

# Enantioselective Catalysis: Influence of Conversion and Bulk Diffusion Limitations on Selectivity in the Hydrogenation of Ethyl Pyruvate

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Several unexpected observations were made in studying the hydrogenation of ethyl pyruvate over dihydrocinchonidine-modified Pt. A marked trend of increasing optical yield with increasing conversion was observed over a wide range of reaction temperatures, ultimately reaching a plateau between 54–58% enantiomeric excess at high conversion. In addition, reactions carried out under bulk hydrogen diffusion limitations exhibited a strong suppression in optical yield. These results reveal the dynamic nature of the catalyst surface as the reaction progresses and demonstrate the need to develop a complete kinetic picture of the reaction. © 1995

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## INTRODUCTION

The concept of developing heterogeneous catalysts for enantioselective synthesis of pharmaceutical and agrochemical intermediates has received increasing attention over the past several years, based partly on expectations, however tenuous, of a substantially increased future market for optically pure compounds (1). The focus of research in this field has been on investigating the role of chiral surface modifiers in directing reactions, typically hydrogenations of prochiral ketone groups, toward one enantiomer of the hydrogenated product. Most studies have concentrated on two particular model systems, hydrogenation of  $\alpha$ -keto esters over supported Pt catalysts modified by cinchona alkaloids (2–15), and hydrogenation of  $\beta$ -keto esters over tartaric-acid-modified Ni catalysts (15–20). Recently some work in expanding the repertoire of substrate/modifier/catalyst combinations has been reported, particularly by Wells and co-workers employing Ir catalysts (21), and by Baiker and co-workers (10) and

Tungler and co-workers (22–25) using Pt catalysts with modifiers other than cinchonidine.

Mechanistic proposals to rationalize the enhanced enantioselectivities observed in these systems have included both geometric/steric and electronic arguments. The effect of particle size has been explored and interpreted in terms of the several different models of the active sites for both the Pt and Ni systems mentioned above. For the Pt system, models which have been discussed include regular arrays of modifier molecules acting as templates on extended planar surfaces (13–15), adsorbed modifier species juxtaposed with coordinatively highly unsaturated metal corner and edge sites (11), and a two- or three-site model where adsorption of the modifier affects 10–20 adjacent surface metal atoms (2, 3). Enantioselectivity has been suggested to be structure-insensitive for the Ni system (18).

Recently, several authors have suggested a fluid-phase interaction between Pt and the modifier to rationalize both the chiral induction and the accelerated rate in  $\alpha$ -keto ester hydrogenation (7–10). The mode of adsorption of the modifier and the role of both the quinuclidine nitrogen and the quinoline ring system of the alkaloid molecule have been discussed (10, 11, 15). The effects of solvent, modifier concentration, and other reaction variables have been explored in many cases to account for both the observed optical yields and for changes in the overall reaction rate.

Still missing from this discussion, however, is a reasonable hypothesis to account for the fact that the observed effects are apparently so system-specific, a point important to any generalized understanding of the phenomenon. However, most of the studies reported in the literature on these systems have not provided a detailed kinetic picture of these reactions. In this paper, we describe several striking and heretofore unreported observations, in-

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cluding a marked trend of increasing optical yield with increasing conversion and a strong suppression of optical yield when reactions are carried out under bulk hydrogen diffusion limitations. These results imply that under conditions similar to those used in this study, reactions which are monitored only at low conversions or under diffusion limitations may not demonstrate the full potential of the chiral catalysts employed. Further careful investigations covering a wider range of conditions than have been explored in the past may ultimately lead to a greater understanding of how chiral surface modifiers direct hydrogenation reactions.

## EXPERIMENTAL

**Materials.** The organic substrate, ethyl pyruvate (Aldrich, >99%) and the solvents 1-propanol and methyl acetate (Aldrich, 99.5%) were used without further purification at a substrate concentration of 1 M. Dihydrocinchonidine was prepared by hydrogenation of cinchonidine (Aldrich) as described previously (11). The catalyst employed in these studies was a 1 wt% Pt/Al<sub>2</sub>O<sub>3</sub> (Aldrich, pre-reduced). The Pt dispersion was determined to be 19.9% D, measured by pulse CO chemisorption using an Altamira Instruments, Inc. AMI-1 catalyst characterization system. The ratio of substrate:modifier:catalyst used in all reaction runs was 1 g ethyl pyruvate:1 mg dihydrocinchonidine:0.5 mg Pt, well within the ranges reported in the literature for this catalytic system.

**Reactions.** Catalytic reactions were carried out in a fully automated reaction calorimeter (Mettler RC1) using a 1-liter jacketed glass vessel with a Hasteloy head and impeller shaft. This system is capable of minimizing and accounting for any heat losses attendant to the process. Reaction temperatures ranged from 263–323 K and pressure was held constant at 487 kPa. Hydrogen was introduced to the liquid by drawing gas in from the head space through a hollow impeller shaft. A subsurface gas diffuser was also used for the distribution of hydrogen in the liquid phase. The agitation speed was 1000 rpm unless otherwise noted.

Reactions were carried out by charging all components to the vessel where they mixed under nitrogen for approximately 2 h while calibrations were carried out to determine parameters for the heat flow measurements, as described previously (26). Agitation of the reactor was then stopped while nitrogen in the head space was replaced with 487 kPa hydrogen, and the reaction was begun when agitation was resumed at the desired speed.

The heat flow of a reaction may be used to give a measure of the overall reaction rate (26–27). An energy balance for an isothermal reacting system shows that the heat flow is proportional to the reaction rate

$$q_r = V_r \sum_i \Delta H_{rxn,i} \left( \frac{dC_i}{dt} \right), \quad [1]$$

where  $q_r$  is the heat released or consumed by  $i$  multiple reactions, occurring simultaneously  $V_r$  is the volume of the reactor contents,  $\Delta H_{rxn,i}$  is the heat of the  $i$ th reaction at the system temperature, and  $(dC_i/dt)$  is the rate of the  $i$ th reaction.

Gas–liquid mass transfer coefficients,  $K_L a$ , were measured by a dynamic method (28, 29) which measures the rate of dissolution of hydrogen in the liquid phase at various agitation speeds in the absence of the catalyst. The liquid was degassed thoroughly by vacuum–fill cycles with nitrogen prior to introduction of hydrogen at 487 kPa with the agitator turned off. Agitation then commenced, and a pressure transducer (Omega, PX305-100A) recorded the pressure of hydrogen in the reactor at a rate of 10 Hz. The rate of gas–liquid mass transfer is given as a function of time, the initial and final pressures,  $P_i$  and  $P_f$ , the vapor pressure  $P_0$ , and the pressure at any time  $t$ ,  $P$ :

$$\frac{P_f - P_0}{P_i - P_0} \ln [(P_i - P_f)/(P - P_f)] = K_L a * t. \quad [2]$$

The total pressure decrease until equilibrium is established also yields the solubility of hydrogen in the solution under the conditions of the experiment. From these parameters the maximum rate of hydrogen delivery from the gas to the liquid may be determined by

$$r_{max} = K_L a * C^{sat,P_f} \quad [3]$$

where  $C^{sat,P_f}$  is the solubility of hydrogen at the final pressure of the experiment.

**Analytical measurements.** Samples, taken periodically as the reaction progressed, were analyzed by gas chromatography (HP 5890 with autoinjector, FID detector), using a Chiraldex B-TA column capable of separating the (R) and (S) ethyl lactate isomers as well as the unreacted ethyl pyruvate. The optical yield is expressed as the enantiomeric excess (% ee) of the (R) lactate using the relationship:

$$ee(\%) = \left[ \frac{[R] - [S]}{[R] + [S]} \right] * 100. \quad [4]$$

## RESULTS AND DISCUSSION

**Influence of conversion on optical yield.** Figure 1 shows the results of the ethyl pyruvate hydrogenation carried out over the dihydrocinchonidine-modified Pt catalyst at 283 K over the full range from 0–100% conversion.

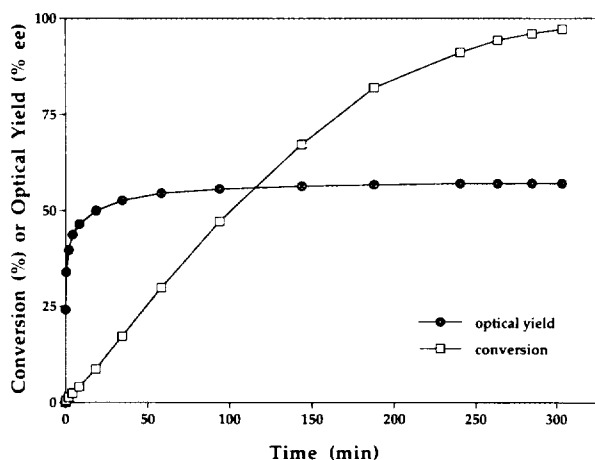


FIG. 1. Conversion and optical yield as a function of time for the hydrogenation of ethyl pyruvate at 283 K and 487 kPa.

At low conversion, an unusual, sharp increase in the optical yield was observed, leveling off at about 10% conversion and holding quite stably there for the duration of the reaction, to give an ultimate optical yield of 57%.

Figure 2 shows that this phenomenon of increasing optical yield with conversion was observed for reactions carried out over a wide temperature range. This observation is all the more striking when the temperature dependence of the reaction kinetics is taken into consideration. Table 1 shows that the plateau in optical yield was approached at a similar conversion level in all cases although the reaction time to reach this conversion varied from 2 min to more than 2 h. An identical trend was found when the solvent employed was methyl acetate, ruling out the possibility that a substrate-solvent interaction specific to alcohol solvents (9) could be responsible for this phenomenon.

To our knowledge, this is the first report of such an optical yield-conversion dependence for a well-mixed and presumably equilibrated system. In all of our reactions, the reaction mixture (including the modifier, substrate, catalyst, and solvent) was allowed to mix for 2 h prior to addition of hydrogen and commencement of the reaction. Margitfalvi and co-workers reported an increase in optical yield with conversion (6, 7) when the modifier was injected into the reacting system after the racemic hydrogenation had progressed to an intermediate conversion, in the interest of monitoring the transient kinetic behavior associated with initial contact between the various components of the reacting system.

Our data suggest that the intrinsic potential of the system to achieve high optical yield was achieved only after a reaction-driven equilibration of the surface environment, with fixed relative amounts of substrate and product required to build the site for chiral hydrogenation. Dynamic

TABLE 1

Reaction Time and Optical Yields at 10% Conversion

Temperature (K)	Reaction time (min)	Optical yield (% ee)
263	135	50
283	22	51
303	3.9	55
323	2.4	53

Note. Reaction conditions: 487 kPa, 1000 rpm;  $C_0 = 1 M$  ethyl pyruvate.

adsorption-desorption processes in the initial stages of the reaction may result in rapidly changing relative coverages of surface species until the surface finally equilibrates to some "steady-state" coverage in which the product species themselves may play a role. An alternative explanation suggests that the catalyst surface itself underwent some change in structure or valence state over the course of the reaction, but it remains inexplicable how the kinetics of such a process would be related not to time or temperature but instead to extent of conversion of ethyl pyruvate, as our data would apparently suggest.

The relationship we found between optical yield and conversion may help to reconcile reports of difficulties in the reproducibility of initial rates and optical yields in studies of this reaction (11), since selectivity values obtained from the very steep part of the ee vs conversion curve at low conversions would be subject to large errors in optical yield for even a very small error in conversion. Our results make clear the necessity of exploring the relationship between optical yield and conversion before interpreting data acquired solely at low conversion. For example, application of the two-site mechanistic model developed by Blaser and co-workers (2, 3) to our initial

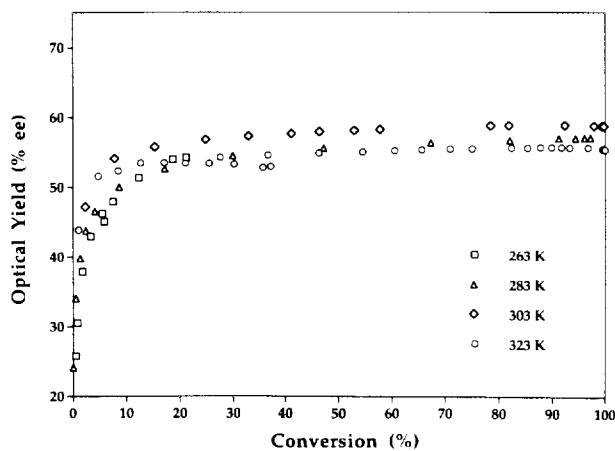


FIG. 2. Optical yield vs conversion for ethyl pyruvate hydrogenation carried out at 487 kPa and 323, 303, 283, and 263 K.

rate/selectivity data might not be valid if, as our data suggest, the number of "modified" surface Pt sites changes in the initial stages of the reaction. Furthermore, at the conversion level where our optical yields became constant, the reaction would not be zero-order in ethyl pyruvate as assumed by the Blaser model.

Much of the work reported in the literature on this system is carried out under pressures 2–20 times higher than those used in our studies. Indeed, high pressure may be a key to obtaining high constant optical yield at low conversion, possibly by leading to the establishment of a different equilibrated surface environment earlier in the progress of the reaction. Further experiments are underway in our laboratory to delineate the role of various species, including products and modifier, to achieve a better understanding of the dynamic nature of the surface environment required for chiral hydrogenation.

*Influence of hydrogen diffusion control.* An issue which has received scant attention in the literature is the potential effect on optical yield of carrying out liquid phase reactions under severe diffusion limitations. The reaction conditions employed in many studies imply that gas–liquid mass transfer of hydrogen, or pore diffusion of hydrogen dissolved in the liquid phase within catalyst pores, may be rate-limiting, and only a few attempts to determine the regime of operation have been reported (5, 18), most notably by Blaser and co-workers (5) who investigated the role of gas–liquid, liquid–solid, and intraparticle diffusion resistances. We focused our investigations on gas–liquid diffusion limitations. Figure 3 makes the intriguing observation that agitation speed can have a significant effect on the optical yield, comparing a reaction carried out at a constant 400 rpm agitation speed to the data of Fig. 1 at 1000 rpm. The trend of increasing optical yield with conversion was again observed, but more nota-

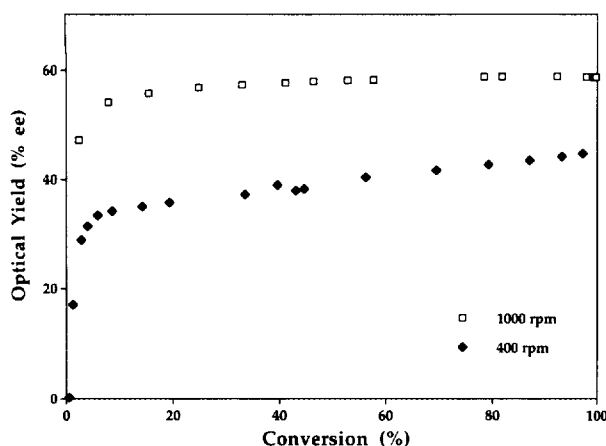


FIG. 3. Optical yield vs conversion for ethyl pyruvate hydrogenation carried out at 303 K at agitation speeds of 1000 and 400 rpm. Data from the experiment at 1000 rpm are reproduced from Fig. 2.

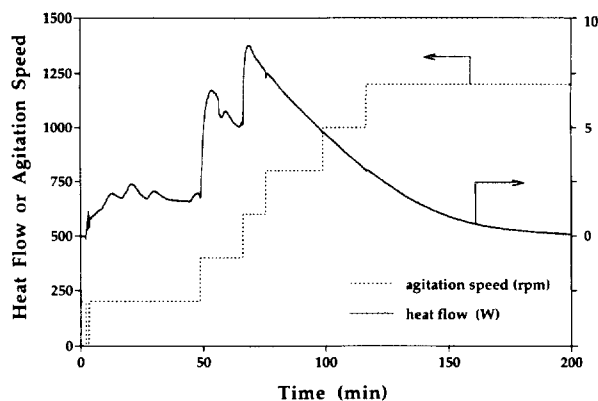


FIG. 4. Heat flow as a function of agitation speed for the hydrogenation of ethyl pyruvate at 303 K and 487 kPa.

bly, it was found that a 25% drop in the ultimate optical yield occurred compared to that achieved for the reaction carried out 1000 rpm. Such a significant change in optical yield due only to a change in agitation speed has not been reported before, although Blaser and co-workers (5) found a small (ca. 5%) change in optical yield between 300–1200 rpm under their high pressure conditions.

Heat flow calorimetry measurements provide an ideal tool to illustrate diffusion limitations by following  $q_r$  as a function of agitation speed (27). Since heat flow is proportional to reaction rate, any change in reaction conditions which causes a change in rate is reflected as an interruption in the decaying heat flow (or rate) profile. In the gas–liquid diffusion regime, changing the agitation speed causes a change in the reaction rate and therefore in the measured  $q_r$ . At agitation speeds where diffusion is not the rate controlling process, changing the agitation speed has no effect on the rate or the heat flow.

Figure 4 shows the effect of changing the agitation speed on the heat flow profile for a reaction carried out at 303 K. At 200 rpm, the heat flow and, correspondingly, the reaction rate were extremely low. At each increase in the agitation speed from 200 to 400 and then 600 rpm, the heat flow went through an immediate, sharp increase followed by a new decay curve corresponding to a new reaction rate profile. When the agitation speed was increased from 600 to 800 rpm, however, the heat flow profile was not affected, continuing instead to follow a smooth decay curve through all further increases in the agitation speed. Figure 4 thus illustrates graphically the threshold for overcoming gas–liquid diffusion limitations.<sup>2</sup>

<sup>2</sup> Since the reaction was progressing throughout this study, the reaction rate at the time the agitation speed was changed to 800 rpm was lower than its initial potential at  $C_0 = 1 M$ . A conclusive indication of the absence of diffusion limitations would entail carrying out the study at 800 rpm and 1 M substrate.

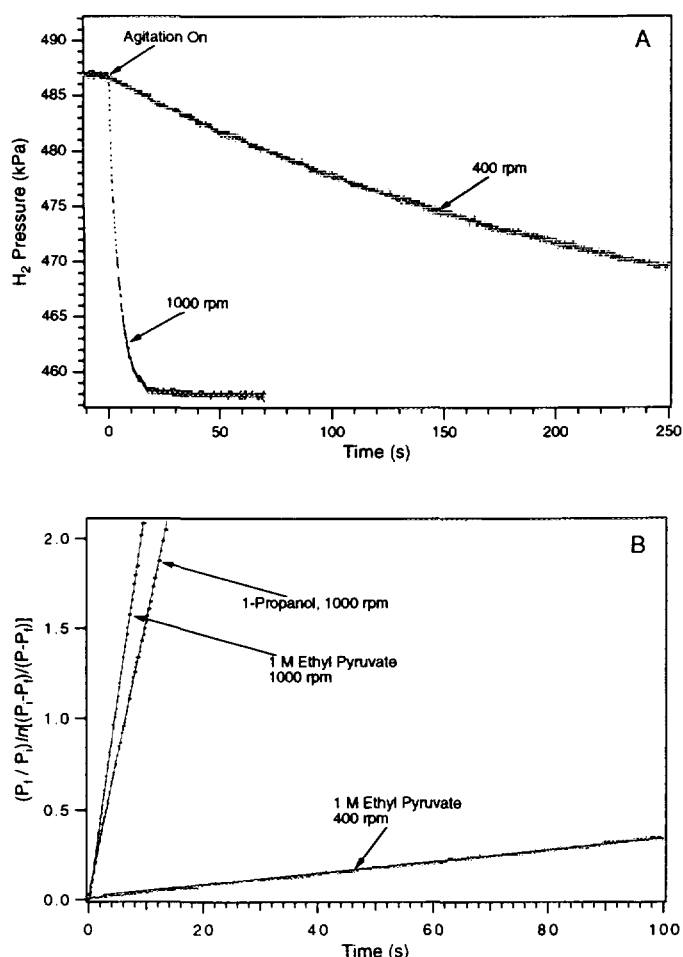


FIG. 5. Hydrogen uptake measurements in 1-propanol and in 1 *M* ethyl pyruvate in 1-propanol (303 K, 487 kPa) to determine gas-liquid mass transfer coefficients,  $K_L a$ , for different agitation speeds. (A) hydrogen pressure uptake vs time; (B) plot of the pressure function of Eq. (2) vs time for 1-propanol and 1 *M* ethyl pyruvate in 1-propanol for different agitation speeds.

While monitoring of the heat flow profile as a function of agitation speed during the reaction can provide a qualitative picture of the conditions under which mass transfer of hydrogen may be rate-limiting, measurements of the mass transfer coefficient,  $K_L a$ , under various conditions provide a quantitative analysis of the regime of diffusion limitations. A dynamic method (28, 29) for measuring  $K_L a$  of hydrogen in the reaction mixture is described under Experimental.

Figure 5 shows both the pressure uptake data and the plot of Eq. [3] vs  $t$  for experiments carried out at 400 and 1000 rpm in the solvent, 1-propanol, and in 1 *M* ethyl pyruvate in 1-propanol at 303 K and 487 kPa. The significant difference in the rate of hydrogen uptake at the two stirring speeds is manifested in the large difference in the slopes of the lines in Fig. 5b, giving  $K_L a$  values for each

agitation speed. Table 2 compares hydrogen mass transfer rates with initial reaction rates (measured in terms of moles hydrogen added to ethyl pyruvate/min) for the hydrogenation reactions carried out at each agitation speed. It is interesting to note that the observed rate of reaction for the experiment carried out at 400 rpm was very close to the maximum rate of hydrogen mass transfer into the bulk at this agitation speed, confirming that the controlling process under these conditions was the gas-liquid diffusion of hydrogen. At 1000 rpm, by contrast, the rate of hydrogen diffusion was about seven times faster than that of the observed initial reaction rate.

It should be noted that our study addresses only the effect on optical yield of hydrogen diffusion through the gas-liquid interface. Other rate processes which might interfere with the measurement of intrinsic kinetics, such as liquid-solid transport and pore diffusion resistances, were not investigated in our work, although Blaser and co-workers (5) have delineated regimes of operation where control by these rate processes may be avoided. The dynamic method described above for determining the rate of diffusion of hydrogen has also been applied to this system by Blaser and co-workers (5).

The result we report is intriguing because it seems counterintuitive to the simple kinetic models which are often applied to these reactions. In his classic discussion of the effects of diffusion on the kinetics of organic reactions, Roberts (30) pointed out that diffusion limitations should have an effect on selectivity for parallel reactions only if the reactions exhibit different reactant concentration dependencies. Our results suggest, therefore, that a simple kinetic model employing the same form of the rate law with different rate constants for the [R] and [S] isomers cannot accurately describe the mechanism of chiral hydrogenation. This concept has been illustrated before by Halpern (31) in the homogeneous asymmetric hydrogenation of prochiral olefins in which his elegant kinetic studies helped to develop different rate laws for the [R] and [S] isomers which accounted for the observed pressure dependence on optical yield.

An interesting inference from this work is that, for studies on this system carried out under conditions where agitation of the reactor is inadequate, higher optical yields than have been reported may well be possible if diffusion control could be eliminated. Some of the large variations in optical yields reported in the literature for seemingly similar catalysts and conditions might thus be rationalized.

## CONCLUSIONS

The hydrogenation of ethyl pyruvate over dihydrocinchonidine-modified Pt exhibited a striking relationship between increasing conversion and increasing optical yield.

TABLE 2  
Gas-Liquid Mass Transfer Parameters<sup>a</sup>

	Solution		
	1-Propanol	Ethyl pyruvate (1 M) in 1-propanol	Ethyl pyruvate (1 M) in 1-propanol
Agitation speed (rpm)	1000	1000	400
Mass transfer coefficient ( $K_{La}$ ) ( $s^{-1}$ )	0.15	0.22	0.003
Hydrogen solubility ( $M$ ) <sup>b</sup>	0.013	0.012	0.013
Maximum gas-liquid mass transfer rate ( $10^2 \times$ mole $H_2$ /liter/min)	11.8	16.6	0.26
Initial hydrogenation rate <sup>c</sup> ( $10^2 \times$ mole $H_2$ /liter/min)	—	2.4	0.32

<sup>a</sup> Gas-liquid mass transfer and hydrogen solubility measurements carried out at 293 K and at an initial pressure of 487 kPa;  $\Delta P$  of the measurement is ca. 30 kPa (see Fig. 5A).

<sup>b</sup> Solubility corrected to 487 kPa using Henry's Law:  $C^{sat,487} = (487 \text{ kPa}/P_2) \times C^{sat,P_2}$ ; variables defined as in Eqs. [2] and [3].

<sup>c</sup> Initial hydrogenation rate estimated initial linear portion of conversion vs time plot.

The optical yield reached a plateau of 54–58% ee at about 10% conversion and remained constant for the rest of the reaction. This trend held over a wide range of reaction temperatures where the reaction time to reach this conversion varied from 2 min to 2 h. This result suggests that dynamic adsorption-desorption processes early in the reaction ultimately established an equilibrated surface environment, allowing the full potential of this system for chiral hydrogenation to be realized.

A second important observation of this work was the suppression of optical yield for reactions carried out under diffusion limitations, suggesting a stronger positive dependence on hydrogen concentration for the formation of the [R] isomer. This emphasizes the importance of obtaining a complete kinetic picture of the reaction and other rate processes of importance under the particular experimental conditions employed before mechanistic analyses are made. Developing an understanding of these phenomena may contribute to our overall understanding of chiral heterogeneous catalysis.

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