Heterogeneously catalyzed asymmetric hydrogenation of C=C bonds directed by surface-tethered chiral modifiers.

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ABSTRACT. Asymmetric hydrogenation of C=C bonds is of the highest importance in organic synthesis and such reactions are currently carried out with organometallic homogeneous catalysts. Achieving heterogeneous metal-catalyzed hydrogenation, a highly desirable goal, necessitates forcing the crucial enantiodifferentiating step to take place at the metal surface. By synthesis and application of six chiral sulfide ligands that anchor robustly to Pd nanoparticles and resist displacement, we have for the first time accomplished heterogeneous enantioselective catalytic hydrogenation of isophorone. High resolution XPS data established that ligand adsorption from solution occurred exclusively on the Pd nanoparticles and not on the carbon support. All ligands contained a pyrrolidine nitrogen to enable their interaction with the isophorone substrate whilst the sulfide functionality provided the required interaction with the Pd surface. Enantioselective turnover numbers of up to ~ 100 product molecules per ligand molecule were found with a very large variation in asymmetric induction between ligands: observed enantiomeric excesses increased with increasing size of the alkyl group in the sulfide. This likely reflects varying degrees of ligand dispersion on the surface: bulky substituent groups hinder close approach of ligand molecules to each other, inhibiting close-packed island formation, favoring dispersion as separate molecules and leading to effective asymmetric induction. Conversely, small substituents favor island formation leading to very low asymmetric induction. Enantioselective reaction most likely involves initial formation of an enamine or iminium species, confirmed by use of an analogous tertiary amine, which leads to racemic product. Ligand rigidity and resistance to self-assembled monolayer formation are important attributes that should be designed into improved chiral modifiers.

Introduction

The major operational advantages offered by heterogeneous over homogeneous catalysis are well known and exploited wherever possible. However, heterogeneously catalyzed *enantioselective* reactions are rarities, despite their huge potential importance in the research laboratory and in the pharmaceutical, fine chemicals and advanced materials industries. Virtually all published work in this field refers to the

asymmetric catalytic hydrogenation of C=O bonds in ketoesters carried out on the surfaces of modified Pt or Ni surfaces.[1] In these systems, a chiral agent is used to modify the otherwise achiral heterogeneous catalyst, thus allowing enantioselective catalysis to occur. Although the means by which such chiral templating of the metal catalyst surface is accomplished in the case of α-ketoester hydrogenation (Pt)[2] appears to differ from that which operates in the case of β-ketoester hydrogenation (Ni),[3] and details of the corresponding reaction mechanisms are the subject of debate, one key aspect is very clear for both classes of reaction: *the crucial step that leads to enantiodifferentiation occurs at the surface of the metal.*

The situation with regard to asymmetric hydrogenation of C=C bonds is very different. Moreover, unlike C=O asymmetric hydrogenation, such processes are of the highest importance in organic synthesis and are often a critical step in an overall synthetic scheme (e.g. the synthesis of L-dopa).[4, 5] Currently, such reactions are carried out with organometallic *homogeneous* catalysts, which depend on costly, usually phosphorus-based ligand systems. There are very few examples of heterogeneously-catalyzed asymmetric C=C hydrogenation. In the late 1990s Nitta *et al.* and others claimed that cinchona alkaloid-modified Pd surfaces may be used for the enantioselective hydrogenation of C=C bonds in large aromatically conjugated hydrogenation substrates, such as (E)-α-phenylcinnamic acid.[6] However large amounts of the chiral agent were required, some of which underwent hydrogenation,[7] so that the behavior was not catalytic in the normal sense of the term. Moreover, the effect was specific to this particular class of substrates and a recent review by Studer *et al*. indicates that no significant progress has been made in extending this approach.[8] Another system, the proline-directed asymmetric hydrogenation of isophorone (Figure 1) and similar molecules, typically carried out with a Pd catalyst, has been investigated by Tungler and co-workers[9,10] who proposed that these reactions proceed by the same general mechanism as that which operates for asymmetric C=O hydrogenation - a reactive encounter between the adsorbed organic substrate and the adsorbed chiral agent (proline) in the presence of hydrogen adatoms.

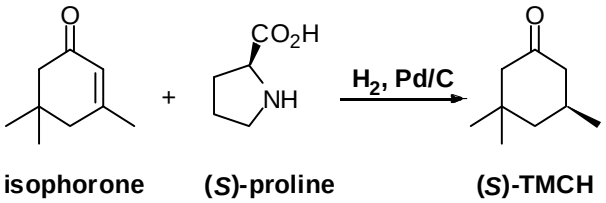


Figure 1. The proline directed asymmetric hydrogenation of isophorone to (*S*)-TMCH ((*S*)-3,3,5-trimethylcyclohexanone).

However, we have shown,[11] and others have confirmed,[12] that this interpretation is not correct. The metal surface merely carries out a *racemic* hydrogenation of adsorbed isophorone and the observed enantiomeric excess (e.e.) in the product (trimethylcyclohexanone, TMCH) is merely due to subsequent kinetic resolution that takes place in solution as a result of one enantiomer of TMCH reacting with the chiral agent much faster than the other. In other words, heterogeneous enantioselective catalytic synthesis was *not* achieved. The mechanism we proposed[11] also explains why the maximum attainable yield of enantiopure TMCH cannot exceed 50% and why the chiral agent (which is necessarily consumed) has to be used in stoichiometric amounts rather than in catalytic quantities.

In order to achieve true heterogeneous enantioselective catalysis it is necessary to force the crucial enantiodifferentiating step to take place *at the metal surface*. In this connection, using single crystal methods,[13] we have shown that a critical obstacle to heterogeneous catalysis in this system is the much faster ($\sim \times 10^5$) and stronger adsorption from solution of the reactant (isophorone) compared to the chiral agent (proline). As a result, the metal surface becomes saturated with isophorone to the complete exclusion of proline so that only racemic hydrogenation is possible at the metal surface. Clearly, overcoming this impediment requires radically changing the surface chemistry so as to tether the chiral agent to the metal surface sufficiently strongly. Here we report a significant advance: the successful attainment of this goal by purposeful synthesis of chiral ligands that anchor robustly to the metal surface, resist displacement, and direct the *heterogeneous* enantioselective catalytic hydrogenation of isophorone. Above all else, the principal object of this work is to demonstrate proof of concept.

Experimental Methods

Enantiomerically pure sulfide ligands **2**, **4**, and **6** were prepared following known procedures (Figure 2),[14] the remaining ligands **1**, **3**, and **5** were prepared analogously. All of the ligands contain the pyrrolidine motif which has had widespread use in enantioselective organocatalysis;[15] however, the carboxylic acid group is replaced by a range of sulfide substituents. The pyrrolidine nitrogen is intended to enable these ligands to interact with isophorone whilst the sulfide functionality provides a strong interaction with the surface,[16] enabling the tethered molecules to behave as true heterogeneous chiral modifiers. A range of structurally diverse sulfide substituents (Figure 2) was used so as to examine possible steric and electronic effects on the effectiveness of the chiral ligand at inducing asymmetry in the heterogeneous enantioselective hydrogenation of isophorone. Molecules analogous to the disulfide ligand **1** undergo S-S scission upon adsorption on a range of metals,[17,18] including Pd.[19] Ligand **1** therefore provides a means of depositing the unsubstituted sulfide on the surface.

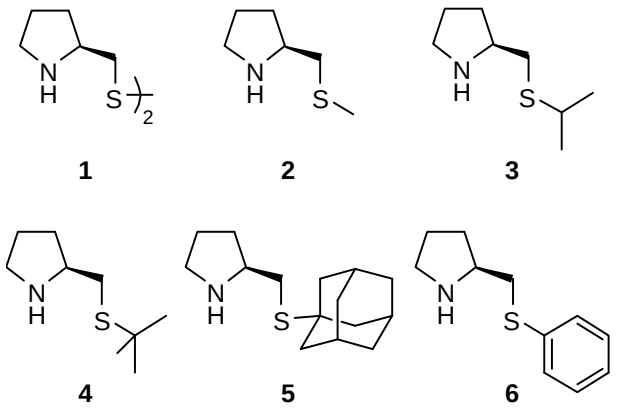


Figure 2. Sulfide ligands used (**1**) 1,2-bis((*S*)-pyrrolidin-2-ylmethyl)disulfane, (**2**) (*S*)-2-(methylthiomethyl)pyrrolidine, (**3**) (*S*)-2-(iso-propylthiomethyl)pyrrolidine, (**4**) (*S*)-2-(tert-butylthiomethyl)pyrrolidine, (**5**) (*S*)-2-(adamantan-1-ylthiomethyl)-pyrrolidine and (**6**) (*S*)-2-(phenylthiomethyl)pyrrolidine.

Catalytic testing of the hydrogenation reactions was carried out by the following procedure: Methanolic solutions of the enantiomerically pure ligands were added to a reaction mixture of isophorone (3 ml, Sigma-Aldrich) and 10% reduced Pd/C catalyst (Alfa Aesar, 0.050 g) in methanol (40 ml, Fisher Scientific HPLC grade), such that the molar ratio of ligand to isophorone was varied up to a maximum of 1:500. These solutions were then hydrogenated by stirring in autoclaves under 15 bar of H_2 (after thorough flushing with H_2 at the start of each reaction) to fixed time (168 h) or fixed conversion (60%). Analysis of reaction products was carried out by dilution of aliquots in 50/50 dichloromethane/methanol (Fisher Scientific HPLC grade) and addition of a decane (Sigma-Aldrich) internal standard. These were then analyzed by a gas chromatograph (Hewlett-Packard 5890 Series II) equipped with an *α*-cyclodextrin capillary column (Chirasil-Dex CB, Varian, Inc.) for chiral separation. The dimethyl acetal of TMCH is formed in varying amounts under the reaction conditions. In cases where the dimethyl acetal was formed a few crystals of pyridinium *p*-toluene sulfonate, one drop of water and one drop of acetone were added to a sample of the crude reaction mixture to allow complete hydrolysis of the acetal back to TMCH. The sample was then analyzed as before. The enantiomeric excess of the TMCH was the same before and after hydrolysis demonstrating that the dimethyl acetal was formed post hydrogenation and not from the isophorone prior to hydrogenation.

High resolution X-ray photoelectron spectroscopy measurements were recorded in NCESS Laboratory, Daresbury, UK using the SCIENTA ESCA300 spectrometer and employing monochromatized Al Kα (hν = 1486.6 eV) radiation. Thin films of (i) carbon support (carbon black, Cabot), (ii) Pd reference sample (powder, Johnson Matthey) and (iii) 10 wt% Pd/C catalyst (Alfa Aesar) reduced in hydrogen at 150 °C for 12 hrs, were obtained by pressing the three powders on Al plates (Advent 99.9%) until no Al signal could be detected by XPS. Adsorption of the (*S*)-2-(tert-butylthiomethyl)pyrrolidine chiral modifier was performed by dipping the plates in a 0.47 mmol dm^{-3} solution of the chiral modifier (**4**) in methanol for 10 minutes. The samples were dried briefly in air then vacuum prior to acquisition of XP spectra.

Results and Discussion

Figures 3a,b show the measured e.e. as a function of modifier concentration for the six different chiral ligands. A measure of the uptake of the ligand by the catalyst is provided by specifying the concentration of the ligand in the initial reaction solution: exactly where on the Pd/C catalyst the ligand resides is revealed by XPS data presented below. Here, it is important to note that *only very small (i.e. catalytic) amounts of ligand were used*, in contrast with the necessarily large stoichiometric amounts of proline that were consumed when the latter was used to achieve kinetic resolution of the TMCH product in the hydrogenation of isophorone.[10]

Reactions were run until a yield of at least 60% was obtained (as monitored by hydrogen gas consumption during reaction and subsequently by chiral gas chromatography). In every case, increasing the ligand concentration decreased the reaction rate and this retardation effect was most pronounced with the largest ligands. For this reason, the concentration range explored was limited because the length of time required to achieve ~ 60% conversion was infeasible.

Two features are apparent. First, there is a large variation in the effectiveness of the ligands to induce asymmetry in the reduction of isophorone: 1,2-bis((*S*)-pyrrolidin-2-ylmethyl)disulfane (**1**), and (*S*)-2-(phenylthiomethyl)pyrrolidine (**6**) are totally ineffective, whereas the other four ligands are effective to varying degrees. Second, for the effective ligands, the e.e. achieved at ~ 60% conversion varies essentially linearly with initial ligand concentration, consistent with strong Langmuir-like adsorption of the chiral modifier from solution.

It is striking that the gradients of the lines in Figure 3 increase systematically with increasing size of the alkyl group in the thioether. Another way of illustrating this trend is shown in Table 1 which lists the e.e. achieved at ~ 60% for each modifier for the same initial modifier concentration of 0.23 mmol

dm^{-3}. (Typically, yields calculated from an internal standard were found to be consistent with conversion to within a few percent for all ligands, indicating that no significant decomposition of the substrate occurred).

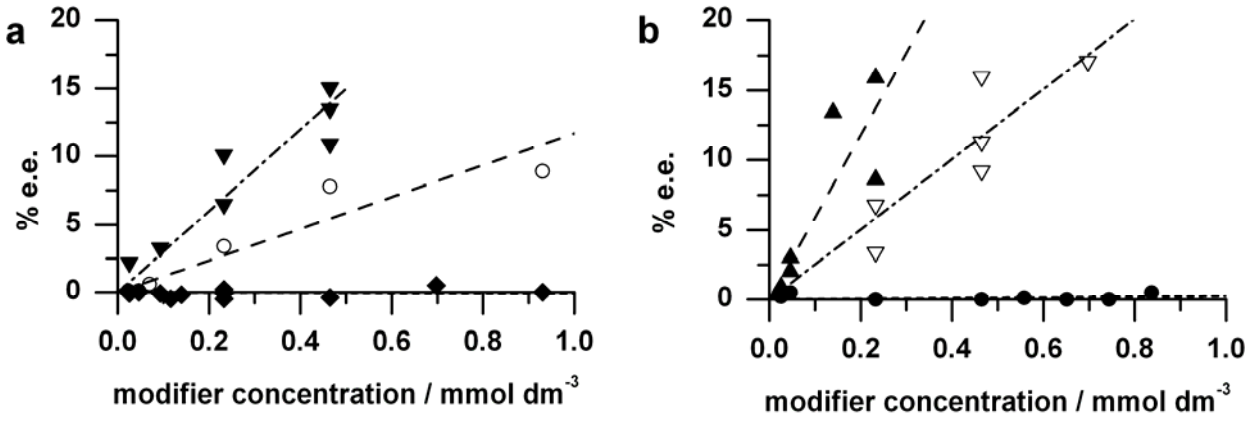


Figure 3. Dependence of TMCH e.e. on initial ligand concentration. Each data point corresponds to running the reaction up to a conversion of ~60%. (a) ▼ (*S*)-2-(tert-butylthiomethyl)pyrrolidine, (**4**); ○ (*S*)-2-(methylthiomethyl)pyrrolidine, (**2**); ◆ (*S*)-2-(phenylthiomethyl)pyrrolidine (**6**); (b) ▲ (*S*)-2-(adamantan-1-ylthiomethyl)-pyrrolidine, (**5**); ▽ (*S*)-2-(iso-propylthiomethyl)pyrrolidine, (**3**); ● 1,2-bis((*S*)-pyrrolidin-2-ylmethyl)disulfane, (**1**). A ligand concentration of 0.47 mmol dm^{-3} corresponds to 0.1 mol% ligand with respect to isophorone.

Modifier Ligand	% e.e. of TMCH obtained
(*S*)-2-(adamantan-1-ylthiomethyl)-pyrrolidine, (**5**)	13.8
(*S*)-2-(tert-butylthiomethyl)pyrrolidine, (**4**)	7.3
(*S*)-2-(iso-propylthiomethyl)pyrrolidine, (**3**)	6.0
(*S*)-2-(methylthiomethyl)pyrrolidine, (**2**)	3.3
1,2-bis((*S*)-pyrrolidin-2-ylmethyl)disulfane, (**1**)	0.0
(*S*)-2-(phenylthiomethyl)pyrrolidine (**6**)	0.0

Table 1. Dependence of TMCH e.e. on identity of ligand for fixed ligand concentration (0.23 mmol dm^{-3}, corresponding to 0.05 mol% ligand with respect to isophorone) as in Figure 2.

These results clearly indicate that *heterogeneous* enantioselective hydrogenation did indeed occur in the presence of adsorbed chiral modifier molecules. Only catalytic amounts of our modifiers were used (typically 1:2000 modifier:isophorone molar ratio) in contrast to the far greater stoichiometric amounts of proline that were required to achieve an enantiomeric excess in the product *via* kinetic resolution.[9,11] Rationalizing the observed dependence of e.e. on the degree of steric hindrance in the vicinity of the stereogenic center on the pyrrolidine moiety requires discussion of the mode of ligand adsorption. First, it must be the case that our ligands adsorb intact and remain so during reaction. Dissociative adsorption of the modifier by cleavage of the C-S bond (see Figure 4) to yield two adsorbed fragments would isolate the stereogenic carbon atom on the pyrrolidine ring from the alkyl or aryl functionality. If this were the case the e.e. achieved would be the same for all the sulfides as all would produce the same chiral entity on the surface. Clearly, this is not what is observed.

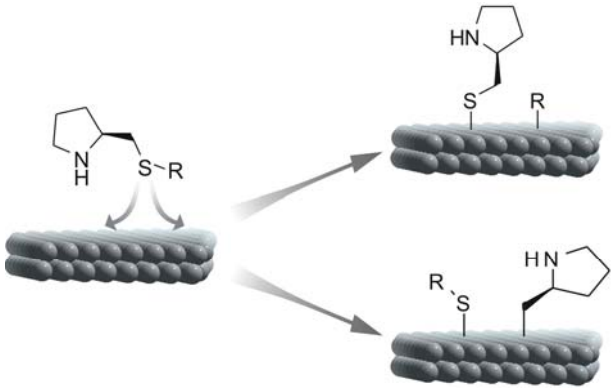


Figure 4. Showing that dissociative adsorption of sulfide ligands would preclude any dependence of e.e. on the **R** group.

How then does the **R** functionality affect e.e.? A plausible hypothesis is that the identity of **R** determines the spatial distribution of the adsorbed chiral modifier on the surface of the Pd catalyst. In general, adsorbates on metal surfaces may be dispersed as an ordered or disordered array of individual molecules, or they may agglomerate into islands of close-packed molecules separated by regions of bare surface, or the islands may be in equilibrium with a "sea" of dispersed molecules. Which of these three possibilities actually occurs depends on the interplay between molecule-surface and molecule-molecule interactions. Consider now the consequences of these alternative behaviors for enantioselective catalysis. Fully dispersed chiral modifiers should be the most effective: each molecule can interact with a neighboring adsorbed substrate molecule (isophorone) allowing asymmetric induction in the subsequent reaction with H adatoms. Close-packed islands of modifier should be very ineffective, only molecules at the periphery can interact with adjacent substrate molecules. And of course only hydrogenation to give racemic product can occur on the "bare" (modifier-free) metal surface. Bulky **R** groups will hinder close approach of modifier molecules to each other, thus inhibiting island formation, favoring dispersion as separate molecules and resulting in effective asymmetric induction. Conversely, small **R** groups should favor island formation leading to very low asymmetric induction. Another factor that may contribute to the observed increase in e.e. with bulkiness of the **R** group is that a larger **R** may push the stereogenic center closer to the surface constraining the reaction conformation during

hydrogenation and promoting enantioselective reaction. The results for **R** = H, Me, ^{i}Pr, ^{t}Bu, adamantyl, where bulkiness and e.e. increase together, are in agreement with these explanations (Figure 3 and Table 1). Interestingly, **R** = phenyl does not fit this pattern: no detectable e.e. was observed in this case. It appears that the presence of an aromatic substituent strongly modifies adsorption behavior compared to the other cases, possibly the consequence of π-π interactions which favor island formation,[20] and hence poor enantioselectivity.

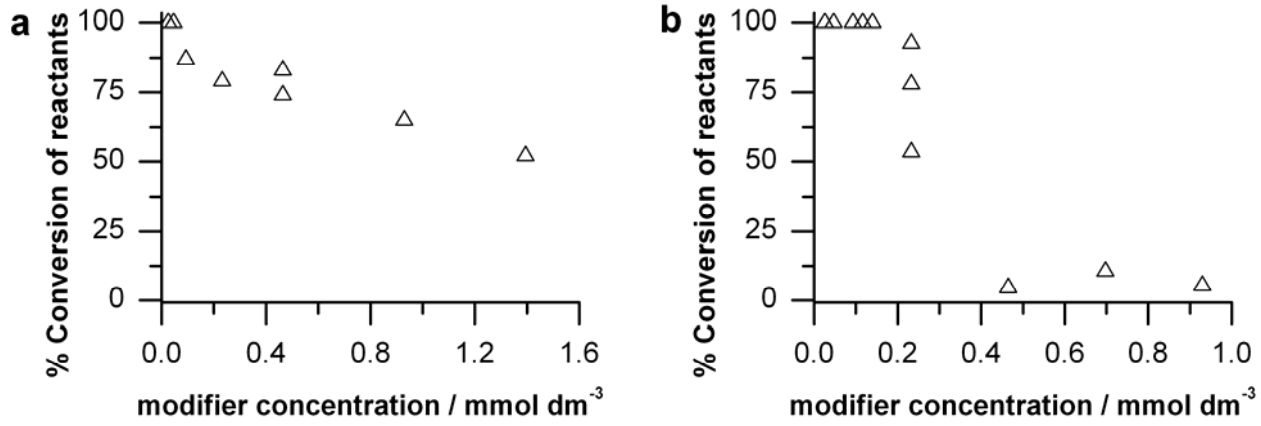


Figure 5. Dependence of activity (reactant conversion after a fixed time (168 h)) on ligand concentration. (a) (*S*)-2-(tert-butylthiomethyl)pyrrolidine, (**4**), (b) (*S*)-2-(phenylthiomethyl)pyrrolidine (**6**).

Support for this explanation is provided by the data shown in (Figures 5a,b) which show the *total conversion of reactant* to TMCH product after a fixed time as a function of ligand concentration for two different ligands. These results provide a direct indication of the extent to which reactant molecules can access the surface and undergo hydrogenation. For **R** = tert-butyl (Figure 5a) the catalytic activity decreases approximately linearly with ligand concentration while at the same time the e.e. rises (Figure 3 and Table 1). This is consistent with well-dispersed ligand molecules which (i) create chiral adsorption sites and (ii) necessarily decrease overall activity simply as a result of denying surface sites to the reactants (hydrogen and isophorone). The behavior for **R** = phenyl (Figure 5b) is dramatically different, with a pronounced step decrease in activity at 0.2 mmol dm^{-3}. This may be rationalized as

follows. Even at low concentration the ligand molecules form islands, likely due to π–π interactions,[20] leaving most of the surface bare (i.e. racemic chemistry). Activity is therefore high, and, because only very few ligand molecules can interact with adjacent reactant molecules e.e. is very low, as indeed observed (Figure 3 and Table 1).[21, 22] Initially, with increasing ligand concentration, the islands grow, most of the surface remains bare, activity remains high and the reaction is essentially racemic. At a certain point, the entire surface becomes covered with close-packed ligand molecules: a self assembled sulfide monolayer that is impervious to reactant molecules, and activity collapses. Further increase in ligand concentration in the solution phase can have no effect on the saturated surface which therefore remains catalytically inert.

Although the e.e.s we report are modest compared to those encountered in the well-established field of homogeneous enantioselective catalysis, their significance is considerable. We have demonstrated a hydrogenation reaction that is both truly heterogeneous and genuinely catalytic and which leads to ***enantioenriched*** product. Furthermore, we have demonstrated that the effectiveness of the stereogenic center on the ligand in inducing enantioselective catalysis depends in no small part on the collective behavior of the adsorbed chiral molecules which depends on the interplay between intermolecular and molecule-surface interactions.

It is revealing to calculate the enantioselective turn-over number[23] because this enables a distinction to be made between a catalytic process and a kinetic resolution by reductive amination, i.e. the mechanism the proline mediated reaction. For example, carrying out the reaction with 0.47 mmol dm^{-3} (corresponding to 0.1 mol% ligand with respect to isophorone) of (**4**) (*S)*-2-(^{t}butyl-thiomethyl)-pyrrolidine modifier present in the initial reaction solution, hydrogenation gave TMCH in 70% yield with an e.e. of 15%. This corresponds to a enantioselective turn-over number of ≥ 100 product molecules per ligand molecule. (Mere kinetic resolution would of course correspond to an enantioselective turn-over number of exactly 1).

To confirm that the observed enantiomeric excess did indeed arise purely from the chirality of the modifier ligand, a control experiment was performed with the opposite enantiomer of the originally used chiral modifier. Thus a concentration of 0.47 mmol dm^{-3} (corresponding to 0.1 mol% ligand with respect to isophorone) of (*R*)-2-(^{t}butyl-thiomethyl)-pyrrolidine produced TMCH with an e.e. of - 14.3% in very good agreement with the result given above (Figure 3) where it was found that the (*S*) form gave an e.e. of + 14.8% at similar reactant conversion.

Our current hypothesis regarding the mechanism of the reaction is as follows (Figure 6). The ligand is tightly bound to the surface of the palladium through sulfur. 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.

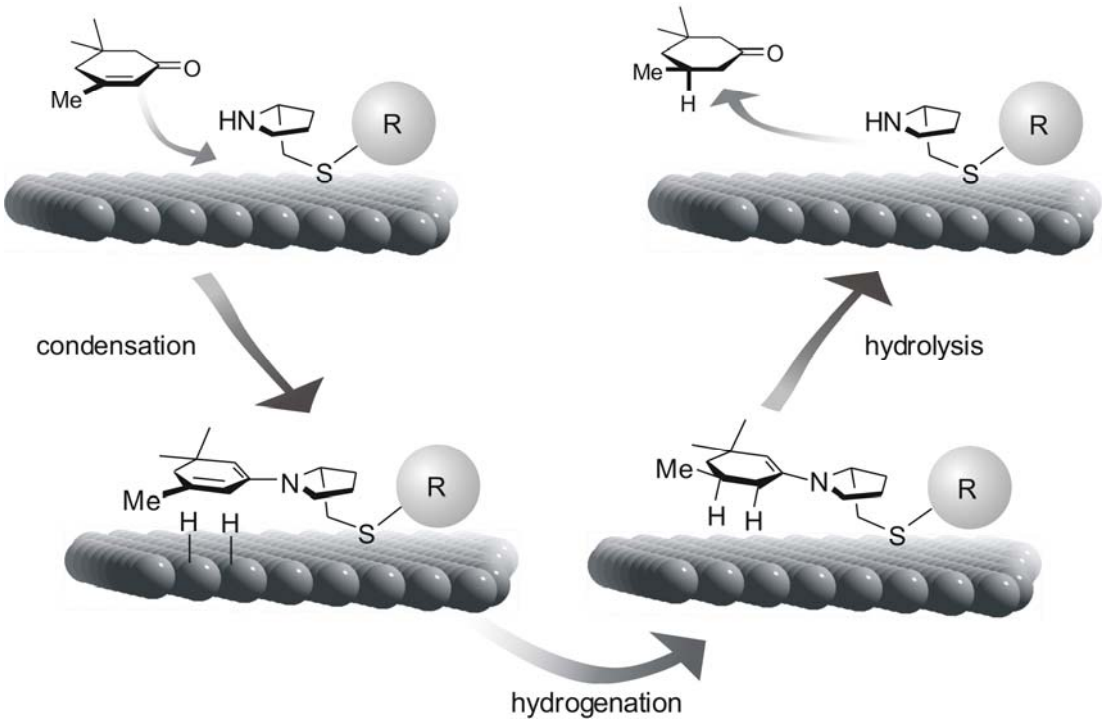
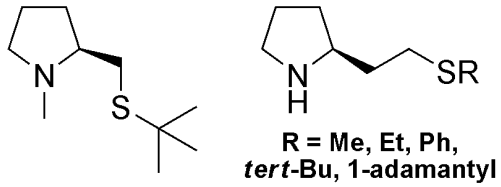


Figure 6. Scheme showing proposed mechanism *via* iminium ion/enamine intermediate.

In order to test the hypothesis that interaction of the ligand with the substrate *via* the nitrogen atom on the pyrrolidine ring is critically important, we synthesized and tested the effectiveness of the analogous tertiary amine (*S*)-2-(tert-butylthiomethyl)-1-methylpyrrolidine (**7**) in order to compare its performance with that of the secondary amine (**4**) (*S*)-2-(^{t}butyl-thiomethyl)-pyrrolidine (15% e.e.). Strikingly, use of the tertiary amine (**7**) as a ligand in the catalytic asymmetric hydrogenation of isophorone resulted in racemic product, a result which is in keeping with our model of enamine/iminium formation.[24]



7 **8**

Figure 7. Modified sulfide ligands used in additional experiments (**7**) (*S*)-2-(tert-butylthiomethyl)-1-methylpyrrolidine and (**8**) ligands containing an additional methylene unit between the pyrrolidine ring and the sulfide.

The effect of the distance between the secondary amine and the sulfide in influencing enantioselectivity of the reduction of TMCH was examined by synthesizing and then using a set of ligands **8** (Figure 7) analogous to **1-6**, but containing an additional methylene unit between the pyrrolidine ring and the sulfide.[25] In every case, only very small enantiomeric excesses were observed (<4% e.e. at ≥ 60% yield). This may be attributed to the tethering sulfur atom now being in a much less rigid relationship with the pyrrolidine allowing the two moieties to rotate with respect to each other so that isophorone molecules interacting with the pyrrolidine ring undergo hydrogenation from both prochiral faces with approximately equal probability.

Finally, we address a point that is critically important to any mechanistic interpretation that might be offered: where does the adsorbed chiral ligand actually reside? On the palladium? On the support? On

both? Accordingly, we carried out high resolution XPS measurements on three samples that had been exposed to (**4**) (*S*)-2-(^{t}butyl-thiomethyl)-pyrrolidine under exactly the same conditions as those used for catalytic testing. These were (i) pure Pd powder (ii) pure carbon support (iii) the Pd/carbon catalyst itself. The key result is given in Figure 8a which shows the relevant S 2p XP spectra.

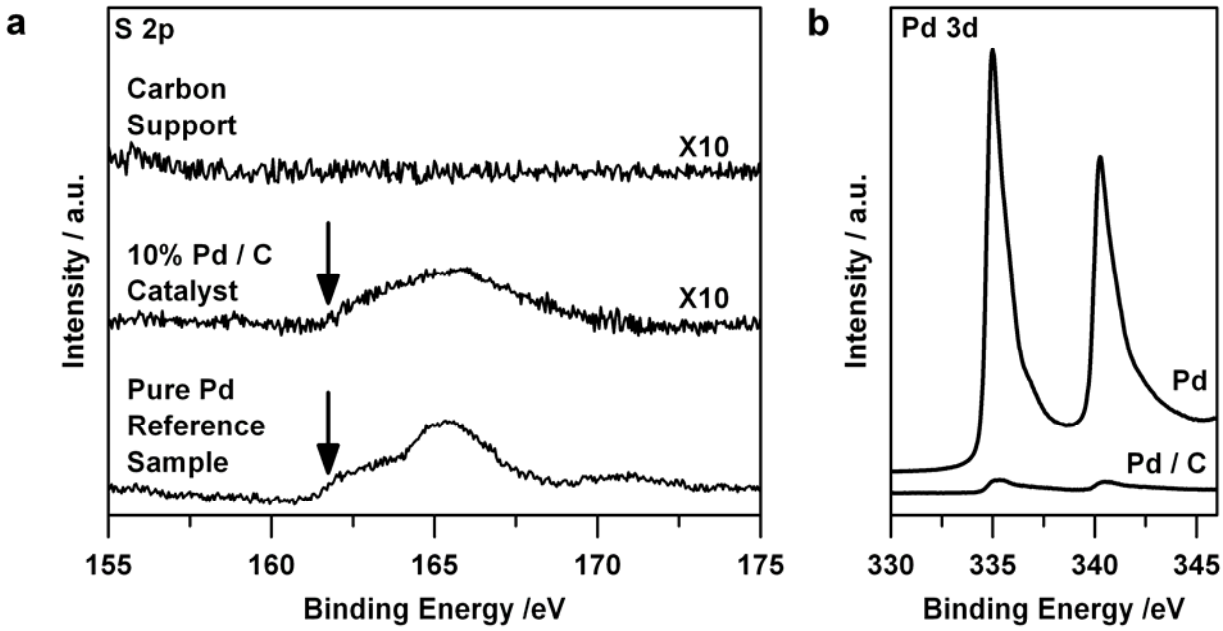


Figure 8. (a) Sulfur 2p XP spectra showing uptake of (*S*)-2-(^{t}butyl-thiomethyl)-pyrrolidine modifier (**4**) from methanol solution by (top to bottom) carbon support, 10wt % Pd/C catalyst, and pure palladium reference sample. Samples were left in contact with ligand solution for 10 minutes. (b**)** Palladium 3d XP spectra for the fresh Pd/C catalyst and pure Pd reference.

Figure 8a confirms extensive adsorption of (**4**) (*S*)-2-(^{t}butyl-thiomethyl)-pyrrolidine by palladium. It is noteworthy that, when due allowance is made for photoionization cross sections, the corresponding N 1s XP spectra (shown in the supporting information) yield a S:N ratio of 1:1 in accord with the stoichiometry of the chiral modifier. Figure 8b shows Pd 3d spectra obtained from the Pd powder reference sample and from the catalyst. It serves to illustrate the point that the metal content of the catalyst is of course far lower than that of pure Pd powder, which is why the S 2p spectrum of the catalyst is ~ 10 × less intense than that of pure Pd powder (Figure 8a). The broadening of the S 2p signal

observed for the (dilute) Pd/C catalyst likely reflects inelastic scattering of the sulfur photoelectrons (kinetic energy 1320 eV) arising from Pd nanoparticles located within the carbon support. Thus it is established that within experimental error ligand uptake occurred exclusively on the Pd nanoparticles, justifying the implicit assumption that underlies the preceding discussion. (The arrow in Figure 8a indicates the S 2p binding energy characteristic of sulfur adatoms on palladium.[20] This indicates that the species we observe contains organically-bound sulfur,[26, 27] confirming our earlier conclusion that adsorption does not destroy ligand integrity.)

Conclusions

Chiral sulfide ligands that anchor robustly to Pd nanoparticles and resist displacement are effective in directing the truly heterogeneous enantioselective catalytic hydrogenation of isophorone. Enantioselective turn-over numbers of up to ~ 100 product molecules per ligand molecule have been found. High resolution XPS data show that ligand adsorption from solution occurred exclusively on the Pd nanoparticles and not on the carbon support. A large variation in asymmetric induction across the series of ligands correlated with size of the alkyl group in the sulfide. This is thought to reflect different degrees of ligand dispersion on the surface, bulky substituent groups inhibiting close-packed island formation, favoring dispersion, and hence resulting in effective asymmetric induction. Control experiments carried out with an analogous tertiary amine lead to purely racemic product, consistent with a mechanism that involves initial formation of an enamine or iminium species. Use of a set of ligands equivalent to the original set of six but containing an extra methylene unit gave only very small enantiomeric excesses. This suggests that placing the tethering sulfur atom in a much less rigid relationship with the pyrrolidine allows the two moieties to rotate with respect to each other so that isophorone molecules interacting with the pyrrolidine ring undergo hydrogenation from both prochiral faces with approximately equal probability. Ligand rigidity and resistance to self assembled monolayer formation are important attributes that should be designed into improved chiral modifiers.

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24. Another mechanistic possibility involves the delivery of the isophorone to the metal surface *via* hydrogen bonding with the secondary amine of the ligand. This would also account for the production of racemic TMCH with the tertiary amine ligand **7**, although is less likely given the previous observation of the condensation product with proline and the lack of asymmetric induction in this reaction by other chiral modifiers with a capacity to hydrogen bond.

25. The ligands **8** were prepared from (*S*)-β-homoproline in an analogous manner to the preparation of the ligands **1**-**6**.

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TOC GRAPHIC


Me
O
Enantioselective
Hydrogenation
Me
H
O
Chirally Modified Pd Surface