the electronic environment of the complex alters the catalytic properties on heterogeneous catalysts, as discussed previously in regards to Figure 6. Steric restrictions can also be incorporated by judicious choice of calixarene in order to control catalytic reactant or product shape and, potentially, enantioselectivity.

Conclusion

Much of the inspiration for incorporating cooperativity between surface and active site in hybrid organic–inorganic heterogeneous catalysts comes from proficient biological catalysts, which are known to achieve high activity and selectivity by exquisitely tuning their active site inner- and outer-sphere environments. Guided by this general principle, we review the synthesis of hybrid organic–inorganic heterogeneous catalysts consisting of a synergistic interaction between active site and surface, and demonstrations of dramatic enhancements in catalyst activity and selectivity in these systems. The examples highlighted in this Concept article demonstrate how new catalytic structures that employ surface acidity functioning in concert with organic and organometallic active sites can be synthesized for enhanced multifunctional catalysis. Often the underlying responsible effects in these systems have no direct counterpart in homogeneous catalysis, because of the unique role played by the surface as acidic macroscopic ligand and the lack of competition from translational entropy when forming interactions between immobilized species. These phenomena may be used for creating new catalytic centers and properties, such as acid–base bifunctional catalyst **3** that follows a mechanism similar to that observed in enzymatic primary amine catalysts. These phenomena also enable the synthesis of the C_2 symmetric vanadium complexes in **12B**. If uncontrolled, surface organometallic species can form inactive agglomerates, but with the proper attention to synthetic control, the nominal pla-

narity and macroscopic rigidity of a surface can be used for stabilizing coordinatively unsaturated species that may not otherwise exist or be catalytically active in solution. Such species can be stabilized by multidendate grafting to SiO_2 or by simultaneous coordination of a multidendate ligand and the surface, as in structure **13B** in Figure 7. The importance of multidendate ligands is also highlighted for this purpose, because of their ability to remain coordinated to the metal center under conditions of ligand exchange, thus allowing for steric and electronic control throughout the heterogeneous catalytic cycle through an inner-sphere approach. It is anticipated that use of functional, multidendate ligands coupled with principles of surface organometallic chemistry will continue to provide new routes by which the selectivity of homogeneous organometallic and biological catalysts will be successfully incorporated into highly active and robust synthetic heterogeneous catalysts.

Acknowledgements

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