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Inversion of the Enantioselectivity in the Hydrogenation of (*E*)-2,3-diphenylpropenoic Acids over Pd Modified by Cinchonidine Silyl Ethers

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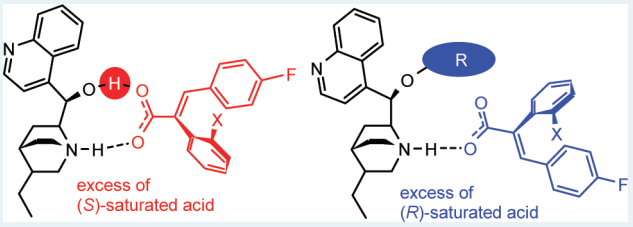
ABSTRACT: Natural cinchona alkaloids and their derivatives were applied as chiral modifiers in the enantioselective hydrogenation of (*E*)-2-(2-methoxyphenyl)-3-(4-fluorophenyl)propenoic acid over Pd/Al_2O_3 catalyst. The effect of the modifier structure on enantioselectivities and reaction rates was investigated. The natural cinchonine and its methyl ether resulted in opposite product enantiomers in excess. However, in the cinchonidine series larger substituents were needed to obtain inversion, such as the *tert*-butyl-dimethylsilyl group. To find an explanation of the phenomenon, stabilities of cinchona alkaloid derivatives under the reaction conditions were investigated by electron-spray ionization mass spectrometry, and the modifiers' relative adsorption strengths were studied using mixtures of cinchona alkaloids and sequentially added modifiers. Decrease in the interaction strength of the cinchona ether derivatives with the acid and the catalyst surface can tentatively explain the observed decrease in the enantioselectivity and the eventual inversion of its sense. Results of these studies suggested the gradual alteration of the shape of the surface chiral sites by increasing the size of the substituent. The presence of benzylamine always increases the amount of the enantiomer which is formed in excess over the parent cinchona alkaloids and accelerates the desorption of the modifier, suggesting the participation of the additive in the surface intermediate. Occasionally, cinchona alkaloid mixtures provided enantioselectivities above or under the values obtained with both sole modifiers, which is suggested to be due to the mutual interaction of the two cinchona derivatives on the surface.



KEYWORDS: chiral surface, enantioselective, hydrogenation, heterogeneous catalyst, palladium, cinchona alkaloid, unsaturated acid

1. INTRODUCTION

Asymmetric hydrogenations of prochiral unsaturated organic compounds are among the most important methods for the preparation of optically pure fine chemicals.[1,2] Chiral catalytic materials obtained by adsorption of optically pure substances over metal particles are convenient alternatives of complexes used in enantioselective hydrogenations.[3] The most successful catalytic systems obtained to date by this approach are based on "modifiers" from the chiral pool, that is, tartaric acid or cinchona alkaloids.[4−6] Pt and Pd catalysts modified by cinchona alkaloids provided excellent enantioselectivities in hydrogenations of activated ketones and olefins, respectively.[6] Thus, in contrast to aliphatic α,β-unsaturated acids,[7−13] in the hydrogenation of (*E*)-2,3-diphenylpropenoic acids over 90% enantiomeric excesses (ee) could be reached over Pd.[14−19]

Conventionally, the origin of the enantiodiscrimination over cinchona alkaloids modified metal catalysts is attributed to the C^9-C^8 stereogenic center of the alkaloid, since modifiers, with opposite configurations of this center afford the opposite product enantiomers in excess. However, in the hydrogenation of activated ketones over Pt, inversion in the sense of the ee was obtained by substitution of the C^9-OH of the modifier without altering the configuration of the stereogenic center.[20−26] Baiker and co-workers demonstrated that the chiral surface sites of Pt are reshaped in the presence of certain substituents, leading to changes in the docking preference of the substrates. Inversion in the sense of the ee over modified Pd were seldom reported.[27−31] Thus, the small excess of (*R*)-2,3-diphenylpropionic acid obtained in the hydrogenation of α-phenylcinnamic acid by using 10,11-dihydrocinchonidine methyl ether was attributed to the lack of H-bonding of the substrate to the C^9-O-CH_3 group.[27] Recently, it was found that in the hydrogenation of several (*E*)-2,3-diphenylpropenoic acids methyl ethers of the cinchonine series lead to inversion of the ee sense and was interpreted by the cooperative effect of the methyl substituent on the shape of the

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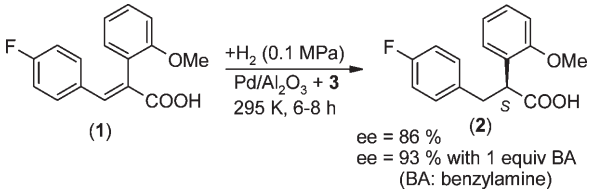
Scheme 1. Enantioselective Hydrogenation of (*E*)-2-(2-methoxyphenyl)-3-(4-fluorophenyl)propenoic Acid over Pd/Al_2O_3 Modified by Cinchonidine (3)



chiral surface sites, the increase in the flexibility of the cinchona-acid interaction, and the steric influence of the aryl moieties of the acids.[32] The sense of the ee in the presence of methyl ethers from the cinchonidine series was strongly influenced by the acid structure.

The interpretation of such unexpected results should take into account the conformational behavior and the adsorption mode of cinchona alkaloids and their derivatives.[33−35] The conformational behavior of cinchona alkaloid methyl ethers found in solution is altered when compared with that of parent alkaloids as effect of the steric hindrance of the ether group. Moreover, the conformational mobility is further changed upon adsorption over metal surfaces.[37−39] However, the most stable surface conformations of the protonated cinchonidine and its methyl ether on Pt were the so-called quinuclidine adsorbed conformations, that is, QA-Open(4) and QA-Open(3), which allowed the simultaneous interaction of reactants with both the quinuclidine N and the C^9-O-R functionality.[38] The behavior of cinchona alkaloids on Pd was characterized by weaker adsorption, higher mobility, and higher population of surface tilted "spectator" species when compared to Pt.[40,41]

During the hydrogenations over catalysts modified by cinchona alkaloids besides the vinyl group, the anchoring quinoline moiety is also partially saturated,[42−45] which may cause significant alteration in the ee. Previous studies demonstrated such transformation of the cinchona alkaloids during the hydrogenation of activated ketones over Pt[46−50] as well as that of 2-pyrones and heteroaromatic acids over Pd.[51−53] It was shown that over Pd the heteroaromatic ring of the quinoline moiety is more prone to hydrogenation than the benzene ring.[53]

Information on the mechanism of the enantiodifferentiation were also obtained from studies using binary mixtures of modifiers either in pre-equilibrated system or by their consequent addition to Pt[24,54−58] or Pd.[27,59−61] The nonlinear behavior obtained over Pd in the hydrogenation of (*E*)-2,3-diphenylpropenoic acids indicated weaker adsorption of the methyl ethers on the Pd surface when compared with the parent cinchona alkaloids.[32]

To sum up, the product chirality in the enantioselective hydrogenation of (*E*)-2,3-diphenylpropenoic acids over Pd is controllable by the substitution of the cinchona alkaloid used as modifier. However, the effect of the modifier structure is not yet fully understood. Here we report a detailed study on the modifier structure-enantioselectivity relationship in the hydrogenation of (*E*)-2-(2-methoxyphenyl)-3-(4-fluorophenyl)propenoic acid (**1**) over cinchona alkaloid-modified Pd (see Scheme 1). Hydrogenations using binary modifier mixtures or sequentially added modifiers were carried out to compare the adsorption strengths of the derivatives used and transformations of modifiers under reaction conditions were also investigated.

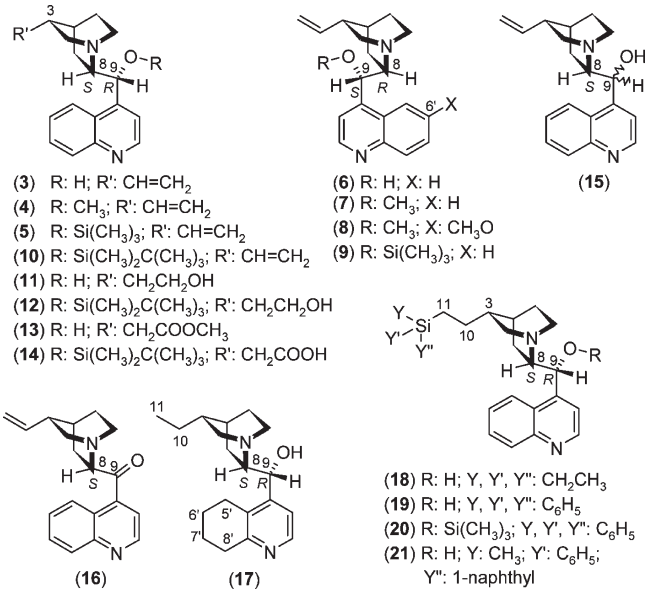


Figure 1. Structure of the cinchona alkaloid derivatives used as modifiers in this study.

2. RESULTS

2.1. Effect of the Modifier Structure on the Enantioselective Hydrogenation of 1. The effect of the modifier structure was examined using the derivatives presented in Figure 1. Mainly the influence of two structural parts of the cinchona alkaloids were studied, namely, (a) the stereogenic center altered by derivatization of the C^9-OH group or epimerization of this chiral center and (b) the quinuclidine part altered by derivatization of the vinyl group at the C^3 position. Results obtained in the absence and presence of benzylamine (BA) are summarized in Table 1 along with those resulted over unmodified catalyst and modified by the parent cinchona alkaloids (**3**, **6**) and methyl ethers (**4**, **7**, **8**), included for comparison.[32] Note that the initial H_2 uptake rates (R_{iH}) of the racemic and enantioselective hydrogenations had close values (in the absence of BA, deceleration occurred) suggesting that there was no ligand acceleration associated with the presence of the modifier, similarly with the previously reported hydrogenation of diketones over Pt.[62]

The modifiers used in this study may be divided in two groups based on whether they favor production of the same or opposite product enantiomer as compared to the parent alkaloid. The first group comprises **4**, **5**, **9**, **11**, **13**, **17**, **18**, **19**, **20**, and **21**, namely, derivatives bearing free C^9-OH along with the methyl ether of **3** and trimethylsilyl ethers. These modifiers provided the same sense of the ee as observed for parent cinchona alkaloids (**3** or **6**). Modification of the surface by modifiers from the second group, namely, **7**, **8**, **10**, **12**, and **14** favored inversions in the sense of the ee as compared to their parent compounds. This group includes the methyl ethers of the $(R)C^8-(S)C^9$ cinchonas and the $C^9-O-SiMe_2{}^tBu$ ethers. Very low ee with retention of its sense was obtained with the hexahydro-**3** (**17**). Modifiers **15** and **16**, which have the C^9 epimerized or symmetric, resulted in close to racemic hydrogenation, the latter giving a small ee in favor of the (*S*)-**2**. Substituents on the C^{10} or C^{11} decreased the ee; this decrease was more pronounced when bulky silyl groups were grafted on the C^{11} atom (**18**, **19** and especially **21**). The trimethylsilyl ethers **5**, **9**, and **20** afforded the same ee as the

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C^9−OH cinchona alkaloids from which are derived (**3**, **6** and **19**). The modifier structure effect on R_{iH} was less pronounced and difficult to rationalize; with few exceptions decreased by substituting the C^{10} or C^{11}.

2.2. Effect of Achiral Amine Additive. The presence of BA had an opposite effect on the ee using cinchona alkaloid derivatives belonging to the above two groups (see Table 1). The enantioselectivity was enhanced in the presence of the achiral amine in reactions over catalyst modified by derivatives, which give the same product enantiomer in excess as their parent alkaloids. In contrast, decrease of ee was observed by addition of BA to the reaction mixture containing catalyst modified by compounds from the second group. Thus, in comparison with reactions in the absence of BA, the presence of the additive always led to the formation of higher amounts of the enantiomer obtained in excess with the parent cinchona modifier. Although, in the presence of the substituents on the C^{11} the ee decreased when compared with **3**, the derivative **13** in the presence of BA afforded the same ee as **3**, in contrast to **11**, **18**, **19**, and **21**. It is known that BA increases the hydrogenation rate over modified sites.[14−19,63] The R_{iH} values increased or were unaltered in the presence of BA using cinchona alkaloids underivatized on the C^9−OH, whereas with the cinchona ethers this value either decreased or remained at the same value by adding BA, with few exceptions (trimethylsilyl ethers and **12**).

Table 1. Hydrogenation of 1 over Cinchona Derivatives Modified Pd/Al_2O_3 Catalyst[a]

entry	modifier	R_{iH} (mmol h^{-1} g^{-1})[b]	X (%)/t (h)[c]	ee (%); (config)[d]
1[16,32]		7; 4	99/6; 99/6	
2[16,32]	**3**	3; 7	98/6; 99/6	86(*S*); 93(*S*)
3[32]	**4**	6; 5	96/6; 96/6	25(*S*); 54(*S*)
4	**5**	4; 5	99/8; 99/6	84(*S*); 90(*S*)
5[32]	**6**	4; 6	98/6; 99/6	55(*R*); 74(*R*)
6[32]	**7**	7; 7	96/6; 95/6	44(*S*); 34(*S*)
7[32]	**8**	4; 4	95/6; 94/6	30(*S*); 0
8	**9**	3; 5	85/8; 98/6	55(*R*); 72(*R*)
9	**10**	5; 4	90/6; 80/6	50(*R*); 4(*S*)
10	**11**	4; 4	98/8; 96/6	72(*S*); 79(*S*)
11	**12**	2; 3	94/8; 88/6	55(*R*); 19(*R*)
12	**13**	2; 7	75/8; 99/8	73(*S*); 93(*S*)
13	**14**	4; 4	84/8; 87/8	20(*R*); 12(*R*)
14	**15**	3; 7	95/6; 96/6	0; 1(*S*)
15	**16**	2; 3	83/8; 88/6	7(*S*); 2(*R*)
16	**17**	4; −	97/6; −	14(*S*); −
17	**18**	3; 3	55/6; 65/6	52(*S*); 58(*S*)
18	**19**	2; 2	72/8; 74/8	52(*S*); 70(*S*)
19	**20**	2; 5	60/8; 70/6	52(*S*); 58(*S*)
20	**21**	1; 2	65/8; 74/8	22(*S*); 34(*S*)

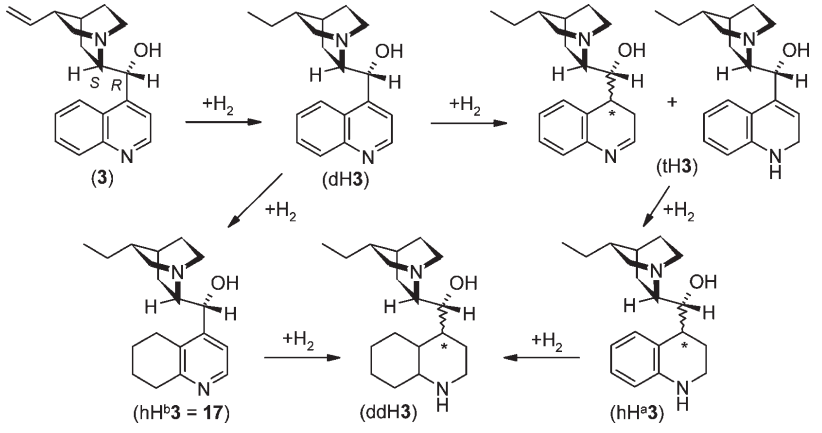
[a] Reaction conditions: 25 mg 5% Pd/Al_2O_3, 5 cm^3 DMF + 2.5 vol % H_2O, 0.5 mmol **1** (c**1** = 0.1 M), 0.025 mmol modifier (c = 5 mM), 0.5 mmol BA (cBA = 0.1 M, when used), 0.1 MPa H_2, 295 K. [b] H_2 uptake rate in the absence; presence of BA. [c] Conversions obtained after hydrogenation times t in the absence; presence of BA. [d] Enantioselectivities and the configuration of the excess enantiomers obtained in the absence; presence of BA.

2.3. Transformation of the Modifiers during the Hydrogenation of 1. Transformation of cinchona alkaloids during the enantioselective hydrogenation of acrylic acids over Pd has not yet been studied. Thus, initially we investigated the transformation of **3** during the hydrogenation of **1** by electron-spray ionization mass spectrometry (ESI-MS). Possible hydrogenation pathways are illustrated in Scheme 2. Although, the method does not allow determination of the concentrations for each derivative, the relative intensities (I_{rel}) of products of different hydrogenation degrees could be compared. R_{iH}, ee, and I_{rel} of the resulting derivatives versus the initial concentration of **3** (c**3**) are presented in Figure 2.

Both in the absence and in the presence of BA even at low c**3** (≤2.5 mM) the residual alkaloid with unreacted quinoline moiety (**3** + dH**3**) was able to provide high ee. The presence of BA accelerated the hydrogenation of the anchoring moiety when compared to reactions in its absence. However, in the former reaction the hydrogenation was less extensive (I_{rel}(tH**3**) > I_{rel}(hH**3**) as compared to I_{rel}(tH**3**) ≤ I_{rel}(hH**3**) in the absence of BA). Increasing c**3** resulted in decrease in the R_{iH} followed by a constant value upon further raising the concentration. The R_{iH} reached its minima at c**3**, which still ensured significant amount (I_{rel} ~ 20%) of cinchona alkaloid with unreacted anchoring moiety.

Transformations of few cinchona derivatives are summarized in Table 2. Only minor differences between hydrogenations of the C^9−O−$SiMe_2{}^t$Bu ethers were observed when compared with **3** or **11** having free C^9−OH groups. Slightly higher amounts of unhydrogenated derivatives were detected using the former derivatives (**10** and **12**). Essential differences were obtained in the transformation of the C^9−O−$SiMe_2{}^t$Bu and C^9−O−$SiMe_3$

Scheme 2. Possible Hydrogenation Pathways of Cinchonidine (3)



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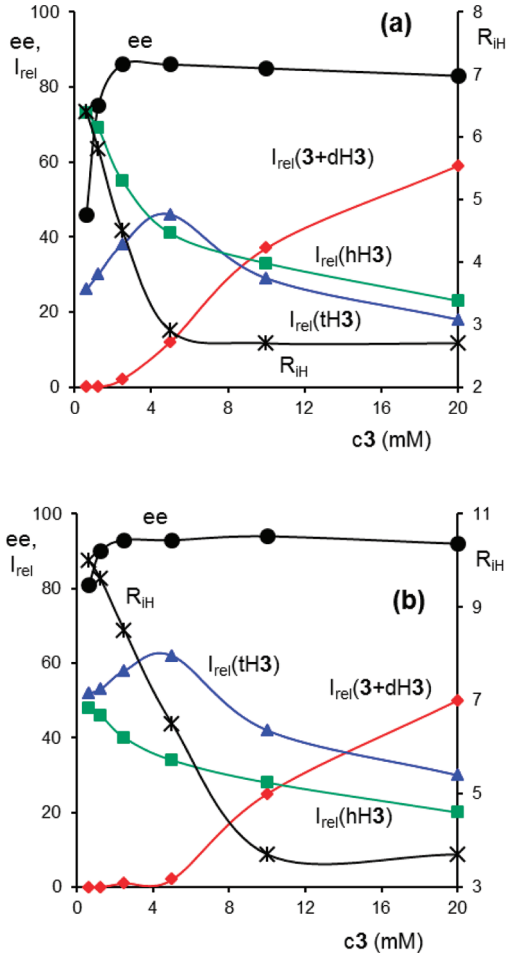

Figure 2. Effect of the concentration of **3** (mM) on the ee (%), R_{iH} (mmol h^{-1} g^{-1}) and the transformation of the modifier expressed as the relative intensities of the **3** derivatives (I_{rel}, %) determined by ESI-MS from the liquid phase: (a) in the absence of BA and (b) in the presence of 0.5 mmol BA (cBA = 0.1 M) (reaction conditions: 25 mg 5% Pd/Al_2O_3, 5 cm^3 DMF + 2.5 vol % H_2O, 0.5 mmol **1** (c**1** = 0.1 M), 0.1 MPa H_2, 295 K, 6 h; for abbreviations see Scheme 2, hH**3** = hH^a**3** + hH^b**3**).

ethers (**10** or **12** and **20**). The former did not suffer C^9O-Si bond hydrogenolysis, whereas the latter was completely transformed during the reaction to the corresponding free C^9-OH derivative followed by hydrogenation of the quinoline moiety to a lesser extent as **10**. The presence of BA had an opposite effect on the hydrogenation of **3** and **10**. Thus, **3** was almost completely transformed by addition of BA (predominantly in tH**3**), whereas close to half of **10** remained unhydrogenated on the quinoline moiety. On the contrary, there was no significant effect of the presence of BA on the transformation of **20**.

2.4. Hydrogenations Using Modifier Mixtures. The above ESI-MS study showed that during reactions the anchoring quinoline moiety of the cinchona alkaloid derivatives are hydrogenated, accordingly, are adsorbed on the metal surface. The relative adsorption strength of cinchona alkaloids can be in situ examined by applying their binary mixtures as modifiers. Therefore, two cinchonidine derivatives giving inversion in the ee, that is, the $C^9-O-SiMe_2{}^tBu$ ethers **10** or **12**, were used in mixture with the parent cinchona alkaloids or their methyl ethers (**3**, **6**, **4**, **7**, or **8**). The results obtained in hydrogenations over catalyst modified by 1:1 binary mixtures are summarized in Table 3.

Prominent nonlinear behavior was obtained using the $C^9-O-SiMe_2{}^tBu$ ethers in mixture with **3**, the latter dominating the enantioselection. The ee's attained using mixtures of the methyl ether **4** with **10** or **12** deviated only slightly from the values calculated assuming linear behavior. Unexpected results were obtained with mixtures of silyl ethers and **6** or **7**. Although, ee's obtained in the absence of BA with **6**, **10**, and **12** were similar (55, 50 and 55% *R*), their binary mixtures resulted in much lower ee's in favor of the *R* enantiomer (30% and 28%, respectively), whereas in the presence of BA the enantioselection was dominated by **6**. When **7** was used in mixture with **10** or **12**, the former dominated the enantioselection, and the presence of BA did not change the ee's, although over the catalyst modified by **7** the use of BA resulted in decrease in the ee. In reactions using mixtures of the methyl ether **8** with **10** or **12** the enantioselection was dominated by the latter.

The nonlinear behavior obtained with 1:1 mixtures promted us to examine the effect of the composition of the **7** + **10**, **7** + **12**, and **8** + **10** modifier pairs. The resultant ee's are presented in Figure 3 along with the plots of ee's calculated assuming a linear behavior and the ee plots that resulted by applying the recently developed kinetic model for the explanation of the nonlinear phenomenon observed over chirally modified metal catalysts.[57]

These experiments proved that the methyl ether **7** dominates the enantioselection when used in a mixture with $C^9-O-SiMe_2{}^tBu$ ethers even at low concentrations of the former. In both sets of experiments (**7** + **10**, **7** + **12**), in the absence of BA, the ee reached values close to that obtained with the sole **7** even at low **7** content ($x(7) \sim 0.25$). Differences observed between the mixtures containing **10** or **12** may be ascribed to the influence of the $C^{11}-OH$ group. In the presence of BA at intermediate compositions the ee reached similar values as in its absence, although, over the **7**-modified catalyst the ee decreases by adding BA. Thus, over a wide range of compositions ($0.1-0.25 < x(7) < 0.75$), the ee was higher than was obtained with the individual modifiers. Because of this surprising behavior the experiments using $x(7) = 1$ were repeated providing the same ee values (reproducibility ±1%). Nonlinear behavior was also obtained using mixtures of **8** and **10**. As effect of the $C^{6'}-OCH_3$ group of **8**, the silyl ether controlled the enantioselection. Up to $x(8) \sim 0.75$ only a slight decrease in the ee was detected when compared with the pure **10**. It is known that flat adsorption with the quinoline moiety parallel to the surface is hindered in the presence of $C^{6'}-OCH_3$ group. Therefore, it is likely that the predominant adsorption mode of silyl ethers is flat, despite of steric constrains of the $C^9-O-SiMe_2{}^tBu$ group.

Application of the kinetic model developed for explaining the nonlinear phenomenon in enantioselective heterogeneous catalysis in the presence of binary modifier mixtures resulted in curves fitting well the data obtained in the absence of BA. The *n* values[57] indicated 7.5−10 kJ mol^{-1} differences in adsorption strengths of the modifiers in each pair examined. However, the model could not fit the data obtained in the presence of BA, when maxima in ee were obtained, suggesting that under these conditions either the BA or the interaction of the modifiers should also be considered in the kinetic treatment. Extension of the applicability of the kinetic model to such cases was recently published (following the submission of this work).[64]

2.5. Sequential Addition of Modifiers. Addition of a modifier during the hydrogenation over catalyst modified by another cinchona alkaloid can be used for evidencing the ability of displacement of one modifier by the other on the surface.[24,52,58]

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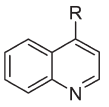
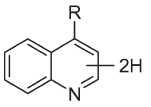
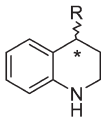
Table 2. Relative Amount of the Cinchona Derivatives in the Liquid Phase Determined by ESI-MS Analysis Following the Hydrogenation of 1 over Modified Pd/Al_2O_3 Catalyst[a]

entry	modifier	additive	I_{rel} (%)[b]		
					
1	**3**	–	12	46	41
2	**3**	BA	2	62	34
3	**10**	–	19	50	31
4	**10**	BA	46	46	8
5	**11**	–	8	64	27
6	**12**	–	14	38	46
7	**14**	–	45	24	29
8	**20**[c]	–	41	29	20
9	**20**[c]	BA	43	29	20

[a] Reaction conditions: 25 mg 5% Pd/Al_2O_3, 5 cm^3 DMF + 2.5 vol % H_2O, 0.5 mmol **1** (c**1** = 0.1 M), 0.025 mmol modifier (c = 5 mM), 0.5 mmol BA (cBA = 0.1 M, when used), 0.1 MPa H_2, 295 K, for the hydrogenation results see Table 1. [b] Relative intensities of the cinchona derivatives in the ESI-MS spectra: derivatives with unhydrogenated quinoline moiety, dihydro-quinoline, and tetrahydro-quinoline derivatives. [c] Only derivatives resulted by hydrogenolysis of the C^9O-Si bond were detected in these samples: **20**-$SiMe_3$+H, **20**-$SiMe_3$+3H, and **20**-$SiMe_3$+5H; the products also contained about 8−9% tetradecahydro-derivative (**20**-$SiMe_3$+15H) and 2−3% of hydrogenated derivatives having a phenyl group less than the parent modifier **20**-$SiMe_3$-Ph+xH, x = 8, 10, 12.

Table 3. Hydrogenation of 1 over Pd/Al_2O_3 Catalyst Modified by 1:1 Binary Cinchona Alkaloid Mixtures[a]

entry	modifier mixture	X (%)[b]	$ee/ee^{calc,c}$	$ee^{BA}/ee^{BA,calc,c}$
1	**3** + **10**	96; 99	79(*S*)/3(*S*)	90(*S*)/61(*S*)
2	**3** + **12**	97; 98	76(*S*)/22(*S*)	87(*S*)/58(*S*)
3	**4** + **10**	90; 85	6(*R*)/8(*R*)	26(*S*)/33(*S*)
4	**4** + **12**	92; 84	7(*S*)/1(*S*)	34(*S*)/27(*S*)
5	**6** + **10**	97; 96	30(*R*)/52(*R*)	63(*R*)/44(*R*)
6	**6** + **12**	91; 94	28(*R*)/55(*R*)	66(*R*)/55(*R*)
7	**7** + **10**	92; 87	44(*S*)/7(*S*)	44(*S*)/23(*S*)
8	**7** + **12**	90; 85	45(*S*)/19(*S*)	41(*S*)/17(*S*)
9	**8** + **10**	78; 72	35(*R*)/10(*R*)	3(*R*)/2(*S*)
10	**8** + **12**	86; 82	42(*R*)/0	6(*R*)/8(*R*)

[a] Reaction conditions: 25 mg 5% Pd/Al_2O_3, 5 cm^3 DMF + 2.5 vol % H_2O, 0.5 mmol **1** (c**1** = 0.1 M), 0.025 mmol 1:1 modifier mixture (c = 5 mM), 0.5 mmol BA (cBA = 0.1 M, when used), 0.1 MPa H_2, 295 K. [b] Conversions obtained in 6 h in the absence; presence of BA. [c] Enantioselectivities (%) and the configuration of the excess enantiomers in the absence and in the presence of BA (suffix BA)/the calculated theoretical values (for the calculation method see the Experimental Section).

Results of experiments using sequential addition of cinchona alkaloids (**3** or **7** in pair with **10**) are presented in Figure 4.

In the hydrogenation started over **3**-modified catalyst, the addition of **10** after 1 h did not change the ee (after both 3 and 6 h 85% (*S*)-**2**). In contrast, the sense of the ee in the hydrogenation over **10**-modified catalyst changed by addition of **3** (at 1 h) from excess of *R* to *S* enantiomer. While in the latter reaction the ee at 3 h was low (58%), the incremental ee (ee^{incr}) was nearly identical with that obtained with **3** (83%) and decreased to 77% at 6 h. In contrast with the catalyst modified by **3**, over the **10**-modified catalyst, the ee obtained after 1 h was lower than at high conversion (entry 9 in Table 1), that is, the ee increased with time (with conversion). Thus, in a separate run modifier **3** was added after 2 h to the reaction slurry containing modifier **10** to ascertain on the displacement of **10** by **3** after reaching metal particles more efficiently modified by **10**. The ee over **10**-modified catalyst reached 49% (*R*) after 2 h which is close to the value observed after 6 h (50%). Accordingly, at higher conversions the ee becomes conversion independent and allowed the analysis of the nonlinear effect observed with modifier mixtures. By addition of **3** and **1**, both the ee and the ee^{incr} were lower than in the experiment in which **3** was added after 1 h and further addition of **10** and **1** at 4 h decreased the ee^{incr} more rapidly. Similarly, over the catalyst modified by **7** the ee after 1 h was lower than the value obtained at high conversion. By addition of **10** to this catalyst after 1 h the ee increased over the latter value (52% as compared with 44% (*S*)-**2**) resulting in surprisingly high ee^{incr} (65%). The addition of **7** to the **10**-modified catalyst resulted in a change in the sense of the ee, similar to the addition of **3**.

2.6. Transformation of the Modifiers in Mixtures. Relative intensities of products formed from cinchona alkaloid derivatives during the reaction using modifier mixtures are presented in Table 4.

No significant differences were observed in the transformation of **3** when used alone or mixed with **10**. In contrast, **10** was less hydrogenated when used in mixture with **3** than as a sole modifier. Namely, more than 50% and 75% of **10** was unaltered in the 1:1 mixture without and with addition of BA, respectively. Moreover, only 17% of **10** was transformed when this modifier was added after 1 h to the reaction mixture containing **3**-modified catalyst. If reversed addition order of modifiers was applied, the distribution of the hydrogenated products of **10** was similar to the simultaneous addition of these modifiers. The transformation of **10** applied in mixture with **6** was similar to that in combination

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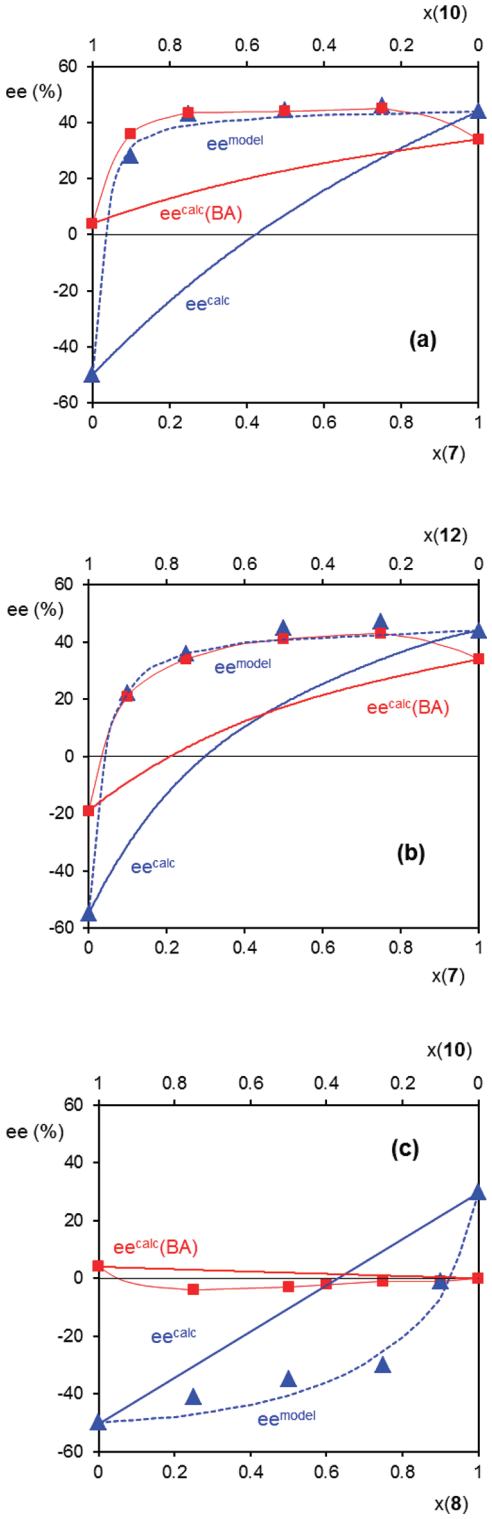

Figure 3. Effect of the composition of binary modifier mixtures on the ee (%) in the absence (blue solid triangles) and presence (red solid squares) of BA obtained in the hydrogenation of **1** using modifier pairs: **7**+**10** (a), **7**+**12** (b), and **8**+**10** (c) (reaction conditions: 25 mg 5% Pd/Al_2O_3, 5 cm^3 DMF + 2.5 vol % H_2O, 0.5 mmol **1** (c**1** = 0.1 M), 0.025 mmol 1:1 modifier mixture (c = 5 mM), 0.5 mmol BA (cBA = 0.1 M when used), 0.1 MPa H_2, 295 K, 6 h). The ee^{calc} curves correspond to the theoretical behavior based on the initial rates obtained over catalyst modified by **7**, **8**, **10**, and **12**. The ee^{model} curves (dotted lines) resulted by using the published kinetic model,[57] n = 0.0193 ± 0.0037 (a), n = 0.0300 ± 0.0041 (b), n = 6.3540 ± 0.9026 (c).

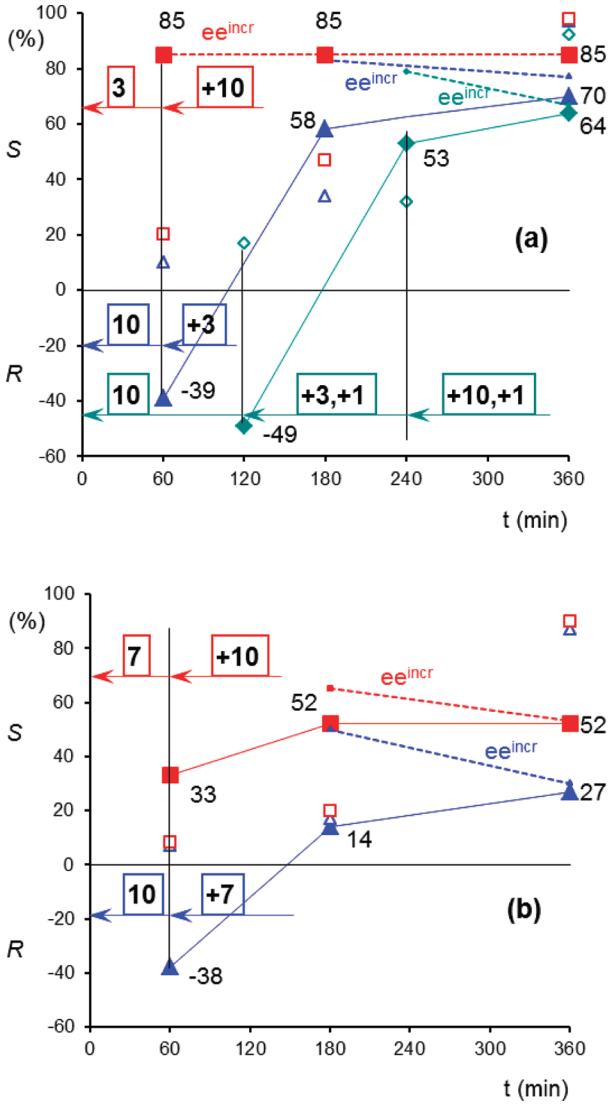

Figure 4. Conversions (X (%), open symbols) and ee (%, closed symbols) obtained in the enantioselective hydrogenation of **1** using sequentially added modifiers (a): **3**+**10** (red solid squares, red open squares), **10**+**3** (blue solid triangles, blue open triangles) and **10**+(**3**+**1**)+(**10**+**1**) (green solid diamonds, green open diamonds); (b): **7**+**10** (red solid squares, red open squares) and **10**+**7** (blue solid triangles, blue open triangles) (reaction conditions: 25 mg 5% Pd/Al_2O_3, 5 cm^3 DMF + 2.5 vol % H_2O, 0.5 mmol **1** (c**1** = 0.1 M), 0.025 mmol of the first modifier (c = 5 mM) followed by addition of 0.025 mmol (c = 5 mM) of another modifier at the given time (t 60, 120, or 240 min), 0.1 MPa H_2, 295 K, t 6 h; when noted parallel with the addition of the modifier 0.5 mmol **1** was introduced; dotted lines are the ee^{incr}, see Experimental Section).

with **3**. The mixture of **6** and **12** resulted in higher conversion of **12** as compared with **10**, approaching that of the sole modifier **12**. It must be noted that the transformations of the C^9—O—$SiMe_2{}^tBu$ ethers were always less extensive as those of the natural cinchona alkaloid **3** or **6**.

Compound **10** in the **4** + **10** mixture was only slightly less hydrogenated in comparison with its use as a sole modifier. In contrast, the hydrogenation of both **10** and **12** were significantly decelerated in the presence of **7**. This deceleration was even more pronounced when **10** was added after 1 h to the **7**-modified catalyst, resembling the results obtained when it was used in a

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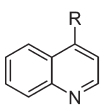
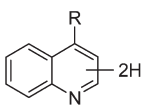
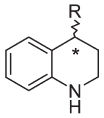
Table 4. Relative Amount of the Cinchona Derivatives Determined in the Liquid Phase by ESI-MS Analysis Following the Hydrogenation of 1 over Pd/Al_2O_3 Catalyst in Presence of Mixtures[a] or Sequentially Added Modifiers[b]

entry	modifier mixture	additive	I_{rel} 1st (%); I_{rel} 2nd (%)[c] 		
1	**3** + **10**	–	15; 52	48; 31	39; 16
2	**3** + **10**	BA	4; 75	59; 18	37; 7
3[b]	**3** + **10**	–	21; 83	37; 11	41; 5
4[b]	**10** + **3**	–	45; 14	31; 31	24; 55
5	**4** + **10**	–	11; 32	45; 36	44; 31
6	**4** + **10**	BA	11; 55	69; 34	20; 9
7	**6** + **10**	–	5; 68	52; 15	43; 17
8	**6** + **10**	BA	10; 79	66; 14	24; 7
9	**6** + **12**	–	5; 22	38; 42	56; 36
10	**6** + **12**	BA	4; 72	48; 18	47; 10
11	**7** + **10**	–	21; 57	60; 26	19; 16
12	**7** + **10**	BA	17; 67	62; 23	22; 10
13[b]	**7** + **10**	–	17; 72	55; 17	28; 10
14[b]	**10** + **7**	–	46; 14	29; 31	24; 55
15	**7** + **12**	–	22; 48	58; 31	20; 21
16	**8** + **10**	–	83; 23	15; 45	2; 31

[a] Reaction conditions: 25 mg 5% Pd/Al_2O_3, 5 cm^3 DMF + 2.5 vol % H_2O, 0.5 mmol **1** (c**1** = 0.1 M), 0.025 mmol 1:1 modifier mixture (c = 5 mM), 0.5 mmol BA (cBA = 0.1 M, when used), 0.1 MPa H_2, 295 K, 6 h, for the hydrogenation results see Table 3. [b] Sequentially added modifiers: 0.025 mmol of 1st modifier followed by addition of 0.025 mmol of the 2nd modifier after 1 h, reaction time 6 h, for the hydrogenations results see Figure 4. [c] Relative intensities of the derivatives in the ESI-MS spectra of both cinchona alkaloids in the order given in column 2.

pair with **3**. By addition of **7** to the **10**-modified Pd, both modifiers were hydrogenated to the same extent as when **3** was used instead of **7** (entries 4 and 14). Interestingly, both **3** and **7** were more hydrogenated when used as the second added cinchona alkaloid than when the catalyst was initially modified by these compounds. The only reaction in which the $C^9-O-SiMe_2{}^tBu$ ether was more hydrogenated than the other cinchona alkaloid was the hydrogenation using the **8** + **10** mixture. We note that the hydrogenation of **10** by using this mixture was similar to that observed with the **4** + **10** mixture and similar to its use as a single modifier and **8** was hydrogenated extremely slowly, consistent with the hindered adsorption of the $C^{6'}-OMe$ substituted quinoline moiety.

3. DISCUSSION

A recent study on the enantioselective hydrogenation of **1** over Pd showed the inversion of the ee sense in the presence of **7**, **8** (i.e., $(R)C^8-(S)C^9$ methyl ethers) when compared with their parent alkaloids. In contrast, the use of cinchonidine methyl ether (**4**) afforded the same *S*-enantiomer in excess as **3**.[32] The results were rationalized in terms of strength of interactions between modifier, substrate acid, and Pd surface. The present work focused on understanding factors controlling the enantiodifferentiation in the hydrogenation of unsaturated acids over Pd through comparative studies using cinchona alkaloid derivatives. For a proper interpretation of the structure-enantioselectivity relationship it was essential to follow the transformation of the cinchona alkaloid derivatives during the hydrogenations. The competitive formation of chiral sites favoring the formation of different enantiomers was studied by applying modifier mixtures and by sequential addition of cinchona derivatives to the slurry.

Alterations in the structure of the cinchona alkaloids demonstrated that the C^9-C^8 stereogenic ensemble transmits the chiral information on the metal surface. The lack of asymmetric C^9 atom, epimerization of this center (**15** and **16**), or decrease in the adsorption strength because of the partial hydrogenation of the anchoring moiety (**17**) results in loss of ee either because of the loss of the enantiodifferentiating ability or because of insufficient coverage of the Pd surface. The effect of the substituents attached to the C^3 correlates well with their nature and size, showing the interference of these groups in the chiral site or the altered adsorption of these derivatives. Most importantly, the present study evidenced that inversion in the sense of ee occurs in the presence of cinchonidine ethers, if the ether group is bulky enough. Inversion was obtained with $C^9-O-SiMe_2{}^tBu$ ethers of **3** and its derivatives (**10**, **12** and **14**). Accordingly, we reached to the conclusion that the inversion observed previously with cinchonine methyl ether is a general feature of the hydrogenation of the 2,3-diphenylpropenoic acids, which is governed mainly by steric factors. Although, the $C^9-O-SiMe_3$ ethers (**5**, **9**, and **20**) led to similar results as the parent alkaloids, the transformation of

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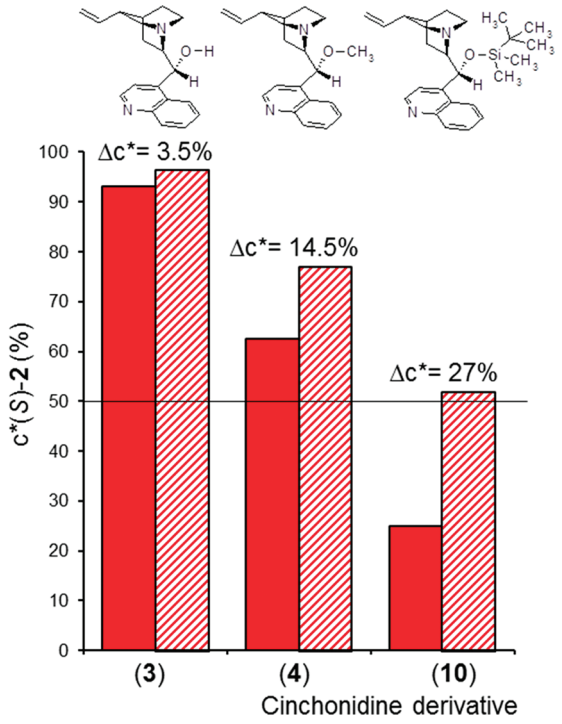

Figure 5. Relative concentrations of the (*S*)-**2** enantiomer: c*(*S*)-**2** (%) = 100 × c(*S*)-**2**/[c(*S*)-**2** + c(*R*)-**2**] using cinchonidine derivatives in the absence (solid columns) and presence (striped columns) of BA (reaction conditions: see Table 1; Δc* (%) is the difference in c*(*S*)-**2** obtained in the presence and absence of BA).

these modifiers showed that this was due to the hydrogenolysis of the O−$SiMe_3$ bond.

The stability of O−$SiMe_2{}^tBu$ ethers under the reaction conditions allowed the examination of the steric effect of the ether group in the cinchonidine series. The size of the ether substituent of cinchonidine had a significant effect on the sense and magnitude of the ee and also on the effect of the BA additive. This is well illustrated in Figure 5 and is supported by results obtained with the other two O−$SiMe_2{}^tBu$ ethers, **12** and **14**. The relative concentration of the *S* enantiomer decreased with increasing bulkiness of the C^9−O− substituent, the C^9−O−$SiMe_2{}^tBu$ ether resulted in c*(*S*)-**2** < 50% (i.e., excess of (*R*)-**2**). A plausible explanation of this inversion is the gradual change in the shape of the surface chiral sites by increasing the bulkiness of the substituent. The higher increase in the c*(*S*)-**2** in the presence of BA over catalyst modified by derivatives bearing bulkier substituents (Δc* in Figure 5) should be due to the stronger accelerating effect of BA on product desorption from sites producing the *S*-enantiomer. However, it could also be explained by the participation of BA in the formation of the chiral site, as one may also deduce from the different effect of the additive over catalyst modified by **10**, **12**, or **14**. According to these, the different C^3 substituents influence the cinchona−**1**−BA interaction to a different extent.

Under reaction conditions used in the present study, the hydrogenation of the parent modifier (**3**) and the C^9−O−$SiMe_2{}^tBu$ ethers (**10** and **12**) was similar. Examination of the effect of the initial concentration of **3** revealed that even traces of derivatives bearing unreacted quinoline, that is, anchoring, moiety are sufficient for retaining the ee at high levels. Accordingly, the partial hydrogenation of the cinchona ethers neither can be responsible for the decreased ee nor for the detected inversion of the ee sense. In the presence of BA the transformation of the modifiers indicated shorter residence time of the alkaloids on the surface, shown by the increased amount of tH-derivatives obtained. Accordingly, BA facilitated the desorption of the hydrogenated cinchona derivatives along with the desorption of the saturated acid, which also points to the possible participation of the additive in the formation of the surface intermediate responsible for the high ee.

The nonlinear behavior obtained with C^9−O−$SiMe_2{}^tBu$ ethers in a mixture with parent alkaloids or methyl ethers showed weaker adsorption of the former derivatives except for the $C^{6'}$−OMe substituted **8**. The relative adsorption strength of modifiers decreases in the order **3** ≥ **6** > **4** ≥ **7** > **10** ≥ **12** > **8**, as shown by the present data and previous results.[32] It is noteworthy that the adsorption strength can be correlated with the size of the ether group and the substitution of the quinoline ring. The above order of adsorption strengths was confirmed by using sequentially added cinchona derivatives during the hydrogenation (Figure 4) and evidenced by the transformation of these derivatives in mixtures with the parent alkaloids.

Finally, during this study several unusual and yet unrevealed observations were made. The modification of the Pd surface by cinchona ethers requires a longer time as compared with **3**, which takes place instantaneously. Changes in ee with conversion over catalyst modified by ether derivatives, indicates a dependence of the ee on the reactant surface coverage either because of adsorption of pro-*S* and pro-*R* intermediates on different number of adsorption sites[65] or because of the influence of modifier−product interactions.[66] The decrease in initial rates obtained in the presence of BA over the cinchona ether-modified catalysts may be rationalized by the participation of the latter in the formation of the surface intermediate of the hydrogenation step. This will influence the shape of the site and the overall hydrogenation rate because of possible adsorption of BA on the metal surface.

The lower ee's obtained in the hydrogenations using the **6** + **10** (or **6** + **12**) mixture when compared with both single modifiers and the beneficent effect on the ee of addition of **10** to the 7-modified catalyst are the most unexpected results. Although, the present study allows to make only assumptions related to these observations, the influence of a cinchona alkaloid on the enantiodifferentiating ability of the other, by altering either its surface conformation or its adsorption mode (tilted vs flat adsorption), or by the interaction of the two modifiers should be examined in further studies as possible causes. However, in the work it was shown for the first time that the enantioselectivity in the hydrogenation of unsaturated acids over Pd can be enhanced in the presence of two cinchona alkaloid modifiers when compared to that induced by either of them alone.

Combining the results obtained in this study, a plausible formulation of the composition and the geometry of the chiral sites may be envisaged also using the previously reported conformational behavior of cinchona alkaloid ethers on metal surfaces.[36−39] The schematic illustration of surface complexes assuming the adsorption of the modifiers in QA-Open(4) conformation,[38] are sketched in Figure 6. It must be noted that based on the results one cannot differentiate between the two most stable surface conformers QA-Open(4) and QA-Open(3); thus, surface complexes with the participation of the latter conformer are possible.

Accordingly, the increase in size of the substituent gradually induces a proportional alteration in the shape of the surface chiral

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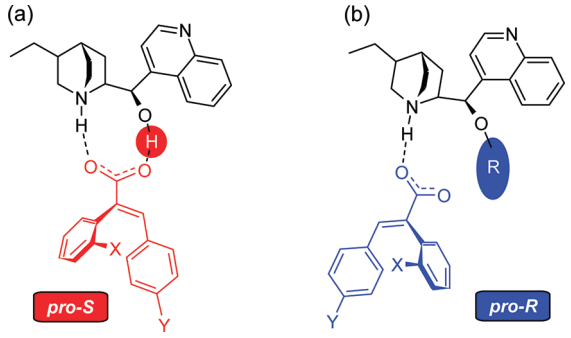

Figure 6. Schematic illustration of the suggested cinchona-acid interaction on the Pd surface modified by (a) dihydrocinchonidine and (b) dihydrocinchonidine ethers (top views).

pocket, which eventually may lead to a change in the docking preference of the acid on the surface and to inversion in the sense of the ee. This is possible because the decrease in the cinchona-acid interaction strength occurred by blocking of an interaction site, that is, the free C^9−OH, and because of the rigid and bulky phenyl substituents of **1**. The surface intermediates formed in the presence of BA should also take into account interactions with the additive, as was recently suggested using cinchonine methyl ether.[32]

4. CONCLUSIONS

The influence of the cinchona alkaloid structure on the enantioselective hydrogenation of (*E*)-2-(2-methoxyphenyl)-3-(4-fluorophenyl)propenoic acid over Pd was studied. This study demonstrated that the chiral information is transmitted by the C^9−C^8 stereogenic ensemble of the alkaloid adsorbed on the metal surface by its quinoline moiety. Substituents attached to the quinuclidine C^3 have effect on the enantioselectivity. Although, results obtained using cinchonidine methyl ether were in contrast to those attained with cinchonine methyl ether, the increase in the size of the ether group in the cinchonidine series also resulted in inversion of the enantioselectivity sense. The presence of benzylamine achiral additive always increased the amount of the enantiomer formed in excess by using the parent modifier of the corresponding derivative. Nonlinear behavior observed in experiments using modifier mixtures and transformations of modifiers during the reaction indicated the decrease in the adsorption strength of surface intermediate complexes by increasing the size of the ether group. The presence of benzylamine facilitated faster desorption of the modifier, favoring the hydrogenation to tetrahydroderivatives.

Results were interpreted by the gradual alteration of the shape of the chiral surface site by increasing the size of the ether group, accompanied by the decrease in the interaction strength of substituted cinchona alkaloids with the acid and the surface. This proposal also rationalized the effect of the benzylamine additive on the ee and H_2 uptake rate. Surprising ee values obtained by using few cinchona alkaloid mixtures, that is, values out of the range determined by the results reached with the sole modifiers, were suggested to be caused by the influence of one cinchona alkaloid on the performance of the other.

5. EXPERIMENTAL SECTION

5.1. Materials. The catalyst used in this study was commercial 5% Pd/Al_2O_3 (Engelhard, 40692, BET 200 $m^2\ g^{-1}$, metal dispersion 0.21)[8,67] pretreated before use at 523 K in 30 $cm^3\ min^{-1}$ H_2 flow for 100 min as earlier reported.[15,16] Cinchonidine (**3**, Alfa Aesar, 99%), cinchonine (**6**, Fluka, ≥98%), 4-fluorobenzaldehyde (Aldrich), 2-methoxyphenylacetic acid (Aldrich), benzylamine (BA, Fluka, ≥99.5%), *N*,*N*-dimethylformamide (DMF, Scharlau, Multisolvent grade), and H_2 gas (Linde AG, 99.999%) were used as received. The preparation of **1** was described previously.[15,16] Cinchona methyl ethers (**4**, **7**, **8**) were prepared by known procedures,[68] other cinchona derivatives (**5**, **9**−**21**, Figure 1), were prepared and characterized as previously reported.[36,69−72]

5.2. Hydrogenation Procedure and Product Analysis. Hydrogenations were carried out in a glass hydrogenation apparatus under conditions used in previous studies,[15,16,32] that is, atmospheric H_2 pressure, 295 K, magnetic agitation (1000 rpm). The H_2 consumption between 0.15 and 0.25 equiv (compared to the acid amount) were used for the calculation of the initial H_2 uptake rates (R_{iH}, mmol $h^{-1}\ g^{-1}$). In a typical run 0.025 g of catalyst was suspended in 3 cm^3 of dimethylformamide (DMF) containing 2.5 vol % dist. H_2O, the apparatus was flushed with H_2, and the catalyst pretreated for 0.5 h by stirring the slurry. Following the pretreatment 0.025 mmol modifier (c = 0.005 M), 0.5 mmol **1** (c_i = 0.1 M), 0.5 mmol BA (when used, c = 0.1 M), and another 2 cm^3 of solvent were added, the system was flushed with H_2, and the reaction was commenced by stirring the mixture. After the specified time the H_2 was released, 5 cm^3 methanol was added, the catalyst was filtered and washed with 5 cm^3 methanol. Samples (~0.2 cm^3) of resulting solutions were used for preparation of methyl esters by reacting with CH_2N_2 solution.

Products were identified by GC-MS analysis (Agilent Techn. 6890N GC + 5973*inert* MSD, DB-1MS, 60 m × 0.25 mm, J & W Sci. Inc., capillary column). Conversions (X, %) and enantioselectivities (ee, %) were calculated from the results of the gas chromatographic analysis of these samples (YL6100 GC - FID) using Cyclosil-B (30 m × 0.25 mm, J & W Sci. Inc.,) chiral capillary column; analysis conditions: hp: 25 psi, $T_{col.}$: 325 K for 100 min, heating by 5 K min^{-1} to 348 K and keeping at this temperature for 15 min; retention times of the corresponding methyl esters: 96.0 min (*R*)-**2**, 97.9 (*S*)-**2**, and 105.5 min **1**.[16,32] The X and the ee were calculated with the formulas:

$$X(\%) = 100 \times [c(S)\text{-}\mathbf{2} + c(R)\text{-}\mathbf{2}]/c_i\mathbf{1}$$

$$ee\ (\%) = 100 \times |c(S)\text{-}\mathbf{2} - c(R)\text{-}\mathbf{2}|/[c(S)\text{-}\mathbf{2} + c(R)\text{-}\mathbf{2}]$$

where c(*S*)-**2** and c(*R*)-**2** are concentrations of product enantiomers and c_i**1** is the initial concentration of **1**. Repeated experiments showed reproducibility within ±1%. Optical rotation measurements (Polamat A polarimeter, l 0.5 dm, c 1, methanol) showed the excess formation of the dextrorotatory *S* enantiomer in the presence of **3**, while with **6** the levorotatory *R* enantiomer resulted in excess.[16,32] The configuration of the major enantiomer resulted by using other cinchona derivatives was assigned by GC analysis using as reference products obtained with **3** and **6**.

Experiments with mixtures of modifiers and the product analysis were carried out similarly as with a single modifier except the corresponding cinchona mixture was added to the slurry.[32] The theoretical ee values (ee^{calc}) corresponding to a modifier mixture were calculated with the formulas:

$$ee^{calc}(\%) = (x_1 \times R_{iH_1} \times ee_1 + x_2 \times R_{iH_2} \times ee_2) / (x_1 \times R_{iH_1} + x_2 \times R_{iH_2})$$

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where x_1 and x_2 are the molar fractions of modifiers 1 and 2; R_{iH1} and R_{iH2} (mmol h^{-1} g^{-1}) are the initial H_2 uptake rates, and ee_1 and ee_2 (%) are enantiomeric excesses obtained with the sole modifiers 1 and 2, respectively. For calculating the ee by the previously reported kinetic model[57] the following equation was used:

$$ee^{model}(\%) = (x_1 \times ee_1 + n \times x_2 \times ee_2) / (x_1 + n \times x_2 + f)$$

where f is equal to zero if the racemic reaction is of minor importance and $n = k_2 \times K_2/k_1 \times K_1$ where K_1 and K_2 are the adsorption equilibrium constants for two modifiers and k_1 and k_2 are rate constants of surface reactions resulting in the formation of adsorbed products interacting with one of the modifier (for details see ref.[57]).

In reactions with sequentially added modifiers, hydrogenations were started over catalyst modified with the first modifier as described above and at the given reaction times samples (0.1 cm^3) were withdrawn for analysis simultaneously with the injection of the second modifier into the reactor dissolved in the same amount of solvent. The incremental ee (ee^{incr}) was calculated using the formulas:

$$ee^{incr}(\%) = 100 \times |[c(S)\text{-}\mathbf{2}^{t2} - c(S)\text{-}\mathbf{2}^{t1}] - [c(R)\text{-}\mathbf{2}^{t2} - c(R)\text{-}\mathbf{2}^{t1}]| / \{[c(S)\text{-}\mathbf{2}^{t2} - c(S)\text{-}\mathbf{2}^{t1}] + [c(R)\text{-}\mathbf{2}^{t2} - c(R)\text{-}\mathbf{2}^{t1}]\}$$

where $c(S)$-$\mathbf{2}^{t2}$, $c(S)$-$\mathbf{2}^{t1}$ and $c(S)$-$\mathbf{2}^{t2}$, $c(S)$-$\mathbf{2}^{t1}$ are concentrations of the (S)-**2** and (R)-**2** enantiomers at t2 and t1 reaction times.

The transformation of the modifiers during hydrogenations was examined by electron-spray ionization mass spectrometry (ESI-MS). The ESI-MSD-ion-trap (Agilent Techn. 1100 LC-MSD TRAP SL ion-trap MS) was operated under positive ion mode using similar analysis parameters with previous studies:[24,73] ESI: capillary (needle) voltage = 3.5 kV, capillary exit voltage = 136 V, drying gas (N_2) = 9 dm^3 min^{-1}, drying gas temperature = 623 K, nebulizer gas = 40 psi; ion-trap: scan range = 80−500 m/z, maximum accumulation time = 300 ms, fragmentation amplitude = 1.5 V, fragmentation time = 40 ms. Solvent/methanol with 0.1 vol. % acetic acid; flow rate: 0.5 cm^3 min^{-1}; sample concentration: 0.1 μmol dm^{-3}; injected volume 2 mm^3. The intensity of a derivative (I_{rel}, %) was expressed as percent of the sum of the intensities of all the derivatives derived from a modifier.

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