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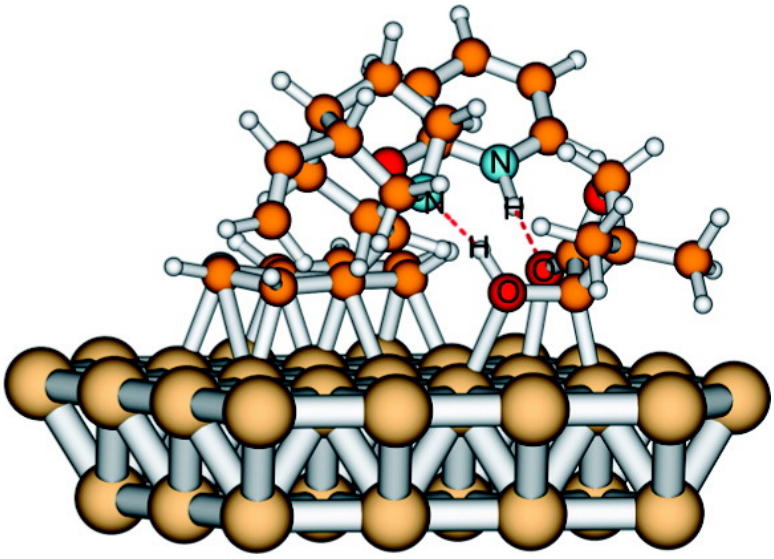

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Role of Guiding Groups in Cinchona-Modified Platinum for Controlling the Sense of Enantiodifferentiation in the Hydrogenation of Ketones

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Abstract: Systematic structural variations of cinchona-type modifiers used in the platinum-catalyzed hydrogenation of ketones give insight into the adsorption mode of the modifier and its interaction with the substrate on the platinum surface under truly in situ conditions. The performance of a new modifier, O-(2-pyridyl)-cinchonidine, is compared to that of O-phenyl-cinchonidine and cinchonidine (CD). In the hydrogenation of ethyl pyruvate, ketopantolactone, and 2-methoxyacetophenone, CD gives the (*R*)-alcohol in excess. Introduction of the bulky O-phenyl group favors the (*S*)-enantiomer, whereas upon replacement of the phenyl by a 2-pyridyl group the (*R*)-alcohol is again the major product. This finding is particularly striking, because the two ether groups have virtually identical van der Waals volumes. A catalytic study including the nonlinear behavior of modifier mixtures, and attenuated total reflection infrared spectroscopy of the solid−liquid interface in the presence of hydrogen, revealed the adsorption mode and strength of the modifiers on Pt. Theoretical calculations of the modifier−substrate interactions offered a feasible explanation for the different role of the bulky ether groups: repulsion by the phenoxy and attraction by the 2-pyridoxy groups. Simulation of the interaction of *o*-pyridoxy-CD with ketopantolactone on a model Pt surface suggests that formation of two N−H−O-type H-bonds—involving the quinuclidine and pyridine N atoms, and the two keto-carbonyls in the substrate—controls the adsorption of the substrate during hydrogen uptake. This mechanistic study demonstrates the potential of insertion of suitable substituents into CD and their influence on adsorption and stereocontrol on the platinum surface.

Introduction

Despite of the compelling development in heterogeneous asymmetric catalysis in the past years, understanding the origin of enantioselection on chirally modified metals is still a challenge.[1−10] A useful approach to learn more about the reaction mechanism is the systematic variation of the modifier structure. This strategy, frequently applied in hydrogenation reactions over Pt,[11−25] Pd,[26−30] Ni,[31] and Rh[32,33] has the intrinsic advantage that the information obtained is related to truly in situ conditions. On the other hand a drawback is that the interpretation of the observations allows a huge freedom for speculations, and for this reason the mechanistic understanding should be supported by a multidisciplinary approach that allows

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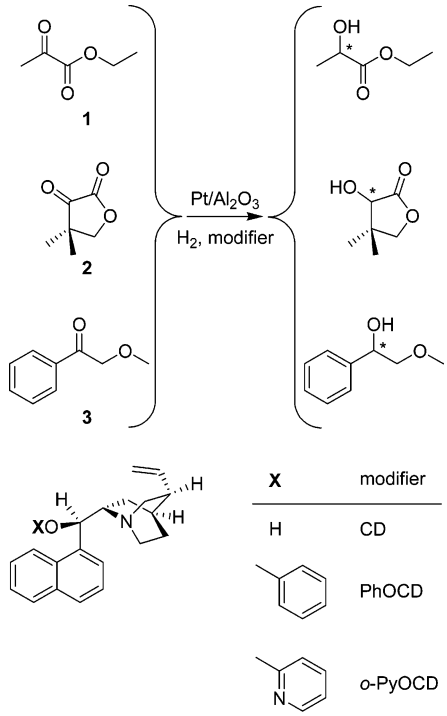
confining the hypotheses. In our case a combined catalytic, spectroscopic, and theoretical study of the changes induced has been chosen.[34−38]

Among the cinchona derivatives tested in heterogeneous enantioselective hydrogenation reactions, the most effective is *O*-methyl-cinchonidine that offers in a few cases higher enantioselectivity than the parent alkaloid cinchonidine (CD).[4,8,39] We have shown in a systematic study of the hydrogenation of some activated ketones on Pt that the key parameter, which determines the stereochemical outcome of the reaction, is the steric bulkiness of the ether group.[40,41] Modifiers containing a small alkoxy group (methoxy, ethoxy) give the same enantiomer in similar excess as CD in the hydrogenation of α-ketoesters, ketopantolactone, and α,α,α-trifluoromethyl ketones. This is an indication that in these transformations the OH function of the alkaloid is not involved in the key substrate−modifier interaction, although it may influence the enantiomeric excess (ee) due to secondary interactions (e.g., additional H-bonds with an O or F atom in the substrate[42]). The enantioselectivity decreases rapidly with increasing bulkiness of the ether group, and in some cases even the opposite enantiomer is formed in good ee. In the case of O-phenyl-cinchonidine (PhOCD, Scheme 1) the enantioselectivity could also be controlled by substitution at the phenyl ring, thus obtaining either the (*R*)- or the (*S*)-alcohol according to the electronic properties of the ring substituent (methyl or trifluoromethyl groups).[43,44] The role of steric bulkiness has recently been confirmed by extending the circle of C(9)-O-substituted CD derivatives.[45] According to a feasible mechanistic explanation the surface chiral pocket, which is available for the adsorption and hydrogenation of the ketone, is reshaped due to the conformational rearrangement of the flexible surface modifier, and thus the major enantiomer of the product is inverted.[43,44]

Here we report a continuation of our effort to understand the remarkable properties of O-substituted cinchonidine derivatives. We synthesized an O-pyridyl derivative of CD and tested it as a chiral modifier of Pt in the hydrogenation of ethyl pyruvate, ketopantolactone, and 2-methoxyacetophenone (Scheme 1). Our working hypothesis was that a comparison with the structurally related PhOCD may give new insight into the mechanism of enantioselection due to the introduction of a chemically interacting moiety, the basic N atom in the pyridine moiety, in proximity of the chiral pocket where the critical interaction takes place. An important point is that the O-phenyl and O-pyridyl moieties have almost identical steric bulkiness but the basic N of the pyridyl moiety can interact with the metal surface or the substrate. The following mechanistic study includes catalytic hydrogenation experiments, attenuated total reflection infrared (ATR-IR) spectroscopic investigation of the adsorption of the new modifier, and high-level computational modeling to help rationalizing the critical interactions leading to enantioselection.

Scheme 1. Hydrogenation of Ethyl Pyruvate (**1**), Ketopantolactone (**2**), and 2-Methoxyacetophenone (**3**) over Pt/Al_2O_3 Modified by CD, PhOCD, and *o*-PyOCD



Experimental Section

Materials. The following chemicals were used as received: toluene (Fluka, >99.7%), CH_2Cl_2 (J. T. Baker, >99.5%), acetic acid (Fluka, p.a.), 1,1,1-trifluoroacetic acid (TFA) (Fluka, >98%), cinchonidine (CD) (Fluka, 98% alkaloid), O-phenylcinchonidine (PhOCD) (Ubichem, >99%),[40] ketopantolactone (Hoffmann−Roche, >99%), 2-methoxyacetophenone (Aldrich, 95%), 2-iodopyridine (Aldrich, 98%). Tetrahydrofuran (THF) (J.T. Baker, 99.5%,) and *t*-BuMe ether (Fluka >99.5%) were freshly distilled from Na before use. Ethyl pyruvate (Fluka, 0.02% ethyl lactate after distillation) was carefully distilled in vacuum before use.

Synthesis of 2-((Pyridin-2-yloxy)(quinolin-4-yl)methyl)-8-vinylquinuclidine (*o*-PyOCD). At first, CD (7.20 g, 24.5 mmol) was dissolved in dry DMSO (50 mL), and NaH (0.70 g, 29.16 mmol) was added at room temperature. After stirring for 1.5 h, dry pyridine (3.92 mL, 49 mmol) and CuI (4.65 g, 24.5 mmol) were added. The mixture was stirred for 40 min, and 5 g (24.5 mmol) of 2-iodopyridine was added. The reaction mixture was refluxed for 3 days at 100 °C and then stirred overnight at room temperature. After this procedure 10 mL of water, 100 mL of CH_2Cl_2, 1.6 g of ethylenediamine tetraacetic acid (EDTA), and 5 mL of ammonia solution were added to the mixture in this order. The mixture was stirred for 1 h, the organic layer was separated, and the aqueous phase was extracted with 30 mL of CH_2Cl_2. The combined organic layer was washed with 5% ammonia solution (4 × 30 mL) until the aqueous phase remained colorless, and finally with 30 mL of

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water. The solvent was removed in vacuum, and the residue was dissolved in 100 mL of EtOAc. The crude product was extracted with 50 mL of 2 M HCl solution, and the acidic solution was washed with 3 × 30 mL of EtOAc and then with 100 mL of CH_2Cl_2. The aqueous solution was neutralized with $NaHCO_3$, and the modifier was extracted with EtOAc (2 × 30 mL). The combined EtOAc layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. Pure product was obtained after washing with hexane (2.1 g). Besides, the CH_2Cl_2 layer was washed with NaOH solution and after that with brine, dried over $MgSO_4$. After evaporation of the solvent 1.8 g of white powder of *o*-PyOCD was obtained. The combined yield of *o*-PyOCD was 3.9 g (43%). The modifier was stored at −15 °C, and a repeated NMR and TLC analysis did not reveal any decomposition even after 20 months of storage. Elemental analysis: found C 76.93, H 7.15, N 11.02; calculated C 77.60, H 6.78, N 11.31. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49−1.94 (m, 3H), 2.32−2.36 (m, 1H), 2.63−2.76 (m, 2H), 3.08−344 (m, 1H), 4.94−5.04 (m, 3H), 5.74−5.87 (m, 1H), 6.78−6.88 (m, 2H), 6.99 (d, 1H), 7.48−7.78 (m, 3H), 7.98 (d, 1H), 8.12−8.16 (m, 3H), 8.34−8.38 (m, 3H), 8.84 (d, 1H). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 23.0, 27.76, 27.94, 39.98, 42.96, 57.11, 60.34, 75.21, 110.97, 114.29, 117.25, 118.45, 123.72, 126.10, 126.56, 128.96, 130.34, 138.76, 141.88, 146.84, 147.17, 148.47, 150.0, 162.38. MS (EI), *m*/*z* (%): 371 (10%) [M^+], 277 (50%) [$M^+ - PyO^-$], 136 (100%) [8-vinylquinuclidine]. HRMS: found [M^+] = 371.1991, calculated [M^+] = 371.1993.

Catalytic Hydrogenations. The 5 wt % Pt/Al_2O_3 catalyst (Engelhard 4759) was pretreated by flushing with nitrogen in a fixed-bed reactor at 400 °C for 30 min, followed by a reductive treatment in flowing hydrogen for 90 min at the same temperature. After cooling to room temperature in flowing hydrogen, the catalyst was flushed with nitrogen for another 10 min and immediately transferred to the reactor without exposure to air. Hydrogenation reactions were carried out in three different reactors. Reactions at 1 bar were carried out in a magnetically stirred 100 mL glass reactor. For higher pressure reactions a stainless-steel autoclave equipped with a 50 mL glass liner and a PTFE cover, and magnetic stirring (1000 rpm), was used. The pressure was held at a constant value with a computerized constant volume−constant pressure equipment (Büchi BPC 9901). For screening the solvent effect, a parallel pressure reactor system Endeavor (Argonaut Technologies) was used. This multiple reactor system contains eight mechanically stirred, 15 mL stainless-steel reactors equipped with glass liners. Under standard conditions 42 mg of catalyst, 1.84 mmol of substrate (0.92 mmol in case of 3), 6.8 μmol of modifier, and 5 mL of solvent were stirred at room temperature and 10 bar for 2 h (6 h in case of 3). The conversion and ee were determined by GC analysis of the reaction mixture, using an HP 6890 gas chromatograph and a Chirasil-DEX CB (Chrompack 7502 25 m × 0.25 mm × 0.25 μm) capillary column. The actual or incremental ee was calculated as $\Delta ee = (ee_1 y_1 - ee_2 y_2)/(y_1 - y_2)$, where y represents the yield to the hydrogenation product and index 2 refers to a sample subsequent to sample 1. The estimated standard deviation of the determination of ee was about ±0.5%.

Spectroscopy. NMR spectra were recorded on Bruker Avance 200 and 500 spectrometers, using deuterated chloroform as solvent.

Attenuated total reflection infrared spectra were acquired by coadding 200 scans at 4 cm^{-1} resolution and 10 kHz scanner velocity with an IFS66 spectrometer (Bruker Optics) equipped with a commercial mirror unit (Specac) and a liquid nitrogen cooled HgCdTe detector. The thin model films for adsorption studies were prepared on a trapezoidal Ge crystal (45°, 52 × 20 × 2 mm^3, Crystran) by electron beam vapor deposition of 100 nm Al_2O_3 (pellet, Umicore), followed by 1 nm Pt (wire, Umicore), in an evaporation unit (Balzers BAE370, equipped with a four-pocket turret allowing consecutive deposition without breaking the vacuum).[46] The coated crystal was mounted into a homemade stainless-steel flow-through cell maintained at 15 °C. Adsorption−desorption experiments were performed as described in detail elsewhere.[47] Prior to adsorption, H_2-saturated CH_2Cl_2 was admitted over the metal film for about 10 min in order to clean the surface. Then, the solution of *o*-PyOCD (0.1 mM) in CH_2Cl_2 saturated with H_2 was admitted to the cell and spectral acquisition started. After about 1 h on stream, the modifier solution was replaced by H_2-saturated CH_2Cl_2 to follow desorption for ca. 30 min.

Computational Methods. Calculations of the chiral modifier adsorbed on platinum (111) were performed using the ADF code,[48] by simulating the Pt(111) surface by means of a Pt 38 cluster, as already shown elsewhere in more detail.[49−51] During all calculations the cluster was kept rigid while all degrees of freedom of the alkaloid were set free to optimize. A zero-order regular approximation (ZORA) Hamiltonian[52] was used to account for relativistic effects, together with relativistically corrected core potentials. Becke−Perdew exchange and correlation functional was used.[53,54] Atoms were modeled using a frozen core approximation reaching 4f for Pt and 1s for second row elements. The basis set used was double-ζ plus polarization functions for second row elements and double-ζ for platinum, within an especially core-steep set of functions optimized for use with the ZORA formalism.

Normal-mode analyses were performed with the Gaussian98 set of programs,[55] using density functional theory with a B3LYP exchange and correlation functional[56,57] and a 6-31G (d-p) basis set of Pople and co-workers.[58,59]

Results

Stability of the Modifier. The stability of *o*-PyOCD during hydrogenation is a critical point in the evaluation of the catalytic experiments, since hydrogenolysis of the ether bond may regenerate CD. Studies of the nonlinear behavior of modifier mixtures revealed that CD adsorbs stronger on Pt than any other modifier[45,60,61] and can control the enantioselection even when it is present in trace amounts (<1 mol %).[22,62]

The stability of *o*-PyOCD, which could be synthesized in high purity and free of traces of CD, was examined under hydrogenation reaction conditions in various solvents. The reactions were carried out under standard reaction conditions but in the absence of any substrate, and the modifier concentration was increased by a factor of 10. The conversion of the modifier was followed by ^{1}H NMR. Hydrogenation in acetic acid and in THF containing 10 μL of TFA led to a partial (50%) or complete conversion of the ether C−O−C bond, respectively, in 2 h of reaction time. In weakly polar, aprotic solvents (toluene, THF, *t*-BuMe ether, CH_2Cl_2) no hydrogenolysis of the C−O−C bond could be detected. Even in these solvents the fast saturation of the vinyl group and the slow hydrogenation of the quinoline ring could be detected, which transformations are typical for

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Table 1. Efficiency of CD, PhOCD, and *o*-PyOCD Used as Chiral Modifiers of Pt/Al_2O_3 in the Hydrogenation of Ethyl Pyruvate (**1**), Ketopantolactone (**2**), and 2-Methoxyacetophenone (**3**); Standard Conditions, 10 bar

		ee, % [conversion, %]		
substrate	solvent	CD	PhOCD	*o*-PyOCD
1	toluene	74 (*R*)[a] [100]	33 (*S*) [100]	48 (*R*) [100]
1	CH_2Cl_2	71 (*R*) [100]	22 (*S*) [100]	41 (*R*) [100]
1	THF	80 (*R*)[a] [100]	36 (*S*) [100]	52 (*R*) [100]
1	*t*-BuMe ether	60 (*R*) [100]	23 (*S*) [100]	44 (*R*) [100]
2	toluene	51 (*R*)[a] [100]	21 (*S*)[a] [100]	28 (*R*) [100]
2	CH_2Cl_2	71 (*R*) [100]	30 (*S*) [100]	36 (*R*) [100]
2	THF	50 (*R*)[a] [100]	21 (*S*)[a] [100]	31 (*R*) [100]
2	*t*-BuMe ether	58 (*R*) [100]	40 (*S*) [100]	12 (*R*) [100]
3	toluene	58 (*R*)[b] [56]	36 (*S*) [92]	1 (*R*) [65]
3	CH_2Cl_2	41 (*R*)[b] [23]	35 (*S*) [55]	2 (*R*) [31]
3	THF	44 (*R*)[b] [34]	48 (*S*) [76]	9 (*R*) [37]
3	*t*-BuMe ether	71 (*R*)[b] [90]	54 (*S*) [95]	6 (*R*) [88]

[a] Data from ref 41, standard conditions, 1 bar. [b] Data from ref 87, standard conditions, 20 bar.

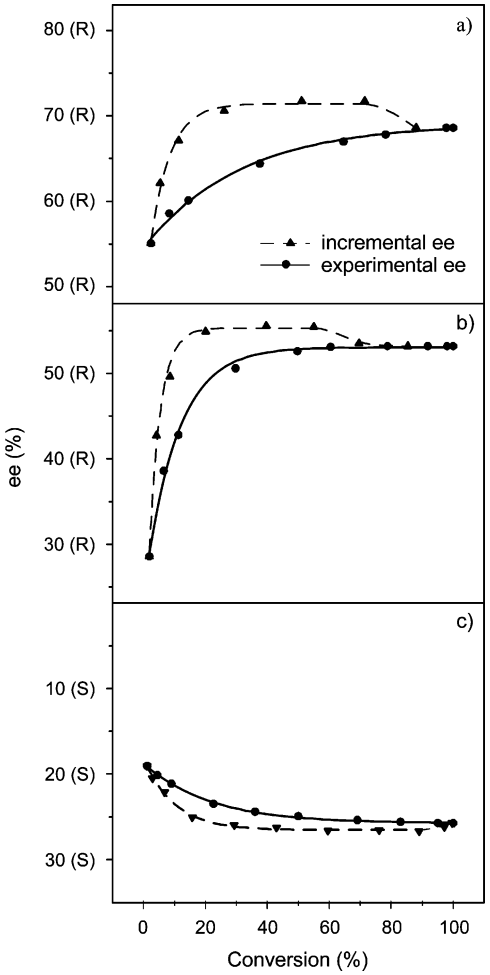

Figure 1. Hydrogenation of ethyl pyruvate over Pt/Al_2O_3 modified by (a) CD, (b) *o*-PyOCD, and (c) PhOCD in THF; standard conditions, 1 bar.

all cinchona modifiers and are not detrimental to the enantioselection until there is sufficient unreduced modifier in solution.[4,8] We can conclude that the ether function of *o*-PyOCD is stable in nonacidic solvents and formation of CD by hydrogenolysis of *o*-PyOCD during ketone hydrogenation can be excluded.

Catalytic Hydrogenation of Ketones. Three ketones, ethyl pyruvate, ketopantolactone, and 2-methoxyacetophenone, were hydrogenated under standard conditions on Pt/Al_2O_3 in the presence of *o*-PyOCD. The enantioselectivities are compared to those achieved with CD and PhOCD in Table 1. The ee was determined at full conversion except in the slow hydrogenation of 2-methoxyacetophenone for which full conversion was not achieved even after 6 h. In all three reactions and in all solvents, CD and *o*-PyOCD gave the (*R*)-alcohol and PhOCD the (*S*)-alcohol in excess. In other words, replacement of the CH fragment of the phenyl ring in PhOCD by a N atom in *o*-PyOCD resulted in the inversion of enantioselectivity. The largest difference was observed in the hydrogenation of ethyl pyruvate in THF, for which 36% ee to (*S*)-lactate was obtained with PhOCD and 52% ee to (*R*)-lactate with *o*-PyOCD. Note also the very low efficiency of *o*-PyOCD in the hydrogenation of 2-methoxyacetophenone. In this reaction CD is far more efficient, which indirectly confirms the stability of *o*-PyOCD under the reaction conditions used, therefore ruling out the formation of CD even when long reaction times are involved.

The dependence of ee on the conversion is shown in Figure 1 for pyruvate hydrogenation. With all three modifiers, there is a significant initial transient period below 20% conversion, which phenomenon is even more visible in the variation of the incremental ee. We assume that the slow removal of surface impurities is the major reason for this behavior. It is known that dimerization and oligomerization of pyruvates are catalyzed by the basic modifier,[63] the basic sites on the alumina support,[64] and the surface Pt sites.[65] The extent of these side reactions can be minimized in acetic acid,[66] in which medium the highest enantioselectivity was achieved,[67,68] but acidic solvents are not allowed here to avoid hydrogenolysis of *o*-PyOCD. The most important conclusion we can deduce from Figure 1 is that the three modifiers behave very similarly and there is no sign of hydrogenolysis of *o*-PyOCD.

Nonlinear Behavior of Modifier Mixtures. In order to estimate the relative adsorption strength of the modifiers on Pt under reaction conditions, the hydrogenation of ethyl pyruvate in the presence of mixtures of PhOCD and *o*-PyOCD was carried out. The nonlinear behavior, a phenomenon analogous

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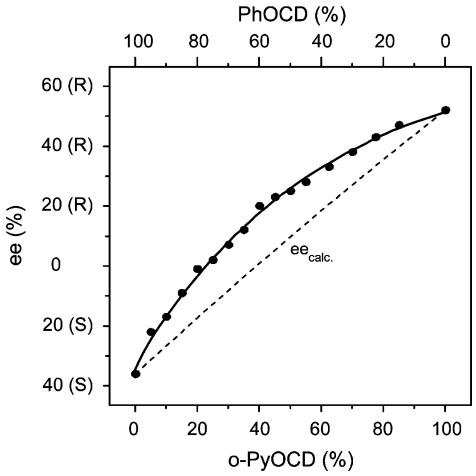

Figure 2. Nonlinear behavior of mixtures of *o*-PyOCD and PhOCD in the hydrogenation of ethyl pyruvate over Pt/Al_2O_3 in THF; standard conditions.

to the thoroughly investigated nonlinear effect (NLE) in homogeneous catalysis,[69−71] is illustrated in Figure 2. The expected or theoretical ee (dashed line) was calculated assuming that the molar ratios of the modifiers in solution and on the Pt surface are identical and the reaction rates and ees are linear combinations of those measured with PhOCD and *o*-PyOCD alone. Clearly, *o*-PyOCD governed the enantioselection in the whole concentration range, leading to higher than expected fraction of (*R*)-lactate. For example, the (*R*)-enantiomer was produced in small excess (2% ee), when only 25 mol % *o*-PyOCD was present, although the expected ee would have been 14% to the (*S*)-enantiomer for this modifier mixture. Albeit this deviation from the linear behavior is considerable, it is still very small compared to that observed for a CD−PhOCD mixture.[22,40] In the hydrogenation of ketopantolactone on the same Pt/Al_2O_3 catalyst, only 0.7 mol % CD was sufficient to produce 33% ee to (*R*)-pantolactone, although PhOCD alone afforded 52% ee to (*S*)-pantolactone.

To visualize the competition between PhOCD and *o*-PyOCD, a transient method was also applied (Figure 3). Hydrogenation of ethyl pyruvate in THF over Pt/Al_2O_3 afforded 27% ee to the (*S*)-enantiomer in the presence of PhOCD and 54% ee to the (*R*)-enantiomer when *o*-PyOCD was applied alone as modifier; both values were measured at full conversion. In a transient experiment the reaction was started with Pt/Al_2O_3 modified by *o*-PyOCD, and after 20 min 1 equiv of PhOCD related to *o*-PyOCD was injected into the slurry. The enantioselectivity was only slightly affected by the addition of PhOCD; the deviation at full conversion was only 5%. This is an indication that PhOCD cannot efficiently compete with *o*-PyOCD at the surface.

In the control experiment (Figure 4) the reaction was started with Pt/Al_2O_3 modified by PhOCD, and after 20 min 1 equiv of *o*-PyOCD was added. The shift of ee, and particularly that of the calculated incremental ee, demonstrates that within a very short time period *o*-PyOCD replaced PhOCD on the Pt surface,

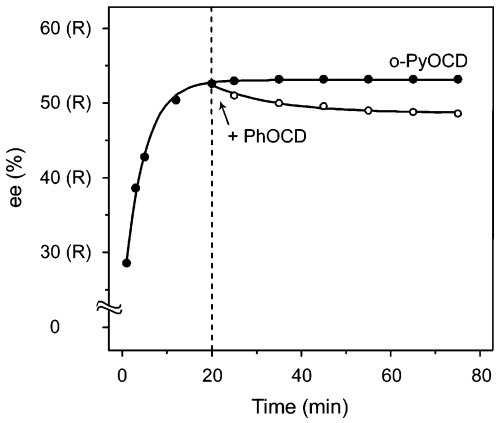

Figure 3. Transient behavior of the hydrogenation of ethyl pyruvate over Pt/Al_2O_3 induced by the addition of 1 equiv of PhOCD to the reaction mixture containing *o*-PyOCD; standard conditions, THF, 1 bar; second modifier added in 1 mL of THF.

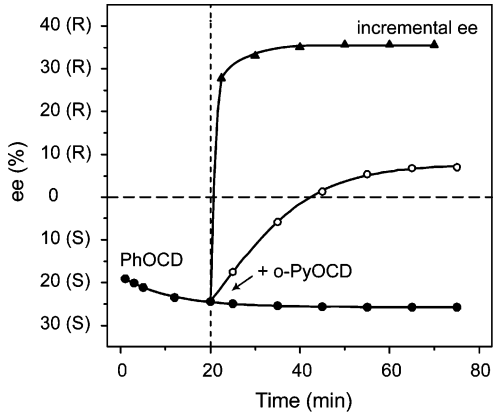

Figure 4. Transient behavior of the hydrogenation of ethyl pyruvate over Pt/Al_2O_3 induced by the addition of 1 equiv of *o*-PyOCD to the reaction mixture containing PhOCD; standard conditions, THF, 1 bar; second modifier added in 1 mL of THF.

resulting in the inversion of the major enantiomer of ethyl lactate. Obviously, *o*-PyOCD adsorbs on Pt stronger than PhOCD.

Infrared Spectroscopy. The adsorption of CD on Pt has been extensively studied by means of IR spectroscopy.[47,72,73] Three main species have been observed on the Pt surface using ATR-IR spectroscopy at the solid−liquid interface.[47] The species differ in the orientation of the quinoline ring with respect to the surface plane. The ATR-IR spectrum of *o*-PyOCD on Pt/Al_2O_3 after about 1 h of adsorption time displays the typical signals associated with these species (Figure 5), which signals are assigned as follows. The signal at 1570 cm^{-1} is attributed to the quinoline ring of a flat adsorbed species, i.e., the quinoline ring of the modifier lies nearly parallel to the surface. The signals at 1594 and 1513 cm^{-1} are characteristic of a species adsorbed via the quinoline ring being in a tilted position to the surface. The signal at 1532 cm^{-1} belongs to the α-quinolyl species, where the α-H is abstracted and the quinoline ring is tilted with respect to the surface. Additional signals at 1468 and 1433 cm^{-1} in Figure 5 are assigned to the stretching modes of the pyridine ring by comparison with the transmission spectrum of the chiral modifier and the calculated spectrum in vacuum. The assignments of the signals are summarized in Table 2.

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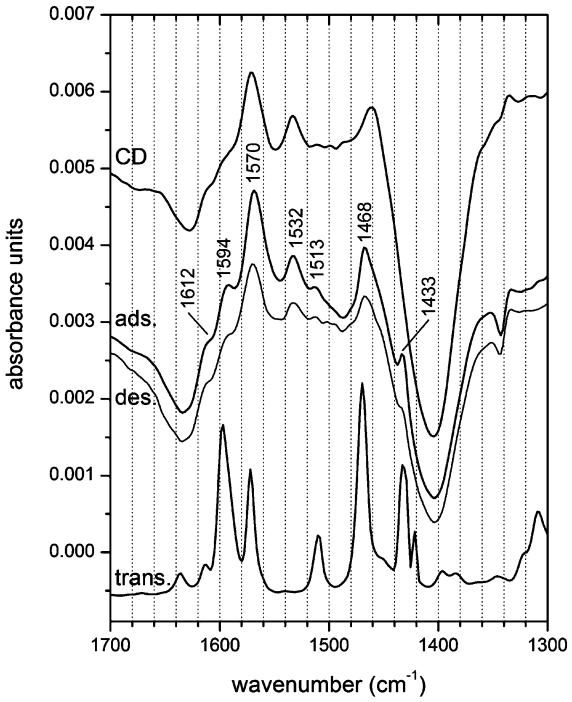

Figure 5. Middle: ATR-IR spectra of *o*-PyOCD on Pt/Al_2O_3 during adsorption (ads.) and after rinsing with H_2-saturated solvent (des.). Bottom: transmission spectrum of *o*-PyOCD (scaled 1:150, CH_2Cl_2, 1 mM). Top: ATR-IR spectrum of CD adsorbed on Pt/Al_2O_3 (after rinsing with H_2-saturated solvent). Spectra are offset for clarity. Conditions: 0.1 mM modifier concentration, 15 °C, H_2-saturated CH_2Cl_2.

Table 2. Assignment of Selected Vibrational Modes of *o*-PyOCD Adsorbed on Pt/Al_2O_3 for Comparison with Adsorbed CD and the Calculated Spectrum of *o*-PyOCD

CD	*o*-PyOCD			assignment	
Pt[a]	sol[b]	Pt[c]	calcd[d]	species	mode
n.o.	1635	n.o.	1670		ν(C═C), vinyl[e]
1610	1614	1612	1619	tilted	ν(C−C) + δ(C−H), Q
			1597		ν(C−C) + δ(C−H), py + Q
1593	1596	1594	1591	tilted	ν(C−C) + δ(C−H), py + Q
			1583		ν(C−C) + δ(C−H), py
1570	1571	1570	1570	flat	ν(C−C) + δ(C−H), Q
1530		1532		α-quinolyl	ν(C−C) + δ(C−H), Q
1511	1510	1513	1509	tilted	ν(C−C) + δ(C−H), Q
sh	sh	n.o.	1481	all	$\delta(CH_2)$, Qd
	1469	1468	1469	all	ν(CC) + δ(C−H), py
			1466		$\nu(CH_2)$, Qd
1460	1454	1460	1457	all	$\nu(CH_2)$, Qd
			1452		$\nu(CH_2)$, Qd
	1433	1433	1428	all	ν(C−C) + δ(C−H), py
	1309	n.o.	1305		δ(C−H), py
	n.o.	1286	1286	all	δ(C−H), py
	n.o.	1265[f]	1271	all	$\delta(C_9(O)-H) + \delta(CH_2)$, Qd
	n.o.	1246	1245	all	δ(C−H), Q + $\delta(C_9(O)-H)$

[a] ATR-IR spectra; $CH_2Cl_2 + H_2$. See ref 47. [b] CaF_2 cell, d = 1 mm. [c] ATR-IR spectra; $CH_2Cl_2 + H_2$; this work. [d] Calculated spectrum of the open (3) conformer in vacuum; see ref 55. [e] The vinyl group is hydrogenated under the present conditions. [f] Partially overlapping with solvent signal; n.o.= not observed; Q = quinoline; Qd = quinuclidine; py = pyridine.

The spectrum recorded after ca. 30 min of desorption time indicates that the flat species resists desorption and dominates the spectrum. The tilted species is more weakly adsorbed, in agreement with the behavior of the parent modifier CD.[47] Adsorption in a flat geometry visibly perturbates the spectrum of the modifier compared to the transmission spectrum, as indicated by the weak signal at 1594 cm^{-1} that, on the contrary, dominates the transmission spectrum. This difference and the negative features[47] at 1400 and 1338 cm^{-1} reveal that *o*-PyOCD adsorbs strongly on Pt. Importantly, the very low intensity of the signal at 1594 cm^{-1} in the adsorbed layer would suggest that the axis of the ring is close to parallel to the metal surface, since this signal is composed of three modes predominantly located on the pyridyl ring and having a dipole moment along its main axis. The signals at 1468 and 1433 cm^{-1} are still observed after desorption indicating that the pyridyl ring of *o*-PyOCD is oriented nonparallel to the metal surface within the adsorbate layer, which is predominantly composed of flat adsorbed species.

Analysis of the spectra allows an estimation of the adsorption geometry of the adsorbed layer. Quantum chemical calculation of the vibrational modes of *o*-PyOCD also indicates that the signals at 1468 and 1433 cm^{-1} and those at higher frequency are not suited to define the adsorption of the pyridine ring. It has been recently proposed[43,74] that the absence or presence of a signal at 1460 cm^{-1} may indicate a specific orientation of the quinuclidine moiety. Figure 5 shows clearly that the spectrum of *o*-PyOCD on Pt exhibits such feature, which overlaps with the signal at 1468 cm^{-1}, indicating that the quinuclidine moiety of *o*-PyOCD is probably oriented toward the metal surface.

Additional information on the adsorption geometry is provided by the pyridine ring which enables the observation of further bands in the 1300−1200 cm^{-1} spectral region which features are absent for other adsorbed cinchona alkaloids. These signals correspond mainly to modes of the pyridine ring. The signal at 1265 cm^{-1} (δ(C−H), not shown) belongs to the stereogenic center at C(9), a signal not present in the parent CD adsorbed on Pt, whereas the band at 1245 cm^{-1} belongs to the quinoline ring, but none of the signals is able to indicate a specific orientation of the pyridyl ring. On the other hand, Table 2 shows that the signal at 1305 cm^{-1}, of medium intensity in the transmission spectrum, is absent in the spectrum of the adsorbed species. This mode exhibits a dynamic dipole moment oriented ca. 30° with respect to the main axis of the pyridyl ring and parallel to the ring plane. According to the surface selection rule, this mode should be silent only when the axis of the pyridyl ring is oriented close to parallel to the surface plane. The absence of the signal at 1305 cm^{-1} on Pt and the observation of the signals at 1468 and 1433 cm^{-1} suggest that in all species within the adsorbed layer the pyridyl ring is oriented in such a way that it closes the chiral space defined by the adsorbed modifier and the metal surface. In the case of the flat adsorbed species, this conformation resembles that exhibited by PhOCD.[43] The pyridyl ring is oriented with the ring plane being approximately perpendicular to the metal surface, with the main axis parallel to it and with the N atom likely pointing toward the surface. In this orientation, the pyridine ring actually generates a closed chiral space more similar to that created by PhOCD than that of CD. Additionally, the quinuclidine N atom also points toward the metal surface. Therefore, the ATR-IR investigations indicate that a species like that represented in Figure 6 populates the Pt surface under the applied experimental conditions.

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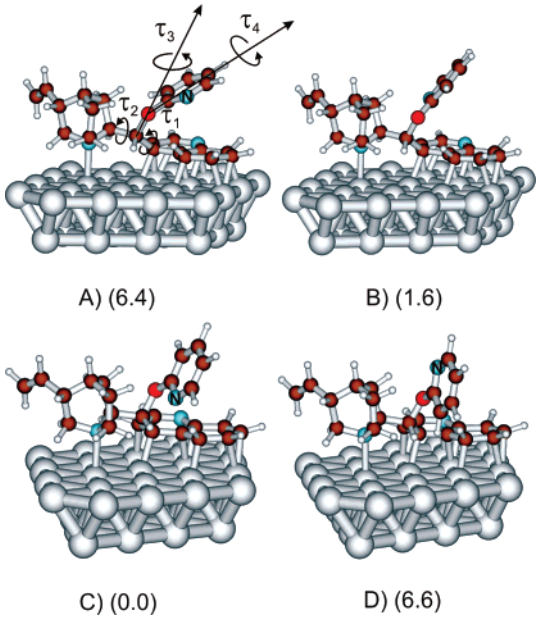

Figure 6. Surface quinuclidine bound (1) conformation of adsorbed *o*-PyOCD. Four structures can be generated according to the position of the *o*-pyridoxy moiety, after rotation of the bonds around τ_3 and τ_4. The relative energies (in kcal/mol) referred to the most stable conformation (C) are reported in brackets. Conformations A and B have an open chiral space, whereas conformations C and D have a closed chiral space, due to the presence of the *o*-pyridoxy moiety in proximity of the metal.

Modeling. Cinchona alkaloids and their ether derivatives have a complex conformational behavior in solution,[75−78] and the conformational complexity is partially retained upon adsorption.[50,51,74,79,80] For CD it was shown that the six possible surface structures can be divided into two groups of three structures in each, according to the values of the angles τ_1 and τ_2.[50,51] The members of the first group may be derived from the conformer SO(3), whereas the conceptual origin of the second group is the conformer SO(4). Structures within the two groups can interconvert by simple conformational rearrangement, whereas a desorption−adsorption step is needed to pass from one group to the other. The first group is composed of the conformers surface closed (2) {SC(2)}, surface open (3) {SO(3)}, and surface quinuclidine bound (2) {SQB(2)}, whereas the second consist of surface closed (1) {SC(1)}, surface open (4) {SO(4)}, and surface quinuclidine bound (1) {SQB(1)}.[50] Excluding the closed conformations, that have the wrong position of the quinuclidine moiety to interact with the substrate adsorbed in the neighborhood, the most stable conformation is the SQB(1), belonging to the SO(4) series. It is expected that the fractional coverage of this species at equilibrium is larger than that of the other conformations, showing therefore a marked difference to the conformational behavior in solution, where the open (3) conformer is the most stable species.[75,76]

Important experimental evidence supporting the considerations above derives from the study of the hydrogenation of CD on a Pt/Al_2O_3 catalyst.[81,82] Two diastereomers of the 1′,2′,3′,4′,10,11-hexahydrocinchonidine were obtained, the 4′-(*R*) and the 4′(*S*), differing in the absolute configuration of the C(4′) carbon atom. The 4′(*S*) diastereomer was formed in excess, which observation is consistent with a surface population dominated by conformers of the SO(4) series.

Accordingly, the following modeling study was confined to those conformers of *o*-PyOCD that are most likely to participate in the enantioselective hydrogenation of ketones (in the following we analyze the simplest case, the hydrogenation of ketopantolactone). In particular, a recent model used to explain the inversion of enantioselectivity with respect to CD when PhOCD is used as chiral modifier was based on the analysis of the chiral space generated by the SQB(1) surface conformation,[43] which is the most stable species among the SO(4) series. The structures of the adsorbed *o*-PyOCD in the SQB(1) conformation were calculated on a platinum surface, simulated by a Pt 38 cluster, and the influence of the position of the *o*-pyridoxy moiety was analyzed. Figure 6 shows the four possible conformers that can be obtained by rotation of the bonds around τ_3 and τ_4. The energy of the most stable conformer, depicted in Figure 6C, was set to zero, while the energy differences between the other conformers and the most stable one are given in brackets.

If we consider the model proposed for PhOCD and its phenyl-substituted derivatives,[43,44] we can conclude that structures A and B have open chiral spaces, and should lead to the formation of (*R*)-pantolactone (similarly to CD), whereas structures C and D have closed chiral spaces, and should lead to the formation of (*S*)-pantolactone, in the hydrogenation of ketopantolactone. For PhOCD the inversion of the major enantiomer was explained by the steric interference of the O-phenyl group in the chiral space available for adsorption of the substrate.[43,44] Since *o*-PyOCD leads to formation of the (*R*)-enantiomer, and still has a closed chiral space in the most stable conformation, the catalytic results seem to contradict to the model. However, there is an important difference between the O-phenyl and the O-pyridyl moieties: the former can mainly cause steric repulsion toward the incoming substrate, whereas the latter can interact with the substrate via the basic nitrogen of the aromatic ring. It has already been shown that hydrogen uptake by amines is a feasible process on platinum in the presence of surface hydrogen.[74,83,84]

On the basis of this concept, an interaction model between *o*-PyOCD and adsorbed ketopantolactone was calculated where both the quinuclidine and the O-pyridyl moieties take part in hydrogen-mediated interactions with the substrate. The simulation was started by addition of hydrogen to the N atoms of the quinuclidine and the O-pyridyl moieties. As shown in Figure 7, after complete optimization of the structures the N atom of the quinuclidine moiety interacts via an H-bond with the keto-carbonyl O atom of ketopantolactone, while the O-pyridyl moiety coordinates the ester carbonyl which is chemisorbed to the metal. Ketopantolactone is adsorbed in a Pro-(*R*) conformation on the metal surface. Figure 7 shows that, in particular, the hydrogen at the quinuclidine N is transferred to the adsorbed ketone at the end of the simulation. A previous simulation[74]

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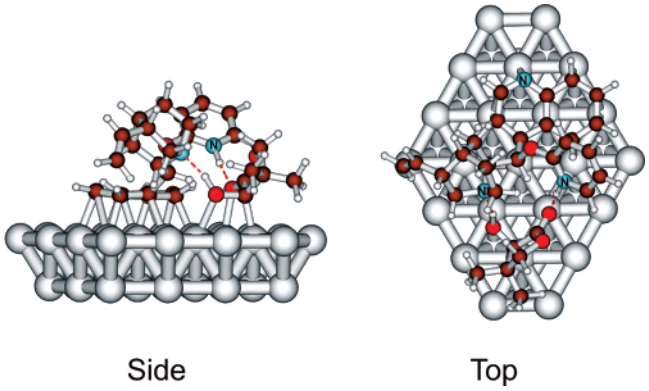
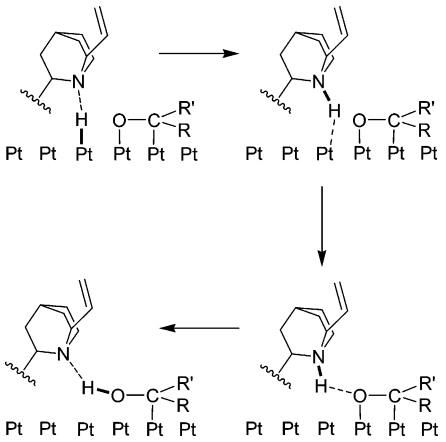


Figure 7. Adsorbed *o*-PyOCD in the surface quinuclidine bound (1) conformation, with the most stable position of the *o*-pyridoxy moiety, interacting with ketopantolactone adsorbed in a Pro-(*R*) conformation. The interaction was obtained by unconstrained energy minimization of the two adsorbed molecules, after hydrogen uptake from the Pt surface at the N atoms of the quinuclidine and pyridine moieties. At the end of the simulation the hydrogen was transferred to the keto-carbonyl group of ketopantolactone (as depicted), therefore forming a semihydrogenated surface species, while the *o*-pyridyl group coordinates to the ester carbonyl group.

Scheme 2. Simplified Scheme for the Interaction of the Quinuclidine N Atom with the Pt−H System and the Subsequent Transfer of the H to the Adsorbed Ketone



showed that hydrogen transfer from the metal to the quinuclidine N occurs without a transition state, and the present result indicates that also the second transfer of the same hydrogen atom to the substrate occurs without a transition state, since a smoothly decreasing energetic pathway is followed during optimization. (For a schematic illustration, see Scheme 2.) Figure 7 also shows that on the other side of the chiral space the substrate (which is Pro-(*R*) adsorbed) is kept coordinated by the other hydrogen-mediated interaction due to the pyridyl moiety.

This interaction model between adsorbed reactant and modifier shows that although *o*-PyOCD generates a closed chiral space on the Pt surface, similarly to PhOCD, it also has the possibility to interact with the substrate via the pyridoxy N atom offering a secondary substrate−modifier interaction. This crucial difference seems to be at the origin of inversion when replacing PhOCD by *o*-PyOCD.

Discussion

The Pt−cinchona system is by far the best heterogeneous catalyst for the enantioselective hydrogenation of activated ketones to alcohols.[4,5,7,8] With the only exception of O-methylcinchonidine, all cinchona derivatives and other types of chiral modifiers tested in these reactions were inferior to CD. Still, analysis of the performance of these modifiers gives a valuable hint to the origin of enantioselection, the real nature of the substrate−modifier−metal surface interactions during hydrogen uptake.

O-Arylation of CD by a phenyl group (in PhOCD) inverted the major product from (*R*)- to (*S*)-alcohol in the hydrogenation of various ketones on Pt.[40,41] The switch in the product enantiomer was associated with the bulky phenyl group that reshapes the chiral space where the enantioselection takes place. The present study reveals another intriguing switch: replacement of the phenyl group by an *o*-pyridyl group (*o*-PyOCD) inverts the enantioselectivity, and again the (*R*)-alcohol is produced in excess. In other words, CD and *o*-PyOCD provide the same enantiomer in excess, despite of the bulky pyridyl group present in the latter modifier, and *o*-PyOCD and PhOCD give the opposite enantiomer of the alcohol, despite of the almost identical van der Waals volumes of the ether groups.

A comparison of the present and former[22,40] studies of the nonlinear behavior of modifier mixtures in ketones hydrogenation shows the following order of adsorption strength on Pt: CD > *o*-PyOCD > PhOCD. The advantage of this approach is that the adsorption strength is related to truly in situ conditions, in the presence of substrate and hydrogen. The ATR-IR investigation confirmed that *o*-PyOCD adsorbs relatively strongly on a model Pt/Al_2O_3 surface, in the absence of substrate. The stronger adsorption of *o*-PyOCD, relative to that of PhOCD, is probably due to the additional interaction of the basic N of the pyridyl group with the Pt surface. In the dominant adsorption mode the quinoline ring is close to parallel to the Pt surface, while the plane of the pyridyl ring is oriented approximately perpendicular to the surface and the basic N interacts with Pt. In this position the bulky ether group closes the chiral space, which is available for adsorption of the ketone in case of CD. This adsorption geometry is similar to that adopted by PhOCD under similar conditions, in the absence of substrate. Hence, on the basis of the adsorption geometries of the modifiers and the similar bulkiness of the ether groups it should be expected that *o*-PyOCD and PhOCD give the same enantiomer, the (*S*)-alcohol, in excess.

The apparent contradiction to the catalytic observations can only be resolved by assuming the involvement of the basic function of the pyridyl group in the enantioselection, as indicated by theoretical calculations including the simulation of the substrate−modifier interaction. ATR-IR spectroscopy revealed that the adsorption features of *o*-PyOCD resemble those already found for CD and PhOCD. This includes the dominant role of the quinoline ring as anchoring moiety, adsorbed (close to) parallel to the metal surface. Theoretical[50,51] and experimental[81,82] evidence in the present and in previous studies strongly suggests that the so-called surface quinuclidine bound (1) conformations of the alkaloids dominate formation of the chiral surface sites. In such conformations the quinuclidine nitrogen interacts with the surface metal atoms to provide a further binding point, thus increasing its stability (adsorption energy). In addition, the quinuclidine N can exchange surface hydrogen, triggered by its proximity to the metal and by the strongly basic nature of the N atom. This concept has already been proven experimentally[83,84] and theoretically.[74] Accordingly, the role of

the surface modifier is twofold: beside forming a chiral environment, it promotes the transfer of hydrogen from the surface to the substrate within the chiral site (Scheme 2), which model is consistent with the rate acceleration often observed on cinchona-modified Pt.

On the basis of this insight, the computational modeling of the docking of ketopantolactone within the chiral space generated by *o*-PyOCD was performed using density functional theory. (The substrate was chosen for its relatively simple conformational behavior.) The calculations confirmed that the adsorbed substrate can interact with the adsorbed *o*-PyOCD via two N−H−O-type bonds. This is a crucial deviation from the model proposed for the CD-activated ketone interaction.[85] Similarly, when the pyridoxy group is replaced by a phenoxy group (in PhOCD), the attractive secondary interaction between the ether group and the ketone becomes a repulsive interaction. This fundamental difference provides a reasonable explanation for the change of the sense of enantioselection in the hydrogenation of α-functionalized ketones.

It is noteworthy to mention that all modifiers bearing large ether substituents yield lower enantioselectivities due to greater steric impediment in the proximity of the chiral space.[41,86] This favors the competing racemic hydrogenation and lowers enantioselectivity. Docking of the ketopantolactone in Pro-(*S*) arrangement within the chiral pocket formed by *o*-PyOCD is unlikely since it would imply the loss of the second binding interaction.

Although the complexity of the system is still a challenge for deriving a complete mechanistic picture, which would require a dynamic analysis of all the steps involved in the hydrogen transfer, the basic elements seem to be present for the assessment of a catalytic system based on the secondary guiding group that is able to adjust a substrate within the surface chiral site.

A final point is the nature of interactions between the basic N atoms of *o*-PyOCD and the Pt−H system. Lee and Masel proposed that under ultrahigh vacuum (UHV) conditions the Pt−H system can protonate pyridine and fluoro-pyridines and produce pyridinium cations on a Pt(110) surface.[83,84] Although we agree with the concept and arrived at a similar conclusion in calculating the interaction of the quinuclidine N of CD with ketones on the Pt−H system,[74] the present study indicates that the term protonation may not be ideal for this case. As discussed previously in relation to the stability of *o*-PyOCD, protonation of the modifier even by a weak organic acid led to its hydrogenolytic decomposition. It seems that at the metal surface the weakly basic pyridoxy N acts as a "hydrogen mediator", rather than a base that is protonated by the Pt−H system.

Conclusions

Systematic variation of the ligand structure is a widely used efficient strategy in homogeneous asymmetric catalysis. Interestingly, this approach is much less popular in heterogeneous catalysis over chirally modified metal surfaces. When considering the strong limitations to the use of in situ spectroscopic methods in analyzing the real nature of substrate−modifier−metal surface interactions, the approach of variation of the modifier structure appears even more attractive. Nevertheless the interpretation of a change in the enantioselectivity, or even a change of the sense of enantioselection, is often not straightforward, giving rise to considerable mechanistic speculation. We have shown in the present work that the number of possible mechanistic explanations can be reduced by the combination of catalytic experiments with spectroscopy under close to in situ conditions and the involvement of computational tools. We consider this approach as presently the most efficient way to unravel the unique features of enantioselection at chiral metal surfaces.

In a previous study of ether derivatives of CD we have shown the crucial role of steric bulkiness of the ether groups that can lead even to inversion of the sense of enantioselection as the bulky ether group occupies the chiral space available for the adsorption of the substrate in case of the parent alkaloid CD.[86] Here, the comparison of PhOCD and *o*-PyOCD provides an even more intriguing example as their van der Waals volumes and adsorption modes on Pt/Al_2O_3 are very similar, but an additional substrate−modifier interaction possible only for *o*-PyOCD inverts the ee.

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Supporting Information Available: Complete references 48 and 55 and Cartesian coordinates of the structure shown in Figure 7. This material is available free of charge via the Internet at http://pubs.acs.org.

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