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Heterogeneous asymmetric hydrogenation and deuteration of 2-methyl-2-pentenoic acid over Pd supported catalysts: proton/deuterium exchange

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Abstract

The asymmetric hydrogenation of *trans*-2-methyl-2-pentenoic acid in hexane over two well defined E-40692 and E-5220 Engelhard Pd/Al$_2$O$_3$ catalysts modified with cinchonidine was re-examined, the literature results have been reproduced and it was found that the E-40692 catalyst lead to the best conversions and %e.e. Deuteration experiments have been conducted under identical (solvent, catalyst, constituents ratios and temperature) conditions: percentage of H/D exchange (in the starting substrate and in the saturated product) as well as percentage of deuteration at all carbons have been determined by ^{1}H NMR and indicated that double bond migration and *cis/trans* isomerization occurred during hydrogenation/deuteration but that these processes contributed less at higher pressure (40 bar) and in the presence of cinchonidine.
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1. Introduction

During enantioselective hydrogenation of type 1 conjugated acids over catalytic amounts of supported palladium catalysts (Pd/Al$_2$O$_3$) in the presence of catalytic amounts of Cinchona alkaloids (Scheme 1) a decrease in the rate of the reaction in the presence of the alkaloid is observed [1–3] together with an enantioselectivity which is significant but does not exceed ∼75/25 [1–5] for **1** suggesting that the adsorbed alkaloid does interact with the substrate (salt formation)[1] while slightly poisoning the catalyst. Moreover, double bond migration, which occurs readily on palladium, [6,7] has been invoked to be directly [8] or indirectly [9] responsible of the low enantioselectivities observed.

To check our ability to reproduce these reactions we studied the asymmetric hydrogenation of *trans*-2-methyl-2-pentenoic acid **1** in hexane over home-made Pd/Al$_2$O$_3$ catalysts and/or over two well defined Engelhard Pd/Al$_2$O$_3$ catalysts (E-40692 and E-5220) modified with CD. To point out possible double bond migration, deuteration experiments have been conducted under identical (solvent, catalyst, constituents

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[1] Aldehydes and esters give 0% e.e. [4].
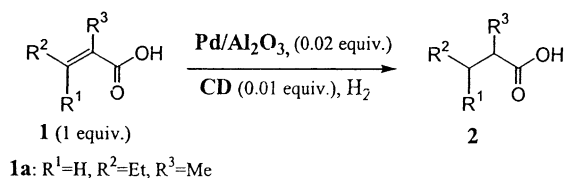
Scheme 1.

ratios and temperature) conditions and it was observed that H/D exchange occurred on the starting substrate (MPEA).

2. Experimental

2.1. Hydrogenation/deuteration

The reactions were conducted in hexane at room temperature (20–25 °C) in a stainless steel autoclave equipped with a magnetic stirring fixed at ∼600 rpm. The catalysts were not pretreated prior to use. The hexane (analytical grade) purchased from Prolabo and the 2-methyl-2-pentenoic acid from Aldrich, were used without further purification. The solvent (S), catalyst (Cat), substrate (MPEA) and modifier (CD), quantities (ratios) were identical in all the cases and are the following: MPEA = 1.53 mmol (0.1 ml), S = 5 ml, Cat (5% Pd) = 50 mg (2.37×10^{-2} mmol of Pd),[2] CD = 1.7×10^{-2} mmol, MPEA/Cat = 64, CD/Cat = 0.7, CD/MPEA = 0.01. The catalyst was added last[3] into a stirred hexane solution of MPEA and CD (for the reactions run with CD). D_2 gas (99.9% D) was purchased from AlphaGaz. The results are gathered in Table 1.

2.2. ^1H NMR determination of percentage of deuteration

The pattern of the C5-methyl signals (^1H NMR, 400 MHz) of MPEA and MPA were narrow triplets

(at 1.08 and 0.97 ppm, respectively) with no traces of other and different patterns due to deuterium exchanges at C5 and/or C4; they have thus been used as 3H surface references to calculate the percentages of deuteration and H/D exchange (Fig. 1). The CH_2 protons at C3 are diastereotopic and the non-equivalence was large enough (Table 3, line 2: $\delta H3a = 1.42$ ppm and $\delta H3b = 1.70$ ppm) to allow determination of the percentage of deuteration on each of them. The spectra have been registered on an Avance 400 Bruker equipped with an inverse BBI probe. The results are gathered in Table 3.

2.3. Determination of enantiomeric purities of MPA

The enantiomeric ratios of the MPA (2-methyl pentanoic acid) obtained have been determined by ^{13}C NMR on the salts obtained by addition of two equivalents of (+)-(R)-α-methyl benzylamine into $CDCl_3$ solutions of MPA. The C2′, C3, C4 and C5 singlets are clearly splitted into two singlets corresponding to the two possible diastereomers of the salt (Fig. 2) and are used for the ratios determination.

2.4. ^2H NMR

^2H NMR spectrum (61.4 and 76.7 MHz) have been registered in $CHCl_3$ as solvent on Avance 400 and Avance 500 Bruker, respectively.

It appeared clearly that no deuterium (<0.5%) has been incorporated at the C5-methyl and at the C4-CH_2 for both recovered starting olefin (MPEA) and product (MPA), which confirm the hypothesis deducted from the ^1H NMR spectra (cf. previously mentioned).

3. Results and discussion

3.1. Asymmetric hydrogenation of 2-methyl-2-pentenoic acid 1 (MPEA) over Pd/Al$_2$O$_3$

Previous results [10] obtained with home-made 2.5%-Pd/Al$_2$O$_3$ catalysts with 4–10 nm particle size has shown that 30% conversion occurred in the presence of CD while 100% conversion was obtained without CD (Table 1, lines 1 and 2).

We now observed that, with home-made 5%-Pd/ Al$_2$O$_3$ catalysts having 20–50 nm particle size, no

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[2] When the 2.5% Pd catalyst was used, 50 mg of catalyst was weighted and all other quantities were divided by two.

[3] Previous results [10] obtained with home-made Pd/Al$_2$O$_3$ catalysts under 40 bar showed that no hydrogenation occurred when the catalyst was impregnated with CD before addition of the substrate (1a) while some conversion (∼30%) occurred when the catalyst was added into the 1a/CD mixture.

Table 1
Hydrogenation of **1a** over supported Pd

Catalyst	CD	Reaction time	Pressure (bar)	Conversion (%)	e.r.	Abs. conf.[a]
2.5% Pd/Al$_2$O$_3$	No	24 h	40	100	–	–
Home-made (4–10 nm)	Yes	24 h	40	30	61/39	S
5% Pd/Al$_2$O$_3$	No	15 min	50	84	–	–
Home-made (20–50 nm)	Yes	15 min	50	0	–	–
5% E-40692	No	5 min	50	100	–	–
	Yes	24 h	20	100	73/27	S
	Yes	15 min	40	100	71/29	S
	Yes	24 h	50	100	71/29	S
	Yes	2 min	50	25	73/27	S
	Yes	5 min	50	72	72/28	S
	Yes	15 min	50	100	73/27	S
	Yes	4 h	50	100	72/28	S
5% E-5220	Yes	15 min	50	36	67/33	S

[a] For determination of the absolute configuration of 2-methyl pentanoic acid (MPA) see [11].

hydrogenation occurred in the presence of CD while 84% conversion was obtained without CD within 15 min (Table 1, lines 3 and 4).

When Pd/Al$_2$O$_3$ catalysts from Engelhard (E-40692) and/or (E-5220) were used, the percentages of conversion were also higher in the absence of CD (100%

versus 72% in 5 min, Table 1, lines 5 and 10) but not so much.

Knowing that hydrogenation is faster without modifier but that catalytic amounts of chiral modifier (CD) are sufficient to produce significant asymmetric inductions, the following route could be proposed
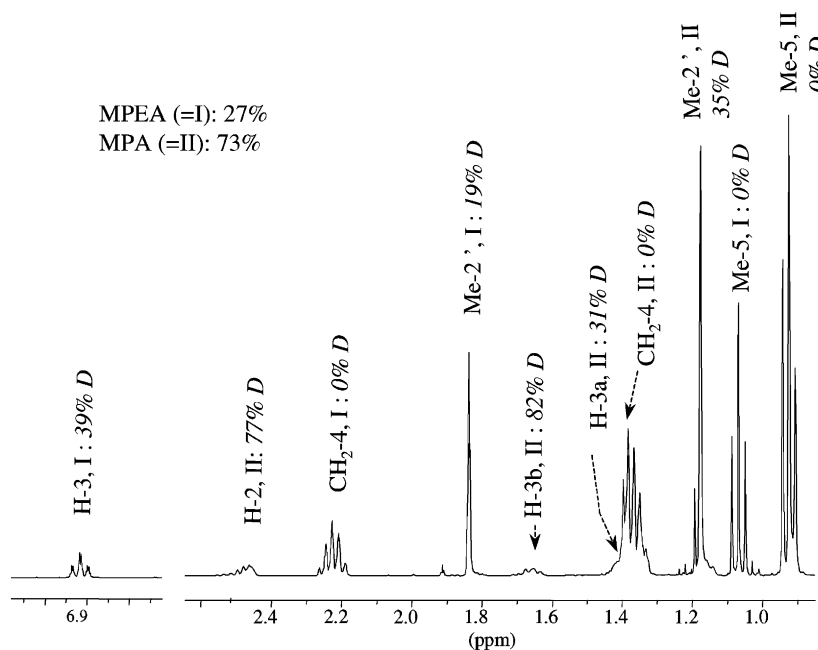

MPEA (=I): 27%
MPA (=II): 73%

Fig. 1. Deuteration of MPEA (2.5 bar, 15 min, with CD).
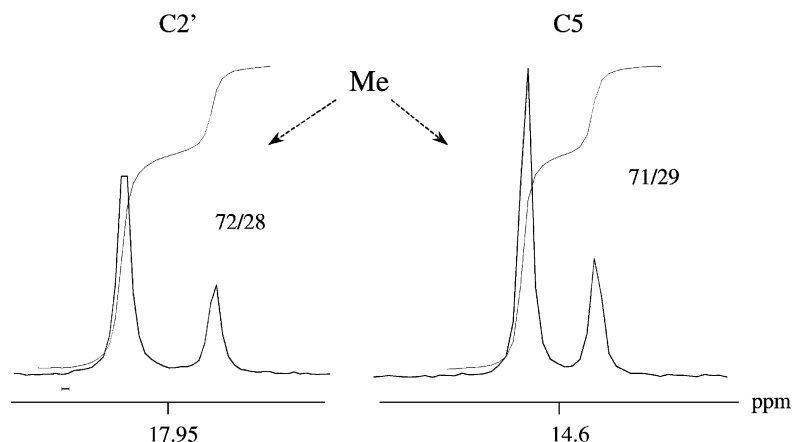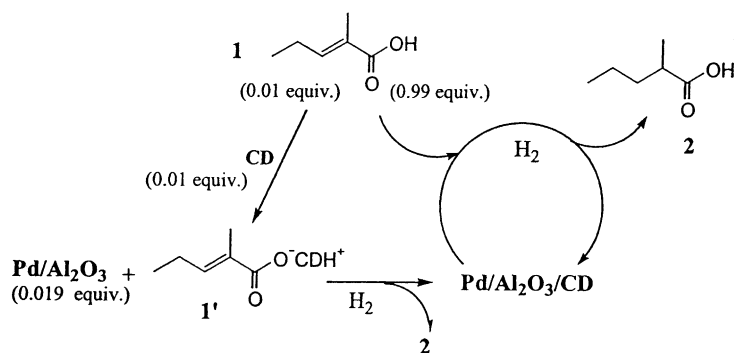
Fig. 2. ^{13}C NMR of MPA in the presence of (+)-(R)-α-methyl benzylamine: methyl signals.

Scheme 2.

(Scheme 2): (i) upon dissolving CD into MPEA, the salt **1′** can be expected to be quantitatively formed (0.01 equivalent) because of the large amount of acid compared to CD (MPEA/CD = 100); (ii) the salt adsorbs on the catalyst and is hydrogenate when H$_2$ is introduced; (iii) MPA (2-methyl pentanoic acid, 0.01 equivalent) is then liberated but not the modifier[4] (CD) leading to the modified now chiral catalyst (Pd/Al$_2$O$_3$/CD); (iv) MPEA adsorbs on the chiral catalyst through salt formation and associative adsorption and the double bond is hydrogenated starting the catalytic cycle (Scheme 2).

It appeared that the Pd 5% catalyst E-40692 was more efficient than the Pd 5% E-5220, leading to, af-

ter 15 min, full conversion and slightly higher enantioselectivity (Table 1, lines 11 and 13). Moreover, the enantioselectivity (in favor of the S-configuration) [11] did not change with time, the variations observed being within the possible range of error because the ratios were determined by C-13 NMR (cf. previously mentioned).

3.2. Deuteration of 2-methyl-2-pentenoic acid over E-40692 (5% Pd/Al$_2$O$_3$)

The enantiomeric ratios obtained during hydrogenation (Table 1) being similar to those found in the literature for hydrogenation of the same conjugated acid (2-methyl-2-pentenoic acid) [4] over the same catalyst (E-40692) in the presence of the same modifier (CD) and the preferred configuration of the resulting saturated acid being the same (S-configuration),

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[4] Less modifier (CD) than Pd (mol) can be used as some Pd atoms must remain free to afford H$_2$ and the conjugate acid for the reaction to occur.

Table 2
Deuteration of **1** in hexane over E-40692

Pressure (bar)	Reaction time (min)	CD	Yield **2** (%)	Remaining **1** (%)
2.5	15	No	100	0
2.5	15	Yes	73	27
40	15	No	100	0
40	5	Yes	82	18
40	15	Yes	90	10

deuteration of 2-methyl-2-pentenoic acid (under various pressure and time conditions) was studied. The results are gathered in Tables 2 and 3.

Deuteration rate at low pressure (2.5 bar) appeared to be slightly more sensitive to the presence of modifier with a 27% decrease in conversion in the presence of CD (Table 2, compare lines 1 and 2) instead of 10% decrease under 40 bar (Table 2, compare lines 3 and 5). Moreover, deuteration was slightly slower than hydrogenation (compare line 5 of Table 2 with line 7 of Table 1) in consistency with the expected isotopic effect [12].

The most important features of these deuterations (Table 3) are:

I concerning C2 and C3b (the double bond of the starting MPEA which undergoes deuteration).

1. Deuteration at C2 and C3b (saturated MPA) is significantly not total under 2.5 bar (Table 3, lines 1 and 2) and significantly lower than under 40 bar (Table 3, lines 3–5).
2. Deuteration at C2 and C3b (saturated MPA) is larger in the presence of CD (Table 3, compare lines 1 and 3 with 2 and 5).

II concerning the other carbons.

3. D incorporation (H/D exchange) is always present at the C2′-methyls, both in the saturated product (MPA) and in the remaining starting olefinic substrate (MPEA) (Table 3, columns 3 and 7).
4. D incorporation (H/D exchange) occurs at C3 in the remaining starting olefinic substrate (MPEA) (Table 3, column 5).
5. D incorporation at C2′-methyl and at C3a is significantly lower in the presence of CD under 40 bar (Table 3, lines 3 and 5).
6. Percentages of D at the diastereotopic positions C3a and C3b are always different, the percent-

ages at C3b is always higher and the percentages at C3a significantly lower in the presence of CD.

7. No *cis*-isomer of the starting MPEA (deuterated or non-deuterated) is detected.

Observation 1 can be explained from possible H/D exchanges between the mobile OH protons of the acid function and the D_2-saturated catalyst as already observed [13,14][5] as well as from transfer of H from the substrate (MPEA) to the catalyst during double bond migration (Scheme 3). The proton concentration at the catalyst surface being nevertheless larger at 2.5 bar of D_2 than at 40 bar of D_2.
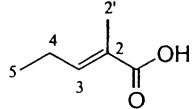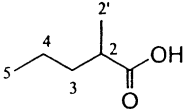
Observation 2 is difficult to explain except by a CD effect which, by trapping the acid function of the substrate to form the salt **1′**, slows down the exchange of these mobile acidic OH with the surface's deuterium. It might also well be that CD slows down double-bond migration and *cis*/*trans* isomerization, which also provide proton to the catalyst surface (as suggested by the results, cf. mentioned later). Moreover, deuteration at C2 and C3b was higher and almost total under 40 bar (∼94%) indicating that under higher D_2 pressure the quantity of H adsorbed on the metallic surface decreases, as expected.

Observation 3 can be explained by the well accepted mechanism of double bond migration (Scheme 3):[6] [15] formation of the half-deuterated state αd (monodeuterated σ-complex) followed by an hydride transfer from the methyl to the palladium surface (Footnote 5) and formation of the π-complex π**2d** which then undergoes deuterium insertion to give the dideuterated

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[5] It must be kept in mind that double bond migration and *cis*/*trans* isomerization which occur in these reactions are accompanied by D/H exchange on the Pd surface which dilutes the adsorbed deuterium and can also modify the percentages of D exchange (which does not represents anymore the equilibria shown in Scheme 3) and of D incorporation.

[6] As C–C bonds are approximately 68% of the palladium diameter and as the π-complexes with palladium are well known, associative adsorption (π-complexation without rupturing the π-bond) followed by formation of the half-hydrogenated (deuterated) state through addition of one H(D) to one of the atom of the former π-bond has been chosen [6] in Scheme 3 and the star stands for Pd. One must note that on the basis of the absence of deuteration at C4 and of the better anchoring effect of a carboxylate group, the σ-complex at C2 was the only one envisaged (but not the σ-complex at C3).

Table 3
Percentages of deuteration (hexane, E-40692) and of H/D exchange

	2-methyl-2-pentenoic acid				2-methyl pentanoic acid					
	H5 1.08 (Me) (%)	H2′ 1.86 (Me) (%)	H4 2.22 (CH$_2$) (%)	H3 7.00 (CH) (%)	H5 0.97 (Me) (%)	H2′ 1.20 (Me) (%)	H4 1.40 (CH$_2$) (%)	H3a 1.42 (CH) (%)	H3b 1.70 (CH) (%)	H2 2.50 (CH) (%)
2.5 bar, 15 min without CD	–	–	–	–	0	42	0	40	66	45
2.5 bar, 15 min with CD	0	19	0	39	0	35	0	31	82	77
40 bar, 15 min without CD	–	–	–	–	0	54	0	53	90	80
40 bar, 5 min with CD	0	6	0	7	0	13	0	13	94	93
40 bar, 15 min with CD	0	15	0	14	0	13	0	11	93	95

Calculated on the ^{1}H NMR spectra and referring to the methyl at C5 for 0% D.
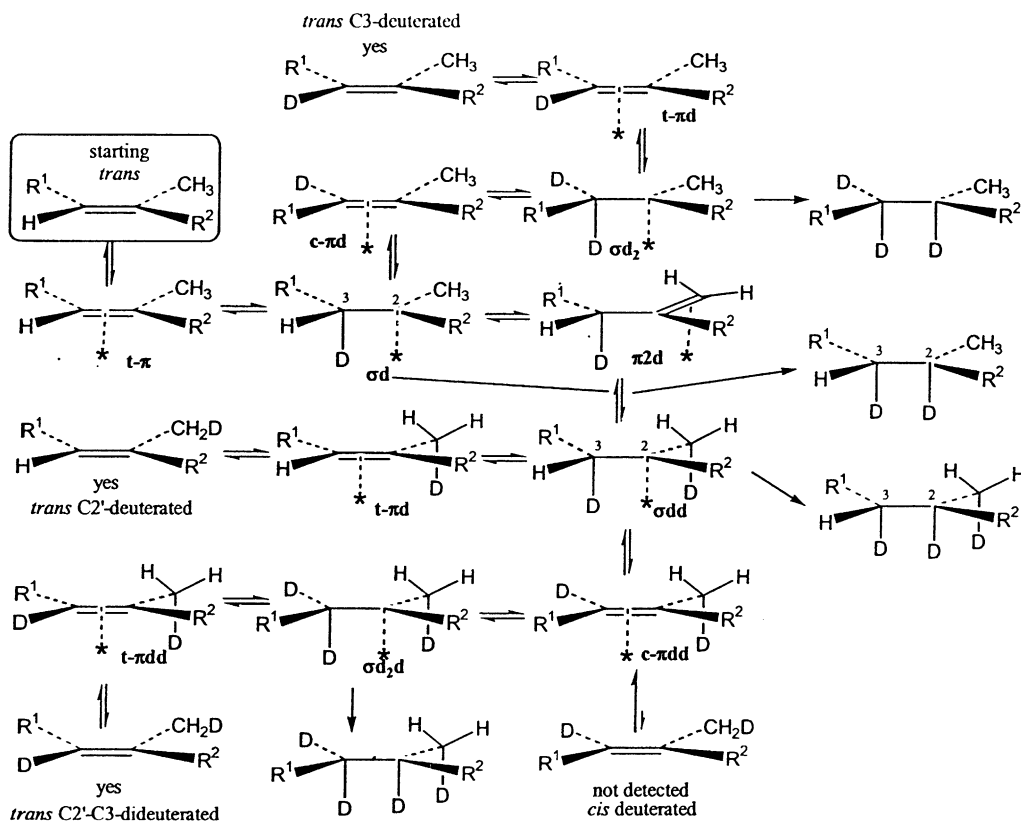
Scheme 3. Simplified equilibrium at the Pd surface: only one enantiomeric approach is drawn (for the sake of simplicity) *t*-π = π-complex of the *trans*-olefinic substrate; *c*-π = π-complex of the *cis*-olefinic substrate; **d** = monodeuterated; **dd** = dideuterated at different positions; **d₂** = gem-dideuterated.

σ-complex σ**dd** and opens the route either toward the C2′-monodeuterated *trans*-olefin MPEA (through formation of the monodeuterated π-complex *t*-π**d**)[7] or to the C3,C2,C2′-trideuterated MPA.[8]

Observation 4 can only be explained by the, also well known, *cis/trans* isomerization (Scheme 3) either from σ**d** (through formation of *c*-π**d**, σ**d₂**, *t*-π**d**) leading to C3-deuterated MPEA or from σ**dd** (through formation of *c*-π**dd**, σ**d₂d**, *t*-π**dd**) leading to C2′–C3-dideuterated MPEA.

Observation 5 (deuteration at C2 and C3a lower in the presence of CD) suggests that under 40 bar (where

the deuterium concentration at the catalyst surface is higher and where, therefore, deuteration should be higher) the modifier (CD) slows down double-bond migration and *cis/trans* isomerization ending in a decrease in percentage of deuteration at C2 and C3a as observed.

Neglecting the H-concentration at the Pd surface, observation 6 suggests that the diastereotopic a and b positions are that indicated in Scheme 4 and that D incorporation at C3a comes only from *cis/trans* isomerization and should correspond mainly to

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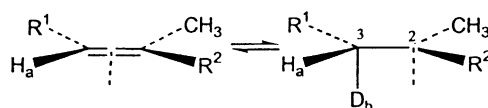
[7] Polydeuteration at C2′ is also possible and would originate by the same double bond migration route from σ**dd**, hydride transfer after rotation around the C2–C2′ bond, deuteration at C2′ and so on.

[8] The possibility of H-transfer is not considered (for simplicity).

Scheme 4.

dideuteration at C3 from σ**d** (either through **c**-π**d**, σ**d₂** or through π**2d**, σ**dd**, **c**-π**dd**, σ**d₂d**, Scheme 3). The lower percentage of deuteration at C3a in the presence of CD corroborates the previous hypothesis that CD slows down *cis/trans* isomerization (cf. previously mentioned observation 5).

Observation 7 indicates that the *cis*-isomer is kinetically/thermodynamically disfavored and not populated.

4. Conclusion

We have shown that double bond migration and *cis/trans* isomerization occurred during hydrogenation/deuteration of conjugated acid (MPEA) on Pd/Al$_2$O$_3$ and that these processes contribute less at higher pressure (40 bar) and in the presence of CD (as chiral modifier).
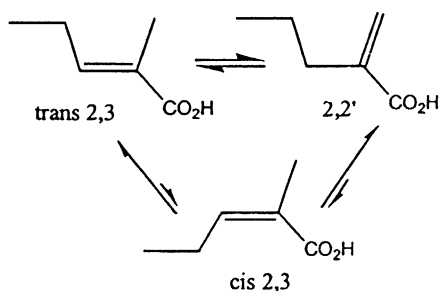
As it had been shown that hydrogenation of *cis*-2-methyl-2-pentenoic acid in the presence of CD leads to lower e.e. (∼27%) [2] than the *trans*-isomer (∼50%) one can conclude that the presence of *cis/trans* isomerization might well be partly responsible of the low e.e. observed.

Moreover, it has been shown also that hydrogenation of 2-ethyl-2-ethenoic acid over Pd–CD system favors formation of the *R*-saturated acid while the *S*-isomer is produced in excess with 2-methyl-2-propenoic acid [5]. Therefore, double bond migration might also be partly responsible of the low e.e. observed, as already suggested by Baiker et al. [8] during

isomerization/hydrogenation of 2-ethyl-2-ethenoic acid.

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