

## Highly Enantioselective Heterogeneously Catalyzed Hydrogenation of $\alpha$ -Ketoesters under Mild Conditions

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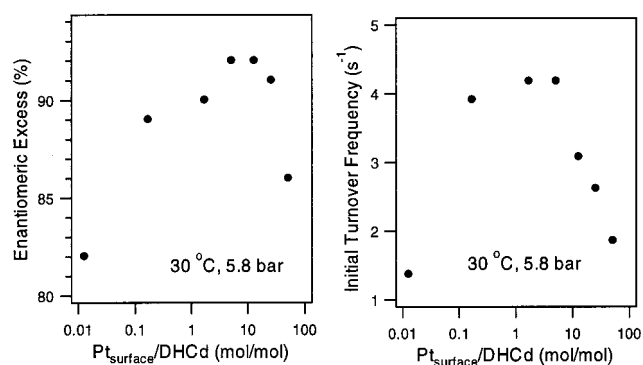
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One of the few heterogeneous catalytic systems identified for asymmetric hydrogenation with synthetically useful enantioselectivities is the cinchona-modified Pt/Al<sub>2</sub>O<sub>3</sub> for hydrogenation of  $\alpha$ -keto esters,<sup>1</sup> where the best reported ee values match if not surpass the best ee's reported for homogeneous catalysis in this reaction. The highest enantioselectivity reported is 92% ee (*R*) using 10,11-dihydrocinchonidine (DHCd) as the chiral modifier and 94% ee (*R*) with the hydroxyl group in the DHCd modifier methylated,<sup>2</sup> in both cases using acetic acid as solvent. These results, however, were achieved under rigorous and commercially impractical conditions of high pressure (100 bar) and high-temperature (400 °C) hydrogen pretreatment of the Pt/Al<sub>2</sub>O<sub>3</sub> catalyst.

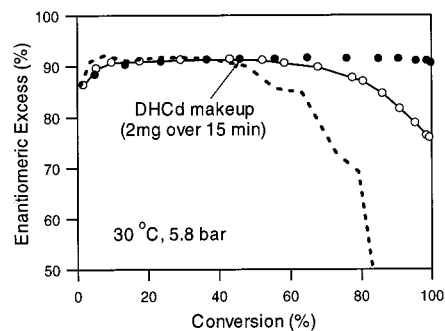
Here, we report that enantioselectivities greater than 90% ee may be achieved in the hydrogenation of ethyl pyruvate using the Pt–cinchona system at pressures nearly 20-fold lower than those previously used to achieve such results. This unprecedented result was obtained by identifying an optimal chiral surface and developing a protocol for maintaining this optimal surface even in the face of the destructive side reactions of the modifier that occur over the course of the reaction in acetic acid. This leads to record enantioselectivities under mild conditions: 94% ee at 5.8 bar and 92% ee at 1.3 bar using DHCd as the chiral modifier. The high enantioselectivity is accompanied by high turnover frequency (4 s<sup>-1</sup> at 5.8 bar),<sup>3</sup> and high turnover numbers (pyruvate/modifier > 28 000, pyruvate/Pt<sub>surface</sub> > 5 500).

We began our studies in order to investigate several curious and apparently contradictory features of the hydrogenation of ethyl pyruvate using cinchona-modified Pt that have been reported in the literature. One is the erosion of ee observed by Blaser and co-workers<sup>4</sup> over the course of the reaction when low levels of the chiral modifier are employed. On the other hand, the results of Baiker and co-workers,<sup>5</sup> as well as our own studies,<sup>6</sup> showed a gradual increase in ee with increasing conversion when higher modifier concentrations were used with acetic acid as solvent. We observed that this ee increase correlates with a decreasing solution concentration of the modifier that results from hydrogenation of the modifier during the hydrogenation of ethyl pyruvate.<sup>6</sup> This result corroborated Blaser's suggestion that the modifier is gradually removed from the solution by hydrogenation and that maintaining an optimal surface coverage is problematic when the solution concentration is too low.<sup>2</sup>

This correlation between the increasing ee and the decreasing modifier concentration in acetic acid led us to examine more carefully the dependence of ee and rate on the molar ratio of the surface Pt atoms to the modifier added in the reactor, Pt<sub>surface</sub>/DHCd. The results, obtained with various DHCd loadings under



**Figure 1.** Best incremental ee<sup>8</sup> (left) and initial rate (right) as functions of Pt<sub>surface</sub>/DHCd for hydrogenation of ethyl pyruvate. See ref 7a for hydrogenation procedure. The DHCd charge was 1 mg which translated to Pt<sub>surface</sub>/DHCd = 5.



**Figure 2.** Profiles of enantiomeric excess over the course of the hydrogenation of ethyl pyruvate commencing with the optimal chiral surface (Pt<sub>surface</sub>/DHCd = 5) without [(○) cumulative ee, (---) incremental ee] and with [(○) cumulative ee] modifier makeup.

otherwise identical conditions,<sup>7</sup> show that both ee and rate exhibit “volcano plot” behavior as functions of DHCd loading (Figure 1). The enantioselectivity increases with decreasing DHCd loading, peaking at a ratio of Pt<sub>surface</sub>/DHCd = 5–12. Reaction rate shows similar behavior. This optimal chiral surface does not “live” indefinitely over the course of a reaction, however, as is graphically illustrated in Figure 2. For a reaction commencing with the optimal amount of chiral modifier, the incremental ee<sup>8</sup> remained constant at 92% until ca. 45% conversion when ee began to erode. At the transition, the reaction rate was also sharply reduced. This downward trend in ee and rate continued to the end of the reaction. As a result, the final cumulative ee was only 76% despite the high incremental ee during the first half of the reaction. The “deactivation” of the modifier is due to the depletion of the modifier from the surface as a result of its hydrogenation

(7) *Reactor*: a reaction calorimeter consisting of a 1-liter jacketed glass vessel. *Catalyst*: 1%Pt/Al<sub>2</sub>O<sub>3</sub> (Aldrich) with 25% Pt dispersion. *Materials*: methyl and ethyl pyruvates (Aldrich, 98%) were vacuum-distilled prior to use. Acetic acid (Fisher, certified ACS, 100.0%) was used as received. *Modifiers*: 10,11-dihydro cinchona were prepared via selective hydrogenation of the vinyl group of the corresponding cinchona (Aldrich) over Pd/C in methanol, followed by purification via crystallization. *Analytical*: samples were analyzed by GC (Chiraldex B-TA). The distilled pyruvate contained a trace amount (~0.9%) of nearly racemic lactate. Only lactates produced by the reaction itself were used in calculating ee. *Hydrogenation*: charge: 1.4 g 1%Pt/Al<sub>2</sub>O<sub>3</sub>; 400 mL HOAc; 0.1 mol pyruvate. Procedure: (a) Standard: add catalyst, DHCd, HOAc, and pyruvate to reactor. Vacuum-evacuate the reactor while stirring before applying H<sub>2</sub> to desired pressure. (b) Add catalyst and HOAc to reactor, hydrogenate for 1 h under the hydrogenation conditions (e.g., 17 °C and 5.8 bar). Evacuate H<sub>2</sub> and add the modifier to the reactor under a N<sub>2</sub> purge. Apply H<sub>2</sub> to desired pressure and quickly add pyruvate to reactor under H<sub>2</sub> pressure using a syringe pump.

(8) Incremental ee ≡ (Δ[R] - Δ[S])/(Δ[R] + Δ[S]), where Δ[R] and Δ[S] are the differences in concentrations of R- and S-enantiomers between two consecutive samples.

(1) Orito, Y.; Imai, S.; Niwa, S. *J. Chem. Soc. Jpn.* **1980**, 4, 670.  
(2) Blaser, H. U.; Jalett, H. P.; Wiehl J. *J. Mol. Catal.* **1991**, 68, 215.  
(3) Expressed as the number of the pyruvate hydrogenated per surface Pt atom per second.  
(4) Garland, M.; Blaser, H. U. *J. Am. Chem. Soc.* **1990**, 112, 7049.  
(5) Mallat, T.; Bonnar, Z.; Minder, B.; Borszky, K.; Baiker, A. *J. Catal.* **1998**, 168, 183.  
(6) Wang, J.; LeBlond, C.; Liu, J.; Sun, Y.-K. Presentation at the 9th International Symposium on Relationship between Homogeneous and Heterogeneous Catalysis, University of Southampton, UK, 1998.

via a parallel/consecutive pathway to much less enantioselective DHCd derivatives.<sup>9</sup>

The results of Figures 1 and 2 together reveal the dilemma for maintaining high ee in this reaction. Formation of the optimal chiral surface requires only a very low loading of the modifier, but its reactivity makes the optimal loading hard to maintain over the entire course of the reaction. A protocol to avoid the surfeit of modifier at the outset of the reaction, as well as to avoid this inexorable erosion of ee at the end, lies in a continuous injection of additional DHCd into the reactor beginning slightly before the transition noted in Figure 2. The gradual addition of the "makeup" DHCd into the reactor allowed the high ee (and rate, not shown) to be maintained over the remaining course of the hydrogenation and avoided a sudden increase in DHCd concentration which could lead to a non-optimally high surface stoichiometry. An alternative one-time dosing of all of the modifier used in the above experiment into the reactor at the outset (producing  $Pt_{\text{surface}}/\text{DHCd} = 1.7$ ) led to a lower best incremental (90% ee) and a lower final ee (86% ee).

The identification of this sensitive concentration dependence of the modifier provides mechanistic insights about the nature of the chiral induction in this reaction. The optimal  $Pt_{\text{surface}}/\text{DHCd}$  ratio of 5–12, along with the fact that DHCd adsorbs strongly on Pt,<sup>6</sup> may correspond to a Pt surface on which DHCd adsorbs in an optimal geometry for efficient enantioselective hydrogenation. Higher modifier concentration may result in "crowding" of the chiral modifier on the Pt surface, forcing DHCd to deviate from the optimal adsorption geometry,<sup>10</sup> whereas lower modifier concentration results in incomplete chiral modification of the active Pt sites on the catalyst, both leading to lower ee and rate.

Further optimization led to the unprecedented result of 94% ee at 5.8 bar hydrogen pressure, a pressure nearly 20 times lower than the 100 bar reported in the literature for obtaining ee over 90%. The optimized conditions include lower temperature (17 °C) and a reverse addition scheme where the pyruvate was added under hydrogenation pressure.<sup>7b</sup> The former increases the intrinsic enantioselectivity obtainable over the optimal chiral surface to 94% ee from 92% ee at 30 °C (5.8 bar). The latter reduces the brief period of lower ee resulting from the transient surface hydrogen starvation at the beginning of the hydrogenation. A cumulative 94% ee up to virtually complete conversion was obtained with modifier makeup at ~95% conversion. This is the highest ee reported for the hydrogenation of ethyl pyruvate on supported Pt catalysts using DHCd as modifier, and matches the highest ee obtained using *O*-methyl DHCd as modifier.<sup>2</sup> This high ee, accompanied by high initial turnover frequency (4 s<sup>-1</sup>) and high turnover numbers (pyruvate/DHCd > 28 000, pyruvate/ $Pt_{\text{surface}}$  > 5 500), is achieved under considerably milder conditions (17 °C, 5.8 bar), and without the need of the high-temperature (e.g., 400 °C) hydrogen pretreatment of the catalyst. Indeed, an intrinsic incremental ee of 92% is obtainable at near atmospheric pressure (1.3 bar).

(9) Results to be published.

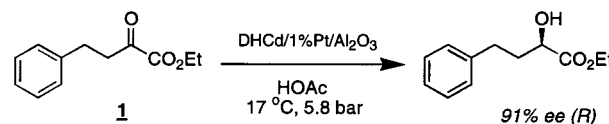
(10) As an alternative to the "three-site model" proposed by Blaser and co-worker,<sup>11</sup> we propose that a coverage-driven change in the adsorption geometry of the modifier on the Pt surface, analogous to the orientational change of pyridine on metal surfaces with pyridine coverage,<sup>12</sup> underlies the decrease in ee with increasing DHCd concentration at high concentrations.

**Table 1.** Abilities of Dihydro Cinchona in Inducing ee for Hydrogenation of Methyl or Ethyl Pyruvate on 1% Pt/Al<sub>2</sub>O<sub>3</sub> Using  $Pt_{\text{surface}}/\text{modifier} = 5$  (17 °C and 5.8 Bar)

cinchona modifier	incremental ee
10,11-dihydrocinchonidine (DHCd)	94% ( <i>R</i> )
10,11-dihydroquinine (DHQn)	94% ( <i>R</i> )
10,11-dihydrocinchonine (DHCn)	91% ( <i>S</i> )
10,11-dihydroquinidine (DHQd)	88% ( <i>S</i> )

Other cinchona alkaloid–Pt catalytic systems were also examined, and the results are summarized in Table 1. The enantioselectivities achieved with the four modifiers using the optimal surface Pt/modifier stoichiometry were consistently higher than those reported in the literature. Differing from DHCd by an extra methoxy at the 6' position, 10,11-dihydroquinine (DHQn) gave the same 94% ee (*R*) as DHCd but exhibited a shorter "useful lifetime" on the catalytic surface as reflected by the lower conversion at which ee begins to erode (75% for DHQn vs 95% for DHCd). In all cases, however, a final ee as high as the best incremental ee may be obtained by the modifier makeup protocol described above.

The surface Pt-to-modifier ratio optimal for ethyl pyruvate holds also for methyl pyruvate with ee being 94% ee (*R*).<sup>13</sup> In the case of the hydrogenation of ethyl-2-oxo-4-phenylbutyrate (**1**),



the optimal ratio is  $Pt_{\text{surface}}/\text{DHCd} = 1$ . The higher modifier loading needed may be a result of a stronger competition between **1** and the modifier for adsorption on Pt. Hydrogenation of **1** over the optimal surface led to an enantioselectivity of 91% ee under mild conditions (17 °C and 5.8 bar). This ee surpasses the best results of 80–87% ee reported in the literature using DHCd as modifier and matches the highest ee using *O*-methyl DHCd as modifier, but without the required high pressure (100 bar) and pretreatment of Pt catalyst in H<sub>2</sub> at 400 °C.<sup>2,14</sup> These results show that the asymmetric hydrogenation of  $\alpha$ -keto esters using a variety of cinchona alkaloids as chiral surface modifiers is possible with higher chiral efficiency and under significantly milder conditions than have been previously reported. The sensitive dependence of ee and rate on  $Pt_{\text{surface}}/\text{modifier}$  provides clues to the nature of the chiral modification of the Pt surface by cinchona, which is currently under further investigation in our laboratory.

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(12) Stöhr, J. *NEXAFS Spectroscopy*. In *Springer Series in Surface Sciences*; Ertl, G., Gomer, R., Mills, D. L., Eds.; Springer-Verlag: New York, 1992; Vol. 25 and references therein.

(13) Note a recent report (Zuo, X.; Liu, H.; Liu, M. *Tetrahedron Lett.* **1998**, *39*, 1941) which showed a significant difference in ee (97.6% vs 92.2%) when hydrogenating methyl and ethyl pyruvate over PVP-stabilized Pt clusters modified by cinchonidine.

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