# Molecular recognition in homogeneous transition metal catalysis: a biomimetic strategy for high selectivity

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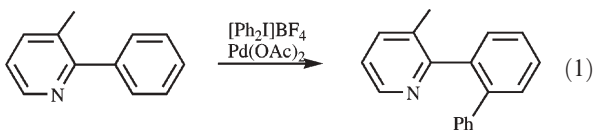
***Received (in Cambridge, UK) 6th July 2007, Accepted 31st August 2007***
***First published as an Advance Article on the web 14th September 2007***
**DOI: 10.1039/b710355g**

Traditional methods for selectivity control in homogeneous transition metal catalysis either employ steric effects in a binding pocket or chelate control. In a supramolecular strategy, encapsulation of the substrate can provide useful shape and size selectivity. A fully developed molecular recognition strategy involving hydrogen bonding or solvophobic forces has given almost completely regioselective functionalization of remote, unactivated C–H bonds.

## Introduction

A satisfactory level of selectivity, one of the most important goals in homogeneous catalysis, can be hard to obtain but can sometimes be achieved in a catalytic reaction thanks to the intrinsic nature of the chemistry. Much more often, the intrinsic selectivity pattern is not fully satisfactory and needs to be improved or modified. Traditionally this is done by changing the metal or tuning the ligands. More bulky ligands naturally tend to steer reaction to the less hindered sites in the substrate. More recently, chelate control has proved valuable in steering reaction to sites adjacent to a preexisting binding site, as in recent work by Sanford and co-workers (eqn (1)).[1] Steering reactivity to intrinsically low reactivity sites remote from existing functionality is a particularly hard challenge. Enzymes can carry out such reactions, however, and a currently emerging biomimetic approach seeks to adapt their strategy to synthetic catalysts.

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## A biomimetic strategy

Enzymes use molecular recognition to orient the substrate in the active site, leading to essentially complete control of the subsequent reaction. The substrate now reacts, not at the intrinsically most reactive site, but at the site that is held adjacent to the reactive center, often a metal ion or cluster. This is achieved by a combination of hydrogen bonding, aromatic stacking, ion pairing and, to some extent, shape selectivity. In so doing, the enzyme controls the environment near the active site to a much greater degree than is possible with conventional synthetic catalysts, bounded as they are by a randomly oriented, dynamic solvent sphere.

The term 'molecular recognition' is usually limited to cases where a number of attractive non-covalent interactions

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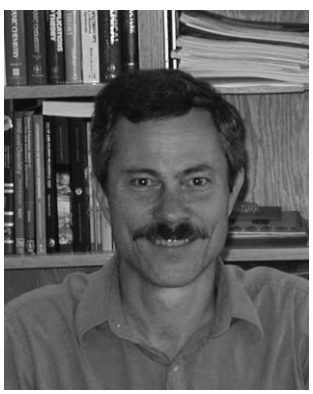

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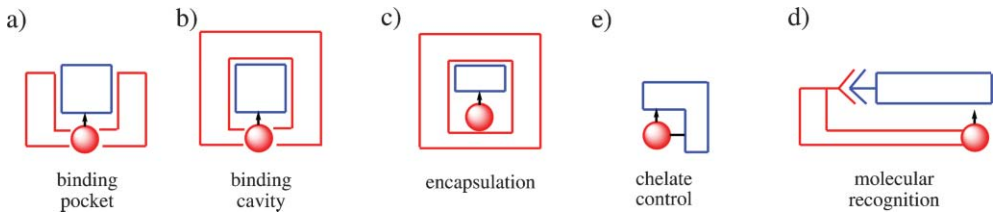



**Fig. 1** Strategies for modifying selectivity in catalysis. Blue represents the substrate, red the catalyst with a sphere for the metal, black the metal–ligand bond and the black arrow represents the attack of the metal on the substrate. A binding pocket is a standard approach, creating a cavity begins to employ supramolecular ideas, and the full molecular recognition strategy employs attractive supramolecular forces to align the substrate. Chelate control allows attack adjacent to a preexisting binding site as in eqn (1). The red V represents the molecular recognition binding site on the ligand and the blue V represents the molecular recognition group on the substrate.

cooperate to achieve selective binding of a substrate molecule. Early work in molecular recognition aimed to characterize adduct formation between host and guest. More recently, organic molecules capable of hydrogen bonding, such as oligopeptides, have shown organocatalytic applications.[2] Still relatively rare are applications where a molecular recognition function is used to orient the substrate to obtain high selectivity in transition metal homogeneous catalysis.

In the predominant and traditional literature strategy for improving selectivity in synthetic catalysts, steric forces define a binding pocket to promote substrate binding in a desired manner, leading to the desired selectivity (Fig. 1(a)). Other such systems operate by site isolation, with a bulky ligand set inhibiting deleterious bimolecular association of catalyst sites. Such is the case for the celebrated picket fence porphyrins in which bulky columnar substituents were erected on one side of the porphyrin plane, the reactive side, and the other was blocked with a bulky axial ligand.[3] Building on this idea, a partially closed cavity can be constructed that limits both the manner of substrate binding and the size or shape of the substrate allowed access to the active site (Fig. 1(b)). The cavity can also contain both an independent catalyst and the substrate (Fig. 1(c)). This fully enters into the spirit of supramolecular chemistry, but all these strategies predominantly employ repulsive steric interactions in distinct contrast to the attractive forces such as hydrogen bonding, aromatic stacking or ionic forces that are more usually associated with molecular recognition. Coordination forces, often included among molecular recognition strategies, are dominant in chelate control (Fig. 1(d) and eqn (1)). The metal first binds to a site on the substrate, such as the pyridine nitrogen in eqn (1), and then causes reaction at an adjacent site, driven by the chelate effect. Although a powerful strategy, this only allows reaction at sites directly adjacent to the binding site, such as in eqn (1). In the most fully developed molecular recognition strategy, attractive forces such as aromatic stacking or hydrogen bonding are used to align the substrate (Fig. 1(e)). In this way, a bimolecular interaction of substrate with catalyst is converted to an effectively intramolecular process involving the bound substrate. In this it resembles the chelate strategy but with the difference that reaction can now occur at a site remote from the molecular recognition group and variation of the length of the linker can in principle allow adjustment of the point of attack. It is this last strategy that has attracted our own attention.[4,5]

## Design factors

In spite of the long independent development of both molecular recognition and transition metal homogeneous catalysis over several decades, successful examples of their use in combination are still very rare. This suggests that there are non-trivial problems in applying molecular recognition to this type of catalysis. Before we can design successful molecular recognition catalysts, we may need to consider what factors could be at work that might cause failure and try to devise effective counter-strategies from the outset. Although failures are not normally reported, as indeed has been the case of one of the present authors (R. H. C.), and reasons for failure are hard to determine with certainty, advance would be facilitated if even negative results were made available for study.

When a substrate binds at the active site of an enzyme, the active site is automatically blocked for unselective reaction with any other unbound molecule of substrate. Such is no longer necessarily the case in synthetic catalysts if the molecular recognition group is not fully occupied by the substrate, in which case blocking of the sort discussed may not be efficient. In that case the active site would be left unprotected by substrate for some fraction of the time, so that an unrecognized substrate molecule could now react unselectively (Fig. 2(a)). This means the molecular recognition cannot be too weak or selectivity may fall off. A similar problem could also arise if the substrate was too sterically undemanding or too flexible or held in too flexible a way so that it did not effectively exclude unrecognized substrate molecules, which could contribute to an undesired unselective background reaction (Fig. 2(b)). A relatively bulky, rigid substrate may therefore be preferred in molecular recognition catalysis. In addition a recognition binding motif such as –COOH···HOOC– or –$CONH_2$···$H_2NOC$–may be favorable in that the two-point pairing imparts no extra degrees of freedom to the groups R and R′ (see Fig. 3), somewhat analogous to the situation in an alkyne R–C≡C–R′. Excessive flexibility is thus restricted. We also need rapid reversibility of substrate and product recognition binding for fast turnover. Simple hydrogen bonded adducts show ps lifetimes so this criterion is certainly met.[6] Should recognition binding be too strong, however, catalyst turnover would be slowed if product decoordination became turnover-limiting.

Any molecular recognition binding partner, at least the proton acceptor partner, is in principle a ligand for a transition metal. Another potential problem is therefore that the affinity

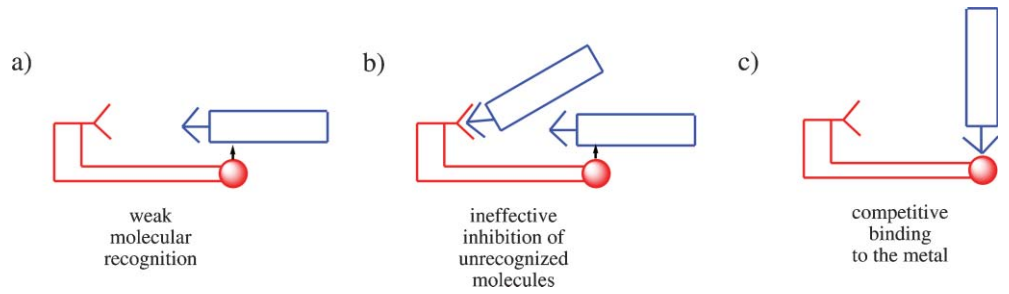



**Fig. 2** Potential problems: (a) weak recognition; (b) ineffective inhibition of unrecognized substrate molecules; (c) substrate binding to the active site. The red V represents the molecular recognition binding site on the ligand and the blue V represents the molecular recognition group on the substrate.

of the metal for the proton acceptor partner, for example a carboxylate, may be such that the carboxylate prefers to bind to the metal than to the molecular recognition binding site on the ligand (Fig. 2(c)). Direct binding is likely to shut down the metal site for the desired reaction. This is another reason for preferring a two-point (or higher) molecular recognition binding motif, such as –COOH···HOOC– or –$CONH_2$···$H_2NOC$–, where the affinity of the recognition binding site on the ligand is enhanced over single-point binding. The binding preferences of the two sites involved must therefore be considered together to ensure full compatibility.

Molecular recognition binding is expected to strongly restrain the motional behavior of the substrate relative to the active site. Any such profound alteration of the dynamics versus the situation of the standard non-recognition catalyst in solution could easily cause one or more steps of the catalytic reaction to fail, since each step is expected to have well-defined stereoelectronic preferences, possibly quite different from each other and possibly all inconsistent with the recognition binding mode. In designing such a catalyst one must therefore take into account the probable nature of the transition state (*ts*) or states. Ideally, analysis of the data from such catalysts could help throw light on the nature of the transition state, so even failures could again have their importance. Fig. 4 shows how the binding of the substrate to the catalyst in the *ts* might be affected if the substrate binding mode is not well adapted to the *ts* structure. For example, if the molecular recognition binding has to stretch and weaken in order to allow the substrate to adopt the required orientation to meet the stereoelectronic requirements of the reaction transition state, this will translate as a relative destabilization of the *ts* for the bound form of the catalyst with an effective increase of the reaction barrier (Fig. 4(a)). Much more desirable is a situation where the molecular recognition binding matches the transition state requirements and no rate change occurs between non-recognition and recognition catalysts (Fig. 4(b)). This consideration suggests that single step reactions such as epoxidation may be easier to bring under control by molecular recognition than multistep processes such as hydroformylation, where numerous steps must each be favored for overall success. It also suggests that the substrate should be held in a manner that allows it to closely adapt itself to the *ts* structure. This is analogous to the near attack conformation (NAC), a concept proposed for enzymes in which the role of the protein is likewise to hold the substrate in a conformation close to the *ts* structure.[7]

Not only must the recognition hold the substrate in a NAC, but the catalyst–substrate adduct also requires appropriate dynamics to allow the system to cross the transition state zone, requiring relative motion of substrate and catalyst units. Enzyme action is increasingly understood in terms of dynamics, the system having internal motions that encourage reaction.[8] This suggests that success in catalysis may requires some degree of flexibility of the molecular recognition unit or

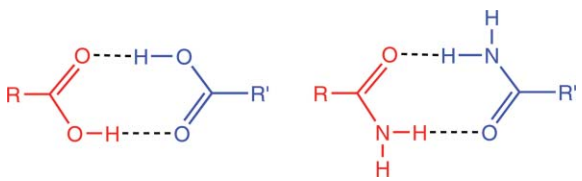



**Fig. 3** The –COOH···HOOC– or –$CONH_2$···$H_2NOC$– binding motifs impart no additional degrees of freedom to the attached groups R and R′ because rotation of the binding motif around the R···R′ axis has no effect on the relative position of R and R′.

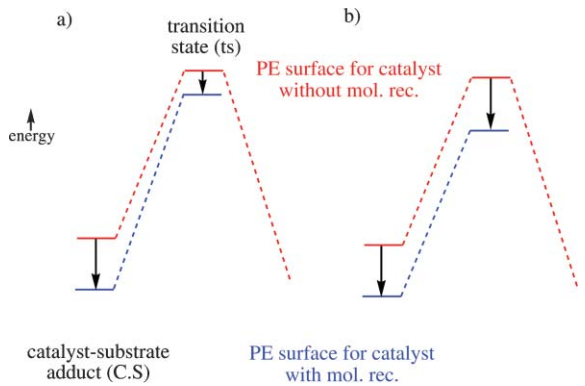



**Fig. 4** The effect of an unfavorable binding mode on the barrier. (a) The molecular recognition system (blue) has to stretch to reach the *ts* conformation, weakening the additional stabilization (black arrow) imparted by molecular recognition binding and raising the barrier relative to the non-recognition standard catalyst (red). (b) The molecular recognition system matches the *ts* conformation, maintaining the additional stabilization (black arrow) imparted by molecular recognition binding and keeping the barrier unchanged or even lowered relative to the non-recognition standard catalyst.

in the substrate itself. Each reaction is likely to have different stereoelectronic requirements leading to different flexibility requirements in the molecular recognition function. These design features will be very challenging to incorporate successfully into synthetic catalysts.

Since each design requirement tends to impose additional restraints on the types of strategies used, it may not be so surprising that synthetic analogues are so rare. The suggestion that an intermediate level of recognition binding strength and of linker and substrate flexibility is required raises the question as to where in the range is optimal and how narrow is the viable range. This will have to be settled by experiment.

As the sophistication of the design increases, the generality of the catalyst may tend to decrease. Just as many enzymes tend to be limited to one substrate or closely related set of substrates, so a more elaborate catalyst recognition architecture may tend to be more limited in substrate scope. Indeed, in early development work, a more efficient research strategy may be to look for a substrate that fits the site, rather than try to design a site for a specific substrate. This is not optimal for target oriented work, as in medicinal chemistry.

Other new strategies in homogeneous catalysis that rely on supramolecular chemistry are not covered here but have recently been reviewed. These include the supramolecular anchoring of catalysts to supports and the formation of new ligands by the selective supramolecular assembly of rationally designed building blocks[9] and molecular recognition effects in organocatalysis.[10]

## Steric forces in catalysis

Although steric forces are indeed non-covalent interactions, they are considered part of a traditional strategy for enhancing selectivity in transition metal catalysis, not as examples of molecular recognition. This is probably because they were recognized very early historically and also because they are repulsive, not attractive in nature. They have nevertheless proved extremely powerful and deserve mention. Numerous catalysts are markedly improved by bulky ligands, for example bulky phosphites in alkene hydrocyanation or bulky phosphines in Buchwald–Hartwig coupling.[11] Perhaps the most dramatic example of the use of steric effects to enhance selectivity is in asymmetric catalysis, dating from the 1970s-era work of Knowles[12] with dipamp and of Kagan[13] with diop asymmetric phosphines on rhodium for asymmetric hydrogenation of amino acid precursors. The developments in this area have been so extensive that whole books have been devoted to them and this article is not the place to review these results.[14]

## Shape selectivity *via* bulky ligands and designed cavities

A more sophisticated use of steric effects in the form of shape selectivity[15] does have a place within the usual definition of supramolecular chemistry. This normally involves construction of a cavity that allows access to the active site only of molecules below a certain size or of a specific shape. Enzymes use shape selectivity as part of a broader mix of effects, but it is rarely if ever the dominant factor. Even in cases where selectivity was originally believed to be dependent on the size of a binding pocket, doubt has been cast by further work. Chymotrypsin's specificity for large hydrophobic residues was believed to be related to the size of the hydrophobic S1 binding pocket formed by residues 189–195, 214–220 and 225–228. Mutational studies on the S1 binding pocket has shown a much more complex behavior, not simply interpretable as a shape selectivity effect.[16] In contrast, shape selective catalysts are much more common in the chemical literature, as in the classic case of zeolites, rigid aluminosilicate materials with well-defined pores and cavities.[17] The difference between synthetic catalysts and enzymes may possibly result from the very great degree of rigidity of a suitably-constructed chemical system such as a zeolite, compared with the more mobile nature of an enzyme, where dynamics of the whole structure seems to be involved in catalysis.[18] If a zeolite, as a crystal lattice held together by covalent bonds, can be considered as very rigid, an enzyme, a structure held together by weaker interactions, must be considered as much less rigid. A cavity is likely to be much more rigidly maintained in a zeolite than an enzyme. The flexibility of the binding pocket in typical synthetic catalysts is probably intermediate between the zeolite and enzyme cases. It is not yet clear how far shape selectivity *via* designed cavities contributes to enzyme selectivity and thus can usefully be considered as an unambiguously biomimetic characteristic.

Perhaps the earliest transition metal example of a designed cavity was Collman's[19] 'picket fence' porphyrin that allowed reversible $O_2$ binding to Fe(II) in the protected pocket of the structure but prevented bimolecular decomposition reactions to give the otherwise ubiquitous Fe(III)–O–Fe(III) dinuclear oxo complex that is a thermodynamic dead-end sink in this system if steric protection is omitted. This operates as much on the authentically biomimetic principle of site isolation as it does on shape selectivity, however.

Moving to true catalysis, Suslick's[20] early alkane hydroxylation by bulky metalloporphyrin catalysts relies upon steric forces within a designed cavity for its shape selective effect. This is achieved with bulky tetrakis(2′,4′,6′-triphenylphenyl) substituents at the meso positions of a manganese porphyrin. Linear alkane substrates showed an unusually high tendency for hydroxylation at the terminal position versus the sterically unconstrained tetraphenyl porphyrin control case. For example, with PhIO as primary oxidant, the bulky porphyrin gave 21, 48, 16 and 15% yield of 1-, 2-, 3- and 4-octanols from *n*-octane, compared with 2, 31, 32 and 28% for the unconstrained Mn(TPP)(OAc) case. In later work,[21] the shape selective catalyst concept was extended by using a MnTPP unit as the core of a dendrimer, with the result that the selectivity, this time for epoxidation, is greatly improved relative to the situation of unconstrained MnTPP in solution.

Porphyrins with chiral buttresses and Fe(III) as central metal have been used as selective catalysts. Groves and Myers[22] used a pivalamido picket fence porphyrin for achiral epoxidations. The related α,β,α,β-porphyrin gave epoxidation in moderate yields (*ca.* 60%) but with low ee's (*ca.* 10%). Other atropisomers gave only racemic products. More recent improvements have led to ee's of up to 75%.[23] Collman

*et al.*[24] used binapthyl bridges in an α,α,β,β arrangement (Fig. 5) and obtained greatly enhanced turnovers and ees.

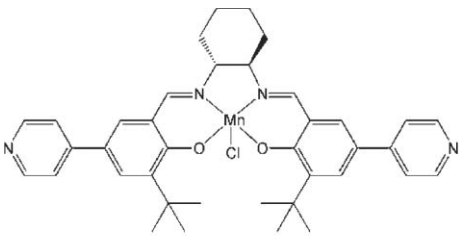
A celebrated example of shape selectivity is seen for zeolite catalysis, where the cavity and exit channel size can be tuned to favor desired pathways. One of the best examples of shape selectivity is the methanol-to-gasoline conversion on the ZSM-5 zeolite. The acid site of the ZSM-5 protonates the methanol and leads to a $CH_2$ equivalent species that oligomerizes, constrained by the pore cavity size, to form gasoline range hydrocarbons.[25] Zeolites have been very widely employed in this type of role with transition metal catalysts in the pores.[26] While of the highest practical importance, this field is usually considered under heterogeneous catalysis.[27]

Placing the catalytic site in a dendrimer environment[28] can induce changes in substrate-, regio- and enantioselectivity, often at the price of lower reaction rates. For example, Pd(II) bis-phosphine complexes showed much higher selectivity for the partial reduction of cyclopentadiene to cyclopentene in a dendrimer environment,[29] possibly because of the slower overall reaction rate. Generally, convenience of reuse is as important an advantage of dendrimer catalysts as any useful change in selectivity.

Porphyrins have been successfully incorporated into microporous solids using strong coordination forces that resist the collapse of the structure that is usually attendant on loss of solvent guest molecules originally present. For example, a non-interpenetrating framework solid, PIZA-1, was made up of ruffled cobalt(III) tetra(*p*-carboxyphenyl)porphyrins coordinated in three dimensions to linear trinuclear cobalt(II) clusters. In catalytic applications of related PIZA frameworks, however, the expected shape selectivity was not apparent because the reaction was mainly confined to the surface of the material.[30]

Iglesia and co-workers have shown how Mn(II) cations within ZSM zeolites catalyze $^t$BuOOH oxidation of *n*-hexane with increased selectivity for attack at the terminal methyl group. Selectivity was highest for Mn within the 10-membered ring channel of ZSM-5 than in other cases.[31]

Metal–organic coordination networks (MOCNs) have shown promise in catalysis.[32] Yaghi and co-workers[33] showed how to design porous solids with controlled pore size and chemical functionality using bifunctional ligands such as 4,4′-bipyridyl as connector rods between metal ion centers. Such materials have been successfully employed for Lewis acid catalysis. A Cd(II) network with 4,4′-bipyridyl as the 'connector rod' gave shape selective cyanosilylation of aldehydes. Bulky 9-anthraldehyde was essentially unreactive while 2-naphthaldehyde gave high yields.[34] A Ti(IV)-framework linked by anthracene-bis-resorcinol 'rods' (**1**) catalyzed the acrolein-1,3-cyclohexadiene Diels–Alder reaction with almost complete selectivity for the *endo* product.[35] Hupp's microporous metal–organic framework material (Fig. 6), $Zn_2(bpdc)_2L{\cdot}10DMF{\cdot}8H_2O$, formed *via* solvothermal synthesis from chiral (salen)Mn rods (L) cross-linked with biphenyl dicarboxylates (bpdc) is an effective asymmetric catalyst for olefin epoxidation. With 2,2-dimethyl-2*H*-chromene as substrate, ee's of 80–90% were obtained. Confinement of the

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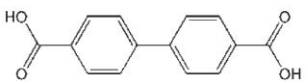



**$H_2$bpdc**

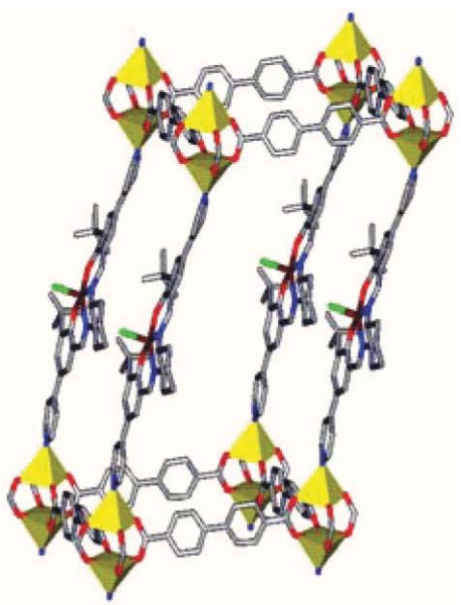


**Fig. 6** Hupp's metal–organic framework material incorporating a Mn-salen catalyst equipped with pyridine groups to convert it into a connector 'rod' between zinc-based corner units (yellow) cross-linked with biphenyl dicarboxylates. [Reproduced from ref. 36 with the kind permission of the Royal Society of Chemistry]

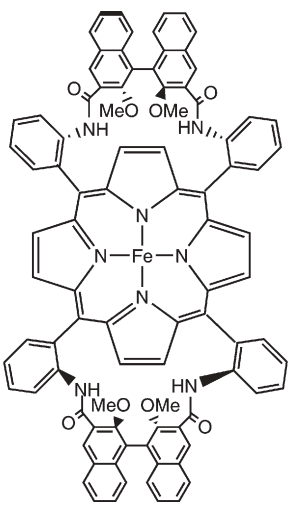
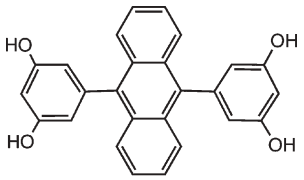



**Fig. 5** Collman's asymmetric iron porphyrin catalyst.

manganese complex enhances catalyst stability, imparts substrate size selectivity, and permits catalyst separation and reuse.[36]

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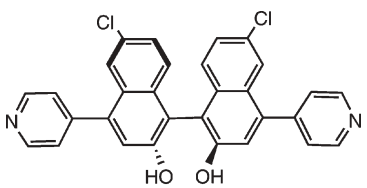
Thomas *et al*. have investigated aluminophosphates (AlPOs), microporous solids consisting of three-dimensional networks of corner-sharing $AlO_4$ and $PO_4$ tetrahedra. Metal ions such as Mn(III) Co(III) or Fe(III) can be incorporated substitutionally in the framework. As an example of a significant selectivity pattern achieved in this way, a Co(III)AlPO-18 material with two framework Co(III) ions separated by *ca*. 7–8 Å, gives double terminal C–H activation, converting *n*-hexane to hexane-1,6-diol, 1,6-dial and ultimately, adipic acid in air.[37] In other work, Johnson and Thomas have shown how a homochiral bis(diphenylphosphino) ferrocene palladium complex shows higher ee in asymmetric Tsuji–Trost allylic amination when confined in a mesoporous silica.[38] Another microporous material, titanosilicalite TS-1, catalyses the $H_2O_2$ oxidation of the linear hydrocarbons methane through nonane to the corresponding isomeric alcohols and ketones. The selectivity imparted by the confinement in this case favors attack in mid-chain for $C_6$ to $C_9$ *n*-alkanes, probably because a hairpin (U-shaped) conformation is adopted by the alkane in the pores.[39]

Much more commonly, confinement has little or no effect on selectivity, however. Lin and co-workers have employed the rod-like linker **2** to provide a MOCN that is inherently chiral. The bipyridine units bind Cd(II) to form the MOCN lattice, then $Ti(O^iPr)_4$ can react with the chiral dihydroxy groups of the BINOL part of the linker to give a catalytic site, capable of catalyzing the nucleophilic addition of $ZnEt_2$ to a range of aromatic aldehydes with complete conversion to the alcohol product. No special confinement effects were noted, the conversion and ee values being comparable to those of the homogeneous BINOL-Ti catalyst.[40]




**2**

## Shape selectivity *via* molecular imprinting and antibody production

Pauling's proposal[41] that enzymes catalyze reactions by selective binding and stabilization of the transition states has been highly influential. It has led to a number of attempts to make catalysts by creating molecular sites that recognize transition state analogues, stable molecules with the charge and shape characteristics inferred for the transition state itself.

In molecular imprinting,[42] a polymer is first formed around a target molecule, the target is then released and the resulting material acts as a selective adsorbent of the target or its close molecular relations. If the target molecule is a transition state analogue, catalysis can result.[43] Applications to separation, sensors and catalysis are all known, but relatively few imprinted transition metal catalysts have yet been reported.[44] A palladium complex of a polymerizable phosphine, $CH_2{=}CHC_6H_4PPh_2$, was used to form a porous polymer and shown to successfully mimic its homogeneous analogue in the Suzuki coupling of an arylboronic acid and a bromoarene. Slightly higher activity and much improved recycling proved possible.[45] Related studies have also appeared.[46] Severin and co-workers immobilized a meso-tetraaryl ruthenium porphyrin with four polymerizable vinylbenzoxy groups by copolymerization with ethylene glycol dimethacrylate. The resulting polymer catalyzed alcohol oxidation with 2,6-dichloropyridine *N*-oxide as primary oxidant. Under similar conditions, the analogous homogeneous catalyst was very inefficient.[47] Reviews by Tada and Iwasawa and by Severin describe a number of related applications to asymmetric catalysis of hydrogenation, transfer hydrogenation and related reactions.[48]

Imprinting seems to be more useful in terms of ease of catalyst recycle and product isolation and sometimes enhanced activity than for altering catalyst selectivity. It also follows the logic of amorphous materials in having a heterogeneous cocktail of sites rather than being a single molecular species such as in classical homogeneous catalysts.

In a biological analogue of molecular imprinting, an antibody is elicited to a transition state analogue for a target reaction. The antibody is then often capable of catalyzing the target reaction. Reaction rates have not always proved as satisfactory as initially hoped,[49] perhaps because the molecular recognition was not sufficiently selective for the transition state. If the reactant or product states are also bound with a comparable binding constant relative to the transition state binding, then the reaction barrier will no longer be lowered. This can only happen if the *ts* is stabilized to a greater extent than the reactant or product. Once again, no transition metal antibody catalysts seem to have yet been reported, although an antibody is known that catalyzes metal insertion into *N*-methylmesoporphyrin IX by causing the porphyrin to distort into a dome shape that directs the N-donor lone pairs towards the approaching metal ion.[50]

Shape selectivity has also been employed by Bergman and Raymond with nanovessels, **4**, constructed from the catechol 'rods', **3**, linked as the catecholates in a tetrahedral fashion to four Ga(III), Al(III) or Fe(III) ions (Fig. 7). The highly negatively charged $[Ga_4L_6]^{12-}$ capsule generates a hydrophobic cavity of approximately 0.5 $nm^3$ that allows encapsulation of a variety of hydrophobic monocationic species, such as $[NMe_4]^+$ and $[NEt_4]^+$, as well as organometallic sandwich complexes, such as $[Cp_2Fe]^+$, $[Cp_2Co]^+$, and even $[CpRu(C_6H_6)]$. Initially prepared in the presence of $NMe_4Cl$ to form $[Na_4(NMe_4)_7][NMe_4Ga_4L_6]$ the cation presumably helps to stabilize the tetrahedral assembly during its formation. The $[NMe_4]^+$ cation binds reversibly to the host interior,

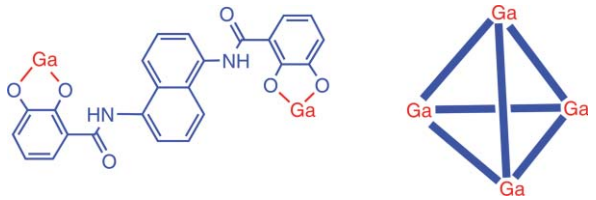



**Fig. 7** The Raymond nanovessel. Catecholate-tipped rods link four Ga(III) corner units to form a $[Ga_4L_6]^{12-}$ capsule.

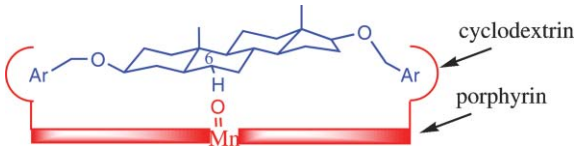
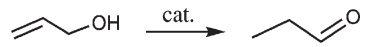


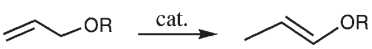

**Fig. 8** Breslow's double recognition catalyst for steroid hydroxylation in cartoon form. Tying down both ends of the steroid leads to exceptionally high selectivity.

however, and can be easily displaced by more strongly binding guests. Encapsulated iridium complexes give C–H bond activation of aldehydes within the host cavity thus controlling the ability of substrates to interact based upon size and shape. The host container acts as an organocatalyst for the sigmatropic rearrangement of enammonium cations by restricting reaction space and orienting the substrate and of orthoformate hydrolysis.[51] In the latter case, the cavity thermodynamically stabilizes the protonated substrate and thus catalyzes the hydrolysis of orthoformates, normally an acid catalyzed reaction, but now possible in basic solution. Rates followed Michaelis–Menten kinetics and were accelerated by up to 890-fold. Competitive inhibition was seen with $NPr_4^+$, and the substrate size selectivity is consistent with the constrained environment of the host.[52] This strategy goes beyond standard encapsulation ideas by including ionic forces to assist binding.

More relevant to the present discussion, the cationic catalyst precursors $[(cod)Rh(Me_2PCH_2CH_2PMe_2)]^+$ and $[(cod)Rh(PMe_3)_2]^+$ (cod = 1,5-cyclooctadiene) were encapsulated as $BF_4$ salts. Rhodium complexes that are too bulky, such as $[(cod)Rh(PEt_3)_2]^+$, fail to undergo encapsulation. After addition of $H_2$ to remove the cod and activate the catalyst, the system became active for the isomerization of allyl alcohol and its methyl ether derivative. Only substrates of the correct size and shape are able to enter the cavity and react. For example, allyl alcohol and allyl methyl ether are isomerized rapidly at room temperature (eqn (2) and (3)), but larger substrates, such as substrates with methyl branching or even allyl ethyl ether do not react at all, in contrast to the results with the unencapsulated catalyst, which reacts with all the substrates tried. This shows the high size selectivity achievable with a supramolecular catalyst.[53]




(2)




(3)

## Molecular recognition catalysis by aromatic stacking and solvophobic effects

Nonpolar aryl groups tend to bind readily to nonpolar cavities such as cyclodextrins as a result of favorable aromatic stacking interactions and exclusion of the more polar solvent that would otherwise be forced to occupy the cyclodextrin. Apart from the enthalpic term, the entropy of solvent release also favors binding. Breslow equipped a Mn porphyrin with four beta cyclodextrin groups (Fig. 8) and provided a substrate steroid with *tert*-butylphenyl groups at each extremity to make it suitable for hydrophobic binding to the cyclodextrins. The steroid was held by the recognition forces such that PhIO induced hydroxylation occurred only at C6 to give the C6-α-hydroxysteroid. Only weak catalytic turnover was reported at first (*ca.* 15 turnovers), but this was later improved to *ca.* 600.[54]

A calix[4]arene-bis-phosphite has been reported that greatly increases the selectivity for linear products in the Pd-catalyzed alkylation of 3-phenylallyl acetate with dimethyl malonate where the linear product was formed with over 98% selectivity. Similarly, in Rh-catalyzed hydroformylation of 1-octene the linear : branched ratio in the aldehyde product can be as high as 80 : 1.[55]

Calixarene modified Zn and Cu complexes have been studied in relation to metallo-phosphodiesterase mimics.[56] Binuclear sites prove optimal, as is the case for catalysis in standard catalysts.[57] Most relevant to the present discussion, flexibility of the calixarene framework (Fig. 9) was identified as an important contributor to successful catalysis by comparison with an analogue where the flexibility was restricted by covalent modification of the system. Applications to hydroformylation with Rh catalysts bearing calix[4]arene-modified phosphites have been reported. Although conversion was excellent, selectivity was not very much improved over the unmodified catalyst.[58]

Cyclodextrins have also been appended a wide variety of ligands with detectable effects on selectivity. In an iron or manganese cyclodextrin-modified porphyrin system (Fig. 10)[59] higher ee's were obtained in polar solvents, consistent with enhanced substrate binding in the hydrophobic cavity. Likewise, other cyclodextrin-modified Mo and Cu catalysts have been successfully employed in asymmetric oxidation,[60a] Pd catalysts in Wacker oxidation,[60b] and Rh catalysts in asymmetric hydrogenation.[61] Cyclodextrins have also been used to incorporate $CpMo(CO)_3CH_2CONH_2$ as a precursor to an alkene epoxidation catalyst. Although activity was similar to the solution version, recycling was facilitated.[62] Likewise, 1-decene hydroformylation proved possible with a Rh complex of tetrasulfonated 1,2-bis(diphenylphosphino)ethane but linear : branched selectivity was not improved.[63] A phosphine was modified as shown in **5** to make it fit a cyclodextrin cavity. The adduct was characterized and the palladium complex showed hydrolytic activity for water-insoluble esters in water.[64] Cyclodextrins also enhance the rates and selectivity of Fenton catalysts for substrates that bind to the cyclodextrin.[65] Fujita and co-workers[66] have reported a dicopper complex of an amine-functionalized cyclodextrin as an efficient amide hydrolysis catalyst.

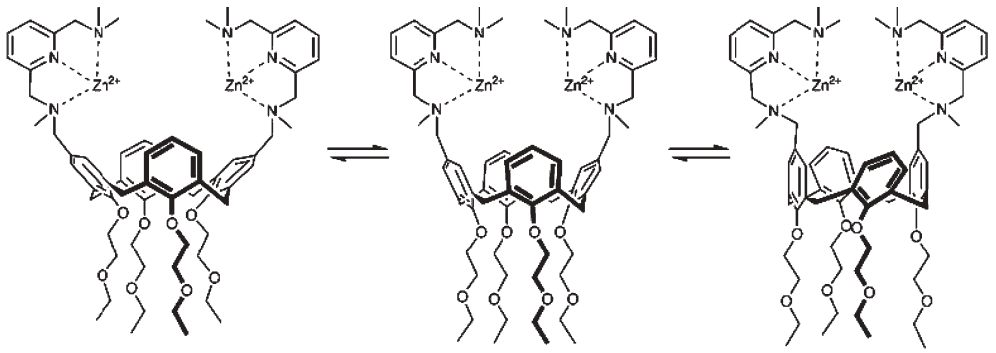
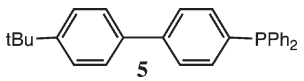


**Fig. 9** A zinc modified calixarene. The controlled flexibility of the structure is believed to be important in permitting phosphodiesterase activity.



**5**

In spite of significant successes in certain cases, the majority of cyclodextrin and calixarene modified catalysts do not deliver exceptional selectivity, perhaps because the cavity imparts too much flexibility to the substrate. In the very successful Breslow case, the substrate is tied down by two cavities, greatly reducing the flexibility.

## Molecular recognition catalysis by hydrogen bonding

Gilbertson and co-workers[67] have reported numerous examples of peptide substituted phosphines (Fig. 11 and eqn (4)) as ligands for metals such as Pd or Rh which are active for asymmetric catalysis of a variety of reactions such as hydrogenation and allylic substitution. An example showing very good ee and yield is illustrated. Not only are peptides very biomimetic in character but combinatorial methods can be used in their synthesis and selection.[68]

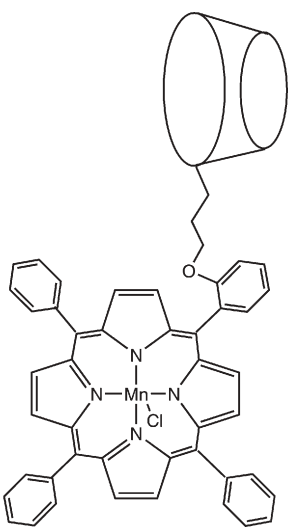


**Fig. 10** A cyclodextrin-modified porphyrin used in oxidation of α-pinene.

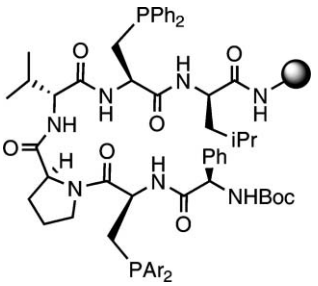
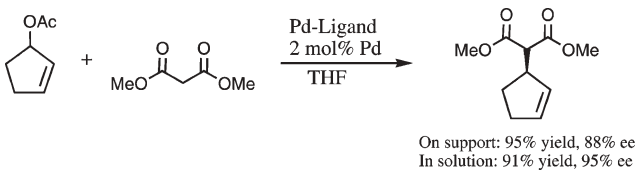


**Fig. 11** Gilbertson's oligopeptide-bis-phosphine ligand for the asymmetric allylic substitution shown in eqn (4).



On support: 95% yield, 88% ee
In solution: 91% yield, 95% ee

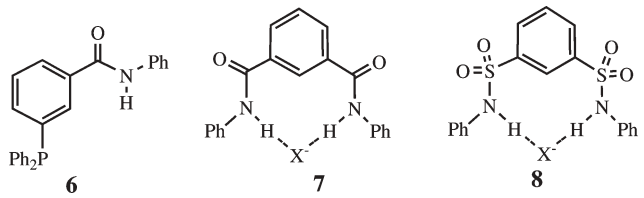
(4)

The most successful systems in asymmetric catalysis are based on a β-turn secondary structure with the phosphines at positions *i* and *i* + 3, the two intervening amino acids being proline and a D-amino acid. The peptide adopts a β-turn secondary structure and shows good selectivity in the alkylation reaction shown. In the pure organocatalytic arena, Miller *et al.* have used related β-turn structures in the development of asymmetric acylation catalysts.[69] Naturally the results are rather sensitive to solvent and conditions and there is every reason to think that hydrogen bonding by the peptide plays a key role in the asymmetric catalysis. This is clearly a powerful method, particularly for asymmetric catalysis, that will no doubt see extensive future development.

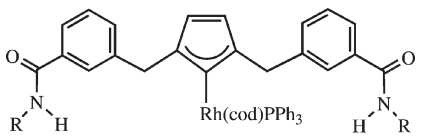
Ward and co-workers have used biotin–avidin recognition in asymmetric catalysis. A biotinylated ligand was attached to a $[Rh(diphosphine)]^+$ or $[\eta^6\text{-(arene)}RuCl(diamine)]^+$ catalyst followed by exposure to avidin. This ensures that the catalyst operates in a chiral polypeptide environment provided by the avidin (or streptavidin). In the transfer hydrogenation of acetophenones with the Ru catalyst, ee's of up to 90% were obtained.[70]

Kavallieratos and Crabtree attached amide groups to a phosphine ligand (**6**) in the hope of influencing catalyst selectivity by hydrogen bonding with substrate proton

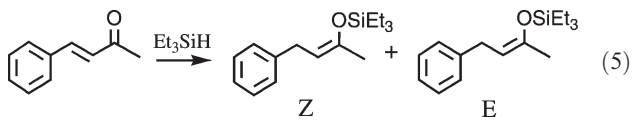
acceptor groups. In fact, no big effects were seen, but in the first series of complexes investigated, [W(CO)$_5$(**6**)], a variety of $X^-$ anions bound so strongly to the hydrogen bonding group that the focus shifted away from catalysis. The observation was put to good use in a pure molecular recognition study in which the related amides **7** and **8** were shown to be excellent 1 : 1 anion receptors. For **8**, $K_a$ values of anion binding were as high as $5.5 \times 10^4$ for $F^-$, and $2.1 \times 10^4$ for $Cl^-$.[71] The sulfonamide even showed significant organocatalytic activity for aldehyde imination,[72] and a ferrocene derivative acted as a halide sensor.[73]




Rivera and Crabtree[5] were able to obtain significant selectivity effects in rhodium catalyzed enone hydrosilylation by appending amide groups to an N-heterocyclic carbene (NHC) ligand, such as in structure **9**.




In particular, the $E$ : $Z$ ratios of the silyl enol ethers (eqn (5)) from enone hydrosilylation were greatly changed, going from 1 : 1 to 5 : 1 when $NaBF_4$ was added (1 equiv./Rh). The interpretation of the results was complicated by the salt effect, implying ion binding was again involved in determining the outcome.

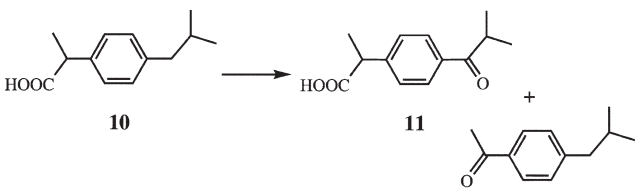



(5)

Das, Brudvig and Crabtree[4] designed a much more effective system that gave large selectivity effects. The dimanganese catalyst core involved, originally developed for its water oxidation activity,[74] also proved to be active for C–H bond hydroxylation.[75] Mechanistic work showed that no freely diffusing radicals were involved with tetrabutylammonium peroxomonosulfate (Oxone) as oxidant, in contrast to the situation with $^t$BuOOH as primary oxidant. For selective reaction by molecular recognition, it is clearly necessary to avoid such diffusing radicals, such as $^t$BuO$^\bullet$, which could escape control by the molecular recognition binding and instead diffuse to other sites on the substrate than simply the one closest to the metal active site.

The terpyridine ligand of the dimanganese catalyst was equipped with a phenylene linker and a Kemp triacid (KTA) U-turn motif to give the final structure shown in Fig. 12. This contains a free –COOH that is capable of binding to a –COOH group of the substrate to bring about selective catalysis by aligning the substrate appropriately for reaction at just one site. This is an advantage in that no functionalization or other pretreatment is necessary to prepare the substrate for the catalytic reaction.

Control reactions without molecular recognition, demonstrating the inherent selectivity of the catalyst, are compared with runs where the molecular recognition group is present. In the control catalyst, a phenyl group replaces the linker–KTA assembly of the molecular recognition catalyst. Ibuprofen (**10**) reacts with the system differently depending on the absence or presence of the molecular recognition: the benzylic $CH_2$ group remote from the substrate –COOH is oxidized to give **11** with 76% selectivity without it, but in >98% selectivity with molecular recognition (eqn (6)). When the molecular recognition site is flooded with excess acetic acid, reaction at the ibuprofen still occurs but all the recognition-induced selectivity is abolished.




(6)

Molecular models show that the reactive, remote benzylic $CH_2$ group is brought close to the metal active site by –COOH···HOOC– binding (as in Fig. 13). The unselective product, **12**, is probably formed by decarboxylation, followed by ketonization of the benzylic position.

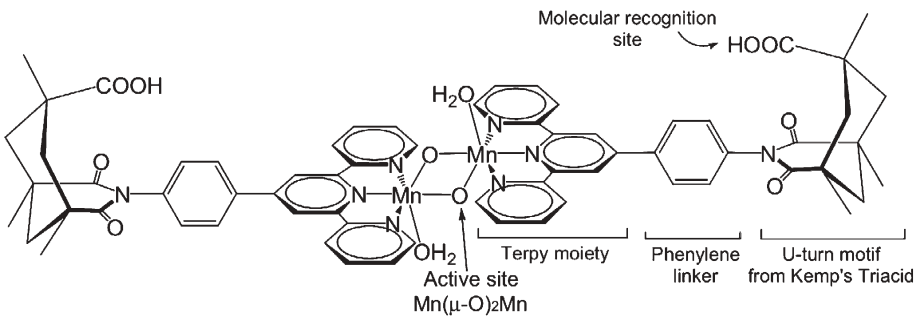



**Fig. 12** The structure of the Mn-terpyridine molecular recognition catalyst. The Mn(III,IV) dioxo unit of the complex as isolated impart a tripositive charge to the dinuclear unit shown.

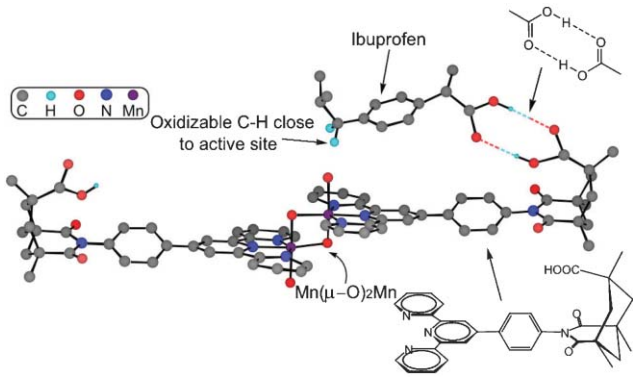



**Fig. 13** The structure with ibuprofen docked at the recognition site as predicted by importing crystallographic data for the component units into Chem-3D.

Of more interest than benzylic C–H activation is the alkyl C–H case. Methylcyclohexane acetic acid **13** (Fig. 14) was chosen in order to maintain a similar distance between the substrate C–H and –COOH groups as in **10** and to provide numerous C–H bonds where reaction could potentially occur. Once again, the control and molecular recognition catalysts were compared. In the control case, a broad mixture of products was formed, few of which could be securely identified. In the recognition case, a single material was formed to the extent of >98%. Extensive $^{1}$H and $^{13}$C NMR analysis, including NOE and *J*(H,H) measurements, together with MS data showed that this material is the tertiary alcohol, **14**. Work with the mixture of isomers of the substrate and with the pure *trans* substrate confirms that both *cis* and *trans* compounds react, the *cis* reacting slightly faster, but that they both give the same isomer, **14**, of the product. The reactive C–H is now one bond closer to the substrate –COOH than in **10** and therefore in a slightly different position relative to the metal active site. Nevertheless, the models indicate that the reactive C–H bond can still come close to the metal site.


(7)

**13** **14**

The results show that the bound substrates do indeed react in preference to unrecognized substrate molecules from the exterior, which would give an undesired and unselective background reaction. This self-inhibition effect has been fully confirmed in extensive but unpublished studies. The fact that

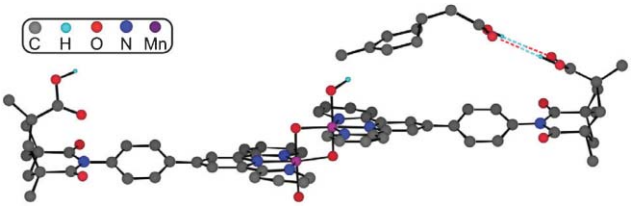
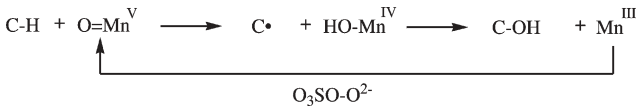



**Fig. 15** The radical intermediate expected from the rebound mechanism, docked at the recognition site with the appropriate conformation to lead to the observed product.

the recognition-bound substrate contains a $–CH_2COOH$ binding site in principle gives it the rotational freedom to bend away from the metal active site as in Fig. 2(b), yet competition from external potential substrates is not found. This may indicate that hydrophobic effects in the polar solvent (MeCN) may help keep the substrate close to the linker/ligand assembly thus protecting the active site. The alternative explanation, that the intramolecularity of the reaction within the catalyst–substrate adduct makes it so fast that it dominates, seems unlikely because the reaction rates with and without recognition are comparable.

The generally accepted rebound mechanism[76] involves a Mn(V) oxo, or more probably its spin isomer, a Mn(IV) oxyl,[77] abstracting a hydrogen atom from the reactive C–H bond to give an intermediate carbon radical. This is converted to the product alcohol by 'rebound' of the OH group from manganese. Applied to our case (eqn (8)), this suggests that the C–H bonds of both *cis* and *trans* methylcyclohexaneacetic acid isomers can approach the reactive site and lose a hydrogen atom. The resulting carbon radical (Fig. 15) is the same whether formed from *cis* or *trans* substrates. The exclusive formation of isomer **14** of the product suggests that the rebound step takes place exclusively from the side opposite the $–CH_2COOH$ group.




(8)

Hydrogen bonding, being directional, may be particularly useful in synthetic recognition catalysts, just as it is in enzymes, because the substrate can be positioned with a considerable degree of precision in this way. The multipoint binding of carboxylic acid dimers is expected to increase the precision even more. High precision is only an advantage if the overall

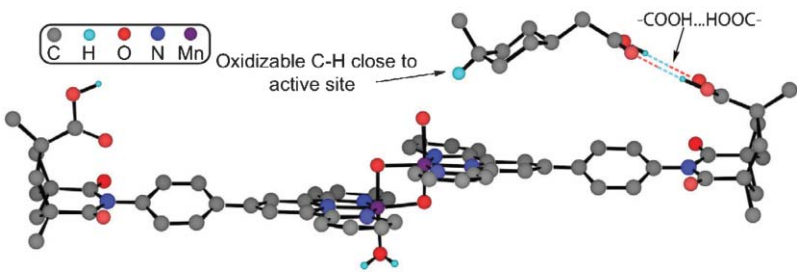



**Fig. 14** *cis*-Methylcyclohexane acetic acid docked at the recognition site, showing the approach of the remote tertiary C–H bond that reacts to the reactive oxo group (red).

design is appropriate, however: a mismatch is harder to correct if flexibility is limited. Other impressive applications of hydrogen bonding in catalysis have also been reported recently.[78]

## Conclusion

Of the methods discussed, molecular recognition *via* hydrogen bonding can give precise regioselectivity control on unmodified substrates at remote locations. Cyclodextrins and related recognition elements can also give excellent results, but greater flexibility of the recognition may degrade selectivity in most cases. Cavities such as are found in zeolites and related molecular analogues, including in molecular imprinting, can provide site isolation and shape and size selectivity. Chelate control allows precise selectivity, but only for attack close to the catalyst binding site (eqn (1)). More traditionally, formation of a binding pocket using selected ligand sets can be highly effective, particularly for asymmetric catalysis. Synthetic catalysts tend to use one particular strategy, while enzymes seem to employ a broad combination of forces.

Biomimetic strategies hold promise for application in homogeneous transition metal catalysis, but their application can be problematic. We have examined a number of possible problems that may be hindering advance and illustrated some of the current work that throws light on the area. For example, the recognized substrate molecule must be able to exclude unrecognized substrate molecules from the site to avoid an unselective background reaction. Assuming the remaining problems can be successfully resolved, the area holds great promise for the development of a generation of homogeneous catalysts having exceptional selectivity.

## Acknowledgements

We thank the NSF and DOE for support of different aspects our work in the catalyst area.

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