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Effect of cinchonidine and dissolved oxygen in continuous enantioselective hydrogenation of ethyl pyruvate

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Continuous hydrogenation of ethyl pyruvate was carried out in a fixed bed reactor over a Pt/SiO_2 fiber catalyst with step changes in cinchonidine and oxygen feed. Presence of cinchonidine always led to a rate deceleration and appearance of enantioselectivity. Trace amounts of O_2 induced overall rate acceleration. A mechanism is proposed which includes ethyl pyruvate hydrogenation and decomposition.

KEY WORDS: ethyl pyruvate; cinchonidine; oxygen effect; continuous hydrogenation; catalyst deactivation.

1. Introduction

Cinchonidine (CD) modified Pt catalysts for hydrogenation of α-keto esters were discovered by Orito *et al.* [1] in late 1970's. The reaction has been studied in detail in *batch reactors* using ethyl pyruvate (EtPy) as reactant. Excellent reviews are available [2–5], which describe the present status of understanding of the Orito reaction mechanism. Trace amounts of cinchonidine induce high enantiomeric excess (ee) >95% of (*R*)-ethyl lactate under optimized conditions. Furthermore, the enantioselective hydrogenation proceeds with up to 100-fold higher reaction rate [6] than the racemic hydrogenation in *batch reactors*.

The effects of dissolved gases in the Orito reaction have been studied in batch reactors [7,8] and by means of *in situ* IR spectroscopy [9], as oxygen was found t be of crucial interest. The original catalyst preparation procedure described by Orito *et al.* [1] involved stirring of the catalyst and modifier solution in air. The presence of small amounts of oxygen is particularly beneficial for the reaction resulting in increased ee and hydrogenation rate. Based on RAIRS measurement [9] it was concluded that hydrogen facilitates CD adsorption on Pt and helps to remove adsorbed CO, whereas oxygen only removes adsorbed CO. In an earlier study the role of oxygen was to reduce CD coverage on Pt in such a way that a larger fraction of the Pt surface would be available for ethyl pyruvate hydrogenation [8].

There are only few reports on continuous operation [10,11] in enantioselective hydrogenation and more specifically on application of transient experiments, were pulses of CD or step changes in CD flow during continuous operation have been investigated. The rate acceleration effect, also called the ligand acceleration effect, has not been studied in continuous operation. Therefore, the aim of this work is to study the effect of oxygen and the role of the modifier in the rate acceleration and increase of ee in *continuous reactor* by means of transient experiments.

2. Experimental

EtPy hydrogenation was studied in a continuous fixed bed reactor ($d_i = 10$ mm) over a 5% Pt/SiO_2 (fiber) catalysts (D = 30%, $d_{Pt} = 4$ nm) using toluene (Baker, >99.5%) as a solvent and cinchonidine as a catalyst modifier (Fluka 27350, >98%). The characterization of the catalyst has been described previously [12]. The experimental setup was described in detail [13], thus only pertinent information is provided below. Additional experiments were carried out with commonly used Engelhard (E4759) 5% Pt/Al_2O_3 powder catalyst. By varying the catalyst amount (0.5–0.1 g) EtPy conversion was adjusted initially below 100%. The liquid and H_2 flow rates were 3.0 and 100 $cm^3\ min^{-1}$, respectively. Prior to the experiments the catalyst was reduced *in situ* at 400 °C under H_2 (1 bar). EtPy (Fluka 15960, >97%) was vacuum distilled before the reaction. The reactant solution was degassed with Ar or saturated with air or H_2 for 40 min prior commencing the reaction. The hydrogenations were carried out at 25 °C and 5 bar H_2. Concentration of EtPy and CD were 0.025 or 0.1 and 3.4×10^{-4} mol dm^{-3}, respectively. Pulse experiments were carried out by injecting 0.5 and 1.0 cm^3 pulses of CD (1.7×10^{-5} and 3.4×10^{-5} mol dissolved in acetic acid) or 0.5 and 1.0 cm^3 oxygen (3 bar) pulses during reaction with a HPLC injection valve. The reaction was

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monitored by taking samples after the catalyst bed for gas chromatographic analysis. Full base line separation of all reaction components was observed with utilized β-dex 225 (Supelco) chiral column. Peaks were identified and the calibration was carried out using EtPy and (−)-ethyl lactate (Fluka 77367, >99%). The enantiomeric excess of (*R*)-ethyl lactate is defined as $ee = (R - S)/(R + S) \times 100\%$ where R and S are concentrations of (*R*)- and (*S*)-ethyl lactate, respectively. Furthermore, it was verified that experiments were conducted in a region free of mass transfer limitations.

3. Results

3.1. The effect of cinchonidine

In analogy to batch reactor experiments it was expected that CD would induce rapid increase of reactant conversion i.e., rate acceleration. Therefore, the reaction should be carried out in the absence of modifier reasonably below 100% conversion in order to observe rate acceleration effects. Previously ethyl pyruvate and ketopantolactone were hydrogenated in continuous mode [10], however, in large excess of catalyst and therefore, the conversion remained virtually at 100% during the whole experiment and no catalyst deactivation or rate acceleration could be observed.

Reaction was started by pumping solution of EtPy + CD + toluene into the reactor where the *in situ* reduced catalyst was kept under flowing hydrogen (100 cm^3/min). Enantioselectivity increased with increasing time-on-stream and after a certain time, dependent of liquid flow rate and CD concentration, the ee attained a steady-state value. The slow increase of ee is related to the specific features of continuous operation mode. The inlet concentration of CD is low and the amount (assuming that rapid adsorption occurs) is not sufficient to cover the catalyst instantaneously with CD. Therefore, the ee gradually increases with time-on-stream as more and more CD adsorbs on the catalyst surface. When the feeding of CD was stopped ee started gradually to decrease. The conversion of the reactant decreased slightly with increasing time-on-stream indicating catalyst deactivation. Gradual catalyst deactivation in continuous operation has been reported also for isopropyl-4,4,4-trifluoroacetate [14] and 1-phenyl-1,2-propanedione [13]. In enantioselective EtPy hydrogenation in ethanol a decrease of activity was reported [15] during repeated use of the catalyst, indicating that also in batch reactor some catalyst deactivation takes place.

Under optimized conditions ee of 76% at 100% EtPy conversion could be obtained, which is a reasonably high value for a SiO_2 supported catalyst in toluene.

The second set of experiments was carried out by starting the reaction as racemic hydrogenation, i.e., without CD, and after 70 min time-on-stream the feeding of CD was initiated (figure 1). In these experiments the reactant solutions were saturated with hydrogen prior to the experiment. In analogy with the *batch reactor* results [2–6] considerable rate acceleration could be expected as the CD flow was initiated. However, the situation was quite the opposite (figure 1). The presence of CD always resulted in gradual development of enantioselectivity, which could be expected in continuous operation mode. However, no overall rate acceleration could be observed when cinchonidine feed was initiated. Moreover, the conversion of EtPy decreased rapidly when CD was introduced into the reactor. This can be rationalized keeping in mind that CD is known to adsorb strongly on Pt surface. Therefore, the decrease of conversion in the presence of CD is probably due to the increasing coverage of strongly adsorbed CD, which blocks some of the active Pt surface. This kind of CD poisoning effect has been reported with acetophenone derivatives [16]. The experiments at low and high EtPy conversions

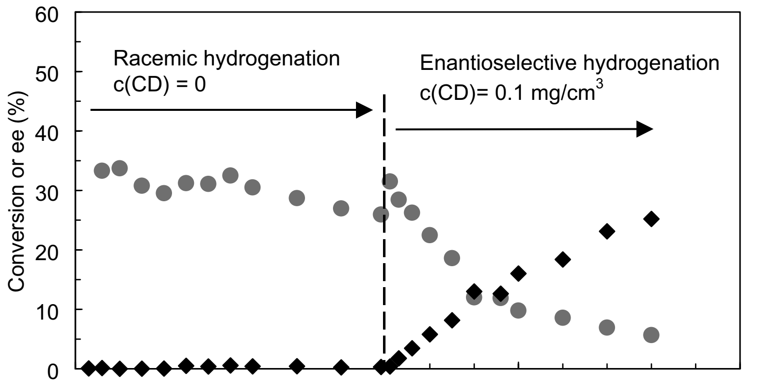


Figure 1. The influence of CD on EtPy conversion (▶) and enantiomeric excess (▶) over Pt/SiO_2 catalysts, $c(\text{EtPy}) = 0.025$ mol dm^{-3}, m(cat) = 110 mg.

demonstrated that introduction of CD induced *overall rate deceleration* combined with enantioselectivity development in continuous reactor. In order to verify that these observations are not just limited to the utilized 5% Pt/SiO_2 catalyst with rather specific support properties additional experiments were carried out using 5% Pt/Al_2O_3 catalyst powder (E4759). Analogous CD induced rate deceleration was observed also with the 5% Pt/Al_2O_3 catalyst. This indicates that the results are not just a specific feature of the utilized 5% Pt/SiO_2 (fiber) catalyst, but can be taken as general observations for Pt catalysts.

Third set of experiments was carried out by injecting CD pulses during racemic reaction. In pulse experiments the utilized CD was dissolved in acetic acid in order to guarantee dissolution of relatively large amount of CD. Solution of EtPy and toluene was flowed through the reactor (standard racemic reaction) and at 40 and 80 min time-on-stream pulses ($V_{\text{pulse}} = 0.5$–$1.0\ \text{cm}^3$) of CD dissolved in acetic acid were injected into the reactor. Interesting results can be seen form figure 2. Instantaneously, as the pulse of CD was injected the activity decreased considerably (EtPy conversion decreased from 40% to 20%) verifying that CD induced catalyst deactivation. At the same time instantaneously ee is obtained, which gradually decreases with increasing time-on-stream. It can be seen that after CD pulse, as the ee decreases, the activity (conversion of EtPy) slightly increases and attains a steady-state level. When the second pulse of CD was injected again an additional drop in activity (EtPy conversion decreased from 20% to 15%) was observed with a peak of enantioselectivity.

These findings indicate that the cinchonidine in fact decreases activity. Furthermore, the enantioselectivity appearance was always accompanied by a decreased activity. Summarizing, no rate acceleration could be observed when CD was introduced under experimental conditions used in this work. In an earlier study Margitfalvi *et al.* [17] also arrived into conclusions, based on CD injection experiments in batch reactor that the rate acceleration and enantiodifferentiation might not be of same origin. These observations indicate that the observed apparent rate acceleration effect in a batch reactor might not be simply caused by "ligand-accelerating" properties of CD as conventionally believed but more likely is a complex phenomenon where additional factors like catalyst deactivation play a central role.

It is noteworthy to mention that although there are several reports in the literature on the rate acceleration for other substrates than ethyl and methyl pyruvate hydrogenation, the lack of overall rate acceleration in connection with heterogeneous asymmetric catalysis is not that uncommon. Batch reactor experiments with ethyl benzoylformate [18] and with methyl pyruvate over Ir-CD [3], have shown lower or equal rates for modified catalysts. No rate enhancement was observed in the hydrogenation of ethyl nipecotinate over Pd-CD catalysts [19], and in the hydrogenation of trifluoroacetophenone [20] derivatives. A decrease of rate in hydrogenation of hydroxymethylpyrone [21] and of 2-methyl-2-pentenoic acid [22] over CD modified Pd/Al_2O_3 has been reported. In 1-phenyl-1,2-propanedione [23] hydrogenation, no overall rate acceleration was obtained either. These observation are not limited to liquid-phase reaction, as in gas phase hydrogenation of methyl pyruvate no rate acceleration could be observed either [24]. Therefore, it can be concluded that the overall rate acceleration is by no means a general feature of asymmetric heterogeneous catalysis.

3.2. The effect of dissolved oxygen

In order to penetrate deeper into the phenomenon of rate acceleration it was deemed important to study effects, which were also reported to lead to reaction rate increase. Presence of O_2 has been beneficial for the Orito reaction and originally the catalyst preparation was

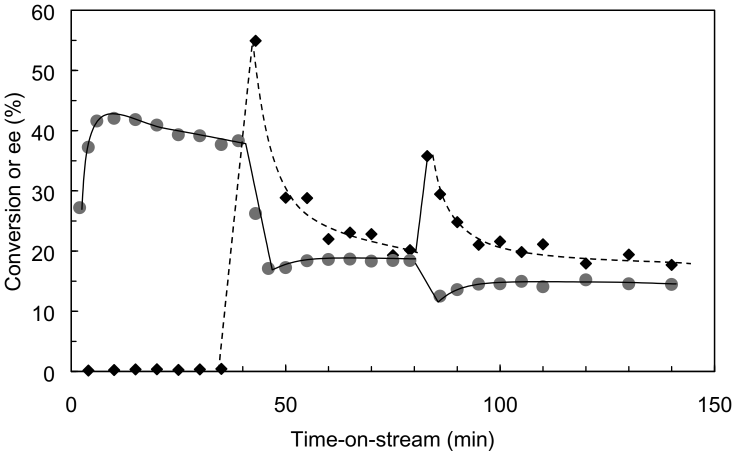


Figure 2. The effect of cinchonidine pulses during racemic hydrogenation; 0.5 cm^3 pulse (at 40 min) and 1.0 cm^3 pulse (at 80 min) of CD dissolved in acetic acid. Symbols: conversion of EtPy (▶) and enantiomeric excess ee (▶), $c(\text{EtPy}) = 0.1\ \text{mol dm}^{-3}$, m(cat) = 120 mg.

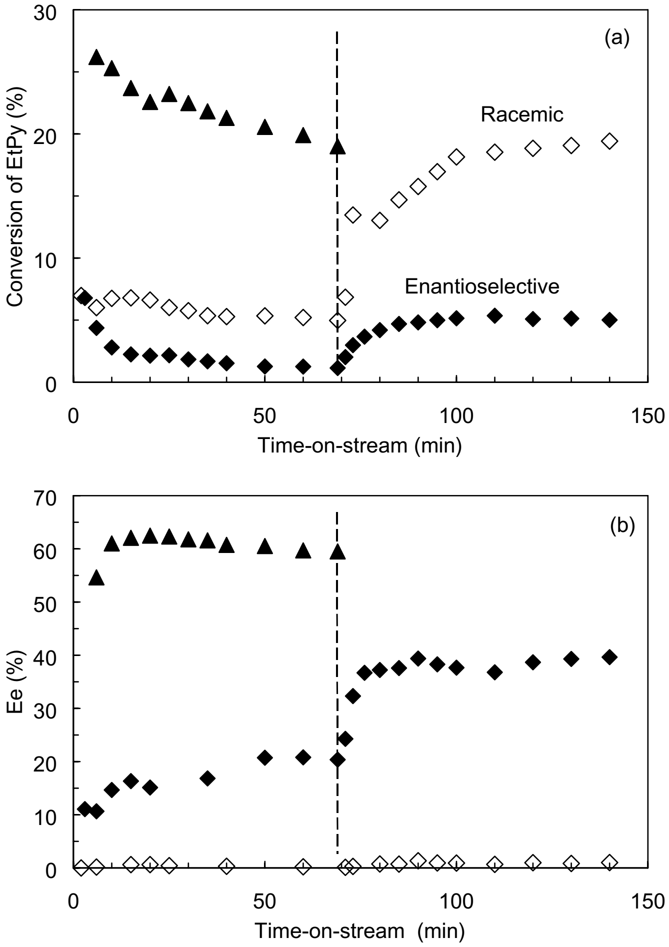


Figure 3. Hydrogenation using aerobic and Ar degassed solutions. Symbols: (▶) aerobic solution with CD, (M) initially anaerobic no CD and switch to aerobic at 70 min and (▶) initially anaerobic with CD and switch to aerobic at 70 min. $c(\mathrm{EtPy}) = 0.1$ mol dm^{-3} and m(cat) = 120 mg.

described to include 20 h stirring of the catalyst and CD in the presence of air. Introduction of air has been reported to induce rate acceleration in a batch reactor [7] as well.

In the present study the role of O_2 was investigated by utilizing Ar or air saturated (40 min saturation prior to reaction) reactant solutions with and without CD. As the reaction was started with Ar degassed solution, the EtPy conversion was initially 7% both in racemic and enantioselective hydrogenations (figure 3(a)). In enantioselective hydrogenation the conversion decreased rapidly with increasing time-on-stream supporting the fact that CD causes catalyst deactivation and rate deceleration by covering the Pt surface. After 70 min time-on-stream the feed was switched from Ar saturated to air saturated solutions (the liquid-phase composition otherwise identical) and notable effects were observed. The EtPy conversion increased rapidly from 1% to 5% and 5% to 20% in enantioselective and racemic hydrogenation, respectively (figure 3(a)). Simultaneously the ee exhibited a rapid increase from 20% to 40% (figure (3b)).

In order to verify that the observed rate acceleration and enhanced ee were due to O_2, several experiments were carried by injecting 0.5 and 1.0 cm^3 pulses of O_2 into the reactor (figure 4) during the continuous experiment. Always the pulse of O_2 induced rapid rate acceleration and improved the ee whenever CD was present. The positive effect in pulse experiments was reversible and after the O_2 pulse the conversion and ee started to decrease gradually towards the initial level, which was before the O_2 pulse.

By comparison the reaction was started with aerobic solution containing CD (figure (3a)). Initially the conversion was fourfold higher compared to the anaerobic situation. Also the steady-state ee was three times higher (ee = 64%) compared to the anaerobic situation (figure 3b). Furthermore, as after 70 min time-on-stream a switch from air to Ar saturated solution was made no significant differences could be observed in ee and EtPy conversion. This indicates that over a modified catalyst, i.e., catalyst in steady-state covered by CD, the absence of O_2 does not induce rapid deactivation. However, when the catalyst surface is initially free of CD the

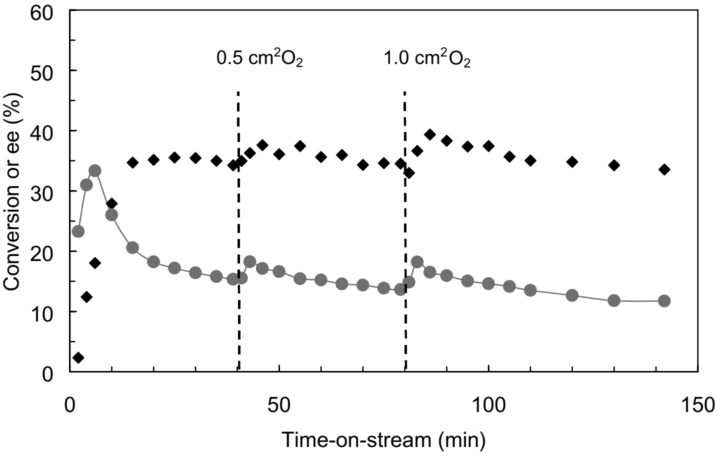


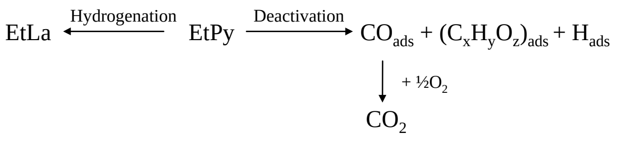
Figure 4. Effect of oxygen pulses (0.5 and 1.0 cm^3, 3 bar) during EtPy hydrogenation. Symbols: enantiomeric excess ee (▶) and EtPy conversion (▶). c(EtPy) = 0.1 mol dm^{-3}, m(cat) = 120 mg.

presence of trace amounts of O_2 is needed for maintaining high activity and high ee.

The results demonstrate clearly that trace amounts of O_2 induced significant overall rate acceleration and enhancement of ee (figure 3). The O_2 effects can be explained taking into account EtPy decomposition during hydrogenation, which produces CO and $C_xH_yO_z$ leading to catalyst deactivation [2] (scheme 1). The EtPy decomposition of Pt has been proposed based on IR measurement on Pt/Al_2O_3 catalysts exposed to EtPy [25]. The schematic representation of the situation where the EtPy undergoes parallel hydrogenation and deactivation reactions is given in scheme 1. The role of trace amounts of O_2 is thus to continuously oxidize the formed CO to CO_2 and therefore prevent catalyst deactivation. Such a beneficial effect of oxygen is not specific for asymmetric catalysis and has been reported for cinnamyl alcohol oxidation, where oxidative removal of adsorbed CO results in considerable rate acceleration [26].

4. Discussion

In present work, CD induced always rate deceleration (both in step change and pulse experiments) in continuous reactor. Cinchonidine is known to adsorb strongly on Pt and it can thus reduce the fraction of free Pt surface leading to decreased hydrogenation rate. However, this is against previous experimental observations, which confirm that presence of CD increases considerably the overall reaction rate [2–6].



Scheme 1. Deactivation and hydrogenation routes of ethyl pyruvate (EtPy) and subsequent oxidation of CO to CO_2.

The main differences between previous batch experiments and present work are the relatively low EtPy concentration (0.025 or 0.1 M) and hydrogen pressure (5 bar) used. Also it can be noted that the ee in the present work was relatively low (typically between 30 and 60%). At the same time Blaser *et al.* [27] previously reported 2.4 and 4.6-fold rate acceleration at 31% and 61% ee, respectively. Based on this one can expect noticeable rate acceleration already at relatively low ee values observed in the present work. Furthermore, the low hydrogen pressure cannot explain the observations as relatively high ee and rate acceleration can be observed already at 1 bar H_2 pressure [17]. The main difference and the possible cause for the lack of rate acceleration can be attributed to low EtPy concentration (0.025 or 0.1 mol dm^{-3}) used in the present investigation. To confirm this hypothesis, additional experiments were carried in a batch reactor over a 5 wt% Pt/Al_2O_3 catalyst in toluene (10 bar H_2, $c_{EtPy} = 0.01$ or 2.0 mol dm^{-3}, $c_{CD} = 3.4 \times 10^{-4}$ mol dm^{-3}, $T = 15$ °C). Details about the catalyst characterization and hydrogenation procedure can be found in [23]. At 0.01 mol dm^{-3} concentration of EtPy a rate deceleration ($R_{e.s.}/R_{rac.} = 0.5$) with respect to racemic hydrogenation in batch reactor was observed with ee of 80%. In analogy with previous hydrogenation results, at high EtPy concentration a six-fold rate acceleration ($c_{EtPy} = 2.0$ mol dm^{-3}, $R_{e.s.}/R_{rac.} = 5.9$) could be observed with ee of 85%. Consequently, CD induces rate deceleration at low EtPy concentration both in batch and continuous reactors, whereas CD induced rate acceleration is observed at high EtPy concentration. The ligand acceleration/deceleration dependence on the EtPy concentration is thus strongly linked to the effect of catalyst deactivation (caused by side reactions of EtPy) on apparent hydrogenation rate. The latter could explain also why relatively strongly adsorbing organic molecules (e.g. quinoline, quinuclidine), which are nonchiral nevertheless cause apparent rate acceleration in methyl and ethyl pyruvate hydrogenation [16,28,29] as i.e., they in fact slow down side reactions, catalyst deactivation. This is then seen as overall activity increase (rate acceleration) with respect to racemic hydrogenation. However, more detailed investigation is needed to quantify the role of EtPy concentration on the ligand acceleration effect.

An excellent review [2] has classified three types of side reactions namely condensation of EtPy catalyzed by CD [30], rapid Pt catalyzed polymerization of methyl pyruvate [31] in the absence of CD and hydrogen, and decomposition of alcohols and ketones on Pt [24] which all can influence the hydrogenation rate. The decomposition of EtPy on Pt produces CO and strongly adsorbed $C_xH_yO_z$ [25] (scheme 1), which leads to catalyst deactivation. This offers a plausible explanation for the observed oxygen effects, i.e., the role of oxygen is to regenerate the catalyst by oxidizing the adsorbed CO to CO_2 and thus maintaining a high catalyst activity for the hydrogenation reaction. The initial reaction rate (figure (3a)) in aerobic hydrogenation was fourfold higher than the anaerobic hydrogenation rate.

5. Conclusions

The ethyl pyruvate hydrogenation at low concentrations over Pt in continuous and batch operation modes indicate that cinchonidine induced *rate deceleration* and enantioselectivity. This indicates that the observed apparent rate acceleration effect might not be simply caused by "ligand-accelerating" properties of CD as conventionally believed but more likely is a complex phenomenon where additional factors like catalyst deactivation play a central role. A possible explanation for the observed lower rates of racemic hydrogenation at higher ethyl pyruvate concentration in batch reactors could be that in the absence of cinchonidine catalyst deactivates rapidly due to side reactions, i.e., ethyl pyruvate decomposition and polymerization. In the presence of cinchonidine the side reactions cannot proceed with as high rate as in the absence of cinchonidine leading to apparent rate acceleration with respect to racemic hydrogenation. Trace amounts of oxygen have beneficial effect on both rate an enantiomeric excess in continuous operation, which can be explained by oxidative removal of surface impurities e.g., CO. The present study suggests that the overall rate acceleration in α-keto ester hydrogenation could be accounted by catalyst deactivation effects and is not associated with intrinsic kinetics of enantioselective α-keto ester hydrogenation.

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