Aspects of heterogeneous enantioselective catalysis by metals

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Abstract

Some aspects of metal-catalyzed heterogeneous enantioselective reactions are reviewed with specific reference to four different systems where the phenomena that control enantioselection appear to be very different. In the case of glucose electro-oxidation it is clear that any intrinsic chirality present at the metal surface plays a vital role. With α-keto hydrogenation, achiral surfaces modified by the adsorption of chiral agents become effective enantioselective catalysts and formation of extended arrays of chiral species appears not to be of importance: instead a 1:1 docking interaction controlled by hydrogen bonding between the adsorbed chiral modifier and the prochiral reactant determines the outcome. Hydrogen bonding also plays a central role in β-ketoester hydrogenation, but here fundamental studies indicate that the formation of ordered arrays involving the reactant and chiral ligand *is* of importance. Asymmetric C=C hydrogenation, though relatively little studied, has the potential for major impact in synthetic organic chemistry both at the laboratory scale and in the manufacture of fine chemicals and pharmaceuticals. The structural attributes that determine whether or not a given chiral ligand is effective have been identified; the ability to form strong covalent bonds with the metal surface while also resisting hydrogenation and displacement by the strongly-adsorbing reactant under reaction conditions are essential necessary conditions. Beyond these, ligand rigidity in the vicinity of the chirality center coupled with resistance to SAM formation are critically important factors whose absence results in racemic chemistry.

Introduction

Chirally pure materials consisting of a single enantiomer are of great interest and utility in a variety of fields including non-linear optical properties, flavor and aroma chemicals, agricultural chemicals, specialty materials, and especially, the manufacture of pharmaceuticals. Such materials can only be prepared either by separating the components of a racemic mixture, intrinsically wasteful, or by chiral synthesis, a far preferable approach in principle. Chiral synthesis necessarily implies asymmetric catalysis, hence the need for enantioselective catalysts, which in turn raises the issue of homogenous *versus* heterogeneous enantioselective catalysis.

With respect to practical implementation, asymmetric catalysis remains firmly in the domain of homogeneous catalysis, despite the well known operational advantages of heterogeneous catalysis. The reason for this state of affairs is readily understood. Clearly enantioselectivity is the key attribute and by their very nature, homogeneous catalysts are typically much more selective than their heterogeneous counterparts because the former are characterized by a single kind of active site, in contrast with the range of adsorption sites presented to the reactants by a typical heterogeneous catalyst. As a direct consequence, homogeneous mechanisms are generally much better understood, thus allowing the possibility of rational catalyst design. In regard to selectivity, achieving enantiospecificity presents the greatest challenge of all, especially in the realm of heterogeneous catalysis. The development of highly selective homogenous chiral transition metal catalysts opened up a major new field of chemistry—the synthesis of pure enantiomers from achiral precursors. The academic and technical consequences of these advances have transformed synthetic chemistry, as recognized by the award of the 2001 Nobel Prize for chemistry to Knowles and Noyori for their seminal work on homogeneously-catalyzed enantioselective hydrogenation.[1] In contrast, effective *heterogeneously*-catalyzed enantioselective reactions are rarities, despite their huge potential importance to the pharmaceutical, fine chemicals and advanced materials industries.

A variety of approaches has been applied in the search for enantioselective heterogeneous catalysts relevant to very many different classes of organic reactions, [2] usually involving immobilization of known homogeneous catalysts either within or tethered to the surfaces of a range of both organic and inorganic solids, including mesoporous materials,[3] polymers,[4, 5] and dendritic systems.[6] In the particular case of heterogeneous asymmetric hydrogenation, the principal focus of this article, most reported work addresses the hydrogenation of α- and β-activated ketones. The former reaction, often referred to as the Orito reaction[7], is the better understood of the two having been extensively investigated, especially by Baiker and co-workers, and a recent review is available.[8] A somewhat earlier wide-ranging review of asymmetric catalysis at metal surfaces by Mallat et al. includes, among other topics, an examination of current understanding of both α– and β- ketone hydrogenation.[9]

Asymmetric catalysis carried out by heterogenized chiral complexes tethered to or confined within materials of various kinds, [10,11] as described above, lies outside the scope of this article. Here we survey some aspects of recent progress, especially with respect to the metal-catalyzed heterogeneous asymmetric hydrogenation of C=C bonds, a subject whose importance is explained below.

When attempting to achieve asymmetric induction during a surface-catalyzed reaction, one may distinguish two cases, whether considering extended metal surfaces or the corresponding metal nanoparticles that are used in practical catalysis. Either the solid surface itself must be intrinsically endowed with chiral adsorption sites or an intrinsically achiral or racemic surface must have chirality bestowed on it by adsorption of one enantiomer of a chiral modifier whose role is to generate an excess of (say) *R* over *S* adsorption sites. Available strategies for achieving the latter condition have been recently reviewed by Roy and Pericas.[12] We begin by considering an elegant example of the former case that demonstrates the catalytic chemistry of intrinsically chiral metal surfaces in the complete absence of any added chiral modifiers or auxiliaries.

Electro-oxidation of glucose

This topic provides the first experimental verification of the catalytic effects of the intrinsic chirality of otherwise unmodified kinked single crystal metal surfaces, originally postulated by Gellman and co-workers in 1996[13] and theoretically predicted by Sholl in 1998.[14] A seminal paper was published in 1999 by Attard and co-workers[15] who went on to carry out important research in this area. Attard et al. investigated the electrooxidation of d- and l- glucose in aqueous sulphuric acid using platinum electrodes with well defined surfaces consisting of either linear or kinked step adsorption sites. A clear diastereomeric response in the voltammetric signal was obtained for electrodes containing either *R*- or *S*-kink sites and the estimated[16] difference in adsorption activation energy responsible for the observed enantiodifferentiation was found to lie in the range predicted by Sholl in his 1998 paper.[14] It was also shown that bimetallic kinked PtPd alloy single crystal surfaces could induce chiral recognition during glucose electrooxidation.[17] Moreover, for molecules related to glucose, Attard et al.[18] found differences in electrosorption behaviour that depended on the absolute stereochemistry of the various carbon atoms constituting the pyranose ring. By these means they were able to identify the adsorption site responsible for the crucial kink-molecule interaction. Comparison with the very different behavior of linear carbohydrates led to the conclusion that the pyranose ring was an important factor in the chiral discriminating power of the electrode surface.[19] Additionally, it was found that the nature of the supporting electrolyte could significantly influence the magnitude of the electrosorption currents observed and the potential at which glucose was electrooxidised.[20] The reaction mechanism is thought to be rather complex and there is no general agreement about the nature of the rate determining step, although most authors agree that the first step is detachment and oxidation of the aldehyde hydrogen bound to the C1 carbon atom.[21, 22] Overall, the experimental findings suggest that weak, hydrogen bonding interactions within the electrochemical double layer control the enantiodifferentiation of glucose electrooxidation. In keeping with this view, molecules that adsorbed more strongly than glucose at the platinum electrode surface did *not* support chiral adsorption effects, in particular the cinchona alkaloids[18,19] which appeared to adsorb randomly from acidic aqueous media onto platinum chiral kink sites. This observation has implications for the mechanism of the so-called Orito reaction, that we shall now consider.

Asymmetric C=O hydrogenation I: the Orito reaction

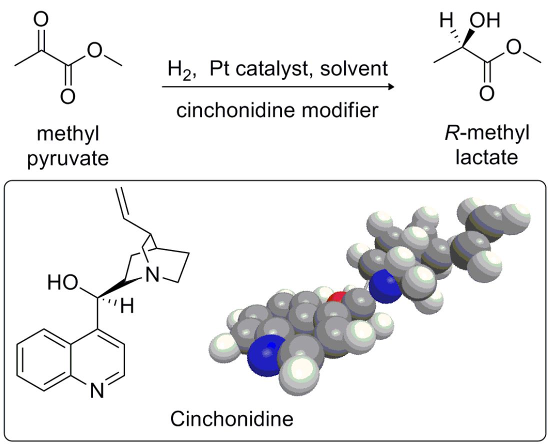

Figure 1. The Orito reaction: enantioselective hydrogenation of methyl pyruvate (a prototypical α-ketoester) using a cinchonidine modified Pt catalyst.

The Orito reaction[7] involves the hydrogenation of an α-ketoester, e.g. ethyl pyruvate, on the surface of a Pt catalyst in the presence of a chiral alkaloid modifier - typically cinchonidine (Figure 1). Platinum-cinchona and related systems are by far the most widely studied cases of heterogeneous asymmetric hydrogenation. The effects of (i) concentration and structure of the chiral modifier, (ii) the structure of the platinum catalyst and (iii) the solvent used, have been thoroughly studied and comprehensively reviewed.[23-25] The generally accepted overall reaction scheme deriving from this body of work involves (i) adsorption of the cinchona alkaloid on the Pt surface thus providing a chiral environment within which stereo-differentiation can occur (ii) adsorption of the reactant on the chirally-modified metal and entailing some kind of specific intermolecular interaction between modifier and prochiral reactant (iii) activation of hydrogen by dissociative chemisorption and its subsequent incorporation by the reactant.[23-25] The key mechanistic question, of course, concerns the nature of the surface-mediated molecular events that result in enantioselectivity and much effort has been expended in addressing this crucial issue, including extensive and detailed studies of the effect of reaction variables on enantiomeric excess.[8,26] The original reaction reported by Orito[7] gave up to 92% yield with 81.9% optical yield with the best substrate, modifier, solvent combination, although subsequent optimization has shown it is possible to get high enantiomeric excesses (> 90%) even in a flow reactor operating at relatively high turn-over frequencies (84000 h^{-1}).[27]

An early proposal as to the origin of enantioselectivity in the Orito reaction was made by Wells and coworkers who suggested that the alkaloid modifier formed an ordered but open array on the metal surface thus giving rise to chiral interstices that preferentially adsorbed the α-ketoester in a configuration that led to preferential formation of one enantiomer upon hydrogenation.[28] However, Schwalm et al.[29] argued that a 1:1 reactant:modifier interaction fitted the available data more closely and offered theoretical calculations in support of their 'docking' model. Subsequently, in the light of LEED results which indicated the chiral modifier was not highly ordered upon adsorption, Wells and co-workers also then suggested a possible role for an H-bonding interaction involving the quinuclidine N atom.[30] Much more recently, Balazs et al. found strong non-linear effects when using mixtures of chiral modifiers,[31] confirming that 1:1 reactant:modifier interactions determine enantioselctivity and that ordered arrays does not play a role. Mallat et al. reviewed a number of models proposed to account for the 1:1 interaction, concluding that the weight of evidence supported an N-H-O hydrogen bond formed between the protonated amine modifier and the carbonyl oxygen of the substrate. [9] On the other hand, McBreen et al.[32] examined the reactive behavior of a large number of α-ketones on the basis of which they proposed a two-point H-bonding model in which two hydrogen bonds are formed, one between the aromatic group of the modifier and the carbonyl of the reactant and a second between the the quinuclidine nitrogen and a side chain on the reactant (Figure 2). Mallat et al. [9] note that this model is at variance with observation in that: (i) it could be argued that the model predicts that quinine and quinidine should be ineffective modifiers, whereas in fact they do induce significant enantioselectivity. (Given that the extent of involvement of the different aromatic hydrogens in H-bonding within the McBreen model is unexplored, and that quinine and quinidine still have one of the two aromatic hydrogens available, further experiments are necessary to clarify this point); (ii) it fails to fully account for observed rate enhancement behavior exhibited by some substrates. Subsequently, McBreen et al.[33] studied the system by means of STM, in particular examining one class of substrates (α-phenyl ketones) that do not undergo the expected rate enhancement. They conclude that this is most likely a consequence of substrate-substrate interactions (observed by STM) leading to rate enhancement in a manner analogous to the rate enhancement induced by chiral modifier-substrate interactions. The net result being no enhancement of the enatioselective reaction over the racemic one.

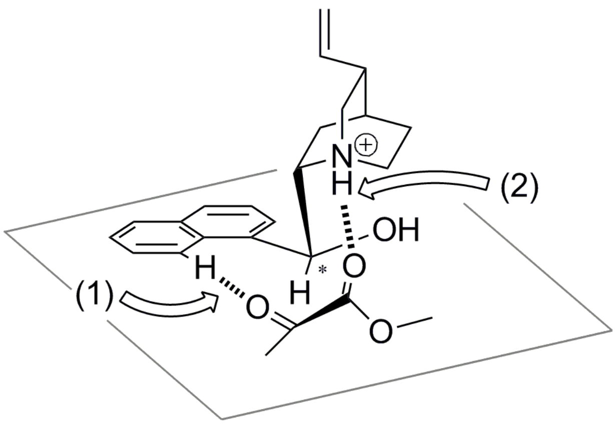

Figure 2. 1:1 docking interaction proposed by McBreen and co-workers whereby the surface activated aromatic ring is able to form a hydrogen bond at the surface (1) with the carbonyl to be hydrogenated while the protonated amine hydrogen bonds to the α-carbonyl of the ketoester (2) preferentially orientating the reactant in a conformation leading to a single enantiomer product on hydrogenation from the surface face.

Stereospecific adsorption of the chiral modifier cinchonidine at chiral kink sites has been suggested as a possible mechanism by which cinchonidine promotes the heterogeneously-catalyzed enantioselective hydrogenation of prochiral alpha-ketoesters.[18] In a series of papers,[34-37] Attard and co-workers used cyclic voltammetry to observe directly the various step, kink and terrace sites at the surfaces of supported Pt nanoparticle catalysts in order to assess the possible role of kink sites. By deliberately decorating chiral kink sites with (otherwise inert) bismuth atoms, a marked decrease in the enantioselective excess was observed as kink sites became progressively blocked. However, more recent work by Baiker and co-workers[38] who used shaped Pt nanoparticles supported on silica seemed to suggest that {111} terraces play an important role in the enantioselective reaction. . It therefore seems possible that phenomena occurring at kinked chiral step sites *and* on extended {111} terraces may both play a role in determining the achievable enantiomeric excess (e.e.) In the former case, the chiral modifier preferentially blocks (say) the *R* kinks leaving the *S* kinks free to carry out chiral hydrogenation. In the latter case, the chiral modifier creates a chiral adsorption site for the reactant on an otherwise achiral surface, as dicussed above. Clearly, despite a great deal of progress over a period of decades, uncertainties remain to be resolved before a complete understanding of this complex system is achieved.

Although the Orito reaction is necessarily carried out in the solution phase, studies performed with well defined single crystal surfaces under vacuum conditions can yield useful insight into aspects of the reaction, fundamental studies of the associated surface phenomena being relatively uncommon. For example, transient kinetic measurements showed that catalytic behavior depended on the order in which the reactants (methyl pyruvate, hydrogen) and modifier were introduced.[39] By means of a combination of complementary methods involving solution phase kinetic measurements on a practical dispersed catalyst and studies on a Pt{111} single crystal surface by means of STM and NEXAFS, Bonello et al. showed that in the absence of the cinchona modifier and under conditions of hydrogen starvation the catalyst deactivated due to blocking of the platinum surface by self-condensation of the methyl pyruvate reactant.[40] Subsequent investigations, in which STM, NEXAFS, XPS and TPR were used, confirmed that in the absence of coadsorbed hydrogen methyl pyruvate polymerizes at room temperature on Pt{111}. The resulting polymer chains, partly dendritic, had an average length of ~ 9 monomer units, and NEXAFS showed that they contained C=O bonds but no C=C bonds. This suggested that polymerization occurred by hydrogen elimination from the monomer, followed by an aldol condensation involving elimination of methanol, detected by TPR. Such a process should be favored on a hydrogen-free metal surface. Very strikingly, coadsorbed hydrogen completely suppressed polymerization, thus confirming the importance of avoiding hydrogen starvation at all stages of catalyst operation.[41] Note that these findings are fully consistent with the model of McBreen and co-workers[33] involving hydrogenbonded networks of enolic species, which of course could exist in the presence of co-adsorbed hydrogen.

Asymmetric C=O hydrogenation II: Tartaric acid-modified Raney Ni

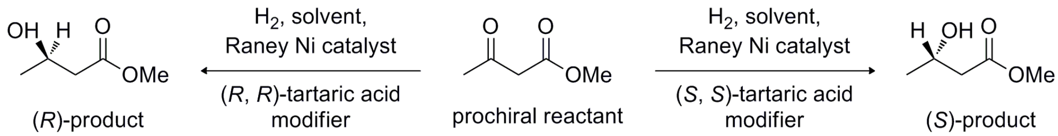

Figure 3. Enantioselective hydrogenation of methyl methacrylate (a prototypical β-ketoester) using a tartaric acid modified Raney Ni catalyst.

The hydrogenation of β-ketoesters and β-diketones using chirally modified Raney Ni has also been extensively studied, with tartaric acid as the most often used chiral modifier (Figure 3). Other chiral glutamate and glutamic acid modifiers have also been used with Raney Ni, the earliest example of this approach being that of Stewart and Lipkin who in 1939 used *d*-glucose but achieved only a less than 1%.[42] Only much later, in the early 1960s, were promising e.e.s obtained by Izumi and co-workers who used tartaric acid, which proved to an effective chiral modifier in the hydrogenation of β-ketoesters.[43] Many variations with respect to catalyst preparation, additives, solvents, ambient pressure and hydrogenation substrates have been explored, and these are well documented elsewhere.[44,45] Metals other than Ni have also been investigated, but found to be significantly less effective.[46] Lack of correlation between kinetic behavior and e.e. have been interpreted to suggest that only some areas of the hydrogenated catalyst surface lead to enantiodifferentiation.[47] This view is at least consistent with the reported effect of added Na+, which promoted enantioselectivity.[48] The effect is stronger when NaBr is used as a co-modifier and less pronounced when other sodium salts are used (NaI, NaCl, NaF, $NaNO_3$). The promotional effect has been attributed to poisoning of the non enantioselective regions of the metal surface. It has also been suggested that the alkali halide modifies the stereochemistry of the product-determining surface complex between the nickel, the tartrate and the substrate.[49] A variety of explanations has been advanced to explain the origin of the observed enantioselectivity – the most widely accepted being a 2-point H-bonding model in which the hydroxyls of tartaric acid H-bond to the β-ketoester or β-diketone oxygen atoms, thus favoring adsorption of one β-ketoester conformer over the other, resulting in enantioselective hydrogenation. (Figure 4). Satisfyingly, this model explains *both* the diastereoisomers formed in the chiral di-hydrogenation of acetyl acetonate[50]. It also accounts for the hydrogenation of prochiral ketones containing sterically hindering alkyl groups, which can form only one hydrogen bond, the net result being a very striking reversal in enantioselectivity.[51]

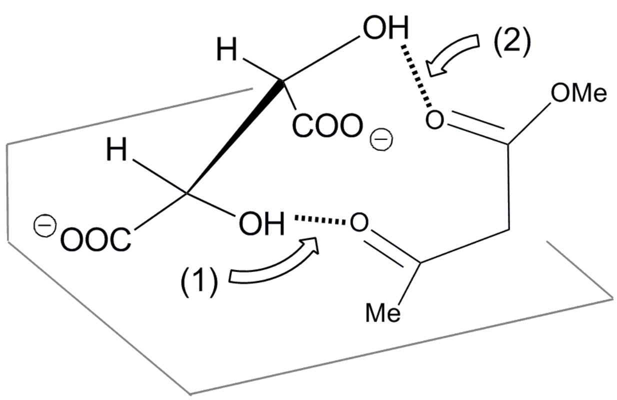

Figure 4. Two point hydrogen bonding model proposed for methyl methacrylate interacting with tartaric acid as shown with one hydrogen bond (1) holding C=O functionality to be hydrogenated near surface, and second hydrogen bond (2) above surface controlling preferential adsorption in conformation leading to a single enantiomer when hydrogenated from the surface face.

As with the Orito reaction, studies carried out with well defined single crystal surfaces under vacuum conditions have provided ~~important~~ insight into aspects of the reaction. Thus Baddeley and co-workers investigated pertinent hydrogen bonding interactions using single crystal Ni surfaces.[52-57] Their results suggest that more complex intermolecular interactions are important in determining the ee. Specfically, they concluded that supramolecular interactions *between modifier-reactant complexes* resulted in formation of domains that favor one chiral hydrogenation product over the other. Their work also demonstrated that the identity of the reactant tautomer actually present under reaction conditions depends critically on the modification procedure used for catalyst preparation. For example, it was found that ~~at~~ on Ni(111) at ~ 300 K, at saturation coverage of the chiral modifiers tartaric acid[52] and glutamic acid both species completely blocked adsorption of the reactant. The significance of this is that both modifiers, when present on their own, can form ordered arrays only at high coverages, when the surface is fully passivated to reaction.[52-54] Revealingly however, when modifier and reactant were co-adsorbed with 1:1 stoichiometry a H-bond stablilised ordered 2-D structure was formed at a modifier coverage of ~ 0.05-0.07 ML – exactly the range of coverage that is found to be optimum for tartaric acid-modified Ni nanoparticle.[58] It appears that these systems involve very different and possibly more complicated effects than those invoked and discussed above in connection with the Orito reaction which is dominated 1:1 reactant/modifier interactions. ~~between and the ordered "chiral pocket template model."~~ Instead, multiple intermolecular H-bonding interactions within the modifier-reactant domains stabilize one enantiotopic face relative to the other, in turn favoring formation of one enantiomer of the hydrogenation product. Such effects may augment the efficacy of the 1 and 2 point H-bonding models described above. Baddeley and co-workers used RAIRS to investigate how different chiral modifiers affected the structure of the co-adsorbed methylacetoacetate reactant.[55-57] In every case it was found that the most effective modification conditions were those that induced adsorption of the diketo tautomer of the β-ketoester.[55-57] Strikingly, with glutamic acid as the chiral modifier, it was shown that the dominant chiral product depended on the modification temperature. [56] With (*S*)-glutamic acid as modifier, treatment at 300 K and pH 5 favored the (*R*)-product, the diketo form of methylacetoacetate being dominant on the surface. Increasing the modification temperature resulted in progressively decreasing e.e.s: after modification at 373 K the enol tautomeric form of the ketoester dominated on the surface and the (*S*)-product was actually favored. Such fundamental information, not available from conventional catalytic experiments, brings important added insight that must be built into the development of future mechanistic models for this system.

Asymmetric hydrogenation of C=C bonds

Although there is undoubtedly more to learn in regard to the fundamentals of enantioselective C=O hydrogenation as exemplified by the two most intensively studied reactions, α- and β-ketoester hydrogenation, our understanding of these two systems may be regarded as relatively well developed. In particular, and irrespective of details, there is general agreement that the critical step, which leads to enantio-differentiation takes place at the surface of the metal catalyst.

In marked contrast to the situation pertaining to α- and β-ketoester hydrogenation, the asymmetric hydrogenation of C=C bonds has received very little attention and understanding is correspondingly limited. All the more surprising, given that C=C asymmetric hydrogenation, unlike C=O asymmetric hydrogenation, is of the highest importance in organic synthesis. Enantioselective hydrogenation is often a critical step in an overall synthetic scheme, e.g. the synthesis of a number of pharacetical products, recent examples including L-dopa (treatment of Parkinson's disease);[59] Tipranavir (HIV treatment);[60] and Ramelteon (insomnia medication).[61] Currently, such reactions are carried out by means of organometallic *homogeneous* catalysts, which depend on costly, usually phosphorus-based ligand systems.

~~Despite C=C bond hydrogenation being more important from the viewpoint of synthetic organic chemistry, very little work on the heterogeneous catalysis of this class of reactions has been reported.~~ Several groups have attempted to extend the methodology used for Pt-catalyzed asymmetric C=O hydrogenation by using chinchona alkaloid-type molecules in Pd-catalyzed asymmetric hydrogenation. Although there are early reports of metal catalyzed C=C hydrogenation[42, 62] including cinchona modified Pd,[63] the major breakthrough in mechanistic understanding and achievable enantiomeric excess arose in connection with the Nitta reaction[64] where highly enantioselective hydrogenation of *(E)*-alpha-phenylcinnamic acid was achieved using a cinchonidine-modified Pd/TiO_2 catalyst. (Figure 5).

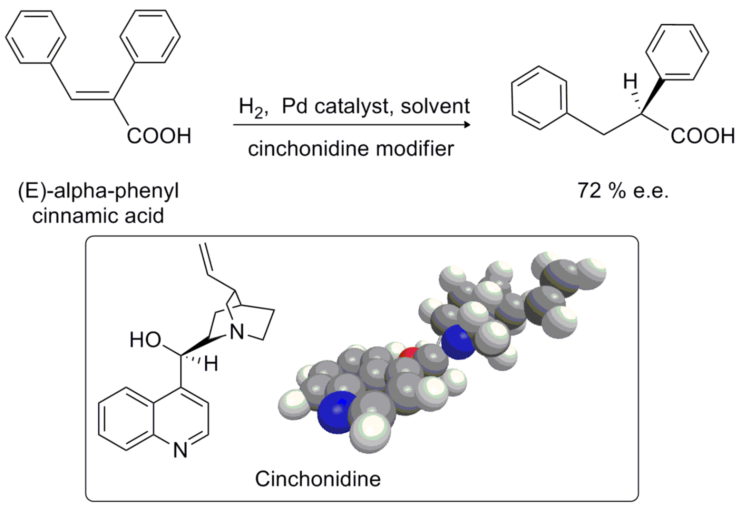

Figure 5. The Nitta reaction: enantioselective hydrogenation of *(E)*-alpha-phenylcinnamic acid using a cinchonidine modified Pd catalyst(72 % e.e. at 100% conversion).

This approach was subsequently extended to achieve enantiomeric excesses of up to 82% with certain heavily phenyl substituted reactants.[65] The use of chirally-modified Pd to catalyze enantioselective hydrogenation has been extended to other reactants,[66] although high modifier/substrate ratios were required Other chiral modifiers containing aromatic rings have also been examined - for example dihydro-vinpocetine, which is thought to anchor to the metal surface by an indole rather than a quinoline ring system.[67]

However, this approach suffers from a serious flaw that precludes its widespread use. Thus in asymmetric C=O hydrogenation, use of a chiral modifier tethered to the surface of a metal catalyst by an aromatic ring system is an effective strategy; however, under Pd-catalyzed C=C hydrogenation conditions, the aromatic rings themselves are inevitably also hydrogenated resulting in loss of the chiral modifier from the surface and consequentially an overall process that is not truly catalytic. This problem was identified by Baiker and co-workers,[68] who noted that hydrogenation of the alkaloid modifier necessitated its replenishment during reaction to achieve effective operation.[69] Attempts to anchor the proline moiety to the metal surface by incorporating quinoline or indole units into the chiral modifier have also been investigated.[70] However this method would suffer from exactly the same problem of hydrogenation of the aromatic anchoring functionalities during reaction, as discussed immediately above for similarly anchored aromatic chiral modifiers on Pd catalysts. In contrast, as will be shown later, chiral organic sulfides that tether covalently to the Pd surface *do* offer a promising way forward in this respect.

In the late 1980s Tungler and co-workers reported on an apparently heterogeneously-catalyzed, asymmetric hydrogenation with a Pd/C catalyst employing the amino acid proline as a chiral auxiliary,[71] as indicated in Figure 6. Much subsequent work focused on varying catalyst and process parameters including support, pre-treatment and solvent.[72]

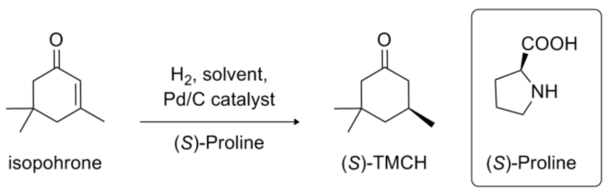

Figure 6. Proposed use of amino acid (*S*)-Proline as a chiral auxiliary in the enantioselective hydrogenation of isophorone to 3,3,5-trimethylcyclohexanone (TMCH) yielding (*S*)-enantiomer product in excess.

On the basis of NMR data, circular dichromism measurements and the observation that the presence of water decreases selectivity (owing to its effect on the condensation equilibrium), it was proposed that an enantio-directed hydrogenation occured at the Pd surface after pre-condensation of proline and isophorone to form an iminium salt intermediate - the rigid structure of the iminium intermediate tethered via the carboxylate function favoring hydrogenation from one enantioface of the prochiral intermediate.[71] In other words, enantioselectivity is proposed to result from the initial formation (in solution) of a proline/isophorone condensation product which then adsorbs on the metal surface where it undergoes *heterogeneous asymmetric* (diastereoselective) hydrogenation. Hydrolysis of the TMCH-proline hydrogenation product then delivers enantio-enriched TMCH. The limited yield and enantiomeric excess were attributed to competing pathways that are either racemic or result in complete hydrogenation of the iminium salt intermediate.[71] However, as discussed in detail below, this mechanism cannot be regarded as correct. Moreover, use of a chiral auxiliary that pre-complexes with the reactant rather than direction by a chiral modifier that is actually tethered to the surface does not represent true heterogeneous catalysis in the usual sense, even if the enantio-differentiating event does occur at the surface—we shall show that it does not. This is so because *stoichiometric* rather than catalytic quantities of the chiral agent are required, and a subsequent separation step is inevitably necessary, just as in conventional homogeneous organocatalysis.

It is also notable that in the proline/isophorone system[71,73] the absolute yield of optically pure TMCH product (e.e. × yield) never exceeds 50 %. As we shall see this is because what happens is no more than a chiral separation: the observed enantiomeric excess arises from an initially *racemic* hydrogenation followed by subsequent kinetic resolution in the solution phase, rather than a true surface-catalyzed asymmetric reaction.[74]

Thus we have shown,[74] and others have confirmed,[75] that interpretation in terms of an adsorbed prochiral intermediate formed by a condensation reaction between proline and isophorone is not correct. We investigated the system in detail in order to (i) test the earlier hypothesis and (ii) clarify key aspects of the mechanism.[74] It was found that the proline/isophorone condensation product, though formed, was merely a spectator and not a key reaction intermediate. Moreover, as noted above, enantioselectivity is the result of kinetic resolution — a process that occurs homogeneously in solution and not at the metal surface. Racemic TMCH is produced by initial *heterogeneous* hydrogenation of isophorone; proline then reacts *homogeneously,* preferentially with one enantiomer of TMCH, leaving an excess of the other. The mechanism we propose also explains why the maximum attainable yield of enantiopure TMCH cannot exceed 50%: stoichiometric consumption of the chiral agent occurs—its role is not catalytic, nor does it act at the metal surface.

Subsequent single crystal studies of the adsorption from solution of the reactant (isophorone), the chiral agent (*R* and *S* proline) and the chiral hydrogenation product (3,3,5-trimethylcyclohexanone) onto a series of Pt single crystal surfaces revealed why the proline/isophorone system *cannot* give rise to significant heterogeneous asymmetric hydrogenation.[76]

In fact, the reactant adsorbs ~ 10^5 times faster than the chiral agent so that under conditions of competitive adsorption the latter is entirely excluded from the metal surface. Moreover displacement and reaction rate measurements carried out with practical Pd/carbon catalysts[76] showed that under reaction conditions isophorone quickly displaced pre-adsorbed proline from the metal surface. Thus regardless of the details of experimental procedure, both kinetics and thermodynamics act to exclude the chiral agent from any surface-mediated process that could lead to enantiodifferentiation. In addition, we showed that there is no preferred diastereomeric interaction between *R*,*S* proline and *R*,*S* step kink sites on Pt{643} and Pt{976} implying that such sites do not play a role in determining the catalytic behavior of supported metal nanoparticles.[76]

It has recently been suggested[77] that a surface-catalyzed asymmetric hydrogenation component may yet make a contribution to the overall reaction. However the data quality suggests that this proposal should be treated with caution. At best, it may be inferred that any surface- catalyzed asymmetric component is significant only in the early stages of the reaction and can only be a very minor component in the proline/isophorone system: for example, in the case of Pd/C the data are noisy and the derived e.e. values are calculated from the difference of two large numbers.

A noteworthy recent report describes e.e. inversion as a function of particle size: large and small Pd particles supported on MgO produced opposite enantiomers of TMCH[78]. For the small particles, which are able to carry out the hydrogenation efficiently, the e.e. is in good agreement with that found from the kinetic resolution of racemic TMCH (and therefore in good accord with our findings described above). For the larger particles, which hydrogenate isophorone far less efficiently, the authors suggest that sufficient time is available for isophrone and proline to interact in solution before adsorption – the Pd/MgO surface then catalyses a reaction producing the opposite enantiomer to that seen for kinetic resolution. Although this does suggest some surface-related effect, the low enantioselectivities, the problem of subsequent separation of the proline auxiliary which remains in solution, and the very slow reaction rates necessary to avoid rapid racemic hydrogenation as the first step in the reaction render this approach of very limited practical value.

Clearly, in order to achieve true heterogeneous enantioselective catalysis it is necessary to force the crucial enantiodifferentiating step to take place *at the metal surface*. Achieving this goal requires changing the surface chemistry so as to tether the chiral agent to the metal surface sufficiently robustly in order to resist both displacement by the strongly-adsorbing reactant and hydrogenation under reaction conditions . This goal has now been achieved[79] by purposeful synthesis of chiral ligands that contain the characteristic pyrrolidine motif present in proline, anchor robustly to the metal surface, resist displacement and direct the *heterogeneously-catalyzed* enantioselective hydrogenation of isophorone, as described below.

The enantio-pure set of chiral ligands that were used is shown in top part of Figure 7.[79] Each contained a sulfur atom in order to achieve covalent tethering to the metal surface. The result of using these chiral sulfide ligands as chiral modifiers in the Pd/C-catalyzed hydrogenation of isophorone is summarized in Figure 7, which shows the measured e.e. as a function of modifier concentration for the six different ligands. The initial modifier concentration provides a measure of the amount subsequently adsorbed onto the Pd surface of the catalyst. Ligand adsorption measurements coupled with X-ray photoelectron spectroscopy adsorption data demonstrated that, unlike proline, these sulfide ligands did indeed anchor robustly to the surface of the palladium component of the Pd/C catalyst.[79]

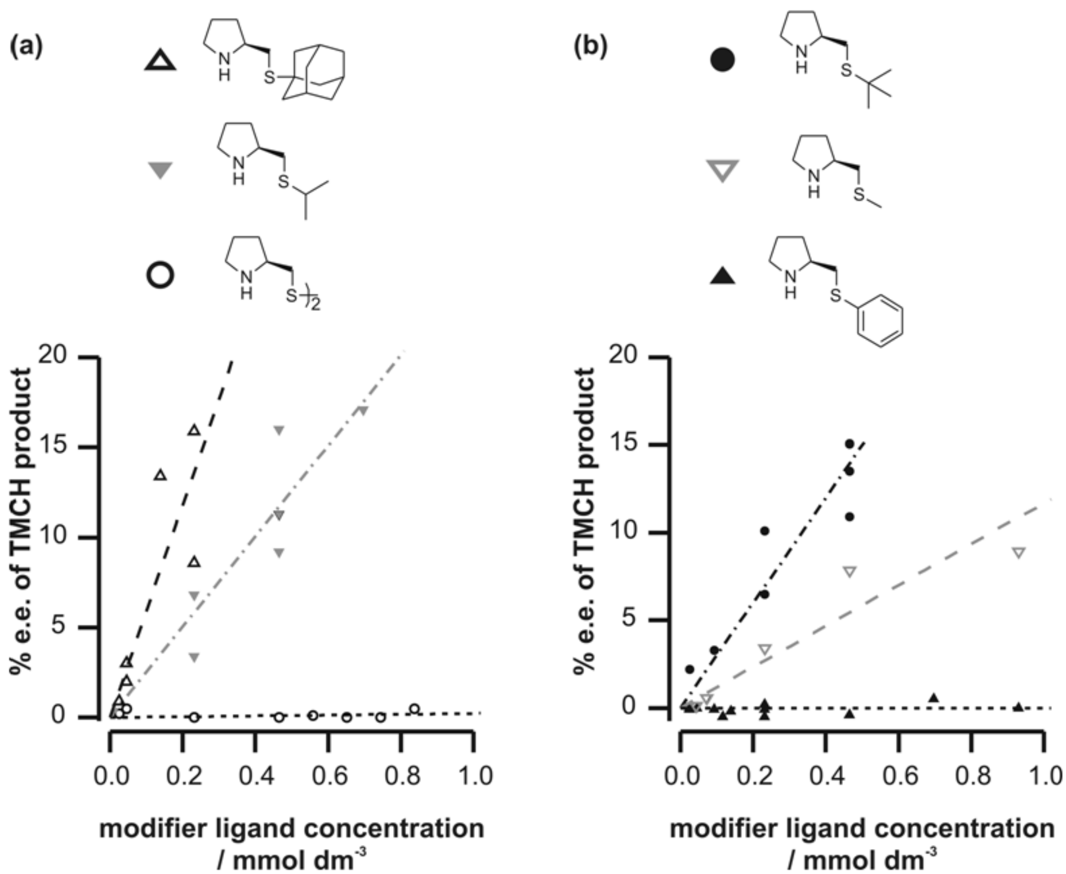

Figure 7. Dependence of TMCH product e.e. on initial modifier ligand concentration. Each data point corresponds to running the reaction up to a conversion of ~60%. (a) △ (*S*)-2-(adamantan-1-ylthiomethyl)-pyrrolidine; ▼ (*S*)-2-(iso-propylthiomethyl)pyrrolidine; ○ 1,2-bis((*S*)-pyrrolidin-2-ylmethyl)disulfane; (b) ● (*S*)-2-(tert-butylthiomethyl)pyrrolidine; ▽ (*S*)-2-(methylthiomethyl)pyrrolidine; ▲ (*S*)-2-(phenylthiomethyl)pyrrolidine. A ligand concentration of 0.47 mmol dm^{-3} corresponds to 0.1 mol% ligand with respect to isophorone.

The key point is that only *very small (i.e. catalytic) amounts of ligand* (typically 1:2000 modifier/isophorone molar ratio under our conditions) were used, in contrast to the necessarily large (stoichiometric) amounts of proline that were consumed when the latter was used to achieve kinetic resolution.[74] Specifically, under our conditions over 100 chiral molecules are produced for every chiral ligand molecule originally present in the reactor. These results clearly indicate that heterogeneous enantioselective hydrogenation did indeed occur in the presence of adsorbed chiral sulfides which act to steer the course of the hydrogenation reaction.

It is striking that the effectiveness of these ligands in inducing asymmetry (proportional to gradients of the lines in Figure 7) increased systematically with increasing size of the alkyl group they contain. This confirms that the ligands must adsorb non-dissociatively on the surface - cleavage of either C-S bond would yield two fragments such that the alkyl group and the stereogenic carbon atom would be separated from each other. There would then be no way for the former to affect the degree of asymmetric induction caused by the latter. How might the degree of steric encumbrance in the vicinity of the stereogenic centre affect the e.e. obtained? A plausible hypothesis is that the bulkiness of the alkyl group determines the spatial distribution and hence the effectiveness of adsorbed chiral modifier molecules on the catalyst surface. In general, adsorbates on metal surface may: (i) be dispersed as individual molecules, (ii) agglomerate into close-packed islands that are separated by regions of bare surface, or (iii) there may be dynamic equilibrium between dispersed molecules and islands. Which of these possibilities actually occurs is determined by the interplay of molecule-surface and molecule-molecule interactions. Bulky alkyl groups hinder the close approach of chiral adsorbates thus favoring dispersion and inhibiting island formation. As a result, the modifier molecules are more accessible for interaction with co-adsorbed reactant species. Conversely, by analogy with the well known behavior of alkane thiols, compact chiral sulfides would be more prone to island formation with the result that only those molecules at island peripheries would be effective for inducing asymmetric hydrogenation of the co-adsorbed reactant molecules, most of which would undergo racemic hydrogenation on the ligand-free portion of the surface. This hypothesis is in very good accord with the results presented in Figure 7 which show a strong correlation between ligand size and the resulting degree of asymmetric induction. Interestingly, and apparently anomalously, the phenyl-containing chiral sulfide was ineffective. However, this is understandable in terms of π-π interactions which promote island formation[80] with the result that this relatively large ligand yields negligible enantioselectivity.[79]

The proposed reaction mechanism is based on well-known homogeneous chemistry, namely the condensation of secondary amines with ketones. Thus in the present case the ligand and surface-bound isophorone react to give an iminium ion (or enamine) with loss of water. The iminium ion or enamine undergoes diastereoselective olefin hydrogenation to give a second iminium ion / enamine which is hydrolyzed to give product which desorbs from the surface. To test the hypothesis that the secondary amine nitrogen is directly involved in the formation of a reaction intermediate, a chiral *tertiary* amine, analogous to (*S*)-2-(*tert*-butylthiomethyl)pyrrolidine but with an additional methyl group, was also prepared, Figure 8. Tertiary amines cannot undergo condensation with isophorone. Used under the same reaction conditions the tertiary amine gave a racemic product, confirming that the mechanism responsible for asymmetric induction is indeed mediated by the nitrogen of the pyrrolidine ring.[79]

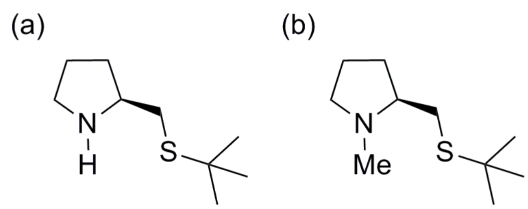

Figure 8. (a) The (*S*)-2-(*tert*-butylthiomethyl)pyrrolidine secondary amine chiral modifier used in the enantioselective hydrogenations above and (b) its tertiary amine analogue.

On this basis, using steric and geometric arguments briefly summarized here, it is possible to construct a fairly detailed model that very satisfactorily accounts for the origin of enantioselectivity during the hydrogenation of isophorone when both chiral modifier and reactant are confined to the metal surface.[81] Given the known adsorption behavior of functionalized pyrrolidine rings[82] and that the sulfur atom provides the tether to the metal via a co-ordinate bond,[83] two possible configurations can result from an encounter of the adsorbed chiral modifier with an isophorone molecule so as to form an iminium intermediate. These are shown in Figure 9(a) – each configuration leading to one of the product enantiomers. It is clear that in these two configurations very different degrees of steric encumbrance arise as a result of the relative proximity of the geminal dimethyl group (Me*) to the bulky alkyl group of the chiral modifier. That shown in the left panel is sterically disfavoured relative to the configuration shown on the right, so that the latter should correspond to the favored product enantiomer. Thus the mechanism we propose predicts that the *(S)*-enantiomer of the product should predominate when using the *(S)*-enantiomer of the chiral modifier, in agreement with experiment.

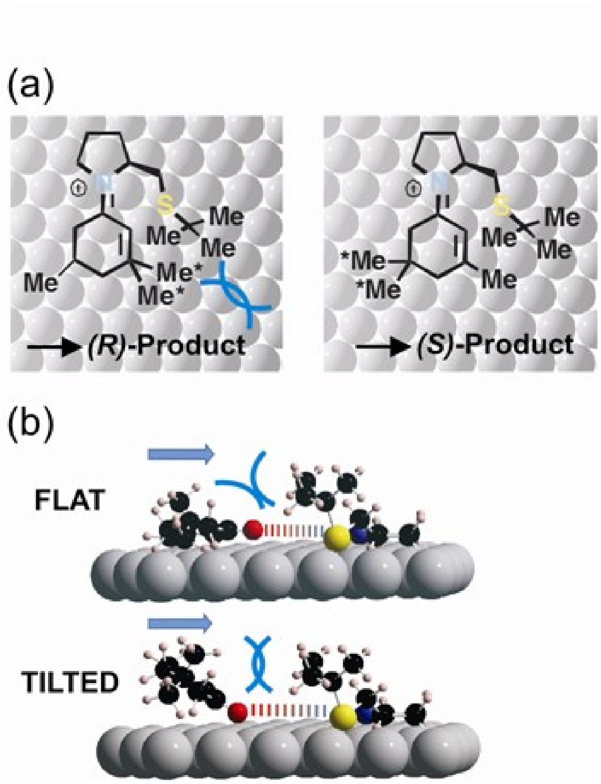

Figure 8. (a) The difference in steric inhibition for reactant– modifier configurations of iminium intermediates leading to the two product enantiomers. (b) Enhanced unfavourable steric interaction between the geminal dimethyl group (Me*) and the *tert*-butyl group of the chiral modifier *in the sterically disfavoured configuration* upon tilting isophorone from flat to ~ 42°.

Additional insight into the influence of the adsorption geometry of the isophorone reactant on e.e. was obtained by means of NEXAFS spectroscopy. This showed that the molecule adopts a strongly tilted adsorption geometry on Pd(111) (~ 42° relative to the surface plane).[81] Figure 9(b) illustrates the consequences of this tilting by showing an isophorone molecule approaching the chiral modifier in both flat (top) and strongly tilted (bottom) geometries. It is clear that when the isophorone molecule is strongly tilted, formation of the (*R*) product becomes even more sterically hindered further disfavoring the formation of the iminium species leading to the disfavored (*R*)-product. Once again, not unexpectedly, stereochemical effects play a leading role. Because the most effective chiral modifiers bear bulky substituents, both the stereochemistry and the adsorption geometry of the reactant molecule are important. In regard to the chiral ligand itself, the results show that molecular rigidity and resistance to self-assembled monolayer formation are attributes that should be designed into improved chiral modifiers for future studies in this area.

Concluding remarks

Given the progress that has been achieved in understanding key aspects of the hydrogenation of α- and β- ketoesters, it seems likely that these reactions will continue to attract attention. However, it is at least of equal importance to broaden the chemistry so as to address reactions that are of practical importance both in the research laboratory and in the production of fine chemicals and pharmaceuticals. Asymmetric C=C hydrogenation is just such a case, as we have tried to emphasize. Here, having identified some of the ligand attributes that are necessary for inducing enantioselection (covalent tethering to the metal surface; bulky R substituents to inhibit SAM formation; ligand rigidity in the vicinity of the chirality center) the time is ripe for exploring substrates other than isophorone and its derivatives so as to enter the arena of practical organic synthesis. For example relatively little work has been carried out exploring metal catalyzed heterogeneous asymmetric hydrogenation involving carbon-nitrogen bonds.[84] In this regard, it would be of interest to investigate the asymmetric hydrogenation of imines, 2-vinylic nitro-compounds and the corresponding nitriles, all of which would be of substantial technical interest, especially if simultaneous reduction of the CN or NO_2 functionality also could be achieved in the latter cases : work is in progress. Equally, the study of new classes of chiral ligands should be a priority. The value of fundamental studies is by now well established. Use of well-defined systems to focus on crucial aspects of enantioselective mechanisms can provide important insight for the development of practical materials. Although it is not likely that theory will lead experiment in the foreseeable future—as is true of the field of heterogeneous catalysis in general—theoretical studies will almost certainly play an increasingly important role in rationalizing observations, not least because of the complexity and intrinsic difficulty of the subject.

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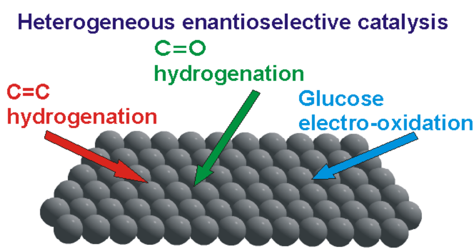
Heterogeneous enantioselective catalysis
C=O
hydrogenation
C=C
hydrogenation
Glucose
electro-oxidation