# The First Case of Competitive Heterogeneously Catalyzed Hydrogenation using Continuous-Flow Fixed-Bed Reactor System: Hydrogenation of Binary Mixtures of Activated Ketones on Pt-Alumina and on Pt-Alumina-Cinchonidine Catalysts

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Abstract Under the experimental conditions of the Orito reaction the competitive hydrogenations of four binary mixtures of ethyl pyruvate (EP), methyl benzoylformate (MBF), pyruvic aldehyde dimethyl acetal (PA) and 2,2-diethoxyacetophenone (DAP) on unmodified Pt/Al<sub>2</sub>O<sub>3</sub> (racemic hydrogenation) and catalyst modified by cinchonidine (chiral hydrogenation) were studied using continuous-flow fixed-bed reactor system (CFBR). Conversions of chiral and racemic hydrogenations were determined under 4 MPa H<sub>2</sub> pressure, at 293 K using toluene/acetic acid 9/1 as solvent. In the competitive chiral hydrogenation of MBF + EP and DAP + PA binary mixtures (S1 + S2) a new phenomenon was observed: namely the EP and PA are hydrogenated faster than MBF and DAP, whereas in racemic one the MBF and DAP are hydrogenated faster than the former ketones. The phenomenon verified for the first time in CFBR is dependent on the adsorption mode of the surface complexes of various compositions (S1-Pt, S2–Pt, S1–CD–Pt, S2–CD–Pt, CD = cinchonidine). In the chiral hydrogenation of DAP a rate decrease, i.e., "ligand deceleration" was observed instead of rate enhancement.

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# **1** Introduction

The investigation of heterogeneous asymmetric syntheses methods is one of the most important fields of research in organic chemistry [1–7]. Such methods are the hydrogenation reactions effected by hydrogen over metal catalysts, particularly in continuous-flow fixed-bed reactor systems (CFBR) [8, 9]. CFBR has been successfully utilized in the chiral hydrogenation of activated ketones [10–23], not only to simplify the practical realization of the reactions, but also to study the mechanism of the Orito reaction [24].

Competitive hydrogenation of mixtures of ketones over metal catalysts is a widely used method in studies on the reaction mechanism of different types of organic compounds (e.g., [25–31]). Research on competitive hydrogenations has yielded new information on the effect of the electronic and 3D structure of the substrates on their adsorption over the catalyst and on surface reactions. In view of the total lack of published results concerning competitive chiral hydrogenation of binary mixtures (with the exception of the Orito reaction [32] and the hydrogenation of prochiral carboxylic acids [33]), it was expected that experimental results obtained in CFBR would provide new information on the enantioselective catalytic hydrogenation of activated ketones, an otherwise widely studied field.

Recently, it was reported that in the competitive hydrogenation of methyl benzoylformate (MBF) + ethyl pyruvate (EP) binary mixture on  $Pt/Al_2O_3$  modified by CD

(enantioselective or chiral hydrogenation) using atmospheric batch reactor under the experimental conditions of the Orito reaction:  $k_{\rm EP} > k_{\rm MBF}$ , but over unmodified catalyst (racemic hydrogenation)  $k_{\rm MBF} > k_{\rm EP}$ . This phenomenon is dependent on the adsorption strength of the surface complexes of various compositions (MBF–Pt, EP–Pt, MBF–M–Pt, EP–M–Pt, M = chiral modifier) [32]. In view of the above unexpected experimental observation, it seemed expedient to study the competitive hydrogenation of binary activated ketone mixtures in the CFBR system so far not studied, as unlike the batch method, this method enables to maintain identical substrate concentration throughout the entire time of the measurement.

The objective of the research was to study the hydrogenation of four binary mixtures (MBF + EP, MBF + PA, MBF + DAP, DAP + PA) using the activated ketones shown in Fig. 1 under the experimental conditions of the Orito reaction (Scheme 1). Comparison of the experiments on unmodified and CD-modified catalysts was the main aim of the study. The present studies on the hydrogenation of these binary mixtures not only confirmed the unexpected experimental observation obtained by the batch method, but generalized it and also contributed to the interpretation of the new phenomenon.

## 2 Experimental

#### 2.1 Materials

Cinchonidine (CD), the activated ketones (EP, MBF, PA, DAP) and solvents were purchased from Aldrich or Fluka. EP, MBF, PA and DAP were distilled under vacuum using a Vigreux-column. Engelhard 5% Pt/Al<sub>2</sub>O<sub>3</sub> (E4759) was pretreated in a fixed-bed reactor by flushing with 30 mL min<sup>-1</sup> He at 300–673 K for 30 min and 30 mL min<sup>-1</sup> H<sub>2</sub> at 673 K for 100 min. After cooling to room temperature in H<sub>2</sub>, the catalyst was flushed with He for 30 min and was stored under air before use [34, 35]. The properties of E4759 catalyst: Pt-content, 5% (w/w); Pt dispersion (after pretreatment), 25%; mean Pt particle size, 4.4 nm.

#### 2.2 Hydrogenations in Flow System

Continuous hydrogenations were carried in H-cube highpressure continuous-flow system. The experimental set-up



Fig. 1 Activated ketones studied in this research

has been described in detail in our previous publication [20]. The same catalyst was used per measurement cycle (160 min), with the catalyst washed (1 h with solvent) in between substrate exchanges (S1, S2, S1 + S2, S1). A typical series of measurements began with pre-hydrogenation of the catalyst (60 min) and continued with chiral or with racemic hydrogenations of individual substrates, followed by chiral or racemic hydrogenation of binary mixtures. The measurement series were ended by a second chiral or racemic hydrogenation under conditions identical with those of the first chiral hydrogenations. The purpose of the latter was to monitor the deactivation of the catalyst in the course of the measurement cycle (160 min).

Standard conditions were: 50 mg E4759 catalyst, 293 K, 4 MPa hydrogen pressure, solvent: toluene/acetic acid (AcOH) 9/1, liquid flow 1 mL min<sup>-1</sup>, modifier concentration: 0.44 mM, substrate concentration 11 mM. In our earlier experiments we verified that our measurements proceed in a kinetic regime, which is also confirmed by the high ee values, since it is well-known that mass transfer limitations can dramatically decrease *ee* values [4]. Conversions and enantiomeric excesses,  $ee\% = |[R] - [S]| \times 100/([R] + [S])$ , were determined by gas chromatography (HP 6890 N GC-FID, 30 m Cyclodex-B chiral capillary column). The reproducibility of the results was  $\pm 1\%$ .

## **3** Results and Discussion

Hydrogenation of activated ketones under the conditions of the Orito reaction in a batch reactor has been discussed in numerous reviews (e.g., [36–40] in the last 4 years). The majority of the reports studies EP, a smaller fraction investigates MBF, whereas only very few publications report experiments on PA [41, 42] and DAP [41]. Results of experiments using CFBR are reported in the publications mentioned [10–23]. However, no experimental observations on the competitive hydrogenation of binary mixtures have been reported yet in the CFBR.

The results of the measurements on binary mixtures are presented in Table 1, and a typical measurement series using DAP + PA mixture is shown as an example in Fig. 2. In both series (chiral and racemic), hydrogenation of the first substrate is followed by that of the second one, and next by hydrogenation of the mixture of the two substrates; finally, the last experiment of the series is again the hydrogenation of the first compound. According to Fig. 2, catalyst activity is somewhat diminished with the progress of reaction time. Deactivation is mainly the consequence of the side reactions of substrates (decomposition accompanied by CO formation, occasional oligomerization). Due to the character of the measurement, steady state cannot be reached within the hydrogenation time of 160 min. The



**Table 1** Conversion (%) of racemic and chiral hydrogenations of individual substrates ( $C_{Si}$ ) and of competitive hydrogenations of binary mixtures ( $C_{Sm}$ ) and enantiomeric excesses (*ee*, %) obtained over chiral catalyst<sup>a</sup>

<u></u> S1 + S2	Racemic hydrogenation (r)				Chiral hydrogenation (c) over modified catalyst							
					Conversion (%)				ee (%, R)			
	$C_{S1i}$	$C_{\rm S2i}$	$C_{\rm S1m}$	$C_{\rm S2m}$	$C_{S1i}$	$C_{\rm S2i}$	$C_{S1m}$	$C_{\rm S2m}$	S1i	S2i	S1m	S2m
$MBF + EP^b$	37	20	23	14	49	77	43	60	83	74	87	77
MBF + PA	80	8	68	4	95	53	88	38	89	90	87	90
MBF + DAP	87	30	80	17	95	20	90	12	92	77	92	76
DAP + PA	35	8	31	7	13	54	10	40	75	90	77	92

<sup>a</sup> Reaction conditions: 50 mg Pt/Al<sub>2</sub>O<sub>3</sub> (E4759) catalyst, 293 K, 4 MPa hydrogen pressure, solvent: toluene/AcOH 9/1, liquid flow 1 mL min<sup>-1</sup>, CD concentration: 0.44 mM, substrate concentration 11 mM

<sup>b</sup> 20 mg E4759 catalyst, 283 K, others as previously given

Subscript i = hydrogenation of the individual substrate, m = hydrogenation of the binary mixture



**Fig. 2** The conversion (*closed symbols*) and *ee* (*open symbols*) as a function of time on stream in the successive hydrogenation of  $PA_i$ ,  $DAP_i$ ,  $PA_m + DAP_m$  and  $PA_i$  using CFBR system over unmodified (PA: *filled diamond*; DAP: *filled triangle*) and CD-modified (PA: *filled circle, open circle*; DAP: *filled square, open square*) Pt/Al<sub>2</sub>O<sub>3</sub> catalysts (for reaction conditions see Table 1, subscript i = individual, m = mixture)

decrease in conversion during hydrogenation of the mixture is a consequence of the double substrate load on the catalyst, since in the case of individual measurements the substrate concentration is 11.25 mM, whereas in the case of a substrate mixture it is 11.25 mM per substrate. Some of the  $C_{\rm Si}$  data in Table 1 indicate inconsistent reproducibility: it is well-known that catalyst systems treated with chiral modifiers are somewhat more sensitive than "ordinary" hydrogenation catalysts. The reason for this is, among others, that, depending on the initial state of the catalyst, the chiral modifier brings about dynamic and continuous changes in the quality of the active sites. This effect of the modifier also depends on its irreversible adsorption under a great variety of conditions [43, 44].

Based on the experimental results summarized in Table 1, the following conclusions can be drawn.

- (i) The experimental data of MBF + EP in Table 1 are not comparable with the other data in all aspects, because there are differences among the experimental conditions. The reason for this is that hydrogenation of MBF + EP had to be conducted under milder experimental conditions, since conversions close to 100% were not suitable for recognition of the supposed and expected tendency [32]. Performing measurements on MBF + EP at a temperature lower by 10 K and using a lower amount of catalyst did not hinder the most important conclusions to be drawn.
- (ii) In racemic hydrogenation, conversion of substrates containing aromatic skeletons (MBF, DAP) is higher than that of substrates without aromatic moiety, most probably due to their stronger adsorption.
- (iii) The course of the conversion in chiral hydrogenations is much more varied than that in racemic hydrogenations, because changes in conversion of the MBF + PA and MBF + DAP mixtures and of

S1 + S2	Racemic hyd	rogenation (r)	Chiral hydro	$C_{\rm c}/C_{\rm r}$				
	C <sub>S1i/S2i</sub>	C <sub>S1m/S2m</sub>	C <sub>S1i/S2i</sub>	C <sub>S1m/S2m</sub>	S1i	S2i	S1m	S2m
$MBF + EP^{b}$	1.9	1.6	0.6	0.7	1.3	3.9	1.9	4.3
MBF + PA	9.0	17.0	1.8	2.3	1.2	6.6	1.3	9.5
MBF + DAP	2.9	4.7	4.8	7.5	1.1	0.6	1.1	0.7
DAP + PA	5.0	4.4	0.3	0.3	0.4	6.8	0.3	5.7

**Table 2** Calculated relative conversions ( $C_{S1/S2}$ ) for racemic (r) and chiral (c) hydrogenations of individual substrates and competitive hydrogenations of binary mixtures<sup>a</sup> and  $C_c/C_r$  values

<sup>a,b</sup> For reaction conditions see Table 1



Scheme 2 Racemic and chiral hydrogenation of DAP + PA binary mixtures

individual substrates are similar to those in racemic hydrogenations. However, in the case of the chiral hydrogenation of MBF + EP and DAP + PA, the conversion of the latter substrates (S2 = EP and PA) exceeds those of MBF and DAP, respectively. The phenomenon is well demonstrated by the experimental data shown in Fig. 2. Namely, in racemic hydrogenation  $C_{\text{DAP}} > C_{\text{PA}}$  (40% > 8%, 31% > 7%), whereas in chiral hydrogenation  $C_{\text{DAP}} < C_{\text{PA}}$  (13% < 54%, 10% < 40%).

(iv) Irrespective of the conversion, high ee values could be attained especially in the chiral hydrogenation of MBF and PA (87–92%), in spite of the fact that no optimization was done.

The several calculated data on the basis of Table 1 are shown in Table 2. The first and second columns of each hydrogenation in Table 2 present the ratio of reactivities of S1 and S2 in chiral or racemic in both individual and competitive hydrogenation. As it is well-known, in the Orito reaction chiral hydrogenation is usually faster than racemic hydrogenation, i.e., rate enhancement (so called "ligand acceleration") takes place [36–40]. The values of  $C_c/C_r$  are the largest for PA both when hydrogenated individually and in binary mixtures. In the chiral hydrogenation of DAP, however, a rate decrease ("ligand deceleration") is observed ( $C_c/C_r < 1$ ) instead of rate enhancement. The essentials of the chemical conversions taking place are illustrated by Scheme 2. From the high *ee* it follows that the Pt-coverage by the modifier is high. The quinoline moiety will strongly adsorb. Because of the non-flatness of the other part (quinuclidine moiety), the ketone substrate can be accommodated with the chiral part of the modifier and catalyst. Smaller ketones (PA in Fig. 2) will be more easily positioned in this way than larger ones (DAP, also lower *ee*). In the absence of modifier DAP will win in a competition with PA due to its relatively strongly adsorbing aromatic ring (Scheme 2).

## 4 Conclusion

The similar tendencies of experimental results obtained in batch and continuous-flow reactors allowed convincing conclusions to be drawn. Namely, results of the competitive hydrogenation of binary mixtures of activated ketones under the conditions of the Orito reaction also confirm the so-called adsorption model of the reaction mechanism [6, 36–38, 40]. Naturally, this does not exclude the possibility that in the case of certain substrates, substrate–cinchona adducts may already form in the liquid phase, i.e., without the participation of Pt, and the structure of such adducts changes favorably or unfavorably for chiral induction in the course of adsorption on the surface of Pt. The interpretation of the differences between the results obtained in batch and in continuous flow reactors necessitates further studies and a more profound knowledge of reaction kinetics.

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