Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Molecular Catalysis A: Chemical 247 (2006) 108–115
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

C9-O-substituted derivatives of cinchona alkaloids as chiral modifiers in the Orito-reaction: Effects of structure of modifiers on sense of enantioselectivity

Szabolcs Cserényi [a], Károly Felföldi [a], Katalin Balázsik [b], György Szöllősi [b], Imre Bucsi [a,*], Mihály Bartók [a,b,*]

[a] *Department of Organic Chemistry, University of Szeged, Dóm tér 8, H-6720 Szeged, Hungary*
[b] *Organic Catalysis Research Group of the Hungarian Academy of Sciences, Dóm tér 8, H-6720 Szeged, Hungary*

Received 25 August 2005; received in revised form 18 November 2005; accepted 18 November 2005
Available online 28 December 2005

Abstract

The effect of the structure of C9-O-substituted cinchona alkaloids as chiral modifiers of Pt on the enantioselectivity of the Pt-alumina-catalyzed hydrogenation of ethyl pyruvate under mild experimental conditions (room temperature, hydrogen pressure of 1 bar, mainly toluene and tetrahydrofurane as solvents) was investigated. Although C9-O-substituted bulky chiral modifiers also have the open3 conformation, which is a prerequisite of high ee, the ee values observed were still low and even opposite to that expected. Based on the experimental data of a great variety of experiments (ESI-ion-trap-MS, modifier mixtures, selective hydrogenation of chiral modifiers, computational studies) the inversion can explain by tilted adsorption of chiral modifier, namely by a conformational change in the adsorbed chiral modifier and reactant 1:1 intermediate complex.

Keywords: Enantioselective hydrogenation; Ethyl pyruvate; Pt/alumina; Cinchona-derivatives; Inversion

1. Introduction

Nowadays it is no more necessary to underline the significance of asymmetric syntheses for a readership of professionals well versed in chemistry and biology. Due to its well-known advantages, the preparation of chiral compounds using heterogeneous catalytic methods is a synthetic method of outstanding significance. The Orito-reaction also is a heterogeneous catalytic hydrogenation procedure, serving for hydrogenation of activated ketones on Pt-alumina catalysts modified with cinchona alkaloids [1]. Orito and coworkers recognized this reaction in the course of studying the hydrogenation of EtPy and EBF (Fig. 1). The main objective of the recent studies on the Orito-reaction has been to expand its field of utilization, to elucidate the reaction mechanism and to interpret chiral induction in this context. Progress in this direction has been reported in several reviews [2–6].

The most frequently used experimental model for studying the mechanism of the Orito-reaction is the EtPy hydrogenation, a reaction producing high enantioselectivities (ee) (97% ee). Various research strategies and methods have been employed [2–6]. Since it has been concluded from these studies that the structure of the chiral modifier plays a decisive role in enantioselection, manifold experiments have been conducted and are in progress to get a better understanding of the relationship between ee and the structure of the chiral modifier. Our results in this field, published over the years [7–13] and very significant new results of Baiker's group [14–16] encouraged us to study the role of C9-O-substituted derivatives (Fig. 2) of the parent cinchona alkaloids in Orito-reaction.

2. Experimental

2.1. Materials

CD, **13–22** (Fig. 2) and solvents were purchased from Fluka and Aldrich and used as received. DHCD was prepared by hydrogenation of CD (Pd/C, 1 N H_2SO_4/H_2O, 1 bar hydrogen

* Corresponding authors. Fax: +36 62 544 200.
E-mail address: bartok@chem.u-szeged.hu (M. Bartók).

1381-1169/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2005.11.038

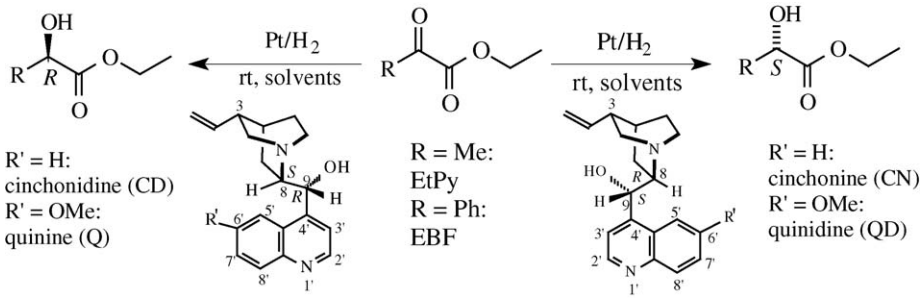


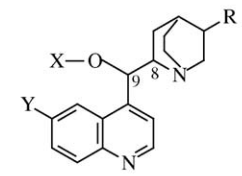
Fig. 1. The Orito-reaction (R = Me (ethyl pyruvate = EtPy, R = Ph (ethyl benzoylformate = EBF).

pressure, 298 K) and used after crystallization. EtPy (Aldrich) was distilled before use to 99.5% purity. The compounds **1**–**3** [17], **4** [14], **5** [18], **6**–**12** [19,20] (Fig. 2) were prepared using literature procedures. The crude products were purified by column chromatography: Fluka 60741 Silica gel 60, eluent CH_2Cl_2/MeOH 85:15. It was found in the course of the enantioselective hydrogenation of EtPy that the individual modifiers purchased as well as the silyl ethers synthesized also contained the parent cinchonas used for modifier synthesis and these affected ee values (**13**, 0.4%; **14**, 0.7%; **15**, 0.4%; **21**, 2.5%; **22**, 1.3%). Silyl ethers proved to be sensitive to purification conditions (hydrolysis on silica gel) and were contained by 0.1–0.8% parent cinchonas. Some of the experiments were performed using these materials; subsequently, the strongly adsorbable parent cinchonas were removed under conditions similar to those of the hydrogenation reaction by stirring for 5 min with Pt-alumina catalyst and the filtrate was used for the Orito-reaction.

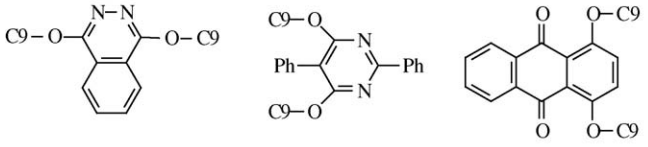
Based on the data in the literature [2–4], from several catalysts the one most often used is Engelhard 4759 (E4759). E4759 was pretreated before use in a fixed bed reactor by flushing with 30 ml min^{-1} helium at 293–693 K for 30 min and 30 ml min^{-1} hydrogen at 693 K for 100 min. After cooling to room temperature in hydrogen, the catalyst was flushed with helium for 30 min and was stored under air before use.

2.2. Hydrogenation

Hydrogenations were performed in an atmospheric batch glass reactor with volume of 10 ml [21]. The agitator speed was 1000–1200 rpm to avoid the diffusion range. The catalytic system including catalyst and 2.5 ml solvent was purged three times with hydrogen and after re-reduction (30 min), the calculated amount of modifier and after 1 min 0.06 ml of EtPy was introduced and stirred in the presence of hydrogen for the required reaction time. Standard conditions are: 25 mg E4759, 2.5 ml solvent, hydrogen pressure: 1 bar, 293–296 K, 1200 rpm, 0.06 ml EtPy. The quantification of conversion and ee are based on GC data [21].



	Modifier	X	R	Y	Configuration	
					C8	C9
1	MeO-CD	Me	vinyl	H	*S*	*R*
2	MeO-DHCD	Me	Et	H	*S*	*R*
3	EtO-CD	Et	vinyl	H	*S*	*R*
4	PhO-CD	Ph	vinyl	H	*S*	*R*
5	AcO-CD	Ac	vinyl	H	*S*	*R*
6	Me_3SiO-CD	Me_3Si	vinyl	H	*S*	*R*
7	Et_3SiO-CD	Et_3Si	vinyl	H	*S*	*R*
8	Me_2PhSiO-CD	Me_2PhSi	vinyl	H	*S*	*R*
9	$MePh_2SiO$-CD	$MePh_2Si$	vinyl	H	*S*	*R*
10	Ph_3SiO-CD	Ph_3Si	vinyl	H	*S*	*R*
11	Ph_3SiO-DHCD	Ph_3Si	Et	H	*S*	*R*
12	Bn_3SiO-CD	Bn_3Si	vinyl	H	*S*	*R*
13	ClBz-DHQ	ClBz	Et	OMe	*S*	*R*
14	ClBz-DHQD	ClBz	Et	OMe	*R*	*S*
15	Phn-DHQ	Phn	Et	OMe	*S*	*R*
16	Phn-DHQD	Phn	Et	OMe	*R*	*S*



17 $(DHQ)_2$ Phal
18 $(DHQD)_2$ Phal
19 $(DHQ)_2$ Pyr
20 $(DHQD)_2$ Pyr
21 $(DHQ)_2$ AN
22 $(DHQD)_2$ AN

Fig. 2. Chiral modifiers studied in Orito-reaction (for abbreviations, see Fig. 1, DH = dihydro, Bn = benzyl).

2.3. Measurements using mixture of modifiers

These hydrogenations were carried out as in 2.2 (25 mg E4759, 273 K, modifier 0.1 mmol/l in THF) with the exception that the reactions were continued after the addition of a second modifier to the mixture containing a first modifier. The procedure was the following: hydrogenation was performed at a modifier concentration of 0.1 mmol/l until 5–15 min; at this point, stirring was stopped and after 1 min a sample was taken. The second modifier was next added and hydrogenation and sampling were continued. ee was measured as described in [21].

2.4. ESI-ion-trap-MS measurements

The ESI-MSD-ion-trap (AGILENT (Palo Alto, CA, USA) 1100 LC-MSD TRAP SL ion-trap MS) was operated under positive ion and auto MS-MS mode using following parameters: ESI, capillary (needle) voltage 3.5 kV, capillary exit voltage 136 V, drying gas (N_2) 9 L min^{-1}, drying gas temperature 623 K, nebulizer gas 40 psi; Ion-trap: scan range 80–350 *m/z*, trap drive 60, max accumulation time 300 ms, fragmentation amplitude 1.5 V, fragmentation time 40 ms.

3. Results and discussion

Preparation and utilization of C9-O-substituted CD-modifiers attracted the attention of researchers as early as the beginning of the nineteen-nineties. Blaser et al. used MeO-DHCD modifier and achieved 95% ee at a hydrogen pressure of 100 bar [22]. AcOH was found to be the best solvent. Nearly 10 years later, in their comprehensive study on the relationship between ee and modifiers Blaser et al. summarized their experimental data on CD-O-derivatives, obtained at hydrogen pressures of 70–100 bar [23]. In recent publications, Baiker et al. proposed an explanation for lower ee values and inversion observed in the case of CD derivatives with bulky C9-substituents [15,16].

Our experimental results obtained under mild conditions (hydrogen pressure 1 bar, room temperature or below, occasionally low modifier concentrations) will be presented below in three groups, i.e. ethers and esters (group 1), ethers developed by Sharpless for the asymmetric dihydroxylation of olefins [24] (group 2) and silyl ethers (group 3).

Selection of the experimental conditions of enantioselective hydrogenation was based predominantly on previous optimization studies using CD and CN chiral modifiers [21,25–27]. Consequently, of the C9-O-substituted cinchona alkaloids shown in Fig. 2, measurements of various types were only conducted in the case of 2 and, for unexpected reasons, **10** and **11**. For these investigations we selected one of the most commonly used catalysts (E4759), toluene, AcOH (these solvents have allowed the highest ee values) and THF (because of UV-detection in HPLC-MS).

3.1. CD, DHCD ethers (*1–4, 15, 16*) and esters (*5, 13, 14*) (*Fig. 2*)

The pertinent experimental data are summarized in Table 1, leading to the following main conclusions: (i) In the case of Me and Et as substituents (entries 1, 2), ee is not decreased as compared to CD, also suggesting—in agreement with earlier investigations [3–6]—that C9-OH does not have a significant role in enantioselection; (ii) as bulkiness of the C9-substituent is increased, ee decreases but the sense of chiral induction is unchanged (entries 3–5; in the case of **4** formation of (*R*)-EtLt is probably due to the presence of CD); (iii) in the case of **16** (entries 6–10), not only is ee significantly decreased, but also the configuration of the product is opposite to that expected (*R*)-EtLt was formed in excess; inversion can be attributed to the effect of steric factors on the adsorption of the chiral modifier, such unexpected inversion was observed in the case of

Table 1
Enantioselective hydrogenation of EtPy on Pt catalyst modified by C9-O-substituted ethers and esters of cinchona alkaloids

	Modifier (mmol/l)	Solvent	Temp. (K)	Catal. (mg)	Time (min)	Conv. (%)	ee (%) *R*	
							tw	Ref.
1	MeO-CD **1** (1)	T	293	12.5	15	100	72	74 [15]
2	EtO-CD **3** (1)	T	293	12.5	15	100	73	76 [15]
3	PhO-CD **4** (1)	T	293	12.5	45	47	14	7 *S* [15]
4	Phn-DHQ **15** (0.1)	THF	293	12.5	60	76	11	T 4 [23]
5	Phn-DHQ **15** (0.1)	THF	273	12.5	60	43	25	–
6	Phn-DHQD **16** (0.1)	THF	293	12.5	60	95	19	T 2 [23]
7	Phn-DHQD **16** (0.1)	THF	293	12.5	2	9	33	–
8	Phn-DHQD **16** (0.1)	THF	293	12.5	15	42	27	–
9	Phn-DHQD **16** (0.1)	THF	293	12.5	30	70	26	–
10	Phn-DHQD **16** (0.1)	THF	273	12.5	60	54	29	–
11	MeO-DHCD **2** (0.1)	AcOH	296	25	10	100	96	93 [23]
12	AcO-CD **5** (0.1)	T	296	25	16	100	42	63 [23]
13	AcO-CD **5** (0.5)	T	296	25	13	100	46	81 [23]
14	AcO-CD **5** (0.1)	AcOH	296	25	70	100	75	67 [23]
15	AcO-CD **5** (0.5)	AcOH	296	25	50	100	81	–
16	ClBz-DHQ **13** (1.6)	T	293	25	30	100	26	22 [23]
17	ClBz-DHQD **14** (1.6)	T	293	25	30	100	0	2 *S* [23]

Standard conditions: 1 bar H_2, T toluene; tw: this work.

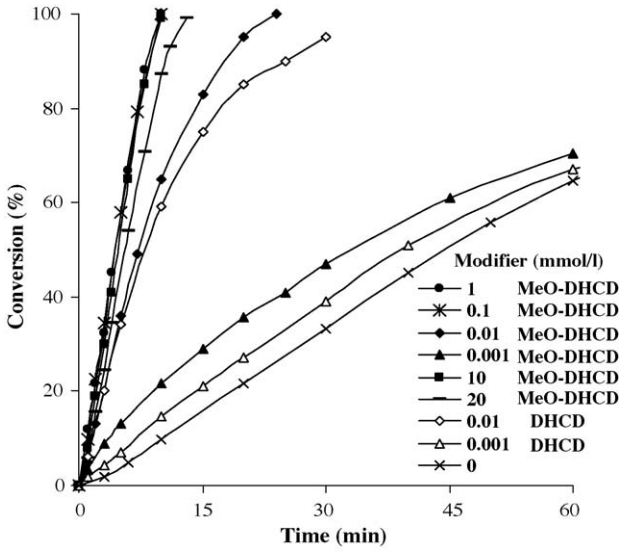


Fig. 3. Enantioselective hydrogenation of EtPy on MeO-DHCD (**2**) modified platinum (25 mg E 4759, 1 bar H_2, 2 ml AcOH, 0.1 ml EtPy, 296 K).

C9-phenoxycinchonidine [14,15]; (iv) in the case of modifiers **15** and **16**, competition of Phn and quinolyl groups for adsorption sites plays an important role, similarly to the anthryl–naphthyl competition [28]; (v) in accordance with the well-known empirical rule [29], low ee values are associated with low reaction rates (see entries 3–7); also, a decrease in temperature results in an increase in ee, similarly to CD [21].

The outstandingly high ee (96%) observed in hydrogenation in AcOH using chiral modifier **2** urged us to compare the data with those obtained with DHCD under identical experimental conditions [21]. We chose the most important parameter, i.e. modifier concentration versus ee (Figs. 3 and 4) as basis for comparison. The figures show that hydrogenation reactions performed in the presence of these two modifiers run somewhat different courses. In the case of **2**, a higher reaction rate results in a higher ee. Maximal ee is attained at a lower modifier/Pt_{surf} ratio in the presence of DHCD than in that of MeO-DHCD, which may have to do with the effects of the solubilities of the two modifiers on the adsorption–desorption equilibrium [30,31].

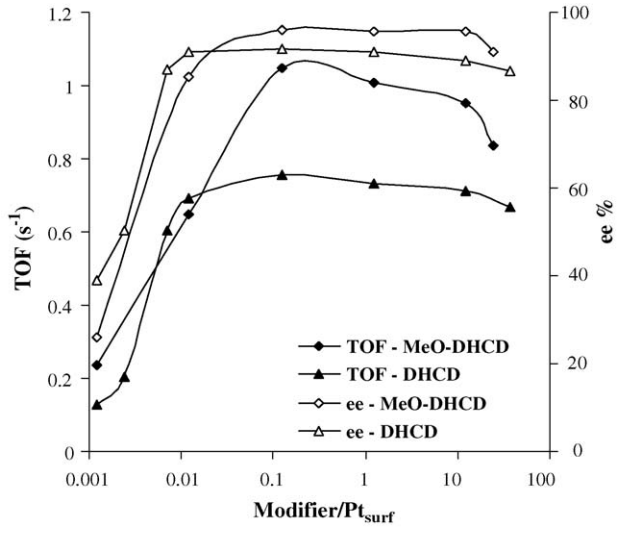


Fig. 4. Initial rate and enantioselectivity as function of Modifier/$Pt_{surface}$ for hydrogenation of EtPy (for conditions and abbreviations, see Fig. 3).

As regards cinchona alkaloid esters, we conducted experiments to study the effect on ee of one modifier with a small-size (**5**) and two with bulky substituents (**13**, **14**) (entries 12–17). When EtPy was hydrogenated in toluene, hydrogenation on Pt modified with AcO-CD at 100 bar allowed a higher ee to be attained [23] than that performed at 1 bar (entries 12, 13). In AcOH, however, ee was higher at 1 bar (81%) than the value published for 100 bar [23] (entries 14, 15). Moreover, ee was not decreased significantly by the small substituent (Ac) relative to DHCD in the case of the CD-ester either, even though the experimental conditions on Pt modified with AcO-CD had not been optimized.

In the presence of modifiers **13** and **14** with bulky ClBz substituents (entries 16, 17) ee was considerably decreased, again as a consequence of hindered adsorption. In the case of **14**, 0 and 2% *S* was formed, respectively [23], with only a less significant decrease in rate (it has to be noted that **13** and **14** contained ~0.4% DHQ and ~0.7% DHQD, respectively). There is a difference between the effects of **13** and **14** on ee ($ee_{13} > ee_{14}$) similar to that observed for CD and CN ($ee_{CD} > ee_{CN}$). In the case of CN this phenomenon was attributed to tilted adsorption due to the surface proximity of the C3-Et group [27].

3.2. DHQ and DHQD derivatives with large substituents at C9 (**17**–**22**) (Fig. 2)

These chiral modifiers were also tested in EtPy hydrogenation in toluene, at 1 bar as compared to 70–100-bar hydrogen pressure [23]. The experimental data are listed in Table 2. When derivatives of **17**–**20** were used (entries 1–4), ee values obtained are as low as those in [23]. The data in Table 2 also reveal that in the case of chiral modifiers **18** and **20**, the major enantiomer was opposite to what was predicted from the absolute configuration of the C8 and C9 atoms, i.e. inversion happened (entries 2, 4).

The data obtained using modifiers **21** and **22**, studied now for the first time, are especially remarkable. The difference between these and the previously discussed modifiers is not only the induction of (*R*)-EtLt with an unexpectedly high (47%) ee, but also the fact that, unlike compounds **18** and **20**, the presence of **22** led to the formation of the product with the expected configu-

Table 2
Enantioselective hydrogenation of EtPy on Pt catalyst modified by cinchona derivatives with large substituents at C9

	Modifier (mmol/l)	Time (min)	Conv. (%)	ee (%) *R*	
				tw	Ref.
1	$(DHQ)_2$-Phal **17** (1.6)	40	100	25	16 [23]
2	$(DHQD)_2$-Phal **18** (1.6)	60	98	0	3 [23]
3	$(DHQ)_2$-Pyr **19** (1.6)	50	100	10	5 [23]
4	$(DHQD)_2$-Pyr **20** (1.6)	45	100	7	9 [23]
5	$(DHQ)_2$-AN **21** (1.6)	30	100	47	–
6	$(DHQD)_2$-AN **22** (1.6)	45	100	13 *S*	–

Conditions: see Table 1, 25 mg E4759, 293 K, T.

Table 3
Enantioselective hydrogenation of EtPy on Pt catalyst modified by C9-O-silyl ethers of CD and DHCD

	Modifier[a] (mmol/l)	Solvent	Time (min)	Conv. (%)	ee (%) *R*	
					tw	Ref.
1	Me_3SiO-CD **6** (1)	T	22	100	17	26 [15]
2	Et_3SiO-CD **7** (1)	T	20	100	13	–
3	Me_2PhSiO-CD **8** (1)	T	15	100	38	–
4	$MePh_2SiO$-CD **9** (1)	T	15	100	53	–
5	Ph_3SiO-CD **10** (1)	T	25	100	62	–
6	Ph_3SiO-CD **10** (1)	THF	10	52	71	–
7	Ph_3SiO-CD **10** (1)	EtOAc	50	100	55	–
8	Ph_3SiO-CD **10** (1)	DMF	60	23	38	–
9	Ph_3SiO-CD **10** (1)	Clb	10	3	13	–
10	Ph_3SiO-CD **10** (1)	Ch	16	96	43	–
11	Ph_3SiO-DHCD **11** (0.1)[b]	THF	40	100	17	–
12	Bn_3SiO-DHCD **12** (0.01)	THF	20	50	37 *S*	–
13	Bn_3SiO-DHCD **12** (0.1)	THF	20	60	10	–
14	Bn_3SiO-DHCD **12** (1)	THF	20	88	30	–

Conditions: see Table 1, 293 K, Ch cyclohexane, Clb chlorbenzene.
[a] Used as prepared, 12.5 mg E4759.
[b] 25 mg E4759.

ration (*S*)-EtLt (entries 5, 6). This unexpected phenomenon may be attributed to the presence of Q (∼2.5%) and QD (∼1.3%) in **21** and **22**, respectively.

3.3. C9-O-silyl ethers (**6–12**) (Fig. 2)

The highest number of tests was done with silyl ethers of group 3, because the first measurements yielded highly unexpected results (Table 3). Namely, silyl ethers containing phenyl and benzyl groups, never before studied as chiral modifiers (**8–10**, **12**) produced relatively high ee values in EtPy hydrogenation (entries 3–10), whereas the less bulky compounds **6** and **7** induced low ee values as expected. The presence of **12** in 0.01 mmol/l concentration led to the formation of (*S*)-EtLt, i.e. inversion happened (entry 12). The unexpected observation was followed up by detailed studies (Fig. 5).

In addition to reproducibility problems regularly arising in enantioselective hydrogenations, high ee made necessary (i) further purification of **10** and **11** and (ii) the development of a suitable analytical procedure for the determination of CD and DHCD, both of which were expected to induce high ee, because data obtained by NMR and TLC were inadequate for the verification of the presence of a few tenths of a percent of DHCD (in the course of hydrogenation, CD is rapidly converted to DHCD). On the other hand, the stability of **10** and **11** had to be tested under the conditions of enantioselective hydrogenation. HPLC-ESI-ion-trap-MS proved to be suitable for solving both problems. **10** and **12** was found to contain 0.7–0.8% and 0.3–0.4% CD, respectively, and **11** was shown to contain 0.2–0.3% DHCD. These amounts of CD and DHCD correspond to molar concentrations of 0.0003–0.0008 mmol/l, respectively, under the given experimental conditions. It is therefore highly probable that the

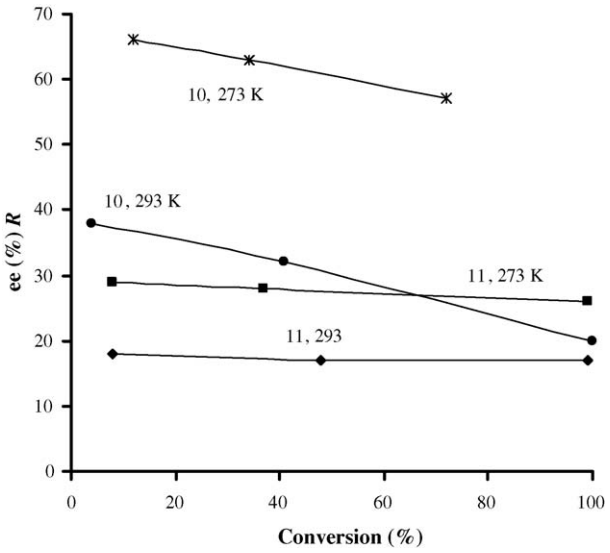


Fig. 5. Enantioselective hydrogenation of EtPy on Pt-alumina catalyst modified by **10** (containing ∼ 0.7% CD) and **11** (containing 0.2–0.3% DHCD) cinchona derivatives: effect of conversion and temperature on ee (standard conditions, solvent THF, [**10**, **11**]: 0.1 mmol/l).

relatively high ee values shown in Table 3 and Fig. 5 are due to the presence of DHCD rather than **10**, **11** and **12**, a conclusion that is in agreement with earlier results obtained at a DHCD concentration of 0.001 mmol/l [21].

Studies on the hydrogenation of **10** under the conditions of EtPy hydrogenation (1 bar H_2, 2.5 ml THF, [**10**] = 0.1 mmol/l, 293 K) was performed using **10** that contained ∼0.5% CD (Table 4). Upon increasing hydrogenation time, hydrogen uptake could be followed conveniently by ESI-MS. The site of hydrogenation could be determined by ESI-MS2. Assumable hydrogenation sites are vinyl and phenyl groups and the quinoline skeleton. On the basis of ESI-MS2 spectra, at the time of the formation of the ion at $m/z = 555$ the vinyl group was hydrogenated, whereas in ions at $m/z = 557$ and 559, hydrogen was added mostly to the quinoline skeleton (Fig. 6), although some MS2 records suggest hydrogenation of phenyl groups [32].

Since silyl ethers are sensitive to moisture and water is always formed in the course of re-reduction of the catalyst, the addition of 100 μl of water under conditions similar to the above led to the results shown in Table 5. Unlike experiments without the addition of water, hydrogenation in the presence of water was faster and the formation rate of the ion at $m/z = 559$ was reduced with increasing hydrogenation time. It is quite remarkable that the vinyl group is hydrogenated in less than 10 min in the pres-

Table 4
Degree of hydrogenation of **10** on Pt/alumina catalyst by measurement of data of ESI-MS

Min	Relative abundance (%)			
	553	555	557	559
30	100	60	50	43
60	77	100	78	91
120	7	61	79	100

Standard conditions: 12.5 mg E4759, THF, 293 K, [**10**]: 0.1 mmol/l.

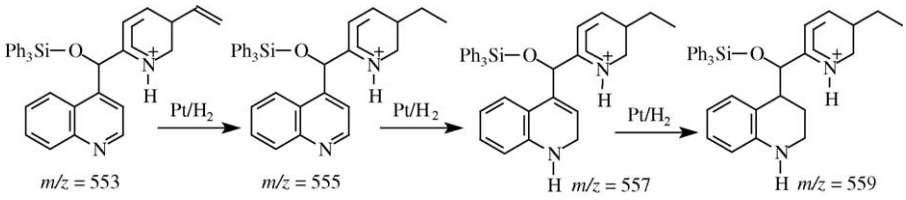


Fig. 6. Formed hydrogenated derivatives in the hydrogenation of Ph_3Si-O-CD on Pt-alumina catalyst (standard conditions).

Table 5
Degree of hydrogenation of **10** on Pt/alumina catalyst by measurement of data of ESI-MS in the presence of 100 μl water

Min	Relative abundance (%)			
	553	555	557	559
10	2	12	100	29
30	2	7	100	29
70	2	4	100	36
120	2	3	100	42

Standard conditions: 12.5 mg E4759, THF, 293 K, [**10**]: 0.1 mmol/l).

ence of water. Most probably, hydrogenation in the quinoline skeleton takes place, due to tilted adsorption, on the σ–π bond linking the N atom close to the surface with C2′ (see Fig. 1). (The product ions of MS2, however, suggest a double bond shift in the course of fragmentation in the ion-trap.) The CD content (∼0.5%) of **10** was also hydrogenated in both cases.

A further conclusion of these studies is that, in the course of the hydrogenation of **10**, Si–O is neither hydrogenated nor hydrated, because the ratio of the hydrogenation products of **10** and CD is not changed relative to the initial composition (10 + 0.5% CD). It is important to note that, according to spectra recorded in the course of EtPy hydrogenation, it is already the ion at $m/z = 557$ that is predominant in the liquid phase even at reaction times shorter than 1 min (557/555 = 100/27), which naturally does not allow conclusions to be drawn regarding the surface conditions [20,32]. These observations, furthermore the data obtained on mixtures of chiral modifiers **10** and CN shown in Fig. 7 support tilted adsorption of the quinoline skeleton of **10**.

According to the "nonlinear effect" in heterogeneous enantioselective hydrogenations [33] Baiker et al. obtained important results using mixtures of chiral modifiers in the Orito-reaction [14,34]. One of the most important conclusions of these studies is the estimation of the relative adsorption strength of the modifiers, which is of importance for the elucidation of the reaction

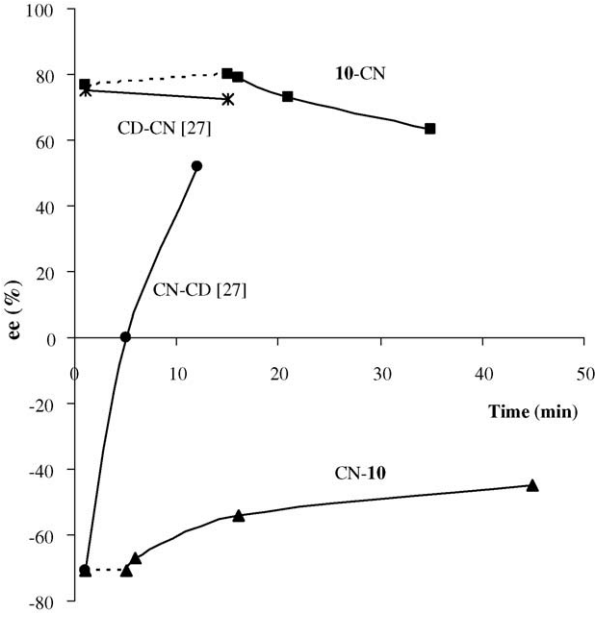


Fig. 7. Enantioselective hydrogenation of EtPy: effect of modifier mixtures (standard conditions, 273 K, 3 ml THF, [CN] and [**10**] (containing 0.2% CD): 0.1 and 0.1 mmol/l, first abbreviation-modifier used first, second abbreviation-modifier added afterwards).

mechanism. We also found it useful to use this approach for studying the significantly divergent behaviours of **10** and CN in the enantioselective hydrogenation of EtPy in THF. According to P. Wells' group results [33], adsorption of CD is stronger than that of CN, a result which, in concert with H-D exchange measurements, supported tilted adsorption of the latter compound [27]. The value of ee (∼77% *R*) obtained in the presence of **10** + 0.8% DHCD was hardly affected at all by CN, whereas the value (∼70% *S*) attained in the presence of CN was decreased more pronouncedly by **10** + 0.8% DHCD. This effect was, of course, caused by the DHCD content of **10** (0.8%) rather than **10** itself.

Table 6
Enantioselective hydrogenation on E4759 catalyst modified by CD and DHCD free silylethers (**6**, **7**, **10**, **12**)

First modifier	1st modifier						+2nd modifier (CD) after 1st			
	Time (min)	Conv. (%)	ee (%)	Time (min)	Conv. (%)	ee (%)	Time (min)	Conv. (%)	ee (%)	Ref.
Me_3SiO-CD **6**	3	6	15 *S*	12	57	28 *S*	–	–	–	5*R* [15]
	2	7	17 *S*	–	–	–	8	75	56 *R*	
Et_3SiO-CD **7**	3	12	13 *S*	18	52	20 *S*	–	–	–	
Ph_3SiO-CD **10**	2	9	0	–	–	–	5	45	51 *R*	
Bn_3SiO-CD **12**	3	8	18 *S*	10	57	19 *S*	–	–	–	

Conditions: 12.5 mg E4759, [**6**, **7**, **12**]: 0.01 mmol/l, [**10**]: 0.1 mmol/l, 293 K, 1 bar H_2, 3 ml THF, 0.06 ml EtPy).

In order to be able to clearly demonstrate the effect of silyl ethers on ee, DHCD was removed by adsorption on E4759 catalyst. Changes in the composition of the filtrate as a function of adsorption time were monitored by ESI-MS. Data obtained using filtrates containing the DHCD-free silyl ether (**6**, **7**, **10**, **12**), followed by addition of CD are shown in Table 6. The evidence shown in Table 6 suggests that, by inhibiting flat-lying adsorption of the chiral modifier via the quinoline skeleton, bulky groups decrease the adsorption strength of the modifier (reviewed in [4] and [5]): on the surface forms a "chiral pocket" of altered stereochemistry [35] that leads to the formation of a product of the orientation opposite to that expected. In addition to the non linear effect-type data presented in Fig. 7 and Table 6, tilted surface conformation of chiral modifiers is also supported by adsorption studies employing H-D isotope exchange [32] and, in the case of **11**, by selective hydrogenation of the N = C2′ bond of the quinoline skeleton.

4. Conclusion

CD derivatives **1**, **2**, **3** and **5** with small substituents at C9 produced ee values similar to that obtained using DHCD in the enantioselective hydrogenation of EtPy, both in protic and aprotic solvents. The following experimental observations, using bulky C9-O-substituted cinchona alkaloids **4** and **6–22** as chiral modifiers in the enantioselective hydrogenation of EtPy need explanations: (i) when the bulkiness of the substituents was increased the ee decreased, and, what is more, in certain cases even the EtLt of the configuration opposite to that expected was formed; (ii) in the case of **16** and **20** (*R*)-EtLt was formed, i.e. the enantiomer opposite to that expected (*S*)-EtLt; (iii) in the case of CD-O-silyl ethers free of CD (*S*)-EtLt was formed, i.e. the product opposite to that produced by DHCD; (iv) cinchona alkaloids with C8(*R*) and C9(*S*) allow the realization of lower ee values than do C8(*S*) and C9(*R*); (v) in the course of assessing the stability of **10** under the conditions of hydrogenation, highly selective hydrogen uptake (*m*/*z* 557(100)) was observed.

According to systematic studies [2–6] from three crucial structural elements for the cinchona alkaloids as chiral modifiers is an anchoring part represented by the flat extended aromatic ring system. To sum up these studies, it appears highly probable that the two most feasible adsorption modes of CD are adsorption via the aromatic system of quinoline or adsorption via the lone pair of quinoline N or C2′-quinoline bonded species. The former results in a flat adsorption of the quinoline ring parallel to the platinum surface, whereas the latter leads to an adsorption where the orientation of the quinoline ring is tilted or even perpendicular to the platinum surface [36,37]. Greater or lesser tilting has already been proposed as possible explanation of the change in behavior of the Pt-catalyst due to bulky substituents at C9-O-CD [16]. Changes in ee in the case of bulky CD-derivatives relative to DHCD may be explained in the way described in [13,15,16]. In this case the chiral modifier is bound to the Pt surface in some kind of tilted conformation.

These investigations also call attention repeatedly to the possibility that, in the course of experiments using cinchona derivatives in the enantioselective hydrogenations, the presence of parent cinchonas may lead to erroneous conclusions, since they have a profound effect on ee even at concentrations of 10^{-3}–10^{-4} mmol/l.

Acknowledgements

Financial support by the Hungarian National Science Foundation (OTKA Grant TS 044690, T 042466, T 048764 and M 045606) is highly appreciated. K. B. and Gy. Sz. thank the financial support of HAS through Bolyai János Research grant. K. B. thanks for postdoctoral research grant financed by Hungarian National Science Foundation (OTKA D 048513).

References

[1] Y. Orito, S. Imai, S. Niwa, J. Chem. Soc. Jpn. 1979 (1118) (1980) 670.
[2] P.B. Wells, R.P.K. Wells, in: D.E. De Vos, I.F.J. Vankelecom, P.A. Jacobs (Eds.), Chiral Catalyst Immobilization and Recycling, Wiley-VCH, Weinheim, 2000, p. 123, and references therein.
[3] A. Baiker, in: D.E. De Vos, I.F.J. Vankelecom, P.A. Jacobs (Eds.), Chiral Catalyst Immobilization and Recycling, Wiley-VCH, Weinheim, 2000, p. 155, and references therein.
[4] M. Studer, H.-U. Blaser, C. Exner, Adv. Synth. Catal. 345 (2003) 45.
[5] T. Bürgi, A. Baiker, Accounts Chem. Res. 37 (2004) 909.
[6] M. Bartók, Heterogeneous Catalytic Enantioselective Hydrogenation of Activated Ketones. Curr. Org. Chem., in press.
[7] M. Bartók, K. Felföldi, B. Török, T. Bartók, Chem. Commun. (1998) 2605.
[8] M. Bartók, K. Felföldi, Gy. Szöllösi, T. Bartók, Catal. Lett. 61 (1999) 1.
[9] M. Bartók, K. Felföldi, Gy. Szöllösi, T. Bartók, React. Kinet. Catal. Lett. 68 (1999) 371.
[10] Gy. Szöllösi, K. Felföldi, T. Bartók, M. Bartók React, Kinet. Catal. Lett. 71 (2000) 99.
[11] M. Bartók, M. Sutyinszki, K. Felföldi, Gy. Szöllősi, Chem. Commun. (2002) 1130.
[12] M. Bartók, M. Sutyinszki, K. Felföldi, J. Catal. 220 (2003) 207.
[13] M. Bartók, M. Sutyinszki, K. Felföldi, I. Bucsi, K. Felföldi, Gy. Szöllősi, F. Bartha, T. Bartók, J. Catal. 231 (2005) 33.
[14] S. Diezi, A. Szabó, T. Mallat, A. Baiker, Tetrahedron: Asymmetry 14 (2003) 2573.
[15] S. Diezi, T. Mallat, A. Szabo, A. Baiker, J. Catal. 228 (2004) 162.
[16] N. Bonalumi, A. Vargas, D. Ferri, T. Burgi, T. Mallat, A. Baiker, J. Am. Chem. Soc. 127 (2005) 8467.
[17] T. Borszeky, T. Bürgi, Z. Zhaohui, T. Mallat, A. Baiker, J. Catal. 187 (1999) 160.
[18] T. Bartók, Gy. Szöllösi, K. Felföldi, M. Bartók, J. Thiel, J. Mass Spectrom. 35 (2000) 711.
[19] A. Lindholm, P. Maki-Arvela, E. Toukoniitty, T.A. Pakkanen, J.T. Hirvi, T. Salmi, D.Y. Murzin, R. Sjöholm, R. Leino, J. Chem. Soc. Perkin Trans. 1 (2002) 2605.
[20] I. Bucsi, Sz. Cserényi, K. Felföldi, M. Bartók, React. Kinet. Catal. Lett., in press.
[21] M. Bartók, K. Balázsik, Gy. Szöllősi, T. Bartók, J. Catal. 205 (2002) 168.
[22] H.U. Blaser, H.P. Jalett, J. Wiehl, J. Mol. Catal. 68 (1991) 215.
[23] H.U. Blaser, H.P. Jalett, W. Lottenbach, M. Studer, J. Am. Chem. Soc. 122 (2000) 12675.
[24] D.J. Berrisford, C. Bolm, K.B. Sharpless, Angew. Chem. Int. Ed. Engl. 34 (1995) 1059.
[25] K. Balázsik, M. Bartók, J. Catal. 224 (2004) 463.
[26] K. Balázsik, M. Bartók, J. Mol. Catal. A: Chem. 219 (2004) 383.
[27] M. Bartók, M. Sutyinszki, K. Balázsik, Gy. Szöllősi, Catal. Lett. 100 (2005) 161.

[28] M. Schürch, T. Heinz, R. Aeschimann, T. Mallat, A. Pfaltz, A. Baiker, J. Catal. 173 (1998) 187.
[29] M. Garland, H.U. Blaser, J. Am. Chem. Soc. 112 (1990) 7048.
[30] A. Gamez, J. Köhler, J. Bradley, Catal. Lett. 55 (1998) 73.
[31] Z. Ma, F. Zaera, J. Phys. Chem. B 109 (2005) 406.
[32] Gy. Szöllősi, I. Bucsi, Sz. Cserényi, M. Bartók, Rapid Commun. Mass Spectrom., in press.
[33] K.E. Simons, P.A. Meheux, S.P. Griffiths, I.M. Sutherland, P. Johnston, P.B. Wells, A.F. Carley, M.K. Rajumon, M.W. Roberts, A. Ibbotson, Recl. Trav. Chim. Pays-Bas 113 (1994) 465.
[34] W.R. Huck, T. Bürgi, T. Mallat, A. Baiker, J. Catal. 216 (2003) 276.
[35] R.L. Augustine, S.K. Tanielyan, J. Mol. Catal. A: Chem. 112 (1996) 93.
[36] J. Kubota, F. Zaera, J. Am. Chem. Soc. 123 (2001) 11115.
[37] D. Ferri, T. Bürgi, J. Am. Chem. Soc. 123 (2001) 12074.