

Heterogeneously Catalyzed Asymmetric C=C Hydrogenation: Origin of Enantioselectivity in the Proline-Directed Pd/Isophorone System

Alexander I. McIntosh, David J. Watson, Jonathan W. Burton, and Richard M. Lambert*

Contribution from the Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, United Kingdom

Received February 15, 2006; E-mail: RML1@cam.ac.uk

Abstract: We have studied the proline-directed, Pd-catalyzed enantioselective hydrogenation of isophorone in the liquid state using a variety of methods. Our results unambiguously reveal the true reaction pathway and demonstrate that all earlier mechanistic hypotheses are wrong: although a proline/isophorone condensation product is formed, it is merely a spectator and not a key reaction intermediate in subsequent heterogeneous hydrogenation. Enantioselectivity is the result of kinetic resolution—a process that occurs homogeneously in solution and not at the metal surface. Racemic 3,3,5-trimethylcyclohexanone (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. Thus in complete contrast to the case of ketoester asymmetric hydrogenation, the metal surface is *not* involved in the crucial enantio-differentiation step. The mechanism we propose also explains why the maximum attainable yield of enantiopure TMCH cannot exceed 50%.

Introduction

The development of homogeneous chiral transition metal catalysts opened up a major new field of chemistry—the synthesis of pure enantiomers from achiral precursors.^{1–3} The academic and technical consequences of these advances have transformed synthetic chemistry. By comparison, effective *heterogeneously* catalyzed enantioselective reactions are rarities, despite their huge potential importance which derives from the major operational advantages offered by heterogeneous over homogeneous catalysis. In addition to the fundamental challenges that it poses, this area is of foremost significance to the pharmaceutical, fine chemicals, and advanced materials industries. Two systems have received intensive study: the enantioselective hydrogenation of α - and β -ketoesters catalyzed by modified platinum metals^{4–11} and by Ni.^{12–15} Although there

is undoubtedly more to learn, our understanding of the fundamentals of enantioselective C=O hydrogenation may be regarded as relatively well developed—a key point being that, irrespective of details, the critical enantio-differentiation step occurs at the surface of the metal catalyst.

In marked contrast, despite its potential importance in organic synthesis, heterogeneously catalyzed asymmetric hydrogenation of C=C bonds has received very little attention. Thus far, essentially all the work in this area has been carried out by Tungler and co-workers^{16,17} who focused on the metal-catalyzed, proline-directed, enantioselective hydrogenation of isophorone (**1**) to dihydroisophorone (**2**) (3,3,5-trimethylcyclohexanone, hereafter TMCH), where relatively modest enantiomeric excesses (ee's) have been achieved. They concluded that enantioselectivity arises from the initial (*homogeneous*) formation 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 enantioenriched TMCH. However, there are significant apparent inconsistencies and gaps in their analysis of the proline/isophorone system. Accordingly, we investigated this system in order to (i) test earlier proposals and (ii) clarify key aspects of the mechanism. We find that the proline/isophorone condensation

- (1) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1999–2007.
- (2) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022.
- (3) Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024–2032.
- (4) Blaser, H. U.; Baiker, A. In *Handbook of Heterogeneous Catalysis*; Ertl, G., Knötzinger, H., Weitkamp, J., Eds.; Wiley-VCH: New York, 1997; Vol. 5, p 2422.
- (5) Blaser, H. U.; Jaleff, H. P.; Muller, M.; Studer, M. *Catal. Today* **1997**, *37*, 441–463.
- (6) Baiker, A. *J. Mol. Catal. A-Chem.* **1997**, *115*, 473–493.
- (7) Wells, P. B.; Wilkinson, A. G. *Top. Catal.* **1998**, *5*, 39–50.
- (8) Jenkins, D. J.; Alabdulrahman, A. M. S.; Attard, G. A.; Griffin, K. G.; Johnston, P.; Wells, P. B. *J. Catal.* **2005**, *234*, 230–239.
- (9) Attard, G. A.; Ahmadi, A.; Jenkins, D. J.; Hazzazi, O. A.; Wells, P. B.; Griffin, K. G.; Johnston, P.; Gillies, J. E. *ChemPhysChem* **2003**, *4*, 123–130.
- (10) Bonello, J. M.; Williams, F. J.; Lambert, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 2723–2729.
- (11) Bonello, J. M.; Lambert, R. M.; Kunzle, N.; Baiker, A. *J. Am. Chem. Soc.* **2000**, *122*, 9864–9865.
- (12) Jones, T. E.; Baddeley, C. J. *Surf. Sci.* **2002**, *519*, 237–249.
- (13) Jones, T. E.; Baddeley, C. J. *Surf. Sci.* **2002**, *513*, 453–467.

- (14) Jones, T. E.; Baddeley, C. J. *J. Mol. Catal. A-Chem.* **2004**, *216*, 223–231.
- (15) Lorenzo, M. O.; Baddeley, C. J.; Muryn, C.; Raval, R. *Nature* **2000**, *404*, 376–379.
- (16) Tungler, A.; Máthé, T.; Petró, J.; Tarnai, T. *J. Mol. Catal.* **1990**, *61*, 259–267.
- (17) Tungler, A.; Kajtár, M.; Máthé, T.; Tóth, G.; Fogassy, G.; Petró, J. *Catal. Today* **1989**, *5*, 159–171.

product is merely a spectator and not a key reaction intermediate. Moreover, enantioselectivity is the result of kinetic resolution—a process that occurs homogeneously in solution and not at the metal surface. Racemic TMCH (\pm)-**2** is produced by initial *heterogeneous* hydrogenation of isophorone (**1**), proline (**3**), then reacts *homogeneously*, preferentially with one enantiomer of TMCH, leaving an excess of the other. Thus in complete contrast to the case of ketoester asymmetric hydrogenation, the metal surface is *not* involved in the crucial enantio-differentiation step. The mechanism we propose also explains why the maximum attainable yield of enantiopure TMCH cannot exceed 50%.

Experimental Methods

Materials. L-Proline (99+%), D-proline (99+%), isophorone (97%), and 3,3,5-trimethylcyclohexanone (TMCH) (98%) were supplied by Aldrich. HPLC grade methanol was supplied by Fisher Scientific, and the 10% Pd/C catalyst was purchased from Alfa Aesar.

Hydrogenation Procedure. Hydrogenation was carried out at atmospheric pressure using standard Quickfit glassware with continuous stirring of the reaction mixture. Proline + isophorone reactions were carried out with 0.004 mol of proline and 0.004 mol of isophorone in 8 mL of methanol in the presence of 20 mg of Pd/C catalyst. Similarly, proline + TMCH reactions were carried out with 0.004 mol of proline and 0.004 mol of TMCH in 8 mL of methanol with 20 mg of Pd/C catalyst. After hydrogenation, the catalyst was removed by filtration using 0.45 μ m grade filters, and the filtrate was combined with an equal volume of dichloromethane. Next, the unreacted proline was extracted by scavenging through a macroporous polystyrene sulfonic acid column (Argonaut Technologies Inc.); the latter was then washed with a 1:1 mixture of methanol and dichloromethane to recover any remaining isophorone and/or TMCH. The combined eluent, which contained all the TMCH product along with unreacted isophorone, was then analyzed by gas chromatography.

Analysis. Reaction mixtures were analyzed using a Hewlett-Packard 5890 Series II gas chromatograph equipped with a β -cyclodextrin capillary column (Chirasil-Dex CB, Varian, Inc.). Chromatograms were acquired using the following temperature program: 90 °C for 10 min then 5 °C/min to 110 °C. Enantiomeric excesses expressed in % terms were calculated according to

$$ee = \frac{[A] - [B]}{[A] + [B]} \times 100$$

where [A] is the concentration of one enantiomer and [B] that of the other enantiomer. Absolute conversions were calculated using a decane internal standard that was added to worked-up solutions prior to GC analysis. Ultraviolet–visible (UV–vis) spectra were recorded with a Cary 100 Bio UV–visible spectrometer using 50 μ M initial concentration for both reactants.

Results and Discussion

In this relatively complex system, identifying the separate roles of homogeneous and heterogeneous chemistry is of paramount importance. Accordingly, we first studied the time dependence of the *homogeneous* reaction between L-proline (*S*)-**3** and isophorone (**1**). Then we examined the *heterogeneous* hydrogenation of the resulting reaction mixtures as a function of elapsed homogeneous reaction time. Finally, we investigated the *homogeneous* reaction of L-proline (*S*)-**3** with the primary hydrogenation product racemic TMCH (\pm)-**2** and then the subsequent *heterogeneous* hydrogenation of the resulting condensation product.

Homogeneous Reaction of Proline with Isophorone. Tun- gler et al. proposed that enantioselectivity in this system arises

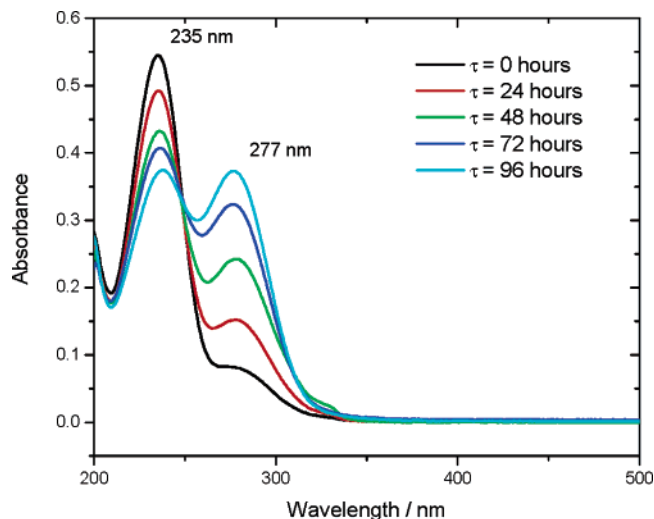


Figure 1. UV–vis spectra of 1:1 isophorone:L-proline reaction mixtures as a function of elapsed time τ . Samples were being withdrawn at 24 h intervals for examination by UV–vis spectroscopy.

from the hydrogenation of one of the condensation products resulting from the homogeneous reaction of proline **3** with isophorone **1**.^{16,17} We therefore studied the time dependence of the homogeneous interaction of a 1:1 mixture of L-proline (*S*)-**3** and isophorone (**1**) in methanol solution at room temperature, samples being withdrawn at 24 h intervals for examination by UV–vis spectroscopy. The results are shown in Figure 1, where τ is the time elapsed between starting the homogeneous reaction and making the measurement.

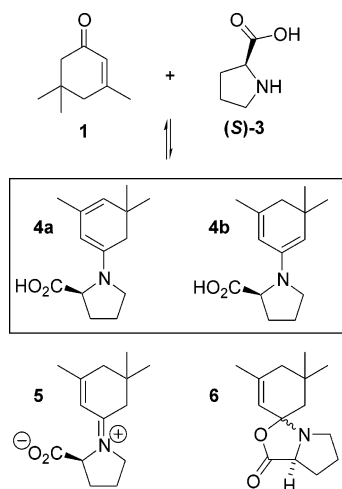
It is apparent that the intensity of the absorbance at 235 nm, which corresponds to the $\pi \rightarrow \pi^*$ transition of the α,β -unsaturated carbonyl system of isophorone,¹⁸ decreased with increasing reaction time. This was accompanied by a corresponding progressive increase in the intensity of an absorbance at 277 nm that we ascribe to the condensation product formed by reaction of L-proline (*S*)-**3** and isophorone (**1**). Note that the occurrence of an isosbestic point provides a clear indication that only one major species is formed by this condensation reaction. Analysis of the solution by means of liquid chromatography–mass spectrometry (LC–MS) and electrospray ionization mass spectrometry (ESI–MS) showed formation of a molecule resulting from the condensation of one molecule of isophorone (**1**) and one molecule of L-proline (*S*)-**3** with elimination of one molecule of water (ESI–MS m/z found: $(M + H)^+$, 236.1642. $C_{14}H_{22}NO_2$ requires M , 236.1651). Scheme 1 illustrates the various possible condensation products.

We assign the condensation product to the linear and/or cross-conjugated dienamines **4** by comparison with the UV absorptions for the dienamines formed between morpholine and isophorone (λ_{\max} 288 nm) and between piperidine and isophorone (λ_{\max} 274 nm).^{19–21}

(18) Flego, C.; Perego, C. *Appl. Catal. A-Gen.* **2000**, *192*, 317–329.

(19) Nozaki, H.; Yamaguti, T.; Ueda, S.; Kondô, K. *Tetrahedron* **1968**, *24*, 1445–1453.

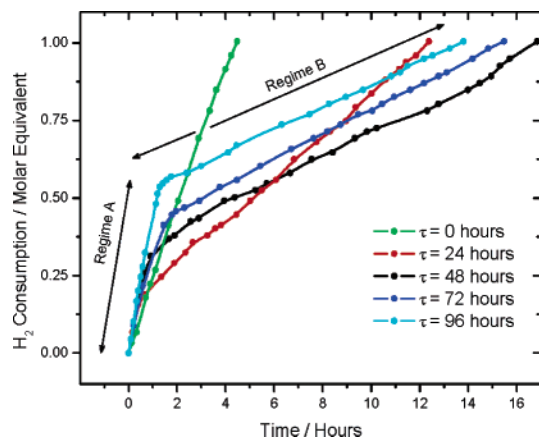
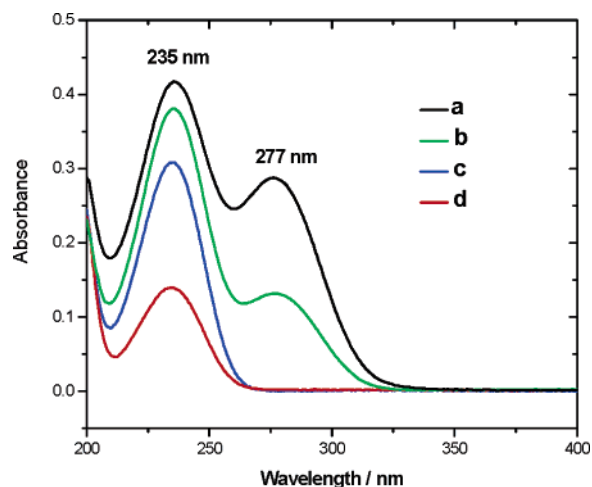
(20) We cannot rule out that the intermediate is the zwitterionic species corresponding to **4** for the following reason: the UV spectrum of aniline shows large shifts in the K (230 nm) and B bands (280 nm) compared with benzene (K band, 203.5 nm; B band, 254 nm), whereas N-protonated aniline shows no such shifts (K band, 203 nm, B band 254 nm).²¹ An ammonium substituent therefore has little effect on the absorption wavelength of the conjugated system to which it is attached; hence the condensation product formed between proline and isophorone may be the zwitterionic species corresponding to **4**.

Scheme 1. Possible Products from the Condensation of Isophorone with Proline**Table 1.** The τ Dependence of TMCH Enantiomeric Excess Produced by Hydrogenation up to One Molar Equivalent H_2 of L-Proline (S)-3 and Isophorone 1 Reaction Mixtures

prereaction time (τ), h	ee (%) $\pm 3\%$
0	49
24	54
48	39
72	33
96	19

Heterogeneous Hydrogenation of the Reaction Mixture as a Function of τ . A corresponding approach was used to examine the τ dependence of the heterogeneously catalyzed hydrogenation of the reaction mixtures resulting from the homogeneous condensation of L-proline (S)-3 and isophorone 1; that is, mixtures of L-proline and isophorone in methanol were stirred for a series of times τ (the same times as used to acquire the UV-vis data in Figure 1), placed under 1 atm hydrogen gas, and the Pd/C catalyst added. In each case, after consumption of 1 molar equiv of hydrogen, the reaction was stopped and the ee of the resulting TMCH 2 was measured by chiral GC. The results are presented in Table 1, from which it is apparent that the ee of the TMCH *decreased* with *increasing* homogeneous condensation time (τ).

This is a key observation as it demonstrates that enantioselective formation of TMCH does *not* involve heterogeneous asymmetric hydrogenation of the condensation product 4 formed between L-proline and isophorone—as was previously suggested.^{16,17} In other words, if enantioselective formation of TMCH 2 *did* involve heterogeneous hydrogenation of the initially formed condensation product 4, the ee of the resulting TMCH should either *increase* with τ , if the hydrogenation of isophorone is competitive with the hydrogenation of the proline/isophorone condensation product 4, or *be independent* of τ , if there is no competitive hydrogenation of isophorone. Both of these scenarios are in direct contradiction to observation. (As we shall show later, the condensation product 4 does undergo hydrogenation, but this is a side reaction and it does not contribute to TMCH formation, racemic or otherwise.)

**Figure 2.** The time dependence of hydrogen uptake during hydrogenation of the various prereacted solutions.**Figure 3.** UV absorption spectra of hydrogenation reaction mixtures corresponding to $\tau = 72$ h. Samples taken (a) before hydrogenation; (b) halfway through regime A (see Figure 2); (c) at the turning point between regime A and regime B (see Figure 2); and (d) after consumption of 1 molar equiv of hydrogen.

The time dependence of hydrogen uptake during hydrogenation of the L-proline/isophorone reaction mixtures described above is shown in Figure 2. The uptakes for $\tau \geq 24$ h show distinctive features: it is apparent that there are two dissimilar regions, designated A and B, characterized by very different reaction rates. The amount of hydrogen consumed in regime A increases with τ and closely follows the increase in intensity of the 277 nm absorbance (Figure 1). This strongly suggests that regime A is associated with the relatively rapid hydrogenation of the 277 nm species 4.

To test this hypothesis, a reaction mixture corresponding to $\tau = 72$ h was hydrogenated, samples being taken for UV spectroscopy (a) prior to hydrogenation, (b) halfway through regime A, (c) at the turning point between regime A and regime B, and (d) after consumption of 1 molar equiv of hydrogen. The results are shown in Figure 3.

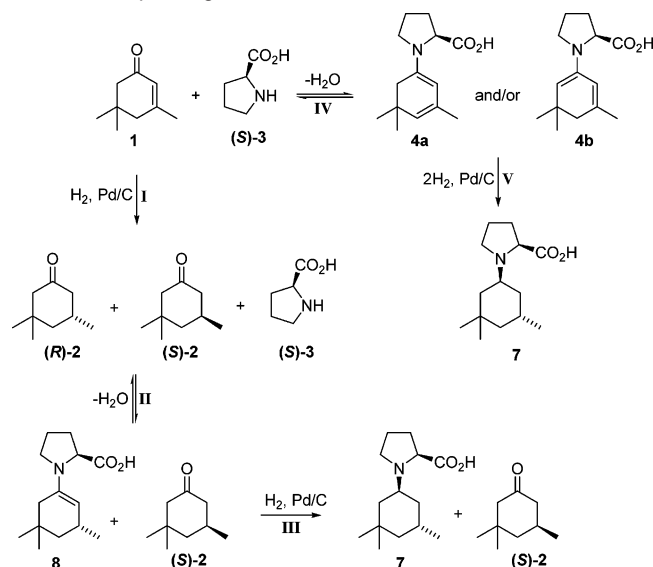
It is apparent that case (a) is equivalent to the $\tau = 72$ h spectrum shown in Figure 1, as would be expected. The spectrum taken in the middle of regime A, and especially that taken at the A/B turning point, clearly demonstrates that during this initial phase it is *principally the 277 nm species 4 that is hydrogenated*. Control experiments carried out with (a) hydrogen in the absence of catalyst and (b) with catalyst in the absence

(21) Jaffé, H. H.; Orchin, M. *Theory and Applications of Ultraviolet Spectroscopy*; Wiley: New York, 1962.

of hydrogen gave a null result, confirming that disappearance of the 277 nm species **4** was indeed due to its hydrogenation and not to some other process. The ee of the TMCH produced by hydrogenation was also measured at the A/B turning point: *this TMCH was racemic*. The UV spectrum of the solution obtained after consumption of 1 molar equiv hydrogen (spectrum d, Figure 3) shows that, in contrast to regime A, substantial hydrogenation of isophorone **1** occurs in regime B. Moreover, even after the consumption of 1 molar equiv of hydrogen, a significant amount of unreacted isophorone remained. Control experiments showed that under our conditions neither L-proline alone nor TMCH alone underwent catalytic hydrogenation. This indicates that the 277 nm condensation product **4** can consume more than 2 equiv of dihydrogen. Support for this proposal was gained by the isolation and full characterization of (2*S*)-1-[(1*S*,5*R*)-3,3,5-trimethylcyclohexyl]pyrrolidine-2-carboxylic acid **7** from the above reaction mixture, the result of hydrogenation of **4** with 2 mol of hydrogen. The amino acid **7** was isolated as the major component (13:1 by ¹H NMR) of an inseparable mixture along with the diastereomer **7'** (for structural assignment and full characterization, see Supporting Information).

To simplify the further discussion of this relatively complex system, we now introduce a reaction scheme that accounts for all our observations—some yet to be described and discussed—as shown below. The key features of this scheme, and indeed

Scheme 2. Proposed Reaction Scheme for the Kinetic Resolution of TMCH **2** by L-Proline (*S*)-**3**. Intermediate **8** May Be the Regioisomeric Enamine, the Corresponding Zwitterionic Species, or the Corresponding Iminium Ion



the principal message of this paper, are readily summarized. Steps I, III, and V are catalytic hydrogenations and necessarily involve the metal surface—however, they do *not* result in the formation of enantioenriched TMCH. Step II is the stereo-determining reaction—however, it does *not* involve the metal surface; it consists of competitive homogeneous reactions involving L-proline (*S*)-**3** and *both* enantiomers of TMCH **2**. Clearly, these two competing reactions *must* have intrinsically different rate constants. Hydrogenation of enantiopure (*S*)-TMCH, (*S*)-**2**, and (*R*)-proline (*R*)-**3** did indeed reveal a much faster hydrogen uptake than the comparable reaction of enantiopure (*S*)-TMCH, (*S*)-**2**, and (*S*)-proline (*S*)-**3**. We shall proceed

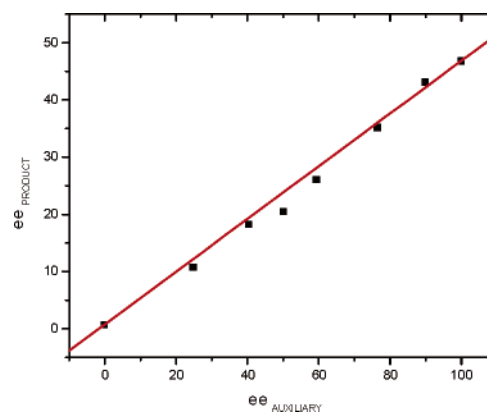


Figure 4. Dependence of the ee of TMCH **2** on the ee of the proline chiral auxiliary at the point corresponding to the consumption of 1 molar equiv of hydrogen. The solid line corresponds to exact linearity: $ee_{\text{product}} = ee_{\text{max}} \times ee_{\text{aux}}$, where ee_{max} is equal to 49%.

to justify this radically new interpretation of the proline-directed enantioselective heterogeneous hydrogenation of isophorone according to which step II is the critical homogeneous process that leads to enantio-differentiation by kinetic resolution of racemic TMCH (\pm)-**2** formed by *racemic heterogeneous hydrogenation* of isophorone **1** (step I). First we describe the results of experiments designed to address certain specific mechanistic issues.

The possible occurrence of nonlinear effects during the catalytic hydrogenation of racemic TMCH (\pm)-**2** and proline **3** was investigated as such behavior has been observed in a number of other catalytic asymmetric processes.²² Clearly, there are no nonlinear effects, consistent with the mechanism proposed in Scheme 2.

Figure 4 shows the dependence of the ee of the hydrogenation product (TMCH **2**) on the *enantiomeric excess of the proline chiral auxiliary* (varied by mixing L- and D-proline) at the point corresponding to the consumption of 1 molar equiv of hydrogen. (The solid line in Figure 4 corresponds to exact linearity: $ee_{\text{product}} = ee_{\text{max}} \times ee_{\text{aux}}/100$, where ee_{max} is equal to 49%.)

Reaction of Proline with the Primary Hydrogenation Product (TMCH). Next we examined the proposed steps II and III in Scheme 2, namely, the hydrogenation of mixtures of L-proline (*S*)-**3**, (\pm)-TMCH (\pm)-**2**. A mixture of L-proline (*S*)-**3**, (\pm)-TMCH (\pm)-**2**, and Pd/C was found to consume significant amounts of hydrogen even at $\tau \sim 0$. Given the control experiments which show that neither L-proline nor TMCH alone undergo Pd-catalyzed hydrogenation, we may conclude that L-proline and TMCH undergo a relatively fast reaction (step II) resulting in a product (**8**) that undergoes subsequent hydrogenation to yield **7** (step III). Indeed, analysis of hydrogenated reaction mixtures revealed the presence of a species corresponding to the fully hydrogenated condensation product of TMCH and L-proline—species **7** [*m/z* (ES) found: ($M + H$)⁺, 240.1971. C₁₄H₂₆NO₂ requires *M*, 240.1964] identical to material isolated from the $\tau = 72$ h reaction mixture above (for full structural assignment of **7**, see the Supporting Information). Most importantly, chiral GC measurements showed that the residual TMCH exhibited significant enantiomeric excess [predominantly the (*S*)-enantiomer]; together, these observations establish step II as the stereo-determining step.

(22) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2923–2959.

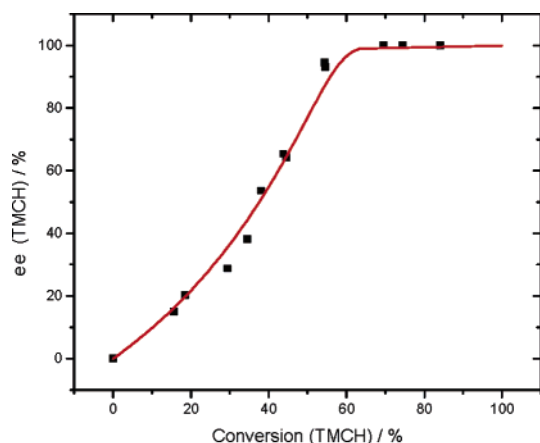


Figure 5. Dependence of TMCH ee on TMCH conversion during the catalytic hydrogenation of a mixture initially containing 0.004 mol TMCH and 0.004 mol L-proline in 8 mL of methanol.

Accordingly, further experiments were conducted to confirm beyond doubt that enantioselectivity in this system is the result of the kinetic resolution of racemic TMCH (\pm)-**2** formed in the initial racemic heterogeneous hydrogenation of isophorone. Figure 5 shows the dependence of the enantiomeric excess of TMCH **2** on TMCH conversion during the catalytic hydrogenation of a mixture initially containing 0.004 mol TMCH and 0.004 mol L-proline (*S*)-**3** in 8 mL of methanol. The data are very striking—they show that as TMCH is consumed the ee of the remaining (unreacted) TMCH rises rapidly, approaching 100% ee [of the (*S*)-enantiomer] at ~60% conversion, thereafter remaining constant until all the TMCH has reacted. This is a clear indication that the (*R*)-enantiomer of TMCH reacts much more rapidly with L-proline than does the (*S*)-enantiomer, quickly leading to a situation in which effectively all the (*R*)-enantiomer is consumed leaving behind essentially just the (*S*)-enantiomer (~100% ee), which reacts slowly with L-proline. Equation 1 relates the efficiency of the kinetic resolution (the *S*-factor) to the ee and the conversion.²³

$$S = \frac{\ln[(1 - c)(1 - ee)]}{\ln[(1 - c)(1 + ee)]} \quad \text{where} \quad S = k_{\text{REL}} = \frac{k_{\text{FAST}}}{k_{\text{SLOW}}} \quad (1)$$

The solid line in Figure 5 shows the fit of eq 1 to the data, from which we calculate $S = 17.8$ for the ratio of the overall reaction rate constants for removal of the (*R*)- and (*S*)-isomers of TMCH by reaction with L-proline.

A control experiment was performed to establish that kinetic resolution depends on equilibrium **II** being followed by step **III**. First, (\pm)-TMCH and L-proline were mixed and allowed to react under hydrogen but *without catalyst*. After 30 min at room temperature, the ee of the remaining TMCH reached 7.7% [excess of (*S*)-**2**] and remained constant thereafter. This observation is fully consistent with equilibrium **II** being followed by step **III**. The (*R*)-enantiomer in racemic TMCH (\pm)-**2** reacts (homogeneously) somewhat preferentially with L-proline to form condensation product **8**, hence yielding a slight excess of the (*S*)-enantiomer. However, in the presence of both hydrogen and catalyst, the irreversible hydrogenation step **III** drives the equilibrium between L-proline and (*R*)-TMCH (*R*)-**2** (step **II**) toward complex **8**, thus enabling high conversion and much larger ee.

In summary, we have shown that in the proline-directed asymmetric hydrogenation of isophorone the catalyst surface does not participate in the key enantio-differentiating event, which actually occurs homogeneously in the solution phase (step **II**). The catalyst does, of course, enable the initial (racemic) hydrogenation (step **I**, Scheme 2); it also plays an important role in driving the kinetic resolution equilibrium step to completion by irreversibly removing (*R*)-TMCH (*R*)-**2** via **8** to the amino acid **7** by hydrogenation (steps **II** and **III**, Scheme 2). Therefore, in the absence of side reactions, the best possible overall performance of this system and systems analogous to it corresponds to ~100% ee in the product TMCH **2**, but at a maximum yield of ~40%, relative to the starting material. Step **V** (Scheme 2) formerly thought to be the critical step involved in surface-mediated enantio-differentiation is actually an undesired side reaction—its effects are minimized by operating at $\tau = 0$, that is, zero pre-equilibration of reactant and chiral additive before commencing hydrogenation.²⁴

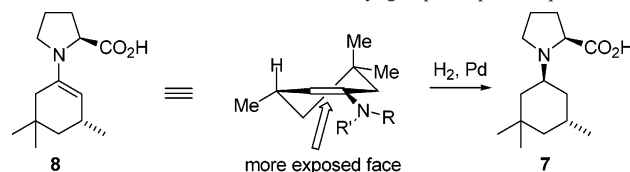
Interestingly, the same major diastereomer of the amino acid **7** is formed from the hydrogenation of isophorone **1** or racemic TMCH (\pm)-**2** in the presence of L-proline (*S*)-**3**.²⁵ The implication from this result is that the hydrogenation of **4**—the condensation product of L-proline (*S*)-**3** and isophorone **1**—occurs at the alkene double bond first and then, in a subsequent step, at the enamine double bond.²⁶

The highly diastereoselective reduction of **4** to yield **7**, coupled with the proposed reduction of the alkene double bond in **4** in the presence of the enamine/iminium ion double bonds, bodes well for the future design and discovery of a truly heterogeneous metal-catalyzed hydrogenation of alkenes which does not operate via a homogeneous kinetic resolution mechanism. However, to develop truly heterogeneous systems for metal-catalyzed asymmetric hydrogenation, it will be necessary to anchor the chiral agent to the metal surface more strongly than any competing adsorbate. Interestingly, our results²⁷ for the separate adsorption from solution of isophorone and proline onto single-crystal surfaces of Pt show that isophorone adsorbs ~10⁵ times faster than proline. This is entirely consistent with what we find here: isophorone adsorption and hydrogenation is so fast that proline itself never gets a chance to become directly involved in a surface reaction step. Work is in progress to develop a truly heterogeneous catalytic asymmetric hydrogenation of olefins.

(24) Steps **IV** and **V** consume one molecule of L-proline and one molecule of isophorone, so the only limit to a high ee of (*S*)-TMCH is that the reaction is routinely run until only 1 equiv of H₂ is consumed—step **V** just reduces the amount of (*S*)-TMCH which can be produced, not the ee of the TMCH which is controlled by hydrogen availability, that is, conversion.

(25) Purification of the hydrogenation mixture from a $\tau = 72$ h experiment which was halted at the turning point between regimes **A** and **B** gave a 13:1 mixture of **7**:**7'**.

(26) If the hydrogenation occurred in one surface-bound event, the two substituents on the cyclohexane in **7** would be *cis* and not *trans* to one another. The *trans* stereochemistry of the cyclohexane substituents in **7** is readily accounted for; hydrogenation of **8** will likely occur from the least hindered face of the enamine (or imine) double bond from the lowest energy conformer in which two of the three methyl groups are pseudoequatorial.



(27) McIntosh, A. I.; Watson, D. J.; Lambert, R. M. Manuscript in preparation.

(23) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

Acknowledgment. A.I.M. acknowledges financial support by the UK Engineering and Physical Sciences Research Council. J.W.B. gratefully acknowledges the Royal Society UK for the award of a University Research Fellowship.

Supporting Information Available: Full structural assignments and characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA061104Y