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Reactions of chlorine substituted (*E*)-2,3-diphenylpropenoic acids over cinchonidine-modified Pd: Enantioselective hydrogenation versus hydrodechlorination

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ABSTRACT

The effect of the chlorine position on the C–Cl bond hydrogenolysis and the enantioselective hydrogenation of Cl substituted (*E*)-2,3-diphenylpropenoic acid derivatives has been studied over cinchonidine-modified Pd/Al_2O_3. In contrast to the fast hydrodechlorination of the β-phenyl-*para*-Cl substituted acids the Cl on the α-phenyl ring was barely hydrogenolized. These observations were interpreted by the different arrangements of the two phenyl rings on the surface, with the α- and β-phenyl rings adsorbed tilted and parallel, respectively. The results confirmed the beneficial effect of the α-phenyl-*ortho*-substituents on the chiral discrimination, thus the 2,3-diphenylpropionic acids substituted by Cl on the α-phenyl ring could be prepared in good yields and optical purities. The conclusions were used for the rational design of an acid, i.e. (*E*)-2-(2-methoxyphenyl)-3-(3,4-difluorophenyl)propenoic acid, which afforded the best optical purity (*ee* up to 95% at 295 K) described until now in this heterogeneous system.

1. Introduction

Optically pure carboxylic acids are often used chiral building blocks in the fine chemicals industry [1,2]. Asymmetric catalytic hydrogenations of the corresponding unsaturated acids are widely used synthetic methods for the preparation of these compounds [3,4]. The increased interest in environmental benign processes motivated the efforts on developing heterogeneous asymmetric catalytic systems to replace the widely used soluble metal complexes [5,6]. A simple method to obtain enantioselective heterogeneous hydrogenation catalysts is the surface modification of an active metal by chiral compounds. However, only a few efficient heterogeneous catalytic systems developed using this approach were reported up to now [7–12]. Among these Pd catalysts modified by cinchona alkaloids were found the most appropriate for the enantioselective hydrogenation of prochiral unsaturated carboxylic acids and other activated olefins [12,13]. The enantioselectivities obtained in the hydrogenation of α,β-unsaturated carboxylic acids over cinchonidine (CD) modified Pd catalysts were found highly dependent on the structure of the acid. The hydrogenation of aliphatic or cycloaliphatic acids afforded moderate or good enantiomeric excesses (*ee*) [14–21], while in the reaction of (*E*)-2,3-diphenylpropenoic acid and its ring substituted derivatives good to excellent, over 90% enantioselectivities were reached [22–29].

For predicting the enantioselectivities obtainable with certain carboxylic acids and thus, to further extend the scope of this catalytic system it is necessary to know the interactions of the acid with the modifier and the metal surface, i.e. the adsorption mode of the acids on chirally modified surface sites. However, in this complex three-phase catalytic system, collecting *in situ* data for evidencing these interactions is difficult even with the fast developing physico-chemical tools available today. Thus, *in situ* methodologies still rely on information gathered under real reaction conditions by controlled alteration of the structure and properties of one of the reaction components, i.e. modifier, substrate, solvent or catalyst. Although, such alterations may influence the reaction rate and *ee* by multiple effects, the collected data may provide valuable mechanistic details for understanding the surface processes and the structure of the intermediates involved.

In the hydrogenation of (*E*)-2,3-diphenylpropenoic acid the importance of the interaction strength of the substrate with the chiral modifier was illustrated by the effect of the methoxy substituents on the phenyl rings [24–28]. The interaction of the substrate with the metal surface was also addressed by using heteroaromatic analogs of (*E*)-2,3-diphenylpropenoic acid [30,31]. The

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present study besides widening the scope of the enantioselective hydrogenation of (*E*)-2,3-diphenylpropenoic acid derivatives over CD modified Pd, was aimed to collect further experimental data to ascertain the adsorption mode of the acid on the metal surface. Due to the well-known hydrogenolysis of the C–Cl bond of chloro-aromatics over Pd catalysts [32–34], we anticipated, that Cl substituted acids are appropriate to indicate the sites of the acid in contact with the surface. Thus, we prepared twelve derivatives of (*E*)-2,3-diphenylpropenoic acid substituted at least with one Cl and examined their hydrogenation on unmodified and CD-modified Pd/Al_2O_3. The position of the Cl in the acid molecule was chosen based on the effect of other substituents (F, CH_3O and CH_3 groups) on the rate and *ee* and taking into account the possible arrangements of the phenyl rings derived from theoretical calculations [35].

2. Materials and methods

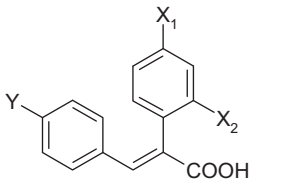
2.1. Materials

The catalyst used was a known commercial 5% Pd/Al_2O_3 (Engelhard, 40692) which was pretreated before use as described earlier [26,27]. Cinchonidine (CD, Alfa Aesar, 99%), the benzaldehyde and phenylacetic acid derivatives (Aldrich) were used without purification. Benzylamine additive (BA, Fluka, ≥99.5%), N,N-dimethylformamide (DMF, Scharlau, Multisolvent grade) and H_2 gas (Linde AG, 99.999%) were used as received. The substituted (*E*)-2,3-diphenylpropenoic acid derivatives were prepared by the Perkin condensation [26,27] and were purified by several crystallizations in ethanol–water to over 98% purities. The acids were identified and their purity was determined by ^1H and ^{13}C NMR spectroscopy (Bruker Avance DRX 400 spectrometer at 400 MHz (^1H) and 100 MHz (^{13}C) in d_6-DMSO) and by GC–MS (Agilent Techn. 6890N GC–5973 MSD, 60 m HP-1MS capillary column) analysis of the methyl esters formed by using CH_2N_2 ethereal solution (for analytical data see the Supplementary material).

2.2. Hydrogenation procedure and product analysis

The hydrogenations were carried out in a glass hydrogenation apparatus under atmospheric H_2 pressure and room temperature using magnetic agitation (1000 rpm). The H_2 consumptions between 0.15 and 0.25 equivalents (compared to the acid amount) were used for calculating the initial H_2-uptake rates (R_{iH}). In a typical run 0.025 g catalyst was suspended in 3 cm^3 DMF containing 2.5 vol% H_2O, the apparatus was flushed with H_2 and the catalyst was pretreated for 0.5 h by stirring the slurry. After the pretreatment 0.025 mmol CD, 0.5 mmol unsaturated acid and 0.5 mmol BA (when used) in 2 cm^3 solvent were added, the system was flushed again with H_2 and the reaction commenced by stirring the mixture. After the given time 5 cm^3 methanol was added, the catalyst was filtered and washed with 5 cm^3 methanol.

Portions (~0.2–0.3 cm^3) of the resulted solutions were concentrated in vacuum and used for the preparations of the methyl esters (using CH_2N_2 ethereal solution). The resulted compounds were identified by GC–MS analysis (see Supplementary material). Conversions (X(%)), chemoselectivities (Sel(%)) and enantioselectivities (*ee* (%)) were calculated from the results of the gas chromatographic analysis of these samples (YL6100 GC–FID) using chiral capillary columns: Cyclosil-B (30 m × 0.25 mm, J&W Sci. Inc.,) and Chiraldex™ G-TA (Astec, 40 m × 0.25 mm, Supelco). The *ee* was calculated with the formulae: $ee(\%) = 100 \times |[S] - [R]|/([S] + [R])$; where [*S*] and [*R*] are the concentrations of the product enantiomers. Experiments carried out several times resulted in product compositions within ±1%. The absolute configurations of the enantiomers formed in excess were assumed to be *S* based on the rotation sign [21–30] of the samples obtained after removal of CD and BA (Polamat A polarimeter, the dextrorotatory enantiomers were formed in excess) and based on the similar chromatographic behaviour of the Cl substituted saturated products with the CH_3O and F derivatives obtained in previous studies [26,27].



(**1a**) X_1 = H, X_2 = Cl, Y = H
(**1b**) X_1 = H, X_2 = Cl, Y = MeO
(**1c**) X_1 = H, X_2 = Cl, Y = F
(**1d**) X_1 = Cl, X_2 = H, Y = H
(**1e**) X_1 = Cl, X_2 = H, Y = MeO
(**1f**) X_1 = Cl, X_2 = H, Y = F
(**1g**) X_1 = MeO, X_2 = H, Y = Cl
(**1h**) X_1 = H, X_2 = MeO, Y = Cl
(**1i**) X_1 = H, X_2 = F, Y = Cl
(**1j**) X_1 = Cl, X_2 = H, Y = Cl
(**1k**) X_1 = H, X_2 = Cl, Y = Cl
(**1l**) X_1 = Cl, X_2 = Cl, Y = H

Fig. 1. The structure of the Cl substituted (*E*)-2,3-diphenylpropenoic acids.

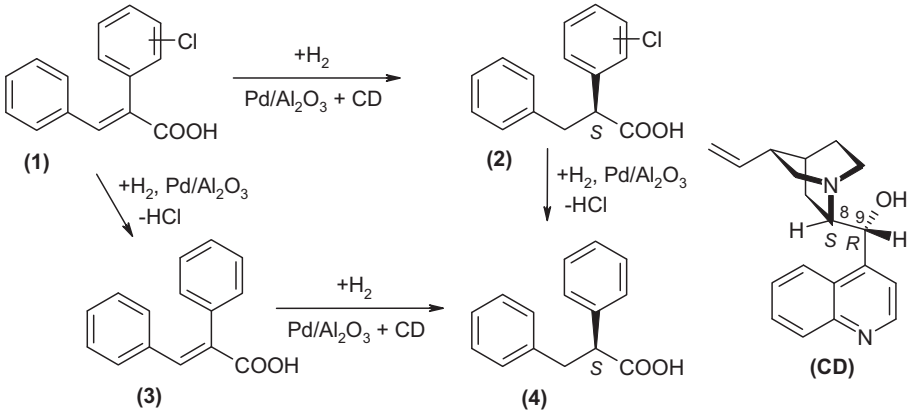
3. Results and discussions

The hydrogenation of (*E*)-2,3-diphenylpropenoic acid over CD modified Pd catalyst results in the excess formation of the (*S*)-2,3-diphenylpropanoic acid in increased *ee* in the presence of BA [22,23]. In the hydrogenation of CH_3O and/or F substituted derivatives the *ee* further increased except with β-phenyl-*ortho*-substituents [24–27]. Beside the effect of the substituents on the interaction strength of the acid with the modifier, the adsorption strengths of the acids were also affected by the substituents, influencing the stereochemical out-come of the reactions [27,30]. Chlorine substituted derivatives may suffer parallel or consecutive C–Cl bond hydrogenolysis (hydrodechlorination) of the unsaturated or/and saturated acids resulting in the corresponding dechlorinated acids (Scheme 1, **3** and **4**). The ratio of the hydrogenation/hydrodechlorination rates is determined by the adsorption mode of the substrate, i.e. the position of the Cl substituent. Thus, to obtain evidence on the adsorption mode of the acids on the Pd surface we investigated the hydrogenation of Cl substituted acids (Fig. 1). To be able to directly compare the reactivity of the differently positioned Cl in the hydrogenolysis reaction these derivatives included dichlorine substituted acids as well.

3.1. Effect of the ortho-chlorine substituent on the α-phenyl ring

The results obtained in the hydrogenation of the acids **1a**, **1b** and **1c** which contained Cl substituent in *ortho* position on the α-phenyl ring are presented in Table 1 and Fig. 2.

The initial H_2-uptake rates (R_{iH}) in the hydrogenation of these compounds showed similar trends as observed in the reactions of other (*E*)-2,3-diphenylpropenoic acid derivatives [22–28], i.e. decreased as effect of modification by CD and the presence of BA increased the R_{iH} over modified catalyst. We point on the following observations:



Scheme 1. Example of the possible reaction pathways in the enantioselective hydrogenation of Cl substituted (*E*)-2,3-diphenylpropenoic acid derivatives over CD-modified Pd catalyst.

(i) In none of these reactions unsaturated dechlorinated acids (**3a**–**3c**) were formed.
(ii) The initial high hydrogenation selectivities (*Sel* (%)) decreased and at extended reaction times significant amounts of dechlorinated saturated acids (**4a**–**4c**) were obtained.
(iii) The hydrogenations of these acids slowed down over modified catalyst at relatively low conversions (the values depended on the substituent on the β-phenyl ring).
(iv) The *ee* of the saturated product (**2a**–**2c**) decreased in time over modified catalyst in the absence of BA, while in the presence of the additive slightly increased.
(v) The *ee* of the side products **4a**–**4c** were initially low and increased by time.

The decrease in the R_{iH} over modified catalyst before reaching complete conversions may be attributed to poisoning of the Pd by the HCl formed during hydrodechlorination. The absence of the unsaturated dechlorinated acids in the product indicated that the hydrodechlorination was slower than the hydrogenation. The low initial *ee* of **4a**–**4c** were indication of coupled hydrogenation–hydrodechlorination over unmodified surface sites even in the presence of CD. The significant increase in these values parallel with the increase in their selectivities showed either a change in the reaction pathway (by readsorption of the optically enriched **2a**–**2c**) or a shift of their preferential formation from unmodified to chirally modified sites during the reaction. However, the similar shapes of the conversion and *ee* (**4a**–**4c**) curves supported the latter assumption (see Fig. 1a). The decrease in the *ee* of **2a**–**2c** by time may be attributed to the transformation of CD in hydrochloride salt changing the enantiodifferentiating ability of the modified sites by possible alterations in the conformation of the modifier [36]. The *ee* decrease could also be due to the hydrodechlorination of the readsorbed **2a**–**2c**; the preferential readsorption of the excess enantiomer may lead to kinetic resolution, as over Ni modified by tartaric acid or cinchona alkaloid modified Pt [37–43].

In the presence of BA the formed HCl is neutralized by this amine. Thus, in these reactions besides increasing the desorption rate of the saturated acids from modified sites [22–28], BA has the additional effect of preventing the alteration of the chiral sites. The time dependence of the *ee* of **2a**–**2c** in the presence of BA was influenced by the β-phenyl substituent. The differences may be explained by the influence of the *para*-substituents on both the substrates acidities and consequently on the strength of the acid–CD interactions and the acids adsorption strength, also having effect on the readsorption rate of the saturated acids.

Altogether, the results indicated that on chiral surface sites the adsorption of these acids does not lead to hydrodechlorination, this process may occur by readsorption of the saturated acids when

Table 1
Hydrogenation of (*E*)-2-(2-chlorophenyl)-3-phenylpropenoic acid (**1a**) and (*E*)-2-(2-chlorophenyl)-3-(4-methoxyphenyl)propenoic acid (**1b**).[a]

Acid	Catalyst condition[b]	R_{iH}[c]	*t* (h)[d]	*X* (%)[d]	*Sel* (%)[e]	*ee* (%)	
					2; **3**; **4**	**2**	**4**
1a	Unmodified	21	0.7	81	96; 0; 4	–	–
			1	100	89; 0; 11	–	–
	CD	5	2	70	99; 0; 1	70	5
			8	77	91; 0; 9	64	30
	CD^{BA}	7	1	70	97; 0; 3	69	15
			2	81	94; 0; 6	70	19
			6	94	86; 0; 14	71	33
1b	Unmodified	12	1.5	44	76; 0; 24	–	–
			6	65	69; 0; 31	–	–
	CD	3	3	25	94; 0; 6	90	23
			6	32	87; 0; 13	88	50
	CD^{BA}	11	3	35	94; 0; 6	92	56
			8	62	86; 0; 14	91	68
			20	84	76; 0; 24	89	78

[a] *Reaction conditions*: 25 mg 5% Pd/Al_2O_3, 5 cm^3 N,N-dimethylformamide (DMF) + 2.5 vol% H_2O, 0.5 mmol acid, 0.1 MPa H_2, 295 K, 0.025 mmol CD (if used), 0.5 mmol BA (if used).
[b] Reactions carried out over unmodified or modified catalyst (CD) in the absence or in the presence of benzylamine (CD^{BA}).
[c] R_{iH}: initial H_2-uptake rate (mmol h^{-1} g^{-1}).
[d] *t*: reaction time needed to obtain the given *X* conversions.
[e] *Sel*: product selectivities (for annotations see Scheme 1 and Fig. 1).

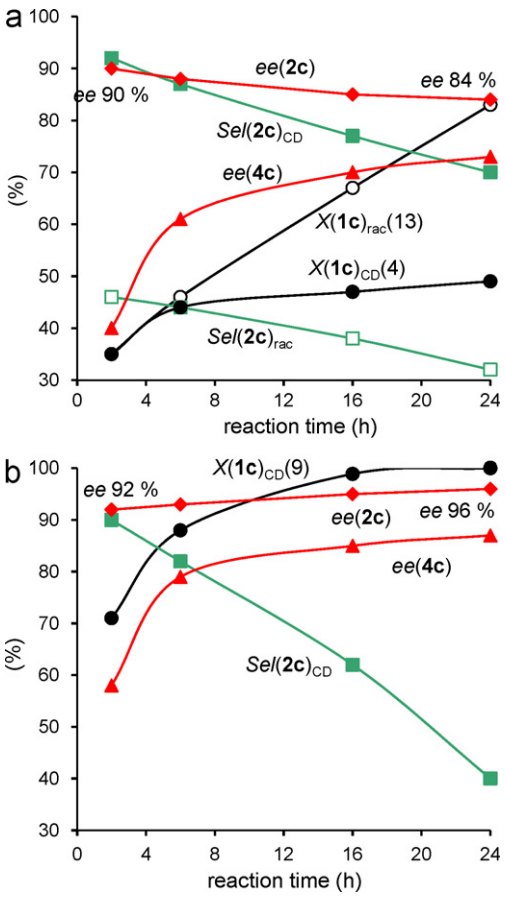


Fig. 2. Hydrogenation of **1c** over unmodified and CD-modified catalyst in the absence (**a**) and presence of BA (**b**). *Reaction conditions*: see Table 1. X_{rac} and X_{CD} are the conversions (in parentheses the corresponding R_{iH} values (mmol h^{-1} g^{-1})); $Sel(\mathbf{2c})_{rac}$ and $Sel(\mathbf{2c})_{CD}$ (%) are the selectivities of **2c** over unmodified and CD-modified catalysts (formation of **3c** was not detected in these reactions, thus, $Sel(\mathbf{4c}) \approx 100 - Sel(\mathbf{2c})$); *ee*(**2c**) and *ee*(**4c**) (%) are the enantioselectivities of **2c** and **4c**.

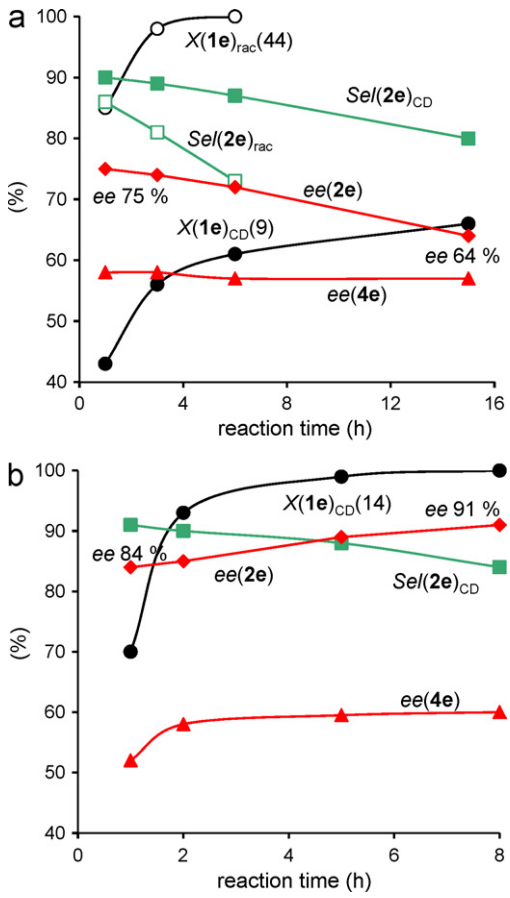


Fig. 3. Hydrogenation of **1e** over unmodified and CD-modified catalyst in the absence (**a**) and presence of BA (**b**). *Reaction conditions*: see Table 2. For abbreviations see Figs. 1 and 2 (the formation of **3e** was detected only over modified catalysts, *Sel*(**3e**) = 4–5% and 2–4% in the absence and presence of BA, respectively).

increased saturated product concentrations are reached. These observations may be interpreted by the tilted arrangement of the α-phenyl ring of the acid on the modified Pd surface. We note that the *ee*s obtained in the hydrogenation of **1b** and **1c** in the presence of BA equalled those reached in the reactions of the compounds bearing F (*ee* 92% and 91%) or CH_3O group (*ee* 90% and 93%) instead of Cl [27], while provided higher *ee*s as the corresponding *ortho*-unsubstituted (*ee* 84%) or CH_3-substituted compounds (*ee* 84% [27]). This led us to suggest that the beneficial effect of the substituents in this position on the *ee* is due to the partial charge of the substituents (due to their electrostatic or dipole–dipole interaction with the modifier [44]) and their steric effect plays a less significant role.

3.2. Effect of the para-chlorine substituent on the α-phenyl ring

The results obtained in the hydrogenations of acids bearing the Cl substituent in *para* position on the α-phenyl ring (**1d**, **1e** and **1f**) are summarized in Table 2 and Fig. 3.

The most important differences and similarities obtained in the hydrogenations of these compounds and the previous acids are the following:

(i) The R_{iH} were much higher as those obtained in the hydrogenation of the corresponding *ortho*-Cl substituted compounds under identical conditions.

(ii) The formation of small amounts of unsaturated dechlorinated acids (**3d**–**3f**) was detected especially over modified catalyst.

(iii) The initially high hydrogenation selectivities decreased by time, longer hydrogenations led to significant amounts of **4d**–**4f** formed by the hydrodechlorinations of **2d**–**2f** and in a smaller part by the hydrogenations of **3d**–**3f**.

(iv) The transformation of these compounds was also decelerated over modified catalyst before reaching full conversions.

(v) The *ee* of the saturated products **2d**–**2f** decreased in time over modified catalyst in the absence of BA, while in its presence increased (except **2d**, which was constant).

(vi) The *ee*s of **4d**–**4f** were constant or increased during these reactions.

According to these results the behaviour of the *ortho*- and *para*-Cl substituted acids (**1a**–**1c** and **1d**–**1f**) were essentially similar, which may be regarded as an indication of the similar reaction pathways occurring during the hydrogenations of these types of chlorinated acids. Thus, it may be assumed that initially the hydrodechlorination did not occur over chiral surface sites. The formation of HCl had similar effect as previously, i.e. inhibited the hydrogenations over modified catalyst in the absence of BA (see Fig. 3a). The low *ee*s obtained in the hydrogenations of **1d**–**1f** may be ascribed to the absence of electrostatic interaction with CD and in some part to the lack of steric influence of the *para*-Cl on this interaction. The above differences may originate mostly from these alterations of the acid-CD interactions. Furthermore, the adsorption on unmodified surface sites of the *para*-Cl compounds through the α-phenyl

Table 2
Hydrogenation of (*E*)-2-(4-chlorophenyl)-3-phenylpropenoic acid (**1d**) and (*E*)-2-(4-chlorophenyl)-3-(4-fluorophenyl)propenoic acid (**1f**).[a]

Acid	Catalyst condition[b]	R_{iH}[b]	*t* (h)[b]	*X* (%)[b]	*Sel* (%)[b]	*ee* (%)	
					2; **3**; **4**	**2**	**4**
1d	Unmodified	27	1	69	91; 0; 9	–	–
			2	97	87; 0; 13	–	–
	CD	12	1	47	98; 0; 2	48	33
			2	74	95; 1; 4	48	33
			4	95	92; 1; 7	47	33
	CD^{BA}	16	1	64	92; 3; 5	49	3
			2	88	89; 2; 9	49	29
			4	99	85; 0; 15	48	34
1f	Unmodified	34	1	44	85; 4; 11	–	–
			3	70	73; 0; 27	–	–
	CD	9	1	43	93; 2; 5	63	22
			6	74	87; 2; 11	54	29
			16	76	77; 1; 22	47	38
	CD^{BA}	21	1	73	88; 2; 10	53	28
			2	96	83; 2; 15	73	59
			3	100	78; 0; 22	73	61

[a] *Reaction conditions*: 25 mg 5% Pd/Al_2O_3, 5 cm^3 DMF + 2.5 vol% H_2O, 0.5 mmol acid, 0.1 MPa H_2, 295 K, 0.025 mmol CD (if used), 0.5 mmol BA (if used).
[b] For abbreviations see Table 1, Scheme 1 and Fig. 1.

ring is not as much hindered as that of the *ortho*-substituted acids, due to the distance of the substituent from the α-C. Consequently, the results obtained with these acids confirmed the tilted adsorption of the α-phenyl ring on the modified Pd.

3.3. Effect of the para-chlorine substituent on the β-phenyl ring

For probing the arrangement of the β-phenyl ring on the Pd surface we studied the hydrogenations of three compounds bearing the Cl substituent in *para* position on this ring (**1g**, **1h** and **1i**). The results are presented in Table 3 and Fig. 4.

These results showed a completely different behaviour of the β-phenyl-*para*-Cl substituted acids, as compared with those substituted on the α-phenyl. The most significant differences are the followings:

(i) The hydrogenated product selectivities are low (*Sel*(**2g**–**2i**) = 13–40% depending on the acid and reaction conditions), and small alteration in these values were observed by time.
(ii) Over unmodified catalyst the major products are the dechlorinated saturated acids **4g**–**4i** and the unsaturated **3g**–**3i** were not formed.
(iii) In contrast, over modified catalyst the initial main products are the dechlorinated acids **3g**–**3i**, which were consecutively hydrogenated to **4g**–**4i** after extended reaction times.
(iv) The R_{iH} values decreased drastically due to chiral modification of the catalyst and increased 6–9 times when BA was also used. The transformation of these compounds were the most severely inhibited over modified catalyst in the absence of BA (*X* 14–15% after 6 h).
(v) The *ee* of the saturated products **2g**–**2i** strongly decreased in time over modified catalyst in the absence of BA. In the presence of BA only small modifications were obtained, dependent on the position and nature of the α-phenyl substituent.
(vi) The *ee* of **4g**–**4i** were low and further decreased in the absence of BA. In the presence of BA the alterations in the *ee*s of **4g**–**4i** followed a similar trend as those of **2g**–**2i**.

The results indicated an adsorption mode of the (*E*)-2,3-diphenylpropenoic acids, which makes possible the fast hydrogenolysis of the C–Cl bond on the β-phenyl ring, i.e. the flat adsorption of this moiety. The rate of hydrogenolysis became the same order of magnitude as that of the hydrogenation of the C=C bond over unmodified Pd, leading to the formation of **4g**–**4i** as the major product. The extensive hydrodechlorination of the substrates implies the formation of higher amounts of HCl and faster transformation of CD in hydrochloride as compared with the previous reactions. This is accompanied by lower *ee* of **2g**–**2i** and also by decrease in these values during the reactions. However, the low *ee*s are also due to the unfavourable effect on the CD–acid interaction of the electron withdrawing Cl. The low *ee* of **4g**–**4i** and the decrease of

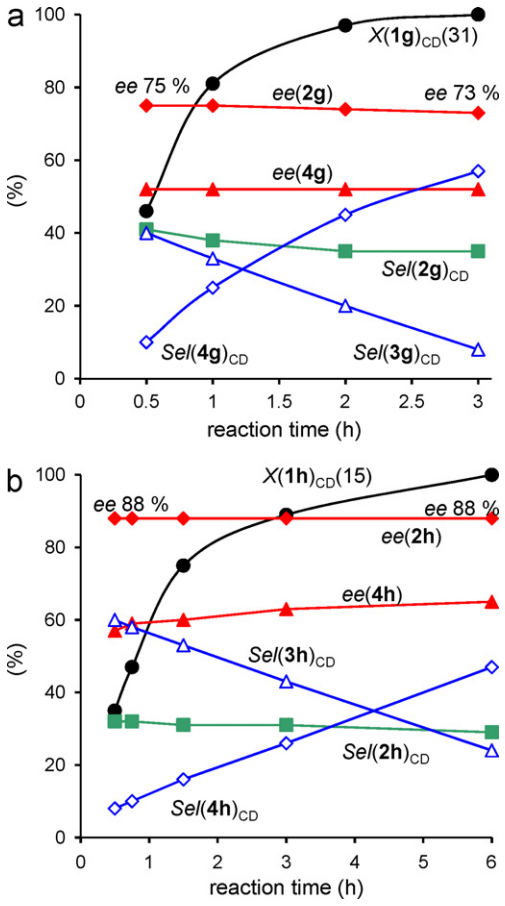


Fig. 4. Hydrogenation of **1g** (**a**) and **1h** (**b**) over CD-modified catalyst in the presence of BA. *Reaction conditions*: see Table 3. For abbreviations see Scheme 1, Figs. 1 and 2.

Table 3
Hydrogenation of (*E*)-2-(4-methoxyphenyl)-3-(4-chlorophenyl)propenoic acid (**1g**), (*E*)-2-(2-methoxyphenyl)-3-(4-chlorophenyl)propenoic acid (**1h**) and (*E*)-2-(2-fluorophenyl)-3-(4-chlorophenyl)propenoic acid (**1i**).[a]

Acid	Catalyst condition[b]	R_{iH}[b]	*t* (h)[b]	*X* (%)[b]	*Sel* (%)[b]	*ee* (%)	
					2; **3**; **4**	**2**	**4**
1g	Unmodified	50	1	60	24; 0; 76	–	–
			4	72	23; 0; 77	–	–
	CD	5	6	15	22; 63; 15	43	2
			20	35	20; 2; 78	20	0
1h	Unmodified	19	2	36	33; 0; 67	–	–
			5	56	30; 0; 70	–	–
	CD	2	6	14	14; 77; 9	64	13
			20	30	16; 9; 75	26	6
1i	Unmodified	24	1	34	25; 2; 73	–	–
			3	54	23; 0; 77	–	–
	CD	3	6	15	16; 73; 11	47	50
			20	40	13; 10; 77	20	n.d.
	CD^{BA}	22	1	70	28; 51; 21	74	78
			3	95	23; 32; 45	78	81
			6	100	21; 7; 72	80	n.d.

[a] *Reaction conditions*: 25 mg 5% Pd/Al_2O_3, 5 cm^3 DMF + 2.5 vol% H_2O, 0.5 mmol acid, 0.1 MPa H_2, 295 K, 0.025 mmol CD (if used), 0.5 mmol BA (if used).
[b] For abbreviations see Table 1, Scheme 1 and Fig. 1; n.d.: not determined.

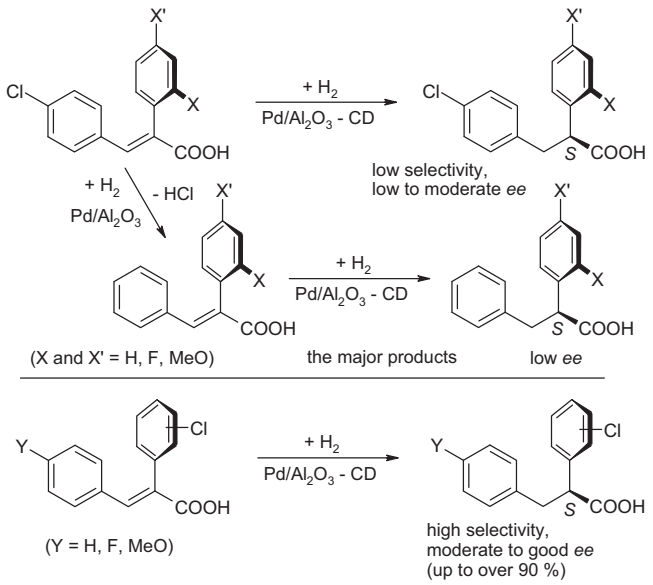
these values by time were indicative of the preferential successive hydrogenation of the dechlorinated unsaturated acids over racemic surface sites (except **1i**). The presence of BA had favourable effect on both the selectivities and the *ee*s of **2g**–**2i** and **4g**–**4i**, thus, the poor results obtained in the absence of BA may be attributed mostly to the effect of HCl on both the surface and the modifier. However, even in the presence of BA the selectivities of **2g**–**2i** were low and the *ee*s were smaller than those obtained in the hydrogenations of the acids bearing F or CH_3O group instead of Cl in the same position or even in that of the corresponding β-phenyl-*para*-unsubstituted acids [26,27], confirming the contribution of the electronic effects of the β-phenyl-*para*-Cl substituent in determining the *ee* of **2g**–**2i**.

3.4. Hydrogenation of dichlorine-substituted derivatives

For the direct comparison of the effect of differently positioned Cl next we studied the hydrogenation of three dichlorine substituted acids (**1j**–**1l**). The hydrodechlorination of these compounds may result in the formation of two pairs of mono-Cl substituted unsaturated and saturated acids, respectively, and a completely dechlorinated unsaturated and saturated acid pair. Fortunately, with each acid the hydrodechlorination occurred predominantly in a specific position. The results obtained were summarized in Table 4.

All these compounds showed preferential hydrodechlorination pathways, which were in accordance with those indicated by the hydrogenolysis selectivities of the mono-Cl derivatives. Thus, the compounds bearing *para*-Cl on the β-phenyl ring suffered fast C–Cl hydrogenolysis, resulting in low saturated product selectivities (**2j**, **2k**) and predominant formation of the acids dechlorinated on the β-phenyl ring. In contrast, when both Cl substituents were situated on the α-phenyl ring (in *ortho* and *para* position, **1l**) high saturated acid (**2l**) selectivities were obtained, with increasing amount of dechlorinated product (**4l**) only after reaching complete conversion of **1l**. The *ee*s also confirmed the interpretations of the hydrogenations of the mono-Cl derivatives. Thus, the alterations in the *ee*s of both **2j** and **4j** obtained in the hydrogenations of **1j** resembled the behaviour observed in the hydrogenation of **1g** (see Table 3 and Fig. 4), with somewhat lower values of the former, ascribed to the effect of the α-phenyl-*para*-substituent (CH_3O vs. Cl). Similarly, small differences were observed when the α-phenyl ring was substituted in *ortho* position with Cl or CH_3O group (compare the behaviour of **1k** and **1h**). In the hydrogenations in the presence of BA the *ee*s of the saturated dechlorinated **4k** and **4h** were almost equal (~60%). The α-phenyl-dichlorine-substituted compound (**1l**) had an intermediate behaviour as compared with the corresponding mono-Cl-substituted **1a** and **1d** as regards the *ee*, being closer to that obtained in the reaction of **1a**, indicating the dominating effect of the α-phenyl-*ortho*-substituent on the *ee*.

Accordingly, the main reaction pathways in the hydrogenations of the (*E*)-2,3-diphenylpropenoic acids substituted by Cl in different positions may be summarized as sketched in Scheme 2. The differences in the reactivities of the Cl on the two phenyl groups indicated without doubt that these moieties are differently arranged on the surface when the acid is interacting with CD, i.e. the α-phenyl is anchored in a tilted orientation, while the β-phenyl is adsorbed parallel with the surface. The suggested arrangement of the (*E*)-2,3-diphenylpropenoic acids interacting with CD on the metal surface is illustrated on Fig. 5. The degree of tilt of the α-phenyl ring should be dependent on the nature and steric effect of the substituents, which will influence the rate and the *ee* of the hydrogenation. Experiments aimed at determining more accurately the arrangement of this moiety on the surface are in progress. Finally, these experiments evidenced, that the CD-modified Pd catalyst, is not suitable



Scheme 2. Reaction pathways observed in the enantioselective hydrogenation of Cl substituted (*E*)-2,3-diphenylpropenoic acids over CD-modified Pd catalyst.

Table 4
Hydrogenation of (*E*)-2,3-di(4-chlorophenyl)propenoic acid (**1j**), (*E*)-2-(2-chlorophenyl)-3-(4-chlorophenyl)propenoic acid (**1k**) and (*E*)-2-(2,4-dichlorophenyl)-3-phenylpropenoic acid (**1l**).[a]

Acid	Catalyst condition[b]	R_{iH}[b]	*t* (h)[b]	*X* (%)[b]	*Sel* (%)[b]	*ee* (%)	
					2; **3**[c]; **4**[c]	**2**	**4**[d]
1j	Unmodified	28	1	50	32; 1[e]; 63[e]	–	–
			4	81	32; 0; 62	–	–
	CD	3	6	17	27; 51; 20	28	1[e]
			20	62	29; 1; 67	12	1
	CD^{BA}	34	1	84	43; 25; 29	50	40
			2	99	37; 0; 49	55	43
1k	Unmodified	22	2	47	14; 0[f]; 81[f]	–	–
			4	65	12; 0; 72	–	–
	CD	2	6	13	6; 84; 10	57	4[f]
			20	38	10; 4; 80	26	4
	CD^{BA}	19	2	98	38; 56; 4	76	60
			6	99	12; 38; 41	82	60
1l	Unmodified	21	1	100	90; 0[g]; 5[g]	–	–
	CD	7	3	59	95; 0; 3	62	n.d.[g]
			6	81	90; 1; 6	68	n.d.
	CD^{BA}	8	2	64	96; 0; 3	65	n.d.
			3	87	92; 0; 5	64	83
			6	100	62; 0;35	48	62

[a] *Reaction conditions*: 25 mg 5% Pd/Al_2O_3, 5 cm^3 DMF + 2.5 vol% H_2O, 0.5 mmol acid, 0.1 MPa H_2, 295 K, 0.025 mmol CD (if used), 0.5 mmol BA (if used).
[b] For abbreviations see Table 1, Scheme 1 and Fig. 2; n.d.: not determined.
[c] The selectivities of the major dechlorinated unsaturated and saturated products.
[d] The *ee*s of the major dechlorinated saturated acids.
[e] **3j**: (*E*)-2-(4-chlorophenyl)-3-phenylpropenoic acid; **4j**: 2-(4-chlorophenyl)-3-phenylpropionic acid.
[f] **3k**: (*E*)-2-(2-chlorophenyl)-3-phenylpropenoic acid; **4k**: 2-(2-chlorophenyl)-3-phenylpropionic acid.
[g] **3l** = **3k**; **4l** = **4k**.

for the preparation of 2,3-diphenylpropionic acids substituted by Cl on the β-phenyl ring, however, may be an appropriate choice for the preparation in good yields and optical purities of acids bearing Cl substituent on the α-phenyl ring.

3.5. Hydrogenation in the presence of HCl and the scope of the catalytic system

The results of the hydrogenations of the chlorinated acids were interpreted by assuming that the HCl formed during the hydrogenolysis of the C–Cl bond poisoned the metal surface in the absence of BA and also changed the intrinsic enantiodifferentiation ability of the chiral sites by transformation of CD in hydrochloride [36]. This assumption was verified by using CD × HCl as modifier and hydrogenation in the presence of added HCl. As a test compound we used (*E*)-2-(2-methoxyphenyl)-3-(4-fluorophenyl)propenoic acid (**1m**, Fig. 6), which provided high *ee* in previous studies (Table 5) [27].

The use of CD × HCl as modifier in the absence of BA resulted in slightly decreased R_{iH} and conversion as well, while the *ee* was much lower as compared with CD. However, when BA was added both the R_{iH} and the *ee* were similar with the hydrogenation using the free base (CD). Addition to the reaction mixture of 0.1 mmol HCl had a striking effect on both the rate and *ee*, the hydrogenation was severely inhibited and the product formed had very low optical purity. We mention that this amount of HCl corresponds to the amount formed by 20% hydrodechlorination of a Cl substituted acid.

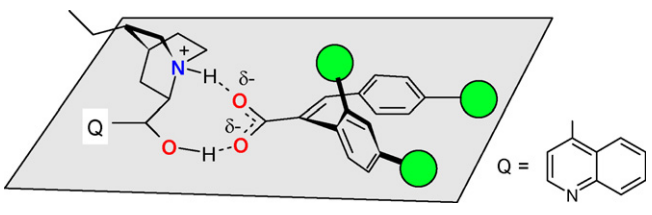


Fig. 5. Schematic illustration of the arrangement on the Pd surface of (*E*)-2,3-diphenylpropenoic acids interacting with the modifier.

However, in the presence of BA this inhibition was not observed and the *ee* was only slightly lower than that obtained in the absence of HCl. These results confirmed the assumption, that the HCl formed during the hydrogenation of the chlorinated acids in the absence of BA alters the enantiodifferentiating ability of the CD and inhibits the reaction by poisoning the catalyst. The added BA neutralized the HCl; the slightly lower *ee* may be attributed to decrease in the amount of free BA available during the reaction.

The low hydrogenolysis rate of both α-phenyl-*ortho*- and *para*-Cl substituted acids was interpreted by the tilted arrangement of this moiety on the surface. To further ascertain on the above assumption the hydrogenation of a derivative bearing F substituents in both *ortho*-positions on the α-phenyl ring was attempted (**1n**, Fig. 6). It is known that the Ar–F bond is several orders of magnitudes more resistant to hydrogenolysis than the Ar–Cl [32,45], thus, the chosen substitution pattern should hinder the adsorption and the hydrogenation of **1n**. Indeed, low conversions were achieved even over unmodified catalyst and beside the saturated acid **2n**, formation of a hydrodefluorinated product was also detected. Over modified catalyst both in the absence and presence of BA decrease by one order of magnitude in the R_{iH} led to low conversions even after 20 h. The presence of BA decreased the rate, the conversion and also the *ee*. Thus, these results showed that substitution on both sides of the α-phenyl ring in *ortho* position dramatically decelerates the hydrogenation as effect of their steric hindrance, confirming the tilted arrangement of this moiety on the surface.

The above conclusions and the results reported up to now [24–28] delimited the scope of this catalytic system. Acids highly substituted on the β-phenyl ring may be hydrogenated in excellent *ee*s depending on the electronic effect of the substituent [24,25], except when this is in *ortho* position [26,27]. The substituents in the latter position exert a strong steric inhibition on the CD-acid interaction resulting in low rate and *ee*. The substituents on the α-phenyl ring have more limited effect, except those in the *ortho* position [26,27]. These were found to increase the *ee* for reasons not fully clarified yet (by their effect on the interaction with CD). The α-phenyl moiety tolerates substitution in *para*, both *meta* [28]

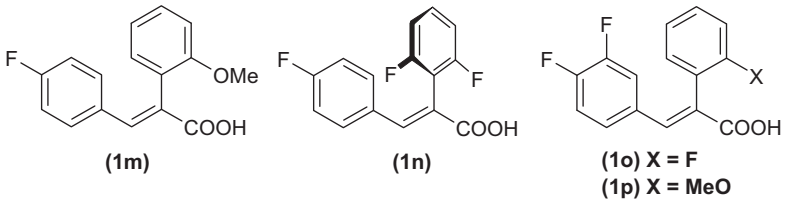


Fig. 6. Methoxy and fluorine substituted (*E*)-2,3-diphenylpropenoic acids examined.

Table 5
Hydrogenation of fluorine- and methoxy-substituted (*E*)-2,3-diphenylpropenoic acids.[a]

Substrate	Modifier	R_{iH}; R_{iH}^{BA}[b]	X/t; X^{BA}/t[c]	*ee*; ee^{BA} (%)[d]
1m	–[e]	9	99/6; –	0; –
	CD[e]	3; 7	94/6; 99/6	86; 93
	CD × HCl	2; 7	74/6; 99/6	67; 94
	CD + HCl[f]	0.1; 7	5/6; 98/6	16; 89
1n	–	4	50(86[g])/6; –	0; –
	CD	0.4; 0.2	50(95[g])/20; 35(90[g])/20	75; 70
1o	–	13	100/3; –	0; –
	CD	6; 9	100/6; 100/6	78; 87
1p	–	10	100/4; –	0; –
	CD	5; 9	100/8; 100/8	88; 95

[a] *Reaction conditions*: 25 mg 5% Pd/Al_2O_3, 5 mL DMF + 2.5 vol% H_2O, 0.5 mmol acid, 0.1 MPa H_2, 295 K, 0.025 mmol CD (if used), 0.5 mmol BA (if used).
[b] Initial H_2-uptake rates (mmol h^{-1} g^{-1}) in the absence and presence of BA.
[c] Conversions (%) obtained after hydrogenation times *t* (h) in the absence and the presence of BA.
[d] The *ee*s (%) obtained in the absence and presence of BA.
[e] Results published previously [27] and repeated during this work.
[f] Addition of 0.1 mmol HCl (as 5 M aqueous solution) following CD and before adding the acid and BA (if used).
[g] Selectivity of the saturated product **2n**.

and one of the *ortho* positions. However, one of the *ortho* C must remain unsubstituted to avoid impeding the adsorption of the acid by the tilted α-phenyl ring.

With these observations and conclusions in mind we attempted to design two fluorinated acids (**1o** and **1p**, Fig. 6), which could be hydrogenated in higher *ee* as the (*E*)-2,3-diphenylpropenoic acid derivatives studied up now (the highest *ee* value obtained in reactions carried out at room temperature was 93% [27]). Although, good *ee* was obtained in the hydrogenation of **1o**, the best value remained below 90% (Table 5). To our delight the replacement of the *ortho*-F on the α-phenyl ring by CH_3O group (**1p**) fulfilled our expectations. Both in the absence and presence of BA the *ee* was higher as obtained in the reactions of **1m** under the same conditions (room temperature), reaching up to 95% *ee* at full conversion.

4. Conclusions

A series of Cl substituted (*E*)-2,3-diphenylpropenoic acids were prepared and their enantioselective hydrogenations over CD-modified Pd/Al_2O_3 was studied in order to obtain *in situ* evidence on the adsorption mode of this type of acids on the chirally modified surface. The low C–Cl hydrogenolysis rates of the acids substituted on the α-phenyl ring by Cl in either *ortho* or *para* position was in contrast with the fast hydrodechlorination of the β-phenyl *para*-Cl substituted acids. This behaviour was attributed to the different arrangement of the two phenyl rings of the adsorbed acids, the β-phenyl parallel, while the α tilted to the surface during the enantioselective hydrogenation. The results obtained also confirmed the beneficial effect of the α-phenyl-*ortho*-substituents on the chiral discrimination, while in β-phenyl-*para* position the substituents should have electron donating effect in order to reach good optical purities. The differences in the effect of the Cl in different positions were also evidenced by the hydrogenations of three dichlorine-substituted acids.

Our present study demonstrated that this catalytic system is appropriate for the preparation of Cl substituted 2,3-diphenylpropionic acids, as long as the Cl is on the α-phenyl ring. The interpretation of the results was supported by hydrogenations in presence of HCl and by the reaction of an α-phenyl-*ortho*,*ortho*-difluorine substituted acid. Moreover, the conclusions of this study were used for the design of an acid, which by hydrogenation in this catalytic system under mild reaction conditions (room temperature) provided the saturated product in the best optical purity (*ee* 95%) reached up to now.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2010.09.013.

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