Heterogeneous Enantioselective Hydrogenation of Ethyl Pyruvate Catalyzed by Cinchona-Modified Pt Catalysts: Effect of Modifier Structure

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Abstract: The effect of the structure of chiral modifiers derived from natural cinchona alkaloids on the enantioselectivity and rate of the Pt/Al_2O_3-catalyzed hydrogenation of ethyl pyruvate was investigated. The influence of the following structural elements was studied: the cinchonidine versus the cinchonine backbone; effect of the nature and the size of substituents attached to C_9; effect of partial hydrogenation of the quinoline ring; effects of changes of the substituent at the quinuclidine moiety. The strongest effects on ee and somewhat less on rate were observed for changes in the $O-C_9-C_8-N$ part of the cinchona alkaloid and for partial or total hydrogenation of the quinoline rings. The nature of the substituents in the quinuclidine part had a comparably minor influence. The solvent was found to have a significant effect on enantioselectivity and rate. In acetic acid, the best results were obtained with *O*-methyl-10,11-diydrocinchonidine (ee's up to 93%), whereas dihydrocinchonidine was the most effective modifier in toluene. In agreement with a basic model proposed by Pfaltz, it was concluded that the minimal requirements for an efficient modifier for the hydrogenation of α-keto esters is the presence of a basic nitrogen center close to one or more stereogenic centers and connected to an aromatic system. The results are in qualitative agreement with mechanistic models based on hydrogen-bonding interactions between an adsorbed modifier molecule and adsorbed ethyl pyruvate or its half-hydrogenated intermediate.

Introduction

Empirical structure−activity and selectivity correlations are an important tool for developing enantioselective catalysts. This is even more pronounced for heterogeneous systems because of a serious lack of understanding of the mode of action of such catalysts. Especially the nature of the chirality transfer from the chiral modifier or ligand to the chiral product is not really understood. In this contribution, we present results concerning the effect of modifier structure for the enantioselective hydrogenation of ethyl pyruvate (etpy) to ethyl lactate (etlac) using Pt-alumina catalysts in the presence of cinchona-type modifiers (Orito reaction; Figure 1).[1] A preliminary report has appeared.[2] This study should contribute to the understanding of the enantioselective hydrogenation of functionalized carbonyl groups with modified heterogeneous catalysts, a topic of interest from both a preparative and a mechanistic point of view.[3−6]

Results

Synthesis of Cinchona Derivatives: Structure and Purity. Nature has provided us with the two diastereomeric families of cinchonidine (Cd)/quinine (Qn) and cinchonine (Cn)/quinidine (Qn) (see Figure 2) that served as starting points for preparing derivatives thereof (see Figure 3). Roughly, one can distinguish three parts where changes seem relatively easy: (i) the substituent at C_9, (ii) the quinoline moiety, and (iii) the quinuclidine moiety. It must be pointed out that some of these transformation are rather difficult to carry out experimentally and very often the resulting product mixtures had to be separated by HPLC (see Experimental Section). Here we very briefly describe the synthesis of the most important derivatives tested in this study and discuss the evidence for our structural assignments.

Figure 1. Test reaction.

Two reaction types were employed for changing the *substituent at* C_9: O-methylation or acylation and substitution of OH. Methylation with MeI had to be carried out in the presence of NaH in order to get good yields of MeO-HCd. Acylation with acid chlorides or related derivatives were usually straightforward; O-substituted derivatives with large groups were originally developed for the asymmetric dihydroxylation.[7] We assume that the substitution reactions to Cl-HCd, Br-HCd, and probably also for F-HCd occur with inversion of configuration as shown for 9-bromoquinine by Braje et al.[8]

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(1) Orito, Y.; Imai, S.; Niwa, S. *J. Chem. Soc. Jpn.* **1982**, 137 and references cited therein.

(2) Blaser, H. U.; Jalett, H. P.; Monti, D. M.; Baiker, A.; Wehrli, J. T. *Stud. Surf. Sci. Catal.* **1991**, *76*, 147.

(3) Blaser, H. U. *Tetrahedron: Asymmetry* **1991**, *2*, 843.

(4) For a recent comprehensive review of the enantioselective hydrogenation of α-keto esters using cinchona-modified platinum catalysts and related systems, see: Blaser, H. U.; Jalett, H. P.; Müller, M.; Studer M. *Catal. Today* **1997**, *37*, 441.

(5) Pfaltz, A.; Heinz, T. *Top. Catal.* **1997**, *4*, 229.

(6) Baiker, A. *J. Mol. Catal. A: Chem.* **1997**, *115*, 473.

(7) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

(8) Braje, W. M.; Wartchow, R.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2540.

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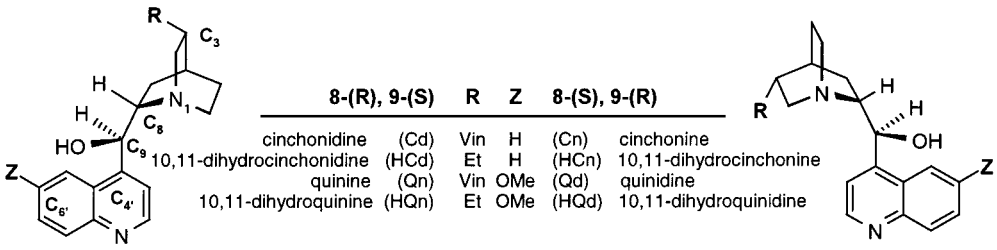

Figure 2. Structures, numbering, and abbreviations for the parent cinchona alkaloids.

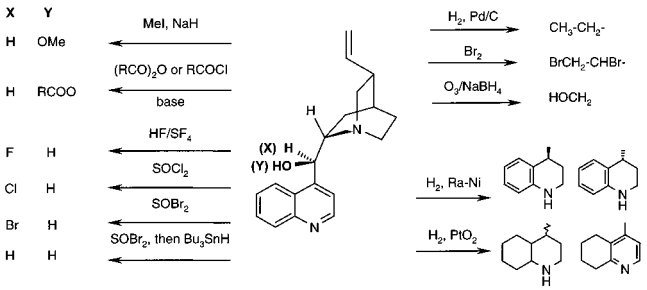

Figure 3. Derivatization of cinchonidine (for abbreviations, see Figures 4 and 5).

The *quinoline moiety* was partially hydrogenated using two different catalysts: Raney nickel for the preferential hydrogenation of the heteroaromatic ring to the two epimers of py-HCd and platinum oxide for reducing the carbocyclic aromatic ring to cyc-HCd as well as to the saturated DHCd isomers in the presence of trifluoroacetic acid. In all cases, complex product mixtures were obtained and purification was carried out using chromatographic methods. For py-HCd, two epimers (called A/B-py-HCd) are expected and were indeed observed in a ratio of ~2:3. While we were able to separate the two epimers, we were not able to make a clear assignment of the absolute configuration at $C_{4'}$ on the basis of the available data. Cyc-HCd exists only as one isomer; the eight isomers possible for DHCd were not separated. The *vinyl group at C_3 of the quinuclidine* moiety was selectively hydrogenated in high yields in the presence of Pd/C to give HCd as an important intermediate for many other derivatives. Ozonization followed by reductive workup lead to norcinchol, one of the few water-soluble cinchona derivatives. In all cases, structures were confirmed by NMR.

Screening Strategy and Quality of Results. A preliminary screening in ethanol indicated that several structural factors influence the effect of cinchona modifiers for the Pt-catalyzed hydrogenation of α-keto esters.[2] Because the enantioselectivity is also significantly affected both by the solvent type and by the modifier concentration,[4,9] a more elaborate procedure was applied and the tests were carried out in toluene (1 and 10 mg of modifier), in acetic acid (1 mg of modifier), and in ethanol (10 mg of modifier), in some cases with additional experiments. This choice was based on the finding that optimal concentrations usually were very low in AcOH, medium in toluene, and high in EtOH. Furthermore, because acceleration is an important characteristic of the Pt cinchona catalysts,[4] not only the ee's but also the initial rates were determined for several test series.

The results reported below were obtained over the course of several years. The conditions, the ethyl pyruvate, and catalyst lots as well as the autoclaves differed slightly for the four different series of experiments (see Table 1). In addition, two different commercially available 5% Pt/Al_2O_3 catalyst types were used that in our hands always gave high ee's. For this reason, the results (especially the rate data) of some series are not directly comparable. However, the major effects discussed below are significant and not affected by these variations.

Table 1. Reaction Conditions for the Various Test Series

	prel series[2]	series 1	series 2	series 3	series 4
catalyst type	4759	5R94	5R94	5R94	4759
catalyst wt, mg	100	50	50	50	50
etpy vol, mL	10	5	5	5	5
solvent vol, mL	20	20	20	25	10
modifier wt, mg	10	1 and 10	1 and 10	1 and 10	1 and 10
temp, °C	25−30	20	20	20	20−30
pressure, bar	70−100	100	100	100	70−100

Hydrogenation Results: Enantioselectivities and Rates Using Different Modifiers. (1) Comparison of the Parent Cinchona Modifiers. As already described by Orito,[1] the results shown in Table 2 confirmed that cinchonidine and quinine always give preferentially ethyl (*R*)-lactate while the pseudo-enantiomeric cinchonine and quinidine led to an excess of *S* product. The same holds true for the partially hydrogenated derivatives HCd and HCn. This means that the absolute configuration at C_8 and/or C_9 controls the sense of induction. Nevertheless, the relative position of the group *R* to the second quinuclidine substituent and the nature of *Z* sometimes had a strong effect on both the magnitude of the enantiomeric excess and the reaction rate: The cinchonidine and quinine families induced higher ee's than the cinchonine and quinidine families, respectively. The presence of a methoxy group in the quinoline ring (Cd vs Qn, Cn vs Qd) led to a lower enantioselectivity. The 10,11-dihydro derivatives in the Cd series gave slightly higher ee's, whereas the effect for the Cn series was ambiguous. Bürgi et al.[10] reported that the introduction of a phenyl group in the 2-position of the quinoline ring of 9-deoxycinchonidine also led to a decrease in ee of ~20%.

The solvent had a significant effect on the magnitude of the enantioselectivity and on the rate of the modified catalytic system. Generally, acetic acid gave the best ee values but in most cases lower rates than ethanol or toluene. The modifier concentration affected rates more strongly than ee's. As a trend, in EtOH, 10 mg of modifier often gave better enantioselectivities; in AcOH and toluene, addition of 1 mg of the modifier was usually superior.

The rates for the unmodified systems varied between 2 and 5 mmol/min·g, depending on the solvent and the series. As described before,[4] all modifiers had a rate-accelerating effect, but with obvious differences for the four families. Generally, higher ee's correlated weakly with higher rates, but more interesting is the fact that the presence of a ring methoxy group affected the rates more than the ee's.

(2) Effect of the Substituents X and Y at C_9 (Figure 4). In this series of experiments, we can distinguish two cases. In the first, the OH group at C_9 of HCd was replaced with relatively

(9) Blaser, H. U.; Garland, M.; Jalett, H. P. *J. Catal.* **1993**, *144*, 569.

(10) Bürgi, T.; Zhou, Z.; Künzle, N.; Mallat, T.; Pfaltz, A.; Baiker, A. *J. Catal.* **1999**, *183*, 405.

Table 2. ee (%), Rate (mmol/min·g), and Absolute Configuration of etlac for the Hydrogenation of Ethyl Pyruvate Catalyzed by Pt Catalysts Modified with Cinchona Alkaloids[a]

	AcOH				EtOH				toluene					
	1 mg		10 mg		1 mg		10 mg		1 mg		10 mg			
modif	ee	rate	ee	rate	ee	rate	ee	rate	ee	rate	ee	rate	ac	ser
Cd	88	110	89	160	71	220	82[b]	70[b]	85	170	81	90	(*R*)	2
HCd	90	120	90	160	67	170	72[b]	50[b]	86	220	83	120	(*R*)	2
Cn	81	40	78	60	52	90	42	80	70	90	67	30	(*S*)	2
HCn	63	70	83	90	43	110	40	90	67	120	69	60	(*S*)	2
Qn	81	7					45	19	73	12	73	10	(*R*)	3
Qd	56	3					27	14	51	5	46	5	(*S*)	3

[a] For conditions, see Experimental Section; for abbreviations, see Figure 2. [b] Series 1.

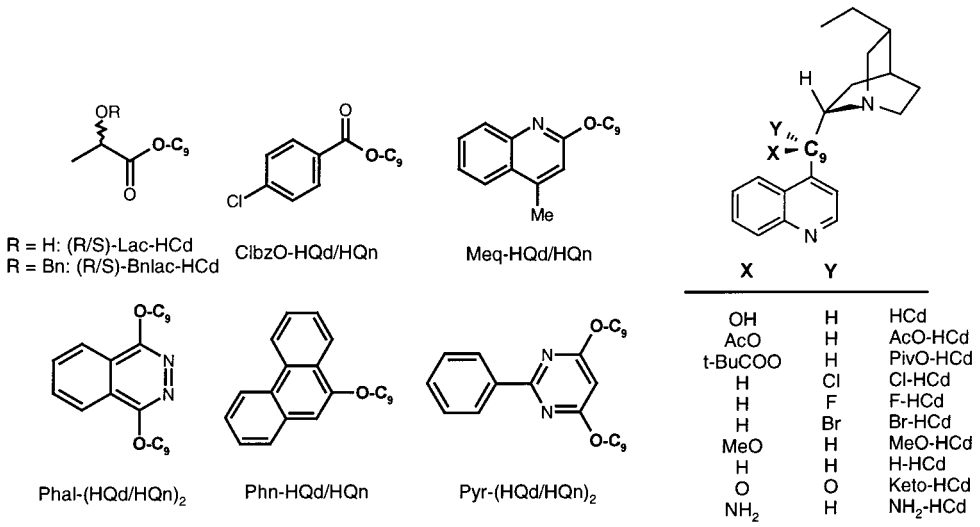

Figure 4. Structures and abbreviations of cinchona modifiers with different substituents at C_9.

Table 3. HCd Derivatives with Small- and Medium-Sized Substituents at C_9: Effect on ee (%), Rate (mmol/min·g), and Absolute Configuration of etlac[a]

	AcOH		EtOH		toluene					
	1 mg		10 mg		1 mg		10 mg			
modifier	ee	rate	ee	rate	ee	rate	ee	rate	ac	ser
AcO-HCd	67	30	54	90	63	40	81	90	(*R*)	2
PivO-HCd							22		(*R*)	prel
(*R*)-Lac-HCd	44	19	43	50	45	30	62	38	(*R*)	4
(*S*)-Lac-HCd	46	23	44	50	43	34	65	25	(*R*)	4
(*R*)-Bnlac-HCd			10	9	20	14	15	4	(*R*)	4
(*S*)-Bnlac-HCd			12	5	24	12	21	6	(*R*)	4
ClbzO-HQn	24	1	15	7	13	4	22	3	(*R*)	3
ClbzO-HQd	13	10	0	30	2	10	0	10	(*S*)	3
Cl-HCd	44	30	37	30	23	10	16	30	(*R*)	2
Cl-HCd			44	na[b]					(*R*)	prel
F-HCd	10	10	13	5	30	5	24	1	(*R*)	2
Br-HCd			20	na					(*R*)	prel
MeO-HCd	93	190	70	120	70	70	67	60	(*R*)	2
NH_2-HCd	8	5	4	10	10	10	21	1	(*R*)	2
H-HCd			44	na					(*R*)	prel
keto-HCd			43	na					(*R*)	prel

[a] For conditions, see Experimental Section; for abbreviations, see Figure 4. [b] na, not available.

small substituents (Table 3); the second group of modifiers consists of ligands developed by Sharpless for the dihydroxylation reaction[7] with large substituents at C_9 (Table 4).

As shown in Table 3 and described in our preliminary report,[2] replacing the X or Y groups of HCd by other small substituents did not change the *sense of induction* but significantly affected the ee values. A recent publication described similar observations: For 9-deoxy-Cd, Bürgi et al.[10] reported an ee of 57%, Bartok et al.[11] obtained ee's of 42 and 22% for epi-Qn and epi-QD, respectively. Bartok et al. also described the effect of using iso-Cn and iso-Qd, where a ring is formed between C_9−O and C_{10}.[12,13] Under our test conditions, a strong decrease in ee was observed for all cases except MeO-HCd and AcO-HCd. An additional stereogenic center in the substituent did not affect the enantioselectivity: both (*R*)- and (*S*)-Lac-HCd give the same ee's. The corresponding benzyl ethers (*R*)- and (*S*)-Bnlac-HCd also showed the same behavior but with much lower ee's. As a rule, oxygen-containing substituents gave better performances and more bulky substituents led to significantly lower enantioselectivities. The effect on the rates was similar as discussed above: without significant exceptions, modifiers with low ee's also had low rates.

Ligands developed by Sharpless for the asymmetric dihydroxylation of olefins carrying very large substituents at C_9 (Table 4) showed distinctly different behavior. In many cases, the major enantiomer was opposite to what was expected from the absolute configuration of the cinchona backbone. This reversal was more pronounced for HQd than for HQn derivatives and, in contrast to all other modifiers, not only the magnitude of the ee values but also the sense of induction showed a strong solvent dependence. The largest differences were found for Phn-HQn (40% ee in AcOH vs 4% in EtOH or toluene) and for Meq-HQd (13% (*S*) in AcOH vs 18% (*R*) in toluene). A similar observation was recently reported by Collier et al.[14] for the

(11) Bartok, M.; Felföldi, K.; Szöllösi, G.; Bartok, T. *React. Kinet. Catal. Lett.* **1999**, *68*, 371.
(12) Bartok, M.; Felföldi, K.; Szöllösi, G.; Bartok, T. *Catal. Lett.* **1999**, *61*, 1.
(13) Bartok, M.; Felföldi, K.; Török, B.; Bartok, T. *Chem. Commun.* **1998**, 2605.
(14) Collier, P. J.; Hall, T. J.; Iggo, J. A.; Johnston, P.; Slipszenko, J. A.; Wells, P. B.; Whyman, R. *Chem. Commun.* **1998**, 1451.

Table 4. HCd Derivatives with Large Substituents at C_9: Effect on ee (%), Rate (mmol/min·g), and Absolute Configuration[a]

		AcOH 1 mg		EtOH 10 mg		toluene 1 mg		toluene 10 mg		
modifier	ac[b]	ee	rate	ee	rate	ee	rate	ee	rate	ser
Phal-$(HQn)_2$	(*R*)	16 (*R*)	26	7 (*R*)	26	10 (*R*)	15	16 (*R*)	29	4
Phal-$(HQd)_2$	(*S*)	4 (*S*)	22	**4 (*R*)**[b]	**23**	**1 (*R*)**	**30**	**3 (*R*)**	**13**	4
Pyr-$(HQn)_2$	(*R*)	**6 (*S*)**	**20**	**2 (*S*)**	**26**	5 (*R*)	27	4 (*R*)	11	4
Pyr-$(HQd)_2$	(*S*)	**6 (*R*)**	**28**	**7 (*R*)**	**24**	**6 (*R*)**	**29**	**9 (*R*)**	**32**	4
Phn-HQn	(*R*)	40 (*R*)	3	5 (*R*)	7	4 (*R*)	4	4 (*R*)	2	3
Phn-HQd	(*S*)	4 (*S*)	1	**18 (*R*)**	**9**	**2 (*R*)**	**5**	**2 (*R*)**	**3**	3
Meq-HQn	(*R*)	28 (*R*)	2	5 (*R*)	7	4 (*R*)	4	2 (*R*)	1	3
Meq-HQd	(*S*)	13 (*S*)	2	**11 (*R*)**	**7**	**11 (*R*)**	**4**	**18 (*R*)**	**1**	3

[a] For conditions, see Experimental Section; for abbreviations, see Figure 4. [b] Absolute configuration expected on the basis of the parent cinchona alkaloid. [c]Boldface type indicates reversed absolute configuration.

Table 5. HCd Derivatives with a Modified or Lacking Quinoline Moiety: Effect on ee (%), Rate (mmol/min·g), and Absolute Configuration of etlac[a]

	AcOH 1 mg		EtOH 10 mg		toluene 1 mg		toluene 10 mg			
modifier	ee	rate	ee	rate	ee	rate	ee	rate	ac	ser
HCd	90	120	72[b]	50[b]	86	220	83	120	(*R*)	2
A-py-HCd	82	10	35	10	50	4	52	4	(*R*)	1
B-py-HCd	47	10	12	10	48	4	57	4	(*R*)	1
cyc-HCd	20	10	5	20	1	5	7	5	(*R*)	1
DHCd	25	5	2	10	5	3	3	4	(*R*)	1
M11					6	na[c]			(*R*)	4
quinuclidine A	2	na					11	na	(*R*)	4
quinuclidine B	1	na					5	na	(*R*)	4

[a] For conditions, see Experimental Section; for abbreviations, see Figure 5. [b] Series 1. [c] na, not available.

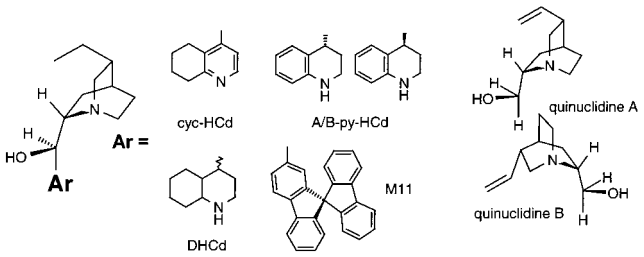

Figure 5. Structures of cinchona modifiers with replaced quinoline moiety.

hydrogenation of etpy using Cd-modified Pd catalysts in different solvents. However, one has to keep in mind that rather low ee's are observed and that only small changes of activation energies can lead to a reversal of induction. Interestingly, the dimeric ligands gave significantly higher rates even though the enantioselectivities were comparable to the monomeric modifiers.

(3) Effect of Change of the Quinoline Moiety. Several potential hydrogenation products of HCd were isolated and tested as modifiers (see Table 5 and Figure 5). With the exception of the A-py-HCd isomer in AcOH, all ee's were considerably lower than for HCd, as also observed by Sun.[15] As already pointed out, at the moment we cannot tell which absolute configuration at the 4′-position of py-HCd is more favorable. The loss in enantioselectivity was more pronounced when the homoaromatic ring was hydrogenated (cyc-HCd) or when a planar aromatic group was lacking completely. It is noteworthy, that both quinuclidines A and B led to an excess of ethyl (*R*)-lactate, albeit in low ee. All these modifiers showed a very weak rate acceleration. Bürgi et al.[10] showed that

(15) Sun,Y. K. Merck Research Laboratories, personal communication.

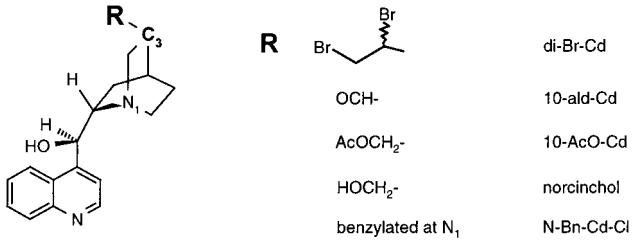

Figure 6. Structures of cinchona modifiers with different substituents at the quinuclidine part.

Table 6. Changes at the Quinuclidine: Effect on ee (%), Rate (mmol/min·g), and Absolute Configuration of etlac[a]

	AcOH 1 mg		EtOH 10 mg		toluene 1 mg		toluene 10 mg			
modifier	ee	rate	ee	rate	ee	rate	ee	rate	ac	ser
di-Br-Cd			60	na[b]					(*R*)	prel
10-AcO-Cd			40	na					(*R*)	prel
10-ald-Cd			72	na					(*R*)	prel
norcinchol	91	37	60	26	75	36	76	44	(*R*)	2
N-Bn-Cd-Cl			1	na					(*R*)	prel

[a] For conditions, see Experimental Section; for abbreviations, see Figure 6. [b] na, not available.

substitution at the 2′-position of the quinoline ring has only a minor effect on ee: 2′-phenyl-9-desoxy-HCd gave 48% ee as compared to 57% for 9-deoxy-Cd.

(4) Effect of Changes at the Quinuclidine Moiety. The limited number of examples (see Figure 6 and Table 6) indicate that the nature of the R substituent at C_3 does not have an important effect on ee as long as arrangement of the substituents of the quinuclidine remains the same (as opposed to the quinidine/cinchonine series). When the quinuclidine nitrogen was alkylated, the modifier was no longer effective.

(5) Detailed Investigations of the Partially Hydrogenated HCd Derivative. Two aspects were investigated in more detail because we became aware of their importance in the course of our project: (i) the variation of the enantioselectivity with reaction time (or conversion); (ii) the effect of the modifier concentration on ee and reaction rate.

The dependence of ee on the conversion was investigated for three partially hydrogenated modifiers. Several studies have shown that the enantioselectivity is often not constant during the course of the reaction.[4] In line with these observations, we noted significant ee increases at the beginning of the reaction for all three modifiers. After the initial increase, the enantioselectivity remained rather constant for A- and B-py-HCd around 80−84 and 60−64%, respectively, whereas it decreased strongly during the very slow reaction in the presence of cyc-HCd from ∼40% to below 20%. While the reason for the initial increase

Table 7. Optimal Concentration, Maximum ee, and Acceleration Factor for Different Modifiers[a]

modifier	opt concn, μM	ee (%) at opt concn (conversion)	acceleration factor	ee (screening)
HCd	0.08	92 (79)	18	90
A-py-HCd	8	74 (37)	6	82
B-py-HCd	9	65 (43)	10	47
cyc-HCd	34	47 (28)	4	20

[a] Conditions: AcOH, JMC94, room temperature, and 100 bar.

is still under debate,[16] the decrease at high reaction times is probably due to further hydrogenation to the saturated DH-Cd.[4,15,17]

To obtain more information concerning modifier adsorption behavior and ligand acceleration, the effect of the modifier concentration on ee and reaction rate was investigated in some detail for three partially hydrogenated modifiers in acetic acid as best solvent.[9,18] In all cases, a maximum for both rate and ee was observed similar to what was observed for several other modifiers; i.e., very high modifier concentrations are detrimental.[4] In Table 7 we have tabulated the optimal modifier concentration, the corresponding ee and acceleration factor (maximum/unmodified rate), and the ee values found in the screening for HCd, cyc-HCd, A-py-HCd, and B-py-HCd. Two facts are noteworthy: First, the ee's observed in these detailed investigations agree well with those found in the screening series. This means that the differences in ee for different modifiers are real and not due to a wrong choice of modifier concentration or of the conversions chosen for screening. Second, the best ee's and rates are observed at much lower concentrations for HCd than for the three partially hydrogenated modifiers; for the two py-HCd's it is ~100 and for cyc-HCd ~400 times higher, respectively, than for HCd. This indicates a much weaker adsorption of the partially hydrogenated cinchona derivatives.

Discussion

Since the publication of our preliminary results on the effect of the modifier structure on the catalyst performance for the enantioselective hydrogenation of etpy,[2] several groups have published on this topic.[5,6,10−13,17,19−21] Of special significance are a number of rather efficient chiral amines prepared by Pfaltz and Baiker[5,6,21] that can be considered to be simple cinchona models. Recently, Bartok et al.[12,13] tested cinchonine and quinidine derivatives with conformational restrictions and Baiker's group[10] described a 2-phenylcinchonidine derivative. In addition, vinca-type alkaloids[20] and Tröger's base[22] were also found to induce moderate enantioselectivity whereas other alkaloids were hardly effective.[19] Even though these efforts have not led to more selective modifiers compared to the cinchona alkaloids, important insights into the decisive structural parameters have been gained. In the following paragraphs, first we will describe the mechanistic models proposed so far, then summarize the effects observed for the various structural variations, and finally try to draw conclusions from the effects described above and integrate these into a slowly emerging general picture on the mechanism of enantioselection by cinchona-modified Pt catalysts.

Several groups have developed structural models to explain the mode of action of the cinchona-modified Pt catalysts or analogues thereof.[4−6,23−25] With the exception of the template model of Wells that has been withdrawn,[23] all other models postulate specific interactions between one cinchona modifier and one molecule of etpy. Augustine[25] explained the observed enantiodiscrimination by a two-point interaction between the adsorbed modifier and adsorbed etpy (N_1 lone pair with keto group and lone pair of the oxygen at C_9 with ester group). Margitfalvi's "shielding effect" model[24] is based on a two-point interaction between modifier and etpy in solution (interaction N_1 with keto group and a $\pi-\pi$ stacking interaction quinoline with ester group). The shielded etpy is thought to interact with the Pt surface and hydrogen would be added to etpy from the unhindered side of this adduct. Baiker[6] and Pfaltz[5] as well as Wells[23] have rationalized the results observed for cinchona alkaloids and also for some analogues thereof by assuming a strong interaction between adsorbed etpy (or a half-hydrogenated intermediate) and the adsorbed modifier on the Pt surface via hydrogen bridging as depicted in Figure 7. Molecular modeling studies have been carried out for several of these mechanistic models in order to confirm the feasibility of the proposed interactions. From modeling results and NMR experiments[27] and from the effect of restricting rotation around the C_8-C_9 axis using isocinchona derivatives,[12,13] it was inferred that an *open conformation* of the adsorbed modifier must be the optimal active species (see Figure 7a). A similar situation was found for aryl ethylamine modifiers (Figure 7b). In contrast, Margitfalvy et al.[24] proposed the interaction between etpy and a *closed conformation* (where the lone pair of N_1 points to the quinoline ring) to be decisive. The calculated results were claimed to be in agreement with both the "shielding effect" model[24] and the hydrogen bridge model![26−28]

Tables 8 and 9 present a summary of all pertinent results obtained for structural variations of cinchona-type modifiers (see Figure 8) for the hydrogenation of etpy with Pt catalysts. We have grouped the results according to the simplified model of Pfaltz,[5] who distinguished two structural elements: an (extended) aromatic system (Ar) that is proposed to serve as anchoring group on the catalyst surface and a basic amino function (N-unit) that is thought to interact with the keto group of the substrate. Table 8 summarizes the effects of various combinations of the Ar and N-unit and Table 9 of changing the substituents X and Y at C_9.

From the results summarized in Tables 8 and 9 and Figure 9, it is evident that an (extended) aromatic system and a basic

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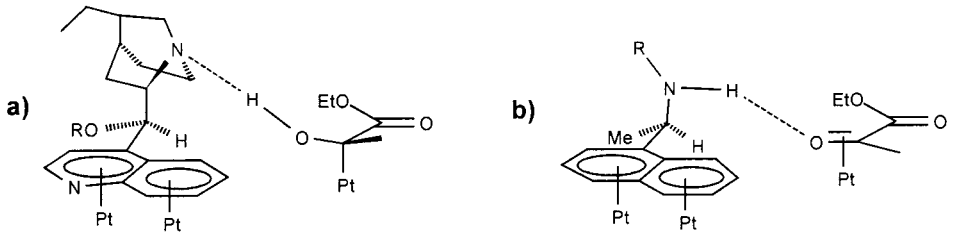


Figure 7. Artist's view of the structure of proposed adsorbed adduct complexes between modifier and etpy or its reaction intermediates: (a) HCd in the open conformation with half-hydrogenated etpy;[23] (b) protonated modifier (aryl ethylamine type) and etpy.[5,6]

Table 8. Best ee's for Various Combinations of Aromatic Groups and Amino Functions

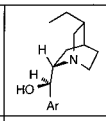
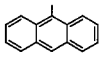
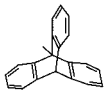
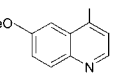
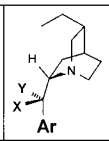
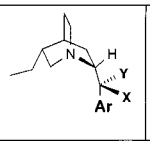
Ar				ref.
			(25%)	this work
	X = CH 0% X = C-NO$_2$ 29%	X = CH 0% X = N 0%		5 7,5
			20%	this work
			A 82% B 57%	this work this work
	X = CH 82%	X = CH 75% X = N 67%	X = N >90%	5 5,this work
		42%		6
		87%		5
			6%	this work
		4%		5

Table 9. Effect on ee: Variation of the Substituents at C_9

Ar: 			
	best ee (major enantiomer)	best ee (major enantiomer)	ref.
Y/X = H/OH, H/MeO, H/AcO	>80 % (R)	~80 % (S)	this work
Y/X = H/lactate, H/H, Cl/H, O/O	40-65 % (R)	na	this work
Y/X = OH/H	42 % (R)	22 % (S)	11
Y/X = H/Bn-lac, F/H, Br/H, H/NH$_2$	<25 % (R)	na	this work
ClbzO-HQn ClbzO-HQd	0-24 % (R)	0-13 % (S)	this work
Meq-HQn Meq-HQd	2-28 % (R)	13 %(S)-18 %(R)	this work
Phn-HQn Phn-HQd	4-40 % (R)	4 %(S)-18 %(R)	this work
Phal-(HQn)$_2$ Phal-(HQd)$_2$	7-16 % (R)	4 %(S)-4 %(R)	this work
Pyr-(HQn)$_2$ Pyr-(HQd)$_2$	4 %(R)-6 %(S)	6-9 % (R)	this work

nitrogen center close to a stereogenic center is a necessary *but not sufficient* prerequisite for an effective modifier. For the aromatic moiety, the following trends can be identified:

(i) Larger aromatic systems generally give better ee's than smaller ones of the same type.

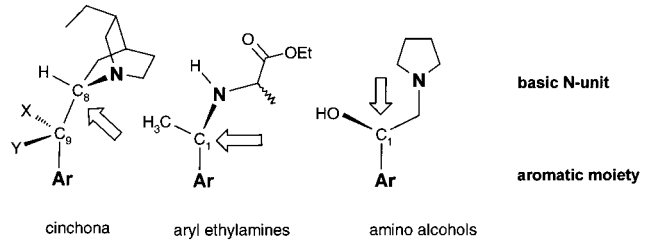


Figure 8. Basic structure of effective cinchona-type modifiers and analogues.

(ii) The presence of an N-atom in the aromatic ring is no prerequisite; homo- and heterocyclic derivatives are of similar effectiveness.

(iii) Modifiers with a simple benzene or pyridine ring show no chiral induction. The minimum requirement seems to be an aminobenzene moiety (see, e.g., Tröger's base or the nitrophenyl derivative in Table 8, which under the reaction conditions is reduced to 1-(4-aminophenyl)ethylamine)).

(iv) Whereas the substitution of small aromatic systems is favorable, the addition of a methoxy or a phenyl group to the quinoline has a slightly negative effect.

(v) If the aromatic system are not flat or are absent, only very low ee's can be obtained.

These trends as well as the results summarized in Table 7 concerning the optimal modifier concentration are in overall agreement with the notion that strong adsorption on the Pt surface is critical and that the aromatic rings adsorb via its π-system and not via the quinoline or quinuclidine nitrogen atoms. This is in agreement with deuteration experiments as well as a recent NEXAFS study.[29] Nevertheless, the results summarized in Table 7 clearly show that the strength of adsorption can by no means explain the differences in chiral induction; otherwise, low ee's could be improved simply by increasing the modifier concentration and we and others have shown that ee's do not increase above a certain modifier specific limit.[4]

Therefore, the precise structure of the chiral unit and the positioning of the basic nitrogen atom relative to the aromatic moiety determines the intrinsic ee and acceleration factor. The necessity for a basic nitrogen atom is inferred from the fact that alkylation of N_1 in cinchonidine or replacement of the amino group by a hydroxy group in the amino alcohol modifiers[5] leads to racemic ethyl lactate. The three most effective modifier classes as depicted in Figure 8 demonstrate that the quinuclidine subunit obviously is very well suited as are the closely related amino alcohols and the more simple aryl ethylamines. However, there are remarkable differences: In the case of the cinchona derivatives and the aryl ethylamines, the absolute configuration of the major ethyl lactate enantiomer is determined by the

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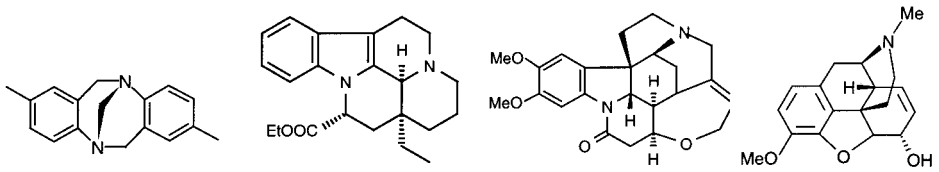

Figure 9. Structures of moderately selective modifiers.

absolute configuration at C_8 and C_1, respectively, i.e. the stereogenic center α *to the N atom*. For the amino alcohols, the sense of induction is controlled by the absolute configuration of the stereogenic center α *to the O atom*, in contrast to the cinchona derivatives where (except for very large groups) the substituents at C_9 affect only the magnitude but not the sense of induction. Nevertheless, it is possible to rationalize the effectiveness of these three classes with the hydrogen-bridging model.

The effects of changing X and Y at C_9 are summarized in Table 9. Obviously, the presence of large substituents at the oxygen atom leads to a strong decrease in enantioselectivity and in some cases even to a reversal of the absolute configuration of the major product enantiomer. If one accepts the open conformation depicted in Figure 7a to be important, the effect of replacing OH by a medium-sized group like acetate or lactate can be explained by hindered adsorption and/or by deviation from the optimal conformations by rotation around the $C_{4'}-C_9$ bond due to steric effects. However, this simple picture does not explain the significant loss in enantioselectivity for some epi or deoxy derivatives where X and Y are about of the same size. For the case of the Sharpless modifiers, where we sometimes observe a reversal of the absolute configuration of the product, one can speculate that the large aromatic substituents at C_9 compete with the quinoline ring for adsorption on the Pt surface leading to a different adsorption complex. This might explain the significant solvent effects on the absolute configuration of the major enantiomer. However, one should be very careful not to overinterpret effects that are the result of a difference in activation energy of the order of only a few hundred calories per mole.

As pointed out above, from a structural point of view, our results do not allow us to discriminate rigorously between these models. We think that the mechanistic picture of Pfaltz, Baiker, and Wells, assuming adsorbed adducts as depicted in Figure 7, can explain more known facts of this complicated reaction than any of the other proposals. The finding of Pfaltz and Baiker that the $O-C_9-C_8-N$ fragment present in cinchona modifiers is no prerequisite for obtaining good ee values is not in accord with Augustine's two-point interaction model. The following points speak against the proposal of Margitfalvi: (i) the negative effect of a methoxy substituent at the quinoline ring (electron-donating groups should give a stronger $\pi-\pi$ stacking interaction) and (ii) the fact that very low modifier concentrations are needed to get the highest ee's and rates (for a 1:1 interaction in solution, the best results would be expected at much higher modifier concentrations). Nevertheless, it must be stressed that none of the preferred models is able to explain all of the many features and especially that it is not possible with any of the models to single out specific interactions that are directly responsible for enantiodiscrimination. This means that at the moment it is not possible to predict in any meaningful way the effect of structural variations of either the substrate or the modifier on enantioselectivity. In other words, finding improved catalytic systems is still a matter of educated guesses and much trial and error!

Conclusions

From our detailed study of a variety of different cinchona derivatives, we find that the best results are obtained with cinchonidine or slightly changed Cd derivatives such as HCd, MeO-HCd, or norcinchol. With few exceptions, modifiers derived from cinchonidine lead to an excess of (*R*)-ethyl lactate whereas cinchonine derivatives preferentially lead to the *S* enantiomer. Three structural elements in the cinchona molecule can be identified where variations affect rate and ee of the enantioselective hydrogenation of ethyl pyruvate (or more generally α-keto acid derivatives): (i) an aromatic moiety Q, (ii) the substitution pattern of the quinuclidine, and (iii) the substituents X and Y at C_9.

Aromatic Moiety. For cinchona-based modifiers, a 4′-substituted quinoline nucleus is optimal; for other chiral modifiers, a larger aromatic ring system is of advantage. With one exception (py-HCd), modifiers with partially hydrogenated systems have much lower ee's between 0 and 50% and low acceleration ratios as well. Substituting the quinoline in the 6′- or 4′-position leads to somewhat lower enantioselectivities.

Substitution Pattern of the Quinuclidine. The absolute configuration at C_8 of the quinuclidine controls the absolute configuration of the major product enantiomer (exceptions are large substituents at C_9). The nature of the substituent at C_3 and the relative configuration at C_3 and C_8 (cinchonidine relative to cinchonine series) have a moderate but significant effect on ee. If N_1 of the quinuclidine moiety is alkylated, optical induction is lost completely.

Substituents X and Y at C_9. The presence of an OH or OMe group at C_9 is optimal. Larger substituents on the O-atom or replacing OH with other substituents leads to lower enantioselectivities.

The choice of the solvent has a significant effect on enantioselectivity and rate. In acetic acid, best results were obtained with *O*-methyl-10,11-diydrocinchonidine (ee's up to 93%), whereas dihydrocinchonidine was the most effective modifier in toluene. In EtOH, ee values were generally lower but rates often higher than in AcOH.

Our results are in qualitative agreement with the closely related mechanistic models proposed by Pfaltz, Baiker, and Wells, namely that a successful modifier needs two structural elements: first, an (extended) aromatic system, which is able to form a strong adsorption complex with the Pt surface; second, a suitable chiral amino function able to interact with the keto group of the adsorbed etpy or its half-hydrogenated intermediate via a hydrogen bridge. This activated complex is thought to be responsible both for enantiocontrol and for rate acceleration.

Experimental Section

Materials. Catalysts: 5R94 (Johnson Matthey) 5% Pt/Al_2O_3, Pt dispersion 0.22 (measured by CO adsorption), particle size 10−30 μm, S_{BET} 131 m^2/g; 4759 (Engelhard) 5% Pt/Al_2O_3, Pt dispersion 0.24 (measured by CO adsorption), particle size 50−120 μm, S_{BET} 168 m^2/g.[2] Before use, the catalyst was reduced for 2 h in flowing hydrogen at 400 °C. Ethyl pyruvate (Fluka purum) was distilled and stored not longer than 2 weeks at 5 °C. Ethanol, toluene, and acetic acid (all Fluka puriss p.a.) were used as received.

Cinchona Derivatives. The following derivatives were obtained from commercial sources and used as received: Cd, Cn, Qn, Qd, N-Bn-Cd^+Cl^- (Fluka purum). The following AD ligand derivatives were obtained either from commercial sources or from the laboratory of Prof. K. B. Sharpless: ClBzO-HQn, ClBzO-HQd, Meq-HQn, Meq-HQd, Phal-$(HQn)_2$, Phal-$(HQd)_2$, Phn-$(HQn)_2$, Phn-$(HQd)_2$, Pyr-$(HQn)_2$, and Pyr-$(HQd)_2$. M11[30] was obtained from Prof. F. Diederich (ETH Zürich); quinuclidines A and B were from Buchler GmbH (D-38110 Braunschweig).

The following cinchona derivatives were synthesized according to the method summarized in Figure 3, and their spectroscopic data are in good agreement with the proposed structure (for synthesis and spectra see Supporting Information): HCd,[31] MeO-HCd, AcO-HCd, PivO-HCd, (*R*)-Bnlac-HCd, (*S*)-Bnlac-HCd, (*R*)-Lac-HCd, (*S*)-Lac-HCd, F-HCd, cyc-HCd, A-py-HCd, B-py-HCd, DHCd, di-Br−Cd,[32] and norcinchol.

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(32) Braje, W. M.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Beil W.; Hoffmann, H. M. R. *Helv. Chim. Acta* **2000**, *83*, 777.

Hydrogenation Procedure. The test reactions were carried out in a 50-mL three-phase-slurry reactor with a magnetic stirring bar and a small baffle. Etpy was added to the solvent followed by the pretreated catalyst and the modifier. The autoclave was closed, and the air was displaced with argon (2 times). Then the autoclave was pressurized with H_2, and the reaction was started by turning on the magnetic stirrer (∼1000 rpm). After hydrogen uptake had stopped, the pressure was released and the hydrogen was displaced by argon. Initial turnover frequencies (tof; s^{-1}) were calculated in terms of accessible platinum atoms obtained from CO adsorption data. For series 1−3, conversion was determined by GLC (column: OV 101, 2 m, 50 °C), ee's by gas chromatography on a chiral capillary column (Chirasil-(L)-Val, 50 m, 150 °C) after derivatization of the ethyl lactate with isopropylisocyanate. For series 4, both conversion and ee of were determined without derivatization by GLC (β-cylodextrin).

Acknowledgment. We thank Prof. B. Sharpless (Scripps) for various samples of AD ligands, Prof. F. Diederich (ETH Zürich) for a sample of the spirofluorene derivative M11, Prof. A. Pfaltz (University of Basel) for a critical reading of the manuscript, and S. Burkhardt, D. Imhof, J. Salathin, and A. Schwendemann for careful experimentation.

Supporting Information Available: Synthetic procedures and spectral data of new cinchona derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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