ACCOUNTS
of chemical research

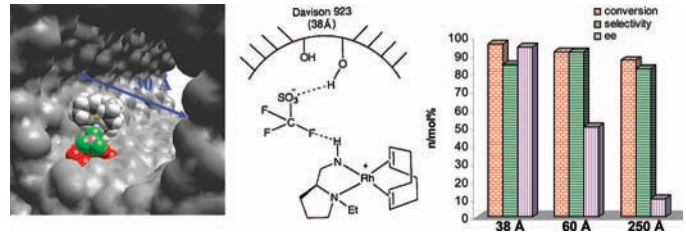
Exploiting Nanospace for Asymmetric Catalysis: Confinement of Immobilized, Single-Site Chiral Catalysts Enhances Enantioselectivity

JOHN MEURIG THOMAS*,† AND ROBERT RAJA*,‡

†Department of Materials Science, University of Cambridge, Cambridge CB2 3QZ, U.K., ‡School of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, U.K.

RECEIVED ON SEPTEMBER 27, 2007

CONSPECTUS



In the mid-1990s, it became possible to prepare high-area silicas having pore diameters controllably adjustable in the range ca. 20−200 Å. Moreover, the inner walls of these nanoporous solids could be functionalized to yield single-site, chiral, catalytically active organometallic centers, the precise structures of which could be determined using in situ X-ray absorption and FTIR and multinuclear magic angle spinning (MAS) NMR spectroscopy. This approach opened up the prospect of performing heterogeneous enantioselective conversions in a novel manner, under the spatial restrictions imposed by the nanocavities within which the reactions occur. In particular, it suggested an alternative method for preparing pharmaceutically and agrochemically useful asymmetric products by capitalizing on the notion, initially tentatively perceived, that spatial confinement of prochiral reactants (and transition states formed at the chiral active center) would provide an altogether new method of boosting the enantioselectivity of the anchored chiral catalyst. Initially, we anchored chiral single-site heterogeneous catalysts to nanopores covalently via a ligand attached to Pd(II) or Rh(I) centers. Later, we employed a more convenient and cheaper electrostatic method, relying in part on strong hydrogen bonding. This Account provides many examples of these processes, encompassing hydrogenations, oxidations, and aminations. Of particular note is the facile synthesis from methyl benzoylformate of methyl mandelate, which is a precursor in the synthesis of pemoline, a stimulant of the central nervous system; our procedure offers several viable methods for reducing ketocarboxylic acids. In addition to relying on earlier (synchrotron-based) in situ techniques for characterizing catalysts, we have constructed experimental procedures involving robotically controlled catalytic reactors that allow the kinetics of conversion and enantioselectivity to be monitored continually, and we have access to sophisticated, high-sensitivity chiral chromatographic facilities and automated high-throughput combinatorial test rigs so as to optimize the reaction conditions (e.g., H_2 pressure, temperature, time on-stream, pH, and choice of ligand and central metal ion) for high enantioselectivity. This Account reports our discoveries of selective hydrogenations and aminations of synthetic, pharmaceutical, and biological significance, and the findings of other researchers who have achieved similar success in oxidations, dehydrations, cyclopropanations, and hydroformylations. Although the practical advantages and broad general principles governing the enhancement of enantioselectivity through spatial confinement are clear, we require a deeper theoretical understanding of the details pertaining to the phenomenology involved, particularly through molecular dynamics simulations. Ample scope exists for the general exploitation of nanospace in asymmetric hydrogenations with transition metal complexes and for its deployment for the formation of C−N, C−C, C−O, C−S, and other bonds.

I. Introduction

Hitherto chemists have not been able to devise a generally applicable strategy for assembling new solid catalysts capable of facilitating the entire sweep of conversions embracing regioselective, shape-selective, and enantioselective processes. This work arose because one of us (J.M.T.) felt that

Published on the Web 05/28/2008 www.pubs.acs.org/acr
10.1021/ar700217y CCC: $40.75

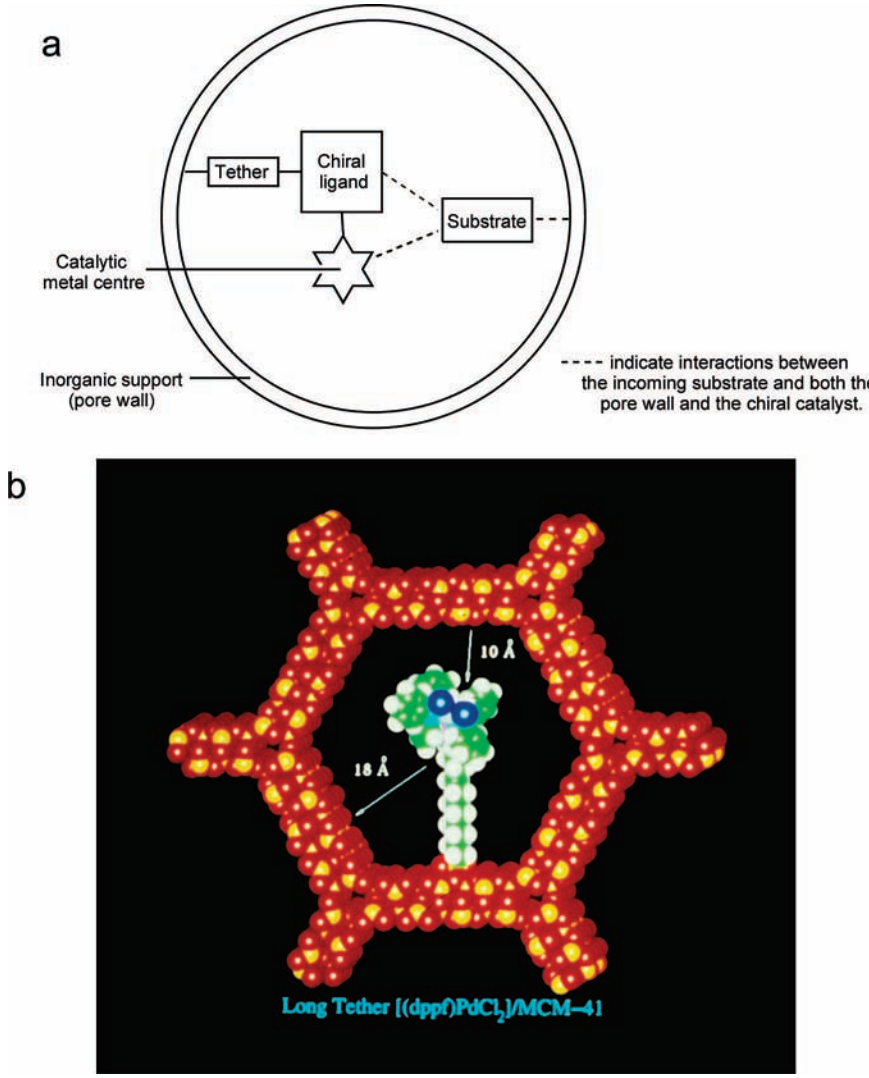


FIGURE 1. (a) Schematic representation of the confinement concept in which a substrate is incarcerated within the cavity of a chirally modified mesoporous host, which leads to chiral heterogeneous catalysis, and (b) an example of the tethered (*S*)-1-[(*R*)-1,2′-bis(diphenylphosphino)-ferrocenyl]ethyl-*N*,*N*′-dimethylethylenediamine palladium dichloride catalyst showing the influence of the pore wall.

such a strategy could be evolved. Late in the 1980s, he realized[1] that open-structure inorganic solids offered opportunities for the design of new heterogeneous catalysts that could contain accessible spatially well-separated and structurally well-defined active centers that simulate the behavior of homogeneous and enzymatic catalysts.

Numerous inorganic single-site heterogenous catalysts (SSHCs, with Brönsted or Lewis acid or coordinatively unsaturated metals or redox-active centers) were designed[2] by us and found to offer environmentally benign, single-step (and often solvent-free) routes for the preparation of heavy chemicals,[3,4] builder molecules,[5] some fine chemicals[6] and vitamins (e.g., niacin).[7] The majority of these regio- and shape-selective SSHCs were based on microporous solids possessing pore diameters up to ca. 10 Å. The active centers were incorporated into the open-structure hosts using proven methods of solid-state syntheses.[5]

In 1995, it was suggested to one of us (J.M.T.) by his post-doctoral colleague, Thomas Maschmeyer, that the newly available family of mesoporous silicas[8] that they had used[9] to anchor organometallic molecules for the preparation of single-site, Ti^{IV}-centered solid epoxidation catalysts might present novel opportunities for improving enantioselectivities in certain chiral conversions. The idea, illustrated in Figure 1a,b, was deliberate restriction of spatial freedom in the vicinity of an active center tethered to the inner wall of a nanopore in such a manner that a prochiral molecule approaching it and its chiral ligands would suffer additional interaction with the pore wall.[10,11] This interaction would be approximately equal to the energy difference between the two transition states that lead

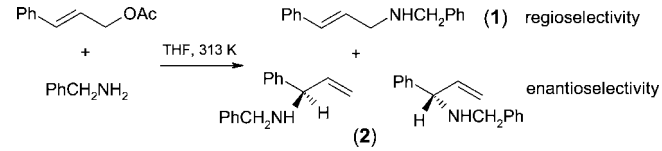
to the chiral products. Specifically, it was felt[11] that a prochiral olefin, approaching a single-site chiral catalyst such as one derived from a diphenyl-phosphinoferrocenyl (dppf) complex with palladium,[12] would, upon hydrogenation, exhibit enhanced enantiomeric excess (ee) compared with the value obtained when the same chiral catalyst functioned in homogeneous solution. If true, this confinement procedure could also yield enhanced enantioselectivities in hydroformylations, carbamate syntheses, and epoxidations using immobilized Mn^{III}−salen complexes, as well as in many other chiral conversions (see below).

By now, numerous examples exist (in our own work) where asymmetric catalysis occurs when appropriately selected chiral active centers are immobilized within the pores of mesoporous materials.[5,13−18] Moreover, short reviews[19−22] have recently appeared that confirm the merit of exploiting nanospace in the manner adumbrated above. Greater light has been shed on the precise way in which enantioselectivities are enhanced as a result of very recent molecular dynamics simulations,[23] which also embraces the fruitful notion of continuous chirality measure introduced by Alvarez and Avnir.[24] In addition, we have conducted specific tests involving a series of mesoporous silcas with well-defined but different values of pore diameter and shown (see below) that there is a progressive diminution in the enantiomeric excess (ee) values for a given conversion as the diameter increases (see Figure 7).

Others have also reported on or hinted at the scope that exists with confined chiral (immobilized) active centers in effecting several kinds of chiral catalytic reactions such as the well-documented examples of reductions, oxidations, epoxidations, Si−H insertions, aminations, cyclopropanations, and dehydrations in the open and patent literature.[22,23]

Some investigators have used polymeric supports or encapsulation within zeolites to construct their confined chiral catalysts. We have used silica exclusively in view of its numerous practical advantages: it (i) does not swell on exposure to solvent or reactants, (ii) has high mechanical and thermal resistance, (iii) has high stability during repeated recycling of the catalyst and separation of products, and (iv) is relatively easy to prepare (compared, for example, with encapsulation within zeolites). Because of the single-site nature of the chiral catalyst tethered inside the siliceous nanopore, the reactions yield molecularly well-defined products, and it is relatively straightforward to characterize in atomic detail (with multinuclear magic angle spinning (MAS) NMR, FTIR and extended X-ray absorption fine structure (EXAFS))[13,14,16] the precise atomic nature of the active centers.

SCHEME 1. Allylic Amination of Cinnamyl Acetate with Benzylamine (Trost−Tsuji Reaction)[16]



Initially, we utilized mesoporous silicas belonging to the so-called MCM-41 family[8] prepared from surfactants as structure-directing agents. Later we used the Davison family of mesoporous silca gels manufactured by the W.R. Grace Co. Whereas the former have highly ordered pores of a sharply defined diameter, controllable within the range 20−100 Å diameter, the Davison mesoporous silicas are disordered, but the pore-size distribution is centered around a particular (desired) diameter ranging from 38 to 250 Å. They are prepared[25] without recourse to the use of a surfactant or liquid-crystal structure-directing agent, as is generally the case with those mesoporous silicas now in extensive use.[26] Moreover they are thermally and mechanically robust and are inexpensive.

The approach we describe below to prepare products of high optical purity has many advantages. First, because the confined and anchored organometallic catalyst is heterogeneous, separation of products is straightforward. Second, when the anchored catalyst exhibits no tendency to leach away on successive use (there are several ways of ensuring this), the method may be used repeatedly without loss of expensive cation (e.g., Rh or Pd) or of even more expensive chiral ligands, in contrast to the situation that exists for homogeneous enantiomeric catalysts. In addition, there is adequate scope with such confined (nanoporous) chiral catalysts to utilize ligands that are relatively inexpensive and quite accessible, such as those involving nitrogen functionalization, rather than the more costly phosphorus ones, as many of the examples cited below show. Lastly, the diameters of the mesoporous silicas are large enough to permit facile diffusion of reactants to and products from the active sites. Quite high turnover frequencies are therefore expected and are indeed often found.

II. Proof of Principle via Heterogeneous Allylic Amination[13,14,16]

Our first practical test involved C−N bond formation in the allylic amination (the "well-known" Trost−Tsuji reaction[16]) of cinnamyl acetate, see Scheme 1. Three different catalysts were used (two heterogeneous (b, c) and one homogeneous (a)), but the chiral active center was identical in all three, see Figure 2.

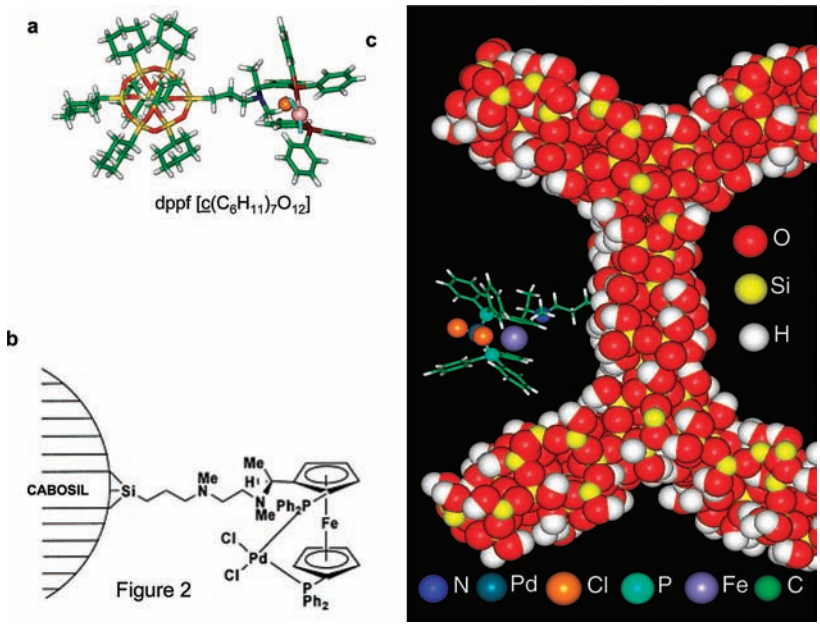


FIGURE 2. Depiction of the catalytically active dppf−diamine palladium dichloride catalyst attached to a soluble silsesquioxane moiety (a), tethered to a nonporous silica, Cabosil (b), and spatially confined within a mesoporous silica, MCM-41 (c).

The chiral ligand attached to the dppfPdCl$_2$, (dppf ≡ (*S*)-1-[(*R*)-1,2′-bis (diphenyl-phosphino)ferrocenyl]), which, in turn, was covalently tethered to the mesoporous silica, was ethyl-*N*,*N*′-dimethylethylenediamine. The confined catalyst used here is tethered inside ca. 30 Å diameter mesopores in an MCM-41 silica. The unconfined catalyst consists of a commercially available nonporous silica known as Cabosil, which has convex surfaces, to which was tethered the same chiral (*S*)-1-[(*R*)-1,2′-bis(diphenylphosphino)ferrocenyl]ethyl-*N*,*N*′-dimethylethylenediamine palladium dichloride active center. The homogeneous analogue (which is soluble in cyclohexane) of these two catalysts consists of the same active center attached to one of the vertices of the cyclohexyl silsesquioxane to form dppf [*c*(C$_6$H$_{11}$)$_7$Si$_7$O$_{12}$]. To ensure that no active sites are bound to the exterior surface of the silica, pretreatment with diphenyl dichlorosilane was carried out so as to convert all the silanol groups initially resident there into chemisorbed phenylated silane (see Figures 51 and 52 of ref 13 for more structural details).

Insofar as the procedural aspects of anchoring the tethered chiral organometallic moiety are concerned, the inner walls of the mesoporous silica were first derivatized with 3-propyltrichlorosilane. The ferrocenyl-based ligand was prepared by Hayashi's method,[12] it was incorporated by using an excess of it into the mesoporous silica (MCM-41), and then it was treated with PdCl$_2$/MeCN to yield the active, immobilized chiral catalyst. As described fully elsewhere,[14] the structural integrity of the organometallic dppf-Pd^{II} entity remained intact after immobilization. The EXAFS studies also indicated this,[13,14] and so did the ^{13}C and ^{31}P MAS NMR spectra.

TABLE 1. Allylic Amination of Cinnamyl Acetate and Benzylamine Using (*S*)-1-[(*R*)-1,2′-Bis(diphenylphosphino)ferrocenyl]ethyl-*N*,*N*′-dimethylethylenediamine Palladium Dichloride in Homogeneous Form, Tethered to Nonporous Silica (Cabosil) and Spatially Confined with Mesoporous Silica (MCM-41)[a]

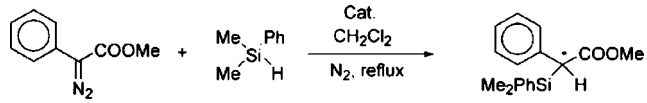
dppf-ferrocenyl-diamine-Pd catalyst	conv (%)	**1** (%)	**2** (%)	ee (%)
homogeneous	76	99+		
tethered silica	98	98	2	43
MCM-41-confined	99+	50	50	95

[a] See Scheme 1 for description of products.

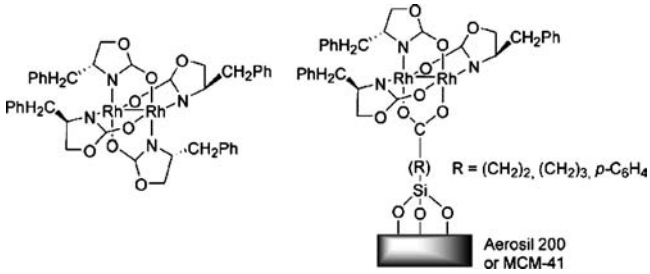
The results of this test (see Table 1.), chosen to probe simultaneously the regio- and enantioselectivity of the process, are very revealing. Whereas the unconfined heterogeneous catalyst yields a minute amount (2%) of the (desirable) branched product, the confined one yields an essentially equal amount of chiral (branched) and straight-chain products. More significantly, in the confined catalyst, we find that the product exhibits an ee value of 95%, far in excess of the 43% seen in the minute amount of branched product seen in the case of the unconfined catalyst. The homogeneous catalyst yields the straight-chain product almost exclusively; this is not surprising because there are no spatial restrictions that would bias the products toward the branched-chain isomer. We note in passing that the regioselectivity seen in the confined catalyst is not high.

It is very likely that with judicious selection of the size and shape of the anchored chiral catalyst and the nanospace

SCHEME 2. Si−H Insertion of Methyl Phenyl Diazoacetate with Dimethylphenylsilane Using Immobilized Dirhodium Carboxamide Catalysts



SCHEME 3. Chiral Dirhodium Carboxamide Complexes Anchored on Aerosil 200[27] Display More than Ten-Fold Increase in Enantioselectivity Compared with Their Homogeneous Analogues in the Si−H Insertion of Methyl Phenyl-Diazoacetate with Dimethylphenylsilane (See Scheme 2)



within which it is confined, many other C−N and C−C forming enantioselective reactions could be designed, utilizing other platinum-group metals (Ru, Os, Ir, and Pt) apart from the Pd and Rh used by us.

In a closely related (later) study, by Hultman et al.[27] involving Si−H insertion reactions (see Scheme 2), a significant improvement in enantioselectivity was observed by immobilizing a chiral dirhodium complex (see Scheme 3) on a silica known as Aerosil 200, the average pore diameter of which was ca. 500 Å. Using the same anchored complex and reagents but an MCM-41 silica (pore diameter 19 Å) for the confinement, there was no observable catalytic activity, probably because the pores of this silica were too small to accommodate the transition-state formed between the two reactants shown in Scheme 2. Given that Aerosil 200 has a rather broad pore-size distribution, it is conceivable that ee values substantially in excess of the 28% reported by Hultman et al. could be achieved if another commercially available nanoporous silica such as Davison 634 (with a sharply defined pore size of 60 Å) were used for this Si−H insertion reaction.

III. Selection of Other Examples Where Confinement in Nanopores Enhances Enantioselectivity

We have focused almost exclusively on our own work on asymmetric hydrogenation, and most of the examples cited below belong to that reaction type. For completeness, a few other reactions in which the confinement effect has boosted enantioselectivity are also given. The reader is also referred to very recent reviews by McMorn and Hutchings[21] and by Li et al.[22] who deal with enantiomeric oxidations in confined spaces especially with anchored Mn(salen) complexes.

SCHEME 4. The Two-Step (Conventional) Hydrogenation Ethyl Nicotinate to Ethyl Nipecotinate

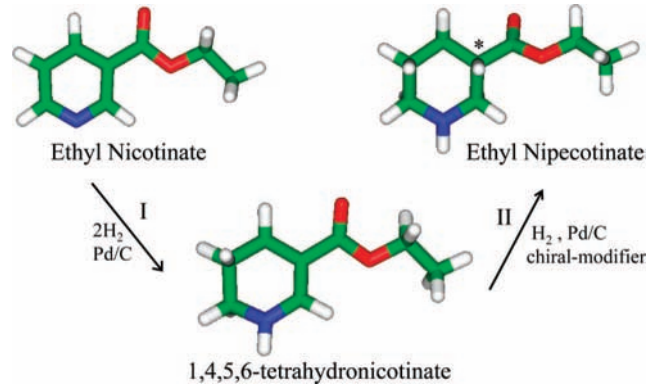


TABLE 2. The Effect of the Homogeneous (**I**), Tethered (**II**) and Spatially Confined (**III**) dppf-Diamine Palladium Dichloride Catalysts for the Asymmetric Hydrogenation of Ethyl Nicotinate to Ethyl Nipecotinate[a]

dppf-ferrocenyl-diamine-pd Catalyst	substrate (reactant)	*t* (h)	conv (%)	ee (%)
homogeneous (**I**)	ethyl nicotinate	72	15.9	
		120	27.2	
tethered silica (**II**)	ethyl nicotinate	72	12.6	2
		120	19.2	2
tethered to MCM-41 and confined inside mesopore (**III**)	ethyl nicotinate	48	35.5	17
		72	53.7	20

[a] See Scheme 4 and Figure 3 for more details.

a. The One-Step Conversion of Ethyl Nicotinate to Ethyl Nipecotinate. Ethyl nipecotinate is an important intermediate in biological and medicinal transformations. Previous efforts to hydrogenate enantioselectively an aromatic ring such as that in ethyl nicotinate had resulted in values of ee that were less than 6%, but a two-step (Scheme 4) process (using a cinchonidine-modified Pd catalyst supported on carbon) raised the ee to 19% at a conversion of 12%.[28] Using our (*S*)-1-[(*R*)-1,2′-bis(diphenylphosphino)ferrocenyl]ethyl-*N*,*N*′-dimethylethylene-diamine palladium dichloride catalyst confined within the 30 Å pores of mesoporous MCM-41, we achieved (in a single step) conversions in excess of 50% and an order of magnitude improvement in the ee (see Table 2.).[18] The homogeneous analogue, which was grafted to the vertex of an incompletely condensed silsesquioxane cube[29] (dppf[*c*(C_6H_{11})$_7$$Si_7O_{12}$]), resulted in a racemic product, thereby proving the chiral advantage achieved by confinement of the dppf-ethyl-*N*,*N*′-dimethylethylenediamine-$PdCl_2$, active center inside the siliceous mesopore (Figure 3).

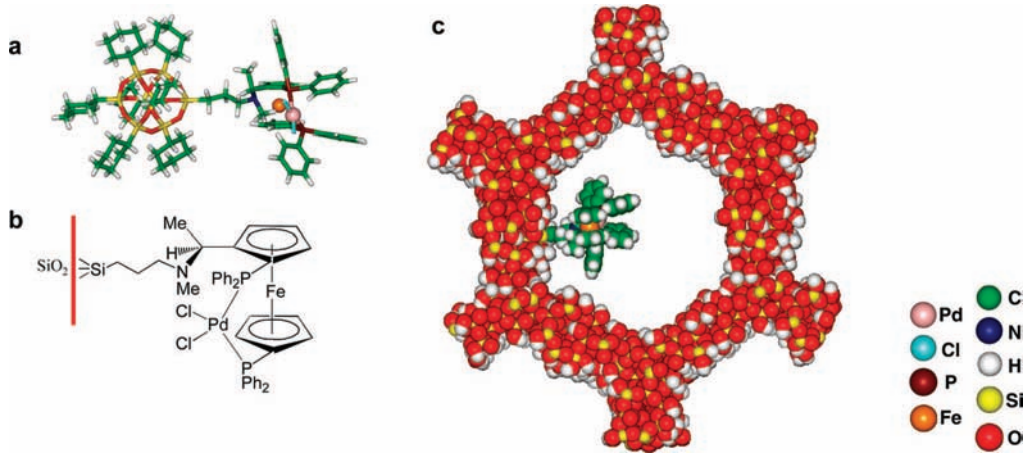
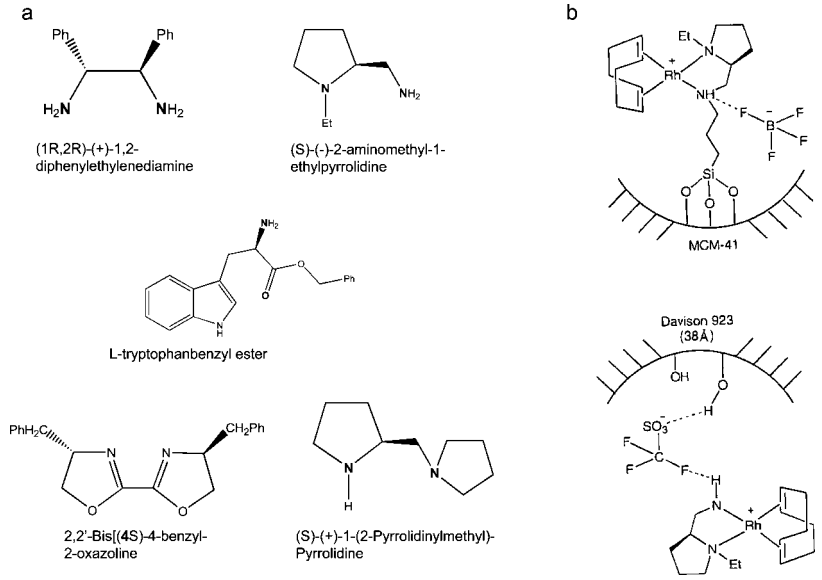


FIGURE 3. The dppf-diamine palladium dichloride catalyst confined within mesoporous silica (c) yields a substantial ee of the desired nipecotinate product compared with the homogeneous silsesquioxane analogue (a) and the nonconstrained variant tethered to nonporous silica, Cabosil (b), see Table 2.

SCHEME 5. Some Asymmetric Diamine Ligands (a) that Can Be Anchored to the Concave Surfaces of Mesoporous Silicas via Covalent (Using BF_4^- Anion) and Non-Covalent Methods (Using $CF_3SO_3^-$ Counterion) (b)



b. Asymmetric Hydrogenation of *E*-α-Phenylcinnamic Acid and Methyl Benzoylformate. Enantiomerically enriched α- and β-hydroxy carboxylic esters are valuable reagents and important intermediates in the preparation of pharmaceuticals and agrochemicals.[30,31] Esters of mandelic acid, for example, are used as precursors in the synthesis of pemoline, a central nervous system (CNS) stimulant, and in the production of artificial flavors and perfumes. Methyl mandelates are currently prepared by direct esterification of mandelic acid with alcohols in the presence of sulfuric acid.[32] This method of direct esterification with strong acids not only has the disadvantages associated with the corrosive nature of the acid but is usually accompanied by side reactions such as carbonization, oxidation, and etherification, which decrease the overall selectivity and enantiopurity.[33] In addition, expensive downstream processing and post-treatment pollution problems make the process commercially and environmentally unattractive.

Even though enzymes are currently more extensively used industrially than asymmetric transition-metal (TM) complexes for enantioselective catalytic conversions involving pharmaceuticals and agrochemicals, TM complexes are of growing importance in this context. Biological processes using microorganisms for asymmetric reduction have the inherent problem of stability of the enzyme and high costs associated with external cofactors.[31] Organometallic chiral complexes have, however, overwhelmingly, been utilized homogeneously, and their heterogeneous asymmetric counterparts have hitherto

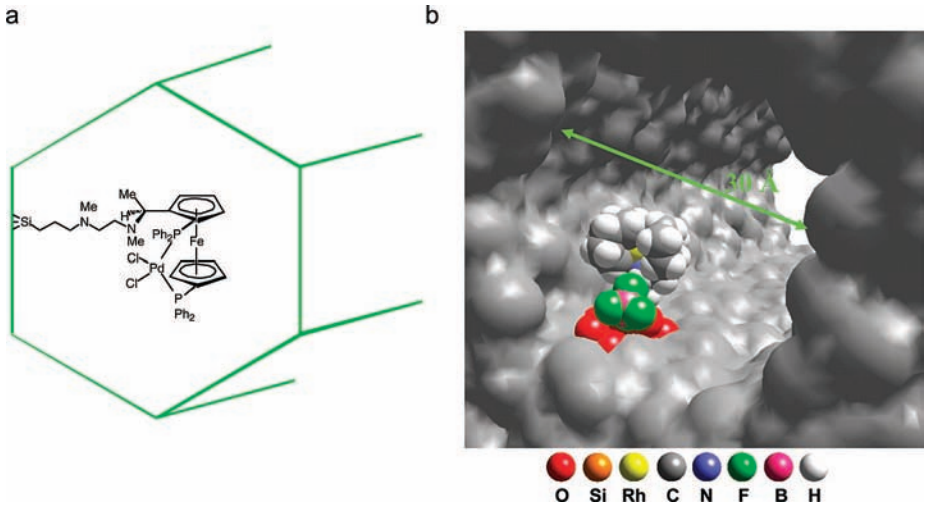
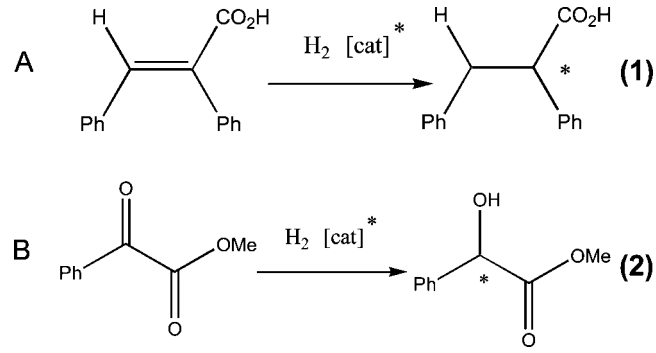


FIGURE 4. Enantioselectivity can be induced by tethering chiral dppf-diamine-based catalysts to the inner walls of mesoporous silica (a) or by anchoring diamine asymmetric ligands (shown in Scheme 5) onto concave surfaces (b). In the case of the former, it is the constraints imposed by the space surrounding the metal center that facilitates the enantioselectivity, whereas in the case of the latter, it is the restricted access generated by the concavity of the pore that is the principal determinant for the ensuing enantioselectivity.

performed disappointingly so far as their enantioselectivity is concerned, largely because they contained a range of different kinds of active centers, each with its own catalytic selectivity, a situation that contrasts markedly with the one prevailing here with single-site solid (chiral) catalysts that we describe below. Moreover, one of the major disadvantages of using customary chiral phosphines is their high cost—the cost of the ligand, in most applications, outweighs the cost of the final product—and sensitivity to oxidation, which limits their industrial applicability.

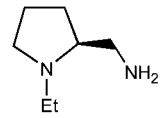
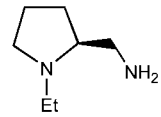
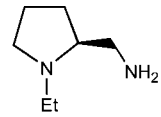
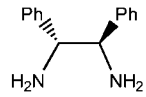
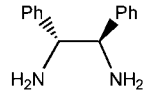
Comparatively few reports have hitherto been published in which Rh^{I} or Pd^{II} asymmetric complexes without phosphine ligands have been used to activate hydrogen, but a growing number employing nitrogen-containing ligands has appeared of late for the purpose of enantioselective conversions.[34] The validity of our earlier strategic principle (see section II), boosted by support from German Chemical Industry,[35–37] led us to evaluate the reality of tethering rather inexpensive diamine asymmetric ligands (Scheme 5), onto the inner walls of non-ordered mesoporous silicas. The argument behind using such an approach was to substantiate the concept that the diamine ligands tethered at concave silica surfaces would boost the enantioselectivity to a far greater degree, in contrast to having them attached to convex surfaces. The idea is that the confining dimensions of the interior of a pore should be able to restrict the possible orientations that a bulky reactant can assume as it approaches a chiral catalytic center that is attached to a concave pore wall (see Figure 4). If a reactant is nudged by its surroundings into the right orientation for a stereospecific reaction, then the reaction should proceed enantioselectively.

SCHEME 6. Schematic Representation of the Asymmetric Hydrogenation of *E*-α-Phenyl Cinnamic Acid and Methyl Benzoylformate



The ligands shown in Scheme 5 can be anchored covalently[17] to the inner walls of the mesoporous silica (MCM-41, in this case) using a BF_4^- anion that is hydrogen-bonded to the nitrogen of the amino group in the ligand to secure the cationic organometallic catalyst in place. It is seen that the molecular cation (that functions as a chiral catalyst) is hydrogen-bonded (visible in the crystal structure)[17] to the BF_4^- anion via the pendant nitrogen of the pyrrolidine. The catalyst itself is pseudo-square-planar where the metal (Rh^{I} or Pd^{II}) is bonded to 1,5-cyclooctadiene (COD). The results for the hydrogenation of *E*-α-phenylcinnamic acid and methylbenzoylformate (Scheme 6) are summarized in Table 3. Further, by grafting the Rh^{I} chiral complex on both a concave silica (using MCM-41, 30 Å diameter) and a convex silica (a non-porous, Cabosil silica), we established beyond doubt that it is

TABLE 3. Asymmetric Hydrogenation of *E*-α-Phenyl Cinnamic Acid and Methyl Benzoylformate[a]) Using Covalently Tethered Rh(I) and Pd(II) Chiral Catalysts[b]

Amine and diene	Catalyst	Substrate	Metal	Time (hr)	Conv.	ee (1)	ee (2)
 COD	Homogeneous	α-phenyl cinnamic acid	Rh(I)	24	74	93	
	Heterogeneous			24	80	96	
	Homogeneous	Methyl benzoyl formate	Rh(I)	24	95		0
	Heterogeneous			1	98		91
 NBD	Homogeneous	α-phenyl cinnamic acid	Rh(I)	24	88	64	
	Heterogeneous			24	99	91	
	Homogeneous	Methyl benzoyl formate	Rh(I)	0.5	85		18
	Heterogeneous			2	100		99
 allyl	Homogeneous	α-phenyl cinnamic acid	Pd(II)	24	100	76	
	Heterogeneous			24	93	93	
	Homogeneous	Methyl benzoyl formate	Pd(II)	2	100		0
	Heterogeneous			2	97		87
 COD	Homogeneous	α-phenyl cinnamic acid	Rh(I)	24	57	81	
	Heterogeneous			24	98	93	
 allyl	Homogeneous	α-phenyl cinnamic acid	Pd(II)	24	95		79
	Heterogeneous			24	75		88

[a] See Scheme 6 for description of products and ref. 17a for experimental details on catalyst preparation. [b] Reaction conditions: substrate = 0.5 g; solvent (methanol) = 30 mL; homogeneous catalyst[17a] = 10 mg; heterogeneous catalyst[17a] = 50 mg; H_2 = 20 bar; T = 313 K; counterion = BF_4^-.

the spatial restrictions imposed by the concave surface at which the active center is located that enhances the enantioselectivity of the catalyst (see Figure 5).

c. The Influence of Pore Diameter on the Efficacy of Anchored Enantiomeric Catalysts. Because we believe that our own approach, adumbrated above, pertaining to heterogenization of asymmetric catalysts within nanoporous silica constitutes a paradigm shift in regard to the development of high-performance chiral (solid) catalysts for enantioselective syntheses and other organic processes, we undertook a systematic study of a range of nanoporous silicas in each of which there was a very narrow spread of pore diameter. In carrying out this study,[15] we abandoned our earlier (see section IIIb) practice of using chiral catalysts covalently tethered to the inner walls of the mesopores. Instead we adopted the noncovalent immobilization approach described by Rege et al.[38] In this method, a surface-bound triflate ($CF_3SO_3^-$) counterion securely anchors the cationic chiral rhodium complex Rh^I(COD)PMP, where COD is cyclo-octadiene and PMP stands for the chiral ligand (*S*)-(+)-1-(2-pyrrolidinylmethyl)-pyrrolidine (see Figure 6 and bottom right drawing of Scheme 5). This straightforward electrostatic method of confining cationic chiral catalysts within the nanopores circumvents the need for ligand modification to secure covalent tethering. Furthermore, catalysts prepared via this method do not require a brominated trichlorosilane tether for anchoring the ligand and hence are an order of magnitude cheaper than the covalently tethered analogues. The methodology is also quick and convenient and results in robust effective catalysts, which make them industrially attractive. Its further advantages are elaborated elsewhere, see Rouzard et al.[17b]

Three other cationic chiral catalysts confined within mesoporous silicas were also used (all with the $CF_3SO_3^-$ anion): Pd^I-(allyl)PMP; Rh^I(COD)AEP, and Rh^I(COD)DED, where AEP stands for (*S*)-(-)-2-aminomethyl-1-ethyl-pyrrolidine and DED for (1*R*,2*R*)-(+)-1,2-diphenyl-ethylenediamine]. The test reaction was the asymmetric hydrogenation of methylbenzoylformate to the corresponding methyl mandelate (see section IIIb;

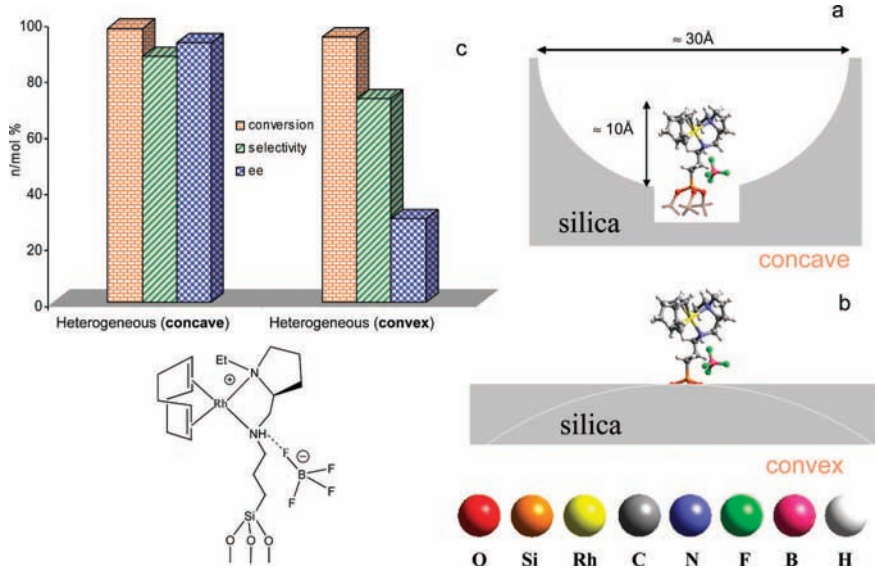


FIGURE 5. Graphical model (to scale) showing the constraints imposed on a Rh(I)-(COD)−(*S*)-(−)-2-aminomethyl-1-ethyl pyrrolidine catalyst when it is anchored on a concave (a) and convex surface (b). The computational model shown here has been derived from the crystal structure of the Rh(I) complex, which clearly indicates that the BF_4^- anion is hydrogen-bonded to the nitrogen of the amino groups. The chiral diamine organometallic catalyst constrained at the concave silica surface (a) surpasses the performance (both in terms of selectivity and ee) of the same catalyst anchored to a convex surface (shown in panel b) in the asymmetric hydrogenation of *E*-α-phenyl cinnamic acid, see Scheme 6A.

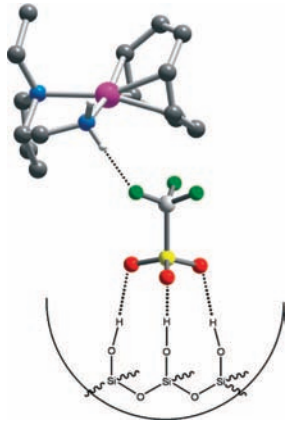


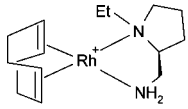
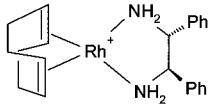
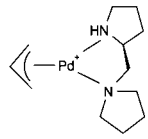
FIGURE 6. Schematic illustration of a cationic chiral organometallic catalyst, [Rh(I)(COD)PMP] (PMP = (*S*)-(+)-1-(2-pyrrolidinylmethyl)-pyrrolidine and COD = cyclo-octadiene), which is noncovalently anchored via a N−H···F hydrogen bond with the triflate ion, $CF_3SO_3^-$, to the curved inner surface of a 38 Å diameter pore of a mesoporous silica support (Davison 923). Atoms are indicated as follows: Rh, purple; N, blue; H, white; F, green; C, gray; S, yellow; O, red.

Scheme 6). In their homogeneous form, only the Rh(COD)PMP and Pd(allyl)PMP exhibit any significant enantioselectivity (ee) under the reaction conditions (see Table 4 and Figure 7) employed by us, whereas the other two homogeneous catalysts (namely Rh(COD)AEP and Rh(COD)DED) did not display any significant ee. This is probably because the bulkiness of PMP in comparison to that of AEP and DED exerts further spatial congestion in the vicinity of the active center.

Figure 7 and Table 4 summarize the results for the Pd^{I}(allyl)PMP, Rh^{I}(COD)AEP, Rh^{I}(COD)DED, and Rh^{I}(COD)PMP chiral catalysts and show that, as expected from arguments given above, chiral restriction does indeed boost the ee values in a manner that logically reflects the declining influence of spatial constraint in proceeding from the 38 Å to the 60 Å to the 250 Å pore-diameter silica. For the heterogeneous catalysts the trend with Rh(COD)PMP is mirrored by both AEP and DED ligands, and it is clear that even when some of the asymmetric catalysts exhibit significant ee's under homogeneous conditions, their performance is much enhanced when immobilized in a constrained environment. It is also noteworthy and reassuring that the noncovalent method of anchoring the organometallic catalyst does not lead to facile leaching when the catalyst is recycled. Further details are given in recently filed patents.[36,37,39]

d. Asymmetric Epoxidations Using Confined Mn^{III}(Salen) Complexes. There is particular interest in the use of immobilized chiral Mn^{III}(salen) complexes for the epoxidation of unfunctionalized olefins,[40] a subject of considerable current interest.[41] A study by Piaggio et al.[42] used this chiral complex anchored to an Al^{III}-framework substituted MCM-41 mesoporous silica for the asymmetric epoxidation of (*Z*)-stilbene with iodosyl benzene (PhIO) as an oxygen donor. When this reaction (see Scheme 7) was carried out with the same catalyst in homogeneous solution, the ratio of the cis/trans products was 0.4. But with the confined catalyst the ratio

TABLE 4. Asymmetric Hydrogenation of Methyl Benzoylformate for the Synthesis of Methyl Mandelate[a] Using Rh(I) and Pd(II) Chiral Catalysts Non-Covalently Anchored onto Mesoporous Silica[b]

Catalyst	Catalyst	Silica Type (pore dimension)	Metal	t (h)	Conv.	TOF (h^{-1})	ee
 Rh(COD)AEP	Homogeneous	-	Rh(I)	2.0	62	46	0
	Heterogeneous	Davison 923 (38 Å)	Rh(I)	0.5	82.6	542	82
		Davison 634(60 Å)		0.5	67.1	440	65
		Davison 654 (250 Å)		0.5	44.6	292	0
 Rh(COD)DED	Homogeneous	-	Rh(I)	2.0	69.9	60	0
	Heterogeneous	Davison 923 (38 Å)	Rh(I)	2.0	98.1	188	79
		Davison 634(60 Å)		2.0	81.5	190	63
		Davison 654 (250 Å)		2.0	83.1	159	4
 Pd(allyl)PMP	Homogeneous	-	Pd(II)	0.5	96.0	264	55
	Heterogeneous	MCM-41(30 Å)	Pd(II)	0.5	89.8	542	62
		Catalyst Recycled		0.5	91.5	551	66

[a] A precursor in the manufacture of pemoline, a CNS stimulant. [b] Reaction conditions: methyl benzoylformate = 0.5 g; solvent (methanol) = 30 mL; catalyst (homogeneous) ≈ 10 mg; catalyst (heterogeneous) ≈ 50 mg; H_2 = 20 bar; T = 313 K; counterion = $CF_3SO_3^-$.

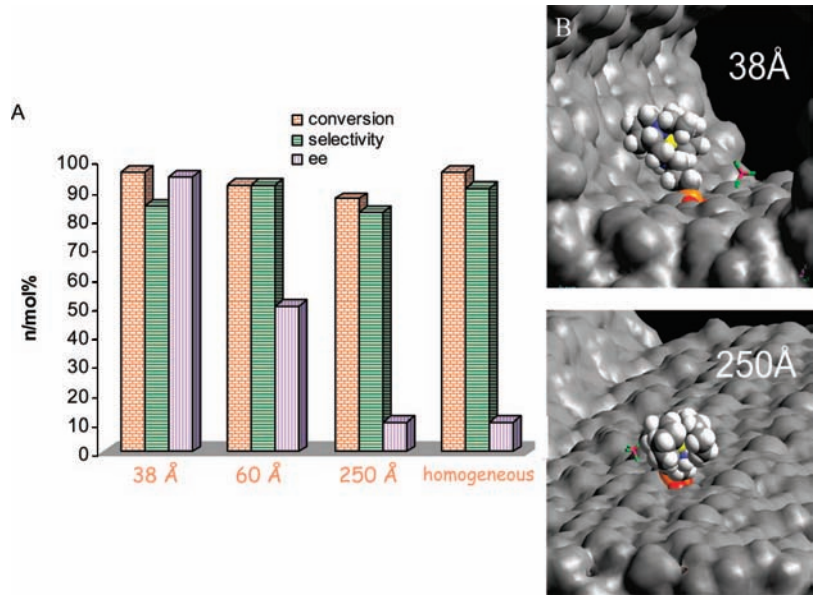
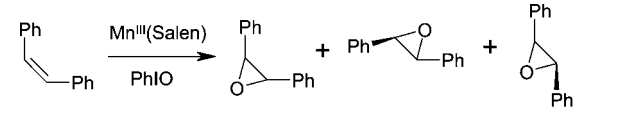


FIGURE 7. The effect of surface curvature and concavity of the support (B) in facilitating the asymmetric hydrogenation of methyl benzoylformate to methyl mandelate (A), using [Rh(COD)−(*S*)-(+)-1-(2-pyrrolidinylmethyl)-pyrrolidine] $CF_3SO_3^-$ catalysts anchored onto mesoporous silicas of varying pore dimensions.

increased 10-fold, the rationale being that rotation of the radial intermediate is retarded in the confined state, thereby favoring the formation of the cis product.

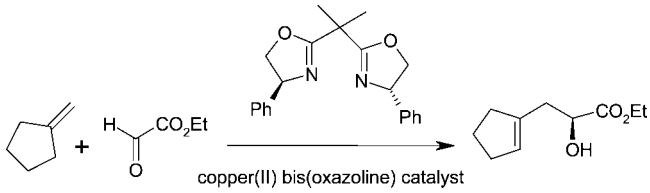
In a recent detailed study, Zhang and Li[43] investigated the asymmetric epoxidation of 6-cyano-2,2-dimethylchromene using chiral Mn^{III}(salen) catalysts immobilized within mesoporous silica. In particular, they varied the length of the axial linkage separating the Mn^{III}(salen) active site from the wall of the nanopores, the diameters of which were also systematically varied. In harmony with the results of Raja et al.[15]

SCHEME 7. Asymmetric Epoxidation of (*Z*)-Stilbene with Iodosyl Benzene Using Immobilized Chiral Mn^{III}(Salen) Complexes



(*Z*)-stilbene cis-epoxide (*R*)-trans-epoxide (*S*)-trans-epoxide

SCHEME 8. Chiral Copper(II) Bis(oxazoline) Complexes Constrained within Confined Spaces Showed Enhanced ee's for the Reaction of Methylenecyclopentane with Ethyl Glyoxylate



reported earlier (dealing with asymmetric hydrogenation), these workers found that the ee values increased as the pore diameter decreased and as the length of the linkage increased. For the confined catalyst, ee values of 90% were obtained, whereas with the epoxidations in homogeneous solution the ee's were ca. 80%. An earlier study by Balkus et al.[44] investigated the asymmetric (Mn^{III}(salen)-catalyzed) epoxidation of α-methyl styrene with hypochlorite and found a distinct enhancement of ee for the confined catalyst over the homogeneous one, 91% compared with 51%.

Earlier still, Corma et al.[45] using Mo^{VI} complexes of chiral ligands derived from (2*S*,4*R*)-4-hydroxyproline, heterogenized into ultrastabilized zeolite-Y that had been treated to produce a range of mesopores, found higher values (47%) of ee for the asymmetric oxidation of geraniol (with *tert*-butylhydroperoxide as oxygen source) than those obtained in homogeneous solution (28%).

e. Other Examples Where Confinement in Nanopores Boosts Enantioselectivity. Leaving aside the well-known work on "ship-in-bottle" systems involving zeolites as host,[46] the work of Hutchings[47] has shown the merit of modifying zeolite-Y with dithiane oxide so as to engender novel enantioselectivity. It transpires that when zeolite-Y is modified by an enantiomerically enriched dithiane 1-oxide, the resulting solid catalyst is selective in the dehydration of one of the enantiomers of butan-2-ol, even though both enantiomers are present in equal concentration at the inlet of the reactor.

Taylor et al.[48] also immobilized copper(II) bis(oxazoline) complexes with both zeolite-Y and Al^{III}-substituted MCM-41 mesoporous silica. Superior enantioselectivity (ee of 93%) was obtained for the confined chiral Cu^{II} complex (compared with 57% for the homogeneous catalyst) in the reaction of methylenecyclopentane with ethyl glyoxalate (see Scheme 8). It was found by Corma et al.[45] that substantially higher values of ee were exhibited by Cu^{II}-bis(oxazoline) anchored on mesoporous silica than in the homogeneous reaction in the Friedel–Crafts hydroxylation of 1,4-dimethoxybenzene with 3,3,3-trifluoropyruvate.

Mayoral and co-workers have recently shown[49] that chiral bis(oxazoline)–copper complexes can be easily immobilized onto anionic solids, such as clays and nafion–silica nanocomposites, or in ionic liquids and used as heterogeneous catalysts in cyclopropanation reactions involving styrene and ethyl diazoacetate. Their theoretical calculations[49b] indicate that supported azabis(oxazoline)–copper complexes are significantly more stable than the bis(oxazoline) analogues due to electrostatic metal–ligand interactions that result in high enantioselectivities (90% ee).

Apart from using other metal centers, besides the Pd and Rh that we have explored, there is also much scope for the use of other ligands such as semicorrine[50] and a diverse range of different nucleophiles.[51,52]

IV. Computational Aspects of the Confinement Effect

First, it is prudent to distinguish between enhancement of ee for a particular reaction carried out heterogeneously in comparison with the homogeneous reaction on the one hand from the situation in which the heterogeneous reaction genuinely involves confinement of the chiral catalyst and spatial restriction in access to the active site by the prochiral reactant on the other. Often there is a higher ee observed by immobilization at the solid surface simply because this prevents the formation of inactive bi- or multinuclear chiral complexes, which tend to occur in homogeneous solution. Here we are concerned only with the influence of confinement. Sometimes, as one might expect, the confinement does not lead to enhanced values of ee. This depends on the system under investigation, but generally the ee's are boosted by the spatial restriction. So far, hardly any quantitative analysis (quantum mechanical or otherwise) has been made to provide insight into these steric effects, which yield such important practical consequences. A very recent molecular dynamics simulation by Malek et al.[23] on anchored Mn^{III}(salen) complexes in mesoporous silica has, however, led to a deeper understanding of the detailed perturbations that contribute to enhanced enantioselectivities. These workers have invoked the concept of the "continuous chirality measure" (CCM)[23] to quantify the chirality content of the Mn^{III}(salen) complex. They showed that the immobilized linker entity influences the enantioselectivity of the catalyst owing to the increasing chirality content of the Mn^{III}(salen) complex. Their simulations with a typical docked olefin (β-methyl styrene) suggest that cis and trans reactants have different levels of asymmetric induction in the Mn^{III}(salen) complex. It transpires that a trans reactant (olefin)

induces higher chirality in the immobilized Mn^{III}(salen) complex than the cis olefin. This fact enabled Malek et al.[23] to interpret why such significant differences in ee result when the confined chiral catalyst is compared with either an unconfined (but immobilized) catalyst or the same catalyst in homogeneous solution. There is doubtless room for further, more sophisticated simulations using, for example, the "ONETEP" procedure of Skylaris et al.[53] where a very large number of participating atoms may be included in the simulation.

We thank Dr. R. Hanko, Dr. W. Stahl, Dr. A. Klausener, and Dr. U. Notheis (Bayer Chemicals Leverkusen) for their keen interest and support and Professor B. F. G. Johnson and Prof. K. D. M. Harris for numerous stimulating discussions. Lanxess (now Saltigo), Leverkusen, Germany, is gratefully acknowledged for financial assistance and EPSRC (U.K.) for a rolling grant (to J.M.T.) up to 2000.

BIOGRAPHICAL INFORMATION

John Meurig Thomas taught and researched at the University of Wales (Bangor and Aberystwyth) for 20 years before becoming the Head of the Department of Physical Chemistry, University of Cambridge (1978−1986). From 1986 to 1991, he was the Director of the Royal Institution of Great Britain, London, and of the Davy-Faraday Research Laboratory there, where he occupied the Chair created for Michael Faraday. He is now Hon. Prof. of Solid State Chemistry at the Department of Materials Science, University of Cambridge. His awards for solid state, materials, and surface chemistry include the Davy Medal, Rutherford and Bakerian Lectureships of the Royal Society, the Faraday Medal, the Stokes medal (and five others from the Royal Society of Chemistry), the Messel Gold Medal of the Society of Chemical Industry, the Willard Gibbs Gold Medal of the American Chemical Society, and the Semenov Medal of the Russian Academy. The European Federation of Catalyst Societies elected him their first peripatetic Francois Gault lecturer, and in 1999, he became the first recipient of the ACS award for creative research in homogeneous and heterogeneous catalysis. His Royal Institution Christmas Lectures on crystals were broadcast nationally on BBC TV in 1987 and 1988. He has wide-ranging interests in solid-state chemistry described, in part, in nine Accounts, but his current activities are devoted mainly to the design of new catalysts for sustainable and green processes and the development of new electron-based techniques in solid-state science. In 1991, he was knighted for his services to Chemistry and the popularization of science.

Robert Raja was awarded an 1851 Exhibition by Royal Commission to pursue an independent postdoctoral research program at the Royal Institution of Great Britain after graduating in 1997. He worked with Bayer Chemicals, Leverkusen, Germany (2000−2003), as a Research Chemist and was instrumental in developing one of the first series of heterogeneous, organometallic chiral catalysts for fine-chemical and pharmaceutical applications. He moved to Cambridge University in 2004 as a Senior Research Associate, where the focal theme of his research entailed the discovery and design of novel microporous and mesoporous solids, for application as heterogeneous catalysts in chemical, fine-chemical, pharmaceutical, and environmental technologies using energy-renewable feedstocks and sustainable processes. In June 2006, he was appointed as Associate Professor/Reader in the School of Chemistry at the University of Southampton. He is the author of over 100 publications and also the inventor or coinventor of 38 International Patents. He was recently awarded the Barrer Award (2005) by the Royal Society of Chemistry and Society of Chemical Industry in recognition of his outstanding contributions to preparative materials chemistry and their application to industrial catalysis.

FOOTNOTES

* Correspondence data. J.M.T.: tel +44-1223-334300; fax +44-1223-740360; e-mail jmt2@cam.ac.uk. R.R.: tel +44-2380-592144; fax +44-2380-593781; e-mail R.Raja@soton.ac.uk.

REFERENCES

1 Thomas, J. M. Uniform heterogeneous catalysts: The role of solid-state chemistry in their development and design. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1673–1691.

2 (a) Thomas, J. M.; Raja, R. Catalytically active centres in porous solids: Design and performance of highly selective new catalysts. *Chem. Commun.* **2001**, 675–687. (b) Thomas, J. M.; Raja, R.; Sankar, G.; Bell, R. G.; Lewis, D. W. Benign by design: New catalysts for an environmentally conscious age. *Pure Appl. Chem.* **2001**, *73*, 1087–1101.

3 Thomas, J. M.; Raja, R. Design of a "green" one-step catalytic production of ε-caprolactam (precursor of nylon-6). *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 13732–13736.

4 Raja, R.; Sankar, G.; Thomas, J. M. Designing a molecular sieve catalyst for the aerial oxidation of n-hexane to adipic acid. *Angew. Chem., Int. Ed.* **2000**, *39*, 2313–2316.

5 (a) Thomas, J. M.; Raja, R.; Lewis, D. W. Single-site heterogeneous catalysts. *Angew. Chem., Int. Ed.* **2005**, *44*, 6456–6482. (b) Thomas, J. M.; Raja, R. The advantages and future potential of single-site heterogeneous catalysts. *Topics Catal.* **2006**, *40*, 3–17. (c) Jones, M. D.; Raja, R.; Thomas, J. M.; Johnson, B. F. G. A new approach to the design of heterogeneous single-site enantioselective catalysts. *Topics Catal.* **2003**, *25*, 71–79.

6 Raja, R.; Thomas, J. M.; Greenhill-Hooper, M.; Doukova, V. A high-performance selective oxidation system for the facile production of fine chemicals. *Chem. Commun.* **2007**, 1924–1926.

7 Raja, R.; Thomas, J. M.; Greenhill-Hooper, M.; Ley, S. V.; Paz, F. A. A. Facile, one-step production of Niacin (vitamin B3) and other nitrogen-containing pharmaceutical chemicals with a single-site heterogeneous catalyst. *Chem.—Eur. J.* **2008**,in press.

8 (a) Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C.; Beck, J. S. Ordered mesoporous molecular-sieves synthesized by a liquid-crystal template mechanism. *Nature* **1992**, *359*, 710–712. (b) Thomas, J. M. The chemistry of crystalline sponges. *Nature* **1994**, *368*, 289–290.

9 Maschmeyer, T.; Rey, F.; Sankar, G.; Thomas, J. M. Heterogeneous catalysts obtained by grafting metallocene complexes onto mesoporous silica. *Nature* **1995**, *378*, 159–162.

10 (a) Thomas, J. M. Tales of tortured ecstasy: Probing the secrets of solid catalysts. *Faraday Discuss.* **1995**, *100*, C9−C27. (b) Maschmeyer, T. Oral presentation at the Annual Progress Meeting of the Davy Faraday Research Laboratories, DRFL Annual Report, 02 April, 1995.

11 Thomas, J. M.; Maschmeyer, T.; Johnson, B. F. G.; Shephard, D. S. Constrained chiral catalysts. *J. Mol. Catal. A* **1999**, *141*, 139–144.

12 Hayashi, T.; Hagihara, T.; Katsuro, Y.; Kumada, M. Asymmetric cross-coupling of organozinc reagents with alkenyl bromides catalyzed by a chiral ferrocenylphosphine palladium complex. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 363–364.

13 Thomas, J. M. Design, synthesis and *in situ* characterization of new solid catalysts. *Angew. Chem., Int. Ed.* **1999**, *38*, 3588–3628.

14 Johnson, B. F. G.; Raynor, S. A.; Shephard, D. S.; Maschmeyer, T.; Thomas, J. M.; Sankar, G.; Bromley, S. T.; Oldroyd, R. D.; Gladden, L. G.; Mantle, M. D. Superior performance of a chiral catalyst confined within mesoporous silica. *Chem. Commun.* **1999**, 1167–1168.

15 Raja, R.; Thomas, J. M.; Jones, M. D.; Johnson, B. F. G.; Vaughan, D. E. W. Constraining asymmetric organometallic catalysts within mesoporous supports boosts their enantioselectivity. *J. Am. Chem. Soc.* **2003**, *125*, 14982–14983.

16 (a) Trost, B. M.; Keinan, E. Steric steering with supported palladium catalysts. *J. Am. Chem. Soc.* **1978**, *100*, 7779–7781. (b) Tsuji, J. *Palladium reagent and catalysis: Innovation in organic synthesis*; Wiley, New York, 1995.

17 (a) Jones, M. D.; Raja, R.; Thomas, J. M.; Johnson, B. F. G.; Lewis, D. W.; Rouzard, J.; Harris, K. D. M. Enhancing the enantioselectivity of novel homogeneous organometallic hydrogenation catalysts. *Angew. Chem., Int. Ed.* **2003**, *42*, 4326–4331. (b) Rouzard, J.; Jones, M. D.; Raja, R.; Johnson, B. F. G.; Thomas, J. M.; Duer, M. Potent new heterogeneous asymmetric catalysts. *Helv. Chim. Acta* **2003**, *86*, 1753–1759.

18 Raynor, S. A.; Thomas, J. M.; Raja, R.; Johnson, B. F. G.; Bell, R. G.; Mantle, M. D. A one-step, enantioselective reduction of ethyl nicotinate to ethyl nipecotinate using a constrained, chiral, heterogeneous catalyst. *Chem. Commun.* **2000**, 1925–1926.

19 Thomas, J. M.; Johnson, B. F. G.; Raja, R.; Sankar, G.; Midgley, P. A. High-performance nanocatalysts for single-step hydrogenations. *Acc. Chem. Res.* **2003**, *36*, 20–30.

20 (a) Song, C. E.; Lee, S,G. Supported chiral catalysts on inorganic materials. *Chem. Rev.* **2002**, *102*, 3495–3524. (b) Song, C. E.; Kim, D. H.; Choi, D. S. Chiral organometallic catalysts in confined nanospaces: Significantly enhanced enantioselectivity and stability. *Eur. J. Inorg. Chem.* **2006**, 2927–2935.

21 McMorn, P.; Hutchings, G. J. Heterogeneous enantioselective catalysts: strategies for the immobilization of homogeneous catalysts. *Chem. Soc. Rev.* **2004**, *33*, 108–122.

22 (a) Li, C. Chiral synthesis on catalysts immobilized in microporous and mesoporous materials. *Catal. Rev. Sci. Eng.* **2004**, *46*, 419–492. (b) Li, C.; Zhang, H. D.; Jiang, D. M.; Yang, Q. H. Chiral catalysis in nanopores of mesoporous materials. *Chem. Commun.* **2007**, 547–558.

23 Makek, K.; Jansen, A. P. J.; Li, C.; van Santen, R. A. Enantioselectivity of immobilized Mn-salen complexes: A computational study. *J. Catal.* **2007**, *246*, 127–135.

24 Alvarez, S.; Alemany, P.; Avnir, D. Continuous chirality measures in transition metal chemistry. *Chem. Soc. Rev.* **2005**, *34*, 313–326.

25 (a) Iler, R. K. *The chemistry of silica: Solubility, polymerization, colloid and surface properties, and biochemistry*; Wiley Interscience: New York, 1979. (b) Acker, E. G. Characterization of acid-set silica hydrosols, hydrogels and dried gel. *J. Colloid Interface Sci.* **1970**, *32*, 41–48.

26 Terasaki, O., Ed. *Mesoporous crystals and related nano-structured materials*; Elsevier: Amsterdam, 2004.

27 (a) Hultman, H. M.; de Lang, M.; Nowotny, M.; Arends, I.W.C.E.; Hanefeld, U.; Sheldon, R. A.; Maschmeyer, T. Chiral catalysts confined in porous hosts I: Synthesis. *J. Catal.* **2003**, *217*, 264–274. (b) Hultman, H. M.; de Lang, M.; Arends, I.W.C.E.; Hanefeld, U.; Sheldon, R. A.; Maschmeyer, T. Chiral catalysts confined in porous hosts II: Synthesis. *J. Catal.* **2003**, *217*, 275–283.

28 Blaser, H. U.; Honig, H.; Studer, M.; Wedemeyer-Exl, C. Enantioselective synthesis of ethyl nipecotinate using cinchona modified heterogeneous catalysts. *J. Mol. Catal. A* **1999**, *139*, 253–257.

29 Feher, F. J.; Newman, D. A.; Walzer, J. F. Silsesquioxanes as models for silica surfaces. *J. Am. Chem. Soc.* **1989**, *111*, 1741–1748.

30 Tashiro, Y.; Nagashima, T.; Aoki, S.; Nishizawa, R. Process for preparing optically active amino acid or mandelic acid, U.S. Patent 4,224,239, 1980.

31 Endo, T.; Tamura, K. Process for producing R(-)-mandelic acid and derivatives thereof. U.S. Patent 5,223,416, 1993.

32 Haslam, E. Recent developments in methods for the esterification and protection of the carbonyl group. *Tetrahedron* **1980**, *36*, 2409–2433.

33 Yadav, G. D.; Bhagat, R. D. Synthesis of methyl phenyl glyoxylate via clean oxidation of methyl mandelate over a nanocatalyst based on heteropolyacid supported on clay. *Org. Process Res. Dev.* **2004**, *8*, 879–882.

34 (a) Togni, A.; Venanzi, L. M. Nitrogen donors in organometallic chemistry and homogeneous catalysis. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497–526. (b) Fache, F.; Schultz, E.; Tommasino, M. L.; Lemaire, M. Nitrogen-containing ligands for asymmetric homogeneous and heterogeneous catalysis. *Chem. Rev.* **2000**, *100*, 2159–2231.

35 Raja, R.; Hanko, R. Process for reducing ketocarboxylic acid esters. European Patent Filing No. EP1491548 A1, 2004.

36 Thomas, J. M.; Johnson, B. F. G.; Raja, R.; Jones, M. D. New substances useful as catalysts for asymmetric reactions comprise a metal complex with an enantiomer-enriched chiral bidentate diamine ligand adsorbed on a micro- meso- or macroporous support. German Patent DE10326915, 2005.

37 Thomas, J. M.; Johnson, B. F. G.; Raja, R.; Jones, M. D. Process for the asymmetric hydrogenation of ketocarboxylic acid esters. European Patent Filing No. EP1469005 B1, 2004.

38 de Rege, F. M.; Morita, D. K.; Ott, K. C.; Tumas, W.; Broene, R. D. Non-covalent immobilization of homogeneous cationic rhodium-phosphine catalysts on silica surfaces. *Chem. Commun.* **2000**, 1797–1798.

39 Thomas, J. M.; Johnson, B. F. G.; Raja, R.; Jones, M. D. Process for reducing ketocarboxylic esters. US Patent Filing No. US2004220347, 2004.

40 (a) Zhang, H. D.; Xiang, S.; Li, C. Enantioselective epoxidation of unfunctionalised olefins catalyzed by Mn(salen) complexes immobilized in porous materials via phenyl sulfonic group. *Chem. Commun.* **2005**, 1209–1211. (b) Piaggio, P.; McMorn, P.; Langham, C.; Bethell, D.; Bulman-Page, P. C.; Hancock, F. E.; Hutchings, G. J. Asymmetric epoxidation of stilbene by manganese(III) chiral salen complex immobilized in Al-MCM-41. *New. J. Chem.* **1998**, *22*, 1167–1169. (c) Corma, A. Attempts to fill the gap between enzymatic, homogeneous and heterogeneous catalysis. *Catal. Rev. Sci. Eng.* **2004**, *46*, 369–417. (d) Bianchini, C.; Barbaro, P. Recent aspects of asymmetric catalysis by immobilized chiral metal catalysts. *Topics Catal.* **2002**, *19*, 17–32.

41 (a) Bell, S.; Wustenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. Asymmetric hydrogenation of unfunctionalized, purely alkyl-substituted olefins. *Science* **2006**, *311*, 642–644. (b) Wills, M. Chemistry—Better asymmetric reactions. *Science* **2006**, *311*, 619–620.

42 (a) Piaggio, P.; McMorn, P.; Murphy, D.; Bethell, D.; Page, P. C. B.; Hancock, F. E.; Sly, C.; Kerton, O. J.; Hutchings, G. J. Enantioselective epoxidation of (Z)-stilbene using a chiral Mn(III)-salen complex: Effect of immobilization on MCM-41 on product selectivity. *J. Chem. Soc., Perkin Trans 2* **2000**, 2008–2015. (b) Rechavi, D.; Lemaire, M. Enantioselective catalysis using heterogeneous bis(oxazoline) ligands: Which factors influence the enantioselectivity. *Chem. Rev.* **2002**, *102*, 3467–3493.

43 Zhang, H.; Li, C. Asymmetric epoxidation of 6-cyano-2,2-dimethylchromene on Mn(salen) catalyst immobilized in mesoporous materails. *Tetrahedron* **2006**, *62*, 6640–6649.

44 Gbery, G.; Zsigmond, A.; Balkus, K. J. Enantioselective epoxidations catalyzed by zeolite MCM-22 encapsulated Jacobsen's catalyst. *Catal. Lett.* **2001**, *74*, 77–80.

45 Corma, A.; Garcia, H.; Moussaif, A.; Sabater, M. J.; Zniber, R.; Redouane, A. Chiral copper(II) bisoxazoline covalently anchored to silica and mesoporous MCM-41 as a heterogeneous catalyst for the enantioselective Friedel-Crafts hydroxyalkylation. *Chem. Commun.* **2002**, 1058–1059.

46 (a) de Vos, D. E., Vankelcom, I. F. J., Jacobs, P. A., Eds. *Chiral catalyst immobilization and recycling*; Wiley-VCH: New York, 2000. (b) Jayaraman, S.; Upilli, S.; Natarajan, A.; Joy, A.; Chong, K. C. W.; Netherton, M. R.; Zenova, A.; Scheffer, J. R.; Ramamurthy, V. Molecular assembly and reactivity of organic crystals and related structures. *Tetrahedron Lett.* **2000**, *41*, 8231–8235.

47 Hutchings, G. J. New approaches to rate enhancement in heterogeneous catalysis. *Chem. Commun.* **1999**, 301–306.

48 Taylor, S.; Gullick, J.; McMorn, P.; Bethell, D.; Page, P. C. B.; Hancock, F. E.; King, F.; Hutchings, G. J. Catalytic asymmetric aziridination of styrene using CuHY: Effect of nitrene donor on enantioselectivity. *J. Chem. Soc., Perkin Trans 2* **2001**, 1714–1723.

49 (a) Fraile, J. M.; Garcia, J. I.; Herrerias, C. I.; Mayoral, J. A.; Gmough, S.; Vaultier, M. Comparison of the immobilization of chiral bis(oxazoline)-copper complexes onto anionic solids and in ionic liquids. *Green Chem.* **2004**, *6*, 93–98. (b) Fraile, J. M.; Garcia, J. I.; Herrerias, C. I.; Mayoral, J. A.; Reiser, O.; Socuéllamos, A.; Werner, H. The role of binding constants in the efficiency of chiral catalysts immobilized by electrostatic interactions: The case of azabis(oxazoline)-copper complexes. *Chem.—Eur. J.* **2004**, *10*, 2997–3005.

50 Muller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. C2-symmetrical 4,4′,5,5′-tetrahydrobi(oxazoles) and 4,4′,5,5′-tetrahydro-2,2′-methylenebis(oxazoles) as chiral ligands for enantioselective catalysis. *Helv. Chim. Acta* **1991**, *74*, 232–240.

51 Lu, Z.; Ma, S. Metal catalyzed enantioselective alkylation in asymmetric synthesis. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297.

52 (a) Noyori, R. Asymmetric catalysis: Science and opportunities (Nobel Lecture). *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022. (b) Noyori, R.; Sandoval, C. A.; Muniz, K.; Ohkuma, T. Metal-ligand bifunctional catalysis for asymmetric hydrogenation. *Philos. Trans. R. Soc. London, Ser. A* **2005**, *363*, 901–912.

53 Skylaris, C. K.; Haynes, P. D.; Mostofi, A. A.; Payne, M. C. Introducing ONETEP: Linear scaling density-functional simulations on parallel computers. *J. Chem. Phys.* **2005**, *122*, 084119.