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New data to the origin of rate enhancement on the Pt-cinchona catalyzed enantioselective hydrogenation of activated ketones using continuous-flow fixed-bed reactor system

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ABSTRACT

A study on the origin of rate enhancement (RE) in the enantioselective heterogeneous catalytic hydrogenation of methyl benzoylformate (MBF), ketopantolactone (KPL) and pyruvic aldehyde dimethyl acetal (PA) under the Orito reaction conditions over Pt catalyst modified with parent cinchona alkaloids, as compared to the unmodified catalyst is presented. The hydrogenations were carried out in continuous-flow fixed-bed reactor system over 20–100 mg Pt/Al_2O_3 catalyst in 1 mL min^{-1} flow of toluene/acetic acid 9/1 solvent mixture under 40–80 bar H_2 pressure, at 283 or 293 K using 0.044–2 mM modifier concentration and 45 mM substrate concentration. Our results obtained using racemic hydrogenations followed by three changes of the chiral modifier (on the same catalyst) supported the so-called "ligand acceleration" phenomenon in the enantioselective hydrogenation of activated ketones such as MBF, KPL and PA. In our opinion, RE produced by the first modifier added after racemic hydrogenation can also be explained by the purifying effect of the cinchona. REs observed following further exchanges of modifiers are indicative of the intrinsic character of the phenomenon. This research suggested that the origin of enantiodifferentiation and rate enhancement is the same, namely, both may be traced back—probably in different ways—to the role of the intermediate complexes of the hydrogenation, to its formation and transformation, which in turn depends on numerous factors.

1. Introduction

The most important aim of the organic catalytic research is the improvement of the reactions selectivities (e.g. [1–6]). Nowadays, ensuring high optical purities in asymmetric catalytic synthetic transformations is also of increased significance. Two of the most intensively studied heterogeneous enantioselective catalytic reactions are the enantioselective hydrogenations of C=O and C=C bonds containing compounds on Pt and Pd catalysts modified by cinchona alkaloids (Orito reaction [7], Scheme 1) and hydrogenation on Ni catalysts modified by tartaric acids [8–12]. The Orito method allows the realization of enantiomeric excess (ee) as high as 90–98% for certain compounds [13–20]. As a result of extensive investigations many details of the reaction became known. Progress has been reported in several reviews (since 2005 [21–27]).

The main objective of the recent studies on the Orito reaction has been to expand its field of utilization, to elucidate the reaction mechanism and to interpret the origin of enantiodifferentiation and rate enhancement (RE) in this context. The investigations on the mechanism of the reaction used mostly ethyl pyruvate (EP) as model substrate. One of the basic starting points of the studies on EP was the observation that the modified reaction is 20–100 times faster than the unmodified reaction [28–31]. The recognition of RE led to application of the concept of ligand accelerated (LA) catalysis to the Orito reaction, introduced for the enantioselective homogeneous transformations in solution: "A reaction is considered ligand accelerated if there is a slower unmodified (unselective) cycle and a faster modified (selective) cycle [29]." "It also appears from the pertinent literature that research groups involved in this research agree that RE and enantiodifferentiation are closely connected effects and should be discussed together" [32].

The so-called CD:EP 1:1 interaction model [28–36] has been accepted for many years for the interpretation of RE and enantiodifferentiation. Based on this model, the interpretation of RE has been supplemented and corrected [37–41], which has also been included in the reviews discussing the Orito reaction [21,26,27,32,38,42–48]. Reviews that do not deal with this subject have also been published [22,49,50]. In connection with ligand acceleration, it is important to recall the observation made by Baiker's group in 1992: "… rate acceleration and chiral induction may not be of the

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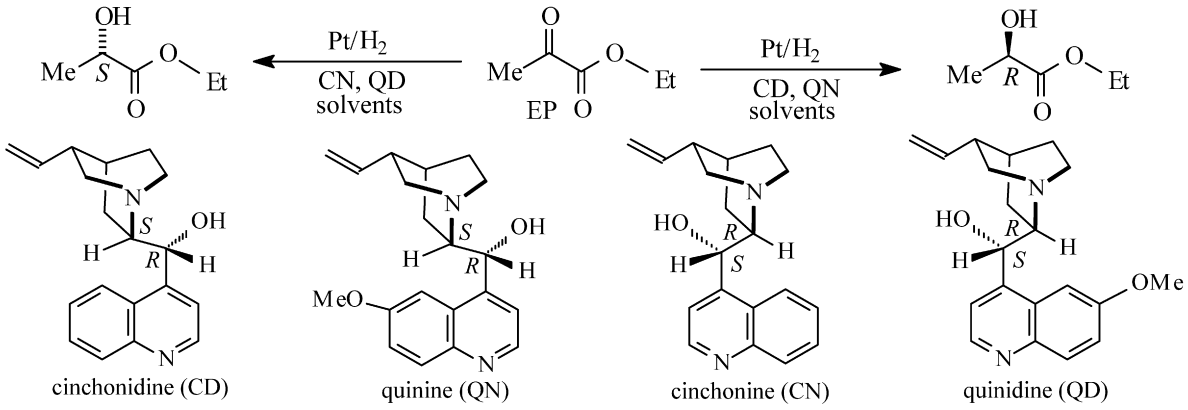


Scheme 1. The Orito reaction.

same origin, although they appear to be correlated" [51], which has apparently not caught the readers' attention. In the coming years, however, experimental data were published on situations where high ee values were attained even though there was no great difference between the rates of racemic and enantioselective hydrogenations [45,52–60]. Moreover in the gas phase hydrogenation the Pt–CD chiral catalyst showed a decrease in reaction rate compared to the unmodified catalyst [61].

These experimental observations as well as catalyst deactivation due to decomposition and oligomerization of EP in the absence of CD and/or H_2 [62–68] led to the suggestion that the origin of RE should be interpreted on the basis of a model other than the one based on ligand acceleration. Experimental evidence for this hypothesis was published by Jenkins et al. in 2005 [69] and Toukoniitty and Murzin in 2006 [70]: "Rate enhancement in the presence of an alkaloid modifier is attributed to the inhibition of pyruvate ester polymerization at the Pt surface and results from reaction occurring at a normal rate at an increased number of sites, not (as was once thought) to reaction occurring at an enhanced rate at a constant number of sites" [69]. "The enantiodifferentiating interactions that induce ee occur between EP and CD whereas the ligand acceleration originates from CD's ability to hinder side reactions, leading to EP decomposition and catalyst deactivation" [70].

The conclusions drawn in refs [69,70] were followed by a debate [71–74] with the following main conclusion according to Mallat and Baiker: "We believe that the chiral modifier induces enantioselection and intrinsic rate acceleration in the Pt-catalyzed hydrogenation of various activated ketones" [74]. In our opinion the experimental data leading to the two different standpoints are not easy to compare, either because catalysts of different types were studied [69], or because the data were obtained under experimental conditions significantly different from those of the Orito reaction (e.g. gas phase [61], low concentration of EP [70]). It has to be noted that, in contrast to his earlier view [70], Murzin very recently comments on the kinetic character of RE [75].

Nearly simultaneously with the debate, a review was published by Blaser and Studer entitled "Cinchona-Modified Platinum Catalysts: From Ligand Acceleration to Technical Processes" [26], in which the authors maintain their earlier standpoint on the role of LA in the enantioselective heterogeneous catalytic hydrogenation of activated ketones: "Kinetic studies aimed at understanding the mode of action of the catalyst revealed that the cinchona modifier not only renders the catalyst enantioselective but strongly accelerates the hydrogenation. This was the first case of ligand acceleration with a heterogeneous catalytic system."

The objective of the present manuscript is to produce further experimental data for elucidate the origin of RE in the Orito reaction. In our opinion the results obtained in the hydrogenation of methyl benzoylformate (MBF), ketopantolactone (KPL) and pyruvic aldehyde dimethyl acetal (PA) as substrates using continuous-flow fixed-bed reactor (CFBR) system under reaction conditions generally applied for the Orito reaction confirmed the intrinsic feature of RE observed in this heterogeneous catalytic reaction.

2. Experimental

2.1. Materials

MBF, PA, KPL, parent cinchona alkaloids (CD, CN, QN, QD) and solvents were from Aldrich or Fluka, and used as received, except MBF (b.p. 391–393 K at 5 Hg mm) and PA (b.p. 325–327 K at 25 Hg mm) were distilled in vacuum using Vigreaux-column. From the catalyst pretreatment methods (high temperature, ultrasound [76–78]) we have used the former method. The catalyst, Engelhard 5% Pt/Al_2O_3 (E4759) was pretreated in a fixed-bed reactor by flushing with 30 mL min^{-1} He at 300–673 K for 30 min then hold in 30 mL min^{-1} H_2 at 673 K for 100 min. After cooling to room temperature in H_2, the catalyst was flushed with He for 30 min and was stored under air until use. Merck 101097 aluminum oxide 90 was used to fill the catalyst cartridge.

2.2. Hydrogenations in CFBR system

Continuous hydrogenations were carried in H-Cube high-pressure continuous-flow system purchased from Thales Nanotechnology Inc. [79]. The experimental set-up has been described in previous publications [80,81]. In the tubular catalyst cartridge of 2 mm inner diameter and 30 mm length the given amount of catalyst was placed and was filled with additional alumina. The catalyst was rinsed 0.5 h with 1 mL min^{-1} flow of toluene/AcOH 9/1 solvent mixture followed by 0.5 h pretreatment with H_2 in the same solvent. After the racemic hydrogenation the reactant and the first modifier were dissolved in the solvent and this solution was delivered to the hydrogenation system via a HPLC pump (Knauer WellChrom HPLC-pump K-120) mixed with H_2 under the desired pressure and passed through the catalyst bed obtaining an ascendant flow of the reaction components. The catalyst cartridge holder was externally cooled to the desired temperature. The modifier was changed by replacing the solutions delivered to the pump. Samples of 1 mL were taken at regular time intervals from the product flow and analyzed [80,81]. Standard conditions were: 50 mg E4759 catalyst, solvent: toluene/AcOH 9/1, liquid flow 1 mL min^{-1}, modifier concentration 0.044 mM, substrate concentration 45 mM, 80 bar H_2 pressure, 283 ± 2 K.

2.3. Product analysis

The products were identified by mass spectrometric (HP 6890 N GC-HP 5973 MSD, HP-1MS, 60 m capillary column) analysis. Conversions and enantiomeric excesses, ee% = ([R] − [S]) × 100/([R] + [S]), were determined by gas chromatography (HP 6890 N GC-FID, 30 m long Cyclodex-B chiral capillary column). Retention times (min): KPL 398 K, 21.65 psi He: 10.6 of (S)-PL, 11.2 of (R)-PL; MBF 383 K, 25 psi He: 21.7 of MBF, 29.9 of (R)-MM, 30.9 of (S)-MM; PA 338 K, 21.65 psi He: 5.2 of PA, 8.6 of (R)-LA, 9.1 of (S)-LA. The reproducibility was ±2%. Turnover frequencies (TOF, h^{-1}) were calculated as described in a recent publication [72]. Transformation of the cinchona alkaloids was checked by ESI-MS measurements (AGILENT 1100 LC-MSD TRAP SL ion-trap MS) operated under positive ion and auto MS-MS mode as described earlier [63,64].

3. Results and discussion

We studied the enantioselective hydrogenation of MBF, KPL and PA in CFBR using the transient method, under experimental conditions similar to those employed by Baiker's group [72,82]. The essence of the transient method is the serial replacement of the cinchona alkaloids serving as chiral modifiers in continuous-flow hydrogenation with others that produce the opposite enantiomer. Continuous sampling allows the determination of changes in ee and conversion. Measurement series were started over unmodified catalyst. After certain time, racemic hydrogenation was followed by the addition of the first cinchona, and continued by replacement of the first one with a second and later with a third one.

The activated ketones to be hydrogenated can be classified into two groups based on their stabilities under the conditions of the Orito reaction. PA, like EP, is a compound capable of enolization; MBF and KPL, however, are not. The products of enolization and of the oligomerization and other transformations of α-methyl ketones are well-known catalyst poisons [62–68], and this deactivation leads to a considerable decrease in enantiodifferentiation and RE. We used the experiences described in [72] for minimizing side reactions, i.e. deactivation. The H-Cube instrument, however, did not allow independent modifier flows as described in Ref. [72]. In contrast to Refs. [67,72], the solvent we used was a 9/1 mixture of toluene/AcOH rather than AcOH, in order to avoid the potential effects of the structural materials of the H-Cube instrument. This circumstance, however, did not prevent the most important conclusions to be drawn, as seen later. The purity of the initial compounds, the conversion of cinchona alkaloids in the course of hydrogenation and the role of potential side reactions were studied by ESI-MS and GC-MS methods.

CFBR measurements were started with EP [83], the most commonly used model compound in the Orito reaction. The objective of these experiments was to demonstrate the suitability of the H-Cube hydrogenator for studying the LA phenomenon using the procedure described by Baiker et al. [72]. The data supplied by the experiments on EP hydrogenation made possible the selection of the experimental conditions [83]. Based on experiments using high-purity EP and assumedly preventing the oligomerization and decomposition of EP (although it cannot be established what exactly happens on the catalyst surface) in their studies using CD, CN and QD as chiral modifiers, Baiker et al. took their stand in favor of the intrinsic character of RE [72].

3.1. Studies on MBF hydrogenation (Figs. 1 and 2)

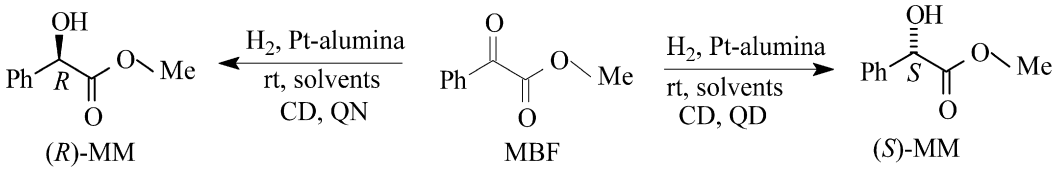
The enantioselective hydrogenation of MBF is shown in Scheme 2. Some of the relevant results of our experiments on MBF hydrogenation are summarized in Figs. 1 and 2. Under the given standard experimental conditions, good mass transport was ensured in the system under a H_2 pressure of 80 bar. In the case of CD feeding the conversion was over 90%. Experiments using catalyst E4759 or its crushed form also indicated good mass transfer, which plays a determinant role especially in enantioselective liquid-phase heterogeneous catalytic hydrogenations [84,85].

Figs. 1 and 2 clearly demonstrate the occurrence of RE in the enantioselective hydrogenations, similar to the case of EP [72], recognized already in the initial phase of the experiments [28–31]. In CFBR studies on the origin of RE we made use of the transient behavior of the cinchonas CD, CN and QN in the hydrogenation of MBF. High ee was to be expected only at nearly 100% conversion, when changes in RE are difficult to detect at the time of the replacement of the chiral modifier [72]. Because of the well-known effect of the adsorption strength of cinchonas on RE [27,86–88], hydrogenation conditions allowing easy determination of the effect of the replacement of the chiral modifier on RE had to be chosen. This means somewhat lower conversion, which can be achieved by applying lower H_2 pressure or less catalyst (see also for KPL). Under such conditions some limitation in mass transfer might occur but, in our opinion, that would not affect the most important conclusions.

The initial conversion in racemic hydrogenation depends on the surface condition of the catalyst. Earlier, it was found that, following the high-temperature pretreatment, the catalyst surface is altered upon standing [16,78]. In addition to freshly pretreated catalyst (e.g. Fig. 1b), we also used catalyst pretreated 1–3 days earlier (e.g. Fig. 1a) that resulted in lower initial conversion. In the racemic hydrogenation the continuous decrease of conversion suggest catalyst deactivation. The larger conversion of enantioselective hydrogenation as compared to racemic hydrogenation points to the importance of the purifying effect of chiral modifiers and/or to the role of the LA concept. These experimental results, however, do not allow differentiation between the two phenomena.

After 40 min hydrogenation over unmodified catalyst (racemic hydrogenation) in case of enantioselective hydrogenation the change of the sense of chirality by replacing CD with CN and again with CD and using the opposite order, that is change of CN to CD and again to CN are shown in Figs. 1a and 1b. The figures show not only the changes in the ee but also in the conversions. From ∼90% (R)-MM in presence of CD the ee changed to ∼60% (S)-MM when CN was fed and then schifted again to ∼90% (R)-MM as effect of feeding CD for the second time.

Changes in conversion due to feeding of various modifiers are easily detected: starting from ∼50% conversion in racemic hydrogenation, the addition of CD increases the conversion to ∼90% (i.e. a significant RE is observed). The conversion of enantioselective hydrogenation is somewhat reduced by CN and is again increased by CD feeding (Fig. 1a). Similar changes in ee and conversion can



Scheme 2. Asymmetric hydrogenation of methyl benzoylformate (MBF) over Pt/Al_2O_3 modified by parent cinchona alkaloids.

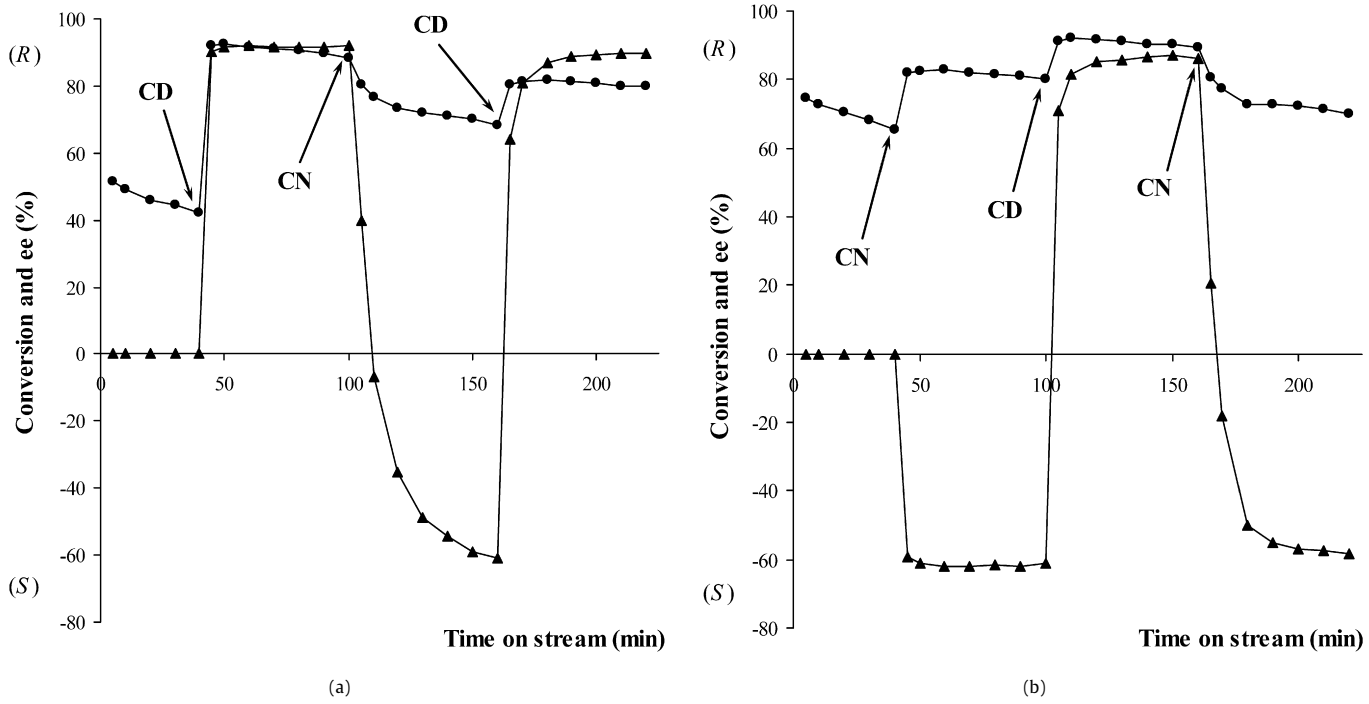


Fig. 1. Transient behavior in MBF hydrogenation using CFBR: changes in conversion (●) and enantioselectivity (▲) by addition—after racemic hydrogenation—of CD followed by CN and again CD (a), and in opposite order (b) using 0.44 mM modifier concentration (otherwise standard conditions, (a) over catalyst stored for 3 days after pretreatment, (b) over freshly pretreated catalyst).

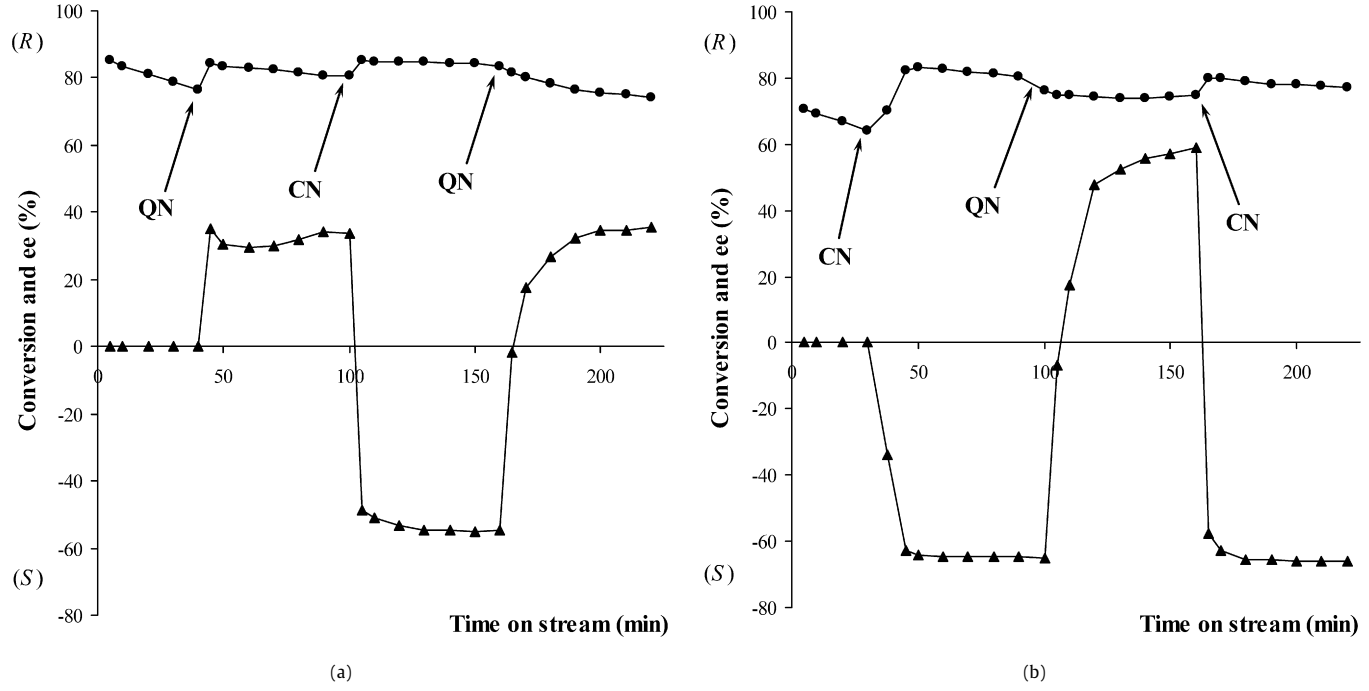
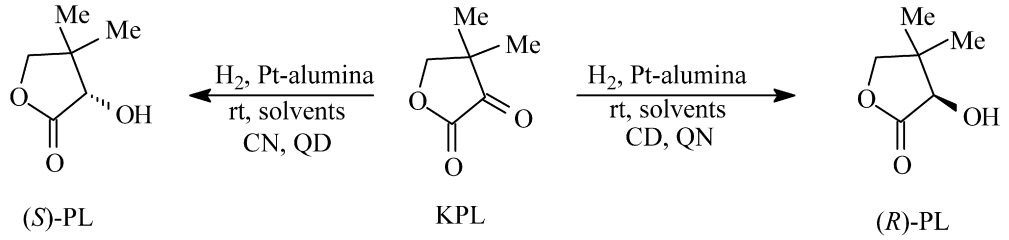


Fig. 2. Transient behavior in MBF hydrogenation using CFBR: changes in conversion (●) and enantioselectivity (▲) by addition—after racemic hydrogenation—of QN followed by CN and again QN (a), and in opposite order (b), for reaction conditions see Fig. 1 ((a) over freshly pretreated catalyst and (b) over catalyst stored for 1 day).

also be observed in the racemic–CN–CD–CN measurements series. Again in this case, the highest conversion is observed in the case of CD feeding: $CD_{conv.} > CN_{conv.} > rac_{conv.}$. Since, according to earlier results, the reaction rate is proportional to the adsorption strength of cinchonas [27,86–88], these measurements also confirm the adsorption strength order: CD > CN.

In our opinion the measurement series presented in Figs. 1a and 1b justifies the assumption of the intrinsic character of RE. In order to interpret RE brought about by CN feeding following racemic hydrogenation (Fig. 1b), one may suppose that RE is a consequence of the so-called purifying effect by CN. However, REs elicited by the effect of subsequently added CD and CN, are indicative of an intrinsic phenomenon, because the suppression of catalyst deactivation of cinchona alkaloids cannot be so different for the individual cinchonas, i.e. it cannot show a regularity of this kind.

Similar interpretations of the racemic–QN–CN–QN and the racemic–CN–QN–CN measurement series (Figs. 2a and 2b) and



Scheme 3. Asymmetric hydrogenation of ketopantolactone (KPL) over Pt/Al_2O_3 modified by parent cinchona alkaloids.

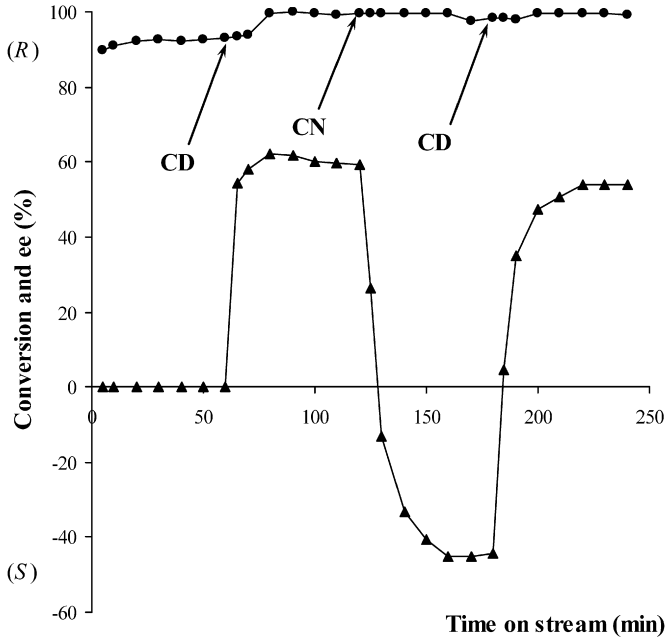


Fig. 3. Transient behavior in KPL hydrogenation using CFBR: changes in conversion (●) and enantioselectivity (▲) by addition—after racemic hydrogenation—of CD followed by CN and again CD under 40 bar H_2 pressure, at 293 ± 2 K and over 30 mg catalyst (otherwise standard conditions).

combination with the conclusions of the measurements shown in Figs. 1a and 1b yielded the adsorption strength order: CD > CN > QN, which is not identical with the order established for EP hydrogenation under similar conditions (CD > QN > CN) [83]. The difference is presumably due to the different properties of the complexes formed by cinchona alkaloids adsorbed on the catalyst surface and the substrates to be hydrogenated.

3.2. Studies on KPL hydrogenation (Figs. 3 and 4)

The enantioselective hydrogenation of KPL is illustrated in Scheme 3. Experimental evidence to date [87,89] showed that, among activated ketones, hydrogenation of KPL is the fastest. Therefore conditions significantly milder than those used for MBF had to be chosen in order to be able to follow and evaluate the conversions of hydrogenation in the presence and absence of various modifiers. As shown in Fig. 3, conversions exceeded 90% even under these milder conditions. The use of KPL "as received" usually allows ee values of 50–60% to be attained in hydrogenations in toluene/AcOH 9/1. In the representative figures selected from numerous measurement series the 60 min racemic hydrogenation on prehydrogenated catalyst was followed by hydrogenations on modified catalysts, also 60 min each.

Similarly to Section 3.1, Figs. 3 and 4 represent the conversions and ee values of the measurement series racemic–CD–CN–CD (Fig. 3), racemic–QN–CN–QN (Figs. 4a and 4b) and racemic–CN–QN–CN (Fig. 4c). Fig. 3 reveals that CD feeding after racemic hydrogenation produced (*R*)-PL in 60% ee and the subsequent CN feeding yielded (*S*)-PL in ~45% ee, followed by another inversion on feeding again CD. Conversion is modified slightly (since even the conversion in racemic hydrogenation is close to 100%) but perceptibly by the various feeding sequences. Identical changes in ee and conversion values can also be observed in the racemic–CN–CD–CN measurement series. The hydrogenation is the fastest on CD-modified catalyst, somewhat slower in the case of CN and the slowest on unmodified catalyst (racemic hydrogenation). Thus, RE also occurs in the enantioselective hydrogenation of KPL.

Important conclusions can be drawn from the experiments using QN–CN cinchona pair (Figs. 4a, 4b and 4c). Changes in conversion are more obvious in these runs than as presented in Fig. 3, which spectacularly showed and consequently demonstrated the changes in RE caused by different cinchona alkaloids, in accordance with the adsorption abilities of cinchona–KPL complexes. The course of all measurement series (the slopes of the curves) clearly show that CD replaces, i.e. desorbs CN from the Pt surface faster than vice versa, and CN desorbs QN from the surface faster than vice versa. By reusing the catalyst (Fig. 4b), the racemic hydrogenation that followed the measurement series presented in Fig. 4a showed some residual ee (the wash with MeOH was too short). After the measurement series shown in Fig. 4b, the catalyst was washed with MeOH for 2 h and the subsequent reuse (Fig. 4c) in racemic hydrogenation no more indicated the presence of any active chiral centers. In our opinion the measurement series in Figs. 4a, 4b and 4c convincingly demonstrate that—similarly to MBF—in addition to the purifying effect of cinchonas, LA is also present in RE.

The TOF values calculated from the data series presented in Fig. 4a showed well that the as effect of QN the TOF increased with ~20% compared with the racemic hydrogenation, which further varied with ~10–10% on subsequent CN and QN feeding. In our opinion in the first TOF enhancement both the so-called purifying effect of the cinchona alkaloid and the LA played role, while the subsequent changes in the TOF may be ascribed to LA. To sum up the above, the order of conversions is: $CD_{conv.} > CN_{conv.} > QN_{conv.}$, and that of adsorption strength is CD > CN > QN, an order that is identical with that identified for MBF (Section 3.1.) and different from that observed in the course of EP hydrogenation [83].

3.3. Studies on PA hydrogenation (Figs. 5 and 6)

The enantioselective hydrogenation of PA is outlined in Scheme 4. PA is a special case of the hydrogenation of activated ketones under the conditions of the Orito reaction, in as much as enantioselective hydrogenation in this case is associated with high ee even at low reaction rates [15,16,90,91]. Ee values of over 90% can be attained on Pt modified by either of the four parent cinchonas in AcOH [20,91], whereas hydrogenation in toluene produces significantly lower ee values (50–60%). Because of this, in the solvent mixture chosen for these studies (toluene/AcOH 9/1) ee values exceeding 90% were not expected; however, to allow comparison with the other substrates, it was expedient to adhere to the above solvent mixture. Because of the slow hydrogenation rate of PA,

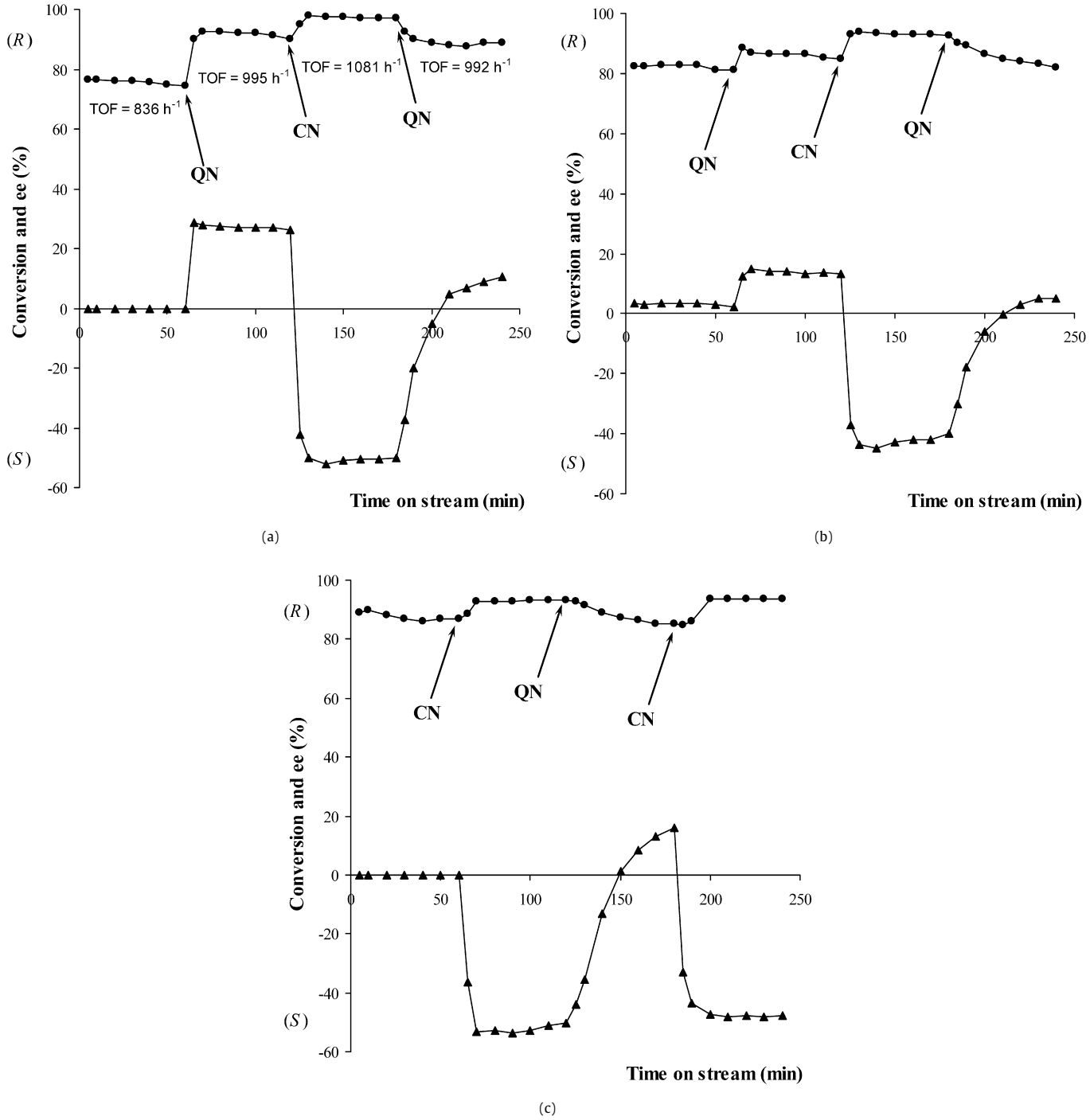
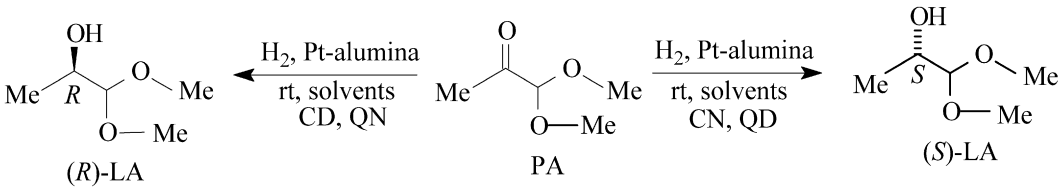


Fig. 4. Transient behavior in KPL hydrogenation using CFBR: changes in conversion (●) and enantioselectivity (▲) by addition—after racemic hydrogenation—of QN followed by CN and again QN (a,b), and in opposite order (c) (for reaction conditions see Fig. 3, using (a) fresh catalyst, (b) reused after (a) series and (c) reuse after (b) series).

however, conditions somewhat more stringent than those applied in the previous cases were needed, namely a larger amount of catalyst (100 mg), a higher cinchona concentration (1–2 mM) and a higher temperature (293 instead of 283 K) to accelerate product desorption. These were the problems that were highlighted by the measurement series outlined in Figs. 5a and 5b, in which a cinchona concentration of 0.044 mM was used. In Fig. 5a the unexpected decrease in ee brought about by the time on stream over QN- and QD-modified catalyst is, in our opinion, a consequence of slow product desorption. The high ee observed after the 160 min reaction time elicited by CD feeding and the maximal conversion on Pt over the entire measurement cycle are quite conspicuous (Fig. 5a). The situation was somewhat improved by slightly increasing the temperature (Fig. 5b), but ee decreased and at the end of the measurement series, conversion decreased even relative to racemic hydrogenation (from 17 to 11%), due to the relatively long reaction time and, more importantly, to the higher temperature. The course of RE in the presence of the four parent cinchonas, however, appears very characteristically even in these preliminary experiments.

In view of the fact that RE is well detectable in PA hydrogenation catalyzed by Pt–CD and Pt–CN (Figs. 5a and 5b), further experiments were performed on the Pt–CN–Pt–QN catalyst system. Experimental parameters (temperature, modifier concentration, H_2



Scheme 4. Asymmetric hydrogenation of pyruvaldehyde dimethyl acetal (PA) over Pt/Al_2O_3 modified by parent cinchona alkaloids.

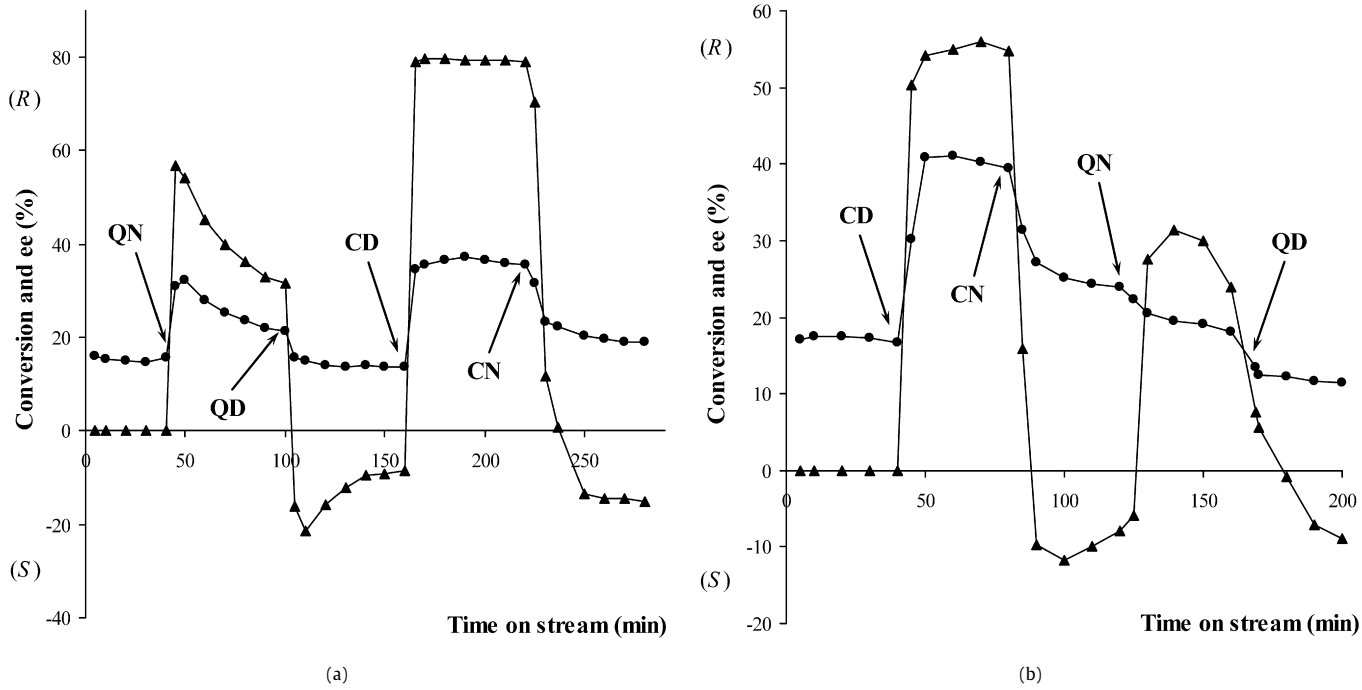


Fig. 5. Transient behavior in PA hydrogenation using CFBR: changes in conversion (●) and enantioselectivity (▲) by addition—after racemic hydrogenation—of QN followed by QD, CD and finally by CN at 283 ± 2 K (a), or addition of CD followed by CN, QN and QD at 293 ± 2 K (b) over 100 mg catalyst (otherwise standard conditions).

pressure, reaction time) were varied in order to optimize the reaction conditions; two characteristic measurement series are presented in Figs. 6a and 6b. Maximal conversions attained are in the range of 50–60%; the ee value for Pt–CD was ~75% (*R*), whereas in the case of Pt–CN catalyst formation of the (*S*) enantiomer in a somewhat lower ee was observed. In the present case, measurement series consisted 40 min cycles, i.e. a 40 min racemic hydrogenation was followed by 40 min hydrogenations on various modified catalysts. Fig. 6a and 6b show changes in the conversion and ee values of the racemic–QN–CN–QN and racemic–CN–QN–CN measurement series, respectively, as a function of time on stream. Changes in conversion on Pt–CN and Pt–QN catalysts are less spectacular than those observed in the case of MBF and KPL. By the evidence of the two measurement series it appears as if hydrogenation on Pt–CN catalyst proceeded at a slightly higher conversion than on the Pt–QN catalyst.

Although the catalyst is strongly deactivated in the course of the time on stream—probably because of the enolization tendency of PA—the occurrence of RE relative to racemic hydrogenation, however, is unambiguous also in the case of PA. We think that because of the multiply-proven differences between the adsorption strengths of cinchonas, the intrinsic character of RE cannot be excluded neither in case of PA. It is remarkable that in the course of racemic hydrogenation, conversion is not changed during the time on stream, even though it is slightly and continuously decreasing in the entire range studied (160–280 min), whereas changes in conversion over modified catalyst show a picture compatible with the intrinsic character of RE. In our opinion the change in RE brought about by different cinchonas can be interpreted on the basis of its intrinsic character. To sum up we obtained the conversion order: CD > CN > QN > QD and the same order of adsorption strength values: CD > CN > QN > QD, respectively, an order nearly identical with that determined for MBF and KPL.

4. Conclusion

Hydrogenation results obtained under the generally utilized experimental conditions of the Orito reaction, in the CFBR system, with methyl benzoylformate, ketopantolactone and pyruvic aldehyde dimethyl acetal substrates on modified and unmodified Pt catalyst, in racemic–cinchona 1–cinchona 2–cinchona 1 measurement series confirm the intrinsic nature of RE. The order of the conversions of the hydrogenations taking place on unmodified (Pt_{um}) and modified catalysts (Pt–CD, Pt–CN, Pt–QN, Pt-QD) is the following: Pt–CD > Pt–CN > Pt–QN > Pt–QD > Pt_{um}. In our opinion such a regular dynamics of the changes in conversions as observed in the presented measurements series is caused by the certain cinchona alkaloids. Consequently, these new experimental data presented in this manuscript not only suggest the validity of the LA based interpretation of RE [29], but also confirm its general character in the conditions of the Orito reaction. As regards the results presented in Refs. [69,70], they reflect phenomena taking place under conditions other than those of the Orito reaction, which are also able to elucidate many of the experimentally observed effects.

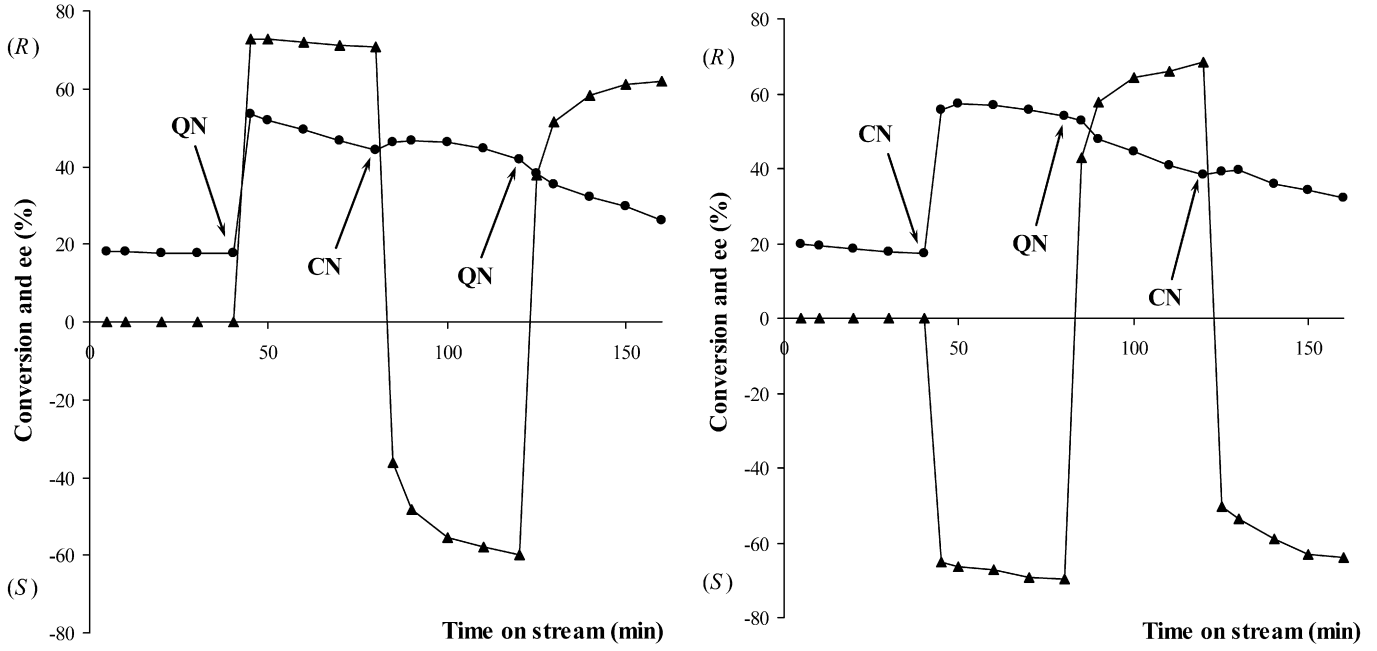


Fig. 6. Transient behavior in PA hydrogenation using CFBR: changes in conversion (●) and enantioselectivity (▲) by addition—after racemic hydrogenation—of QN followed by CN and again QN (a), and in opposite order (b) using 2 mM modifier concentration, at 293 ± 2 K, over 100 mg catalyst (otherwise standard conditions).

Manifold studies carried out to date have verified that in the Orito reaction (i) cinchona alkaloids inhibit the deactivation of the Pt catalyst, (ii) they form chiral surface active sites and (iii) surface intermediate complexes with the substrate. These three effects of cinchonas are responsible for enantioselection and RE. The contribution of these three effects to chiral induction and RE depend on numerous, probably as yet unknown factors. The role of any of the above effects cannot be doubted. Based on the results to date, in our opinion the novel experimental data published in the present manuscript confirm that LA cannot be excluded from the interpretation of RE occurring in the Orito reaction.

Since it cannot be known what exactly is happening on the surface of Pt, indirect experimental data are needed to determine the dominant character of the various factors in the context of the most important parameters of the Orito and Orito-type reactions (catalyst, substrate, modifier, experimental conditions of hydrogenation). Among others it should be revealed the role of the following phenomena: (i) adsorption–desorption processes, (ii) the role of irreversible adsorption of modifiers, (iii) continuously restructuring of Pt surface during hydrogenation, (iv) structure of intermediate complexes, etc. [16,92–100]. It must be stressed, the regularities of the hydrogenation of ketones [101] hold true for the enantioselective hydrogenations only with reservations, because hydrogenation of the modifier-ketone complex rather than that of the ketone has to be considered, which has also been confirmed by the results of nonlinear phenomenon studies in the heterogeneous enantioselective hydrogenation of activated ketones.

One of the immediate tasks of the near future could be to elucidate (i) the so-called unexpected inversion recognized in hydrogenations on Pt modified with certain cinchonas [102,103] and (ii) rate deceleration due to repulsive interactions arising among modifiers, certain substrates and Pt as a consequence of stereochemical factors (e.g. [104], where there is high ee, but no RE).

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