

Constrained chiral catalysts

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Abstract

Some of the approaches previously used to perform reactions enantioselectively using heterogeneous catalysts, together with a few illustrative examples, are first briefly summarised. We then outline various advantages and opportunities that nowadays exist for the confinement of large and rather complicated chiral organometallic catalytic entities as well as reactant and product species inside the cavities of mesoporous silicas, the pore diameters of which fall in the range 25 to 100 Å. The unique opportunities afforded by chiral chelate ligands based on bis-diphenyl-phosphinoferrocene (BPPFA) held within mesoporous silica are adumbrated. Examples of potentially useful reaction systems and general synthetic possibilities are discussed with the view to highlight the emerging potential of the mesoporous dimension in regio- and enantioselective catalysis. © 1999 Published by Elsevier Science B.V. All rights reserved.

Keywords: Catalysis; Regio- and enantioselectivity; MCM41; dppf; Solid-state NMR; Confinement

1. Background

In the pharmaceutical and agrochemical industries, as well as in the expanding fields of fragrances and flavours, there is a growing demand for enantiomerically pure products. Not surprisingly, therefore, increased attention is now being given to the design of powerful enantioselective catalysts. After all, only a relatively minute amount of the requisite chiral catalyst is needed to generate large amounts of the targeted chiral product. But how does one set about designing the requisite catalyst? Leaving aside engineered enzymes and other biological macromolecular chiral catalysts, the most

popular procedure to date has been to ‘construct’ the right homogeneous transition-metal-based complex, which generally operates at low temperatures and at moderately high pressures [1–5].

To date, homogeneous catalysts in which metal-ion complexes are attached to carefully designed chiral ligands are still the most effective enantioselective catalysts. But it has been appreciated for some time—see, for example, the early review by Burwell [6]—that heterogeneous catalysts would be preferable, owing to a variety of intrinsic practical advantages that are directly connected to such factors as ease of separation, handling and recovery, not to mention their higher potential for regeneration and re-use. Awareness of such advantages prompted Schwab [7] several decades ago to modify metal surfaces such as Raney nickel with certain stere-

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ospecific adsorbents so as to confer enantioselectivity on the resulting catalyst. Much later, Akobori et al. [8] in Japan reported the first reasonably reliable metal-catalysed asymmetric hydrogenation. Their preparation consisted of metallic Pd supported on silk; and this was successful in the hydrogenations of oximes and ketones.

As Swiss workers have recently emphasised [9–11], there are only a limited number of possible approaches to the design of enantioselective heterogeneous catalysts. One of these seeks to find (or prepare) solids in which the active sites are located in a chirally discriminating environment. To be precise, this approach encompasses (but is not restricted to) the use of chiral solids (i.e., those that exhibit a chiral space group, such as $P_{2,1,2,1}$, so that an active site in any one of the three, mutually perpendicular crystallographic screw axes is intrinsically prochiral). Stratagems of this kind were used in early work on photoactive pro-chiral molecular crystals [12,13].

Another approach entails the phenomenon of chiral-leaching, in which a cavity may be created in a solid by a stereospecific etchant (such as that which occurs when D- or L-tartaric acid attacks the sites of screw dislocations at the cleavage surfaces of calcite [14]). Related to this is the recent ingenious achievement of Gellman et al. [15] in creating chiral kinks (produced when monatomic terraces interact) on single crystal faces of metallic Ag. However, neither of these two approaches seem particularly well-suited for routine use or scale-up. Chiral imprinting, which involves the interaction of a chiral template with a solid such that upon careful removal of the template a chiral imprint or ‘footprint’ is being left, might prove to be a powerful technique for the preparation of enantiomerically discriminating catalysts, but is still in its very early stages.

In contrast, the last family of approaches now to be considered, namely the creation of a chiral environment for the active sites, already has shown to be viable for a range of reactions.

One way forward, therefore, is to graft a chiral ligand/modifier (which exerts stereochemical control) to a catalytically active (but not itself stereoselective) solid. Another is to graft an ‘ordinary’ active site to a chiral solid support. Yet another entails the heterogenization (or immobilisation) of chiral homogeneous transition metal complexes on a high-area solid support. We have focused on the last of these three options, but before we highlight possible specific strategies capitalising on this approach, it is instructive to recall other work relevant to options one and two.

2. Some previously considered examples

(a) Chirally modified metals, in which finely divided metals such as Ni, Pt, Pd (which themselves are supported on high area alumina) have adsorbed upon their exterior surfaces a chiral auxiliary. Well-known examples of this kind are the Ni-tartaric acid system for the hydrogenation of β -ketones, β -ketoesters [9], and the Pt-cinchona alkaloid system [10,11,16–18] for the hydrogenation of carbonyl compounds activated by an electron-withdrawing group in an α -position. For both the Ni and Pt treated surfaces enantiomeric excesses (e.e.) as high as 95 per cent have been reported; but the range of reactants that may be transformed enantioselectively in this way is rather narrow.

The precise manner in which the adsorbed chiral auxiliary remains somewhat obscure; but fresh insights have been gained recently [19,20] in the case of the Pt-cinchona system. Evidently, the chiral modification effect induced by the cinchona alkaloids is much dependent upon the anchoring part of the flat aromatic ring system (quinoline) which is thought to be bound to the Pt surface by multicentre bonding. It is also much governed by the stereogenic region (at C_9 and C_8 of the alkaloid) since it determines the chirality of the product.

(b) ‘Ship in bottle’ or ‘Tea bag’ catalysts. Construction of a chiral entity (the ship) inside a

micropore (the bottle)—a cavity of molecular dimension—is not an insuperable task [21]. With non-chiral entities such constructions have been accomplished on numerous occasions. The concept here is to allow the catalytic entity to rattle inside the constraining cavity, so long as it is accessible to the reactant and it does not prevent the product from being washed away so as enable the regeneration of the original catalyst. Such ‘tea-bag’ catalysts (a term coined by one of us [22] eight years ago) have become more feasible following the recent work of Bein et al. [23], who designed an intrazeolitic epoxidation catalyst based on a Mn complex with a trimethyl triazacyclononane (tmtacn) ligand. (Although the as-prepared $[\text{Mn}(\text{tmtacn})]^{2+}$ -NaY catalyst was initially inactive, it becomes very active following an induction period, during the course of which a Mn^{III} - Mn^{IV} dinuclear complex is formed.)

Two other recent contributions that entail ‘ship-in-bottle’ or ‘tea-bag’ concepts of encapsulation are noteworthy. The paper by Ogunwumi and Bein [24] describes a novel epoxidation catalyst which entails the intra-zeolitic assembly of a chiral Mn-salen complex; and Corma et al.’s recent paper [25] on zeolite encapsulation also deals with the same kind of complex, active for the enantioselective epoxidation of alkenes, inside zeolite Y.

(c) Chirally-modified zeolites have recently been shown by Hutchings et al. [26,27] to exhibit quite significant kinetic resolution in the catalytic dehydration of butan-2-ol. Zeolite H^+ -Y, modified beforehand by impregnation with chiral sulfoxides, display good-quality heterogeneous enantioselectivity for the gas phase reaction above 100°C . The rate of dehydration of the *S*-enantiomer butan-2-ol is nearly twenty times as fast as that of the *R*-enantiomer. The chiral modifier introduced to the achiral zeolite remains stable up to about 200°C ; and computer simulation suggests that the observed stability of the *R*-1,3-dithiane 1-oxide in the faujasitic zeolite is due to proton transfer between the zeolite and the molecule. Very recent work [28]

suggests that extra-framework aluminium ions may play a not insignificant role in anchoring the chiral modifier securely within the cavities of the host zeolite.

3. Constrained chiral catalysts

Following on from the above, the next logical extension to the idea of confinement is the use of confined spaces large enough to accommodate complicated organometallic catalytically active molecules as well as the relevant substrate and product species.

Here, we may turn our attention to the recently discovered families of mesoporous oxides, particularly the mesoporous siliceous oxides with channel apertures ranging from 25 to 100 \AA [29]. They unlock new possibilities in solid state catalysis as they provide unique supports for the development of new chiral catalysts. Indeed, the large diameter (ca. 30 \AA) channels of the so-called MCM-41 mesoporous silicas permit the direct grafting of complete chiral metal complexes and organometallic moieties onto the inner walls of these high surface area (typically $> 850 \text{ m}^2 \text{ g}^{-1}$) solids by a variety of ways, including tethering by functionalising the surface with organic groups such as alkylhalides, -amines, -carboxyls and -phosphines. This opens routes to the preparation of novel catalysts consisting of large concentrations of accessible, well-spaced and structurally well-defined active sites.

Various organometallic chiral catalysts may be tethered as shown below (cf. Fig. 1).

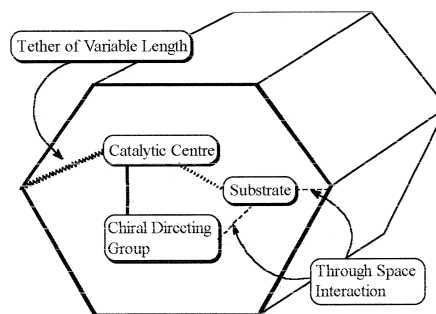


Fig. 1. Schematic representation of the confinement concept.

The key concept in this approach is the substrate's interaction with, both, the pore wall and the chiral directing group. The confinement of the substrate in the mesoporous channel should lead to a larger influence of the chiral directing group on the orientation of the substrate relative to the reactive catalytic centre when compared to the situation in solution. Of course, this is not only the case for enantioselective reactions but also for regioselective ones.

The chiral chelate ligands based on bis-diphenyl-phosphinoferrrocene (BPPFA, Fig. 2) would be particularly attractive for tethering into MCM41 as, e.g., their planar chirality never undergoes racemisation, they are synthetically very accessible [30], and they possess functionalities suitable for reaction with pore-bound tethers. The opportunities for variations of the 'R' groups and hence the steric/electronic characteristics for both metal complexation and tailoring of the chiral environment offer great scope (cf. Fig. 3).

The homogeneous transition metal complexes of BPPFA are active for a large variety of stereoselective reactions, such as cross-coupling of organometallic reagents with alkenyl or aryl halides, aldol-type reactions, substitutions of allylic substrates with nucleophiles, hydrogenation and hydrosilylation of olefins and ketones and hydroboration. Thus, with the chiral MCM-41 derivatives, catalytic regio- and enantioselective syntheses (i.e., the altered selectivity of the chiral complexes tethered in siliceous MCM-41 vs. that of their homogeneous analogues) might be explored in the fashion typified by Corma et

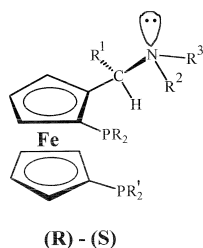


Fig. 2. The chiral chelate ligand family based on bis-diphenyl-phosphinoferrrocene (BPPFA), R = alkyl, aryl or functional group.

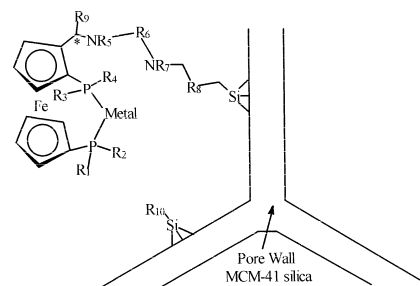


Fig. 3. Schematic showing possible variations of the 'R' groups on and around the catalyst.

al. [31] in the rhodium/USY system, where an increase in enantiomeric selectivity from 75% to 95% could be achieved and is thought to have been caused by the additional substrate-pore wall interaction as shown above.

We already have reported tethered of various transition metal complexes to the *internal* surface of the MCM-41 silica support [32,33]. This directed tethering has been achieved by deactivation/strengthening of the particle's external surface using 10% of a stoichiometric (relative to the total number of silanols estimated) amount of R_2SiCl_2 under non-diffusive conditions, and subsequent insertion of bifunctional bromo-alkyl tethers under diffusive conditions.

It would be possible to derivatise a chiral phosphine (e.g., BPPFA) to yield a *N,N'*-dimethylethylene diamine tail which might then be reacted with the surface bound bromo-alkyl group to give a tether incorporating two tertiary amine groups. This type of modification of the BPPFA ligand for the homogeneous case is known to induce significant directing capacities in catalytic reactions [34,35].

The capacity of chiral phosphines to bind the platinum group metals has led to an enormous diversity in the metals/reactions available to such sites. It would be possible to insert not only, analogous to Hayashi, et al. [36,37], gold (aldol cyclisation), palladium (Trost–Tsuji reaction) and platinum (hydroformylation), but also a further set of metal centres, sourced from various ruthenium cluster species which potentially allows an assessment of catalyst disper-

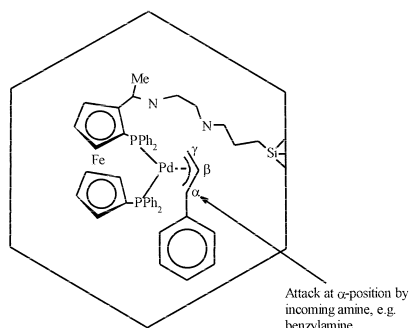


Fig. 4. Intermediate in the Pd-centred Trost–Tsuji reaction.

sion by electronmicroscopy [38–40]. The addition of the group VIII and IX metals would allow access to asymmetric hydrogenations [41], hydroformylations [42] and carbamate synthesis [43].

Analogously, it would be possible to generate tethered chiral catalysts made from the commercially available BPPM (BPPM = (2*S*,4*S*)-4-(diphenylphosphino) - 2 - [(diphenylphosphino) methyl]pyrrolidine) in a similar fashion to Stille et al. to compare the relative merits of the homogeneous vs. heterogeneous catalysts [44].

Preliminary results of some initial synthetic, structural and catalytic investigations with MCM41 immobilised chiral complexes point to the potential of the concepts discussed above being realised (cf. Fig. 4).¹

For example, the Pd-centred Trost–Tsuji reaction (also called allylic amination) wherein the cationic Pd(allyl) species undergoes nucleophilic attack at one of two possible sites (α , γ) in non-symmetric allylic substrates was used to investigate confinement induced selectivity and some differences in selectivity between homogeneous and heterogeneous catalysts could be observed. Furthermore, when comparing the homogeneously and the heterogeneously catalysed reactions of the BPPM systems, preliminary results also indicate significant selectivity changes for linear vs. branched products, sug-

gesting that further investigations along this general route should be profitable.

In conclusion, the various developments in the area of confined chiral catalysis and the related discussion of possibilities in mesopore derivatisations with chiral, catalytically active dppf complexes, highlight an exciting area of chemistry in which the mesoporous dimension has significant potential to make an impact.

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¹The full details of these investigations will be described elsewhere.

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