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A new origin for stereo-differentiation in the Orito reaction: Residual chiral induction and enantiomeric excess reversal during piecewise continuous experiments using a chiral fixed-bed reactor

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Abstract

The Orito reaction with ethyl benzoylformate on Pt/Al_2O_3 was performed in a piecewise continuous manner with a chiral fixed-bed reactor (CFBR), using a variety of chemical and physicochemical methods to pretreat or clean the chiral fixed bed between multiple hydrogenation reactions. It was observed that after an enantioselective hydrogenation with cinchonidine as modifier at 0 °C, the CFBR could be effectively cleaned at 0 °C, and that a *racemic* unmodified hydrogenation could be performed thereafter. This implies the effective desorption of chiral species from the surface during cleaning. In sharp contrast, it was observed that after the same enantioselective hydrogenation at 0 °C, and after a cleaning treatment of the CFBR at 50 °C, a reproducible unmodified *enantioselective* hydrogenation, with a marked (ca. −9% to −18%) enantiomeric excess (e.e.), resulted. This reversal in the e.e. was stable over time. Similar experiments were conducted with ethyl pyruvate and (a) Pt/Al_2O_3 and cinchonine or (b) Pt/C and powdered Pt catalysts with cinchonidine. The e.e. reversal was again observed in (a), and residual chiral induction but e.e. retention was observed in (b). It is suggested that the e.e. reversal in the unmodified hydrogenation on Pt/Al_2O_3 can be explained by a superposition of two more or less irreversible modifications of the surfaces during the 50 °C cleaning phase. One modification is associated with a more or less irreversible change of the Pt and a minor e.e. retention effect, and the other modification is associated with the presence of the support Al_2O_3 and a predominant e.e. reversal effect. These two effects constitute a previously unknown origin for stereodifferentiation in the Orito reaction.
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Keywords: Enantioselective hydrogenation; Residual chiral induction; Enantiomeric excess reversal; Platinum surface reconstruction; Support surface modification

1. Introduction

The enantioselective hydrogenation of α-ketoesters to the corresponding alcohols over cinchona alkaloid-modified Pt catalysts has been well studied [1]. Various catalysts, modifiers, and substrates have been tested for the Orito reaction [2–10]. The kinetics of the reaction have also been studied in considerable detail [11–13]. The most widely accepted model for stereodifferentiation in the Orito reaction involves the reversible adsorption of the cinchona alkaloid, coadsorption of substrate, and hydrogen activation on the platinum crystallites. The adsorbed cinchona alkaloid provides a chiral environment in which stereodifferentiating hydrogenation can occur.

Concerning the catalytic mechanism, there is wide agreement that some very specific interactions between the substrate and modifier are responsible for inducing the observed enantioselectivity. But there is less agreement on whether the interactions with the catalyst surface are decisive in the stereodifferentiating step. Accordingly, two types of mechanisms—modified catalyst [11,14–16] and shielding effect [17,18]—have been proposed.

Most experimental approaches to understanding the chirally modified catalysis rely on batch reaction system configurations. Because of the high reaction rates of this ligand-accelerated re-

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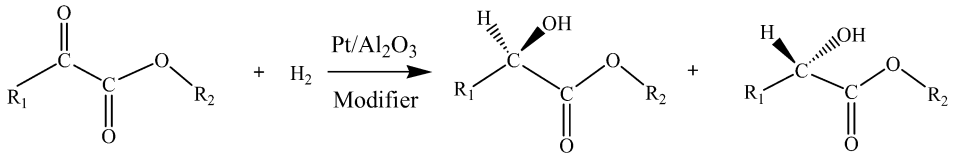
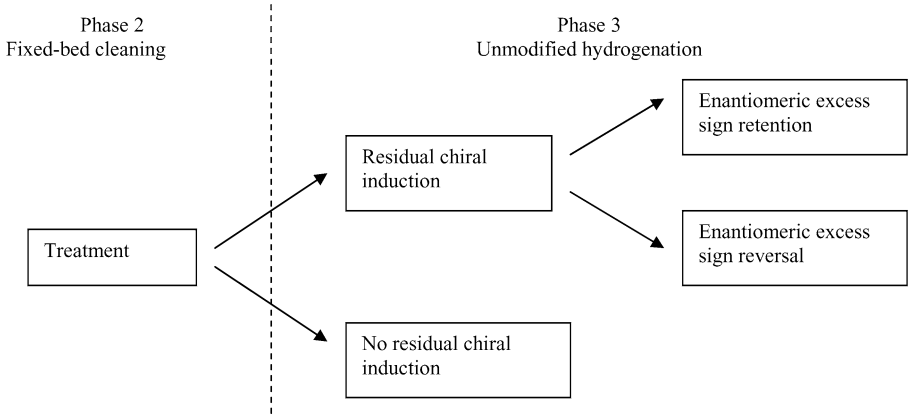


Scheme 1. Hydrogenation of α-ketoesters catalyzed by cinchona modified platinum catalysts.



Scheme 2. An overview of the potential outcomes of a CFBR cleaning phase followed by an unmodified hydrogenation.

action, gas–liquid, liquid–solid mass transfer, and intraparticle diffusion problems can and often do arise, leading to a rapid decrease in enantiomeric excess (e.e.) [19].

Continuous three-phase enantioselective hydrogenation using a chiral fixed-bed reactor (CFBR) has been successfully demonstrated [20–22]. By conducting the Orito reaction in such a manner, continuous dosing of fresh modifier can be performed, which successfully overcomes the continuous degradation of the chiral modifier. Recently a two-phase CFBR system was successfully demonstrated [23]. In that study, the enantioselective hydrogenation of α-ketoesters (Scheme 1) was studied over cinchona-modified Pt/Al_2O_3 catalyst. Despite the unusual contacting pattern, this reaction produced α-hydroxyesters with relatively high e.e.'s. Successful multiple hydrogenations, in a piecewise continuous fashion, were also demonstrated with the same CFBR. One unexpected observation was a substantial and reproducible change in the predominant stereoisomer obtained after the fixed bed was regenerated and a subsequent unmodified hydrogenation was performed. This change in the predominant stereoisomer is demonstrated by a reversal in the sign of the experimentally determined e.e.'s.

In the present study, various experimental sequences were performed using the CFBR. The individual phases involved in these sequences included fixed-bed pretreatment, initial modified enantioselective hydrogenation, in situ cleaning of the CFBR, unmodified hydrogenation, and modified enantioselective hydrogenation on the same catalyst bed. All of the experimental designs contained three or four sequential phases. Phase 2 was always a cleaning phase, and phase 3 was always unmodified hydrogenation. The objective of this study was to reinvestigate the factors that can induce residual chiral induction and e.e. sign reversal on Pt/Al_2O_3 after the in situ high-temperature cleaning phase 2 and during the unmodified hydrogenation phase 3, and hence identify the possible origins of this effect. The observation of residual chiral induction indicates that some sort of *stereodifferentiating information* [24] is retained by the system. An overview of the potential outcomes of a CFBR cleaning phase followed by an unmodified hydrogenation is shown in Scheme 2.

2. Experimental

2.1. Chemicals

Ethyl benzoylformate (EB; Aldrich, 95%) and ethyl pyruvate (EP; Merck, 98%) were distilled under vacuum and stored at 0 °C. Cinchonidine (Fluka, 98%, containing $\leqslant$2% quinine and $\leqslant$8% quinidine) and cinchonine (Fluka, 99%) were used without further purification in the reactions. The pure *R* and *S* enantiomers of ethyl mandelate (EM; Aldrich, 99%) and ethyl lactate (EL; Fluka, 99%) were used without further purification as standards for analysis. Absolute ethanol (Merck, 99.8%) was filtered before use. The catalyst Pt/Al_2O_3 (Engelhard 4759, 5%), platinum powder (Alfa Aesar, 99.9%), and Pt/C (Strem, 5% on activated carbon) were prereduced before reaction [3,4,25].

2.2. Experimental apparatus

A 2.1-mm-i.d. × 50-mm-long high-performance liquid chromatography (HPLC) cartridge with stainless steel frits was used for the fixed-bed reactor. This volume was fully or partially packed with the catalyst powder. The solutions of substrate or substrate in ethanol and modifier in ethanol were pumped quantitatively by a HPLC quaternary pump, in which the flow rates

Table 1
Experimental designs to investigate the effect of chiral fixed bed pretreatment and in situ cleaning on subsequent unmodified and modified hydrogenations of ethyl benzoylformate on Pt/Al_2O_3[a]

Expt. No.	Phase 1 Initial chiral fixed bed treatment $t = 0$–90 min	Phase 2 In situ cleaning $t = 90$–220 min	Phase 3 Unmodified hydrogenation $t = 220$–310 min	Phase 4 Modified enantioselective hydrogenation $t = 310$–400 min
1 (standard)	C_{Cind}, C_{EB}, x_{H_2}, F_{total}, 0 °C	$x^*_{H_2}$, F_{total}, 50 °C	C_{EB}, x_{H_2}, F_{total}, 0 °C	C_{Cind}, C_{EB}, x_{H_2}, F_{total}, 0 °C
2	No substrate	Same	Same	Same
3	No substrate and hydrogen	No hydrogen	Same	Same
4	Same	0 °C	Same	Same
5	C^*_{Cind}, 50 °C	Same	Same	C^*_{Cind}, 50 °C

[a] Further reaction details are: cinchonidine concentration, $C_{Cind} = 4.3 \times 10^{-5}$ M, $C^*_{Cind} = 4.3 \times 10^{-4}$ M, ethyl benzoylformate concentration, $C_{EB} = 4.3 \times 10^{-3}$ M, H_2 mole fraction, $x_{H_2} \approx 0.007$, $x^*_{H_2} = 0.006$. Experimental conditions in all experiments are: total liquid-phase flow rate, $F_{total} = 0.65$ ml/min (LHSV, 225 h^{-1}) and total pressure, $P = 60$ bar.

of each channel could be controlled independently. A vapor–liquid equilibrated solution of hydrogen in ethanol was prepared in a separate autoclave and pumped through a three-way valve to be mixed with substrate and modifier before the CFBR. Then the piecewise experiments were performed with the catalyst cartridge immersed in a temperature-controlled water bath. A back-pressure regulator was used to control the reaction pressure. A detailed schematic diagram has been provided elsewhere [23]. Samples of the liquid phase were taken at regular intervals for gas chromatography (GC), HPLC, and UV–vis circular dichroism (CD) analysis.

2.3. Experimental design

In principle, a vast number of permutations involving fixed-bed pretreatment, enantioselective hydrogenation, in situ cleaning, and unmodified hydrogenation can be performed. To maintain a tractable problem, and to achieve rather straightforward oversight on the experimental design, two sets of experiments were performed. For each experiment, a new fixed bed was prepared with fresh catalyst and then used immediately.

In the first set of five experiments, each piecewise continuous run was restricted to four phases. Importantly, the last two phases were always conducted as unmodified hydrogenation followed by modified enantioselective hydrogenation, thus revealing the effect of pretreatment and in situ cleaning. These hydrogenations were conducted with EB as the substrate on the Pt/Al_2O_3 catalyst. Cinchonidine was used as a modifier if necessary. Details of the experimental design and experimental conditions are given in Table 1.

The second set of three experiments was designed to demonstrate the generality of the phenomena observed and to further probe the origins of residual chiral induction and e.e. sign reversal. In this set of experiments, each piecewise continuous run was restricted to exactly three phases, and the last phase was always unmodified hydrogenation. The hydrogenations were conducted with EP and (a) Pt/Al_2O_3 or (b) Pt/C and powdered Pt catalysts. If necessary, cinchonine was used as a modifier in (a) and cinchonidine was used as a modifier in (b). Details of the experimental design and conditions are given in Table 2.

Table 2
Experimental designs to investigate the effect of chiral fixed bed pretreatment and in situ cleaning on subsequent unmodified hydrogenation of ethyl pyruvate with different catalysts[a]

Expt. No.	Catalyst	Phase 1 Initial treatment $t = 90$ min	Phase 2 In situ cleaning 50 °C	Phase 3 Unmodified hydrogenation $t = 90$ min, 0 °C
6	Pt/Al_2O_3	C_{Cin}, C_{EP}, x_{H_2}, F_{total}, 0 °C	$x^*_{H_2}$, F_{total}, 90 min	C_{EP}, x_{H_2}, F_{total}
7	Pt/C	C^*_{Cind}, x_{H_2}, F_{total}, 0 °C	$x^*_{H_2}$, F_{total}, 360 min	C_{EP}, x_{H_2}, F_{total}
8	Pt powder	C_{Cind}, C_{EP}, x_{H_2}, F_{total}, 22 °C	$x^*_{H_2}$, F_{total}, 130 min	C_{EP}, x_{H_2}, F_{total}

[a] Further reaction details are: catalyst loading, Pt/Al_2O_3 ca. 0.2 g, Pt/C ca. 0.04 g, Pt powder ca. 0.5 g, cinchonine concentration, $C_{Cin} = 5.1 \times 10^{-5}$ M, cinchonidine concentration, $C_{Cind} = 5.0 \times 10^{-5}$ M, $C^*_{Cind} = 7.3 \times 10^{-3}$ M, ethyl pyruvate concentration, $C_{EP} = 0.24$ M, H_2 mole fraction, $x_{H_2} \approx 0.007$, $x^*_{H_2} \approx 0.006$. Experimental conditions in all experiments are: total liquid-phase flow rate, $F_{total} = 0.65$ ml/min (LHSV, 225 h^{-1}) and total pressure, $P = 60$ bar.

2.4. Data analysis

The conversions of EB in experimental designs 1, 2, 4, and 5 were almost 100% because of the high catalyst loading, whereas the conversions in terms of dissolved hydrogen were ca. 3%. This means that the hydrogenations occurred under conditions with dissolved hydrogen in large excess. The conversions of EB in phases 3 and 4 of experimental design 3 were ca. 32% and 70%, respectively. The lower conversions in this case suggest that catalyst deactivation occurred due to lack of dissolved hydrogen during phase 2. The conversions of EP in phases 1 and 3 of experimental design 6 were ca. 50%. The conversions in terms of dissolved hydrogen were ca. 100%, which means that this experiment was performed under limited hydrogen availability. The conversions in experimental designs 7 and 8 were <2% due to the low activities of the catalysts under reaction conditions.

The e.e. is calculated using the following formula:

$$\text{e.e. } (\%) = \frac{[R] - [S]}{[R] + [S]} \times 100. \quad (1)$$

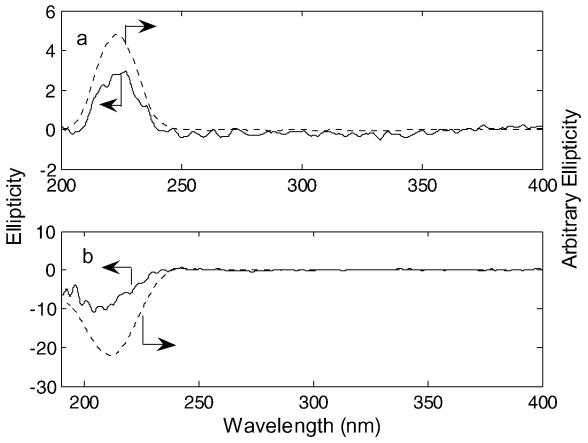


Fig. 1. The circular dichroism (CD) spectra of the product ellipticities for phase 3 after signal processing and the pure enantiomer references. Solid line is experimental ellipticities of the products and dotted lines are ellipticities of pure enantiomer references. (a) Ellipticities for experimental design 1; (b) ellipticities for experimental design 6.

In experimental designs 1–6, the e.e.'s were determined using a recently developed HPLC-CD method [26]. Due to the high conversions of the substrate and/or the analytical method applied, only information on product concentrations is provided in Section 3. In experimental designs 7 and 8, the e.e.'s were determined by GC analysis with a chiral capillary column (CP-Chirasil-Dex CB, 25 M × 0.25) because of the low conversions involved. The e.e.'s in phase 3 of experimental design 6 were also confirmed by GC analysis.

In the present experiments, a positive e.e. corresponds to an excess of the *R* enantiomer, and a negative e.e. corresponds to an excess of the *S* enantiomer. The CD spectra of the products for phase 3 in experimental designs 1 and 6 after signal processing, as well as the pure enantiomer references, are plotted in Figs. 1a and 1b, respectively. Obvious CD signal similarity to *S* EM was obtained in phase 3 of experimental design 1, and obvious CD signal similarity to *R* EL was obtained in phase 3 of experimental design 6.

During the cleaning process, no substrate was added; only ethanol dissolved with/without hydrogen was fed in. Therefore, after a short transition period, no product was formed. The product concentration was unobservable, and the e.e. was set to 0.

3. Results

3.1. Experimental design 1: Standard experimental design

The standard experiment, against which all other results in set 1 are compared, is designated as experimental design 1. This experiment consisted of two modified enantioselective hydrogenations, separated by one cleaning phase and one unmodified hydrogenation. The yield and e.e. of EM as a function of time for the standard experiment are shown in Fig. 2. The data indicates considerable stability of the catalytic systems. The yield and e.e. of EM remained essentially constant during experimental phases 1, 3, and 4. The three most important observations

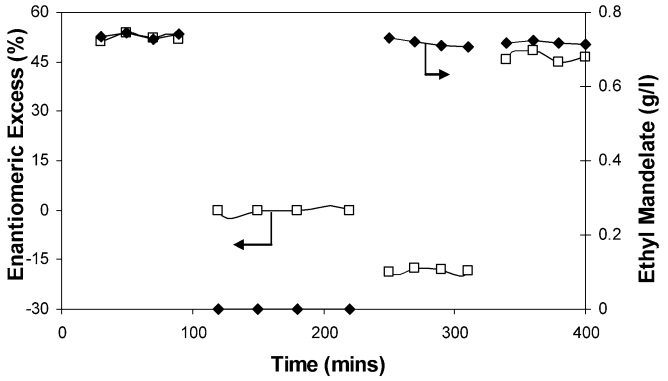


Fig. 2. The yield and e.e. of ethyl mandelate as a function time in experimental design 1. Open symbols, enantiomeric excess; filled symbols, ethyl mandelate concentration.

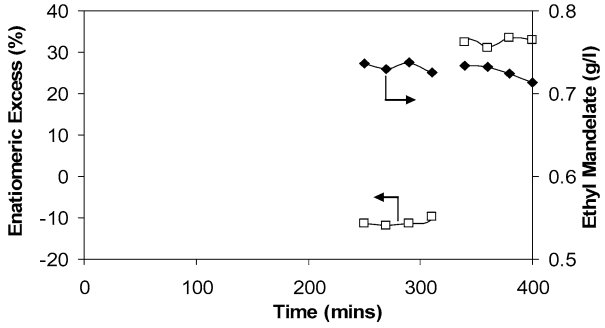


Fig. 3. The yield and e.e. of ethyl mandelate as a function time in experimental design 2. Open symbols, enantiomeric excess; filled symbols, ethyl mandelate concentration.

are: (i) the ca. −18% e.e. observed during the unmodified hydrogenation phase 3, (ii) the essential similarity of the rate of the unmodified phase 3 and the rate of the first enantioselective phase 1, and (iii) the essential similarity of the rate of the first enantioselective phase 1 and that observed during the final enantioselective phase 4 but with a slightly decreased e.e. in the former. Observation (iii) reconfirms that it is possible to clean a CFBR and thus return it to almost its original condition, and that more or less reproducible multiple syntheses can be carried out on the same catalyst bed.

3.2. Experimental design 2: Lack of reagent during pretreatment

The omission of the substrate during phase 1 was the only change in experimental design 2. The experimental results in terms of yield and e.e. of EM as a function of time are shown in Fig. 3. The most important observations were as follows: (i) The yields of EM remained essentially constant in time for both the unmodified hydrogenation phase 3 and the final modified enantioselective hydrogenation phase 4; (ii) the yields of 0.72 g/l in phases 3 and 4 of experimental design 2 were similar to those in phases 3 and 4 of experimental design 1; and (iii) a noticeable change in selectivity pattern occurred between experimental designs 1 and 2. The e.e. in the unmodified phase 3 of Fig. 3 was ca. −11% (compared with ca. −18% in Fig. 2), and the e.e. in

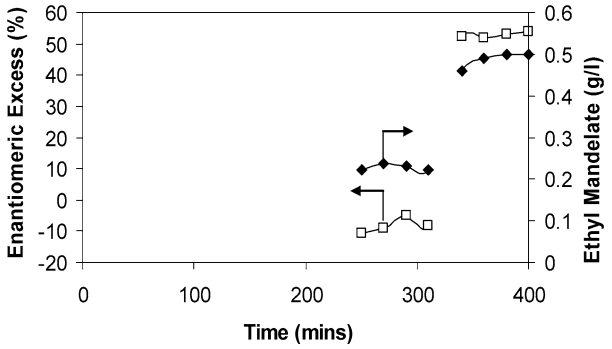


Fig. 4. The yield and e.e. of ethyl mandelate as a function time in experimental design 3. Open symbols, enantiomeric excess; filled symbols, ethyl mandelate concentration.

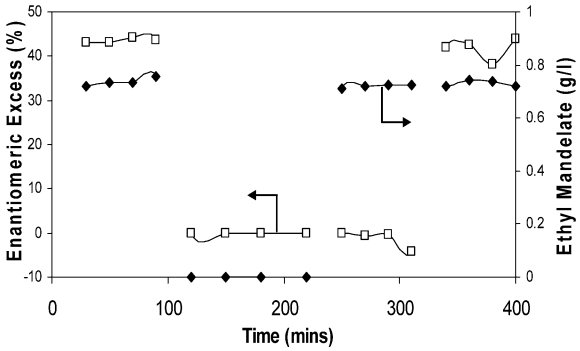


Fig. 5. The yield and e.e. of ethyl mandelate as a function time in experimental design 4. Open symbols, enantiomeric excess; filled symbols, ethyl mandelate concentration.

the final modified enantioselective phase 4 was ca. 32% (compared with ca. 46% in Fig. 2).

3.3. Experimental design 3: Lack of reagent and hydrogen during pretreatment

In experimental design 3, both substrate and hydrogen were omitted during phase 1, and only solvent ethanol was fed in during phase 2. The experimental results in terms of yield and e.e. of EM as a function of time are shown in Fig. 4. Four observations are worth noting:

(i) Reversal of e.e. was observed again during the unmodified hydrogenation phase 3, but lower e.e. (ca. −8%) was achieved (compared with ca. −18% in Fig. 2).
(ii) Deactivation of the catalyst also occurred. The yields of EM in the unmodified hydrogenation phase 3 and the enantioselective hydrogenation phase 4 in experimental design 3 were lower than those observed in experimental designs 1 and 2. Indeed, the yields decreased by ca. 70% and 35%, respectively, compared with either experimental design 1 or 2.
(iii) The e.e. of the final modified hydrogenation phase 4 was ca. 52%, higher than the e.e.'s observed in phase 4 in either experimental design 1 (ca. 46%) or experimental design 2 (ca. 32%).
(iv) The e.e. of the final modified hydrogenation phase 4 (ca. 52%) was identical to the e.e.'s observed in fresh catalyst, such as in phase 1 of experimental design 1 (ca. 52%).

3.4. Experimental design 4: Thermal treatment

The only difference between the operating conditions of experimental design 4 and those in experimental design 1 was the use of 0 °C during the in situ cleaning phase 2. The experimental results in terms of yield and e.e. of EM as a function of time are shown in Fig. 5. The primary observations are that: (i) yields and e.e.'s were similar in the enantioselective phases 1 and 4 of both experimental designs 1 and 4, and (ii) almost no chiral induction occurred during the unmodified hydrogenation phase 3. This last finding contrasts sharply with the result of phase 3 in experimental design 1 (ca. −18% e.e.).

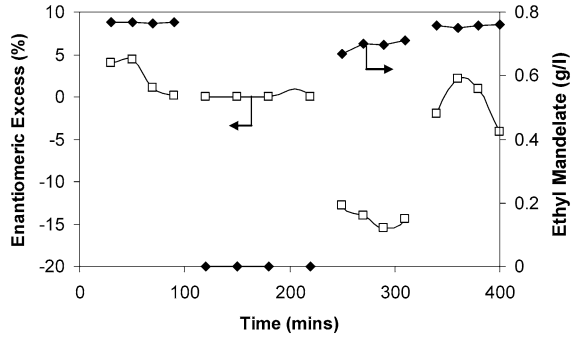


Fig. 6. The yield and e.e. of ethyl mandelate as a function time in experimental design 5. Open symbols, enantiomeric excess; filled symbols, ethyl mandelate concentration.

3.5. Experimental design 5: Confirmation of e.e. reversal during the high-temperature enantioselective reaction

Experimental design 5 addressed the issue of enantioselective syntheses at elevated temperatures. Thus 50 °C was chosen for both phases 1 and 4. Furthermore, because it is known from batch studies that e.e. decreases dramatically at elevated temperatures, the concentration of cinchonidine was increased by a factor of 10. The experimental results in terms of yield and e.e. of EM as a function of time are shown in Fig. 6. It was observed that: (i) very low e.e. (nearly racemic) was achieved at 50 °C in the initial modified enantioselective phase 1; (ii) e.e. reversal was again observed in the unmodified hydrogenation phase 3 at 0 °C, and the value of ca. −14% was very similar to that observed in phase 3 of the standard experiment; (iii) very low e.e. (nearly racemic) was observed again in the final modified hydrogenation phase 4 at 50 °C; and (iv) the yields of the EM were essentially constant at ca. 0.7 and 0.76 g/l in phases 3 and 4, respectively (similar to the yield obtained in phase 1).

3.6. Experimental design 6: Confirmation of e.e. reversal with cinchonine as a modifier on Pt/Al_2O_3 catalyst

Experimental design 6 was performed to address the generality of residual chiral induction and e.e. reversal on the Pt/Al_2O_3 catalyst. Thus in the enantioselective hydrogenation

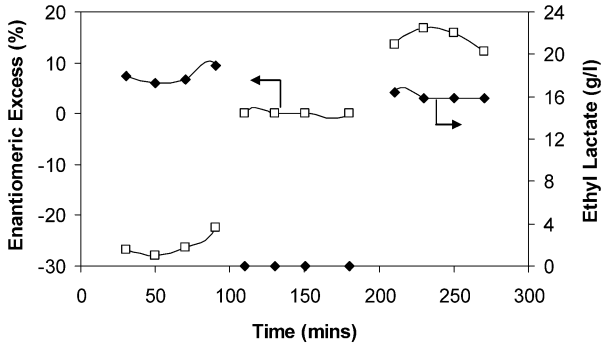


Fig. 7. The yield and e.e. of ethyl lactate as a function time in experimental design 6. Open symbols, enantiomeric excess; filled symbols, ethyl lactate concentration.

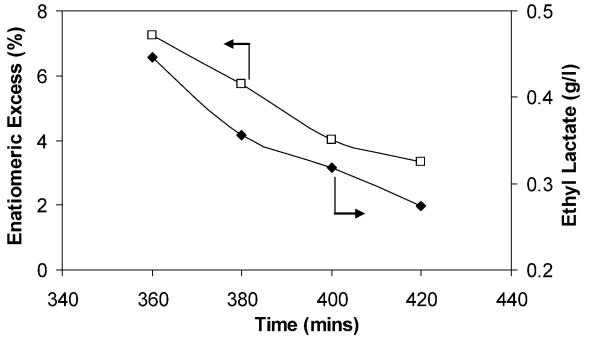


Fig. 8. The yield and e.e. of ethyl lactate as a function time in experimental design 7. Open symbols, enantiomeric excess; filled symbols, ethyl lactate concentration.

phase 1, the modifier was cinchonine instead of cinchonidine and the substrate was EP instead of EB. The experimental results in terms of yield and e.e. of EL as a function of time are shown in Fig. 7. The figure shows that: (i) an e.e. of ca. −26% for the *S* enantiomer in excess was achieved at 0 °C in the initial modified enantioselective phase 1, and (ii) e.e. reversal was again observed in the unmodified hydrogenation phase 3, and a value of ca. 15% was obtained with the *R* enantiomer in excess.

3.7. Experimental design 7: Residual chiral induction with the Pt/C catalyst

Experimental design 7 was performed to address the issue of residual chiral induction when the support was changed; thus a Pt/C catalyst was used. A high concentration of cinchonidine was pumped through the chiral fixed bed in pretreatment phase 1. (A high-alkaloid pretreatment is the standard method for Pt/C catalyst.) To thoroughly flush the system, the cleaning phase 2 was done for ca. 4 h (instead of the normal 130 min). Previous studies have shown that using Pt/C catalyst with cinchonidine as a modifier and ethyl pyruvate as the substrate gives the *R* enantiomer in excess [4,25].

The experimental results in terms of yield and e.e. of EL as a function of time are shown in Fig. 8. It can be seen that a very low e.e. occurred in the unmodified hydrogenation phase 3 and that a value of ca. 5% was obtained. The *R* enantiomer was in excess. No reversal in enantioselectivity was observed. Deactivation was apparent.

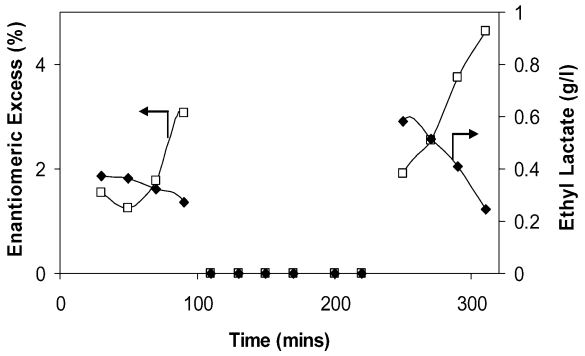


Fig. 9. The yield and e.e. of ethyl lactate as a function time in experimental design 8. Open symbols, enantiomeric excess; filled symbols, ethyl lactate concentration.

3.8. Experimental design 8: Residual chiral induction with Pt powder

Experimental design 8 was performed to address the issue of residual chiral induction when no support was used. Thus, Pt powder was used as the catalyst in this experimental design. The experimental results in terms of yield and e.e. of EL as a function of time, shown in Fig. 9, reveal that: (i) very low e.e. (ca. 2%) was achieved at 22 °C in the initial modified enantioselective phase 1, and (ii) very low e.e. was also observed in the unmodified hydrogenation phase 3, and a value of ca. 3% with the *R* enantiomer excess was obtained. No reversal in enantioselectivity was observed. Deactivation was apparent.

3.9. Overview of results

The primary results of the eight different experimental designs, in terms of yields and e.e.'s in the individual steps of the piecewise continuous operations of the Orito reaction, are summarized in Table 3.

4. Discussion

As indicated by Scheme 2, there are three possible outcomes of a CFBR cleaning phase followed by an unmodified hydrogenation: (i) the total or almost total loss of chiral induction; (ii) the retention of some residual chiral induction, resulting in the same predominant enantiomer and hence the same sign in the e.e.; and (iii) the retention of some residual chiral induction, resulting in a change in the predominant enantiomer and hence a change in the sign of the e.e. All three possible outcomes were observed in the present study.

We first consider case (i), the almost total loss of chiral induction. This occurred in experimental design 4. The design involved an initial modified enantioselective hydrogenation phase 1, followed by a cleaning phase 2 conducted in the presence of both hydrogen and solvent at 0 °C. The e.e. obtained in the unmodified synthesis phase 3 was ca. −0.4%. Most, if not all (within experimental error), of the chiral induction was lost in phase 3. This indicates that the cleaning phase 2 used was effective in removing most, if not all, adsorbed chiral molecules having the ability to induce stereodifferentiation in

Table 3
The yield and e.e. of α-hydroxyester produced in the 8 experimental designs with multiple perturbations

Expt. No.	Phase 1 Initial chiral fixed bed treatment		Phase 2 In situ cleaning	Phase 3 Unmodified hydrogenation		Phase 4 Modified enantioselective hydrogenation	
	Conc. of product (g/l)	e.e. (%)	T (°C)	Conc. of product (g/l)	e.e. (%)	Conc. of product (g/l)	e.e. (%)
1	0.73	52	50	0.72	−18	0.72	46
2	NA	NA[a]	50	0.73	−11	0.72	32
3	NA	NA	50	0.23	−9	0.50	52
4	0.73	43	0	0.72	−0.4	0.73	42
5	0.77	2	50	0.70	−14	0.76	0
6	17.9	−26	50	16.0	15	NA	NA
7	NA	NA	50	0.35	5	NA	NA
8	0.3	2	50	0.4	3	NA	NA

[a] NA means not applicable since (i) for phase 1, no substrate was used in this step and (ii) no phase 4 was performed for the second set of experiments.

the organic reaction (Scheme 1). Essentially a racemic reaction in the unmodified hydrogenation resulted. The cleaning phase used both hydrogen and solvent at 0 °C. The results of phase 4 are a further indication that the cleaning phase resulted in a similar catalytic surface, because essentially identical yields and e.e.'s were obtained during the first and final modified hydrogenations. The ability to properly clean a CFBR has been reported before, so this is a reproducible observation [23].

Case (ii), retention of residual chiral induction resulting in the same predominant enantiomer, was observed in experimental designs 7 and 8. These designs involved different catalysts Pt/C and Pt powder and various pretreatments in phase 1. These designs also involved cleaning procedures all conducted at 50 °C. The e.e.'s obtained in the unmodified hydrogenation phase 3 were ca. 5 and 3%, respectively. These observations indicate that the cleaning phase 2 resulted in retention of some sort of chiral information on the catalyst surface, because the "cleaned" surface was able to induce stereodifferentiation in the organic reaction. The unmodified hydrogenation phase 3 was not racemic, and the same predominant enantiomer was produced in both experimental designs.

Case (iii), retention of residual chiral induction with a change in the predominant enantiomer, was observed in experimental designs 1, 2, 3, 5, and 6. These designs involved various initial modified hydrogenations or pretreatments on Pt/Al_2O_3 in phase 1. These designs also involved various cleaning procedures, all conducted at 50 °C. The e.e.'s obtained in the unmodified synthesis phase 3 for experimental designs 1, 2, 3, 5, and 6 were ca. −18%, −11%, −9%, −14%, and 15%, respectively. Therefore, retention of residual chiral induction occurred, and there was a change in the predominant enantiomer. The use of Al_2O_3 as a support and a temperature of 50 °C in phase 2 were the common factors in the five experimental designs.

4.1. Admissible explanatory theories for reversal in enantioselectivity on Pt/Al_2O_3 catalyst

The reversal in enantioselectivity on Pt/Al_2O_3 during the unmodified hydrogenation phase 3 was present in experimental designs 1, 2, 3, 5, and 6. This residual chirality must have had either an organic or an inorganic origin. In other words, either (i) there was some sort of chiral organic species on the surface leading to this effect or (ii) there was no chiral organic species on the surface, but rather an inorganic species was leading to the observed effect.

4.1.1. Simple redistribution of adsorbed alkaloids

In experiments 1–5, 7, and 8, the commercial Fluka cinchonidine modifier used was a 90:8:2 (weight percentage) mixture of cinchonidine, quinine, and quinidine (quinine and quinidine are diastereomeric). From previous studies, it is known that pure cinchonidine and pure quinine result in the *R* enantiomer and that pure quinidine results in the *S* enantiomer [3].

Comparative experiments in acetic acid have shown that the rates of hydrogenation with cinchonidine, quinine, and quinidine alone are similar and that the absolute values of the e.e.'s are also rather similar [27]. The same study, using competitive experiments conducted with 1:1 cinchonidine and quinidine, also showed that the *R* enantiomer is predominantly formed. This implies that quinidine is less strongly adsorbed than cinchonidine. The heterogeneous enantioselective hydrogenation of ethyl pyruvate over Pt/Al_2O_3 with hydrogenated derivatives of cinchonidine [28] as a modifier, namely 1′,2′,3′,4′,10,11-hexahydrocinchonidine, results in lower rates and e.e.'s. It has been rationalized that in general, hydrogenation of the aromatic rings of the modifier leads to lower absorption constants on platinum and hence the lower observable rates and e.e.'s. Formation of such hydrogenated derivates can be anticipated during the course of the enantioselective syntheses [29,30].

If the aforementioned alkaloids can be desorbed effectively at 0 °C, then they should also be effectively desorbed at 50 °C. Simple redistribution of the aforementioned alkaloids, which normally gives rise to predominantly the *R* enantiomer, to a set of alkaloids giving rise to predominantly the *S* enantiomer, is not a viable argument to explain the anomalous results observed at 50 °C.

In experimental design 6, cinchonine was used instead of cinchonidine. The cinchonine was of very high purity (99%). Again, considerable reversal in enantioselectivity in phase 3 was observed. The arguments concerning alkaloid redistribution seem particularly weak in this case.

4.1.2. New oligomeric or polymeric chiral species

The brief high-temperature treatment might produce higher-molecular weight organics, namely oligomeric or polymeric chiral molecules. Such higher-molecular weight chiral residues

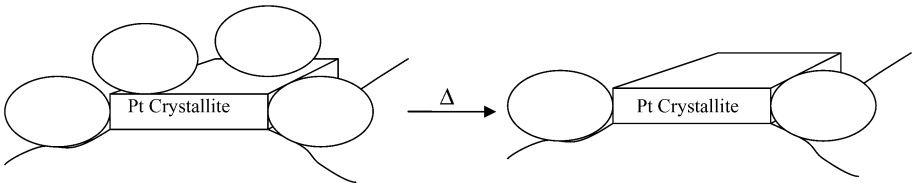


Fig. 10. A representation for the appearance of new stereo-differentiating sites upon thermal treatment, by alkaloid interaction/reaction with platinum at the crystallite/support edge, or by alkaloid reaction with support in immediate proximity to the crystallite.

left on the catalyst surface might not be removed (or not as readily removed) by flushing the fixed bed with the hydrogen/ethanol solution. This formation of new chiral species, occurring during the high-temperature syntheses and cleaning phases, might be promoted by the considerable acidity of the alumina surface. Any resulting oligomeric or polymeric molecules, with their considerable number of aromatic rings, would be expected to be significantly absorbed by π-orbital–platinum interactions on the catalyst surface. Depending on which monomers are polymerized and in what ratios, the higher-molecular weight compound(s) could induce the observed reversal in enantioselectivity in phase 3.

In particular, experimental designs 1 and 5 are not consistent with this explanation. If oligomerization or polymerization were responsible for the observed effect, then a modified hydrogenation conducted at 50 °C in phase 1 of experimental design 5 should induce an even more pronounced e.e. reversal in phase 3 (compared with phase 3 of experimental design 1). This is not the case, however.

4.1.3. Morphological changes in the platinum crystallites

The surface reconstruction of metallic single crystals on adsorption, reaction, and desorption is now well established in the surface science literature, where most of the known examples involve small achiral adsorbate molecules [31–34]. In contrast, only a few well-documented examples of chirality-inducing surface reconstruction due to adsorption of chiral molecules are known. Such intrinsic surface chirality is generally associated with kink sites and high Miller index surfaces [35–37]. This chirality can be created by absorption of a chiral organic, leading to imprinting or faceting on the inorganic material [37] and is associated with the inorganic material alone. In most cases, the naturally chiral structures created on the inorganic material or single-crystal metal surface persist even after the imprinting/faceting agents are removed.

Apparently, all presently known examples of chiral imprinting and faceting involve processes in which chiral adsorbates induce chiral reconstructions on well-defined achiral single-crystal metal surfaces [37–40]. All of these reports of chiral reconstruction have involved copper, which has a low surface energy and corrodes much more readily. Although random cinchonidine adsorption on single-crystal surfaces has been studied by STM [41], apparently there has been no documentation of chiral surface imprinting/faceting in cinchona alkaloid/platinum systems. But this does not exclude the possibility of chiral surface imprinting/faceting on small crystallites.

Residual chiral induction and e.e. retention was observed in experimental designs 7 and 8. The catalysts used were Pt/C catalyst and Pt powder, which have either a rather inert support or no support at all. The results of these experiments seem to support the presence of some kind of chiral surface imprinting/faceting or platinum crystallite modification due to residual organic fragments.

4.1.4. Support-related issues

The e.e. reversal observed in the unmodified hydrogenation phase 3 on Pt/Al_2O_3 catalyst after the cleaning at 50 °C, in contrast to the e.e. retention observed over the Pt/C catalyst and Pt powder after the same thermal treatment, indicates that the support plays some type of role in the retention of chiral information. Plausible reasons for this observation could include: (i) some sort of support-assisted or -induced differences in platinum chemistry or morphology whereby the platinum interacts/reacts differently with the chiral modifiers or (ii) support reaction with the alkaloids.

With respect to (i), it is known that Pt/Al_2O_3 can exhibit strong support–metal interaction (SMSI) behavior. SMSI has been observed after low-temperature reduction at 200 °C [42]. This was attributed to the presence of hydrogen spillover and was manifested as an electronic rather than morphological effect. Changes in morphology and composition of supported Pt nanocrystals have been observed after high-temperature hydrogen reduction at 773 K and above [43]. It was suggested that surface reconstruction under hydrogen and alloy formation occurred. Therefore, support-assisted or -induced differences in the platinum chemistry or morphology, and subsequent differences in the interaction of platinum and the chiral modifiers, cannot be entirely ruled out for the present system.

With respect to (ii), the alumina support is acidic and the chiral alkaloids are Lewis bases. Moreover, the surface chemistry of pure alumina is known to be very complex, having numerous functionalities [44], and alumina impregnated with hexachloroplatinic (IV) acid is even more complex due to the formation of Pt_n^+ sites, chloride-containing sites, and other sites [45–48]. If higher temperature promotes the complexation/reaction of the alkaloids and support surface, then some modified support sites will be produced, and some must be produced in the immediate vicinity of platinum crystallites. The formation of alkaloid–support complexes in the vicinity of the crystallite/support edge would provide stereodifferentiating environments in close proximity to hydrogen activation.

In summary, several types of active sites may be produced on the crystallite, at the crystallite/support edge, or even on the support in close proximity to the crystallite. Fig. 10 illustrates a representative appearance of new stereodifferentiating sites on thermal treatment by alkaloid interaction/reaction with plat-

inum at the crystallite/support edge or by alkaloid reaction with support in immediate proximity to the crystallite.

4.2. Rationalization of residual chiral induction and remodification on the Pt/Al_2O_3 catalyst

Taking into consideration the Pt/C and Pt powder experiments and their e.e. retentions, the observations for Pt/Al_2O_3 in experiments 1, 2, 3, 5, and 6 are most easily rationalized in terms of the superposition of two different phenomena. One of these phenomena is associated with the platinum (and is thus similar to the Pt/C and Pt powder cases), and the other is associated with the same sort of support effect. Together, these two effects constitute a previously unknown origin for stereodifferentiation in the Orito reaction on Pt/Al_2O_3 catalyst.

The unmodified but enantioselective catalysis observed in phase 3 with Pt/Al_2O_3 could arise from hydrogenation on (i) altered platinum crystallites inducing some e.e. retention (as in the Pt/C and Pt powder cases and mentioned in Section 4.1.3) and (ii) sites arising from some sort of support effect, as mentioned in Section 4.1.4, that is, a SMSI-associated effect on the platinum, an alkaloid interaction/reaction with platinum at the crystallite/support edge, or an alkaloid reaction with the support in immediate proximity to the crystallite. The second effect appears to be dominant for Pt/Al_2O_3 catalysts, producing an overall observable e.e. reversal.

In phase 4 of experimental designs 1–5, fresh cinchonidine was again introduced to the fixed bed with substrate and hydrogen. This resulted in modified enantioselective hydrogenation, in which the observed e.e. was consistent with that observed in the initial enantioselective experimental phase 1. Readsorption of cinchonidine on the platinum is the obvious and predominant outcome, which returns the catalyst to almost its original state.

5. Conclusion

Retention of chiral induction and reversal in enantioselectivity after cleaning of Pt/Al_2O_3/cinchonidine was observed in sequential multiple hydrogenations in the same fixed-bed reactor. The same phenomenon was observed when cinchonine was used as modifier. This observation contrasts sharply with fixed-bed cleaning conducted at 0 °C (experimental design 4), in which only minimal retention of chiral induction was observed ($\leqslant -1.0\%$). The latter finding suggests that obtaining effective desorption of chiral modifier from platinum is easy. The retention of chiral induction during the unmodified hydrogenations of α-ketoesters in phase 3, and the associated reversal in sign of the e.e.'s, clearly indicates a second and previously unreported phenomenologic basis for stereodifferentiation in the Orito reaction on Pt/Al_2O_3 catalyst.

Although the exact origins of the stereodifferentiation remain somewhat unclear, a superposition of two more or less irreversible modifications of the surfaces is consistent with the present results. These modifications can be summarized as (i) alteration of platinum crystallites inducing some e.e. retention and (ii) some sort of support effect inducing a reversal in e.e. The changes in platinum as well as the support effects would represent new mechanisms for stereodifferentiation for the Orito reaction on Pt/Al_2O_3 catalyst.

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