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From zeozymes to bio-inspired heterogeneous solids: Evolution of design strategies for sustainable catalysis

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ABSTRACT

Bio-derived transition-metal complexes containing well-defined and well-characterized active sites can be anchored, in a site-isolated fashion, on to the inner walls of porous inorganic supports, for generating highly active and selective single-site heterogeneous catalysts, which can serve as effective functional mimics of metalloenzymes. The nature of an active site in an enzyme and its ability to harness a particular catalytic function with remarkable selectivity, via its protein tertiary structure, could be judiciously transposed to zeolitic architectures with specifically engineered active sites. Throughout this article we follow the progress and evolution of engineering enzymatic activity and selectivity in synthetically designed catalysts, emphasizing the importance and the advantages of the different synthesis methodologies in immobilizing bio-inspired catalytically active single-sites on varying solid supports. The benefits of such systems are highlighted in terms of their environmental impact by reduction of waste, mitigating the generation of greenhouse gases, boosting the enantioselectivity in heterogeneously catalyzed reactions and in the utilization of 'greener' oxidants; with conclusions drawn on how specific supports affect catalytic properties via modification of the local environment of the active site. The seminal contributions of Dr. Ratnasamy in this field have paved the way for a more fundamental understanding of how the support environment, and its interactions with the active site at a molecular level, can lead to development of structure–activity relationships, which in the future can provide avenues for specifically tailoring catalytic outcomes from a mechanistic standpoint.

1. Introduction and overview

Catalytic oxidation reactions play a key role in many areas that benefit the chemical industry, ranging from the production of pharmaceuticals to large-scale commodity chemicals [1]. Oxidation catalysis is one of the most dynamic, challenging and fruitful areas of catalytic chemistry with the design of catalytically active structures and the control of their reactivity being crucial in achieving high catalytic performance with good selectivity. Research in the last few decades [1–4] has demonstrated impressive progress in terms of catalyst design for oxidation processes, which can be accredited to the increasing need to facilitate these reactions in a cleaner, more efficient manner. Especially in the manufacture of commodity chemicals, there are a large number of environmentally unacceptable features, which are magnified due to the scale of production and quantity of diverse target materials. Compounds of strategic industrial importance such as various alcohols, ketones, aldehydes, acids and phenols and a variety of epoxides and esters are synthesized in this way on the scale of many millions of tons per annum [2,3]. Other specific oxidation processes, such as the production of KA oil from cyclohexane, benzene to phenol (and its subsequent selective oxidation to catechol) and oxyfunctionalization of alkanes (e.g. methane to methanol) are among the top 10 challenges of modern chemistry [4]. A significant spectrum of these compounds consume large amounts of energy in their manufacture, involve the use of aggressive, corrosive and explosive reagents and generate copious quantities of waste. Oxidation reactions that are highly prevalent within the pharmaceutical and fine-chemical industries invariably involve numerous individual steps, which also require stoichiometric amounts of oxidants, thereby consuming large amounts of reagents. It is now evident that the next generation of catalysts must be designed with a view to mitigate the consumption of energy and materials, minimize the liberation of waste and reduce the reliance on aggressive oxidants such as $KMnO_4$, HNO_3 and $K_2Cr_2O_7$. These harsh reagents can be substituted with more sustainable and environmentally benign oxidants such as molecular oxygen and can be used in conjunction with the emerging class of new bio-inspired catalysts that can function under more practical conditions.

1.1. Green oxidations: difficulties and inspiration

Selective oxidation with benign oxidants has received much attention recently; but it is still difficult to activate molecular

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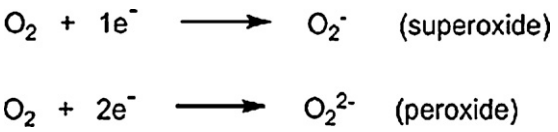
oxygen with commercially available catalysts. Reactions of O_2 with organic substrates without a catalyst are thermodynamically favorable, but kinetically extremely slow, because they are spin-forbidden and the one-electron reduction potential of O_2 is unfavorable. At the same time, natural metalloenzymes facilely execute these transformations in a single-step by simply adding one oxygen atom to the substrate molecule and; there is an increasing number of bio-transformations that are currently being carried out on an industrial scale utilizing biocatalytic processes [5]. Further to the reactions being carried out in an environmentally benign fashion, one the biggest asset of utilizing enzymes is their ability to facilitate excellent stereo-control. In many cases enzymes can achieve enantioselectivities of >99% enantiomeric excess (ee), are highly active under mild pH conditions at low-temperatures and pressures and in aqueous media. Despite these attractive benefits, enzymes have inherent drawbacks; notably a lack of substrate diversity and versatility; but more importantly on issues relating to stability and durability [6]. Enzymes also require co-substrates and co-factors which lead to increasing costs and processing complexities. These drawbacks could, in principle, be suitably addressed by exploiting the robustness and myriad array of pore architectures prevalent in structural and functional enzyme mimics, through the incorporation of well-defined transition-metal complexes containing designed organic ligands, natural amino acids or by the utilization of de-novo designed artificial proteins [7]. Furthermore, the heterogenization of a functional mimic of the active site in an enzyme not only improves stability, but aids the recovery and reusability of the catalyst and offers avenues for use in flow chemistry that can be applied in continuous processing. In practice, however, this idea is difficult to realize and attempts to understand and reproduce this unique ability of oxygenase metalloenzymes have been hindered by challenges in creating artificial systems that are highly active for the activation of molecular oxygen. It is therefore imperative to understand the nature of the active site at a molecular level and the mechanism by which substrates can be functionalized, in order to devise effective methodologies that could be implemented for designing effective functional mimics of the active sites of enzymes and further creating a rationale for subsequent immobilization. Some notable examples will now be discussed in order to illustrate the capability and diversity of natural enzymes.

2. Enzyme cataltyic potential and mechanistic viewpoints

Metalloenzymes are biocatalysts that rely on transition-metals for their catalytic activity. A metalloenzyme is usually a huge protein that contains a small, well-defined metal complex in the active site. The metal-ion is coordinated by a few amino acids from the protein scaffold that stabilizes and isolates the active metal center, as well as providing a specific binding pocket for a substrate molecule. Metal active centers possess a well-defined coordination when surrounded by the proteins' amino acids that give a precise shape to the cavity in which it is situated. Metalloenzymes that activate molecular oxygen possess great potential as catalysts for specific oxidation reactions and serve as effective models for the development of other diverse efficient biocatalysts [8]. Iron and copper ions are the most commonly occurring metal centers in biological oxidation systems and also play important roles in heterogeneous and homogeneous catalysis, mainly due to their inherent electronic properties and accessible redox potentials

Dioxygen reduction (oxidase activity) and activation for incorporation into organic substrates (oxygenase activity) are catalyzed by iron heme enzymes, non-heme iron and copper enzymes [9]. Oxidases catalyze one-, two- or four-electron oxidation of the substrate molecule to two- or four-electron reduction of dioxygen to



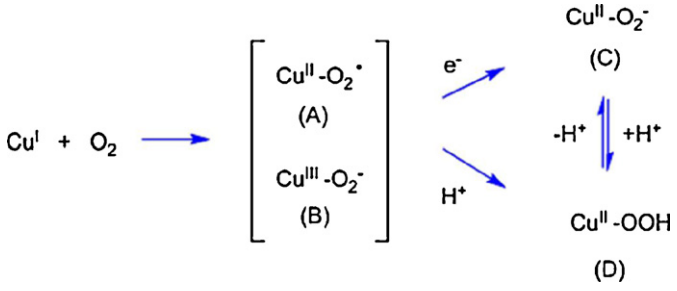
Scheme 1. Reductive activation of O_2 to superoxide and peroxide.

hydroperoxide or water. Oxygenases can incorporate either one (monooxygenases) or two (dioxygenases) atoms of oxygen into organic substrates. In monooxygenase systems, the oxygen atom that is not incorporated is reduced to water by additional two-electron reductants or by the substrate itself. Transition-metal ions, particularly Fe and Cu, are ideal catalysts for oxidation reactions involving molecular oxygen, as they readily react with O_2 to afford metal-containing active oxidants, such as iron-superoxo (Fe^{III}—O_2^-), iron-peroxo (Fe^{III}—O_2^{2-}), iron-oxo (Fe^{IV}=O and Fe^{V}=O) and copper superoxo (Cu^{II}—O_2) or copper peroxo [$(Cu^{II})_2O_2$] species. Mechanistic pathways of O_2 activation by metalloenzymes are determined by the electronic and geometric properties of the metal-ion and by the environment of the surrounding protein [10].

The direct oxidation of organic substrates by O_2 is challenging due to high energy barrier for electron transfer from the organic substrate to the oxidant. For molecular oxygen, this high energy barrier is nature's way of protecting organic compounds from destructive oxidation. Dioxygen in its ground state is a spin-polarized triplet and, as such, is inert toward substrate oxidation; whereas the singlet or doublet (radical) states are far more reactive. Metal catalysts promote spin-forbidden transitions from the triplet to singlet or doublet state. Dioxygen is activated from its abundant triplet ground state to reactive singlet or doublet (radical) species by oxidase and oxygenase metalloenzymes. In biological systems, O_2 is reductively activated and the dioxygen moiety undergoes a partial reduction toward a superoxide or a peroxide (Scheme 1). The source of the activating electrons can involve a transition-metal located within the active site of the metalloenzyme, organic cofactor (e.g. flavin, pterin), second redox-active metal or organic substrate itself.

The mechanism of O_2 activation by iron-containing enzymes (Fig. 1) involves the initial formation of Fe^{II}—O_2 species that can be converted to end-on hydroperoxide Fe^{III}—OOH, which can undergo heterolytic cleavage that results in high-valent Fe^{V}=O species formation. The O—O bond could also be cleaved homolytically affording the lower oxidized Fe^{IV}=O intermediate. These intermediates are key active species employed in iron-catalyzed oxidation chemistry [11,12].

The reaction between the reduced form of Cu^{I} and O_2 coupled with either the addition of an electron or protonation can result in active intermediates, such as copper^{II}-peroxo and copper^{II}-hydroperoxo species (Scheme 2). A Cu^{II}-hydroperoxo species was suggested to be the key reactive intermediate in enzymatic copper-based oxidation reactions, although recent studies indicate that



Scheme 2. Dioxygen activation at mononuclear copper active centres in metalloenzymes.

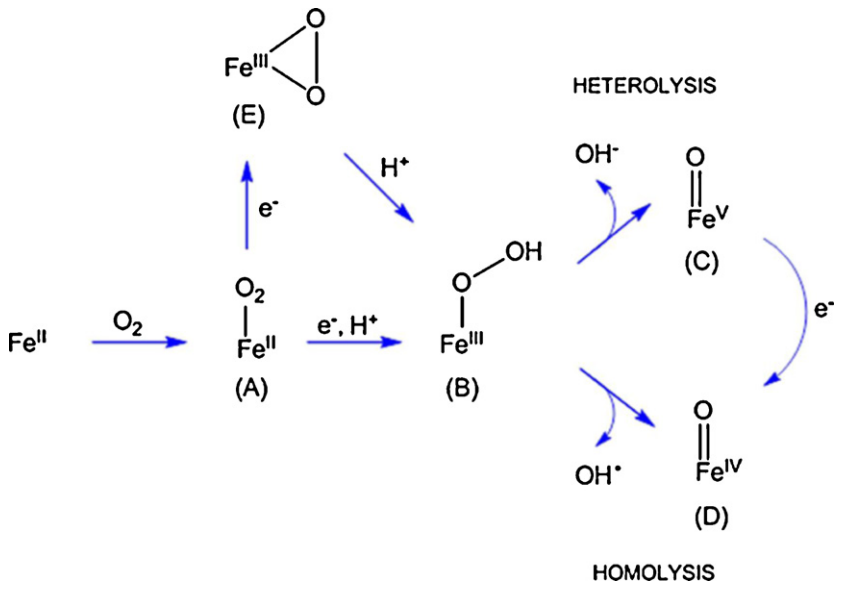


Fig. 1. Proposed mechanistic pathways in oxidation reactions catalyzed by iron-containing metalloenzymes.

Cu^{II}-superoxo species are more likely to be the reactive oxidant for the C—H bond activation of the organic substrates [13]. In binuclear copper enzymes like tyrosinase, the oxygen intermediate is fundamentally different from the high-valent iron-oxo species (Fig. 2). In oxy-tyrosinase, the active species is the side-on μ–η^2:η^2-peroxo complex that has an extremely weak O—O bond, which is cleaved and one oxygen atom is transferred to the substrate molecule and the second oxygen atom is used to produce water.

Metalloenzymes containing iron active sites comprise a large group of dioxygen-activating enzymes that possess the capability for functionalizing a wide-range of organic substrates with high efficiency and selectivity. Iron containing enzymes can be classified depending on the structure of the active site as heme enzymes (Cytochrome P450), mononuclear non-heme enzymes (Rieske dioxygenase, Bleomycin, Intradiol dioxygenase and Lipoxygenase) and dinuclear non-heme enzymes (Methane monooxygenase) [14].

Cytochromes P450 (heme enzyme) constitute a large family of cysteine thiolate-ligated heme monooxygenase enzymes that are present in all forms of life and play a key role in the transfer of an oxygen atom from dioxygen into a wide variety of biological substrates, with the second oxygen atom being reduced by two electrons to a water molecule. P450 are called monooxygenases as they insert only one of the two oxygen atoms present in O_2 into the substrate and play critical roles in the biological hydroxylation of saturated carbon–hydrogen bonds, epoxidation of double bonds, oxidation of heteroatoms (N-, O-, S-oxidation), aromatization and dealkylation reactions. Heme forms the active site of many proteins that fulfill a diverse range of biological functions,

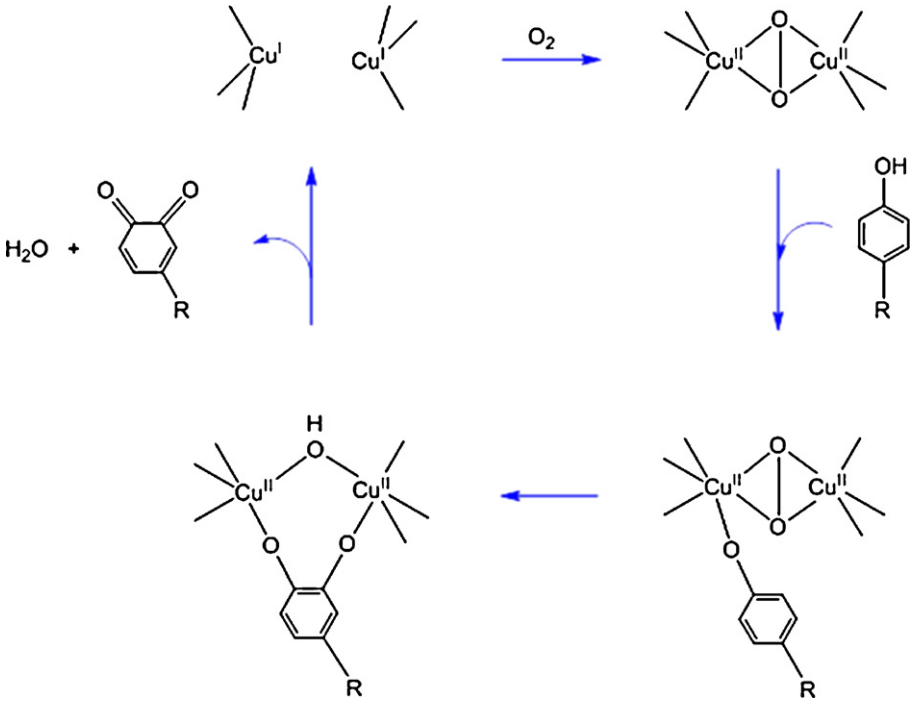


Fig. 2. Dioxygen activation at coupled binuclear copper active sites in the enzyme tyrosinase.

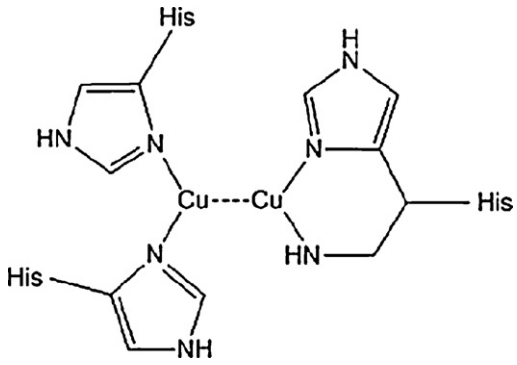
including metabolic oxidation reactions and the transportation of gases, such as oxygen. The iron atom acts as a source or sink of electrons for redox reactions, and it is the binding site for dioxygen. In some enzymes, the porphyrin ring also acts as an electron source [15].

Mononuclear non-heme iron enzymes comprise of a large collection of dioxygen activating enzymes that are very different from their heme counterparts, due to electronic and geometric differences arising from the ligand environment. Non-heme metalloenzymes overcome the barriers involved in dioxygen reactions by substrate activation (oxidized metal center induces radical character), or dioxygen activation (reduced metal site through two-electron reduction) [16] (Fig. 3). Non-heme iron enzymes catalyze oxidative transformations either by involving high-spin ferrous (Fe^{II}) ions or by the utilization of high-spin ferric (Fe^{III}) active centers, both having different modes of activation (dioxygen and substrate activation respectively). The Fe^{III} site is usually utilized to activate substrates for reactions with dioxygen and include intradiol dioxygenases and lipoxygenases [17]. The Fe^{II} site activates oxygen by direct binding to O_2, resulting in iron–oxygen intermediates that react with the substrate and include Rieske dioxygenases, pterin-dependent hydroxylases or extradiol dioxygenases [18].

Binuclear iron enzymes involved in O_2 activation primarily exist in two oxidation states: the fully reduced bi-ferrous $[Fe^{II}]_2$ and the oxidized bi-ferric $[Fe^{III}]_2$ form. A particular example of a di-iron containing enzyme is soluble methane monooxygenase (sMMO) which consists of a carboxylate-bridged dinuclear iron center that is capable of dioxygen activation, producing active species of much superior activity than other monoooxygenases. In addition to hydroxylation of alkanes and aromatics, MMO exhibits a unique ability to convert even methane, which is known to be the most inert hydrocarbon (C—H bond energy, 104 kcal/mol), into methanol using dioxygen as the oxidant. One oxygen atom is reduced to water, and the second is incorporated into substrate molecule, yielding the alcohol [19]. The sMMO system requires three proteins to complete its catalytic cycle: MMOH, MMOB and MMOR, all of which have specific functions in order to oxidize the substrate molecule efficiently with high selectivity (Fig. 4) [20].

Copper-containing enzymes include monoooxygenases, dioxygenases, and oxidases which play a major role in biological dioxygen activation systems [21–24]. Active sites of copper metalloenzymes contain one or more copper ions and some contain additional metal ions such as iron or zinc. Copper enzymes are involved in hydroxylation reactions (particulate methane monooxygenases pMMO, tyrosinase), reversible dioxygen binding (hemocyanin), two-electron reduction of O_2 to peroxide coupled with oxidation of organic molecules (galactose oxidase GO, amine oxidase, catechol oxidase) and four-electron reduction to water coupled with substrate oxidation (ascorbate oxidase, laccase). Copper enzymes can be classified depending on the structure of the active site as mononuclear copper center (amine oxidase and galactose oxidase), non-coupled dinuclear copper center (dopamine β-hydroxylase), coupled dinuclear copper center (tyrosinase, catechol oxidase and hemocyanin), trinuclear copper center (laccase, ascorbate and oxidase) and polymetallic center (superoxide dismutase (SOD) and cytochrome c oxidase).

The majority of biological Cu sites serve as a one-electron shuttle, alternating between Cu^{I} and Cu^{II}. The Cu^{III} oxidation state is generally considered to be inaccessible because of the highly positive Cu^{III}/Cu^{II} redox potentials that result from ligation of amino acid side chains like imidazole and phenolate ions. An important example of a mononuclear copper enzyme is galactose oxidase (GO) which efficiently catalyzes the two-electron oxidation of a wide variety of primary alcohols and poly-alcohols, in a highly regio and stereoselective way, to their corresponding aldehydes (Fig. 5). This enzyme is capable of catalytic oxidations in water, making



Scheme 3. Schematic representation for a proposed di-copper active site of pMMO.

direct use of the molecular oxygen from air. The galactose oxidase active center contains a copper ion coordinated by two nitrogen and two oxygen donor atoms originating from two histidine and two tyrosine residues, respectively. The mononuclear Cu center is also bound by the water molecule to form a distorted five-coordinate metal complex.

A significant example of a copper-containing enzyme in this category is particulate methane monooxygenase (pMMO), which is analogous in function to the diiron sMMO, for the conversion of methane to methanol. Whereas diiron sMMO is selective towards alkanes, alkenes, aromatics, and halogenated hydrocarbons, the pMMO is more selective toward alkanes and alkene substrates that have five carbons or less. There are three metal sites in pMMO: mononuclear copper center, dinuclear copper and a zinc center. The dinuclear copper site is the most likely candidate for O_2 binding and activation (Scheme 3). A dinuclear copper center is coordinated by three histidine residues through the imidazole nitrogen, together with the amino-terminal nitrogen of one histidine. It is likely that exogenous ligands are also present at this site. However, due to difficulties in isolation of membrane pMMO, the detailed structure, mechanism and actual reaction sites for methane hydroxylation still remain under investigation [25].

All these examples show the prodigious ability and diversity of natural enzymes in being able to perform selective oxidations on the most difficult of substrates. Attempting to harness this aptitude in bio-mimetic systems has been widely investigated, in the realms of designing selective heterogeneous catalysts, for clean catalytic transformations. Different methods can be used to immobilize functional mimics of the enzymatic active site onto solid supports, thereby creating catalytically active single-sites, which facilitate demanding chemical transformations in a more industrial practical manner.

2.1. Zeolite encapsulated functional mimics

Encapsulation of catalytically active species within the pores of host solids can be achieved post-synthetically (e.g. ion-exchange followed by flexible-ligand methods) or in-direct synthesis (e.g. zeolite synthesis methods). Zeolites have been identified as suitable hosts for the encapsulation of metal complexes that mimic the catalytic function of the natural enzymes because, the microporous open-framework can readily control access of substrate molecules to the active site or elution of products, based on size, shape and molecular dimension. In such systems, the zeolite or *molecular sieve*, with its intricate array of channels and cages, can serve as a substitute for the protein mantle of natural enzymes and provide a controlled steric environment, where the catalysis ensues. Zeolites are thermally stable, chemically robust and easy to separate from the reaction products; so with a careful combination of metal complexes, isolated as single-sites throughout the inorganic

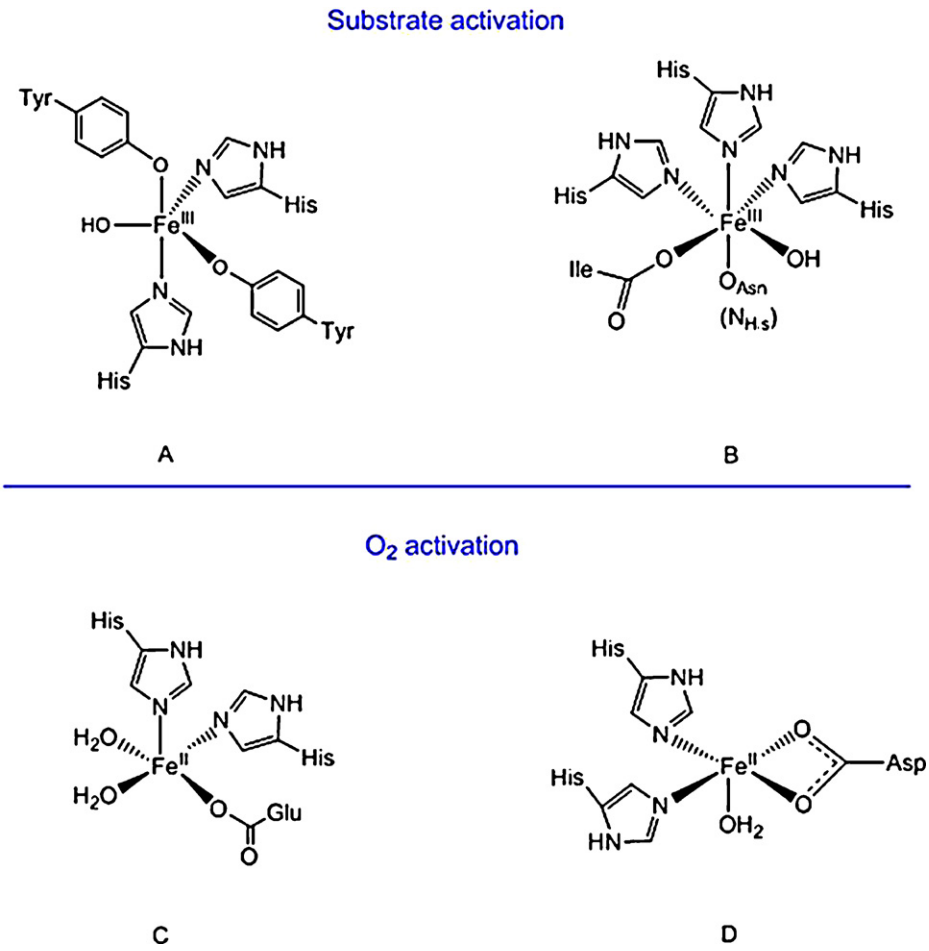


Fig. 3. Non-heme iron active sites for substrate activation: intradiol dioxygenases (A) and lipoxygenases (B). Non-heme iron active sites for O_2 activation: sextradiol dioxygenases (C) and *cis*-dihydroxylating dioxygenases (D).

matrix, can result in catalysts that mimic the functional aspects of enzyme activity.

Phthalocyanines, synthetic porphyrins and salen metal complexes encapsulated within zeolites (Fig. 6) have been widely studied as biomimetic catalysts and have revealed promising oxidation potential. Attempts have also been made to immobilize these complexes on solid supports such as silica, activated carbon, alumina and polymers [26]. Immobilizing phthalocyanine metal complexes within zeolite Y was reported by Romanovsky et al. [27,28] and involved the formation of the zeolite-entrapped metal phthalocyanine via template condensation of four dicyanobenzene molecules around the intrazeolite metal species. Raja and Ratnasamy [29] also illustrated that, via a 'ship-in-bottle' type methodology, single-site heterogeneous catalysts, consisting of entrapped complexes of Fe and Cu phthalocyanine, in which all or most of the hydrogen atoms have been replaced by electron-withdrawing substituents, converted methane in air to methanol and formaldehyde. To some degree, these heterogeneous catalysts effectively imitate the function of methane monooxygenase enzymes, by employing an analogous transition-metal, when compared to the active sites in pMMO and sMMO; thereby encouraging the oxidation of methane, albeit at lower levels of conversion.

Metallophthalocyanine (MPc) complexes are also attractive potential oxidation catalysts, because of their rather cheap and facile large scale preparation coupled with their intrinsic chemical and thermal stability. Their macrocyclic structure is similar to that of porphyrin ligands which are widely used in nature in the active sites of oxygenase enzymes, but phthalocyanines containing electron-withdrawing groups, are relatively stable to degradation and more readily available than porphyrins. Metallophtalocyanine complexes encapsulated in zeolites have been widely investigated in oxidation of hydrocarbons. Iron phthalocyanine was employed as a catalyst for the selective cyclohexane oxidation with PhIO and cyclohexanol was obtained as the sole product [30]. Zeolite encapsulated perfluorinated Co-phthalocyanine and Cu-phthalocyanine incorporated inside zeolite Y were found to be more active in cyclohexane oxidation than their corresponding unsupported analogues (Table 1) [31]. Given their promising potential, metallophthalocyanines have also been immobilized onto zeolites embedded in polydimethylsiloxane membranes, activated carbon black and MCM-41 by sol–gel synthesis [32,33]. Metallosalens, metallophthalocyanines and metalloporphyrins have also been covalently grafted onto silicas and organic copolymers [34], which are other types of supports with inherent benefits, which will be discussed later.

Synthetic metalloporphyrins have been studied as cytochrome P-450 models and are found to be efficient catalysts for alkene epoxidation and alkane oxidation [35]. The use of homogeneous metalloporphyrin systems has many drawbacks due to the increased propensity of the porphyrin ring to undergo oxidative self-degradation and aggregation. Furthermore, oxidation of hydrophobic substrates by water-soluble cationic metalloporphyrins is difficult, as the catalytically active species remains dissolved in the aqueous phase. To overcome these difficulties metalloporphyrins have been encapsulated within zeolitic frameworks that stabilize the porphyrin ring. This approach was described by

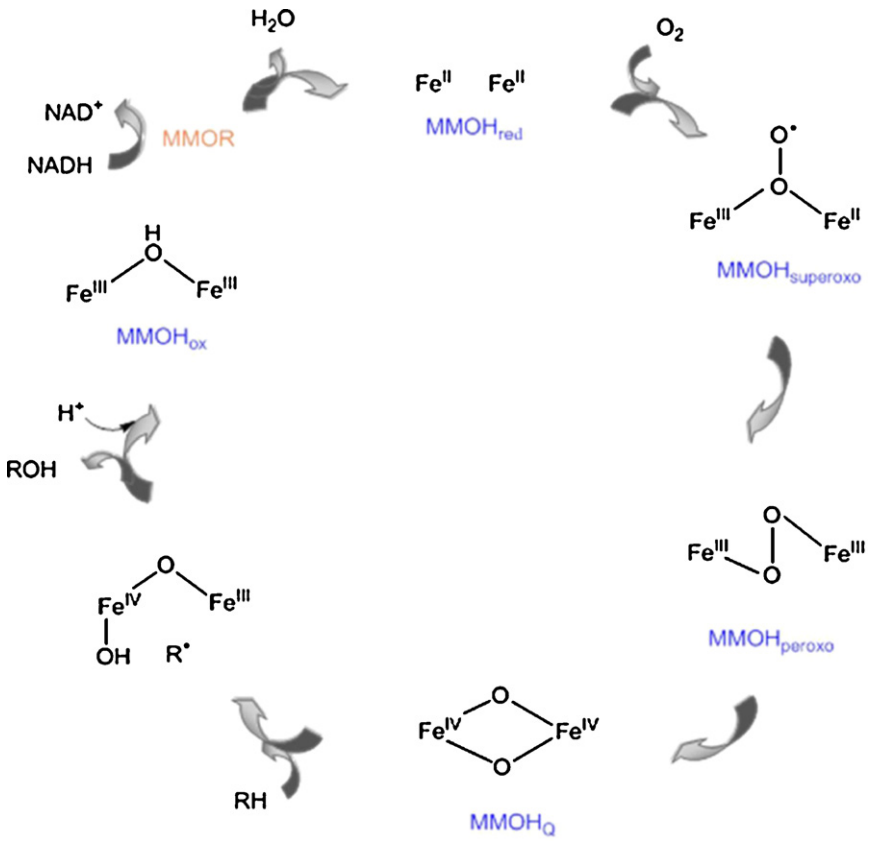


Fig. 4. A proposed mechanistic pathway for the catalytic cycle involving Fe-containing sMMO.

Table 1
Summary of catalytic performances of metallophtalocyanine and metalloporphyrin-based catalysts in oxidation reactions. PhIO (iodosylbenzene) has been often chosen as oxygen source in oxidation reactions with metalloporphyrins, because it has been successfully used with P-450 to support the proposed $Por^{\bullet+}—Fe^{IV}=O$ formation as an active species in cytochromes P-450 [31,39–41,68].

Catalyst	Substrate	Oxidant	Conversion (%)	Selectivity (%)
Cu-Pc	cyclohexane	TBHP	1.1	cyclohexanol (70) cyclohexanone (30)
Cu-Pc-Y	cyclohexane	TBHP	26	cyclohexanol (50) cyclohexanone (50)
	cyclohexane	H_2O_2	7	cyclohexanol (44) cyclohexanone (56)
Co-F_{16}Pc	cyclohexane	H_2O_2	0.82	cyclohexanol (46) cyclohexanone (54)
Co-F_{16}PcY	cyclohexane	H_2O_2	0.91	cyclohexanol (58) cyclohexanone (42)
Co-F_{16}Pc	cyclohexane	TBHP	5.0	cyclohexanol (55) cyclohexanone (55)
Co-F_{16}Pc-Y	cyclohexane	TBHP	1.0	cyclohexanol (50) cyclohexanone (50)
Ru-F_{16}Pc	cyclohexane	TBHP	8	cyclohexanol (33) cyclohexanone (67)
Ru-F_{16}Pc-X	cyclohexane	TBHP	70	cyclohexanol (1.6) cyclohexanone (98.4)
Fe-PorCl_4	cyclohexane	PhIO	15	cyclohexanol (99)
Fe-PorCl_4-Y	cyclohexane	PhIO	25	cyclohexanol (99)
Fe-Por	(Z)-cyclooctene	PhIO	50	(Z)-cyclooctene epoxide (99)
Fe-Por-X	(Z)-cyclooctene	PhIO	86	(Z)-cyclooctene epoxide (99)

Key: Pc = phtalocyanine, Por = porphyrin.

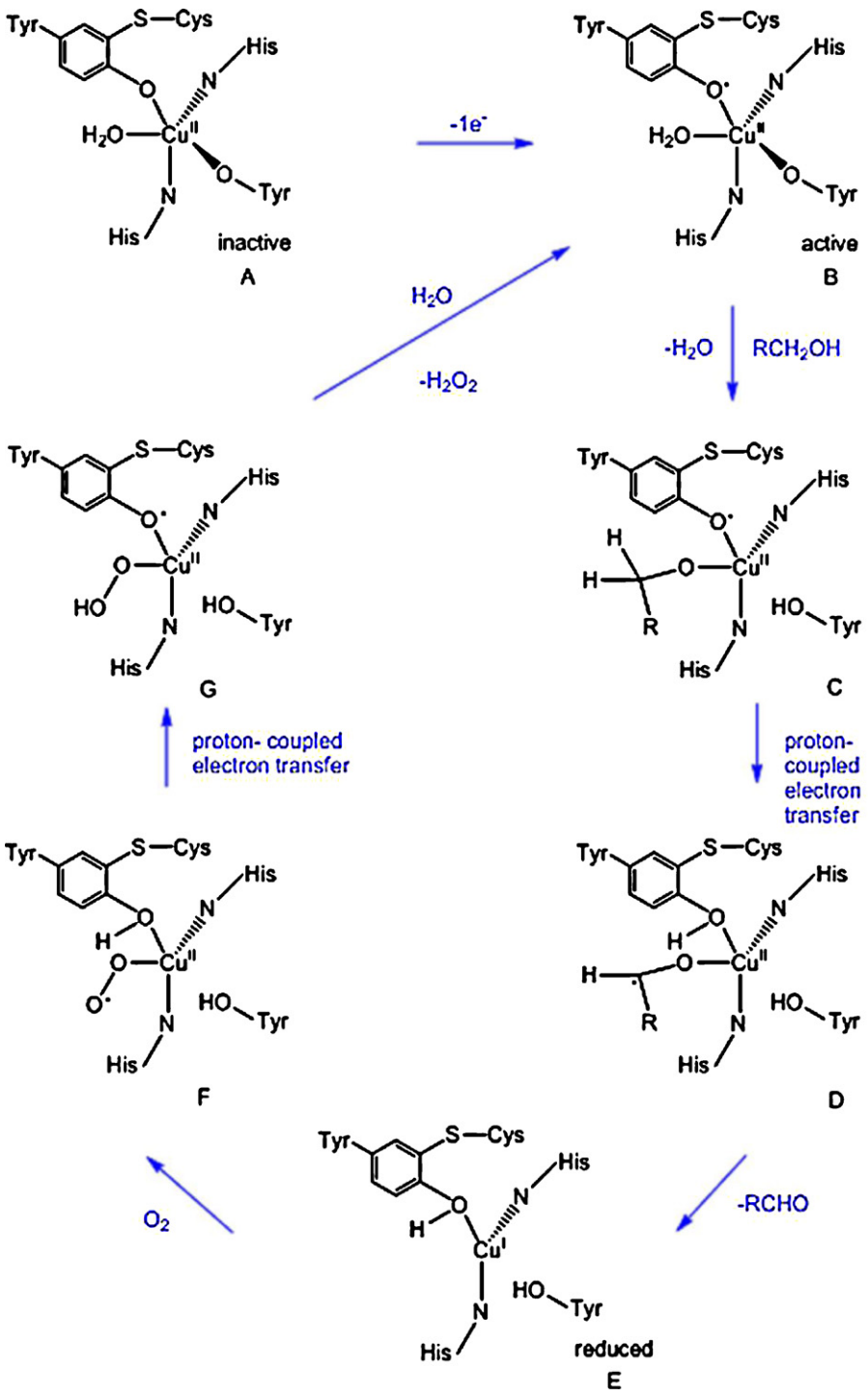


Fig. 5. Mechanistic insights into the oxidation of alcohols catalyzed by galactose oxidase.

Nakamura [36] and involved iron^{III} and manganese^{III} 5,10,15,20-tetramethylporphyrin complexes synthesized within the cages of NaY. These materials showed catalytic activity in the oxidation of cyclohexane with hydrogen peroxide. Supporting metalloporphyrins onto a rigid solid host provided the site-isolation of the active centers and prevented the formation of less reactive dimers (oxo metalloporphyrin dimers). The complex synthesized within zeolitic supercages is too large to pass through the channels, which effectively retards dimerization and deactivation and favorably influences the catalytic activity. The chemical modification of the metalloporphyrin microenvironment for the improvement of the catalytic efficiency has been achieved by the introduction of electron-withdrawing substituents into the porphyrin ring to restrict the formation of unreactive oxo-dimers and hence improve the activity and stability of metalloporphyrins (e.g. porphyrin substituted with NO_2 groups) [37,38].

Ratnasamy and his colleagues were also instrumental in the design of haloperoxidase enzyme mimics, whereby $CuCl_{16}Pc$ complexes were encapsulated within the supercages of zeolites X and Y and were shown to be effective in the oxychlorination and oxybromination of a wide range of aromatic compounds, using molecular oxygen as the oxidant, in the presence of a suitable

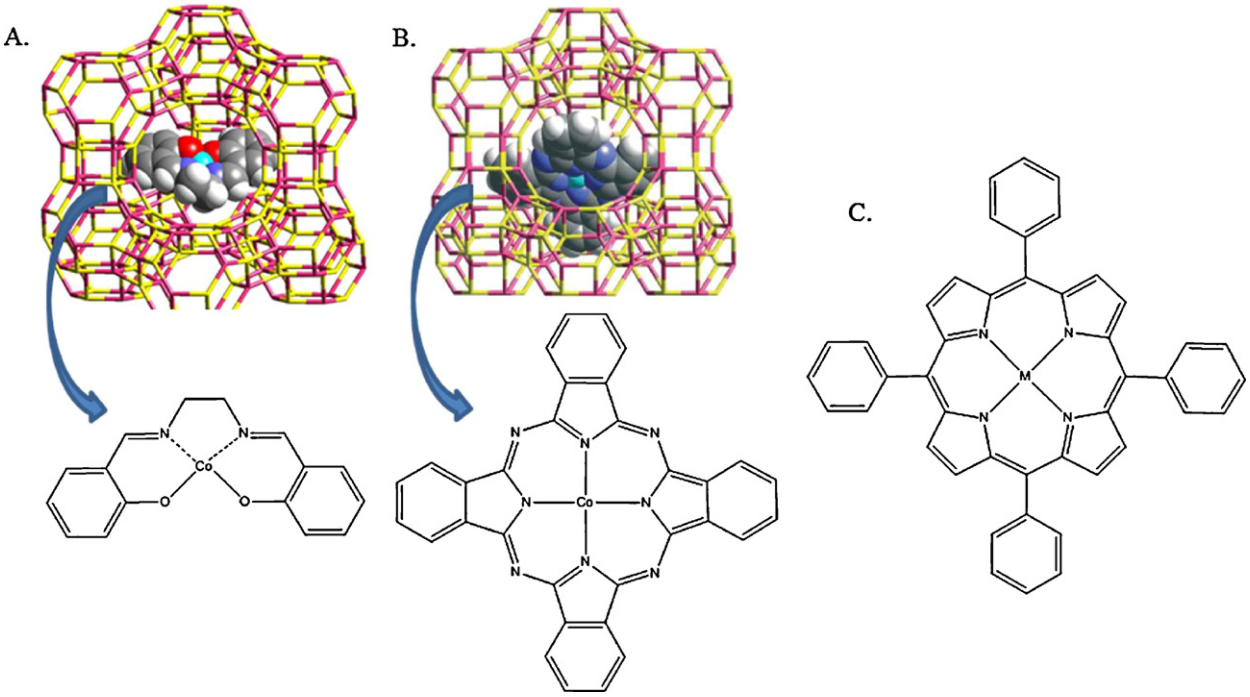


Fig. 6. Graphical representation of Co(salen) (A) Co-phthalocyanine (B) encapsulated within the supercages of zeolite Y accompanied by skeletal forms and structure of a metallopophyrin (tetraphenyl porphyrin) complex (C).

alkali halide (e.g. KBr) [42]. Mimics of hydroxylases have also been prepared by encapsulating Pd(0) and Fe(II) entities within zeolite A [43] for the regioselective hydroxylation of terminal methyl groups in linear alkanes. Raja and Ratnasamy [44] have also shown that dimeric copper–acetate complexes, encapsulated within zeolites X and Y, were effective in converting L-tyrosine to L-DOPA (Fig. 7), which, when perceived from a substrate specificity point of view, mimics the catalytic function of the enzyme tyrosinase. These encapsulated bio-inspired catalysts displayed high substrate specificity (only monophenols were oxidized) and regioselectivity (hydroxylation at the ortho position) and improved turnover frequencies were observed upon heterogenization, which can be attributed to single-site nature of the isolated active sites. The mechanism of this reaction is thought to directly mimic the

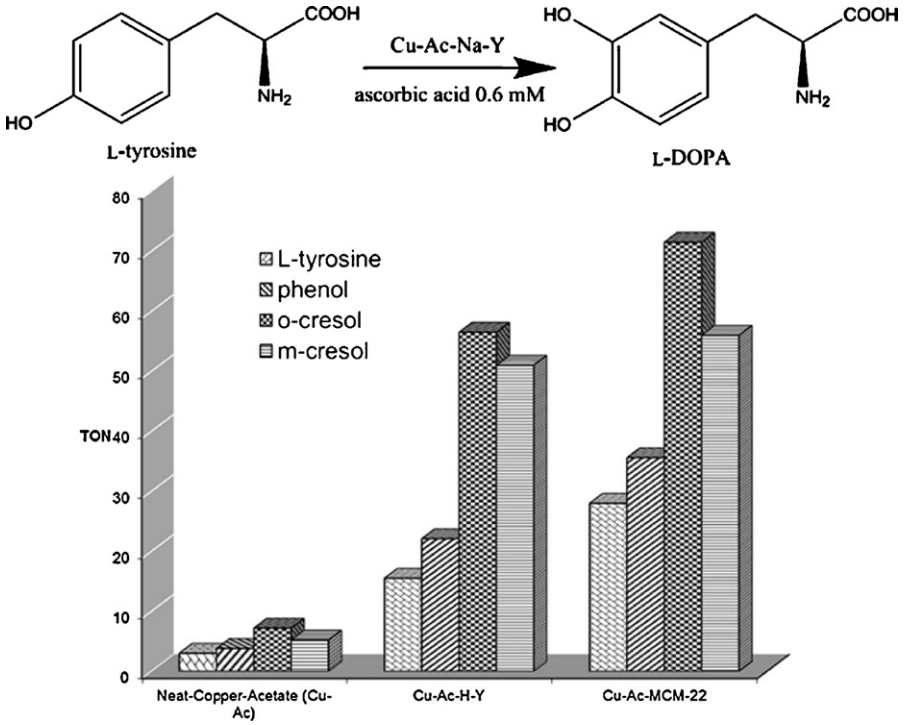


Fig. 7. Comparison of the catalytic performance (TON) of the copper-containing catalysts for the oxidation of monophenols (L-tyrosine, phenol) and ortho-diphenols (ortho- and meta-cresol) after 24 h, at 298 K, using molecular oxygen (100 psi) as oxidant.

Table 2
Metallosalen-based catalysts have also proved effective in oxidation reactions [45,49,55–57].

Catalyst	Substrate	Oxidant	Conversion (%)	Selectivity (%)
Cu-Sal	cyclohexane	H_2O_2	6.1	cyclohexanol (43) cyclohexanone (57)
	cyclohexene	O_2	33.6	2-cyclohexen-1-ol (55) 2-cyclohexen-1-one (41)
Cu-Sal-Y	cyclohexane	H_2O_2	4.0	cyclohexanol (26) cyclohexanone (74)
Cu-Sal	styrene	O_2	84.2	styrene oxide (62.4)
Cu-Sal-SBA	styrene	O_2	47.3	styrene oxide (49.4)
Fe-Sal-Y	cyclohexane	TBHP	1.9	cyclohexanol (23) cyclohexanone (77)
Fe-Sal	styrene	O_2	83.1	styrene oxide (51.2)
Fe-Sal-SBA	styrene	O_2	80.9	styrene oxide (59.7
Co-Sal	styrene	O_2	85.9	styrene oxide (54.4)
Co-Sal-SBA	styrene	O_2	49.2	styrene oxide (72.4)
Mn-SalMn-Sal-X	styrene	O_2	78.8	benzaldehyde (52.0) styrene oxide (32.5)
	styrene	O_2	54.8	benzaldehyde (66.7) styrene oxide (27.7)
Mn-Sal-Y	cyclohexane	TBHP	7.9	cyclohexanol (33) cyclohexanone (67)

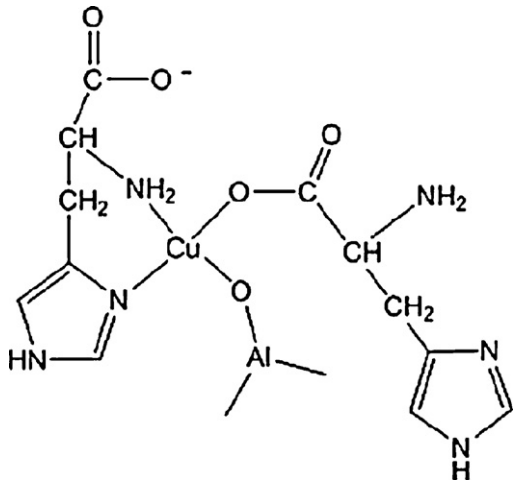
Key: Sal – salen.

catalytic function of tyrosinase, as discussed earlier (Figs. 1 and 2 and Scheme 2), by reversibly binding O_2 through antiferromagnetically coupled copper ions and hydroxylating the phenol derivative.

Another zeolite-encapsulated system that has been explored involves the tetradentate salen ligand (*N*,*N*′-bis(salicylaldehyde)ethylenediimine) that possess two oxygen and two nitrogen atoms and can form stable complexes with transition metal ions (Fig. 6A). The salen ligand is able to diffuse freely through the zeolite pores where upon complexation with previously exchanged metal-ions it becomes too large and rigid to escape the cage. The flexible ligand method has been adopted for the encapsulation of a large variety of Co, Mn, Fe, Cu, Rh, Pd, Ni salen complexes within faujasite supercages [45]. These types of complexes proved to be active and selective catalysts for hydrogenation reactions and in the oxidation of alkanes, alkenes and alcohols [46]. Mn-salen-X showed high activity for the oxidation of styrene and *p*-xylene whereas Mn-salen-Y was reported as an effective heterogeneous enantioselective catalyst for the epoxidation of alkenes [45,47,48]. Cu-salen-Y showed high activity in phenol oxidation; whilst Fe-salen-Y and Mn-salen-Y complexes were used in the oxidation of cyclohexane (Table 2) [49]. The substituted copper salens that contain electron-withdrawing groups like —Cl, —Br or —NO_2 showed higher activity compared to their unsubstituted analogues in oxidation reactions with H_2O_2 and TBHP. Substitution of the aromatic hydrogen atoms of the salen ligand by electron-withdrawing groups has two major effects: (I) retention of the copper complexes in the zeolite cavities is enhanced (due to the larger size of the substituents) and (II) the electronic properties of the encapsulated complex are modified [50]. A significant drawback in utilizing zeolite-encapsulated salen complexes is the availability of space within the supercages; which not only hinders the diffusion of substrate molecules but also limits the choice of reactants, because of the restricted amount of space that is available within the pore for interactions with substrate and generation of active transition-states for a satisfactory catalytic outcome. This can be suitably overcome by employing diverse immobilization strategies for improving active-site separation [48] or by reducing the size of the salen structure through loss of steric bulk [46]. Although altering the structure of the ligand can have an adverse effect on the resulting ee in the reaction, more recent advances have highlighted the merits of utilizing versatile supports for these types of complexes, in order to maintain ee and increase catalytic efficiency [51–54].

A further class of bio-inspired catalysts have been designed by drawing inspiration from studies involving active metal centers in metalloenzymes that are coordinated to the protein scaffold. Amino acids datively bond to the metal centers in natural enzymes; therefore its function may be replicated somewhat by preparing transition-metal complexes with amino acids as ligands. The amino acid–transition-metal complexes can be heterogenized by encapsulation within inorganic host matrices such as aluminosilicates or covalently bonded to mesoporous silica frameworks and polymers.

There have been numerous efforts aimed at the activation of molecular oxygen by metal complexes [43,58,59] and extensive studies have been reported for the selective oxidation of organic compounds [60,61]. A particularly noteworthy example of a stable, catalytically active zeolite immobilized transition-metal complex containing amino acid ligands is Cu^{II}-histidine; which was synthesized by the ion exchange method [62]. The strategy involves ion-exchanging a sodium-enriched zeolite Y (NaY) with a solution of Cu^{II}-histidine at pH 7.3. The capability of the copper complex to undergo ion-exchange is dependent on its charge and stability, which are both influenced by the pH of the reaction media. At low pH values of around 2, only 0.83% of the Cu^{II} is coordinated to the histidine ligand. On increasing the pH to 3, Cu^{II} forms mono-histidine complexes and within a pH range 6–10 bis complexes



Scheme 4. Illustration of a Cu^{II}–histidine complex that is coordinated with framework oxygen of zeolite Y.

are formed. Bis complexes are formed by coordination of nitrogen atom from the imidazole and the nitrogen atom from the amine group, carboxylate oxygen can also coordinate to the metal [63]. In solution, at pH values ranging from 6 to 10, two histidine ligands coordinate to the Cu^{2+} ion in a square-planar geometry. However, in a confined space in the cages of the zeolite, where the complex is encapsulated by the ion-exchange method, a framework oxygen atom replaces the oxygen atom from carboxyl group of histidine (Scheme 4) [64,65]. These studies provide conclusive evidence on how the nature of the active site can be altered by using different supports; in this case the coordination sphere around the metal center is different to that of the homogeneous complex because of bonding to the framework oxygen atom. Cu^{II}-histidine complexes encapsulated in Zeolite Y proved to be active catalysts for the oxidation of alcohols, alkanes and alkenes with *tert*-butyl hydroperoxide (Table 3); and similar procedures of encapsulation within zeolite Y were also employed for Cu^{II} complexes with lysine and arginine at pH 10.

Table 3
Cu^{II}–histidine complex encapsulated in zeolite Y are versatile bio-inspired solids for oxidative transformations [62–65].

Substrate	TON	Selectivity (mol%)
cyclohexane	450	cyclohexanol (50) cyclohexanone (50)
benzyl alcohol	2421	benzaldehyde (67) benzoic acid (33)
1-pentanol	1425	pentanoic acid (100)
cyclohexene	3230	1,2-cyclohexanediol (89) cyclohexene oxide (9) 2-cyclohexene-1-one (1.7) 2-cyclohexene-1-ol (0.3)

Table 4
Cu^{II}–lysine and Cu^{II}–arginine complexes encapsulated in zeolite Y are effective for the oxidation of cyclohexene [66].

Catalyst	TON	Selectivity (mol %)
Cu^{II}-lysine	735	1,2-cyclohexanediol (84) cyclohexene oxide (10) 2-cyclohexene-1-one (4.5) 2-cyclohexene-1-ol (1.5)
Cu^{II}-arginine	669	1,2-cyclohexanediol (85) cyclohexene oxide (8) 2-cyclohexene-1-one (5) 2-cyclohexene-1-ol (2)

The catalytic activity of Cu^{II}-lysine and Cu^{II}-arginine complexes encapsulated in zeolite Y for the oxidation of cyclohexene were much lower than that obtained with Cu^{II}-histidine (c.f. Tables 3 and 4). The lower activity afforded by the former set of complexes was attributed to the fact that the coordination geometries of the encapsulated complexes of NNOO Cu^{II}-lysine and Cu^{II}-arginine were probably less stable than that of the Cu^{II}-histidine system (Table 4) [66].

Building on some of these design strategies that have been pioneered earlier by Romanovsky [27], Herron [43], Weckhuysen [62], Jacobs [32], Balkus [67], Ratnasamy [68] and others, we in our own

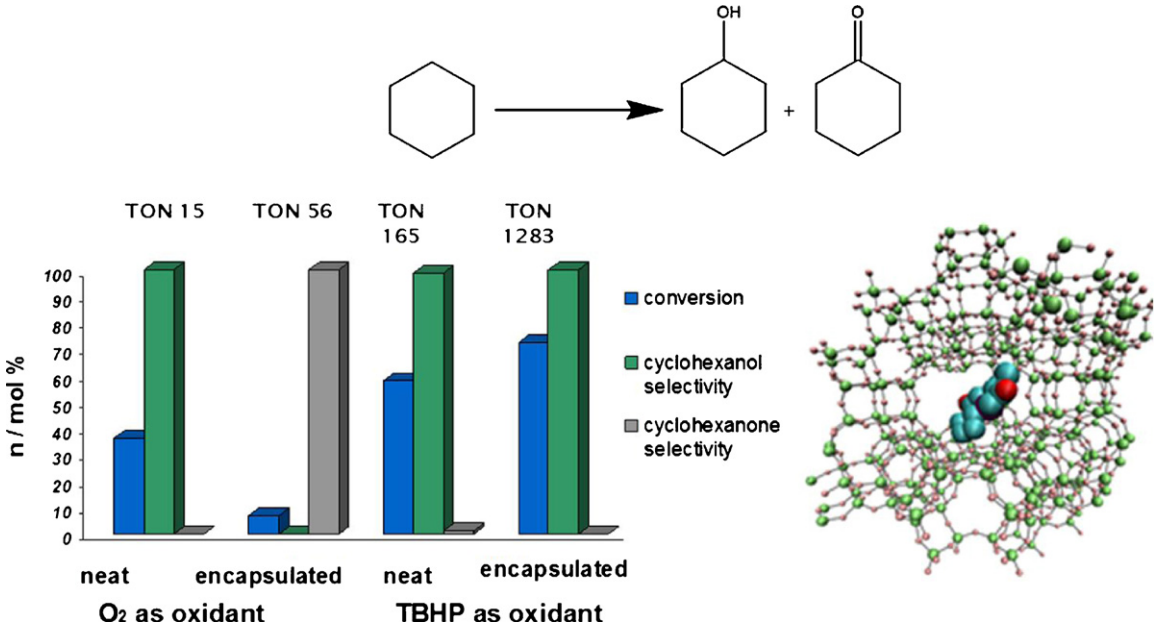


Fig. 8. A summary of results from cyclohexane oxidation (left) employing different oxidants catalyzed by Fe^{3+}proline in zeolite X (right).

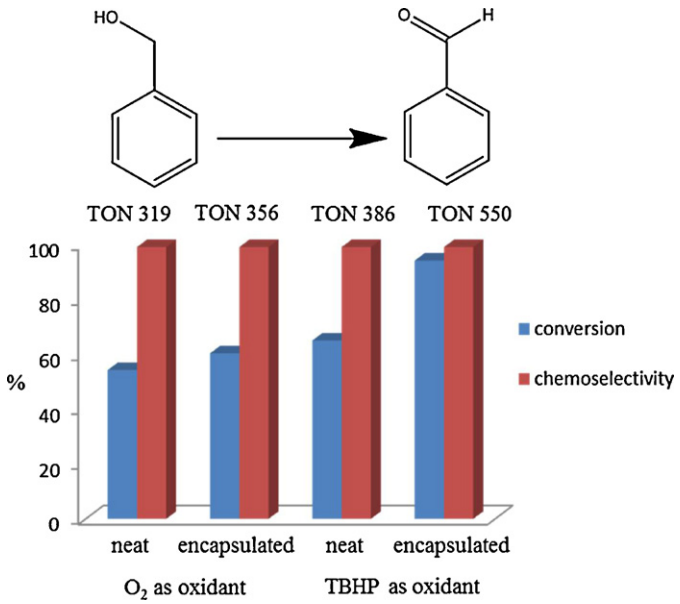


Fig. 9. Fe^{3+} proline complexes encapsulated in zeolite X, using the "zeolite synthesis method" display high chemoselectivities in the oxidation of benzyl alcohol.

work recently, designed heterogeneous Fe^{3+}-proline complexes, which have been synthesized by adopting the zeolite-synthesis and flexible ligand methods that have been described earlier [69]. These new class of catalysts have shown promising potential in the oxidation of cyclohexane (Fig. 8) and benzyl alcohol (Fig. 9); which are industrially important chemical transformations, as the former aerobic oxidation yields cyclohexanone, a vital precursor in the manufacture of ε-caprolactam (for nylon-6) and adipic acid (for nylon 6,6), whilst benzaldehyde (from the latter oxidation) is employed extensively in the production of fine-chemicals and in the perfume industry. Interesting changes in activity and selectivity were observed by simply changing the oxidant; but in both cases, far more conversion was achieved with the heterogeneous analogues, due to the formation of isolated, catalytically active single-sites, that are generated as a result of the encapsulation methodology that was adopted [70].

Catalyst activity, selectivity and stability of the complex may be altered through modifications in immobilization procedure or by changing the type of support and it is now possible to correlate these molecular factors that influence catalysis for the development of hybrid systems [71,72]. Influential properties of the support include diffusion limitations due to pore size and the degree of hydrophilicity or hydrophobicity, which can play an important role in determining the catalytic outcome. It has been established that the hydrophobic–hydrophilic properties of a heterogeneous catalyst plays a fundamental role in influencing both the activity and selectivity of a reaction [73], due to different polarities of the reactant and transition-states. Choice of support is based upon consideration of experimental conditions of intended reaction, with each support and method of heterogenization having explicit benefits, most notably in terms of activity and selectivity. The immobilized complexes (anchored via covalent or non-covalent methods) interact with the support, mainly through polarity-type forces; hence by altering the support type or its associated physical properties, plays a major role in influencing the nature and coordination geometry of the active site, therefore impacting the resulting catalytic outcome.

2.2. *Extending the immobilization strategy to mesoporous silica, polymer matrices and clays*

The immobilization of metal-substituted amino acid complexes has been rationally extended to the adsorption on clays [74,75] and anchoring amino-acid-derived ligands and related complexes on polymer matrices [76]. These heterogeneous catalysts have been utilized in a wide-range of oxidations and organic transformations such as epoxidations, aldol reaction, Baeyer–Villiger oxidations and Kharasch–Sosnovsky reactions. Overall these examples illustrate the particular advantages of using the different supports. In clays, the peptide bond formation derived from the structure–composition effect activates the reactant and, due to the nature of the support, provides ease of access to the catalytic site. More importantly, the use of in situ vibrational spectroscopic techniques has shown that amino acid complexes that were covalently anchored to polymeric supports, displayed a greater stability, with retention of higher activities, for electron transfer reactions [77]. Immobilization on a diverse range of supports further elicits the merits of immobilising single-site homogeneous catalysts and establishes structure–property relationships of the interface between catalyst and support, for potential exploration into industrial exploitation [78,79].

As illustrated above, there are many examples and progress has been met with fervency in encapsulating metal complexes that mimic the function of enzymes in microporous inorganic solids. This strategy can be adapted and modified for anchoring well-defined and isolated catalytic active centers in larger channel architectures, such as hydrophilic mesoporous silicas, primarily to accommodate a broader scope of substrates (Fig. 10). A drawback of zeolites as supports is the microporous nature of the pore architecture, which hinders the diffusion of reactant molecules to, and product molecules from, the active site. With mesoporous silicas, a

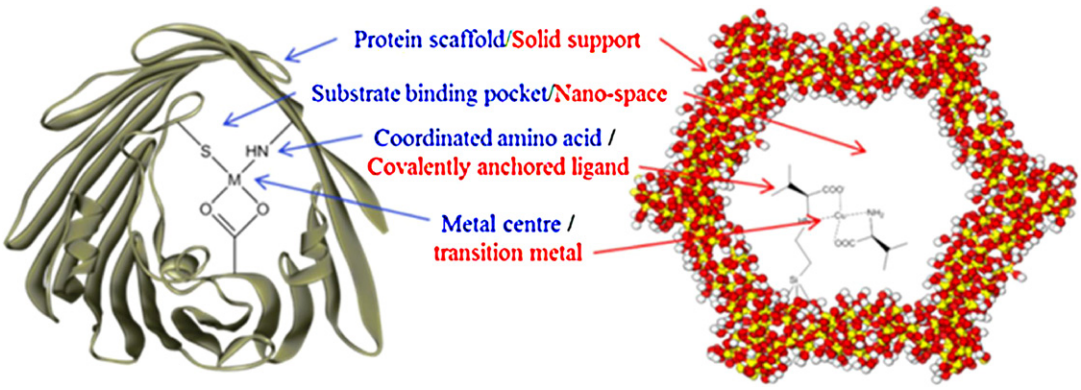
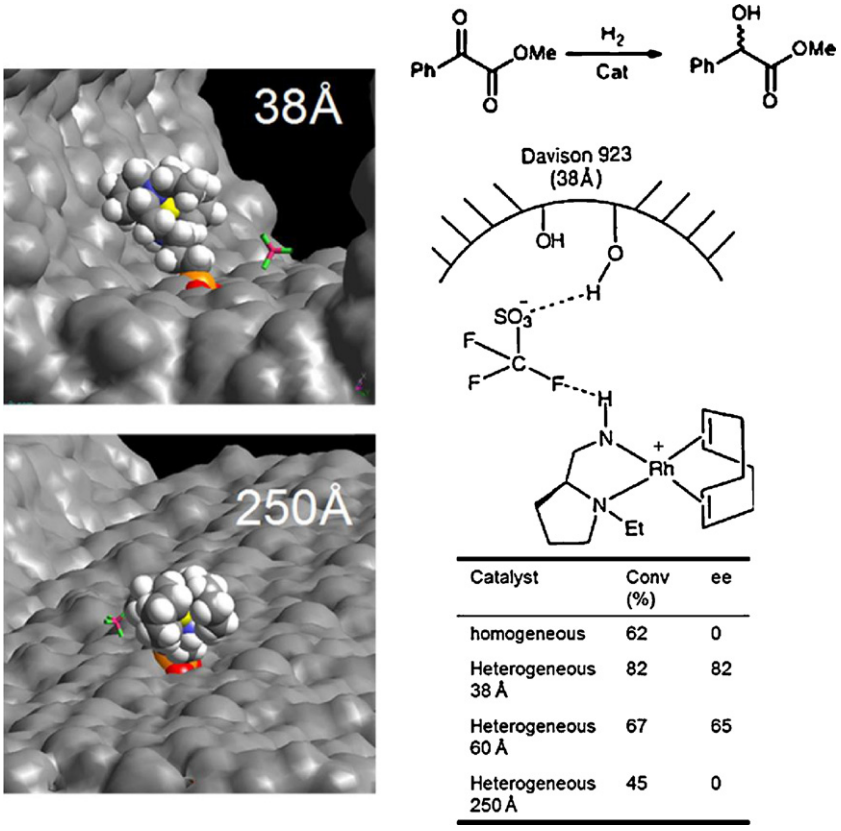


Fig. 10. (Left) Inorganic bio-inspired solids (a metal complex immobilized within mesoporous silica is shown here) bear a number of striking similarities to the protein mantle of natural enzymes containing a metal active center coordinated to an amino acid residue (right).



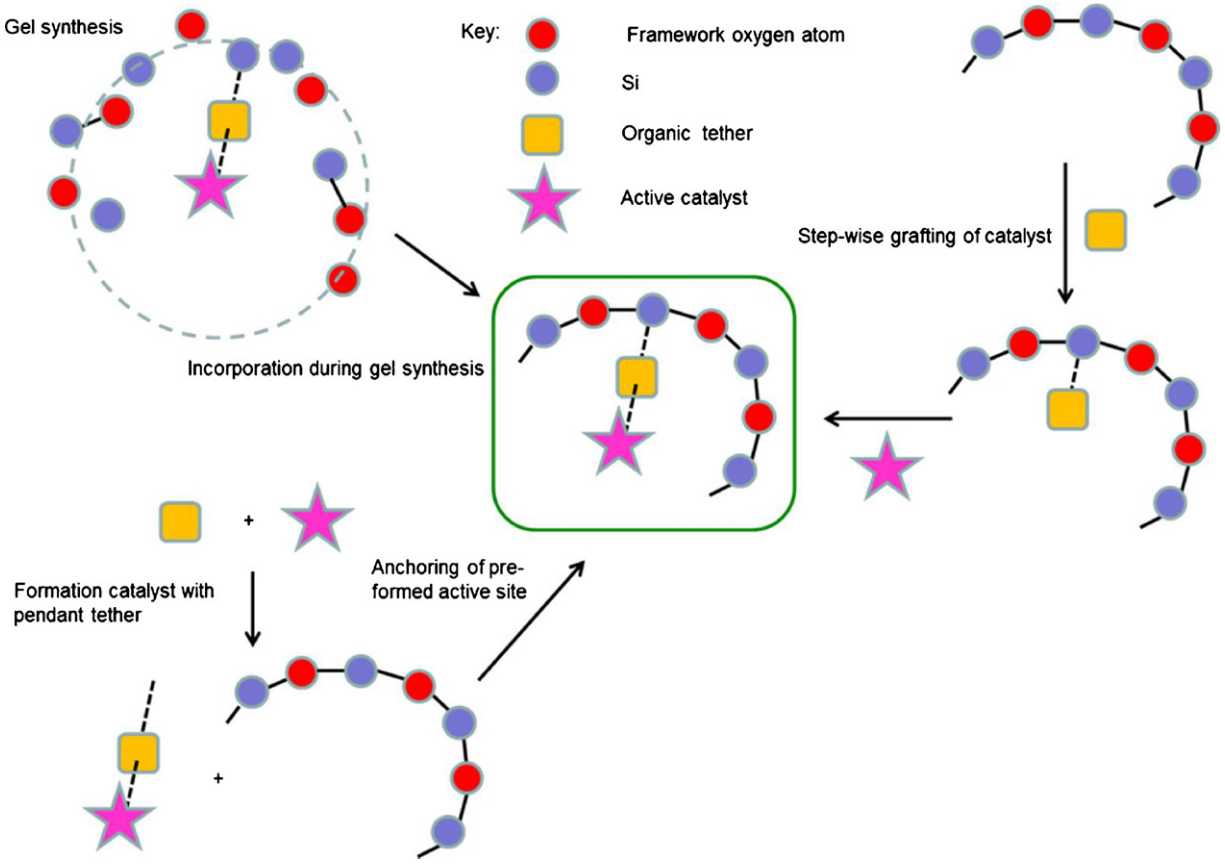
Catalyst	Conv (%)	ee
homogeneous	62	0
Heterogeneous 38 Å	82	82
Heterogeneous 60 Å	67	65
Heterogeneous 250 Å	45	0

Fig. 11. The confined space within mesoporous silica (38 Å, top) radically influences the enantioselectivity in the hydrogenation of methylbenzoylformate catalyzed by Rh^1(COD)AEP.

range of pore diameters are potentially available (from 25 to 250 Å); hence judicious choice of pore aperture imparts desired spatial constraints or freedom with respect to the substrate, transition-states and the mechanistic pathway. As with most solid supports, practical advantages include high thermal stability and straightforward recovery of the catalyst from the reaction mixture, which can be recycled without degrading and in addition, silica frameworks also do not swell on exposure to solvent or reactants.

A profound realization that emerged from this approach was that, deliberate restrictions of space inside the cavities of porous supports, particularly in the vicinity of a tethered active site, induces chirality in a target molecule for effecting asymmetric industrial hydrogenations [80]. The prochiral compound experiences interactions with the chiral auxiliaries of the immobilized complex that act in concert with the metal center, but more significantly with the inner wall of the support. The sum of these interactions would be comparable to the energies of two transition-states that determine stereomeric excess in the product; therefore the additional interaction of the pore wall will alter the stereoselective outcome. The influence of pore diameter of the support on effecting the stereoselectivity of the reaction has been demonstrated on numerous occasions in the allylic amination of the Trost-Tsuji reaction [81], one step conversion of ethyl nicotinate to ethyl nipecotinate [82] and in the asymmetric hydrogenation of *E*-α-phenylcinnimic acid and methylbenzoylformate [83,84]. In these instances, heterogenization was carried out using a covalent anchoring approach (discussed later), but one can also immobilize complexes onto silica via a non-covalent way by using ionic interactions, an approach that was adopted by de Rege et al. [85]. By utilizing the dipole charges in the ligand, a negatively charged counter-ion could be used to attract a metal-cation-containing complex, anchoring the compound through hydrogen bonding with the surface silanol functionalities. This was achieved with a Rh^1(COD)AEP catalyst and used in the industrially significant hydrogenation of methylbenzoylformate to methyl mandelate (Fig. 11) [86,87]. The confined, non-covalently anchored catalyst gives the same correlation in results to that of the covalently anchored series, illustrating that spatial restriction improves enantioselectivity. Understanding this effect and the influence the support can have mechanistically on the stereo-chemical outcome of a desired catalytic transformation can be a great asset in being able to establish structure–property relationships, predict product-distribution and explain enantiomeric excesses.

The covalent anchoring of transition-metal complexes can be achieved in a number of ways (Scheme 5): the in situ immobilization strategy involves reacting the ligand first with a tethering group containing an oxysilane functionality, followed by addition to the gel mixture for the synthesis of the silica framework. The silicon source in the catalyst precursor can act as a framework substituent and graft into a tetrahedral site, within the framework, forming bonds with adjacent silicon atoms via bridging O linkages, leaving a well-defined organic moiety at the surface within the pores during formation of the channels. Post synthetic anchoring is the most commonly used technique which derivatizes the silanol groups of the silica surface with a tether consisting of functionality, such as an amine or alkene, which can be further reacted with a desired ligand that coordinates to the metal center. This covalent approach has been developed for immobilization of solitary amino acids or peptides with sequential solid-phase grafting onto amino-functionalized mesoporous silica by solid-phase peptide synthesis (SPPS) methodology [88]. An analogous route to immobilization of organic moieties to an already functionalized framework atom employs 'click' chemistry protocols [89], which generate facilely and reliably the organocatalyst by joining smaller units together.



Scheme 5. An outline of various strategies for grafting organic moieties onto mesoporous silica supports.

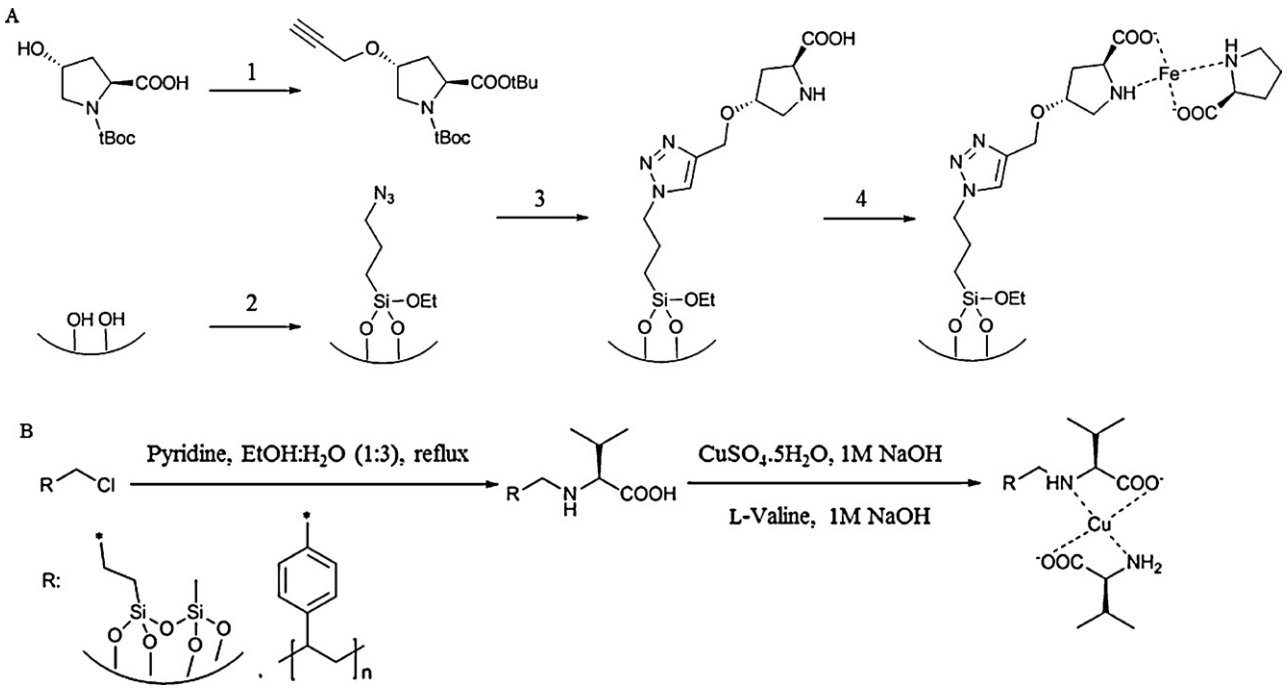
First the silica is pre-functionalized by using an allyl oxysilane, which can be converted to amino functionalities and then tethered by an azide alkyne Huisgen cycloaddition. The hydrophilic character inside the pores, due to pendant silanol groups, can be minimized by co-functionalization with other species, e.g. methyl groups and this also influences the stability of other grafted functionalities. It has been established that grafting a mixture of 3-aminopropyl and methyl groups to the surface improves hydrothermal stability due to a decreasing basic character inside the pores [90].

2.3. Novel methodologies for covalently anchoring metal-substituted bio-inspired solids

Various amino acids and short peptide complexes with copper and iron have been anchored on mesoporous silica via SPPS and have shown encouraging trends in the oxidation of hydrocarbons [91,92]. This useful method was implemented by Pringruber et al. [91] in order to mimic the active core of the enzyme methane monooxygenase (MMO). A short peptide chain, found in the active site of the enzyme of His-x-x-Glu, was covalently attached and coordinated to transition-metal centers via an auto-assembly route, in order to mimic the structure of the metalloprotein. Improvements in catalytic results were observed by complexation of the metal-ions to the peptide chain in comparison to that of the grafted single amino acids. Chiral copper proline-derived complexes have also been grafted on mesoporous silica and employed as heterogeneous catalysts in the asymmetric epoxidation of α-β-unsaturated ketones, using H_2O_2 as the oxidant [93,94]. The heterogeneous copper complex produces conversions in excess of 85% with greater than 82% ee for a range of substrates and is also recycled effectively for up to 5 times with no drop in stereoselectivity and minimal loss in yield.

Our most recent work provides a platform for making a direct comparison between the catalytic results of covalently anchored transition-metal-amino acid complexes to mesoporous silica and polymer supports with traditional zeolite encapsulated analogues (reported earlier). The comparisons seek to highlight the advantages of our recent immobilization strategies (Scheme 6), in terms of a design approach, that we and others have employed in the past, utilizing the same metal complex. The adaptation of well-known anchoring methodologies (Scheme 6) provides reliable routes for the generation of stable, well-defined catalytically active single-sites, thoroughly dispersed, in a site-isolated fashion, throughout the material. Comparing the activity and selectivity of the same immobilized complex on different supports provides valuable insights into structure–property relationships, which can be directly linked to the support influence on the local environment of the active site and surface interactions with substrates and solvent molecules. These characteristics are valuable in terms of adopting the above protocol (Scheme 6) to flow-chemistry-based practices and can be utilized in continuous processing; notwithstanding the fact that the heterogeneous nature of the immobilized catalyst is still attractive for batch processes, as the solid catalysts can be simply recovered through filtration and recycled effectively.

Amongst the numerous applications and wide-range of industrially significant substrates that can be oxidized employing these metal-substituted, bio-inspired heterogeneous catalysts, we have very recently explored the possibility of supporting metal-free amino acids, in order to evaluate their potential as heterogenized organocatalysts.



Scheme 6. (A) Amino acid immobilization to silica supports through the side-chain and (B) covalent attachment onto silica and organic polymers through the amino functionality of the amino acid.

3. A new era of heterogeneous organocatalysis

Organocatalysis has become a prominent aspect in some of the most essential transformations in organic chemistry and, in recent years, amino acids and derivatives have been used to catalyze essential transformations used in the fine chemical and pharmaceutical industries [95]. Furthermore, recent advances in catalyst immobilization approaches have initiated the development of implicit industrial applications; as organocatalysts can be anchored within the mesopores of silica supports [96] to facilitate asymmetric transformations that are vital in the total syntheses of many natural products. Organocatalysts provide avenues for catalyzing asymmetric transformations with exceptionally high stereoselectivities, as recent advances in operando spectroscopy enable transition-states and reaction intermediates to be readily isolated and characterized, providing vital information on the mechanistic

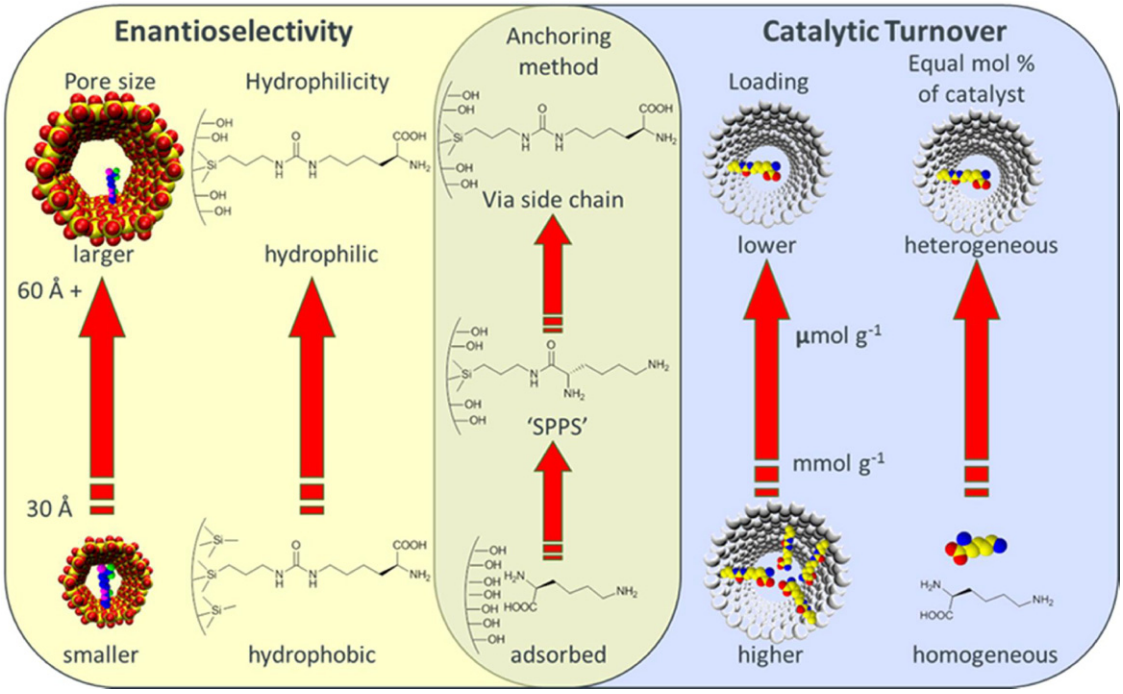


Fig. 12. Summary of catalytic trends observed in lysine catalyzed asymmetric aldol reaction between acetone and 4-nitrobenzaldehyde, particularly highlighting the various anchoring strategies employed with supports with different pore diameters and varying degrees of hydrophilicity.

pathway. This provides the opportunity to design organocatalysts for specific transformations with targeted selectivities, as these new generation catalysts are more amenable for facilitating structure–property relationships, compared to their metallic counterparts, due to their pure organic nature. Apart from the above-mentioned intrinsic benefits, employing organocatalysts has many inherent shortcomings, because of their homogeneous nature, which necessitates the use of high molar ratios of catalyst and gives rise to difficulties associated with recovery and reusability. Through heterogenization, these pitfalls can be suitably overcome and could even lead to more desirable improvements on rate and stereoselectivity. Heterogeneous organocatalysts offer a more complementary mode of catalysis in comparison to that of their metal-based analogues, especially in terms of reducing cost (of metal), eliminating chemical waste, aiding recyclability and decreasing the overall number of steps in the synthesis of fine-chemicals. Our work in this exciting field of research has shown that amino acids that act as organocatalysts can be covalently anchored to porous inorganic supports (using analogous strategies outlined earlier – see Section 2.3), providing a significant increase in activity, due to the single-site nature of the catalyst.

By suitably tailoring the nature of the support, the catalytic outcome can be advantageously altered, as the local environment of the active site can be indirectly modified. By altering the catalyst loading, varying the pore diameters and corresponding degree of order, regulating the degree of hydrophilicity/hydrophilicity and by judicious choice of anchoring strategy, the activity, but more importantly the enantioselectivity of the catalyst can be significantly influenced. A generalized summary of active site modification and effect on catalysis (Fig. 12) implies that the support characteristics can be suitably optimized, in order to maximize a particular conversion to yield the highest enantiomeric excess with the least mol% of catalyst over a reasonable time period. With a lower catalyst loading activity can be increased; which can be interpreted in terms of the catalytic sites existing in more well-defined isolated fashion throughout the support architecture.

The expanding scope of organic transformations that can be catalyzed by heterogenized amino acids and their derivatives is ever increasing and immobilization of these organic moieties offers the opportunity for developing highly active, selective, single-site heterogeneous catalysts [97]. By further correlating spectroscopic information with observed catalytic trends, we hope to establish structure–property relationships and envisage the properties of the framework architecture can be suitably attuned for enhancing the activity and selectivity of the organocatalyst.

4. Future outlooks and potential

Further to the pivotal contributions initiated by Ratnasamy and his colleagues 18 years ago in the area of zeozymes, we have, in this article, emphasized the importance and benefits of design methodologies for immobilizing bio-inspired entities on inorganic supports, in order to achieve stable heterogeneous catalysts, as alternatives for facilitating demanding industrial significant transformations in a cleaner, more sustainable manner. This new generation of bio-inspired solids have shown encouraging results in laboratory-based experiments; but still have to undergo rigorous tests before they can be employed on an industrial scale. Our preliminary results reveal that changing the environment of the active site, i.e. through intricate support modification, judicious choice of pore architectures with intrinsic control over the degree of hydrophilicity/hydrophobicity and astute choice of immobilization strategies can all have a profound influence on the activity and selectivity of the active sites. Moreover, quantifying the characteristics of support with established trends in catalytic performance, leads to development of support tailoring, tuning and optimization via established catalyst–interface interactions and structure–property correlations. Although our initial results are promising and, given the fact that significant advances have been made from a design point of view in recent years, there is still a considerable need for an improved understanding of the function of the host and its mechanistic influence on the catalytic outcome. Advances in in situ characterization and development of *operando* techniques, which are closely aligned with computational modeling on these solid systems, will facilitate a more quantitative understanding of structure–activity relationships that could lead to the design of more active and selective bio-inspired catalysts.

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