Tetrahedron: Asymmetry Vol. 4, No. 8, pp. 1803-1827, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
© 1993 Pergamon Press Ltd

ENANTIOSELECTIVE HETEROGENEOUS CATALYSIS I. A WORKING MODEL FOR THE CATALYST:MODIFIER:SUBSTRATE INTERACTIONS IN CHIRAL PYRUVATE HYDROGENATIONS

Robert L. Augustine,* Setrak K. Tanielyan and Lisa K. Doyle
Department of Chemistry, Seton Hall University, South Orange NJ 07079 USA

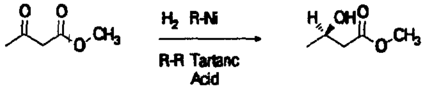
(*Received in UK* 19 *April* 1993; *accepted* 21 *May* 1993)

Abstract: The room temperature and atmospheric pressure hydrogenation of ethyl pyruvate over Pt/Al_2O_3 catalysts modified by varying amounts of dihydrocinchonidine was examined. Data were obtained which showed that the hydrogenation occurred on the corner atoms and adatoms on the Pt crystallites in the catalyst. The formation of (S) ethyl lactate was observed when very low concentrations of the alkaloid modifier were used while at higher modifier concentrations the (R) lactate was produced. The formation of the (R) lactate was accompanied by an increase in the hydrogenation rate. A working hypothesis was formulated to explain these results and to serve as a model for the design of future experiments. This model suggested that the initial adsorption of the dihydrocinchonidine takes place on the face atoms adjacent to the corner atoms on the metal crystallite. This will place the chiral portion of the alkaloid close to the corner atom active site. Enantioselective pyruvate adsorption would be facilitated by a hydrogen bond between the C_9 OH of the alkaloid and the ethoxy oxygen of the pyruvate and hydrogenation of the keto group will lead to (S) lactate formation. In order to place the chiral portion of the modifier near an adatom it is proposed that the alkaloid is adsorbed in an edge-on manner on the face near the adatom active site. In this way the modifier can interact directly with the pyruvate to change its adsorption characteristics. This will lead to an increase in reaction rate and the formation of the (R) lactate.

Introduction

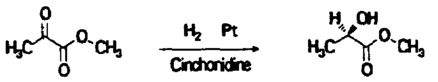
Interest in enantioselective synthesis has been increasing steadily over the past several years particularly because of the need to develop more efficient and safe chiral drugs and agrichemicals. Many of the techniques utilized for the production of single enantiomers rely on an enzyme which is the ultimate enantioselective catalyst. The active site of an enzyme has a chiral environment which sterically directs a prochiral substrate to approach the active site in only one way. In addition there are also other components of the enzyme which interact with specific atoms or groups of atoms in the substrate to enhance the enantioselective adsorption of the substrate onto the active site. It is this combination of a chiral environment and the ability to interact with a specific type of substrate which is responsible for the high substrate specificity and enantioselectivity of enzyme reactions. Almost all of the non-enzyme enantioselective catalysts are soluble metal complexes containing some type of chiral ligand.[1 - 10] Because many of these catalytic species can promote reactions on a number of different types of substrates it appears that such catalysts are effective because of the chiral environment created around the active metal center by the chiral ligands. The chirality of the product is due to the steric environment of the complex and not, necessarily, to any specific ligand-substrate interactions such as those which are present in an enzyme.

Even though there are a wide variety of enantioselective reactions promoted by chiral homogeneous catalysts, these reactions are not easily adapted to large scale liquid phase processes. One of the problems with these systems is that the soluble catalyst and, possibly, some dissociated ligands must be separated from the product of the reaction, a process which frequently results in the destruction of the catalyst complex and the loss of the metal and chiral ligand.[11, 12] An obvious solution to this separation problem is the use of a heterogeneous catalyst which can be removed from the reaction mixture by filtration or centrifugation and then, potentially, be reused. There are two general categories of heterogeneous catalysts which can be adapted for enantioselective synthesis: supported metals and the so-called "heterogenized homogeneous" catalysts. These later species are usually produced by attaching a ligand species such as a phosphine or amine to an insoluble matrix, generally a polymer, and then using these insoluble ligands to complex with the active metal species.[5, 11, 12]

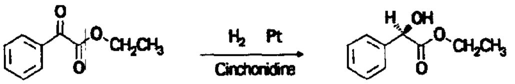


(1)

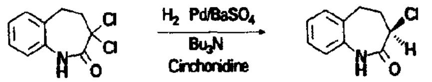
The other type of chiral heterogeneous catalyst can be either a supported metal which has been treated with a chiral modifier[13 - 16] or an active metal on a chiral support.[17] Most of these catalysts give products with low or non-reproducible enantiomeric excesses but there are two such systems which have been developed into viable, highly enantioselective heterogeneous catalysts. These are the Ni/tartaric acid catalysts which promote the hydrogenation of β keto esters to the corresponding alcohols having enantiomeric excesses (ee's) as high as 92% (Eqn. 1).[14 - 16] The other system is the cinchona alkaloid modified Pt catalyst used for the enantioselective hydrogenation of α keto esters giving α hydroxy esters with ee's up to 95% (Eqns. 2 and 3).[13,16] In addition, a Pd/cinchona alkaloid catalyst has been reported which promotes a moderately enantioselective hydrodehalogenation of α, α-dichloro-2-benzazepinone (Eqn. 4).[18]



(2)



(3)

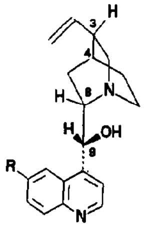


(4)

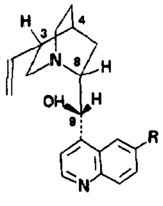
The tartaric acid modified Ni catalyst used for the enantioselective hydrogenation of β keto esters has been extensively investigated.[14 - 16] This reaction is highly selective toward β keto esters and gives the chiral β hydroxy ester with high ee's especially in the presence of a NaBr co-modifier. Despite the large amount of data published concerning this reaction there is essentially no consensus as to the nature of the chiral hydrogenation site or the cause of the observed enantiodifferentiation. One reason for these difficulties is the corrosive nature of the tartaric acid reaction with the Ni so the morphology of the metal surface changes on contact with the tartaric acid. In fact, one proposal suggested that nickel tartrate was the enantioselective catalyst and that the nickel metal surface promoted only the racemic hydrogenation of the substrate.[16] The enantioselective nickel tartrate is thought to be weakly bonded to the nickel metal surface or adsorbed onto the support. It is also considered possible that in liquid phase reactions some of this nickel tartrate complex goes into solution and acts as a homogeneous catalyst for the hydrogenation.[16] It appears from the available data that this system cannot be considered simply as a modified metal surface so it is not a useful model for the general development of chirally modified supported metal catalysts.

On the other hand, the use of cinchona alkaloids to chirally modify Pt catalysts is not expected to result in a corrosive interaction so a detailed examination of this system should provide the basic information needed to develop enantioselective heterogeneous catalysts for other reactions. The enantioselective hydrogenation of α keto esters over supported Pt catalysts modified by cinchonidine was first reported by Orito and coworkers in 1979[19] and the work continued until 1982[20 - 22] with published reports concerned with various aspects of the reaction. Additional work on this catalyst system has been reported by two research groups: Wells and his co-workers[16, 23 - 26] and a collaborative effort between Blaser and Baiker and their co-workers.[27 - 40] Both of these groups have examined the effect of reaction variables on the enantioselective hydrogenation of methyl and ethyl pyruvate using conditions generally similar to those which were reported by Orito et al.[19 - 22] They expressed the need to obtain an understanding of this reaction so the concepts developed could be extrapolated to other enantioselective reactions. To accomplish this they examined the effect which variations in the type of catalyst, solvent, substrate concentration, temperature, H_2 pressure and quantity and type of modifier have on both reaction rate and product ee.

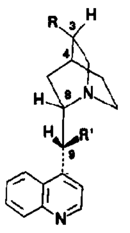
Each of the major cinchona alkaloids was used as a modifier. As seen from structures **1** and **2** these alkaloids are composed of two heterocycles, the quinuclidine and a quinoline ring. Quinine (**1b**) and quinidine (**2b**) have a methoxy group on the quinoline ring while cinchonidine (**1a**) and cinchonine (**2a**) do not. These alkaloids all have four chiral centers with those at C_3 and C_4 the same for all of the cinchona alkaloids.[41 - 43] The major alkaloids are differentiated by their configuration at C_8 and C_9. The use of Pt catalysts modified with either cinchonidine (**1a**) or quinine (**1b**) gives the (R) α hydroxy ester while modification with cinchonine (**2a**) or quinidine (**2b**) gives the (S) enantiomer.[20] It appears that the chiral centers at C_8 and C_9 are those which are primarily involved in the enantioselection while that at C_3 is not. If one discounts the chirality at C_3 the two structures **1** and **2** would be mirror images. In quinine and cinchonidine there is an 8(S)-9(R) configuration while in quinidine and cinchonine it is 8(R)-9(S).[43] The modifier not only provides the chiral environment which the catalyst needs to promote reaction enantioselectivity but it also increases the rate of the hydrogenation. It appears that only the cinchona alkaloids can provide a suitable chiral environment on the Pt catalysts for these hydrogenations. A small product ee was observed with some ephedrine derivatives but nothing else was reported to be even marginally effective.[28] The use of dihydrocinchonidine (**3a**) was reported



1a; R = H
b; R = O-CH$_3$



2a; R = H
b; R = O-CH$_3$



3a; R = CH$_2$CH$_3$ b; R = ⟋⟍
R' = OH R' = OCH$_3$
c; R = ⟋⟍
R' = H

to give a higher product ee than did cinchonidine.[24, 28] Since the presence of a C_9 methoxy group (**3b**) did not influence the ee[27] it can be concluded that the OH itself is not needed for any hydrogen bonding to the substrate. However, with the C_9 desoxy alkaloid, **3c**, the product ee decreased significantly showing that the oxygen on C_9 is beneficial.[27]

Studies on the effect which modifier:catalyst ratios have on the reaction rate and product ee showed that for a given amount of catalyst the addition of relatively small amounts of alkaloid gives a maximum in the reaction rate and product ee with further addition of the alkaloid having little or no further effect.[26, 28] Under the conditions used the adsorption of the modifier was shown to be reversible. Addition of cinchonine to a cinchonidine modified catalyst resulted in an increasing amount of (S) lactate formation as the reaction proceeded.[34]

A number of supported Pt catalysts were shown to be effective. Wells[23 - 26] used the well characterized standard catalyst, EuroPt-1[44] which is a 6.3% Pt/SiO$_2$. Orito and co-workers[21 - 22] and the Swiss workers used both Pt/C and Pt/Al$_2$O$_3$ catalysts.[28 - 30] Blaser[30 - 32] prepared a large number of Pt/Al$_2$O$_3$ catalysts using different aluminas, Pt sources, impregnation methods and reduction procedures. Several series of catalysts were made in which the Pt or alumina sources or the reduction temperatures used for catalyst preparation were varied. In any given series there was no clear correlation between the metal surface area or catalyst dispersion and the performance of specific catalysts in the pyruvate hydrogenation.[28 - 32] However, when comparing the dispersions of the entire group of catalysts with the product ee there appeared to be a possible, general relationship between catalyst dispersion and product ee. Catalysts having the lowest dispersion or largest metal particle sizes gave the highest ee's.[32]

The mechanistic proposal made by Wells[16, 23] was based on this apparent dispersion versus ee relationship. He proposed that the alkaloid was adsorbed in a chiral, L shaped, mode on the faces of the metal particles leaving chiral areas between the modifier molecules for the selective adsorption of the pyruvate. The rate enhancement was envisioned as resulting from the formation of a hydrogen bond between the half-hydrogenated pyruvate and the quinuclidine N of the alkaloid.[16, 25] This was expected to stabilize the intermediate and facilitate the reaction.[25] With this mechanistic interpretation, the C_9 chiral center should have little influence on the reaction. In contrast, Blaser[33] has examined the reaction rates and product ee's from reactions run using varying amounts of alkaloid. These data were used to develop a kinetic model based on a two cycle mechanism.[33, 38] The results of this kinetic evaluation suggest that the enantioselective site consists of a single cinchona alkaloid molecule adsorbed on an ensemble of Pt atoms and not the well ordered array of cinchona alkaloid molecules proposed by Wells.[16] The accelerated rate was explained by having the modifier promote an enhanced adsorption of the pyruvate on the modified metal surface.[28]

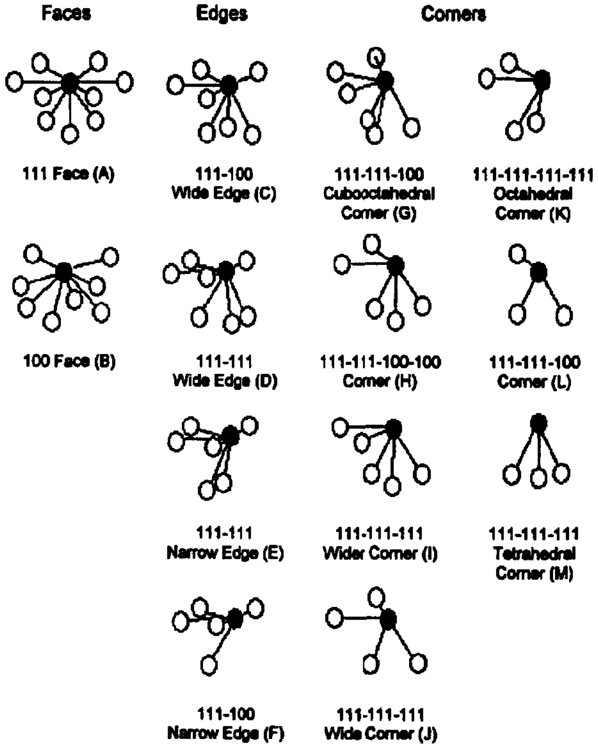


Figure 1. Structural representations of the various types of atoms present on the surface of an fcc metal.[50]

Even with these published data there are a number of questions which must be addressed before any effort can be made toward the general development of enantioselective heterogeneous catalysts. Of most importance is the nature of the catalyst:modifier:substrate interactions which lead to the enantioselective reaction. Before any assumptions can be made about these interactions the nature of the "active site" on which the reaction takes place must be more clearly defined. Wells'[16, 23] proposal that the active site was an ensemble of atoms on the face of the Pt crystallites was made even though ample evidence has been published showing that the catalytically active sites for hydrogenation reactions are the more coordinately unsaturated single corner atoms or adatoms on the faces of the metal crystallites.[45 - 51]

The Nature Of Active Sites On Dispersed Metal Catalysts

In order to understand the different aspects of a problem such as this, some information concerning the various types of surface sites present on a dispersed metal catalyst is needed. Comparison of homogeneous and heterogeneous catalysts reveals that the heterogeneous species are usually less selective than their homogeneous counterparts. While a homogeneous catalyst is a discrete chemical entity, the surface of the metal crystallites found in dispersed metal catalysts is composed of atoms having different environments and

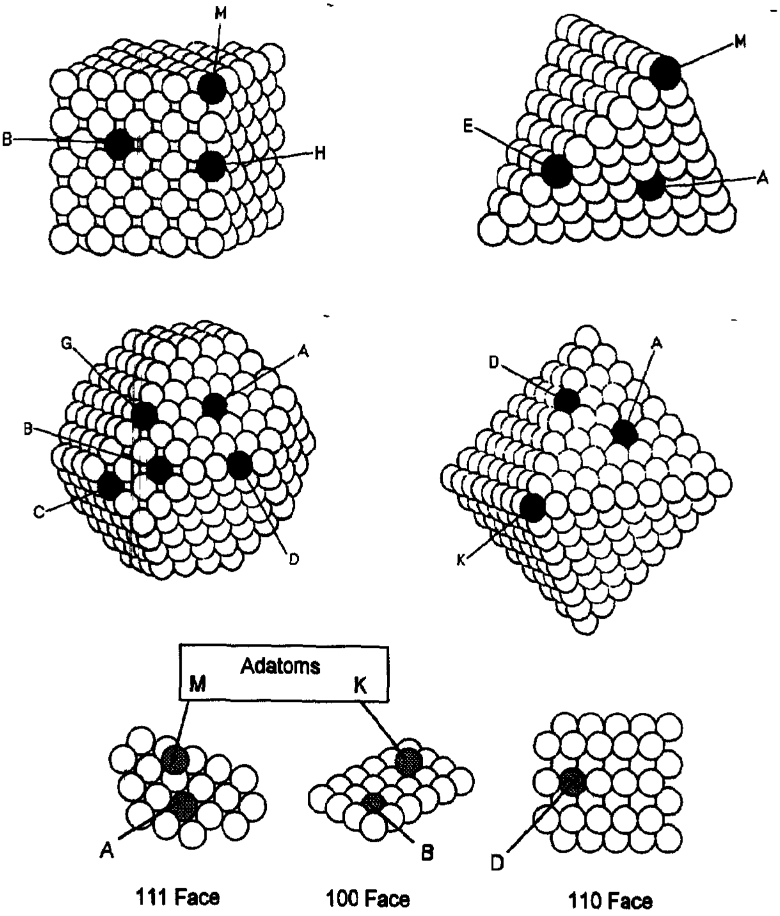


Figure 2. Different types of surface sites present on various crystalline arrangements.

numbers of nearest neighbor atoms. Most of the catalytically active metals have an fcc crystalline arrangement with a metal atom in the bulk bonded to twelve nearest neighbor atoms.[52] Atoms on the surface of the metal crystallites are, obviously, bonded to fewer neighbors and are, consequently, coordinately unsaturated to varying degrees. Figure 1 depicts the various surface sites possible on an fcc crystalline metal.[50] The fewer the number of nearest neighbor atoms the more coordinate unsaturation of the site. Figure 2 shows these various types of sites in a different perspective. Of particular interest is the difference between corner atoms such as K and M which are also still a part of an extended facial atomic arrangement and these same atom types as adatoms on top of the 100 and 111 crystal faces, respectively.

Not surprisingly, there has been considerable experimental data accumulated over the past several years which indicates that these different types of surface atoms can have varying adsorption and reaction characteristics[45 - 51, 53 - 56] presumably because of the differences in the extent of their coordinate unsaturation.

The conclusions drawn from this work are that reactions involving C - C bond breaking, such as alkane hydrogenolysis or rearrangements, take place on ensembles of face atoms on the catalyst surface. Reactions such as hydrogenations and dehydrogenations are promoted by single atom active sites which are the more coordinately unsaturated corner atoms or adatoms on the metal. These later are the sites on which the hydrogenation of a pyruvate is expected to take place. If this is established, then the problem becomes one of determining how a modifier can provide a chiral environment to sites such as the M and K adatoms as well as the various corner atoms pictured in Figures 1 and 2.

Single Turnover Procedure

While the above mentioned work[45 - 48] has provided some conclusions concerning the nature of the active sites involved in these reactions, such steady state procedures cannot give any indication of the numbers of such sites present on a given catalyst. It is reasonable to expect that the different types of sites on the metal surface would react at different rates so no direct correlation between the product composition and numbers of specific types of sites present can be drawn. It is not inconceivable that one could have a small concentration of very active sites which could dominate product formation. In order to have a direct relationship between the number of the various types of active sites present and the amounts of the different products obtained it is necessary that the activity differences between the sites be eliminated. One way of doing this is to run the reaction in such a manner that each site reacts only once so there is only one product molecule produced from each site during the reaction sequence. In other words, the catalyst surface is used in a stoichiometric reaction. This approach is the basis for our Single Turnover (STO) reaction sequence for characterizing dispersed metal catalysts. By using this technique it is possible to measure the amounts of five different types of sites present on a dispersed metal catalyst.[50, 57 - 59] There are three different kinds of saturation sites which were shown to be corner atoms or adatoms of one type or another.[49] These have been labeled ^3M_I, ^3M_R and ^3MH sites for reasons not important to this present discussion.[58] There are also double bond isomerization sites, called ^2M, which are presumably edge atoms. Other sites, termed ^1M, adsorb hydrogen but do not take part in an alkene hydrogenation and are probably atoms on the faces of the metal particles.[58] The relationship of these STO saturation sites with the specific atomic arrangements shown in Figures 1 and 2 is not clear. There is, however, some circumstantial evidence which suggests that the ^3MH site may be a corner atom which is part of a facial arrangement and the ^3M_I and ^3M_R sites are adatoms on the surface of a crystallite face.[60]

Since each of these different types of saturation sites will probably react at different rates the overall rate of a steady state reaction is the sum of the individual site rates as described by Eqn. 5.[50, 61] Here the **Rate** is the experimental rate of H_2 uptake described as a molar Turnover Frequency (TOF) (moles of H_2/mole of Pt/min) for a specific catalyst and the [ ] are the STO saturation site densities (moles of site/mole of Pt) for that same catalyst. The **A**, **B**, and **C** are the specific site TOFs for the ^3M_I, ^3M_R and ^3MH sites, respectively, given in moles of H_2/moles of site/min. Since this equation has three unknowns it can only be solved if it is applied to a series of catalysts having different active site densities. This approach has been used to determine the specific site TOF's for a number of reactions.[50, 61, 62]

$$\text{Rate} = \mathbf{A} * [^3M_I] + \mathbf{B} * [^3M_R] + \mathbf{C} * [^3MH] \qquad (5)$$

To obtain catalysts having different site densities all that is necessary is to reduce samples of the same supported salt, or catalyst precursor, in a stream of hydrogen at different temperatures. In this way series of catalysts having the same metal load and support but with varying active site densities are readily acquired. Such catalysts not only have varying site densities but also different dispersions and metal crystallite size.[59, 63]

Experimental

The ethyl pyruvate (Aldrich, >97% purity) was distilled under vacuum each morning for use during the day (bp 67°, 10mm). The pyruvate was collected in a dried, septum sealed, distillation receiver and kept there, under dry He, until used. Aliquots were extracted using gas tight syringes. The methyl acetate used as the solvent was Fisher Certified which was further purified by distillation from CaH_2 under He using a Labglass Solvent Still. The distilled solvent was stored under He in the septum sealed distillation receiver until use and kept from contact with the atmosphere by transferring it to the reaction vessel using gas tight syringes.

Dihydrocinchonidine (**3a**) was obtained by hydrogenating 2g of cinchonidine (**1a**) (Aldrich) in 100 mL of methanol at room temperature and 4 atm pressure over 0.5g of 5% Pd/C. After H_2 uptake ceased the catalyst was removed by filtration and the filtrate evaporated to dryness. After several recrystallizations from ethanol pure **3a** was obtained: mp 229.5 - 230°C; lit[64] mp 230°C. Portions of the alkaloid modifier were dissolved in distilled methyl acetate and stored in septa sealed flasks under He until use. Appropriate quantities of the chiral modifier solution were transferred to the reaction vessel using gas tight syringes.

Two series of Pt/Al_2O_3 catalysts were prepared by incipient wetness.[65] A 4% Pt/Al_2O_3 was prepared from a solution of 2.1g of H_2PtCl_6 in 16mL of H_2O which was added to 25g of γ Al_2O_3 (Surface area, 102 m^2/g). This was dried in a rotary evaporator under vacuum at 50°C for 3 hr and stored in a closed vial until used. Portions of this supported salt were heated to the desired temperature in He and then reduced isothermally at 200°, 250°, 300° or 400°C in a 30 cc/min stream of H_2. Other portions were reduced in a stream of H_2 while the temperature was ramped from 25°C to the desired temperature at a rate of 5°C/min. A 6% Pt/Al_2O_3 catalyst was prepared from a solution of 3.15g of H_2PtCl_6 in 16mL of H_2O which was added to 25g of γ Al_2O_3. After drying and reducing portions as described above each catalyst sample was calcined at 400°C for 12hr and then re-reduced using the initial reduction procedure. One portion of the 4% Pt/Al_2O_3 reduced material was also calcined at 400°C for 12 hr before isothermal re-reduction at 400°C. Table 1 lists the individual catalysts and their respective reduction procedures. A commercial 5% Pt/Al_2O_3 catalyst obtained from Strem Chemical was also used.

Physisorption measurements Nitrogen BET surface areas and pore volume data were obtained using an Omnisorp 100CX surface area and pore volume analyzer with the sample outgased prior to the study in a high vacuum system at 200°C for 8hr at 10^{-4} -10^{-5}kPa. The BET surface areas were determined from the adsorption isotherm with a data sampling rate of 0.5/min and a cut off pressure 20 kPa.

Chemisorption measurements All chemisorption studies were carried out using an Omnisorp 100CX apparatus according to the procedure proposed by Benson, Hwang and Boudart.[66] Samples (ca 0.5-1.0 g) were placed in a Pyrex cell for subsequent pretreatment and chemisorption measurements. The samples were heated at a rate of 20°/min up to 100°C and He was passed through the sample for 10 min at a rate of 20 cc/min. The temperature was further increased to 150°C and the sample was exposed to a flow of hydrogen for 30 min.

Table 1

Details of the Procedures Used for the Preparation of the 4% and 6% Pt/Al_2O_3 Catalysts

Catalyst[a]	% Pt	Calcined	Temp. at Start of H_2	Temp. at End of H_2	Time in H_2
4-I-N-200	4	No	200°	200°	4 hr
4-I-N-250	4	No	250°	250°	4 hr
4-I-N-300	4	No	300°	300°	4 hr
4-I-N-400	4	No	400°	400°	4 hr
4-P-N-200	4	No	50°	200°	3.5 hr
4-P-N-250	4	No	100°	250°	1 hr
4-P-N-400	4	No	50°	400°	3.5 hr
4-P-C-400	4	Yes	50°	400°	3.5 hr
6-I-C-200	6	Yes	200°	200°	4 hr
6-I-C-250	6	Yes	250°	250°	4 hr
6-I-C-300	6	Yes	300°	300°	4 hr
6-I-C-400	6	Yes	400°	400°	4 hr
6-P-C-200	6	Yes	50°	200°	3.5 hr
6-P-C-250	6	Yes	100°	250°	1 hr
6-P-C-400	6	Yes	50°	400°	3.5 hr

a) A-B-C-D: A, % Pt; B, I = isothermal reduction, P = programmed reduction; C, N = non-calcined, C = calcined; D, temperature of isothermal reduction or maximum temperature in programmed reductions.

Following this step, the samples were evacuated to 10^{-5}-10^{-6} kPa with a simultaneous increase of the temperature to 300°C. At that point the evacuation was continued for 2 hr followed by cooling to 40°C under vacuum. Successive calibrated pulses of H_2 were admitted into the sample and the pressure was monitored until it reached equilibrium which was about 10-15 min after the admission of the pulse. A total of 20-25 pulses was commonly used to reach a pressure of 30 kPa.

Single-turnover measurements (STO) The STO apparatus, reaction sequence and pulse injection techniques have already been described.[57, 58] A 2 - 5 mg sample of each catalyst was placed in the STO reactor (6-mm Pyrex tube). The reactor was purged with oxygen-free He for 30 min and the STO characterization sequence initiated. Several initial STO sequences were required to remove the surface oxygen from the catalyst and to obtain reproducible results from further sequential STO reactions. The sequences consisted of an initial 20 µl pulse of H_2 to saturate the metal surface, followed after 2 minutes by a same pulse size of but-1-ene to react with the adsorbed H_2, producing butane from the direct, ^3M, hydrogenation sites and cis- and trans -but-2-en from the ^2M isomerization sites. A second H_2 pulse, performed 6 minutes after the butene pulse, was passed over the catalyst to react with the stable half-hydrogenated metalalkyl species still present on the metal surface,

Table 2

STO Site Densities and Dispersions of the 4% and 6% Pt/Al_2O_3 Catalysts

Catalyst	$^{3}M_{I}$[a]	$^{3}M_{R}$[a]	^{3}MH[b]	^{2}M[c]	^{1}M[d]	STO Dispersion[e]	H_2 Dispersion[f]
4-I-N-200	0.037	0.015	0.019	0.030	0.269	0.365	0.417
4-I-N-250	0.081	0.033	0.047	0.041	0.371	0.573	0.687
4-I-N-300	0.085	0.038	0.048	0.026	0.320	0.517	0.640
4-I-N-400	0.075	0.027	0.08	0.043	0.282	0.507	0.609
4-P-N-200	0.035	0.017	0.017	0.014	0.217	0.300	0.352
4-P-N-250	0.047	0.024	0.028	0.030	0.388	0.517	0.588
4-P-N-400	0.029	0.018	0.014	0.009	0.119	0.189	0.236
4-P-C-400	0.088	0.044	0.048	0.034	0.251	0.465	0.597
6-I-C-200	0.064	0.043	0.045	0.038	0.270	0.460	0.567
6-I-C-250	0.074	0.040	0.047	0.039	0.363	0.563	0.677
6-I-C-300	0.085	0.042	0.049	0.027	0.320	0.523	0.650
6-I-C-400	0.078	0.042	0.045	0.039	0.256	0.460	0.580
6-P-C-200	0.083	0.042	0.052	0.034	0.317	0.528	0.653
6-P-C-250	0.067	0.040	0.044	0.036	0.307	0.494	0.601
6-P-C-400	0.059	0.034	0.035	0.020	0.310	0.458	0.551

a) Direct saturation sites, Adatoms.
b) Two step saturation sites, Corner atoms.
c) Alkene isomerization sites, Edge atoms.
d) Sites unreactive in alkene hydrogenation, Face atoms.
e) Sum of the STO site densities.
f) Dispersion determined using the H_2 chemisorption data and a 1:1 H:Pt stoichiometry.

releasing the "second" butane in an amount, equal to the number of the ^{3}MH two step hydrogenation sites. Increasing the time between the first hydrogen and the butene-1 pulse to 60 minutes provides the numbers for $^{3}M_{I}$ and $^{3}M_{R}$ site densities. The detailed site calculation procedure has been described.[58, 59] All products were analyzed by on-stream gas chromatography. The STO site densities and the dispersion data are listed in Table 2 for the 4% and 6% Pt/Al_2O_3 catalysts which are described in Table 1.

The pyruvate hydrogenations were run using the recently developed computerized constant volume - constant pressure apparatus.[67] In this system the computer monitors the pressure inside the reaction vessel and injects a standard size pulse of hydrogen into the reaction vessel when the pressure drops below a preset value. At atmospheric pressure a pressure drop of 0.5 mm Hg was commonly used along with hydrogen pulses of 0.25 mL. The time each pulse was injected was recorded by the computer. This sensitivity permits a very careful determination of the progress of the reaction to be made. Typical hydrogen uptake curves are shown in Figure 3. The initial rate of the reaction was determined from the data obtained for the first 5% of the reaction.

The standard conditions chosen for this study were the hydrogenation of 0.25 mL of ethyl pyruvate in 15 mL of methyl acetate over 10 mg of a Pt/Al_2O_3 catalyst at 25° ± 0.1°C and a 760mm Hg pressure of hydrogen. Varying amounts of the dihydrocinchonidine modifier were used. To maintain a constant pressure throughout this study the reactor pressure was adjusted to 760mm for every run regardless of the external atmospheric pressure for any particular day. To eliminate all traces of water from the reaction mixture the reaction flasks were carefully washed and dried in an oven at 110°C for several hours. On removal from the oven they were quickly sealed with a closed stopcock adapter which was connected to a dry nitrogen or helium gas supply. The stopcock was opened and the flask was allowed to cool with the dry gas inside. After cooling, the weighed catalyst was quickly added to the reaction flask and it was then attached to the reaction system by way of the gas inlet adapter described below. The flask was evacuated and filled with dry H_2 several times, 10 mL of methyl acetate was added through the septum and the catalyst:solvent mixture was shaken under hydrogen for 15 min. The appropriate volume of modifier solution was added, followed by sufficient methyl acetate to bring the total volume to 15 mL. The flask was then evacuated and refilled with hydrogen several more times and the mixture agitated under H_2 for an additional 15 min. Agitation was stopped, 0.25mL of the pyruvate was added by syringe and agitation resumed and data acquisition initiated. After the appropriate hydrogen uptake the catalyst was separated by filtration and the composition of the reaction mixture determined by gas chromatography on an HP 5890 FID gas chromatograph using a 30m x 0.25mm Chiraldex B-TA chiral column run isothermally at 75°C. This gave base line separations of the (R) and (S) ethyl lactates and the unreacted ethyl pyruvate. The optical yield is expressed as the enantiomeric excess (ee) of the (R) lactate using the relationship:

$$\text{ee}\ (\%) = ([R] - [S]) \times 100/([R] + [S])$$

Two types of reactors were used. One was a 50 mL jacketed flask with a standard taper joint. This was fitted with a Teflon adapter which permitted the evacuation of the reactor and the filling with gas through an inlet port and a second port which was sealed with a septum for use in adding materials to the reactor or removing samples from the reaction mixture. This apparatus was placed in a modified Parr shaker and agitated at 200 strokes per minute, a rate which was shown to be more than adequate to keep the reaction from being controlled by any mass transport limitations.[68] The reaction temperature was controlled by the circulation of water through the jacket from a bath capable of maintaining a 25°C temperature to within ±0.1°C. The second type of reactor was a 25 mL standard taper Erlenmeyer flask with the same type of adapter described above. In this case the flask was immersed in a constant temperature bath held at 25° ± 0.1°C and the reaction mixture stirred using a glass covered magnetic stirring bar. Again, the reaction run with this system was shown not to be controlled by any mass transport limitation.[68] Data from the two reactor systems were shown the be reproducible and interchangeable.

The hydrogenation run at 10 atm was performed in a 300cc Parr Stirred Autoclave using 75mg of 5% Pt/Al_2O_3 (Strem, freshly reduced in a 30 cc/min stream of H_2 at 200°C for 2hr) to hydrogenate 1.25mL of ethyl pyruvate in 75mL of methyl acetate containing 1.8mL of a 1μmole/mL solution of dihydrocinchonidine. This was the same dihydrocinchonidine:Pt ratio which gave the maximum ee at 760mm pressure.

The thermal desorption of dihydrocinchonidine from the catalyst was examined by stirring 15mg portions of the 5% Pt/Al_2O_3 (Strem) catalyst in 12 mL of methyl acetate under hydrogen for 15 min at 25°C. The temperature of the suspension was then changed to that desired and 3 mL of a 1 µmole/mL solution of dihydrocinchonidine in methyl acetate was added. After 15 min the catalyst was removed and the amount of alkaloid present in the supernatant solution was measured by the uv absorption at 276 and 316nm. The results are depicted in Figure 4.

Results and Discussion

Before it is possible to develop a reasonable understanding of the processes which are taking place on the catalyst surface during an enantioselective hydrogenation of a pyruvate it is necessary to develop a set of reaction conditions which would be amenable to obtaining the kind of information needed for such a task. The previously described reaction conditions,[19 - 22, 23 - 40] which involved high hydrogen pressures and high substrate concentrations, were such that details of the surface interactions could easily have been obliterated. Also, since there are many different types of sites on the surface of the Pt catalyst (Figures 1 and 2), the conditions used would almost certainly have favored those reactions taking place on the most reactive of these sites thus making it difficult to understand what is happening over the entire surface. To answer these problems a different set of standard reaction conditions was selected. These conditions were chosen to facilitate the necessary experimental manipulation and to permit a more detailed investigation of the different facets of the substrate:modifier:catalyst interactions.

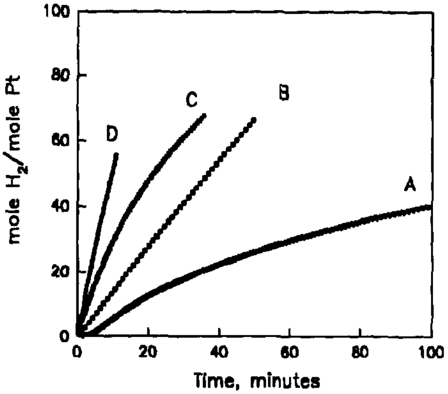


Figure 3. Hydrogen uptake data for the hydrogenation of ethyl pyruvate over 5% Pt/Al_2O_3. A) Freshly distilled pyruvate in cyclohexane solvent. B) Freshly distilled pyruvate in methyl acetate solvent. C) Pyruvate distilled and stored overnight at 5°C and hydrogenated in methyl acetate solvent. D) Freshly distilled pyruvate with 100 µl of water in methyl acetate.

Reaction Conditions

Pressure

The higher pressures used in the published reports[19 -22, 23 - 40] are not necessary for the hydrogenation of a ketone,[69] particularly one as active as that of a pyruvate. These hydrogenations take place readily at room temperature and atmospheric pressure as shown by the hydrogen uptake curves in Figure 3. The initial rates of hydrogenation, which were determined using the data for the first 5% of the hydrogenations, are comparable to those reported in the literature.[23 - 40] As a comparison of enantioselectivity, the hydrogenation run at atmospheric pressure using the dihydrocinchonidine modified commercial 5% Pt/Al_2O_3 gave a maximum enantioselectivity of 50% ee. Repeating this hydrogenation under 10 atm of hydrogen raised the product ee to 60%. Blaser[30 - 32] has found that the product ee data are dependent on the specific catalyst used. This 60% ee is within the range of ee's reported previously so we feel that our results are compatible with the previous data.

Solvent

The solvent used in this reaction must be one in which both the pyruvate and the modifiers are soluble but which interacts only minimally with the catalyst surface. The solvents used in the previous work, benzene, toluene, ethanol and methanol have been shown to have a strong interaction with Pt and other metal catalysts[70] so these solvents could interfere with the adsorption of the substrate and modifier on the catalyst surface. At first, cyclohexane was considered as a potential solvent but, as shown by the H_2 uptake curve in Figure 3 (A), reactions run using this solvent showed appreciable curvature of the hydrogen uptake curve indicating possible product inhibition of the reaction in this solvent. Methyl acetate was finally selected as the standard solvent because it readily dissolved the pyruvate and the cinchona alkaloids. In addition it was shown to have little, if any, tendency to interact with the catalyst surface[70] so its use should not present any problems in this regard.

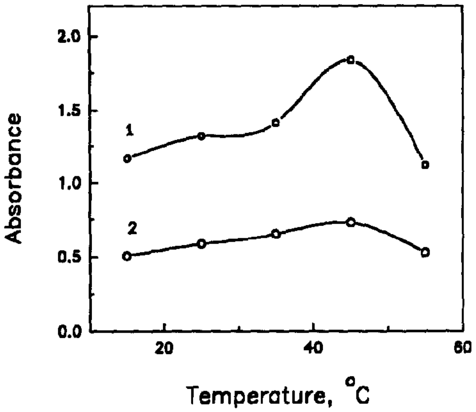


Figure 4. Uv absorbance of the supernatant liquid at 276 nm (Curve 1) and 316 nm (Curve 2) as a function of temperature: 15mg 5% Pt/Al_2O_3 (3.85 μmole Pt), 0.89mg dihydrocinchonidine (3μmole) 15 mL of methyl acetate.

Temperature

All of the hydrogenations were run in glass reaction vessels thermostatted at 25° ± 0.1°C. It was thought that the reported loss of enantioselectivity at temperatures greater than 40°C[23, 28] could have been caused by the thermal desorption of the modifier from the catalyst at these elevated temperatures. To see if this were true, 15mg portions of the commercial 5% Pt/Al_2O_3 catalyst were stirred with a solution containing 3μmoles of dihydrocinchonidine at temperatures between 20° and 50°C and the amount of non-adsorbed alkaloid determined by uv analysis of the supernatant liquid. The results, depicted in Figure 4, show that as the temperature was increased to 50°C the amount of alkaloid found in the supernatant liquid also increased. This shows that thermal desorption of the modifier is a factor up to this temperature but the observed decrease in the uv absorbance at 55° indicates that something more is happening. This factor is presently being investigated in more detail and the results will be described later.

Substrate

The use of pure pyruvate is essential for obtaining reliable and reproducible data. We found that it was not only necessary to distill the pyruvate before use but that it had to be distilled fresh every day and then kept for the day in the distillation receiver under He and accessed via a syringe through a septum seal. Figure 3 shows hydrogen uptake curves for the hydrogenation of freshly distilled pyruvate (B) and samples which had been distilled and then stored overnight at 5°C (C). With the proper precautions the rate data obtained were reproducible to within an experimental error of ±5%, usually better. Failure to follow this regimen resulted in hydrogen uptake data which were difficult to reproduce and frequently showed product and/or substrate inhibition patterns. Attempts were also made to purify the pyruvate by passing it through an alumina column immediately before use. The gas uptake data from the hydrogenation of such material were difficult to reproduce and the hydrogenation uptake curves showed distinct curvature. Some preliminary results indicated that the use of ethyl pyruvate gave more reproducible data than was obtained with methyl pyruvate, even when the methyl ester was distilled and used fresh, so all work was done using the ethyl ester. No transesterification was observed between the solvent and the pyruvate under these reaction conditions.

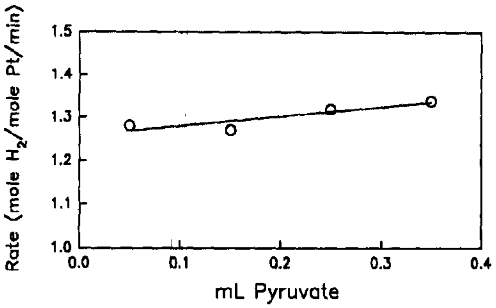


Figure 5. Effect of the amount of freshly distilled ethyl pyruvate on the rate of hydrogenation run over 25mg of a 5% Pt/Al_2O_3 catalyst in 15mL of methyl acetate.

The previous reports stated that the reaction was zero order in pyruvate at the high concentrations of pyruvate used.[23] As the data in Figure 5 show, we have also found that in the absence of the alkaloid modifier the reaction was essentially zero order in pyruvate even at concentrations between 0.05mL to 1.0mL of pyruvate in 15 mL of solvent. This is not too surprising given the high π electron density in the α keto ester, a functional group which would be expected to adsorb very strongly on the catalyst surface.

It was also found that traces of water in the reaction mixture resulted in a marked increase in the reaction rate as shown by the reaction data in Figure 3 (D). Letting the reaction vessel stand open in air was frequently sufficient for the adsorption of enough water on the walls of the vessel to cause this rate increase. This factor caused considerable difficulty in obtaining reproducible results. To eliminate all traces of water from the reaction mixture and insure reproducibility of the reaction data the regimen described in the Experimental had to be carefully followed.

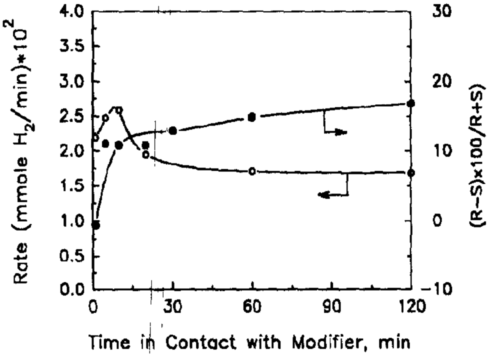


Figure 6. Effect of the modification time on the initial rate of ethyl pyruvate hydrogenation over 25mg of the 4-P-N-250 catalyst (5.12 μmole Pt) and 0.74mg (2.5 μmole) of dihydrocinchonidine.

Modifier

Orito[19 - 22] and Wells[23, 24] prepared the alkaloid modified catalyst by stirring the catalyst with a solution of the alkaloid in air for 1 - 20 hours. The catalyst was then separated by decantation and transferred to a reactor for use. Blazer,[29 - 33] on the other hand, added the modifier directly to the catalyst in the reactor and, after an appropriate time, added the pyruvate to begin the hydrogenation. We opted for the later, more simple, catalyst modification so in the present study the catalyst pretreatment was limited to stirring or shaking it in the reaction vessel under H_2 with a methyl acetate solution of the alkaloid in the desired concentration. After an appropriate time the pyruvate was added through a septum and the measurement of hydrogen uptake was begun. Figure 6 shows the effect which the time of catalyst contact with the dihydrocinchonidine modifier before addition of the pyruvate has on both the hydrogenation rate and product ee. Because of these data 15 min was the normal time used here for treatment of the catalyst with the alkaloid before the pyruvate was introduced into the reactor.

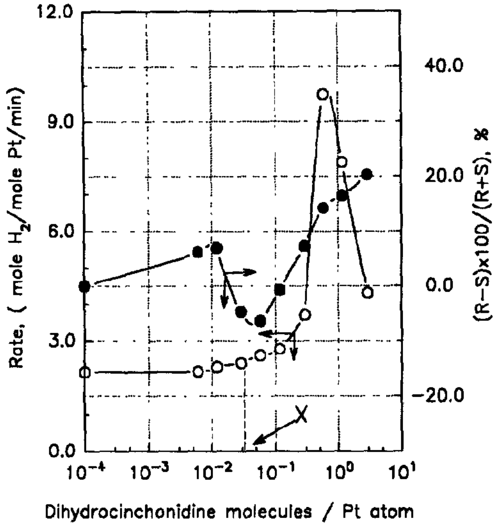


Figure 7. Effect of the dihydrocinchonidine concentration on the rate of ethyl pyruvate hydrogenation and product ee using 15mg of the 4-I-N-300 catalyst.

Figure 7 shows the effect which the addition of small amounts of dihydrocinchonidine has on reaction rate and product selectivity. In contrast to previous reports for reactions run under higher hydrogen pressures,[26, 28] the reaction rate goes through a maximum at a specific modifier concentration and then decreases. The alkaloid:Pt ratio affecting this rate maximum varies from catalyst to catalyst. For the 4-I-N-300 Pt/Al_2O_3 catalyst the rate maximum was observed near a dihydrocinchonidine concentration of one molecule of the alkaloid per Pt atom in the catalyst. More interesting, though, is the effect which small amounts of modifier had on the product stereochemistry. With very small amounts of dihydrocinchonidine, initial formation of (S) ethyl lactate was observed but on further addition of the alkaloid, product formation shifted to the production of the (R) enantiomer. Similar results were observed with a number of the other catalysts listed in Table 1 as well.[71] Such behavior has previously gone undetected.

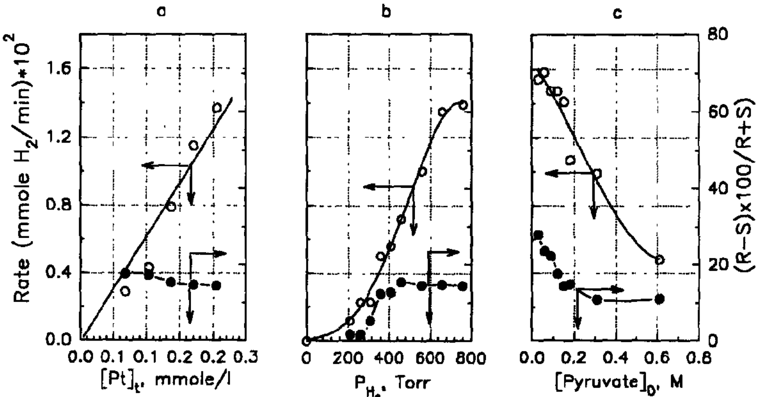


Figure 8. Ethyl pyruvate hydrogenation rates and product ee's as a function of a) catalyst quantity, b) H_2 pressure and c) pyruvate concentration over 15 mg of the 4-I-N-300 catalyst (b and c) at 760 Torr (a and c) with0.25mL of ethyl pyruvate (a and b). The [modifier] corresponded to a 1:1 ratio between the number of dihydrocinchonidine molecules and the total number of Pt atoms in the catalyst used.

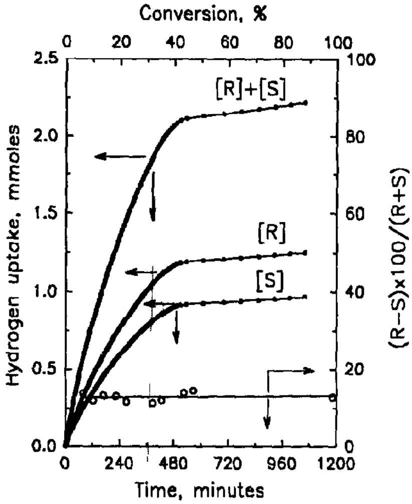


Figure 9. Hydrogenation uptake and product ee data for the hydrogention of 0.25mL of ethyl pyruvate in 15mL of methyl acetate over 15mg of the 4-I-N-300 catalyst (3.85 μmole Pt) modified with 0.89mg (3 μmole) of dihydrocinchonidine.

In Figure 8 are plots which show the effect of changing catalyst quantity (Figure 8a), H_2 pressure (Figure 8b) and pyruvate concentration (Figure. 8c) for reactions run using dihydrocinchonidine modified catalysts. In all runs there was a 1:1 ratio between the molecules of dihydrocinchonidine and the total number of Pt atoms in the catalyst used. As shown in Figure 7, this ratio gave the maximum reaction rate and product ee for the catalyst used. The data in Figure 8a indicate that the pyruvate hydrogenation run under the present conditions is essentially first order in catalyst. This reaction was previously reported to be about first order in hydrogen in the pressure range of 5 - 11 atm using a 3.8 M solution of methyl pyruvate and to have an order in pyruvate of -0.1 ± 0.3 for pyruvate concentrations between 1.9 and 7.5 M at 10 atm H_2 pressure.[23] In contrast, the data in Figure 8b and c show the reaction to be near second order in hydrogen and to have a definite negative order in pyruvate under our reaction conditions.

For expediency, most reactions were run to between 10% and 25% completion for the determination of initial rate values and the ee's of the products. A few representative reactions were run to 100% completion with samples extracted periodically for product analysis. Some typical data are presented in Figure 9. These results show that the ee of the product remained constant throughout the entire reaction so sampling at 10% or 25% was not only efficient but also a valid method for the determination of product selectivity.

The Nature Of The Active Sites Responsible for Pyruvate Hydrogenation

The enantioselective mechanism proposed in the literature stated that the chiral site on the catalyst surface was composed of an ordered array of cinchona alkaloid molecules adsorbed on the faces of the Pt crystallites present on the support material.[16, 23] Other kinetic evidence, however, did not support the premise of an ordered array of alkaloid molecules on the face of a Pt crystallite but rather an active site composed of a single cinchona alkaloid molecule in association with an ensemble of surface platinum atoms.[33, 38] Before developing any type of understanding concerning the nature of the interactions taking place on the metal surface, the type(s) of site(s) on which the hydrogenation is taking place must first be determined. This can be done by running the catalyzed reaction over a series of STO characterized catalysts and then plotting the observed rates against the various site densities and catalyst dispersions A direct correlation is observed with those sites on which the reaction is taking place. This approach has been used to determine the types of sites on which

Table 3

Observed and Calculated Hydrogenation Rates for Reactions Run in the Absence and Presence of Dihydrocinchonidine

Catalyst	Unmodified Cat.[a] Obs. Rate	Unmodified Cat.[a] Calc. Rate[c]	Modified Cat.[b] Obs. Rate	Modified Cat.[b] Calc. Rate[c]
4-I-N-200	0.882	0.954	4.3	4.28
4-I-N-250	2.016	2.037		
4-I-N-300	2.247	2.160	9.8	9.99
4-I-N-400	1.890	1.856		
4-P-N-200	0.882	0.956		
4-P-N-250	1.330	1.205	5.8	5.66
4-P-N-400	0.808	0.828	2.3	3.61
4-P-C-400	2.310	2.379	10.5	10.54
6-I-C-200	1.869	1.948		
6-I-C-250	1.984	2.051		
6-I-C-300	2.331	2.295		
6-I-C-400	2.184	2.102		
6-P-C-200	2.184	2.267		
6-P-C-250	1.869	1.884		
6-P-C-400	1.722	1.604		

a) Hydrogenations run in the absence of dihydrocinchonidine.

b) Maximum rates observed for the hydrogenations run in the presence of dihydrocinchonidine.

c) Rates calculated using Eqn. 5.

reactions as varied as the hydrogenation of alkenes,[49, 62] the heterogeneous Pd catalysed Heck arylation,[72] Pt catalyzed oxidation of secondary alcohols[73] and the heterogeneous Pt catalyzed Claissen rearrangement.[74]

In the present case the 4% and 6% Pt/Al_2O_3 catalysts listed in Table 1 were used for the hydrogenation of ethyl pyruvate under the standard reaction conditions but in the absence of any modifier. The plots of reaction rates, given in Table 3, versus the various STO site densities and catalyst dispersions taken from Table 2 are shown in Figures 10 and 11. It is apparent from these data that there is a linear relationship between the STO saturation site densities (^3M_I, ^3M_R and ^3MH) and the rates of the hydrogenations run using these catalysts. Since these sites have been shown to be the corner or adatoms on the metal surface,[49] these results indicate that, contrary to the previous proposal,[16] the hydrogenation of the pyruvate is taking place over the more coordinately unsaturated corner atoms and adatoms on the Pt surface and not on the face atoms (^1M) of the Pt crystallites. This is not unexpected since the corner atoms and adatoms are also the sites responsible for the hydrogenation of alkenes[49] and the dehydrogenative oxidation of alcohols.[73] Interestingly, the rate versus dispersion plot in Figure 11c is very similar to the published plots showing the absence of any relationship between product ee and catalyst dispersion for specific series of catalysts.[31, 32]

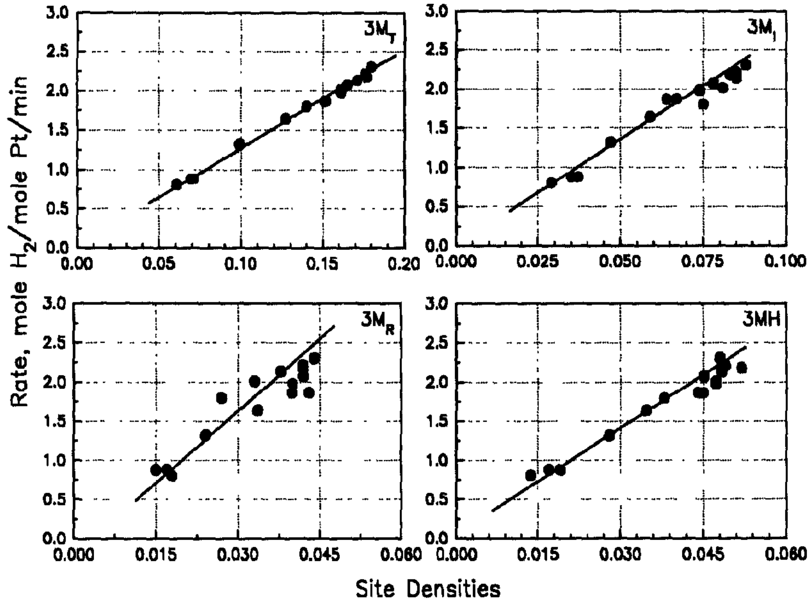


Figure 10. Relationship between the STO determined ^3M site densities and the initial rate of ethyl pyruvate hydrogenation for the catalysts listed in Table 1. ^3M_T is the sum of all ^3M site densities.

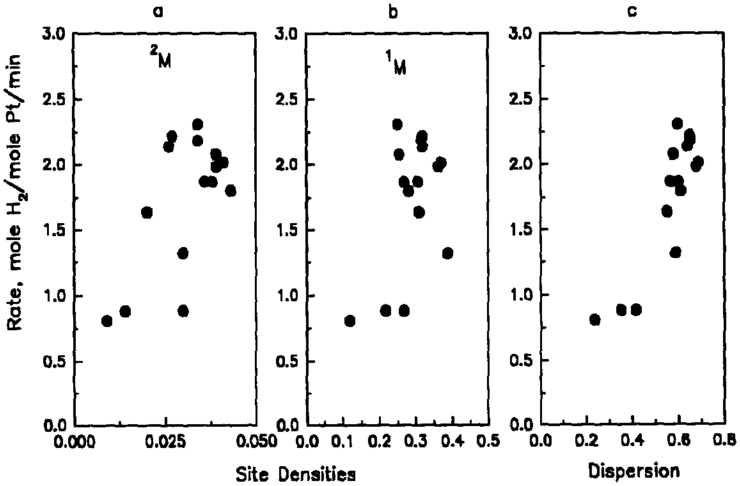


Figure 11. Relationship between the inital rates of ethyl pyruvate hydrogenation and the STO determined ^2M and ^1M site densities and the dispersions of the catalysts listed in Table 1.

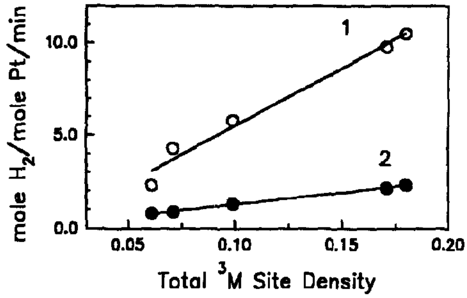


Figure 12. Relationship between the total ^{3}M site densities for some 4% Pt/Al$_2$O$_3$ catalysts and 1) the maximum hydrogenation rates obtained in the dihydrocinchonidine modified ethyl pyruvate hydrogenations run over these catalysts and 2) the ethyl pyruvate hydrogenation rates observed with these catalysts in the absence of alkaloid.

While these data show that for the unmodified catalyst the pyruvate hydrogenation takes place on the corner atoms and adatoms on the Pt crystallites of the catalyst, it does not necessarily follow that this conclusion is valid for the modified catalysts. An examination of the effect of modifier concentration on reaction rate and product enantioselectivity for a number of catalysts has shown that the alkaloid concentration giving the maximum rate varies from catalyst to catalyst.[71] Obtaining precise maximum rate data is not straightforward because of the difficulty in determining the optimum concentration of the alkaloid . We have, however, obtained such data for five of these catalysts with the hydrogenation rate maxima also shown in Table 3. Figure 12 shows the plot of these maximum rates versus the total STO saturation site densities for these catalysts. This linear relationship verifies that even with the modified catalysts the pyruvate hydrogenation takes place on the corner atom and adatom active sites on the Pt catalysts. Also shown in Figure 12 is a plot of the STO saturation site densities versus the hydrogenation rate data for the same catalysts obtained in the absence of dihydrocinchonidine. The difference between the two plots illustrates how the modifier induced rate enhancement can vary from catalyst to catalyst.

It was thought that the specific site rate factors described by Eqn 5 in the Introduction might be useful in obtaining more information about the catalyst:modifier interaction. A rate equation (Eqn. 5) for hydrogenations run in the absence of dihydrocinchonidine was set up for each of the catalysts listed in Table 1 using the STO site densities given in Table 2 and the rate data from Table 3. From this series of equations the specific site TOF's for the ^{3}M$_I$, ^{3}M$_R$ and ^{3}MH sites (A, B and C in Eqn. 5, respectively) were calculated using matrix algebra. Another series of equations was set up with the five catalysts for which the rate maxima for the alkaloid modified hydrogenations were available (Table 3). The specific site TOF's for the non-modified and modified active sites are listed in Table 4 along with the percentage increase in site rate brought about by interaction with the alkaloid. Using these TOF values along with the appropriate site

Table 4
Specific Site Turnover Frequncies (TOF's) for STO Saturation Sites

	^{3}M$_I$^{a}	^{3}M$_R$^{b}	^{3}MH^c
Unmodified reaction^d	17.7	14.5	2.2
Modified reaction^e	95.9	46.8	4.7
% Increase	540	320	210

a) A in Eqn. 5.
b) B in Eqn. 5.
c) C in Eqn. 5.
d) For pyruvate hydrogenations run over Pt/Al$_2$O$_3$ catalysts in the absence of dihydrocinchonidine.
e) For pyruvate hydrogenations run over Pt/Al$_2$O$_3$ catalysts in the presence of dihydrocinchonidine.

Table 5

Calculated Rates For Partially Modifed Catalysts in Pyruvate Hydrogenation over the 4-I-N-300 Catalyst

Site Modified	A	B	C	Calculated Rate[a]
^3MH	17.7	14.5	4.7	2.28
^3M_R	17.7	46.8	2.2	3.38
^3M_I	95.9	14.5	2.2	8.81

a) Calculated using Eqn. 5, the site densities of the 4-I-N-300 catalyst and the listed values for **A**, **B** and **C** taken from Table 4.

densities from Table 3 one can use Eqn. 5 to give the calculated hydrogenation rates also listed in Table 3. In almost every case the difference between the experimentally observed rate and the calculated value is less than ±5%, which is the experimental error for these hydrogenations.

If it is assumed that these sites are modified sequentially by the addition of increasing amounts of the alkaloid, these specific site TOF's can give an indication as to which type of site the dihydrocinchonidine adsorbs on first. The rate and product ee data in Figure 7 were obtained by adding increasing amounts of dihydrocinchonidine to individual portions of the 4-I-N-300 catalyst. At the modifier concentration labeled X in Figure 7, there is a maximum in (S) lactate formation and the observed rate is 2.38 mole H_2/mole Pt/ min. In Table 5 are listed the rates calculated for the 4-I-N-300 catalyst having only one of the three sites modified at a time. With the modifier only on the ^3MH sites the calculated rate is 2.28 mole H_2/mole Pt/ min, very close to the experimental value. The rates calculated for this catalyst with either the ^3M_R or ^3M_I sites modified are much higher. These data, then, suggest that the initial interaction between the Pt catalyst and the dihydrocinchonidine takes place on the STO labeled ^3MH sites. If, as suggested previously, these sites are corner atoms which are an extension of the crystallite face, then it would appear that these corner atoms are modified before the alkaloid interacts with the adatoms on the crystallite faces.

These conclusions are, however, based on rather incomplete data but they are useful in developing the working model discussed below. Obviously, more work in this area is needed. Some of this is presently underway and will be published in a future paper.

Working Hypotheses For The Nature Of The Catalyst:Modifier:Substrate Interactions

Any hypothesis made concerning the interactions which occur between the catalyst and the modifier and substrate must take into account the nature of the sites on which the reaction is taking place, the enantioselectivity and rate data shown in Figure 7 and the possible sequence of site modification described above. The reported[27] effects which changes in modifier structure have on the reaction selectivity[27] must also be considered even though these later data were obtained under conditions different from those involved in this present study. There are two ways in which a chiral modifier can interact with the catalyst. In one the modifier is adsorbed on the surface of the catalyst to create a chiral environment around the active site on which the reaction takes place. In the other the modifier interacts not only with the catalyst but also with the substrate so the chiral environment is enhanced by specific, chiral, interactions between the modifier and the substrate. The first type is that commonly found in homogeneous chiral catalysts. Because there is no specific type of interaction between the modifier and substrate, such catalysts are usually not very substrate specific and can be used to promote a chiral reaction on a number of different types of substrates provided they respond favorably to the chiral environment in the neighborhood of the active site.[1] The second type of effect is that commonly found in enzymes. Here the modifier:substrate interaction imparts to the chiral environment around the active site a substrate specificity which is not present in systems in which the modifier merely establishes a chiral environment.

The rate and selectivity data given in Figure 7 indicate that both effects are probably present in this chiral hydrogenation. The rate enhancement is probably the result of a change in the adsorption characteristics of the keto group caused by the presence of the modifier. This can be the result of an interaction between the modifier and the keto ester which can change the adsorption mode of the keto group. Alternately, the modifier could change the electronic characteristics of the catalyst and, thus, influence the rate of reaction. It is also possible that both factors could be operative at the same time. Since a rate increase is also observed on addition of small amounts of water to the reaction system, as shown in Figure 3(**D**), it would appear that some type of interaction between the modifier and substrate is taking place since one does not normally see any general rate increase caused by the addition of small amounts of water in other hydrogenations. This does not, however, rule out the possibility that an alkaloid modifier could be changing the electronic character of the catalyst as well as interacting with the keto ester.

Assuming that this rate increase is the result of an interaction between the pyruvate and the alkaloid or water, what is the nature of that interaction? It has to be one which is logical chemically but also explains the rate enhancement. Two possibilities come to mind. One is the hydrogen bond stabilized half-hydrogenated ketone proposed by Wells.[16, 25] The other is a nucleophilic attraction of an electron rich center in the modifier molecule to the carbonyl carbon of the keto group of the pyruvate. The available evidence does not support the hydrogen bond stabilization effect. Such bonding is possible with any compound containing an oxygen or nitrogen atom. Ethanol is such a material, yet ethanol was a common solvent in the previous work and a substantial rate increase was observed on addition of the alkaloid even in an ethanol solution. It may be that because of its basicity the quinuclidine nitrogen could form a hydrogen bond with an OH group more readily than the oxygen in the alcohol, but why would this bond only be formed with the half-hydrogenated pyruvate and not with ethanol solvent molecules?

On the other hand, the nucleophilic character of the quinuclidine nitrogen of the alkaloid would be much stronger than that of the oxygen atom in water or alcohol. A nucleophilic interaction between either this nitrogen atom or the oxygen atom of a water molecule and the ketone carbonyl group would weaken the π bond of the carbonyl group. This would change the strength with which the keto group is adsorbed and thereby, change the rate of reaction. The more nucleophilic quinuclidine nitrogen should be attracted to the more electron deficient ketone carbon rather than the ester carbon. The C_9 oxygen could also be involved in a similar attraction. The reported alkaloid modification, product ee data[27] supports the conclusion that the C_9 oxygen is involved in establishing the chirality of the product but not necessarily the entire O-H group. Given that the <u>trans</u> anti parallel orientation of the carbonyl groups on the pyruvate is favored, the attraction between the

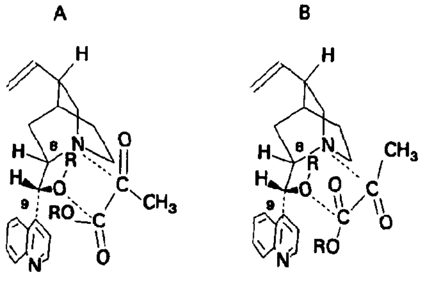


Figure 13. Two modes of interaction between a cinchona alkaloid and a pyruvate.

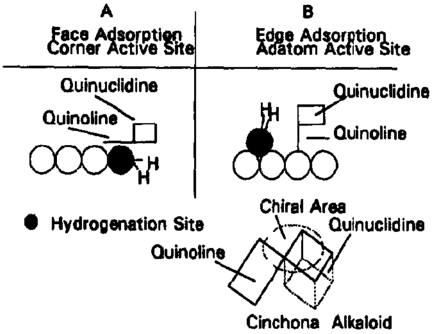


Figure 14. Two modes of interaction between a cinchona alkaloid and a Pt catalyst in which the alkaloid can provide a chiral environment to the corner atom and adatom hydrogenation sites.

alkaloid and the pyruvate can be pictured as in Figure 13. Here the nucleophilic attraction between the quinuclidine nitrogen and the keto carbon as well as the C_9 oxygen and the ester carbon gives a favorable six membered ring interaction. This interaction can take place in the two ways shown in Figure 13 with the one pictured in A apparently less hindered on the basis of molecular model studies.

The modifier can adsorb on the catalyst to provide a chiral environment to the corner atoms and adatoms as pictured in Figure 14. In mode A the adsorption takes place between the face of the quinoline ring of the alkaloid and an ensemble of face atoms which are adjacent to an active corner atom site. The C_8 and C_9 chiral portion of the alkaloid sits over the corner atom to provide the chiral environment. In mode B the adsorption occurs through the nitrogen of the quinoline ring so this ring is adsorbed upright on the metal surface. Examination of molecular models of the alkaloid and various possible metal sites on a large random model of an fcc metal lattice (both in the same scale) indicates that an edge-on mode of adsorption such as that pictured in Figure 14B appears to be needed for the chirality to be transferred to the substrate adsorbed on an adatom on a 111 or 100 face of the metal (K or M in Figure 2). The data presented in Figure 7 indicate that both modes of adsorption may be present in the enantioselective hydrogenation of α keto esters. With the addition of a small amount of dihydrocinchonidine an initial formation of the (S) lactate is observed. Since the rate of the reaction does not increase significantly until the added modifier reaches the concentration needed for the shift to (R) lactate formation, it can be assumed that until this point the surface reaction does not involve any alkaloid-pyruvate interactions such as that pictured in Figure 13 which is used to explain the observed rate enhancement.

As a working hypothesis, then, it is assumed that the alkaloid interacts with the atoms on the Pt surface in varying ways to produce chiral centers with different enantioselectivities. The proposed initial interaction is a facial adsorption of the quinoline ring on Pt face atoms adjacent to corner atoms as shown in Figure 15. The quinuclidine nitrogen may or may not be adsorbed on the corner atom. The enantioselectivity is produced by hydrogen bonding between the C_9 OH and an ester

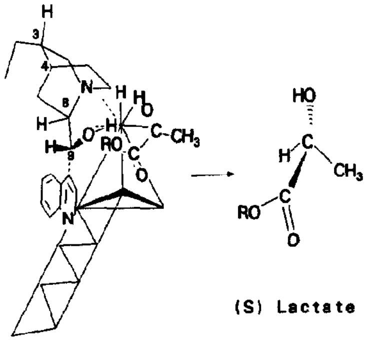


Figure 15. A depiction of a possible interaction beween a cinchona alkaloid molecule, the corner atom on the catalyst and a pyruvate molecule which would lead to (S) lactate formation.

oxygen. Transfer of hydrogen to the pyruvate takes place to the side of the carbonyl group facing the alkaloid resulting in (S) lactate formation. Since no (S) lactate formation was previously observed with a cinchonidine modifier this proposed hydrogen bonding does not contradict the reported alkaloid modification data which is applicable only to the formation of the (R) enantiomer under the high hydrogen pressures and substrate concentrations previously used.[27]

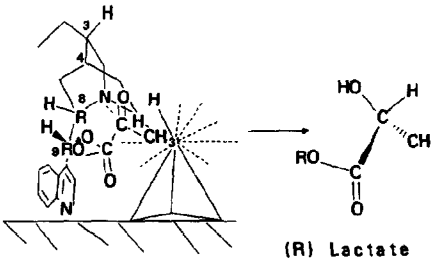


Figure 16. A depiction of a possible interaction between a cinchona alkaloid molecule, an adatom on the catalyst and a pyruvate molecule which would lead to (R) lactate formation.

Further addition of the alkaloid results not only in a shift in the enantioselectivity of the reaction but also in a rate enhancement (Figure 7). From the statements made earlier this would imply that the surface species being hydrogenated under these conditions is the alkaloid-pyruvate "complex" pictured in Figure 13. Edge-on adsorption of the quinoline ring of the alkaloid on face atoms adjacent to an adatom places the quinuclidine ring with the C_8 and C_9 chiral centers somewhat above and sufficiently away from the site so the pyruvate can be adsorbed between the chiral centers of the alkaloid and the active site on the metal. In this configuration the hydrogen is transferred to the keto group from the side away from the alkaloid to give the (R) lactate as depicted in Figure 16.

We recognize that this working hypothesis may contain concepts which are not totally unambiguous. However, we feel that it most reasonably describes the observed changes in enantioselectivity and reaction rate and, therefore, are using it as a model for the design of further experiments to modify or validate these premises.

Conclusions

The problems associated with the use of enantioselective heterogeneous catalysts are very complex. In the first place the surface of the metal catalyst is composed of a number of different types of atoms having varying environments and numbers of nearest neighbors. An understanding of the chiral modification of such catalysts must take into consideration the type(s) of site(s) on which the reaction occurs. It has been shown that the Pt catalyzed hydrogenation of ethyl pyruvate takes place on the corner or adatoms on the metal catalyst surface. The data presented here also indicate that there must be at least two different ways in which the chiral modifier is adsorbed on the catalyst surface to create the necessary chiral environment around these corner atom and adatom sites. A working hypothesis has been proposed which rationalizes the observed changes in product enantioselectivity and reaction rate on the addition of increasing amounts of dihydrocinchonidine to the catalyst. It is suggested that this modifier can be adsorbed on the face atoms adjacent to the corner atoms with the chiral portion of the modifier molecule extending over the corner catalyst atom to provide the required environment to that type of site. For adatoms this type of facial adsorption will not give a chiral environment near the active site so with these sites the modifier must adsorb in an edge-on orientation near the adatom. In this way the chiral portion of the modifying molecule is somewhat above the adatom so the chirality can be transferred to the prochiral substrate. These proposals will be used as a working model for the design of future experimentation to either validate or modify this model. Such work is presently on-going and will be reported in the future.

Acknowledgment

This work was supported, in part, by a grant from the Seton Hall University Research Council. The platinum metal salts were obtained from Johnson Matthey, Inc. through their Precious Metal Loan Program.

References

1. Ojima, I.; Clos, N.; Bastos, C., *Tetrahedron* **1989**, 45, 6901.
2. Brown, J. M.; Chaloner, P. A.; Parker, D., *Adv. Chem. Ser.* **1982**, 196 (Catal. Aspects Met. Phosphine Complexes), 355.
3. Arntz, D.; Schaefer, A., *Catal. Met. Complexes* **1991**, 12 (Met. Promoted Sel. Org. Synth.), 161.
4. Rossiter, B. E., *Chem. Ind. (Dekker)* **1985**, 22 (Catal. Org. React.), 295.
5. Stille, J. K., *Chem. Ind. (Dekker)* **1985**, 22 (Catal. Org. React.), 23.
6. Paganelli, S.; Matteoli, U.; Scrivanti, A, *J. Organomet. Chem.* **1990**, 397, 119.
7. Gladiali, S.; Pinna, L, *Tetrahedron: Asymmetry* **1991**, 2, 623.
8. Mukaiyama, T.; Takashima, T.; Kusaka, H.; Shimpuku, T., *Chem. Lett.* **1990**, 1777.
9. Fiaud, J. C., *Catal. Met. Complexes* **1991**, 12 (Met. Promoted Sel. Org. Synth.), 107.
10. Doyle, M. P., *Recl. Trav. Chim. Pays-Bas* **1991**, 110, 305.
11. Stille, J. K., *J. Macromol. Sci.-Chem.* **1984**, A21, 1689.
12. Stille, J. K., "*IUPAC Macromolecules*", (Ed. by Benoit, H. and Rempp, P.), Pergamon Press, New York, **1982**, p. 99.
13. Blaser, H. U., *Tetrahedron:Asymmetry* **1991**, 2, 843.
14. Izumi, Y., *Angew. Chem., Int. Ed.* **1971**, 10, 871.
15. Izumi, Y., *Adv. Catal.* **1983**, 32, 215.
16. Webb, G.; Wells, P. B., *Catal. Today* **1992**, 12, 319.
17. Akamatsu, A.; Izumi, Y.; Akabori, S., *Bull. Chem. Soc. Japan* **1961**, 34, 1067.
18. Blaser, H. U.; Boyer, S. K.; Pettelkow, U., *Tetrahedron:Asymmetry* **1991**, 2, 721.
19. Orito, Y.; Sumi, I.; Shuichi, N.; *Nippon Kagaju Kaishi* **1979**, 1118.
20. Orito, Y.; Imai, S.; Niwa, S., *Nippon Kagaku Kaishi* **1980**, 670.
21. Orito, Y.; Imai, S.; Niwa, S., Hung, N. G., *Yuki Gosei Kagaju Kyokaishi* **1979**, 37, 173.
22. Niwa, S.; Imai, S.; Orito, Y., *Nippon Kagaju Kaishi* **1982**, 137.
23. Sutherland, I. M.; Ibbotson, A.; Moyes, R. B.; Wells, P. B., *J. Catal.* **1990**, 125, 77.
24. Meheux, P. A., Ibbotson, A., Wells, P. B., *J. Catal.* **1991**, 128, 387.
25. Bond, G.; Meheux, P. A.; Ibbotson, A.; Wells, P. B., *Catal. Today* **1991**, 10, 371.
26. Bond, G.; Simons, K. E.; Ibbotson, A.; Wells, P. B.; Whan, D. A., *Catal. Today* **1992**, 12, 421.
27. Blaser, H. U.; Müller, M., *Stud. Surf. Sci. Catal.* **1991**, 59 (Heterog. Catal. Fine Chem. 2), 73.
28. Blaser, H. U.; Jalett, H. P.; Monti, D. M.; Reber, J. F.; Wehrli, J. T., *Stud. Surf. Sci. Catal.* **1988**, 41 (Heterog. Catal. Fine Chem.), 153.
29. Blaser, H. U.; Jalett, H. P.; Monti, D. M., *Appl. Catal.* **1989**, 52, 19.
30. Wehrli, J. T.; Baiker, A.; Monti, D. M.; Blaser, H. U.; Jalett, H. P., *J. Mol. Catal.* **1989**, 57, 245.
31. Wehrli, J. T.; Baiker, A., Monti, D. M.; Blaser, H. U., *J. Mol. Catal.* **1989**, 49, 195.
32. Wehrli, J. T.; Baiker, A.; Monti, D. M.; Blaser, H. U., *J. Mol. Catal.* **1990**, 61, 207.
33. Garland, M.; Blaser, H. U., *J. Am. Chem. Soc.* **1990**, 112, 7048.
34. Margitfalvi, J. L.; Marti, P.; Baiker, A.; Botz, L.; Sticher, O., *Catal. Letters* **1990**, 6, 281.
35. Blaser, H. U.; Jalett, H. P.; Wiehl, J., *J. Mol. Catal.* **1991**, 68, 215.
36. Garland, M.; Jalett, H. P.; Blaser, H. U., *Stud. Surf. Sci. Catal.* **1991**, 59 (Heterog. Catal. Fine Chem. 2), 177.
37. Margitfalvi, J. L.; Jalett, H. P.; Tàlas, E.; Baiker, A.; Blaser, H. U., *Catal. Letters* **1991**, 10, 325.

38. Garland, M.; Jalett, H. P.; Blaser, H. U., *Preprints, ACS Div. Fuel Chem.* **1992**, 37, 320.
39. Blaser, H. U., *Tetrahedron:Asymmetry* **1991**, 2, 843.
40. Blaser, H. U.; Jalett, H. P.; Monti, M.; Baiker, A.; Wehrli, J. T., *Stud. Surf. Sci. Catal.* **1991**, 67 (Struct.-Act. Se. Relat. Heterog. Catal.), 147.
41. Turner, R. B.; Woodward, R. B., "*The Alkaloids, Vol III*" (Manske, R. H. F.; Holmes, H. L., Eds.), Academic Press, New York **1953**, p 1.
42. Uskokovic, M. R.; Grethe, G., "*The Alkaloids, Vol. XIV*" (Manske, R. H. F., Ed.), Academic Press, New York **1973**, p 181.
43. Verpoorte, R.; Schripsema, J.; van der Leer, T.,"*The Alkaloids, Vol. 34*" (Brossi, A., Ed.), Academic Press, New York **1988**, p 331.
44. Bond, G. C.; Wells, P. B., *Appl. Catal.* **1985**, 18, 221.
45 Sinfelt, J. H.; Carter, J. L.; Yates, D. J. C., *J. Catal.* **1972**, 24, 283.
46 Kirlin, P. S.; Gates, B. C.; *Nature* **1987**, 325, 38
47. Ledoux, M. J., *Nouv. J. Chim.* **1978**, 2, 9.
48. Ledoux, M. J.; Gault, F. G., *J. Catal.* **1979**, 60, 15.
49. Augustine, R. L.; Thompson, M. M., *J. Org. Chem.* **1987**, 52, 1911.
50. Augustine, R. L., *Catal. Today* **1992**, 12, 139.
51. Patterson, W. R.; Rooney, J. J., *Catal. Today* **1992**, 12, 113.
52. "*Magnetism and the Chemical Bond*", Goodenough, J. B., Interscience, New York, **1963**.
53. Goodman, D. W., *Chem. Ind. (Dekker)* **1985**, 22 (Catal. Org. React.), 171.
54. Somorjai, G. A.; Davis, S. M., CHEMTECH **1983**, 13, 502.
55. Davis, S. M.; Zaera, F.; Somorjai, G. A., *J. Catal.* **1984**, 85, 206.
56. Herz, R. K.; Gillespie, W. D.; Petersen, E. E.; Somorjai, G. A., *J. Catal.* **1981**, 67, 371.
57. Augustine, R. L.; Warner, R. W., *J. Org. Chem.* **1981**, 46, 2614.
58. Augustine, R. L.; Warner, R. W., *J. Catal.* **1983**, 80, 358.
59. Augustine, R. L.; Baum, D. R.; High, K. G.; Szivos, L. S.; O'Leary, S. T., *J. Catal.* **1991**, **127**, 675.
60. "Heterogeneous Catalysis for the Synthetic Chemist", Augustine, R. L., Marcel DEkker, Ind., New York, To be published.
61. Augustine, R. L.; Thompson, M. M.; Doran, M. A., *J. Chem. Soc., Chem. Commun.*, **1987**, 1173.
62. Augustine, R. L.; Tanielyan, S. K., *J. Mol. Catal.*, **1993**, 80, 277.
63. Augustine, R. L.; Kelly, K. P.; Lay, Y.-M., *Appl. Catal.* **1985**, 19, 87.
64. Skita, A.; Brunner, W., *Ber.*, **1916**, 49, 1597.
65. Haber, J., *Pure & Appl. Chem.* **1991**, 63; 1227.
66. Benson, J. E.; Hwang, H.; Boudart, M., *J. Catal.*, **1973**, 30 146
67. Augustine, R. L.; Tanielyan, S. K.; Wolosh, G., *Chem. Ind. (Dekker)* **1993**, Catal. Org. React., In Press.
68. Roberts, G. W., "*Catalysis in Organic Synthesis, 1976*", (Rylander, P. N.; Greenfield, H. Eds.) Academic Press, New York, **1976**. p 1.
69. "*Catalytic Hydrogenation: Techniques and Applications in Organic Synthesis*", Augustine, R. L., Marcel Dekker, Inc., New York, **1965**.
70. Augustine, R. L.; Warner, R. W.; Melnick, M. J., *J. Org. Chem.* **1984**, 49, 4853.
71. Augustine, R. L.; Tanielyan, S. K., Unpublished results.
72. O'Leary, S. T.; Augustine, R. L., *Chem. Ind. (Dekker)* **1992**, 47 (Catal. Org. React.), 351.
73. Augustine, R. L.; Doyle, L. K., *J. Catal.* **1993**, 141, 58.
74. Lay, Y.-M., Ph. D. Dissertation, Seton Hall University, **1991**.