Available online at www.sciencedirect.com
ScienceDirect
Journal of Catalysis 254 (2008) 339–348
JOURNAL OF CATALYSIS
www.elsevier.com/locate/jcat

Hydrogenation of 1-phenyl-1,2-propanedione over Pt catalysts modified by cinchona alkaloid *O*-ethers and the kinetic resolution of the 1-hydroxyketones generated

Igor Busygin [a], Johan Wärnå [b], Esa Toukoniitty [b], Dmitry Yu. Murzin [b,*], Reko Leino [a,*]

[a] *Laboratory of Organic Chemistry, Åbo Akademi University, 20500 Åbo, Finland*
[b] *Laboratory of Industrial Chemistry, Åbo Akademi University, 20500 Åbo, Finland*

Received 18 December 2007; revised 10 January 2008; accepted 12 January 2008

Available online 28 January 2008

Abstract

Nine cinchona alkaloid *O*-ethers together with cinchonidine and cinchonine were studied as chiral modifiers in the enantioselective hydrogenation of 1-phenyl-1,2-propanedione over Pt/Al_2O_3. The influence of the *O*-substituent on the reaction rate, selectivity and product distribution was investigated. Apparent rate constants for all hydrogenation steps were calculated using a first-order kinetic approach resulting in a good agreement between the experimentally recorded and predicted concentrations. The experimentally observed structure–selectivity effects indicate that the mechanisms of enantiodifferentiation over the catalyst modified by parent cinchona alkaloids and their ether derivatives differ from each other. Moreover, the modifier structure–selectivity dependence and the solvent effect were different for enantio- and diastereoselection in the 1-phenyl-1,2-propanedione and 1-hydroxyketone hydrogenations. Correlation between the modifier substituent bulkiness and diastereoselectivity of the 1-hydroxyketone hydrogenation was observed. Data on the inversion of enantioselectivity of 1-phenyl-1,2-propanedione hydrogenation, diastereoselectivity and the sense of kinetic resolution of the 1-hydroxyketones were presented. Due to the complexity of the reaction network, several competing mechanistic pathways may be present in a single reaction system.

Keywords: Cinchona alkaloids; Heterogeneous catalysis; Hydrogenation kinetics; 1-Phenyl-1,2-propanedione; Inversion of enantioselectivity; Inversion of diastereoselectivity

1. Introduction

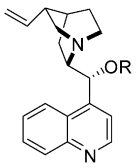
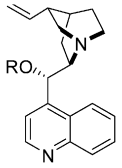
Chiral induction over heterogeneous metal catalysts is one of the most rapidly progressing methods for generating asymmetric centers in organic molecules [1,2]. Enantioface discriminating hydrogenation of a prochiral C=X functionality produces one enantiomer of the molecule in excess over the other. Cinchona alkaloids are efficient chiral surface modifiers for enantioselective hydrogenation of various activated ketones over heterogeneous catalysts. A micromolar quantity of the chiral modifier in the reaction milieu allows producing one product enantiomer in high enantiomeric excess (*ee*). Since the first report on the enantioselective hydrogenation of methyl pyruvate over a heterogeneous catalyst by Orito and co-workers in 1978 [3], applications of the Pt/cinchona alkaloid system have been successfully extended to a number of substrates. Several recent reviews are available on this subject [4–10].

Three functional parts of the cinchona alkaloids can be distinguished, namely, the bicyclic quinuclidine part, the aromatic quinoline ring, and the stereogenic region which couples the two rigid moieties together by two carbon–carbon bonds (Table 1). It is well documented that cinchonidine (CD) and cinchonine (CN) induce an excess of opposite product chirality in hydrogenations. Recently, *O*-ether derivatives of cinchona alkaloids have attracted considerable attention as modifiers for enantioselective hydrogenations of activated ketones [11–17]. This interest originates from the capacity of changing the sense of product chirality by derivatization of the hydroxyl group in

* Corresponding authors. Faxes: +358 2 2154479, +358 2 2154866.
E-mail addresses: dmitry.murzin@abo.fi (D.Yu. Murzin), reko.leino@abo.fi (R. Leino).

0021-9517/$ – see front matter
doi:10.1016/j.jcat.2008.01.012

Table 1
Structures of the modifiers

R	
CD	–H
MeOCD	$–CH_3$
PhOCD	$–C_6H_5$
TMSOCD	$–Si(CH_3)_3$
TBDMSOCD	$–Si(CH_3)_2t$-Bu
ADMSOCD	$–Si(CH_3)_2A$[a]
DPMSOCD	$–Si(C_6H_5)_2CH_3$

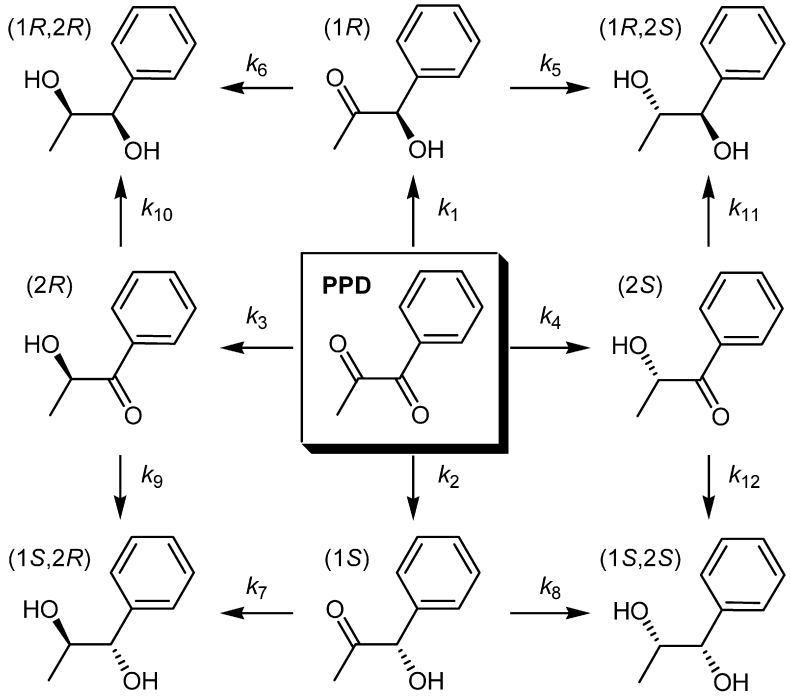
R	
CN	
MeOCN	
PhOCN	
TMSOCN	
–	
–	
–	

[a] A = $–CH_2C(H)=CH_2$.

the alkaloid while retaining the same the absolute configurations of the alkaloid asymmetric centers. Isocinchonas, which are cyclic *O*-ether derivatives of cinchona alkaloids, have been studied actively as well [18–20]. Studies on the structure–selectivity relationships provide valuable information for understanding the experimentally feasible reaction mechanisms and potentially broaden the application area of heterogeneous catalysts in enantioselective hydrogenation [21–23].

Study of the reaction kinetics is one of the approaches for elucidating the reaction mechanisms and interpreting the role of the chiral modifier in enantiodifferentiation. Several reports on studies of kinetics of ethyl pyruvate hydrogenation [24–26] are available. Kinetic analysis of the complex reaction systems consisting of parallel and consecutive steps is represented in the literature only by a few examples. When considering the kinetics of butane-2,3-dione [27,28] and cyclohexane-1,2-dione hydrogenation [29], at least six rate constants should be accounted for. The hydrogenation of unsymmetrical diketones, such as 1-phenyl-1,2-propanedione (PPD), is even more complex and consist of nine steps (Scheme 1). In our laboratories, kinetics of the enantioselective hydrogenation of PPD (Scheme 1), have been studied for some years [14,15,30–32]. Some characteristic features have been revealed: (1) The presence of two inequivalent keto groups in the molecule raises the issue of regioselectivity; Hydrogenation of the carbonyl adjacent to the phenyl ring is always preferred over hydrogenation of the aliphatic one [33]; (2) Under the currently optimal conditions, the main product, (*R*)-1-hydroxy-1-phenyl-2-propanone (depicted as (1*R*) in Scheme 1), can be obtained in 65% *ee* using cinchonidine as the chiral catalyst modifier; (3) When *O*-methyl or *O*-silyl ethers of cinchona alkaloids are used as chiral modifiers, a loss or inversion of enantioselectivity results [14,15,34]. This observation is indicative of a significant difference in the enantioselection mechanisms operating in the diketone and the classical keto ester hydrogenations, as in the latter case, the *O*-methyl derivatives of CD and CN induce, in toluene [13], enantioselectivities similar to those obtained with the parent alkaloids, and in acetic acid even higher selectivities than the parent modifiers [22].

Baiker and co-workers [35] reported the phenomenon of enantioselectivity inversion in the hydrogenation of 4,4,4-trifluoroacetoacetate which is related to the hydrate formation from the ketone in THF. This opened a new approach to research on the nature of modifier–substrate–metal surface interactions in the Orito reaction [4–10]. Since then several investigation have been published reporting inversion of enantioselectivity due to changes in the modifier structure, change



Scheme 1. 1-Phenyl-1,2-propanedione hydrogenation reaction scheme.

of a solvent [36–40] and even changes of the modifier concentration have resulted in inversion of chirality of the main product [41–43]. Studying the kinetics of complex asymmetric reactions raises the issues of enantioselectivity and regioselectivity for the initial steps; kinetic resolution and diastereoselectivity for the consecutive steps. In the present study, we observed the inversion of enantioselectivity of PPD hydrogenation, diastereoselectivity and the sense of kinetic resolution of the 1-hydroxyketones by *O*-derivatization of cinchona alkaloid modifiers. Nine derivatives of cinchonidine and cinchonine (Table 1), possessing substituents with different nature and bulkiness, were examined as chiral modifiers in the enantioselective hydrogenation. Reaction kinetics of the PPD hydrogenation was analyzed by first-order kinetic approach, considering for the first time the complete reaction network.

2. Experimental

2.1. Materials

For use in the catalytic hydrogenation reactions, 1-phenyl-1,2-propanedione (Aldrich, 99%) was vacuum distilled, whereas toluene (J.T. Baker, >99.5%), acetic acid (J.T. Baker, 99.9%), cinchonidine (Fluka, 98%) and cinchonine (Fluka, 98%) were used as received.

2.2. Catalytic hydrogenation

Hydrogenations were carried out using a pressurized batch reactor (Parr, 300 cm^3) equipped with constant flow–constant pressure equipment. According to the standard procedure, the 5 wt% Pt/Al_2O_3 catalyst (Strem Chemicals, 78–1660) (100 mg) was pre-reduced *in situ* by flushing with hydrogen (50 $cm^3\,min^{-1}$) for 2 h at 400 °C. After cooling to room temperature in hydrogen flow, a solution of the chiral modifier (3.4×10^{-5} mol in 50 mL of toluene or acetic acid), preliminary saturated with hydrogen (50 $cm^3\,min^{-1}$) for 10 min in a separate injection chamber, was injected into the reactor. The reaction was commenced by starting the agitation immediately after the injection of the solution of 1-phenyl-1,2-propanedione (0.74 g, 5 mmol) pre-treated in the same manner. The reactions were carried out under kinetic regime in the absence of external and internal mass transfer limitations [31]. The constant hydrogen (AGA, 99.999%) pressure of 10 bar, temperature of 15 or 17 °C (for the hydrogenations in toluene and acetic acid, respectively) and stirring rate of 2000 rpm was applied. The initial concentrations of chiral modifiers and 1-phenyl-1,2-propanedione were 3.4×10^{-4} mol dm^{-3} and 0.05 mol dm^{-3}, respectively. The reaction was followed by a Varian 3300 Gas Chromatograph (GC) equipped with a chiral column (β-Dex 225). Details of the catalyst characterization and analytical procedure and modifier synthesis can be found elsewhere [30–32,44]. The reproducibility of catalytic results was examined by carrying out of repeated experiment with *O*-methyl derivatives in toluene and acetic acid.

2.3. Kinetic model

The reaction kinetics can be described as follows. The disappearance of the reactants and the generation of the products can be calculated by the solution of the molar balances for the components in a batch reactor:

$$r_{\mathrm{PPD}} = \frac{V}{m_{\mathrm{cat}}}\frac{\mathrm{d[PPD]}}{\mathrm{d}t} = -(k_1+k_2+k_3+k_4)[\mathrm{PPD}],$$

$$r_{(1R)} = \frac{V}{m_{\mathrm{cat}}}\frac{\mathrm{d}[1R]}{\mathrm{d}t} = k_1[\mathrm{PPD}] - (k_5+k_6)[1R],$$

$$r_{(1S)} = \frac{V}{m_{\mathrm{cat}}}\frac{\mathrm{d}[1S]}{\mathrm{d}t} = k_1[\mathrm{PPD}] - (k_7+k_8)[1S],$$

$$r_{(2R)} = \frac{V}{m_{\mathrm{cat}}}\frac{\mathrm{d}[2R]}{\mathrm{d}t} = k_1[\mathrm{PPD}] - (k_9+k_{10})[2R],$$

$$r_{(2S)} = \frac{V}{m_{\mathrm{cat}}}\frac{\mathrm{d}[2S]}{\mathrm{d}t} = k_1[\mathrm{PPD}] - (k_{11}+k_{12})[2S],$$

$$r_{(1R,2S)} = \frac{V}{m_{\mathrm{cat}}}\frac{\mathrm{d}[1R,2S]}{\mathrm{d}t} = k_5[1R] + k_{11}[2S],$$

$$r_{(1R,2R)} = \frac{V}{m_{\mathrm{cat}}}\frac{\mathrm{d}[1R,2R]}{\mathrm{d}t} = k_6[1R] + k_{10}[2R],$$

$$r_{(1S,2R)} = \frac{V}{m_{\mathrm{cat}}}\frac{\mathrm{d}[1S,2R]}{\mathrm{d}t} = k_7[1S] + k_9[2R],$$

$$r_{(1S,2S)} = \frac{V}{m_{\mathrm{cat}}}\frac{\mathrm{d}[1S,2S]}{\mathrm{d}t} = k_8[1S] + k_{12}[2S].$$

The system of differential equations was solved numerically with the backward difference method using the Odessa solver in the ModEst program package [45]. The differential equation solver operated under a parameter estimation routine, which minimized an objective function, the residual sum of squares

$$Q = \sum w(c_{\mathrm{exp}} - c_{\mathrm{model}})^2,$$

where c_{exp} and c_{model} denote the experimental and predicted concentrations, and w is a weighting factor. A hybrid Simplex–Levenberg–Marquardt algorithm was used in the minimization of the objective function Q. The numerical algorithm is included in the program package ModEst [45]. The quality of the model fit and the model parameters were tested by calculating the standard deviations of the parameters and the degree of explanation of the model. The values of estimated rate constants (k_i) are lumped constants, which might include the reactant and modifier adsorption coefficients as well as concentrations of modifier and hydrogen. The first-order kinetic approach essentially assumes nonsignificant coverage of adsorbed reactant, which can be justified by utilization of low substrate concentration, as well as experimentally observed kinetic regularities (Fig. 1), following closely first-order behavior.

2.4. Definition of selectivities

It is well known that the origin of enantioselectivity is directly related to the altered formation rates of the enantiomers in the presence of the chiral modifier [31]. Therefore, concentrations of the (*R*)- and (*S*)-enantiomers in the classic enantiomeric excess definition (ee_1 in Eq. (1)) were replaced by apparent rate constants of the single hydrogenation step (Eq. (2)),

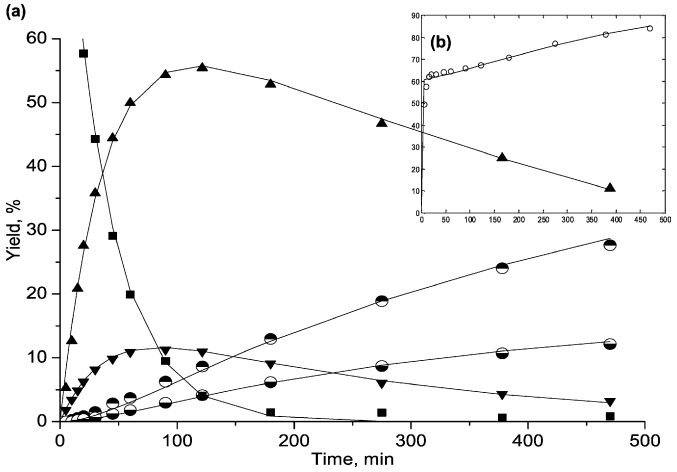


Fig. 1. Comparison of the model prediction (solid lines) with experimental data (symbols) of PPD hydrogenation over cinchonidine modified Pt/Al_2O_3 in toluene: (a) conversion versus time (■) PPD; (▲) (1*R*); (▼) (1*S*); (◓) (1*R*,2*S*)-diol and (◒) (1*S*,2*R*)-diol. 2-Hydroxyketones and *threo*-diols are not displayed. (b) Enantioselectivity versus time data.

obtained from the kinetic model.

$$ee_1 = \frac{[(1R)] - [(1S)]}{[(1R)] + [(1S)]} \times 100\%, \tag{1}$$

$$Er_1 = \frac{k_1 - k_2}{k_1 + k_2} \times 100\%, \tag{2}$$

where k_1 and k_2 are the rate constants identified in Scheme 1. Considering the mechanistic aspect, enantioselectivity expressed as *Er* results in more accurate interpretation of enantioselectivity in the first hydrogenation step. The *Er* value is independent of the conversion whereas the *ee* based on experimental concentrations is altered by kinetic resolution taking place in the second hydrogenation step.

The kinetic resolution of the (1*R*)/(1*S*) mixture was quantified by the rate constants (Eq. (3)) for estimation of the modifier structure effect:

$$k(1R)/k(1S) = \frac{k_5 + k_6}{k_7 + k_8}. \tag{3}$$

At high conversion of 1-hydroxyketones, a first-order kinetic approach is not able to describe all the processes on the surface. As will be discussed later, the selectivity of the second hydrogenation step depends on the conversion of the hydroxyketones. Consequently, and in order to avoid overestimation of the accuracy of the values reported, $k(1R)/k(1S)$ will be represented as a proper fraction.

Diastereoselectivity of the (*R*)-1-hydroxy-1-phenyl-2-propanone hydrogenation (d*r*(1*R*)) is defined in

$$\mathrm{d}r(1R) = \frac{k_5 - k_6}{k_5 + k_6} \times 100\%. \tag{4}$$

Diastereoselectivity of the (*S*)-enantiomer (d*r*(1*S*)) hydrogenation is defined in an analogous fashion.

The ratio of the *erythro*- ((1*R*,2*S*)- and (1*S*,2*R*)-diol) and *threo*-diols ((1*R*,2*R*)- and (1*S*,2*S*)-diol) was quantified by the rate constants. The experimentally observed (Eq. (5)) and calculated (Eq. (6)) *erythro/threo* ratios are defined as

$$erythro/threo = \frac{[(1R,2S)] + [(1S,2R)]}{[(1R,2R)] + [(1S,2S)]}, \tag{5}$$

$$erythro/threo = \frac{k_5 + k_7 + k_9 + k_{11}}{k_6 + k_8 + k_{10} + k_{12}}. \tag{6}$$

The regioselectivity (*rs*) is defined as shown in

$$rs = \frac{[(1R)] + [(1S)]}{[(2R)] + [(2S)]}. \tag{7}$$

3. Results and discussion

In the present study, the kinetics of PPD hydrogenation in toluene and acetic acid was explicitly addressed using several new modifiers. A typical experiment was followed for 8–14 h which allows studying the hydrogenation of hydroxyketones, the primary hydrogenation products of PPD. All of the modifiers presented in Table 1 were hydrogenated in toluene. Instability of the *O*-silyl ether derivatives under acidic conditions prevented their use as chiral modifiers in acetic acid. The stability of *O*-phenyl derivatives of cinchona alkaloids under the conditions employed for catalysis was previously questioned by Baiker and co-workers [46]. Hence, in the present study, stabilities of the *O*-phenyl ethers were investigated in both acetic acid and toluene under the actual hydrogenation conditions. The results are discussed in the following section.

3.1. Modifier stability and influence of the impurities

The stability of a chiral modifier under the employed reaction conditions is particularly important for mechanistic studies. Column purification of silyl ethers promotes partial cleavage of the Si–O bond [13]. Therefore, micro amounts of cinchonidine and cinchonine may be present in the *O*-silyl ether modifier samples. Thus, in the present study, *O*-silyl derivatives of cinchona alkaloids were purified by adsorption over the Pt/Al_2O_3 catalyst [13] and the results were compared with the data obtained from experiments with column-purified modifiers. The kinetics of the hydrogenation reaction, as demonstrated for *O*-(allyldimethylsilyl)cinchonidine (ADMSOCD), was not affected by the purification procedure, indicating that amounts of free cinchonidine sufficient to influence the results of the catalysis experiments were not present in the modifier samples.

This observation can easily be rationalized by considering the effect of modifier concentration in the hydrogenation of PPD. Enantioselective hydrogenation of PPD over cinchona-modified oxide-supported platinum catalysts requires higher alkaloid concentrations than commonly applied for enantioselective hydrogenations of α-keto esters [31]. As little as 0.7 mol% of cinchonidine in admixture with PhOCD can control the enantioselection in ketopantolactone hydrogenation [47]. For PPD, a cinchonidine concentration of 1.4×10^{-5} mol dm^{-3} (corresponding to approx. 4 mol% with the commonly utilized modifier amounts and constant catalyst loading) is required for obtaining a minimal noticeable effect of chiral modification (*ee* = 8% in ethyl acetate) [31]. Thus, taking into consideration the experimental conditions, it can be concluded that the

PPD hydrogenation is less sensitive to minor impurities in the modifier than the hydrogenation of keto esters.

Impurities may also be formed during the experiment by cleavage or hydrogenolysis of the *O*-ether substituent. In PhOCD, the phenoxy moiety is cleaved under strongly acidic conditions [46]. Consequently, in the present study, stability of the *O*-ether bond under currently employed reaction conditions was investigated. Solutions of one silyl ether (ADMSOCD) in toluene and two *O*-phenyl derivatives (PhOCD and PhOCN), both in toluene and acetic acid, were exposed to hydrogen pressures of 10 bar over the platinum catalyst for 12–16 h. After work-up, the samples were analyzed by NMR. The compounds observed were identified as *O*-(propyldimethylsilyl)-10,11-dihydrocinchonidine (PDMSODHCD), *O*-phenyl-10,11-dihydrocinchonidine and *O*-phenyl-10,11-dihydrocinchonine, respectively. The samples were also examined for the presence of decomposition product traces. In short, the NMR detection limit for eventual impurities is considerably lower than the amounts of modifier needed for obtaining enantioselection in the PPD hydrogenation. Products of C(9)–O hydrogenolysis or O–R hydrolysis were not detected in the ^{1}H and ^{13}C NMR spectra of the hydrogenated modifiers, demonstrating that the C(9)–O and O–R bonds are stable under the conditions employed in the catalytic hydrogenation experiments and, accordingly, the impurity traces should have no effect on the reaction kinetics.

3.2. Catalytic hydrogenation

Hydrogenation of PPD proceeds in two steps (Scheme 1). First, two regioisomers, 1-hydroxy-1-phenyl-2-propanone and 2-hydroxy-1-phenyl-1-propanone are formed, which both exist as their (*R*)- and (*S*)-enantiomers. Further hydrogenation of the hydroxyketones produces the corresponding diastereomeric (1*R*,2*R*)-, (1*S*,2*S*)-, (1*R*,2*S*)- and (1*S*,2*R*)-1-phenyl-1,2-propanediols as two pairs of enantiomers. Kinetic resolution of the 1-hydroxy-1-phenyl-2-propanones is commonly observed during the second hydrogenation step.

3.2.1. Kinetic modeling

The apparent rate constants of all hydrogenation steps were estimated using the first-order kinetic approach (Tables S1 and S2, Supplementary material). Quantitative treatment of the hydrogenation kinetics is based on the reaction scheme depicted in Scheme 1. Despite the apparent simplicity, the first-order kinetic model, which neglects the differences in adsorption and, strictly speaking, is valid in the cases of low surface coverage only, still allows the estimation of the rate constants in PPD hydrogenation with high accuracy. Examples of the fit are provided in Figs. 1 and 2 showing very good agreement between the experimentally recorded and predicted concentrations. Furthermore, the selectivities calculated from experimentally measured concentrations and from estimated rate constants are in good agreement with each other (Tables 2 and 3) giving further support for the reliability of the kinetic modeling.

In the model developed in our earlier study [31], kinetic resolution was not considered resulting in deviation between the calculated and experimental concentrations. In the present investigation, for the first time, the complete hydrogenation scheme is evaluated. The other features of the earlier model, adsorption of the modifier, active and spectator species and multicentered adsorption, are, however, not considered here since experiments were conducted only at one concentration level both for the substrate and for the modifier.

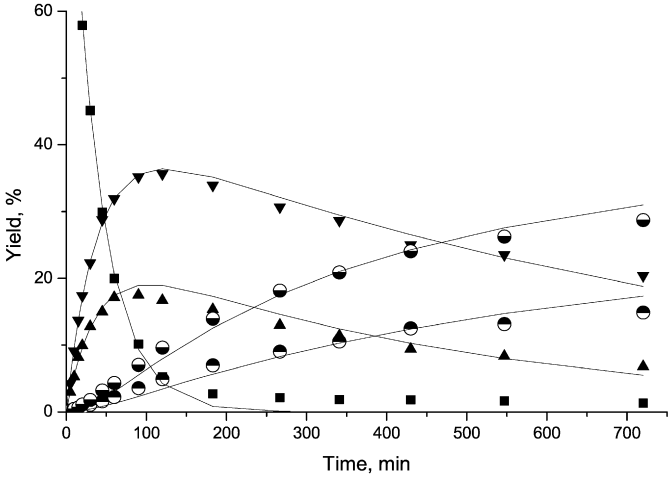


Fig. 2. Comparison of the model prediction (solid lines) with experimental data (symbols) of PPD hydrogenation over TBDMSOCD modified Pt/Al_2O_3 in toluene. Designations are identical to Fig. 1.

3.2.2. Influence of the modifier structure on the first hydrogenation step

The hydrogenation results are presented in Table 2. The rate of the PPD hydrogenation is lower in the presence of a chiral modifier being in line with our previous reports [14,15,30,31]. Generally, but with some exceptions, the rate of hydrogenation in toluene is gradually decreasing with increase in the C(9)-*O*-substituent bulkiness, while in acetic acid it is almost independent on the modifier structure.

Regioselectivity (*rs*) of the hydrogenation in toluene was always lower when *O*-ethers were used as chiral modifiers (*rs* = 2.0–3.1) instead of the parent cinchona alkaloids (*rs* = 3.0 and 4.8). With these modifiers, the *rs* was also lower than in the hydrogenation in the absence of modifier (racemic hydrogenation *rs* = 4.1), indicating that the cinchona alkaloid *O*-ether modified chiral sites slightly disfavor the hydrogenation of the C1=O1 carbonyl group in comparison with the unmodified surfaces. The nature of the *O*-ether substituent has only marginal effect on the regioselectivity in toluene within the ROCD and ROCN series.

The modifier hydroxyl group is essential for achieving high enantioselectivity in the hydrogenation of the PPD C1=O1 keto group in toluene. This observation is in line with our earlier investigations [14,15]. In all examples presented here, the cinchona alkaloid *O*-ethers induced either an inversion or complete loss of enantioselectivity in comparison with their unsubstituted counterparts (Fig. 3). Similar observations have been described in the literature for hydrogenation of various aromatic α-hydroxy ketones [12], substituted acetophenones [49] and 1,1,1-trifluoro-2,4-diketones [50]. Obviously,

Table 2
The efficiency of ether derivatives of cinchonidine and cinchonine used as chiral modifiers of Pt/Al_2O_3 in the heterogeneous hydrogenation of ethyl pyruvate (EtPy) and 1-phenyl-1,2-propanedione (PPD)

EtPy	Modifier	PPD				
ee, %		*rs*[a]	Initial rate[b]	k_{PPD}[c]	ee_1[a], %	Er_1, %
74 [46]; 85 [23]; (89) [23]	CD	4.8 (3.2)[d]	11.3 (17.3)[d]	31.8 (52.2)[d]	63 (13)[d]	60 (11)[d]
72 [13] (91) [22][e]	MeOCD	2.2 (2.5)	7.6 (16.2)	19.8 (48.6)	−10[f] (1)	−10[f] (2)
14 [13]; −7 [46]; −21 [48]	PhOCD	3.1 (3.1)	10.9 (13.7)	30.1 (39.1)	−28 (−5)	−27 (−5)
−28 [13][g]; 26 [46]	TMSOCD	2.4	12.2	31.2	0 (−)	0 (−)
–	TBDMSOCD	2.6	11.1	31.6	−27 (−)	−28 (−)
–	ADMSOCD	2.5	7.8	20.6	−1 (−)	0 (−)
–	ADMSOCD[g]	2.3	7.8	21.1	2 (−)	0 (−)
−20 [13][g,h]	DPMSOCD	2.2	8.6	22.4	−3 (−)	−3 (−)
−70 (−81) [23]	CN	3.0 (3.0)	7.3 (12.9)	15.0 (38.5)	−19 (−3)	−18 (−3)
−32 [22]; (−85) [22][e]	MeOCN	2.1 (2.5)	13.1 (13.3)	37.9 (36.3)	32 (−2)	32 (−2)
–	PhOCN	2.3 (2.8)	12.6 (13.1)	33.4 (42.4)	33 (3)	30 (3)
–	TMSOCN	2.0	10.8	30.9	30 (−)	28 (−)
	–[i]	4.1	21.2		0	

[a] At 50% conversion of PPD.
[b] $\times 10^{-4}$ mol min^{-1} g_{cat}^{-1}.
[c] $k_{PPD} = (k_1 + k_2 + k_3 + k_4)$ [h^{-1} g_{cat}^{-1}].
[d] The first number attributed to the hydrogenation in toluene, the number in parentheses to the hydrogenation in acetic acid.
[e] Dihydro derivative.
[f] Negative value corresponds to the excess of (*S*)-enantiomer.
[g] Purified by adsorption over the metal catalyst.
[h] Ph_3SiOCD.
[i] Racemic hydrogenation; taken from [15].

Table 3
The efficiency of ether derivatives of cinchonidine and cinchonine in the second step of PPD hydrogenation

	Yield of diols after 8 h	$k(1R)/k(1S)$[a]	d$r(1R)$, %[b]	d$r(1S)$, %[c]	*erythro*/*threo*	
					Calculated	Experimental[d]
CD	51 (38)	1/3 (1/3)[e]	58 (33)[e]	38 (100)[e]	4.1 (3.6)[e]	3.7 (4.9)[e]
MeOCD	48 (30)	10/9 (2/5)	33 (21)	49.5 (100)	5.2 (3.2)	4.0 [5.5 (38)]
PhOCD	51 (19)	3/2 (3/5)	2 (−14)	22.5 (35)	5.8 (4.4)	2.8 [2.9 (21)]
TMSOCD	43	7/6	2	23	4.9	2.8
TBDMSOCD	45	3/2	12	7.4	4.2	2.4
ADMSOCD	45	5/6	2	26.2	3.2	2.3
DPMSOCD	37	1/1	3	27.1	4.1	2.7
CN	32 (32)	1/1 (2/1)	25 (96.5)	38 (58)	4.2 (1.5)	3.5 (36) (3.6)
MeOCN	55 (30)	3/4 (17/6)	29 (100)	4.6 (60)	3.6 (2.3)	2.9 [6.3 (36)]
PhOCN	54 (21)	5/7 (1/1)	26 (3)	−17 (7)	1.7 (2.9)	2.6 [1.9 (27)]
TMSOCN	39	2/3	34	−21	2.7	2.2

[a] $k(1R)/k(1S) = (k_5 + k_6)/(k_7 + k_8)$.
[b] d$r(1R) = [(k_5 - k_6)/(k_5 + k_6)] \times 100$, %.
[c] d$r(1S) = [(k_7 - k_8)/(k_7 + k_8)] \times 100$, %.
[d] When diols yield is 50%, unless otherwise specified as a superscript value.
[e] The first number attributed to the hydrogenation in toluene, the number in parentheses to the hydrogenation in acetic acid.

on the Pt surface, the cinchona alkaloid *O*-ethers adopt an adsorption mode or conformation that favors the formation of the product (*S*)-enantiomer in the case of the substituted cinchonidine derivatives and the product (*R*)-enantiomer in the case of the substituted cinchonine derivatives. This is an important observation concerning the nature of the chiral site on the Pt surface. Clearly, the observed inversion of enantioselectivity induced by the cinchona alkaloid ether modifiers in toluene indicates that the enantiodifferentiating steps over the cinchona alkaloid/Pt and cinchona alkaloid ether/Pt systems do not proceed via the same type of substrate–modifier complexes. Besides of the hydroxyl group blocking and subsequent inability to form hydrogen bonding between the reactant carbonyl group and the modifier C(9)–OH group, the bulky substituent could induce differences in the modifier adsorption mode [46]. If the latter is the case, the enantioselectivity should correlate the substituent bulkiness. The size of the C(9)-*O*-substituent increases in the series MeOCD–TMSOCD–ADMSOCD–TBDMSOCD–DPMSOCD. As it was studied for this series (Fig. 3 and Table 2), the substituent bulkiness does not correlate with enantioselectivities observed in toluene which supports the interaction between the modifier hydroxyl group and the reactant carbonyl group on the platinum surface [51].

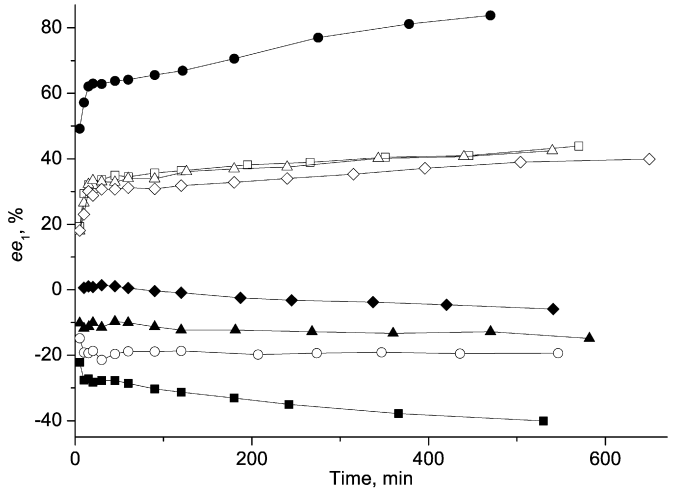


Fig. 3. Enantioselectivities of PPD hydrogenation in toluene over Pt/Al_2O_3 catalysts modified with: (●) CD; (○) CN; (■) MeOCD; (□) MeOCN; (▲) PhOCD; (△) PhOCN; (◆) TMSOCD; (◇) TMSOCN.

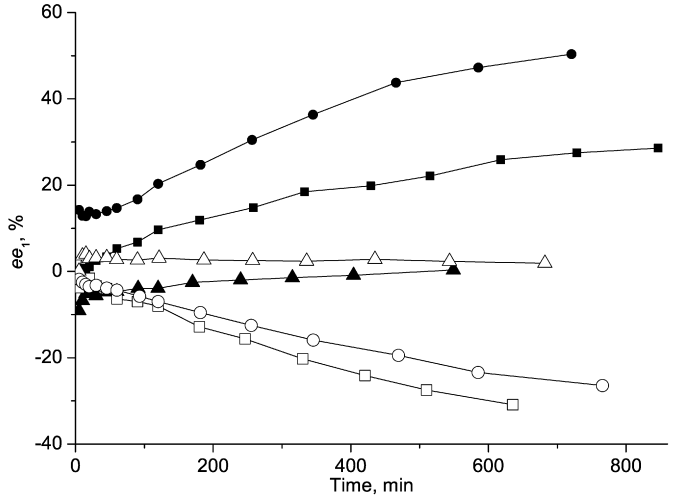


Fig. 4. Resolution of 1-hydroxyketones in acetic acid over Pt/Al_2O_3 catalysts modified with: (●) CD; (○) CN; (■) MeOCD; (□) MeOCN; (▲) PhOCD; (△) PhOCN.

In the present study, the complete reaction profile was also followed in acetic acid with *O*-phenyl and -methyl ethers of CD and CN utilized as modifiers. Clearly, for both CD and CN and their corresponding ether derivatives, a correlation between the substituent bulkiness and *ee* can be observed (Table 2, Fig. 4). The correlation is more pronounced in the cinchonidine case while being considerably less pronounced in the cinchonine series. In acetic acid, both *O*-phenyl ethers induce an inversion of enantioselectivity. The solvent employed plays a significant role in the enantiodifferentiation of PPD over chirally modified platinum catalysts [52]. For hydrogenation in acetic acid, the observed enantiomeric excesses are low, and the results obtained should be critically assessed when drawing mechanistic conclusions on the hydrogenation.

To summarize the results from the hydrogenation of PPD in acetic acid, neither the regioselectivity nor the initial rate of reaction directly correlates with the size of the C(9) substituent. The enantiomeric excess, however, appears to show a correlation.

3.2.3. Kinetic resolution of the 1-hydroxy-1-phenyl-2-propanones

Due to the consecutive reaction network, the relative concentrations of the 1-hydroxy-1-phenyl-2-propanone enantiomers change significantly during the course of the reaction. Following the reaction over a long period of time enables to study the effect of the C(9) substituent on the kinetics of the second hydrogenation step. Kinetic resolution of the primary hydrogenation products is influenced by the presence of the modifier. When cinchonidine is utilized as a chiral modifier, both in toluene and acetic acid, the enantiomeric excess increases with higher conversion of PPD being indicative of higher rate of (*S*)-enantiomer hydrogenation (Fig. 1b) [15]. The opposite is observed in the cinchonine case where the (*R*)-enantiomer is reacting faster than its (*S*)-enantiomer, but only in acetic acid. In toluene both enantiomers are reacting almost with the same rate (Fig. 3).

In toluene the substitution of the modifier hydroxyl group did not affect the rate of hydroxyketone hydrogenation, while in acetic acid the substituent bulkiness appears to be crucial. The yield of the diols after 8 h of reaction is gradually decreasing with increase in the substituent group size (OH–OMe–OPh, Table 3). The relationship holds for both cinchonidine and cinchonine derivatives.

Kinetic resolution of the 1-hydroxyketones results from the lower hydrogenation rate of enantiomer produced in excess during the first hydrogenation step. Thus, (1*S*)- reacts faster than its (1*R*)-enantiomer when the catalyst surface is modified by cinchonidine, and an inversion in the sense of the enantiomer preference is observed in toluene when the hydroxyl group is substituted. The most effective resolution was observed when cinchonidine was used as a chiral modifier and the (1*S*)-enantiomer reacts three times faster than its (1*R*)-enantiomer. Almost no preference for one of the 1-hydroxyketones was detected with MeOCD, TMSOCD, ADMSOCD and CN modifiers in toluene, while PhOCD and TBDMSOCD modifiers induced (1*R*)-enantiomer higher reaction rate (Table 3).

In acetic acid, the (*S*)-enantiomer also reacts faster than the (*R*)-enantiomer in the presence of cinchonidine and its derivatives and slower in the presence of cinchonine derivatives (Fig. 4). The effect of substituent bulkiness is evident in the case of cinchonidine, as the increase in the size of the C(9)-*O*-substituent results in less effective resolution of the 1-hydroxyketones. Cinchonine and its derivatives do not show clear correlation. The lack of correlation may originate from the structure of cinchonine, where the vinyl group at C(3) is spatially closer to the hydroxyl group than in cinchonidine. The present observations explain the high selectivity towards the formation of (1*R*,2*S*)- and (1*S*,2*R*)-diols in acetic acid at the early stage of the reaction when MeOCN [15] and *O*-methyl-10,11-dihydrocinchonidine were used as chiral modifiers, respectively [14,15].

It is noteworthy, that in the case of the *O*-methyl ether derivatives the solvent plays a determinative role in favoring the

reaction of one enantiomer over another. In the second hydrogenation step, the (1*R*)-enantiomer is consumed slightly faster than the (1*S*)-enantiomer when MeOCD is employed as the chiral modifier in toluene, whereas in acetic acid the opposite is observed. For MeOCN the solvent-dependent inversion of the sense of kinetic resolution is well pronounced.

3.2.4. Diastereoselective hydrogenation of 1-hydroxy-1-phenyl-2-propanone

In the present investigation, kinetics of 1-hydroxy-1-phenyl-2-propanone hydrogenation and the influence of the modifier structure effect on it has been considered for the first time (Table 3). In particular, it is interesting to compare the mechanisms of enantio- and diastereoselection for PPD and the 1-hydroxyketones. More specifically, the same type of modifier structure–selectivity dependence and solvent effect in the two cases indicate similar modifier–reactant complexes active in enantio- and diastereoselection, and vice versa.

Recently, we have also investigated the hydrogenation of enantiomerically enriched (>90% *ee*) (*R*)-1-hydroxy-1-phenyl-2-propanone (1*R* in Scheme 1) over cinchonidine modified platinum catalyst, the results of which will be addressed in more detail in a separate study [53]. In brief, the experimentally observed diastereoselectivity in this reaction was approximately 60% in favor of the (1*R*,2*S*)-diol when cinchonidine was used as the chiral modifier in toluene. Moreover, the hydrogenation of (1*R*) proceeds diastereoselectively even over the unmodified platinum catalyst ($de = 49\%$) [53]. In the present study, we apply the kinetic approach to estimate the diastereoselectivities in the hydrogenation of the 1-hydroxy-1-phenyl-2-propanones being present as component of the complex mixture of PPD hydrogenation products. This task is very challenging since the hydrogenation of two different isomeric hydroxyketones results in the formation of identical diols. For example, hydrogenation of both (1*R*)-hydroxyketone and (2*S*)-hydroxyketone potentially provides the (1*R*,2*S*)-diol as one of the two products. Diastereoselectivities in the hydrogenation of the (1*R*)- and (1*S*)-hydroxyketones (d*r*(1*R*) and d*r*(1*S*), respectively) were here calculated using the apparent rate constants (Table 3). Diastereoselectivity of the (1*R*)-hydroxyketone hydrogenation (d*r*(1*R*) value in Table 3) calculated from the PPD hydrogenation experiments over the CD-modified catalyst in toluene in the present work is in very good agreement with the diastereoselectivity observed experimentally under similar conditions in the hydrogenation of (*R*)-1-hydroxy-1-phenyl-2-propanone alone [53]. This observation supports the reliability of the diastereoselectivity estimation method utilized in the present study.

Hydrogenation of the 1- and 2-hydroxyketone mixture always gives rise to the preferential formation of *erythro*-diols (Table 3). In toluene, the *O*-ether cinchonidine derivatives are less effective for diastereoselective hydrogenation of (1*R*) than the parent alkaloid, while the *O*-ether cinchonine derivatives are as effective as CN. The hydrogenation of (1*S*) is also diastereoselective, with MeOCD being the most efficient modifier in toluene. Diastereoselectivity inversion was observed for two modifiers, PhOCN and TMSOCN, resulting in an excess of *threo*-(1*S*,2*S*)-diol. Moreover, a correlation between the substituent bulkiness and diastereoselectivity of the (1*R*)-hydroxyketone hydrogenation was observed for cinchonidine and its derivatives. When the bulkiness of the group at the C(9) position of the modifier was increased in the order OH → OMe → OR (R = Ph, Me_3Si, $Me_2(CH_2{=}CHCH_2)Si$, *t*-$BuMe_2Si$, Ph_2MeSi), the diastereoselective excess gradually decreased from 58% to almost 0% (Table 3). In the cinchonine series, however, diastereoselectivity of the (1*R*) hydrogenation did not depend on the C(9)-substituent. A striking resemblance was observed for the (1*S*)-hydroxyketone hydrogenation, taking into consideration that for the cinchonine derived modifiers, diastereoselectivity correlates with the substituent bulkiness (Table 3), whereas in the case of cinchonidine and its derivatives direct correlation was not observed. It is evident that the modifier structure–selectivity dependence is different for the enantio- and diastereoselection in PPD and 1-hydroxyketone hydrogenations in toluene. Substitution of the modifier hydroxyl group results in a dramatic change in enantioselectivity of the PPD hydrogenation. In contrast, the diastereoselectivity of 1-hydroxyketone hydrogenation gradually decreases with increase in the substituent bulkiness. Therefore, it can be concluded that the OH group of the modifier is not directly involved in the formation of the complex between the 1-hydroxyketone and the chiral modifier on the catalyst surface, whereas for PPD opposite observations have been reported [14,15,51].

The model presented predicts highly diastereoselective hydrogenation of 1-hydroxyketones in acetic acid (Table 3). This is in line with the previous observations [15]. The high diastereomeric excess in the hydrogenation of 1-hydroxyketones in acetic acid and the low *ee* observed in the hydrogenation of PPD in the same media also support the hypothesis that the mechanisms for stereoselection are different for the aromatic and aliphatic ketones.

Experimentally, it was observed that the ratio of the diols strongly depends on the conversion of 1-hydroxyketones both in acetic acid and toluene. When the conversion is low, *erythro*-diols are produced in large excess over the *threo*-diols. With an increase in conversion, the ratio is gradually decreasing. Obviously, the first-order kinetic approach cannot describe all the processes on the surface at higher metal coverage by diols (cf. the values for experimentally observed and calculated *erythro*/*threo* in Table 3). Earlier it has been shown by in situ ATR-IR monitoring of a Pt/Al_2O_3 film during the hydrogenation of ethyl pyruvate in supercritical CO_2 [54] that desorption of ethyl lactate is slower than the adsorption of ethyl pyruvate and the hydrogenation reaction. Clearly, the solvent plays an important role in the adsorption–desorption processes over heterogeneous catalysts which has been observed for ethyl pyruvate hydrogenation [55]. Nevertheless, the accumulation of the diol products on the catalyst surface and the subsequent alteration of the chiral site cannot be excluded entirely.

Another possible explanation is that kinetic resolution of the hydroxyketones results in regio and enantiomers reacting separately during the time scale studied. When CD was used as a modifier in the hydrogenation of PPD in toluene (Fig. 1) the diols were observed in 1% yield already after 15 min of reaction.

The amounts of the 1-hydroxyketones and 2-hydroxyketones were 25.7% and 5.7%, respectively, and increased until almost all of PPD was consumed. Thus, after 2 h of reaction the yield of the hydroxyketones was at its maximum (79.6%) and gradually decreased after this point. After 8 h, both (1*S*) and (2*S*) were almost completely consumed indicating that the diols obtained at this point and thereafter are produced from the hydrogenation of the (1*R*)- and (2*R*)-hydroxyketones, while the diols obtained earlier result from the hydrogenation of all four hydroxyketones.

3.3. Conformational equilibria versus selectivity

The central role of the *Open(3)* conformation of cinchonidine is commonly accepted as crucial for obtaining high enantioselectivity in the hydrogenation of carbonyl compounds over cinchona-modified platinum catalysts [56]. The decrease of *ee* for *O*-substituted cinchona alkaloids in enantioselective hydrogenation of ethyl pyruvate in apolar solvents was related to the population of the *Open(3)* conformation in the liquid phase and consequently on the metal surface [56]. As a result of modifier adsorption–desorption processes, the conformational equilibria in the solution can provide some valuable information on the distribution of the adsorbed species.

Although the conformational equilibria of the parent cinchona alkaloids in the liquid phase have been studied in detail earlier [57,58], only a few studies have addressed the conformational behavior of the ether derivatives [58–60]. Considering that the modification of the cinchona alkaloid structure induces changes in the conformational equilibria [58], it is challenging to investigate whether the selectivity over the cinchona alkaloid *O*-ether modified metal catalysts correlates with the population of *Open(3)* or any other conformation in the liquid phase. Structures and conformational behavior of selected modifiers in solution (NMR), in vacuum (DFT) and in the solid state (X-ray) were also investigated and will be reported in a separate paper [44]. The conformational equilibria of cinchona alkaloid *O*-ethers will be discussed in the light of the results presented in this paper.

4. Conclusion

In the hydrogenation of 1-phenyl-1,2-propanedione using cinchona alkaloid *O*-ethers as chiral modifiers, apparent rate constants of all hydrogenation steps were estimated by the first-order kinetic approach. Very good agreement between the experimentally recorded concentrations and the ones predicted by the kinetic model was achieved, which is particularly remarkable considering the complexity of the reaction. The modifier structure–selectivity dependence and the solvent effect were different for enantio- and diastereoselection in the PPD and 1-hydroxyketone hydrogenations. The sense of enantioselectivity in the PPD hydrogenation was either inverted when compared with the corresponding unsubstituted alkaloids or, alternatively, no chiral induction was observed. A sense of kinetic resolution of the 1-hydroxyketones was also inverted with the *O*-ethers of cinchonidine in toluene, whereas the *O*-ethers of cinchonine were better kinetic resolution agents than the parent alkaloid. In acetic acid, the sense of kinetic resolution was retained with the highest value obtained for the *O*-methyl derivatives as modifiers within the cinchonidine and cinchonine series. Correlation between the substituent bulkiness and diastereoselectivity of the 1-hydroxyketone hydrogenation was observed for the reactant–modifier pairs: (1*R*)-hydroxyketone–cinchonidine *O*-ethers and (1*S*)-hydroxyketone–cinchonine *O*-ethers. Hydrogenation of (1*S*)-hydroxyketone was highly diastereoselective when cinchonidine and *O*-methyl cinchonidine were used as modifiers in acetic acid. Moreover, in the same solvent hydrogenation of (1*R*)-hydroxyketone was also highly diastereoselective with cinchonine and its *O*-methyl derivative.

It should be emphasized that the hydrogenation of PPD is very complex and mechanistically different from the well established keto ester hydrogenation. The experimentally observed structure–selectivity effects indicate that the mechanism of enantiodifferentiation over the catalyst modified by parent cinchona alkaloids and their ether derivatives differ from each other.

Acknowledgments

Financial support by the Magnus Ehnrooth Foundation (I.B.) and by the Academy of Finland (project 204724, E.T.) is gratefully acknowledged.

Supplementary material

The online version of this article contains additional supplementary material.

Please visit DOI: 10.1016/j.jcat.2008.01.012.

References

[1] See Curr. Org. Chem. 10 (13) (2006), volume dedicated to the topic of the use of heterogeneous catalysts in organic synthesis.
[2] M. Heitbaum, F. Glorius, I. Escher, Angew. Chem. Int. Ed. 45 (2006) 4732.
[3] Y. Orito, S. Imai, S. Niwa, in: 43rd Catalyst Forum, Japan, 1978, p. 30.
[4] M. Bartók, Curr. Org. Chem. 10 (2006) 1533.
[5] D.Yu. Murzin, P. Mäki-Arvela, E. Toukoniitty, T. Salmi, Catal. Rev. 47 (2005) 175.
[6] G.J. Hutchings, Annu. Rev. Mater. Res. 35 (2005) 143.
[7] T. Bürgi, A. Baiker, Acc. Chem. Res. 37 (2004) 909.
[8] M. Studer, H.-U. Blaser, C. Exner, Adv. Synth. Catal. 345 (2003) 45.
[9] C.J. Baddeley, Top. Catal. 25 (2003) 17.
[10] T. Mallat, E. Orglmeister, A. Baiker, Chem. Rev. 107 (2007) 4863.
[11] S. Diezi, A. Szabo, T. Mallat, A. Baiker, Tetrahedron: Asymmetry 14 (2003) 2573.
[12] O.J. Sonderegger, G.M.W. Ho, T. Bürgi, A. Baiker, J. Mol. Catal. A Chem. 229 (2005) 19.
[13] S. Cserényi, K. Felföldi, K. Balázsik, G. Szöllősi, I. Bucsi, M. Bartók, J. Mol. Catal. A Chem. 247 (2006) 108.
[14] E. Toukoniitty, I. Busygin, R. Leino, D.Yu. Murzin, J. Catal. 227 (2004) 210.
[15] I. Busygin, E. Toukoniitty, R. Leino, D.Yu. Murzin, J. Mol. Catal. A Chem. 236 (2005) 227.
[16] N. Bonalumi, A. Vargas, D. Ferri, A. Baiker, Chem. Eur. J. 13 (2007) 9236.
[17] K. Balázsik, I. Bucsi, S. Cserényi, G. Szöllősi, M. Bartók, J. Mol. Catal. A Chem. 280 (2008) 87.
[18] M. Bartók, M. Sutyinszki, K. Felföldi, G. Szöllösi, Chem. Commun. (2002) 1130.

[19] J.L. Margitfalvi, E. Tálas, Appl. Catal. A Gen. 301 (2006) 187.
[20] F. Hoxha, T. Mallat, A. Baiker, J. Catal. 248 (2007) 11.
[21] A. Pfaltz, T. Heinz, Top. Catal. 4 (1997) 229.
[22] C. Exner, A. Pfaltz, M. Studer, H.-U. Blaser, Adv. Synth. Catal. 345 (2003) 1253.
[23] H.U. Blaser, H.P. Jalett, W. Lottenbach, M. Studer, J. Am. Chem. Soc. 122 (2000) 12675.
[24] H.U. Blaser, H.P. Jalett, M. Garland, M. Studer, H. Thies, A. Wirth-Tijani, J. Catal. 173 (1998) 282.
[25] J.L. Margitfalvi, E. Tálas, E. Tfirst, Top. Catal. 39 (2006) 77.
[26] H.U. Blaser, M. Garland, H.P. Jalett, J. Catal. 144 (1993) 569.
[27] J.A. Slipszenko, S.P. Griffiths, P. Johnston, K.E. Simons, W.A.H. Vermeer, P.B. Wells, J. Catal. 179 (1998) 267.
[28] M. Studer, V. Okafor, H.-U. Blaser, Chem. Commun. (1998) 1053.
[29] O.J. Sonderegger, T. Bürgi, A. Baiker, J. Catal. 215 (2003) 116.
[30] E. Toukoniitty, P. Mäki-Arvela, M. Kuzma, A. Villela, A.K. Neyestanaki, T. Salmi, R. Sjöholm, R. Leino, E. Laine, D.Yu. Murzin, J. Catal. 204 (2001) 281.
[31] E. Toukoniitty, B. Ševčíková, P. Mäki-Arvela, J. Wärnå, T. Salmi, D.Yu. Murzin, J. Catal. 213 (2003) 7.
[32] E. Toukoniitty, P. Mäki-Arvela, A.N. Villela, A.K. Neyestanaki, R. Leino, T. Salmi, R. Sjöholm, E. Laine, J. Väyrynen, T. Ollonqvist, P.J. Kooyman, Catal. Today 60 (2000) 175.
[33] V. Nieminen, A. Taskinen, M. Hotokka, D.Yu. Murzin, J. Catal. 245 (2007) 228.
[34] A. Lindholm, P. Mäki-Arvela, E. Toukoniitty, T.A. Pakkanen, J.T. Hirvi, T. Salmi, D.Yu. Murzin, R. Sjöholm, R. Leino, J. Chem. Soc. Perkin Trans. 1 (2002) 2605.
[35] M. von Arx, T. Mallat, A. Baiker, Angew. Chem. Int. Ed. 40 (2001) 2302.
[36] M. Bartók, M. Sutyinszki, I. Bucsi, K. Felföldi, G. Szöllősi, F. Bartha, T. Bartók, J. Catal. 231 (2005) 33.
[37] (a) M. Bartók, K. Balázsik, I. Bucsi, G. Szöllősi, J. Catal. 239 (2006) 74;
(b) K. Szőri, K. Balázsik, K. Felföldi, M. Bartók, J. Catal. 241 (2006) 149.
[38] E. Orglmeister, T. Mallat, A. Baiker, J. Catal. 233 (2005) 333.
[39] F. Hoxha, L. Königsmann, A. Vargas, D. Ferri, T. Mallat, A. Baiker, J. Am. Chem. Soc. 129 (2007) 10582.
[40] M. Maris, T. Mallat, A. Baiker, J. Mol. Catal. A Chem. 242 (2005) 151.
[41] R.L. Jenkins, N. Dummer, X. Li, S.M. Bawaked, P. McMorn, R.P.K. Wells, A. Burrows, C.J. Kiely, G.J. Hutchings, Catal. Lett. 110 (2006) 135.
[42] N.F. Dummer, R. Jenkins, X. Li, S.M. Bawaked, P. McMorn, A. Burrows, C.J. Kiely, R.P.K. Wells, D.J. Willock, G.J. Hutchings, J. Catal. 243 (2006) 165.
[43] N.J. Colston, R.P.K. Wells, P.B. Wells, G.J. Hutchings, Catal. Lett. 103 (2005) 117.
[44] I. Busygin, J. Sinkkonen, V. Nieminen, R. Sillanpää, E. Toukoniitty, D.Yu. Murzin, R. Leino, manuscript in preparation.
[45] H. Haario, Modest 6.1, Profmath Oy, Helsinki, 2002.
[46] S. Diezi, T. Mallat, A. Szabo, A. Baiker, J. Catal. 228 (2004) 162.
[47] N. Bonalumi, A. Vargas, D. Ferri, T. Bürgi, T. Mallat, A. Baiker, J. Am. Chem. Soc. 127 (2005) 8467.
[48] S. Diezi, S. Reimann, N. Bonalumi, T. Mallat, A. Baiker, J. Catal. 239 (2006) 255.
[49] (a) R. Hess, A. Vargas, T. Mallat, T. Bürgi, A. Baiker, J. Catal. 222 (2004) 117;
(b) R. Hess, F. Krumeich, T. Mallat, A. Baiker, J. Mol. Catal. A Chem. 212 (2004) 205.
[50] R. Hess, S. Diezi, T. Mallat, A. Baiker, Tetrahedron: Asymmetry 15 (2004) 251.
[51] I. Busygin, O.P. Tkachenko, V. Nieminen, V.Yu. Borovkov, R. Sillanpää, E. Toukoniitty, L.M. Kustov, D.Yu. Murzin, R. Leino, J. Phys. Chem. C 111 (2007) 9374.
[52] E. Toukoniitty, P. Mäki-Arvela, J. Kuusisto, V. Nieminen, J. Päivärinta, M. Hotokka, T. Salmi, D.Yu. Murzin, J. Mol. Catal. A Chem. 192 (2003) 135.
[53] I. Busygin, A. Taskinen, V. Nieminen, E. Toukoniitty, T. Stillger, M. Müller, D.Yu. Murzin, R. Leino, manuscript in preparation.
[54] M.S. Schneider, J.-D. Grunwaldt, T. Bürgi, A. Baiker, Rev. Sci. Instrum. 74 (2003) 4121.
[55] A. Gamez, J. Köhler, J. Bradley, Catal. Lett. 55 (1998) 73.
[56] T. Bürgi, A. Baiker, J. Am. Chem. Soc. 120 (1998) 12920.
[57] G.D.H. Dijkstra, R.M. Kellogg, H. Wynberg, J.S. Svendsen, I. Marko, K.B. Sharpless, J. Am. Chem. Soc. 111 (1989) 8069.
[58] G.D.H. Dijkstra, R.M. Kellogg, H. Wynberg, J. Org. Chem. 55 (1990) 6121.
[59] (a) A. Vargas, D. Ferri, N. Bonalumni, T. Mallat, A. Baiker, Angew. Chem. Int. Ed. 46 (2007) 3905;
(b) N. Bonalumni, A. Vargas, D. Ferri, A. Baiker, Chem. Eur. J. 13 (2007) 9236.
[60] A. Vargas, N. Bonalumni, D. Ferri, A. Baiker, J. Phys. Chem. A 110 (2006) 1118.