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Hydrogenation of α-ketoesters and ketopantolactone on rhodium modified by cinchona and isocinchona alkaloids

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Abstract

Various Rh catalysts and cinchona-type modifiers were tested in the hydrogenation of ethyl pyruvate, ethyl 3-methyl-2-oxobutyrate, and ketopantolactone. The experiments were completed with the study of the nonlinear behavior of modifier mixtures, and UV and NMR analysis of hydrogenation of the modifiers. From this study, β-isocinchonine emerged as an outstanding modifier of Rh/Al_2O_3 that gave up to 68% ee in the hydrogenation of ketopantolactone to (*R*)-pantolactone in toluene, at full conversion and without the formation of any detectable byproducts. Careful prereduction of the catalyst at elevated temperature is critical to achieve good enantioselectivity. The loss of ee, or even the formation of the opposite enantiomer in small excess, in protic solvents is attributed to the formation of solvent–substrate and solvent–modifier complexes that disturb the enantioselection on cinchona-modified Rh. In the weakly interacting solvent toluene, only a few ppm of β-isocinchonine related to ketopantolactone was sufficient to induce enantioselection. This unique feature of the conformationally rigid isocinchona alkaloid is attributed to the stronger adsorption on Rh and weaker adsorption on Al_2O_3, and to the higher resistance against hydrogenation of its quinoline ring "anchoring moiety" compared with the corresponding values of cinchonine and cinchonidine.

Keywords: Ethyl pyruvate; Ethyl 3-methyl-2-oxobutyrate; Ketopantolactone; β-Isocinchonine; Asymmetric hydrogenation; Nonlinear phenomenon; Inversion of enantioselectivity

1. Introduction

From a synthetic standpoint, there are only three attractive chirally modified metal catalysts that offer better than 90% ee: (in historical order) the Ni-tartaric acid [1,2], Pt-cinchona [3–6], and Pd-cinchona systems [7,8]. Whereas in homogeneous catalysis, the enantioselectivity of chiral Rh complexes is excellent in the hydrogenation of ketones [9], application of chirally modified, supported Rh in the reduction of C=O bonds is characterized by moderate chemoselectivity and enantioselectivity [10–18]. An exception is the hydrogenation of hydroxyketones on cinchonidine (CD)-modified Rh/Al_2O_3, with up to 80% ee [19]. Even in this reaction, however, the reaction rate was low and a high modifier/substrate molar ratio (M/S) was necessary, due mainly to the competing hydrogenation of the modifier itself. In cinchona alkaloids, the quinoline ring anchors the modifier to the metal surface, and its saturation leads to a successive loss of enantioselection [20,21].

A possible reason for the limited success is that up to now, only a few chiral modifiers have been tested with Rh. The best modifiers are cinchona alkaloids [10–16] and *O*-phenylcinchonidine [19]. The less bulky ether derivatives and the N-alkylated and N-arylated derivatives of CD [14,15] are barely efficient.

Interesting derivatives of cinchona alkaloids are the isocinchona alkaloids [22], for example, β-isocinchonine (β-iCN, Scheme 1). Its structure is more rigid than that of the parent alkaloid and does not contain a free OH group, the function of which may interact with the ketone substrate (beside the basic quinuclidine N atom [23]). Application of this and other isocinchona alkaloid modifiers in the Pt-catalyzed enantioselective hydrogenation of α-ketoesters [24–30] and ketopantolactone [28] did not reveal any advantage compared with the performance of CN or CD. Because α-isocinchonine exists only in "open" conformation, the reasonably good enantioselectiv-

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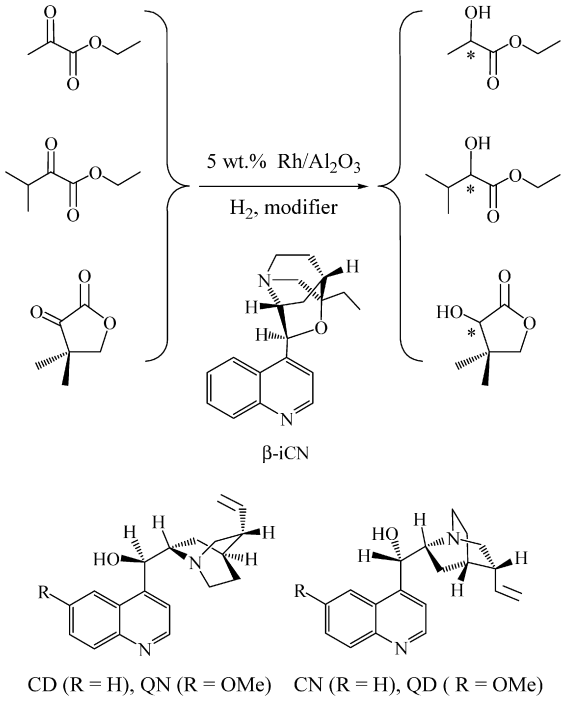


Scheme 1. Hydrogenation of ethyl pyruvate, ethyl 3-methyl-2-oxobutyrate, and ketopantolactone on a 5 wt% Rh/Al_2O_3 catalyst in the presence of cinchona and isocinchona alkaloids.

ity achieved with this modifier in pyruvate hydrogenation on Pt [31] confirmed the relevance of this conformation in various mechanistic models [23].

The situation is different on rhodium, as we discuss later in the hydrogenation of some activated ketones (Scheme 1). We compare the performance of the conformationally rigid β-iCN with that of the commonly used cinchona modifiers CD, CN, QD, and QN (Scheme 1).

2. Experimental

2.1. Materials

Most of the chemicals were used as received: 2-propanol (Acros, extra dry, water <50 ppm), *t*-butanol (Fluka, over molecular sieve, ⩾99.7%), dichloromethane (Fluka, over molecular sieve, ⩾99.5%, water ⩽0.005%), dimethylformamide (DMF) (Acros, over molecular sieve, ⩾99.9%, water <50 ppm), acetic acid (Fluka, p.a.), 1,1,1-trifluoroacetic acid (TFA) (Fluka, >98%), cinchonidine (CD) (Fluka, ⩾98% alkaloid), cinchonine (CN) (Fluka, ⩾98% alkaloid), quinine (QN) (Fluka, ∼99% alkaloid), quinidine (QD) (Fluka, 99% alkaloid), ketopantolactone (Roche AG, 99%), molecular sieve (Zeochem, Z4-01, 2–3 mm), 5 wt% Rh/Al_2O_3 (Engelhard 8001, ESCAT 34). The solvents toluene (Fluka, 99.7%), tetrahydrofuran (THF) (J.T. Baker, 99.5%), and *t*-BuMe ether (Fluka ⩾99.5%) were freshly distilled from Na before use. Acetonitrile (Fluka, ⩾99.5%) was distilled from P_2O_5. The substrates ethyl pyruvate (Acros, 98%, 0.02% ethyl lactate after distillation) and ethyl 3-methyl-2-oxobutyrate (Aldrich, 97%) were carefully distilled in vacuum before use.

Beta-isocinchonine (β-iCN) was synthesized according to the method described by Bartók and coworkers [26], but with some changes in the reaction and separation conditions to improve the yield and purity; 5 g CN (16.98 mmol) was dissolved in 85% concentrated sulphuric acid (30 ml). The reaction mixture was stirred for 7 h at 70 °C and then overnight at room temperature. After cooling to 0 °C, ammonia was added dropwise until a pH of 11 was achieved. The white suspension was diluted with ethanol, stirred for 10 min, and filtered off. The filtrate was concentrated in vacuum and the product was purified by repeated column chromatography on silica gel. The eluent was ethyl acetate:ethanol = 1:1 in the presence of 0.002 vol% ammonia. Finally, 1 g of pure β-iCN was obtained (ca. 20% yield). The product was identified by NMR spectroscopy (Bruker Advance spectrometer operating at 500 MHz). The NMR spectrum agreed well with that published by Thiel et al. [22]. GC/MS analysis indicated 99.5% purity and the absence of cinchonine.

2.2. Catalyst pretreatment methods

The 5 wt% Rh/Al_2O_3 catalyst was always pretreated at elevated temperature before use. According to this standard pretreatment procedure, the catalyst was flushed in a fixed-bed reactor at 400 °C with nitrogen for 30 min, followed by a reductive treatment in flowing hydrogen for 90 min at the same temperature. After cooling to room temperature in hydrogen, the catalyst was flushed with nitrogen for another 10 min and immediately transferred to the reactor (under solvent) without exposure to air.

Alternatively, additional catalyst treatments (after the standard reductive heat pretreatment) were used. In method 1, an ultrasonic pretreatment of the catalyst [32] was performed at room temperature in a 50-ml glass reactor equipped with a gas inlet and a rubber septum. Before sonication, β-iCN and the 5 wt% Rh/Al_2O_3 catalyst were added in the solvent and flushed with nitrogen (or hydrogen) for 15 min. The irradiation was performed for 30 min in a closed nitrogen (or hydrogen) atmosphere. An ELMA TI-H-5 multiple-frequency ultrasonic device was used at 25 kHz. The sonication in air was performed directly without flushing the reactor. In method 2, the pretreatment in the liquid phase at 111 °C was performed in a 25-ml two-necked reaction flask equipped with a cooler, a gas inlet, and a rubber septum. The catalyst and β-iCN were added to the solvent (toluene), flushed with nitrogen (or hydrogen) for 15 min, stirred under refluxing toluene for 30 min, and then the mixture was transferred to the autoclave under nitrogen (or hydrogen). In method 3, the catalyst and β-iCN were stirred in toluene under air, nitrogen, or hydrogen in a 50 ml glass reactor for 30 min at room temperature.

2.3. Catalytic hydrogenation

Hydrogenations were carried out in a 100-ml stainless steel autoclave equipped with a 50-ml glass liner, a PTFE cover, and a magnetic stirrer. The autoclave was also equipped with

a valve for sample collection or substrate addition. Under standard conditions, 21 mg of catalyst, 0.92 mmol of substrate, 6.8 μmol of modifier (M/S = 0.74 mol%), and 5 ml of solvent were stirred magnetically (750 rpm) at 10 bar and room temperature for 60 min. The pressure was held at a constant value with a computerized constant volume–constant pressure device (Büchi BPC 9901). At the end of the reaction, 40 ml of ethyl acetate was added to the slurry and stirred for 5 min before filtration. The conversion and enantioselectivity (ee) were determined by GC analysis of the filtrate, using an HP 6890 gas chromatograph and a Chirasil-DEX CB (Chrompack 7502 25 m × 0.25 mm × 0.25 μm) capillary column. All experiments were carried out at least twice; the average values are shown in the tables and figures. The estimated standard deviation of enantiomeric excess (ee) was about ±0.5% (±1% at <5% ee). In most cases, the ee was determined at full conversion of the ketones.

Hydrogenation of the modifiers β-iCN, CN, and CD was carried out in the same autoclave as the ketone hydrogenations. The conversion was followed by UV spectroscopy with a Cary 400 spectrometer and a 25-mm path length quartz cuvette. The conditions were as follows: 2 mg of modifier in 5 ml mixture of toluene (90 vol%) and THF (10 vol%) was added to 21 mg of 5 wt% Rh/Al_2O_3 and hydrogenated at 90 bar and room temperature. The samples were diluted fourfold before UV measurements. A calibration curve was used to calculate the modifier concentration in solution. NMR spectroscopy (Bruker Advance spectrometer operating at 500 MHz) was used to confirm the structure of the hydrogenation products. The NMR analysis was performed in CCl_3D and CH_3COOD for β-iCN and CN, respectively.

3. Results and discussion

In a preliminary screening, 10 different commercial Rh catalysts were tested in the hydrogenation of ethyl pyruvate, ethyl 3-methyl-2-oxobutyrate, and ketopantolactone (Scheme 1). The catalysts contained carbon or alumina as supports; unsupported Rh black was also tested. In weakly polar solvents in the presence of CD, a 5 wt% Rh/Al_2O_3 (Engelhard) proved to be the most promising, and this catalyst was applied in the further experiments. Recently, an in situ prepared $Rh(CD)/Al_2O_3$ using cinchonidine as a stabilizer of Rh particles and additional QN as modifier has been proposed as an outstanding catalyst for ethyl pyruvate hydrogenation [16]. Unfortunately, we could not reproduce the good enantioselectivity reported earlier and found a low reaction rate.

3.1. Comparison of β-iCN with cinchona alkaloids in different solvents

Hydrogenation of the activated ketone substrates was carried out in a broad range of solvents in the presence of β-iCN and four cinchona alkaloids as chiral modifiers (Tables 1–3). In the weakly polar solvent toluene, in which the solvent effect would be expected to be the smallest, the (*R*)-alcohol always formed in excess in the presence of CD, QN, and β-iCN, and the (*S*)-alcohol formed in the presence of CN and QD.

An interesting observation was the significant variation in the efficiency of cinchona alkaloids in the hydrogenation of the structurally closely related ketones. In the hydrogenation of ethyl pyruvate, ethyl 3-methyl-2-oxobutyrate, and ketopantolactone, the best modifiers were QN, CD, and β-iCN, respectively. In addition, QD and QN, which are reasonably good modifiers in the hydrogenation of the flexible pyruvate molecule, were barely efficient in the reduction of the cyclic

Table 1
The efficiency of cinchona alkaloids and β-isocinchonine as chiral modifiers of Rh/Al_2O_3 in the hydrogenation of ethyl pyruvate; standard conditions

Solvent	ee (%) [Conversion (%)]				
	β-iCN	CN	CD	QN	QD
Toluene	27 (*R*) [100]	40.5 (*S*) [100]	45.5 (*R*) [100]	56.5 (*R*) [100]	40 (*S*) [100]
2-Propanol	34 (*R*) [100]	15 (*S*) [100]	27 (*R*) [100]	–	–
Acetic acid	7 (*R*) [100]	3 (*R*) [100]	8 (*R*) [100]	13.5 (*R*) [100]	11.5 (*S*) [100]
Toluene + 10 μL TFA	3 (*S*) [97]	6 (*R*) [92]	4 (*S*) [98]	–	–

Table 2
The efficiency of cinchona alkaloids and β-isocinchonine as chiral modifiers of Rh/Al_2O_3 in the hydrogenation of ethyl 3-methyl-2-oxobutyrate; standard conditions

Solvent	ee (%) [Conversion (%)]				
	β-iCN	CN	CD	QN	QD
Toluene	33 (*R*) [100]	43 (*S*) [99]	50.5 (*R*) [100]	29 (*R*) [90]	19 (*S*) [78]
t-Butanol	28 (*R*) [100]	2 (*R*) [99]	9 (*R*) [99]	–	–
Acetic acid	21 (*R*) [100]	4 (*R*) [98]	4 (*R*) [99]	9 (*R*) [99]	6 (*S*) [97]
Toluene + 10 μL TFA	4 (*R*) [20]	5.5 (*S*) [14]	13.5 (*R*) [15]	–	–

Table 3
The efficiency of cinchona alkaloids and β-isocinchonine as chiral modifiers of Rh/Al_2O_3 in the hydrogenation of ketopantolactone; standard conditions, ee at full conversion

Solvent	ee (%)				
	β-iCN	CN	CD	QN	QD
Toluene	54 (*R*)	25 (*S*)	47 (*R*)	11.5 (*R*)	4 (*S*)
t-BuMe ether	46 (*R*)	9 (*S*)	38 (*R*)	–	–
THF	51 (*R*)	9 (*S*)	38 (*R*)	–	–
CCl_2H_2	35.5 (*R*)	–	–	–	–
DMF	47 (*R*)	–	–	–	–
t-Butanol	35.5 (*R*)	7 (*R*)	6.5 (*R*)	–	–
Acetonitrile	29 (*R*)	–	–	–	–
2-Propanol	35.5 (*R*)	2 (*R*)	20 (*R*)	–	–
Acetic acid	11 (*R*)	1 (*R*)	4 (*R*)	4 (*R*)	2 (*S*)
Toluene + 10 μL TFA	9.5 (*R*)	4 (*S*)	10.5 (*R*)	–	–

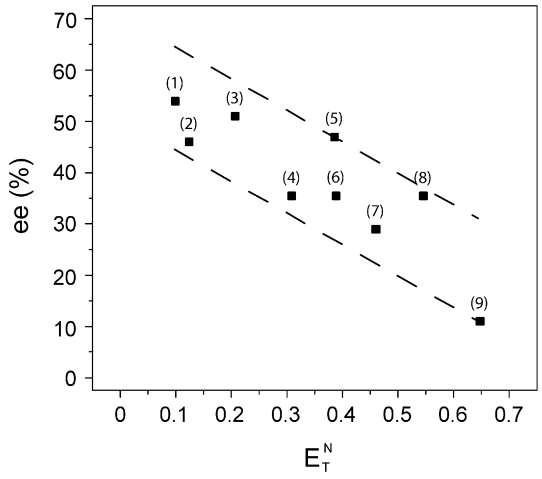


Fig. 1. Solvent effect on the enantioselectivity in the hydrogenation of ketopantolactone over β-iCN-modified Rh/Al_2O_3; standard conditions, ee to the (*R*)-enantiomer was determined at full conversion. Solvents: toluene (1), *t*-BuMe ether (2), THF (3), dichloromethane (4), DMF (5), *t*-butanol (6), acetonitrile (7), 2-propanol (8), acetic acid (9).

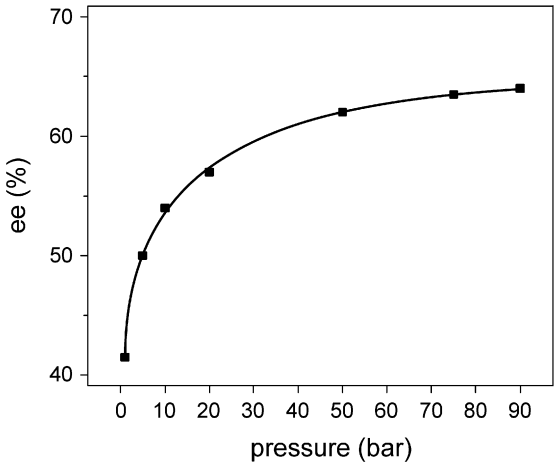


Fig. 2. Influence of hydrogen pressure on the enantioselectivity in the hydrogenation of ketopantolactone to (*R*)-pantolactone over β-iCN-modified Rh/Al_2O_3; standard conditions, toluene, full conversion.

and rigid ketopantolactone. Apparently, aryl-substitution of the quinoline ring in QN and QD at the 6′ position (Scheme 1) disturbs the enantioselection in ketopantolactone hydrogenation.

Considering the role of solvents, in the hydrogenation of all ketones with all five modifiers, the highest enantioselectivities were obtained in toluene. The ee decreased with increasing solvent polarity, as illustrated in Fig. 1 for the example of ketopantolactone hydrogenation in the presence of β-iCN as a modifier. The solvents are characterized by their empirical solvent parameter E_T^N [33]. A similar negative effect of polar solvents on the enantioselectivity was observed in earlier studies in the hydrogenation of ketopantolactone on Pt [34] and Rh [15] modified by CD and its ether derivatives.

The loss of ee relative to that achieved in toluene was particularly significant in acidic medium, and even the opposite enantiomer formed in excess in the hydrogenation of ethyl pyruvate in the presence of β-iCN, CN, and CD (Table 1) and in the reduction of ketopantolactone on CN-modified Rh (Table 2). Note that inversion of the major enantiomer caused by replacing toluene with acetic acid as solvent was also observed in the hydrogenation of ethyl pyruvate [25–27] and ketopantolactone [28] on β-iCN-modified Pt.

Rationalization of the change in the sense of enantioselection in protic solvents is not straightforward. Bartók et al. [25] proposed that protonation of the quinuclidine N and the resulting shift in the reaction mechanism from a nucleophilic attack by the quinuclidine N in toluene to an N–H–O type modifier–substrate interaction in acetic acid would be the origin of inversion. This proposal cannot interpret the inversion observed by replacing toluene with *t*-butanol and 2-propanol in the presence of CN (Tables 2 and 3) and the formation of the same enantiomer in both acidic and nonacidic solvents, which is the general case in the hydrogenation of α-ketoesters and ketopantolactone on Pt modified by cinchona alkaloids. It also must be considered that the ee's to the opposite enantiomers are minor in most cases, and such low values cannot support a mechanistic model. It is more likely that H-bonding interactions between the protic polar solvents and the substrate and/or modifier are responsible for the loss of enantioselectivity and that the occasional minor inversion is insignificant due to the corresponding very small energy difference. We have shown earlier [35,36], based on FTIR studies [37], that CD forms various 1:1- and 1:2-type complexes with carboxylic acids, and these complexes may be the actual modifiers that interact with the substrate.

The results in Tables 1–3 show that, compared with the state of art [10–19], the most promising reaction is the hydrogenation of ketopantolactone in the presence of β-iCN. We analyze the characteristics of this reaction below.

3.2. Ketopantolactone hydrogenation on β-iCN-modified Rh

The Rh-catalyzed hydrogenation of ketopantolactone in the presence of β-iCN was very fast, with full conversion reached within 7 min under standard conditions at 10 bar. The aim of the present study was to analyze the influence of reaction conditions on the enantioselectivity at high (full) conversion to avoid possible complications at low conversion (initial transient period [38–41]).

The influence of pressure on the hydrogenation of ketopantolactone was investigated under standard conditions at a M/S ratio of 0.74 mol%. As shown in Fig. 2, the higher the pressure and thus the surface hydrogen concentration, the higher the enantioselectivity. For comparison, using CD and the same Rh/Al_2O_3 catalyst, the ee reached a (broad) maximum at 20 bar in the same reaction (M/S = 0.37 mol%) [15]. The lower ee at higher pressure was attributed to hydrogenation of the quinoline moiety of CD. An even greater effect of modifier stability was reported for the very slow hydrogenation of α-hydroxyketones on Rh, where the positive effect of increased pressure could be utilized only by increasing the amount of CD considerably (M/S = 11.8 mol%) [19]. Because (partial) saturation of the quinoline ring weakens the adsorption of the alkaloid, it is replaced on the metal surface by CD from the solution. Note that Rh belongs to the best catalysts for the hydrogenation of

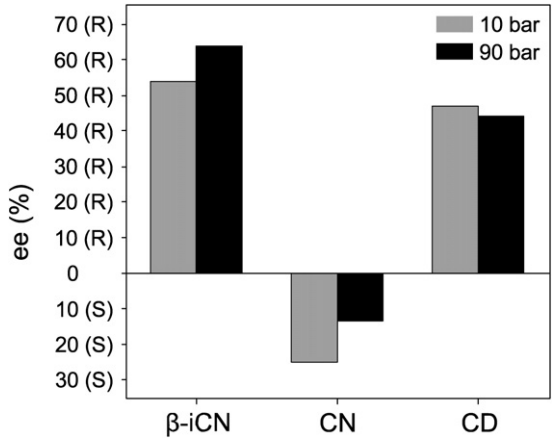


Fig. 3. Comparison of the catalytic performance of Rh/Al_2O_3 modified with β-iCN, CN, and CD in the hydrogenation of ketopantolactone at 10 and 90 bar, respectively. Standard conditions, 6.8 μmol modifier, full conversion.

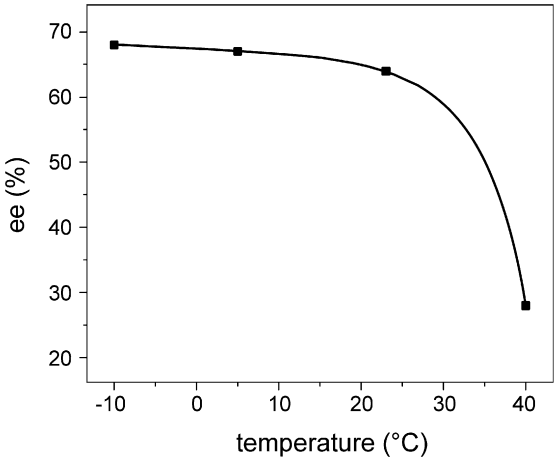


Fig. 4. Influence of temperature on the enantioselectivity in the hydrogenation of ketopantolactone to (*R*)-pantolactone over β-iCN-modified Rh/Al_2O_3; standard conditions, toluene, 90 bar, full conversion.

aromatic and heteroaromatic compounds [42]. The enantioselectivities achieved at 10 and 90 bar in the presence of β-iCN, CN, and CD are shown in Fig. 3 for comparison. The most interesting result is the contradictory effect of high pressure when β-iCN or the parent alkaloid CN is used. This deviation is due mainly to the different resistance of the modifiers against self-hydrogenation, as we discuss later.

The good performance of β-iCN-modified Rh/Al_2O_3 was limited to room temperature or below, as illustrated in Fig. 4. This is a general feature of the hydrogenations on cinchona-modified Rh [11–13,16] and Pt [43–47], and only tartaric acid-modified Ni gives high enantioselectivities at 60–80 °C [1,2]. The 68% ee to (*R*)-pantolactone achieved at −10 °C and 90 bar was the highest enantioselectivity in this reaction on Rh. This enantioselectivity was obtained at full conversion and without the formation of any detectable byproducts.

The influence of modifier/substrate molar ratio (M/S) was studied by varying the amount of modifier at constant substrate concentration (Fig. 5). The correlation is characterized by a broad maximum at a M/S ratio of about 0.4 mol% (corresponding to 0.37 mmol L^{-1} β-iCN). Note that even a M/S molar ratio of only 10 ppm (i.e., <1 μmol L^{-1} β-iCN in the reaction mixture), is sufficient for a significant enantioselection (28% ee). For comparison, a racemic mixture was obtained when <4 μmol L^{-1} β-iCN was applied in the hydrogenation of ethyl pyruvate on Pt/Al_2O_3 [27]. Apparently, β-iCN is a more effective modifier on Rh than on Pt.

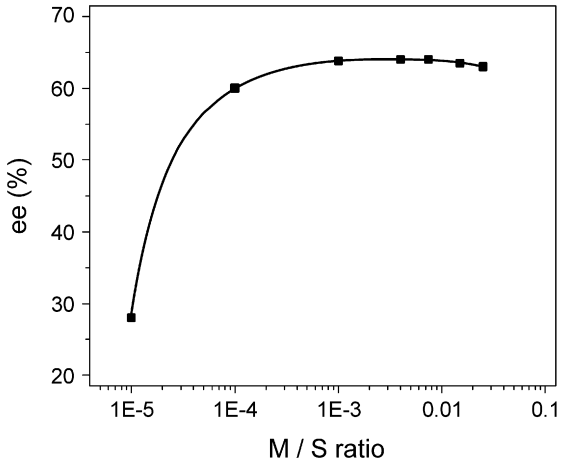


Fig. 5. Influence of modifier/substrate molar ratio (M/S) on the enantioselectivity in the hydrogenation of ketopantolactone to (*R*)-pantolactone over β-iCN-modified Rh/Al_2O_3; standard conditions, toluene, 90 bar, full conversion.

Table 4
Influence of catalyst treatments on the enantioselectivity in the hydrogenation of ketopantolactone to (*R*)-pantolactone over 5 wt% Rh/Al_2O_3 modified by β-iCN (standard conditions, toluene, 90 bar, full conversion). SP: standard pretreatment at 400 °C in flowing hydrogen. Additional treatments: mixtures of freshly reduced catalyst (after SP) and β-iCN were sonicated (method 1), refluxed (method 2), or stirred (method 3) in toluene for 30 min

Method	Atmosphere	*p* (bar)	*T* (°C)	ee (%)
No	–	–	–	44
SP	H_2	1	400	64
1	air	1	25	61
1	N_2	1	25	60.5
1	H_2	1	25	52
1	N_2	1	111	56.5
2	H_2	1	111	53.5
3	air	1	25	58
3	N_2	1	25	59.5
3	H_2	1	25	52
3	H_2	90	25	63.5

Finally, we attempted to improve the enantioselectivity with additional treatments of Rh/Al_2O_3, as summarized in Table 4. A reductive treatment at 400 °C in a continuous-flow reactor, the method used in all reactions discussed up to now, improved the ee by 20%. The likely explanation for this significant change is the complete reduction of surface metal oxides and the cleaning of the surface from impurities originating from the catalyst preparation and storage. Unfortunately, none of the additional treatments applied in the liquid phase after the standard gas-phase prereduction increased the enantioselectivity. We assume that the special effect of these treatments is covered by the

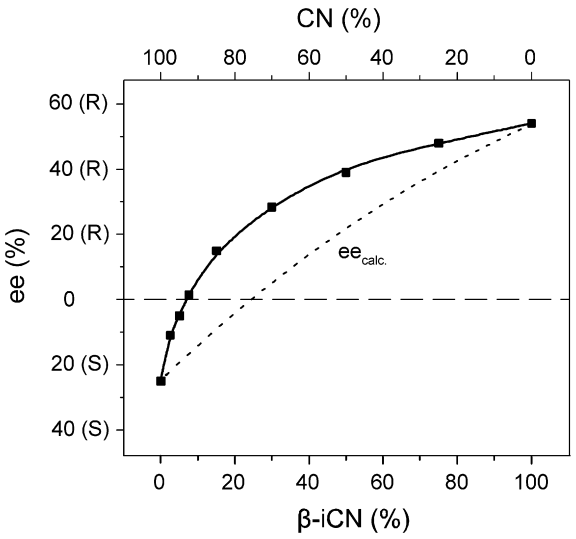


Fig. 6. Hydrogenation of ketopantolactone over Rh/Al_2O_3 modified by β-iCN–CN mixtures; standard conditions, toluene. The dashed line represents the ideal (calculated) behavior.

detrimental effect of (slow) reoxidation of the surface of Rh particles. This interpretation is supported by the negligible changes when the treatment according to method 3 was carried out under hydrogen at high pressure (Table 4, last line).

3.3. Nonlinear phenomenon

The study of the nonlinear behavior of modifier mixtures by the classical "static" method in batch reactors [48–50] and by transient methods in batch [51] and continuous-flow reactors [52] is presently the only possible way to estimate the relative adsorption strength of modifiers under truly in situ conditions. A key requirement is that two modifiers alone give the opposite enantiomers of the product in excess.

Here we applied the classical method commonly used in homogeneous catalysis [53]. The nonlinear behavior of mixtures of β-iCN and CN in the hydrogenation of ketopantolactone is illustrated in Fig. 6. The "expected" or theoretical ee (dashed line) was calculated assuming that the molar ratios of the modifiers in solution and on the Rh surface are identical, the modifier–modifier interactions on the surface are unimportant, and the hydrogenation rates and ee's are linear combinations of those measured by using the modifiers alone. There was considerable deviation from the ideal behavior, and β-iCN governed the enantioselection in the entire concentration range. Only 7.5% β-iCN in the mixture was sufficient to produce the (*R*)-pantolactone in slight excess (1.5% ee), although the calculated ee for this modifier mixture was 16.5% to the (*S*)-enantiomer (corresponding to 18% deviation from linearity). With equimolar amounts of β-iCN and CN, the deviation from the theoretical value was 16% to the (*R*)-enantiomer.

In contrast to the large differences in the adsorption strength on Rh, very similar adsorptions of β-iCN and CN on Pt/Al_2O_3 were reported by Bartók et al. [27,28]. These authors used the transient method in a batch reactor [51] in the hydrogenation of ethyl pyruvate and ketopantolactone. It seems that the superior behavior of β-iCN in mixtures with CN is limited to Rh.

Table 5
Some characteristic data of β-iCN, CN, and CD used to modify Rh/Al_2O_3[a]

Modifier	r_S^0 (mmol min^{-1} g$_{cat}^{-1}$)	r_M^0 (μmol min^{-1} g$_{cat}^{-1}$)	Ads. (%)
β-iCN	12.5	14	12
CN	8.5	24	21
CD	10	25	21

[a] r_S^0—initial reaction rate in the hydrogenation of the substrate ketopantolactone; standard conditions, 10 bar. r_M^0—initial reaction rate in the hydrogenation of the quinoline ring of the modifiers; standard conditions, 90 bar. Ads.—the relative decrease of modifier concentration (in %) in solution due to adsorption on Rh/Al_2O_3, as determined by UV spectroscopy; standard conditions, the mixture of modifier and catalyst in toluene + 10% THF were stirred for 5 min under nitrogen.

The solubility of CN in toluene was much lower than that of β-iCN; we can speculate that the inferior behavior of CN deduced from Fig. 6 is only apparent and due to differences in the actual concentrations of dissolved modifiers. Because the enantioselection with CN in polar solvents was poor (Table 3), we conducted some control experiments in a 90% toluene–10% THF mixture and introduced a 5-min preadsorption period under nitrogen before starting ketopantolactone hydrogenation, to allow equilibration (a deviation from the standard procedure). Under these modified conditions, hydrogenation of ketopantolactone gave 25% (*S*)-pantolactone and 42% (*R*)-pantolactone in the presence of CN and β-iCN, respectively. (The lower enantioselectivities may be due in part to the detrimental effect of stirring in nitrogen; for comparison, see the effect of method 3 in Table 4.) Using the same procedure with equimolar amounts of β-iCN and CN, the ee was 30% to the (*R*)-enantiomer, confirming the inferior behavior of CN in the presence of β-iCN. Clearly, the low solubility in toluene is not the origin of the nonlinear phenomenon.

Previous studies showed that on Pt, CD adsorbs stronger than any other chiral modifier. Modifiers β-iCN and CD cannot be compared directly, because they provide (*R*)-pantolactone in excess, therefore we compared them with CN. The hydrogenation of ketopantolactone was carried out under standard conditions in toluene on Rh/Al_2O_3. In the presence of an equimolar mixture of CN and CD, the ee was 19% to the (*R*)-enantiomer. The "expected" or theoretical value was 16.5% to (*R*)-pantolactone, revealing a minor deviation of only 2.5% to the (*R*)-enantiomer. Note that this relation is similar to that observed on Pt/Al_2O_3 [48]. It demonstrates that on Rh, CD adsorbs more strongly than CN, although the difference is significant smaller than that between β-iCN and CN (16%, Fig. 6). From this comparison, we can deduce the following order of adsorption strength on Rh: β-iCN > CD > CN.

The initial hydrogenation rates of ketopantolactone on Rh/Al_2O_3 in the presence of β-iCN, CN, and CD are given in Table 5. Interestingly, the order of initial reaction rates in the presence of the three modifiers is the same as the order of the adsorption strength of the modifiers. This is not a general situation; many exceptions have been reported using Pt [51,54].

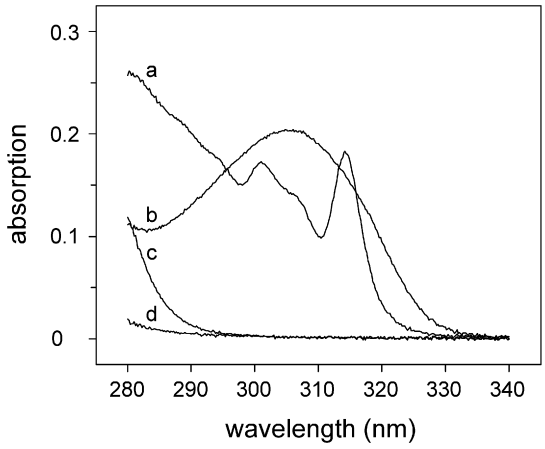


Fig. 7. UV spectrum of quinoline (a), 1,2,3,4-tetrahydroquinoline (b), 5,6,7,8-tetrahydroquinoline (c), and decahydroquinoline (d). Concentrations: 0.34 mmol L^{-1} in a mixture of toluene (90 vol%) and THF (10 vol%).

3.4. Stability of modifiers under reaction conditions: UV and NMR spectroscopy

As discussed previously, a major limitation of Rh is its high activity in the saturation of aromatic rings, leading to extensive degradation of cinchona-type modifiers during ketone hydrogenation [19]. Saturation of the quinoline ring of the modifier leads to weaker adsorption on the catalyst, and the hydrogenated modifier is replaced by an intact modifier from the solution [51,55–57]. This side reaction necessitates uneconomic high M/S ratios and produces waste. To estimate the stability of β-iCN on Rh/Al_2O_3, we compared the hydrogenation of the quinoline rings of β-iCN, CN, and CD under standard conditions used in the enantioselective hydrogenation of ketones. (Note that another side reaction, the hydrogenation of the vinyl group of CN and CD is even faster but does not influence enantioselection.) In each experiment, the modifier and catalyst in 5 ml mixture of toluene (90 vol%) and THF (10 vol%) were stirred for 5 min in nitrogen before hydrogenation. Disappearance of the modifier from solution during this period was considered adsorption on the catalyst. The change of modifier concentration in solution was followed by a UV spectroscopic method in the range of 280–350 nm [51]. A comparison of the UV spectra of quinoline, 1,2,3,4-tetrahydroquinoline, and decahydroquinoline (Fig. 7) with the spectra of CD (not shown), CN, and β-iCN confirmed that the UV spectra of the modifiers were determined by the quinoline chromophore (Figs. 8A and 8B). The concentration of modifiers with intact aromatic ring was determined by the quinoline chromophore at 315 nm.

The amounts of modifiers adsorbed on the catalyst including both Rh and alumina are shown in Table 5. Adsorption of CN and CD was similar and almost twice that of β-iCN. A major reason for the difference is that β-iCN has no free OH-group to interact with the basic sites of the support. Earlier we found a similar difference between the adsorption of CD and its *O*-methylated derivative MeOCD on Pt/Al_2O_3 [58]. The interaction of β-iCN with alumina is limited mainly to that of the basic quinuclidine N with the OH groups of the support

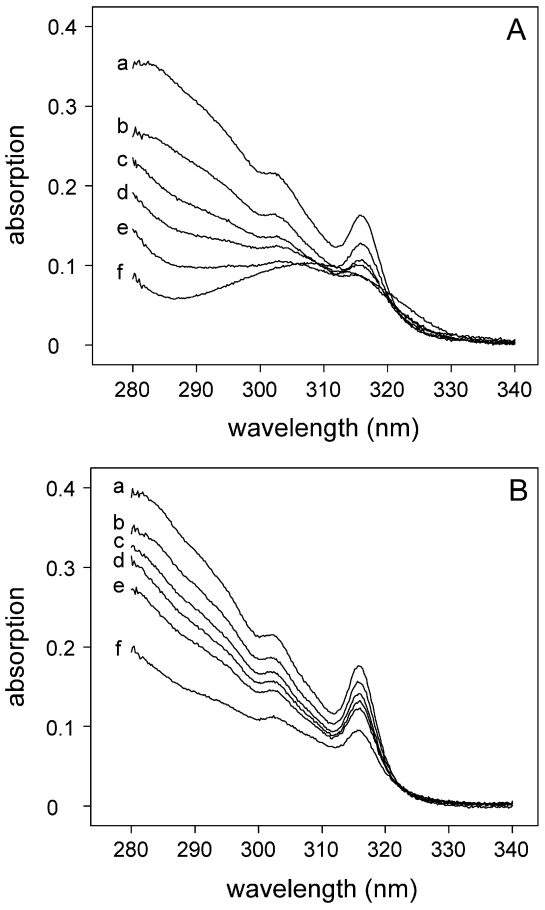
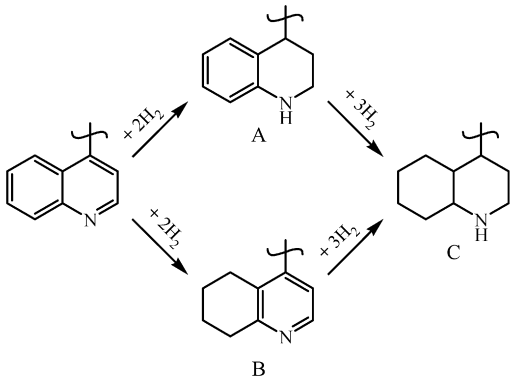


Fig. 8. Hydrogenation of the quinoline ring of CN (A) and β-iCN (B) over Rh/Al_2O_3 followed by UV spectroscopy; standard conditions, 5 ml mixture of toluene (90 vol%) and THF (10 vol%), 90 bar. (a) Initial solution before contacting with the catalyst; (b) the mixture of modifier and catalyst was stirred for 5 min under nitrogen; (c–f) hydrogenation for 2, 5, 10, and 30 min, respectively.



Scheme 2. Hydrogenation pathways of the quinoline moiety of CN and β-iCN over Rh/Al_2O_3.

[59–61]; adsorption via the quinoline N seems to be less important, based on the basicity difference by about six orders of magnitude [62].

In the hydrogenation of CN (Fig. 8A) and CD (not shown), the rapid saturation of the quinoline ring resulted in the first step preferentially in the formation of the 1,2,3,4-tetrahydroquinoline derivative A (Scheme 2). Because the broad band of the UV

spectrum (max. at 308 nm) of the 1,2,3,4-tetrahydroquinoline ring interfered with the characteristic band of the quinoline ring at 315 nm (Fig. 7), hydrogenation of these modifiers could be followed quantitatively only at low conversion, in the first 2 min (Fig. 8A). Thus, these values were used to determine the initial rate of modifier conversion in Table 5.

Hydrogenation of the quinoline ring of β-iCN was significantly different. After 30 min (a multiple of the time required to reach full conversion of ketopantolactone), the concentration of β-iCN in solution was still more than half the initial concentration. The initial hydrogenation rates of the modifiers (Table 5) followed the order CD $\approx$ CN $>$ β-iCN. The UV spectra indicate another major difference, the chemoselectivity of the saturation of the quinoline ring. In the case of β-iCN, the formation of the 1,2,3,4-tetrahydroquinoline derivative was not important.

NMR analysis corroborated the observation made with UV spectroscopy. Hydrogenation of CN for 2 min was sufficient to completely hydrogenate the vinyl group. The conversion of the quinoline ring was around 15%. The saturation was nonselective, and both products A and B in Scheme 2 were formed in similar amounts. (In the hydrogenation of CN over Pt/Al_2O_3, the product B was formed in excess [63].) The conversion of β-iCN was about 20% after about 10 min, confirming the much lower reactivity of this modifier compared with that of the parent alkaloid CN. Both products A and B (Scheme 2) were formed with a ratio of approximately 1:3. Complete saturation of the quinoline rings of modifiers CN and β-iCN (product C in Scheme 2) were observed only in trace amounts.

4. Summary

Hydrogenation of activated ketones on cinchona-modified Rh is moderately enantioselective and complicated by the extensive hydrogenation of the quinoline ring, the "anchoring moiety" of the modifiers to the metal surface. Here we report that β-iCN, a cinchona derivative that has not yet been used to modify Rh, is an outstanding and reasonably stable modifier in the hydrogenation of ketopantolactone. This is the first report of β-iCN being superior to other cinchona alkaloids.

This conclusion is based on the screening of 11 different catalysts and 5 cinchona alkaloids (CD, CN, QN, QD, and β-iCN) in the hydrogenation of ethyl pyruvate, ethyl 3-methyl-2-oxobutyrate, and ketopantolactone. The highest ee (68%) was achieved in the transformation of ketopantolactone to (*R*)-pantolactone on a commercial 5 wt% Rh/Al_2O_3 catalyst. This enantioselectivity is the best reported so far in ketopantolactone hydrogenation on Rh. A further advantage is the high resistance of β-iCN against hydrogenation of its quinoline moiety compared with those of the commonly used CD and the parent alkaloid CN. This attractive feature allows the use of low M/S ratios.

The higher stability of β-iCN was expected to be accompanied by its weaker adsorption on Rh. In contrast, our study of the nonlinear behavior of β-iCN, CD, and CN revealed this order of adsorption strength of the alkaloids. The initial rates of ketopantolactone hydrogenation followed the same order: β-iCN $>$ CD $>$ CN. UV and NMR analysis showed different chemoselectivities of the saturation of the quinoline moieties of the three alkaloids. Our data suggest that the adsorption modes of β-iCN and the parent alkaloid CN during enantioselective hydrogenation on Rh are considerably different. We are currently investigating the origin of this difference in our laboratory using ATR-IR spectroscopy.

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