Asymmetric Synthesis of 2-Methyl Cyclohexane Carboxylic Acids by Heterogeneous Catalysis: Mechanistic Aspects

Michèle Besson,* Françoise Delbecq, Pierre Gallezot, Samuel Neto, and Catherine Pinel[a]

Abstract: The catalytic hydrogenation of (*S*)-alkyl-*N*-(2-methylbenzoyl)pyroglutamates was studied over supported rhodium and ruthenium catalysts at room temperature and a pressure of 5 MPa. The reaction was diastereoselective with the predominant formation of (1*S*,2*R*)-2-methylcyclohexane carboxylic acid with a diastereomeric excess (*de*) of up to 96%. The most stable conformation was determined by means of a combination of modelling calculations, NMR spectroscopy and X-ray structural determination. In this conformation, the carbonyl group of the pyroglutamate auxiliary shields one face of the aromatic ring. The observed selectivity may thus be explained by a preferential adsorption at the unshielded face which avoids steric repulsion by the C=O group to result in a *cis* hydrogenation. The addition of an amine, the nature of the support (alumina or active carbon) or of the metal (Rh or Ru) were shown to give additional stabilisation of the adsorption at the unshielded face to increase the diastereoisomeric excess.

Keywords: aromatic rings · diastereoselectivity · heterogeneous catalysis · hydrogenations · steric hindrance

Introduction

Chiral cyclohexyl derivatives are present in a large number of natural products of biological importance.[1, 2] They can also be used as chiral auxiliaries.[3] Thus, the development of methods for the asymmetric synthesis of these compounds generates considerable interest. The conventional synthesis of optically active cyclohexyl molecules is painstaking and costly; it involves an asymmetric Diels–Alder reaction between butadiene and *N*- or *O*-propenoyl derivatives,[4] or the use of enzymatic resolution.[5] An attractive method for the preparation of these compounds would be the hydrogenation of substituted aromatic compounds by heterogeneous catalysis in an enantioselective or diastereoselective approach. In the former, the metallic surface is modified with an adsorbed chiral organic compound. However, there are, to date, only two efficient catalytic systems: the tartaric acid-modified nickel catalysts and the platinum–cinchona alkaloid system. Both of these systems are substrate specific and not directly applicable to aromatic compounds.[6, 7] The interaction between the reactant and the chiral modifier is responsible for the enantioselectivity. However, the major obstacle to the expansion of the applicability of these catalysts, or in developing new catalysts for the asymmetric conversion of other functionalities, is the lack of understanding of the nature and strength of this interaction. Covalent bonding should provide the strongest interaction and the asymmetric induction can then be accomplished with the help of a chiral auxiliary temporarily grafted to the substrate, thus sterically blocking the reaction at one face of the substrate.[8–11] We have already reported the catalytic hydrogenation of unsymmetrically substituted aromatics, such as *o*-toluic acid, by means of chiral auxiliaries, such as proline alkyl esters.[12] The asymmetric reaction of (*S*)-methyl-*N*-(2-methylbenzoyl)proline ester with supported Rh and Ru catalysts yielded the corresponding *cis* cyclohexyl hydrogenated products with $de \leq 68\%$. The *de* and configuration were found to be remarkably dependent on the nature of the metal, the support and on the presence of the bulky achiral amine (ethyldicyclohexylamine = EDCA).[12] Ranade et al. reported the diastereoselective hydrogenation of anthranilic acid[13, 14] and of *o*-toluidine covalently bonded to (*S*)-proline. Diastereoselectivities of up to 96% were reported for the former, probably as a consequence of the rigidity of the substrate; however, the yield was moderate on account of the large amount of the *trans* compounds. The best *de* for the hydrogenation of the aromatic amine was 57%. The diastereoselectivity was also shown to be dependent on the nature of the metal (Rh or Ru), the support and the process conditions. Simultaneously, Tungler et al.[15] and Besson et al.[16] described the diastereoselective hydrogenation of pyridine derivatives with proline as the chiral auxiliary ligand over metallic supported catalysts.

[a] Dr. M. Besson, Dr. F. Delbecq, Dr. P. Gallezot, Dr. S. Neto, Dr. C. Pinel
Institut de Recherches sur la Catalyse-CNRS
2, Avenue Albert Einstein, 69626 Villeurbanne Cedex (France)
Fax: (+33) 4-7244-5399
E-mail: mbesson@catalyse.univ-lyon1.fr, pinel@catalyse.univ-lyon1.fr

  0947-6539/00/0606-0949 $ 17.50+.50/0

Other chiral auxiliaries with a structure close to proline (prolinol, (*S*)-(2-pyrrolidinylmethyl)pyrrolidine, (*R*)-pantolactone) were screened for the hydrogenation of *o*-toluic acid, but their diastereoselectivity was less than that of proline.[17] We recently reported[18] that high selectivities ($\leq 95\%$) could be achieved by the use of (*S*)-pyroglutamic acid methyl ester as the chiral auxiliary. The present study was designed to provide a better understanding of the origin of the asymmetry in this reaction. In order to get a molecular picture of the adsorption–hydrogenation step and to obtain information on the reaction mechanism, molecular modelling and NMR analyses were performed along with an X-ray structure determination of the molecule. Additionally, the influence of the nature of the ester group (Et, *i*Pr, *t*Bu, *n*-octyl) has been studied.

Results

Identification of the reaction products: The asymmetric hydrogenation of the aromatic substrate **1**, formed by covalent bonding of *o*-toluic acid and alkyl pyroglutamate in ethanol at room temperature and under 5 MPa hydrogen pressure, gave four cyclohexane diastereoisomers: the *cis* isomers **3a** and **3b** and the *trans* isomers **4a** and **4b** (Scheme 1).

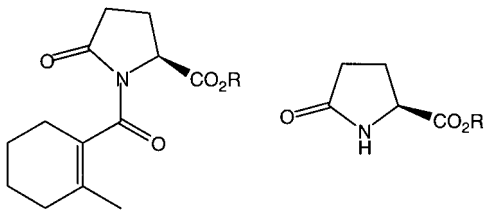
For the hydrogenation of the esters *i*Pr, *t*Bu and *n*-octyl, gas chromatography (GC) was adequate for the separation of the four isomers. The synthesis of (*S*)-octyl-*N*-(2-methyl cyclohexane carbonyl)pyroglutamate allowed the assignment of the *cis* and *trans* isomers by the measurement of the optical rotation in ethanol of a sample that contained no *trans*-hydrogenated products. A rotation ($[\alpha]_D < 0$) in the same sense as that of (1*S*,2*R*)-2-methyl cyclohexane carboxylic acid ($[\alpha]_D^{25} = -5.2$, $c = 1$ in EtOH)[19] was observed, which suggested that the major hydrogenated isomer was (−)-(1*S*,2*R*,2′*S*)-methyl-*N*-(2-methylbenzoyl)pyroglutamate **3b**.

In the case of the methyl and ethyl esters, the four alicyclic isomers were not all separated by GC: only three peaks were detected and were subsequently assigned.[20]

The *de* of the *cis* isomers was defined by Equation (1), which uses the relative percentages of the chromatographic areas of the two peaks assigned to **3a** and **3b**.

$$de = [(\%\,\mathbf{3a} - \%\,\mathbf{3b})/(\%\,\mathbf{3a} + \%\,\mathbf{3b})] \times 100 \quad (1)$$

In addition to the products described above, some other peaks were detected during the course of the reaction. One was attributed to the alkyl pyroglutamate **5**, formed by hydrolysis of the amide bond in the aromatic compound. The



2 **5**

presence of the cyclohexenic intermediate **2** was also established by comparison with a reference prepared by an alternative route. Similar compounds have been also observed for the hydrogenation of the (*S*)-methyl-*N*-(2-methylbenzoyl)proline ester.[12] The remaining products could not be identified unambiguously, but they were shown to have no influence on the diastereoselectivity.

The selectivity of the cyclohexanoic compound for the hydrogenation reaction is given by Equation (2). Typically, a low selectivity reflects the formation of a large amount of side-products. As a result of the conversion of the C=C intermediate, the selectivity increases slightly after total conversion of the aromatic ring.

$$S = [\%\,(\mathbf{3a} + \mathbf{3b} + \mathbf{4a} + \mathbf{4b})/\%\ \text{conversion}\,\mathbf{1}] \times 100 \quad (2)$$

Hydrogenation of (*S*)-methyl-*N*-(2-methylbenzoyl)pyroglutamate over rhodium catalysts: Figure 1 gives the product

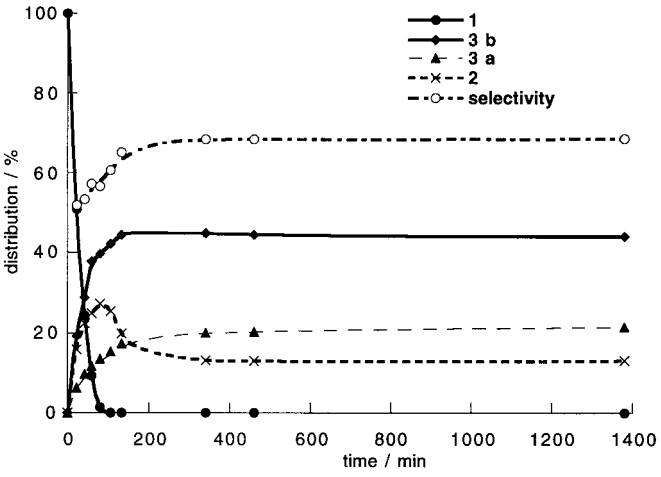
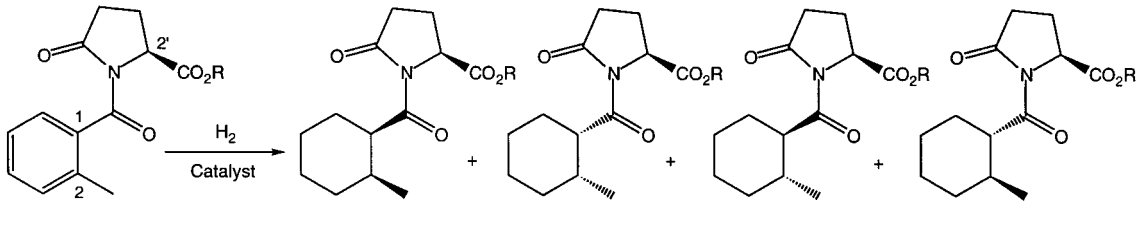


Figure 1. Distribution of the products as a function of time for the hydrogenation of **1** (R = Me) over 3.6% Rh/C. Reaction conditions: 2.27 mmol **1**, 0.105 mmol Rh, 130 mL ethanol, room temperature, 5 MPa hydrogen.



Scheme 1. Diastereoselective hydrogenation of (*S*)-alkyl-*N*-(2-methylbenzoyl)pyroglutamates.

0947-6539/00/0606-0950 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 6

distribution as a function of time for the hydrogenation of (*S*)-methyl-*N*-(2-methylbenzoyl)pyroglutamate over a 3.6 wt% Rh/C catalyst. The cyclohexane derivatives **3a** and **3b**, which result from a *cis* hydrogenation of the aromatic ring, were detected in high proportions. Throughout the reaction, the *de* was 50% in favour of **3b** and was constant with the conversion of the aromatic substrate. The cyclohexenic compound **2** was formed with a maximum yield of 27% and was consecutively hydrogenated to **3a**, so that the *de* decreased progressively to 35%. The percentage of *trans* diastereoisomers formed did not exceed 5%.

While in the case of the methyl prolinate auxiliary, the hydrogenation of the cyclohexenic compound was total,[12] in the case of the pyroglutamate auxiliary, the reaction stopped although 13% of compound **2** still remained. Allowing the reaction to proceed for an additional period of 16 h did not result in any further conversion. This may possibly be the result of the steric hindrance of the tetrasubstituted double bond, which would significantly inhibit the approach of **2** towards the metallic surface. Molecular modelling of this intermediate is underway to confirm this hypothesis. In a similar study of the hydrogenation of (*S*)-proline-modified anthranilic acid on Rh and Ru catalysts, a lower rate of hydrogenation of the cyclohexenic intermediate, relative to the aromatic substrate, was also observed.[13] Methyl pyroglutamate, formed by hydrogenolysis of the amide bond in the aromatic compound, appeared from the beginning of the reaction and attained its maximum (9% chromatographic area) at 100% conversion of **1**. Toluic acid, which is formed during this hydrolysis process, may also poison the catalyst. Because of the presence of many by-products, the selectivity of the reaction in favour of the cyclohexanoic compound was modest: from an initial 52% up to 65% after partial reduction of **2** to **3a** and **3b**.

A bulky amine (ethyldicyclohexylamine, EDCA), which was found to have a beneficial effect on the diastereoselectivity during the hydrogenation of (*S*)-methyl-*N*-(2-methylbenzoyl)proline ester,[12] was added to the reaction medium (molar ratio EDCA/Rh = 2). The product distribution obtained is shown in Figure 2. As expected (and as previously observed[12]), the initial reaction rate decreased (4.3 instead of 23.5 $mol\,h^{-1}\,mol_{Rh}^{-1}$); this was caused by the partial covering of the rhodium particles by the amine. The catalyst then deactivated rapidly and the reaction ceased after 60% conversion. However, with the addition of EDCA, the diastereoselectivity was improved to 91% in favour of the same configuration **3b**. The *de* was also constant with conversion of **1**. The semi-hydrogenated compound **2** was formed with a maximum yield of 3.5% compared with 27% on the same catalyst without the amine EDCA. No *trans* isomers were detected; this was confirmed by the hydrolysis of the hydrogenated solution and the analysis of the 2-methylcyclohexane carboxylic acids obtained. The selectivity of the reaction for the cyclohexane isomers was improved to 85%. The amount of methyl pyroglutamate was only 3% (compared with 9% in the absence of amine) and the other by-products were negligible. The origin of the poisoning observed in this reaction is not clear, but it may be caused by the presence of EDCA, which may react with by-products and yield poisoning compounds.

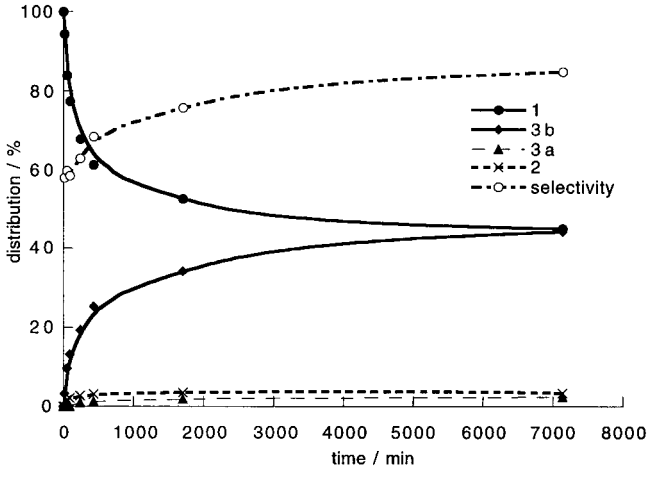


Figure 2. Distribution of products as a function of time for the hydrogenation of **1** (R = Me) over 3.6% Rh/C in the presence of EDCA. Reaction conditions: 2.27 mmol **1**, 0.105 mmol Rh, 0.22 mmol EDCA, 130 mL ethanol, room temperature, 5 MPa hydrogen.

The distribution of products over 3.7 wt% Rh/Al_2O_3 catalyst is given in Figure 3. As previously observed in the case of the methyl prolinate,[15] a great improvement in the diastereoselectivity was obtained by the use of an alumina

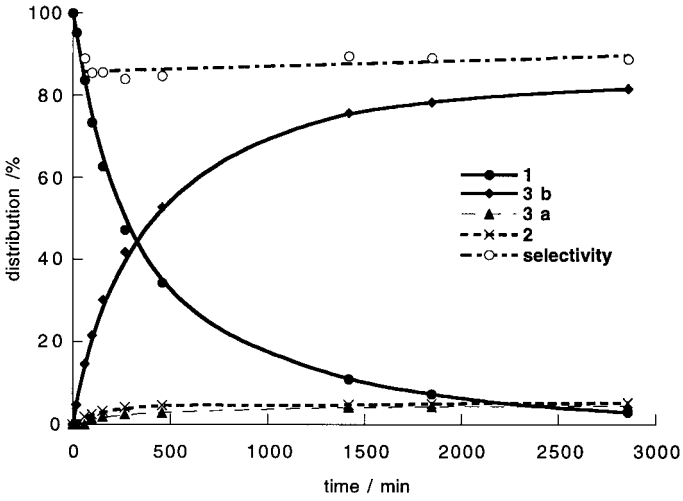


Figure 3. Distribution of products as a function of time for the hydrogenation of **1** (R = Me) over 3.7% Rh/Al_2O_3. Reaction conditions: 2.27 mmol **1**, 0.108 mmol Rh, 130 mL ethanol, room temperature, 5 MPa hydrogen.

support rather than activated carbon. Indeed, although the reaction rate was seven times lower (3.3 $mol\,h^{-1}\,mol_{Rh}^{-1}$ compared with 23.5 $mol\,h^{-1}\,mol_{Rh}^{-1}$), the *de* was 90% in favour of **3b**. *Trans* isomers were not observed and the cyclohexenic **2** compound was formed with a yield of 5%. Only 6% methyl pyroglutamate at its maximum was detected as a by-product. Thus, a very selective reaction was achieved (>90% for the cyclohexane isomers). A decrease in the reaction rate was observed after 50% conversion of **1**. The reason for this deactivation is unclear, but it is probably caused by some modifications of the metallic surface (i.e., change of morphology or the oxidation state). Indeed, as

reported earlier for XPS studies of the catalyst in the hydrogenation of the prolinate derivative of *o*-toluic acid[12], and as observed by Ranade et al[14] in EXAFS and XANES studies, the rhodium catalyst loses its activity when it is prereduced, or reduced during the course of the experiment.

The addition of the amine to 3.7 wt % Rh/Al_2O_3, in a molar ratio EDCA/Rh = 2, slightly decreased the initial reaction rate (2 $mol\,h^{-1}\,mol_{Rh}^{-1}$), but further improved the diastereoselectivity to $\leq 95\,\%$ in favour of **3b**. No *trans* product and very low amounts of cyclohexenic compound **2** were formed.

Influence of the nature of the ester group over the rhodium catalysts: To check whether the diastereoselectivity showed a dependence on the nature of the substituent R in the pyroglutamate ester, the hydrogenation of the substrate **1** (R = Et, *i*Pr, *n*-octyl and *t*Bu) was investigated over the Rh/C and Rh/Al_2O_3 catalysts, with and without EDCA. For both rhodium catalysts, and with all the substituted esters, the product distributions as a function of time were very similar to those obtained with the methyl ester. Complete conversion of **1** could be obtained with Rh/C in the absence of the amine; the conversion was 50–80 % in the other cases. An example is given for the hydrogenation of *N*-(2-methylbenzoyl)-(*S*)-*tert*-butyl pyroglutamate in the presence of Rh/C (Figure 4). The data are summarised in Table 1.

Without EDCA (Figure 4a), the aromatic substrate **1** (R = *t*Bu) was rapidly converted into the *cis* and *trans* alicyclic compounds and the cyclohexenic compound **2**. The latter attained a maximum at 100 % conversion of **1** and was subsequently hydrogenated; however, as observed with the methyl ester, the reaction stopped and the percentage of **2** remained constant, even after a period of 50 hours. In the presence of EDCA (Figure 4b), the reaction was much slower and although the substrate was not totally hydrogenated, the *de* improved from 66 to 92 %.

As regards the diastereoselectivity data, it can be seen from Table 1 that the *de* on Rh/C without amine increased with the bulkiness of the R group of the ester: Me (35 %) < Et ≈ *i*Pr ≈ *n*-octyl < *t*Bu (60 %). The maximum amount of semi-hydrogenated **2** formed was almost the same (≈25 %) in all experiments. The addition of EDCA to the reaction medium in the presence of Rh/C improved the *de* (90–92 %).

In the absence of the amine, significantly higher diastereoselectivities (*de* = 88–90 %) could be achieved on Rh/Al_2O_3 as compared with the Rh/C catalyst (35–60 %). In the presence of the amine (EDCA/Rh = 1.5–2), the *de* was slightly improved and was not dependent on the size of the ester group. The best *de* found was 96 % in favour of **3b**, for the hydrogenation of the octyl ester.

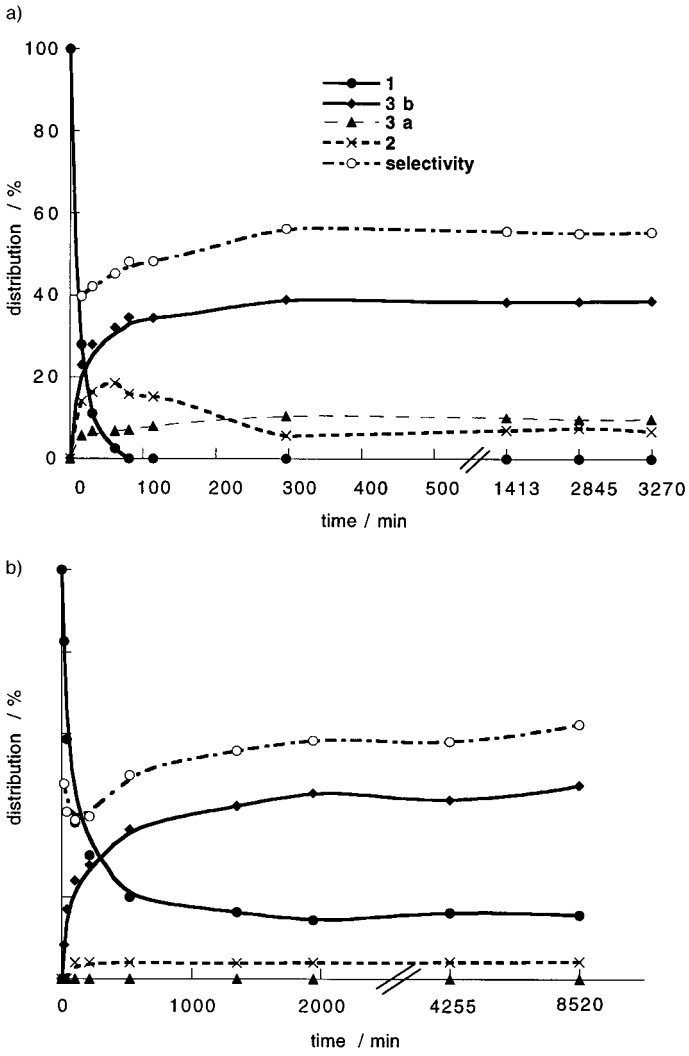


Figure 4. Product distribution as a function of time for the hydrogenation of **1** (R = *t*Bu) in the presence of Rh/C. Reaction conditions: 2.27 mmol **1**, 0.105 mmol Rh, 130 mL ethanol, room temperature, 5 MPa hydrogen, a) without amine, b) EDCA/Rh = 1.5.

Influence of the formation of the by-products on the selectivity: Although the by-products formed were not considered in the measurement of the diastereoselectivity, some tendencies may be noted as regards the selectivity in alicyclic compounds and the amount of alkyl pyroglutamate formed. The data obtained are collected in Table 2.

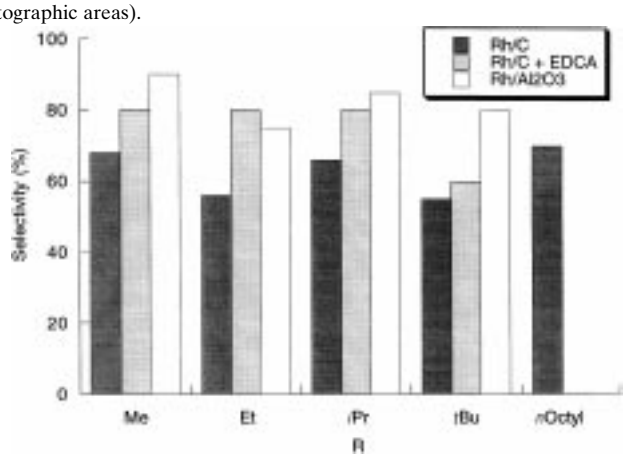
Table 1. Data for the hydrogenation of **1** over 3.6 % Rh/C and 3.7 % Rh/Al_2O_3.

	Rh/C		Rh/C + EDCA		Rh/Al_2O_3		Rh/Al_2O_3 + EDCA	
R in **1**	*de* [%][a]	% **2**[a]	*de* [%]	% **2**	*de* [%]	% **2**	*de* [%]	% **2**
Me	50 (max) – 35	27 (max) – 13	91	4	90	5	94	3.5
Et	65 (max) – 46	32 (max) – 21	90	3	88	5	89	2.5
*i*Pr	56 (max) – 44	22 (max) – 10	90	6	90	5	94	2.5
*t*Bu	66 (max) – 60	18 (max) – 7	92	4	> 90	4	95	2.7
n-octyl	58 (max) – 53	27 (max) – 10	–	–	–	–	96	2.5

[a] From the beginning of the reaction, **1** was hydrogenated mainly to *cis*-**3a** and *cis*-**3b** with a *de* in favour of **3b** which attained a maximum at 100 % conversion of **1**. The intermediate **2** was then hydrogenated preferentially to **3a** with, as a consequence, a decrease in the *de*. The values are given at maximum and at the plateau.

0947-6539/00/0606-0952 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 6

Table 2. Selectivity for the cyclohexanoic derivatives and amount of alkyl pyroglutamate formed during hydrogenation of **1** (percentages of chromatographic areas).



R	Alkyl pyroglutamate [%] Rh/C[a]	Rh/C + EDCA	Rh/Al_2O_3
Me	9–4	3	6
Et	9–5	3	13
*i*Pr	10–4	7	11
*t*Bu	25–10	15	20
n-octyl	13–7	–	–

[a] Percentages at maximum (at almost complete conversion of **1**) and at the end of the reaction.

The by-products detected were alkyl pyroglutamate esters and a compound with a GC retention time very close to that of the semi-hydrogenated compound **2** (i.e., in the case of the methyl ester, compounds were detected at 14.53 and 14.83 min, compared with 14.63 min for compound **2**). We verified that none of these by-products corresponded to a transesterification reaction with the ethanol solvent, but their structures could not be elucidated. Owing to the formation of these by-products and the formation of compound **2**, which is not totally hydrogenated, the selectivity for cyclohexanoic derivatives was in the range 55–90%.

In all experiments, alkyl pyroglutamate was formed by hydrolysis, with a maximum percentage of 25% attained with the *tert*-butyl ester over Rh/C. This compound was formed continuously from the aromatic substrate until its complete conversion. Subsequently, its concentration in the reaction medium decreased in all experiments performed with Rh/C without amine, while its concentration remained constant in the other experiments (Table 2). The addition of an amine to Rh/C or Rh/Al_2O_3 limited the extent of that hydrolysis.

Considering all the esters, the use of Rh/C yielded numerous by-products. It is noteworthy that both the disappearance of alkyl pyroglutamate and the formation of these by-products occurred only over the Rh/C catalyst used without amine. One might assume that these two phenomena correspond to the occurrence of the same type of modification of the auxiliary, whether it is bound to the surface or to the aromatic ring or not. The carbon support might be responsible for that transformation.

Hydrogenation of methyl ester over ruthenium catalysts: The initial reaction rate, maximum percentage of intermediate **2** formed and *de* obtained with the different Ru catalysts tested are given in Table 3.

The hydrogenation was quasi-quantitative in each case, but lower reaction rates were obtained when catalysts on oxide supports were used. After a rapid initial disappearance of substrate **1** up to 75% conversion, the reaction rate decreased. The semi-hydrogenated compound **2** was reduced at a low rate. High diastereoselectivities of 74%, 85% and 78% were achieved with Ru/C, Ru/Al_2O_3 and Ru/TiO_2 catalysts, respectively, the major product being **3b**. These *de* values were obtained from the start of the reaction and remained constant up to complete conversion. Only 3–6% methyl pyroglutamate was formed and no other by-products were detected.

Table 3. Hydrogenation of **1** (R = Me) on supported ruthenium catalysts.

	Initial reaction rate [$mol\,h^{-1}\,mol_{Ru}$]	Max. yield **2** [%]	*de* at max. **2** [%] (conversion of **1** [%])
5% Ru/C	14.4	19	74 (99)
5% Ru/C + EDCA	4.8	10	83 (61)
3.5% Ru/Al_2O_3	2.6	11	85 (61)
2.8% Ru/TiO_2	1.7	19	78 (70)

The addition of EDCA to the Ru/C catalyst (EDCA/Ru = 2.2) slowed down the reaction by a factor of three ($4.8\,mol\,h^{-1}\,mol_{Ru}^{-1}$ compared to $14.4\,mol\,h^{-1}\,mol_{Ru}^{-1}$), but the diastereoselectivity improved slightly from 74% to 81%.

Discussion

Preferred conformation of substrate 1: In order to show the influence of several factors described on the diastereoselectivity, the structure of the aromatic substrate was determined by different techniques, which included molecular modelling, ^1H NMR spectroscopy and X-ray structure determination.

Molecular-modelling calculations were carried out in order to predict the major conformations of **1** (R = Me), by allowing rotation about C2–C1, C1–N, C12–C13 and C13–O3 (Figure 5). As a result of these investigations, four stable

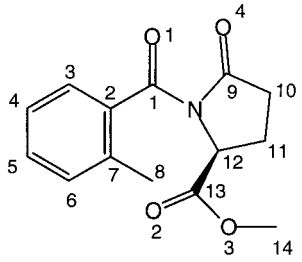


Figure 5. Numbering scheme for **1**.

conformations were found. Figure 6 shows the ball-and-stick drawings of these lowest-energy conformations as well as the respective corresponding calculated energies.

The geometry of the four isomers is very similar to that obtained by conformational analysis of the *o*-toluic acid/prolinate substrate. The main difference between the conformers is the position of the pyroglutamate group with

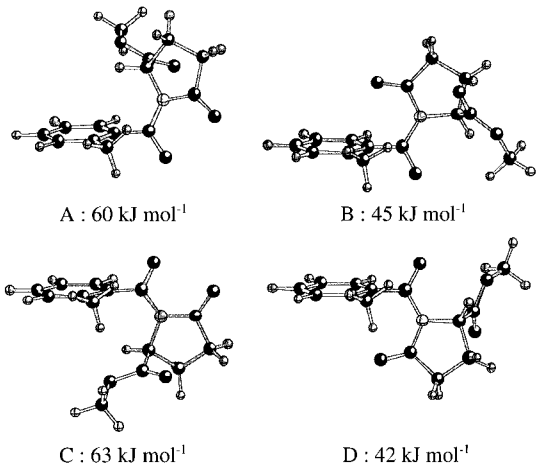


Figure 6. Conformers of substrate **1** after geometry optimisation.

respect to the aromatic ring. In conformers **A** and **B** the chiral auxiliary is situated above the aromatic ring, while in conformers **C** and **D** this moiety is situated below. The pairs of conformers (**A**+**B** and **C**+**D**) vary by rotation of the pyroglutamate about the C1–N bond; this results in the auxiliary being directed over or pointed away from the aromatic ring. The molecular-modelling calculations of the prolinate derivative revealed the existence of four energetically equivalent isomers; this was also confirmed by ^{1}H NMR spectroscopy. So, in contrast to the calculation performed previously for the prolinate auxiliary,[12] these four conformers with the pyroglutamate auxiliary do not have the same calculated energies. The conformer **D** is more stable than the other three by more than 3 kJ mol^{-1}. Thus, we can assume that conformer **D** represents the most probable structure of this substrate.

Figure 7 shows the rotational barriers as a function of the rotation angle about the bond C1–C2. The two energy minima correspond to the isomers **D** and **B**. There are two very high

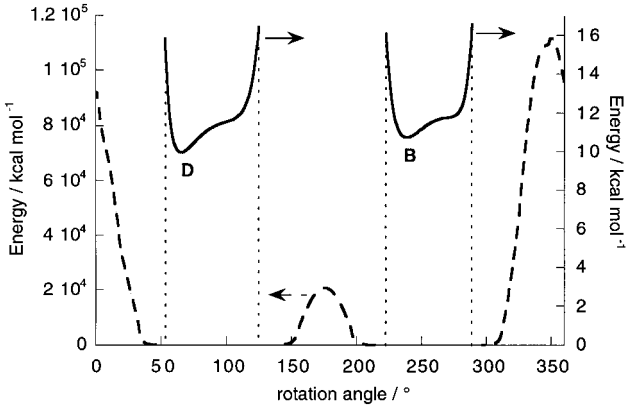


Figure 7. Rotational barriers for the aromatic substrate **1** for rotations around the C2–C1 bond.

energy barriers for total rotation about this bond which changes from one isomer to the other. This is attributed to significant steric hindrances between the oxygen of the amido function (C1=O) and the two *ortho* substitutents of the aromatic ring; namely the hydrogen atom on C3 (Figure 5 and rotation angle ≈180° in Figure 7) and the more bulky methyl group on C7 (Figure 5 and rotation angle ≈360° in Figure 7) which prevent the free rotation about that bond.

Similarly, the energy barrier required for free rotation about the C1–N bond was calculated (Figure 8). This calculation yielded high energy barriers, which are again indicative

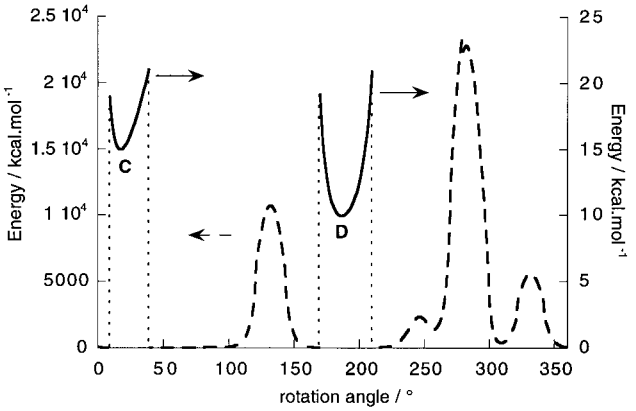


Figure 8. Rotational barriers for the aromatic substrate **1** for rotations around the C1–N bond.

of relatively hindered rotations, mainly as a result of interactions between the aromatic ring and the ester group.

The substrate was crystallised in Et_2O and its crystal structure was determined by X-ray structural analysis (Figure 9).[21] When compared with molecular-modelling calcula-

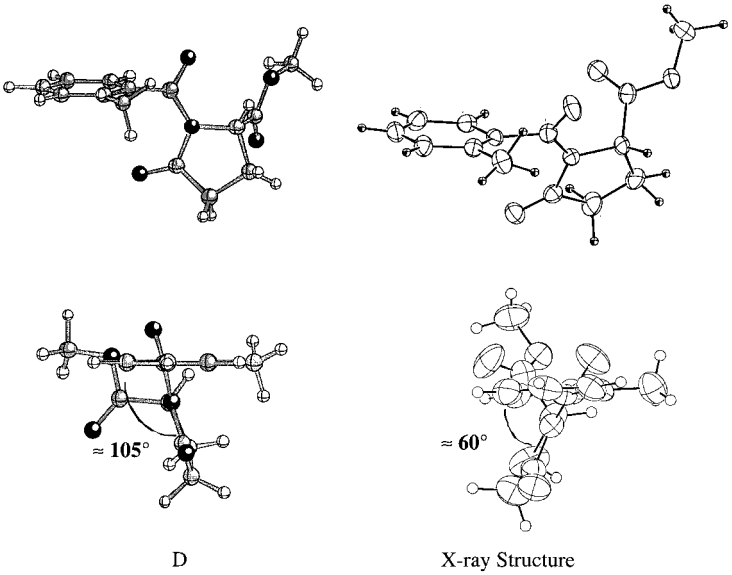


Figure 9. Comparison of the crystallographic form of substrate **1** obtained by X-ray analysis (right) and the most stable conformer obtained by molecular-modelling calculation (left).

tions, the structure obtained is very close to the most stable conformation **D**. The only difference observed is the value of the dihedral angle formed between the average plane of the pyroglutamate ring (C9-C10-C11-C12-N) and the aromatic ring. This is illustrated in Figure 9, with the representation of

0947-6539/00/0606-0954 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 6

the aromatic substrate in profile and the ester group pointing to the back left. From molecular modelling, the aromatic ring shows a deviation of 105° relative to the plane of the pyroglutamate ring, while it is shown to be twisted by 60° in the X-ray analysis. This implies that the oxygen atom O4 attached to the pyroglutamate is oriented towards the aromatic ring in two different directions, either below the C2–C7 bond, or below the C2–C3 bond, as illustrated by the distance between the non-bonded atoms O4 and C3 (3.92 and 2.95 Å, respectively) and O4 and C7 (2.86 and 3.76 Å, respectively). These observed differences can be explained by considering that molecular modelling calculates the energy of the molecule in the gas phase rather than in the solid state. These small differences are not crucial and do not modify the conclusions that can be drawn on the approach of the molecule to the metallic surface. In both cases, one of the faces of the aromatic ring is shielded by the presence of the ligand.

Solution ^{1}H NMR spectrometry confirmed the existence of only one stable conformer. Indeed, in the substrate with the prolinate auxiliary, a splitting was observed in the ^{1}H NMR spectrum attributed to the existence of the substrate in the form of two stable conformers of nearly the same energy in a 80/20 ratio.[12] In contrast, in the ^{1}H spectrum of the pyroglutamate substrate (Figure 10), the line widths were narrow and integrations were assigned unambiguously, which suggests that only one diastereoisomer, or a very rapidly equilibrating mixture of diastereoisomers of **1**, exist in solution at room temperature.

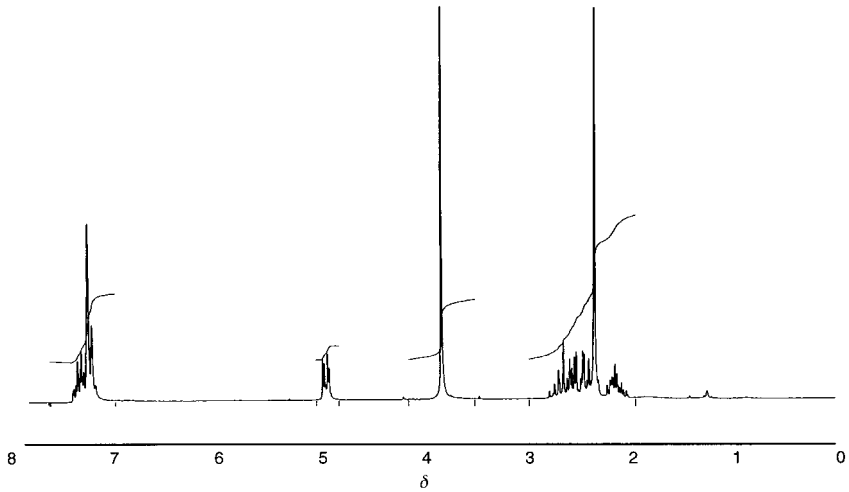


Figure 10. ^{1}H NMR spectrum at 200 MHz of substrate **1** (R = Me).

From the results of the three techniques described above, it may be assumed that substrate **1** presents the molecular structure of conformer **D**.

Interpretation of the selectivity data: Figure 9 shows that one face of the aromatic ring **1** is shielded by the carbonyl group. We now consider the adsorption of the aromatic ring on the metal surface, which generally proceeds by π-bonding. The adsorption of the shielded face of the aromatic ring is unfavourable as a result of steric hindrance. Hence, the aromatic ring can only adsorb at the unshielded face and the *cis* addition of hydrogen on this adsorbed intermediate gives rise to the preferential formation of **3b**; this is in agreement with the experimental results. Indeed, results given in Tables 1 and 3 show that high diastereoselectivities were obtained.

The selectivity data given in Table 1 for the Rh/C and Rh/Al_2O_3 catalysts show that the asymmetric induction is higher than for the alumina-supported catalyst. TEM and XPS studies have shown that in Rh/Al_2O_3, the rhodium particles have a flat morphology and that there are partially oxidised species present.[22] As proposed in the case of prolinate auxiliary,[22] this promoting effect may be attributed to a stronger interaction between the rhodium atoms with a low valence state on alumina and the oxygenated groups of the ester, which optimises the adsorptive effect.

The nature of the ester group in the pyroglutamate was found to have only a small positive effect on the diastereoselectivity (Table 2). This can be easily explained by the observation that in the most stable conformation of the substrate **1** (R = Me), the ester is in an external position relative to the aromatic ring (Figure 9). Therefore, one may expect that the ester will exert only a small steric constraint during adsorption.

With respect to the nature of the metal (rhodium or ruthenium), in the absence of the amine EDCA, a higher diastereoselectivity was observed in the presence of ruthenium supported on active carbon than in the presence of rhodium (74% compared with 50%, in favour of **3b**, Tables 1 and 2). The mode of adsorption of the aromatic substrate onto the unshielded face of the aromatic ring dictates the major configuration of the hydrogenation product. However, as already noted with the prolinate auxiliary,[22] an additional anchoring interaction between the oxygen atoms (ester group and benzoic carbonyl) and the ruthenium metallic surface, which is more electropositive than rhodium, may still promote a preferential adsorption of the molecule onto one specific face. This leads to an enhancement of the diastereoselectivity.

Interestingly, the addition of EDCA to the Rh/C catalysts greatly improved the *de* (Table 1). There is some evidence that the amine molecules adsorb onto the metal surface, so they may exert a supplementary favourable orientating effect. As a result of the competitive adsorption between the substrate and the amine, the conversion of the pyroglutamate was not complete. Thus, the addition of EDCA, in the presence of the ruthenium catalyst only had a weak beneficial effect (Table 3). These findings are supported by our observation of a smaller decrease in the initial reaction rate as the amine was adsorbed onto the catalyst, which indicated a lesser covering of ruthenium by the amine as compared with rhodium on carbon.

Conclusions

Cis-2-methyl cyclohexane carboxylic acids have been prepared with diastereoisomeric excesses of up to 96%. The efficiency of the pyroglutamate auxiliary relative to prolinate is attributed to the presence of the carbonyl group. A combination of molecular-modelling calculations, NMR spectroscopy and X-ray analysis strongly suggest that substrate **1** exists as one single conformation in which one face of the aromatic ring is shielded by the carbonyl group of the pyroglutamate auxiliary. To minimise the steric requirements imposed by the adsorption of the aromatic substrate on the catalyst surface, the adsorption must occur onto the unshielded face; this induces high diastereoselectivities for the hydrogenation of the aromatic ring. In all experiments, the hydrogenated compound with configuration (1*S*,2*R*,2′*S*) was obtained.

A change in the size of the ester groups did not greatly influence the selectivity, since this ester group is located in an outer position relative to the aromatic ring and does not participate much in the adsorption.

A small change in the structure of the chiral auxiliary (pyroglutamic acid versus proline) dramatically improved the *de* of the hydrogenation reaction (max. $\leq$95% and 68%, respectively). Two phenomena are responsible for this higher selectivity: firstly, only one conformer of the substrate is formed during its synthesis and secondly, the additional C=O group significantly increased the steric hindrance of the aromatic face. The pyroglutamate auxiliary should have a large potential for other diastereoselective hydrogenations of aromatic substrates on metal catalysts.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on AC100 and AC200 Bruker spectrometers and referenced to the residual solvent ($CDCl_3$: δH = 7.24, δC = 77). FT-IR spectra were recorded on a Bruker Vector22 apparatus. Elemental analyses were performed at the "Service Central d'Analyse", CNRS. Gas chromatography (GC) was performed on a Shimadzu GC14A apparatus with a J&W DB1701 column (30 m, T_{inj} = 270 °C, T_{det} = 290 °C, T_{oven} = 170 °C: 1 min, then 5 °C min^{-1} up to 260 °C, then 260 °C for 25 min).

Synthesis of the alkylpyroglutamates: Ethyl and octyl pyroglutamates are commercially available. The preparation of the other esters is described below.

(*S*)-Methyl pyroglutamate (5, R = Me): $SOCl_2$ (34 mL, 5 equiv) was added dropwise to a stirred solution of L-pyroglutamic acid (12 g, 0.09 mol) in MeOH (130 mL) under argon at 0 °C. The solution was refluxed for 1.5 h and excess $SOCl_2$ was removed. The residue was distilled (145 °C, 3.5 mbar) to give a pure pale yellow oil (10.2 g, 76%). ^{1}H NMR (100 MHz, $CDCl_3$): δ = 7.5 (s, 1H; N*H*), 3.9 (dd, ^3J(H,H) = 4.4 Hz, 8.2 Hz, 1H; C*H*N), 3.4 (s, 3H; CH_3), 1.7–2.1 (m, 4H; CH_2–CH_2); ^{13}C NMR (25 MHz, $CDCl_3$): δ = 178.4 (C), 172.7 (C), 55.3 (CH_3), 52.0 (CH_2), 29.0 (CH_2), 24.5 (CH_2); IR (film): $\tilde{\nu}$ = 3230 (N–H), 2957 (C–H), 1744 (C=O) cm^{-1}; $[\alpha]_D^{24}$: +10 (c = 6 in methanol); MS (70 eV, E.I.): *m/z* (%): 56, 84 (100), 143 [M^+]; elemental analysis calcd (%) for $C_6H_9O_3N$: C 50.35, H, 6.29, N 9.79; found C 50.06, H 6.16, N 9.74.

(*S*)-*iso*-Propyl pyroglutamate (5, R = *i*Pr): $SOCl_2$ (14 mL, 5 equiv) was added dropwise to a stirred solution of L-pyroglutamic acid (5 g, 0.04 mol) in *i*PrOH (100 mL) under argon at 0 °C and the solution was refluxed for 90 min. Excess $SOCl_2$ and *i*PrOH were removed by filtration. The solid was recrystallised in iPr_2O to yield beige needles (5.6 g, 85%). M.p. 68 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7 (s, 1H; N*H*), 5 (sextet, ^3J(H,H) = 6.2 Hz, 1H; C*H*Me$_2$), 4.15 (m, 1H; C*H*N), 2.5–2.1 (m, 4H; CH_2–CH_2), 1.20 (d, ^3J(H,H) = 6.2, 6H; CH*Me*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 180.0 (C), 171.8 (C), 69.3 (CH), 55.8 (CH_2), 30.7 (CH_2), 24.9 (CH_2), 21.7 (CH_3); IR (film): $\tilde{\nu}$ = 3475 (N–H), 2986 (C–H), 2933 (C–H), 1755 (C=O), 1668 (C=O) cm^{-1}; $[\alpha]_D^{24}$: +6 (c = 5 in methanol); elemental analysis calcd (%) for $C_8H_{13}O_3N$: C 56.14, H 7.60, N 8.19; found C 56.12, H 7.81, N 8.19.

(*S*)-*tert*-Butyl pyroglutamate (5, R = *t*Bu): Perchloric acid 70% (3 mL, 0.7 equiv) was added dropwise to a solution of pyroglutamic acid (12.9 g, 0.1 mol) in *tert*-butyl acetate (185 mL, 11 equiv). The solution was stirred overnight at room temperature then $NaHCO_3$ was added slowly until pH 6 was reached. The aqueous layer was extracted with Et_2O (100 mL) then AcOEt (100 mL). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum to give a yellowish powder which was recrystallised from Et_2O to yield white crystals (10.5 g, 57%). M.p. 102 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7 (s, 1H; N*H*); 4.1 (m, 1H; C*H*N), 2.0–2.5 (m, 4H; CH_2–CH_2), 1.4 (s, 9H; 3 CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.3 (C), 171.3 (C), 82.2 (C), 56.3 (CH), 29.5 (CH_2), 28.0 (CH_3), 24.9 (CH_2); IR (film): $\tilde{\nu}$ = 3260 (N–H), 2989 (C–H), 2969 (C–H), 2946 (C–H), 1737 (C=O), 1679 (C=O) cm^{-1}; $[\alpha]_D^{24}$: +11 (c = 3 in methanol); elemental analysis calcd (%) for $C_9H_{15}O_3N$: C 58.38, H 8.11, N 7.57; found C 58.67, H 8.20, N 7.51.

Synthesis of (*S*)-alkyl-*N*-(2-methylbenzoyl)pyroglutamates (1): The synthesis of **1** (R = Me) is described below as a representative example.

(*S*)-Methyl-*N*-(2-methylbenzoyl)pyroglutamate (1, R = Me): Triethylamine (19.5 mL, 2 equiv) and followed by *o*-toluoyl chloride (11 mL, 1.2 equiv) were added dropwise to a stirred solution of (*S*)-methyl pyroglutamate (**5** (R = Me); 10 g) in toluene (130 mL) at 0 °C under argon. The mixture was stirred for 5 h at 80 °C and then cooled to room temperature. The organic layer was treated with saturated $NaHCO_3$ (2 × 20 mL), NaCl (20 mL), then dried ($MgSO_4$) and concentrated to give a yellowish powder. The product was recrystallised from Et_2O to yield white needles (15 g, 82%). M.p. 108 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.2 (m, 4H; CH_{arom}), 5.0 (dd, ^3J(H,H) = 3.4 Hz, 9.0 Hz, 1H; C*H*COO), 3.8 (s, 3H; COOCH_3), 2.7–2.0 (m, 4H; CH_2–CH_2), 2.4 (s, 3H; ArCH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.0 (C), 171.5 (C), 170.4 (C), 135.5 (C), 135.0 (C), 130.4 (CH), 130.2 (CH), 126.9 (CH), 125.3 (CH), 57.9 (CH), 52.8 (CH_3), 31.6 (CH_2), 21.6 (CH_2), 19.2 (CH_3); IR (film): $\tilde{\nu}$ = 3480 (N–H), 3041 (C–H), 2960 (C–H), 2928 (C–H), 1751 (C=O), 1679 (C=O) cm^{-1}; t_R = 16.9 min; MS (70 eV, EI): *m/z* (%): 91, 119 (100%), 261 [M^+]; $[\alpha]_D^{24}$: −29 (c = 1 in chloroform); elemental analysis calcd (%) for $C_{14}H_{15}O_4N$: C 64.37, H 5.75, N 5.36; found C 64.62, H 5.77, N 5.32.

(*S*)-Ethyl-*N*-(2-methylbenzoyl)pyroglutamate (1, R = Et): Yield: 47%; white crystals; m.p. 52 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.45 (m, 4H; CH_{arom}.), 5.0 (m, 1H; C*H*COO), 4.2 (q, ^3J(H,H) = 7.0 Hz, 2H; COOCH_2), 2.8–2.0 (m, 4H; CH_2–CH_2), 2.3 (s, 3H; ArCH_3), 1.3 (t, ^3J(H,H) = 7.0 Hz, 3H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.3 (C), 171.3 (C), 170.6 (C), 135.7 (C), 135.3 (C), 130.6 (CH), 130.4 (CH), 127.1 (CH), 125.6 (CH), 62.2 (CH_2), 58.3 (CH), 31.9 (CH_2), 21.9 (CH_2), 19.5 (CH_3), 14.4 (CH_3); IR (film): $\tilde{\nu}$ = 3629 (N–H), 3495 (N–H), 3064 (C–H), 2983 (C–H), 2935 (C–H), 1754 (C=O), 1681 (C=O) cm^{-1}; t_R = 18.2 min; MS (70 eV, EI): *m/z* (%): 91, 119 (100%), 202, 275 [M^+]; $[\alpha]_D^{24}$: −35 (c = 1 in chloroform); elemental analysis calcd (%) for $C_{15}H_{17}O_4N$: C 65.38, H 6.18, N 5.09; found C 65.91, H 6.32, N 4.99.

(*S*)-*iso*-Propyl-*N*-(2-methylbenzoyl)pyroglutamate (1, R = *i*Pr): Yield: 70%; white powder; m.p. 70 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30 (m, 4H; CH_{arom}.), 5.1 (sextet, ^3J(H,H) = 6.2 Hz, 1H; COOC*H*), 4.9 (dd, ^3J(H,H) = 3.5 Hz, 8.9 Hz, 1H; C*H*COO), 2.7–2.0 (m, 4H; CH_2–CH_2), 2.4 (s, 3H; ArCH_3), 1.3 (d, ^3J(H,H) = 6.2 Hz, 3H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.1 (C), 170.6 (C), 170.5 (C), 135.4 (C), 135.2 (C), 130.3 (CH), 130.1 (CH), 126.9 (CH), 125.3 (CH), 69.6 (CH_2), 58.3 (CH), 31.6 (CH_2), 21.8 (CH_2), 21.7 (CH_3), 21.6 (CH_3), 19.2 (CH_3); IR (film): $\tilde{\nu}$ = 3475 (N–H), 3054 (C–H), 2986 (C–H), 2933 (C–H), 1755 (C=O), 1668 (C=O) cm^{-1}; $[\alpha]_D^{24}$: −41 (c = 1 in chloroform); elemental analysis calcd (%) for $C_{16}H_{19}O_4N$: C 66.44, H 6.57, N 4.84; found C 66.60, H 6.62, N 4.84.

(*S*)-*tert*-Butyl-*N*-(2-methylbenzoyl)pyroglutamate (1, R = *t*Bu): Yield: 87%; white powder; m.p. 86 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30 (m, 4H; CH_{arom}), 4.8 (dd, ^3J(H,H) = 3.5 Hz, 8.9 Hz, 1H; C*H*COO), 2.8–2.0 (m, 4H; CH_2–CH_2), 2.4 (s, 3H; ArCH_3), 1.5 (s, 9H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.2 (C), 170.3 (C), 170.1 (C), 135.4 (C), 135.2 (C), 130.3 (CH), 130.0 (CH), 126.9 (CH), 125.2 (CH), 82.2 (C), 58.8 (CH), 31.6

0947-6539/00/0606-0956 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 6

(CH_2), 21.5 (CH_2), 19.2 (CH_3); IR (film): $\tilde{\nu}$ = 3500 (N–H), 3300 (N–H), 3050 (C–H), 2977 (C–H), 2950 (C–H), 1751 (C=O), 1680 (C=O) cm^{-1}; $[\alpha]_D^{24}$: −50 (c = 1 in chloroform); elemental analysis calcd (%) for $C_{17}H_{21}O_4N$: C 67.33, H 6.93, N 4.62; found C 67.76, H 7.02, N 4.72.

(*S*)-Octyl-*N*-(2-methylbenzoyl)pyroglutamate (1, R = *n*-octyl): Yield: 67%; brown oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30 (m, 4H; CH_{arom}), 4.9 (dd, ^3J(H,H) = 3.1, 8.9 Hz, 1H; C*H*COO), 4.2 (t, ^3J(H,H) = 6.6 Hz, 2H; COOCH_2), 2.7–2.0 (m, 4H; CH_2–CH_2), 2.4 (s, 3H; ArCH_3), 1.6 (m, 2H; CH_2), 1.3 (m, 10H; 5CH_2), 0.9 (m, 3H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.8 (C), 170.8 (C), 170.0 (C), 135.2 (C), 134.9 (C), 130.0 (CH), 129.8 (CH), 126.7 (CH), 125.0 (CH), 63.7 (C), 57.8 (CH), 31.5 (CH_2), 21.3 (CH_2), 28.9 (CH_2), 28.3 (CH_2), 25.5 (CH_2), 22.4 (CH_2), 22.3 (CH_2), 21.4 (CH_2), 18.9 (CH_3), 13.8 (CH_3); t_R = 32.2 min; MS (70 eV, EI): m/z (%): 91, 119 (100%), 202, 359 [M^+]; $[\alpha]_D^{24}$: −23 (c = 1 in chloroform); elemental analysis calcd (%) for $C_{21}H_{29}O_4N$: C 70.19, H 8.08, N 3.90; found C 69.82, H 8.20, N 3.31.

2-Methyl-1-cyclohex-2-ene carboxylic acid: Ethyl 2-methyl-1-cyclohex-2-ene carboxylate (2 g, 12 mmol) was added to a solution of KOH (1.13g, 1.7 equiv) in MeOH/H_2O (6:1, 12 mL).[23] The solution was refluxed for 4 H, then cooled to room temperature and washed with Et_2O (2 × 20 mL). The aqueous phase was acidified with HCl (pH 1) and extracted with Et_2O (4 × 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to yield a white solid (1.4 g, 82%). M.p. 80 °C; ^{1}H NMR (100 MHz, $CDCl_3$): δ = 11.9 (s, COO*H*), 2.4–1.4 (m, 8H; CH_2), 2.04 (s, 3H; CH_3).

(*S*)-Methyl-*N*-(2-methyl-cyclohex-1-enecarbonyl)pyroglutamate (2): $SOCl_2$ (0.2 mL, 4 equiv) was added to a solution of 2-methyl-1-cyclohex-2-ene carboxylic acid (100 mg, 7 mmol) in $CHCl_3$ (2 mL) at 0 °C under argon. The solution was stirred overnight and the solvents were removed under vacuum. The crude product was used in the next step without purification. (*S*)-Methyl-*N*-(2-methylbenzoyl)pyroglutamate (**1** (R = Me), 100 mg, 7 mmol) in toluene (7 mL) was placed in a three-necked round-bottomed flask. Triethylamine (0.3 mL, 3 equiv) followed by the crude acid chloride were added and the mixture was stirred for 3 h at 70 °C. The solution was washed with $NaHCO_3$ (2 × 10 mL) then NaCl (2 × 10 mL), dried ($MgSO_4$) and concentrated under vacuum to yield 100 mg of a brownish oil. The mixture was analysed by GC/MS without purification; t_R = 14.6 min; MS (70 eV, EI): m/z (%): 79, 122 (100), 265 [M^+].

(*S*)-Methyl-*N*-(2-methyl-cyclohexanecarbonyl)pyroglutamate (3a,b/4a,b; R = Me) (synthetic route): $SOCl_2$ (4 mL, 4 equiv) was added dropwise to a solution of a commercial mixture (*cis*:*trans* = 85:15) of 2-methyl-cyclohexane carboxylic acid (2 g, 14 mmol) in $CHCl_3$ (10 mL) at 0 °C under argon. The mixture was stirred overnight at room temperature and the solvents were removed. The yellow oil was used without purification in the next step. (*S*)-Methyl-*N*-(2-methylbenzoyl)pyroglutamate (**1** (R = Me), 2 g, 14 mmol) in toluene (20 mL) was placed in a three-necked round-bottomed flask. Triethylamine (3.8 mL, 2 equiv) followed by the crude acid chloride were added and the mixture was stirred for 3 h at 80 °C. The solution was washed with $NaHCO_3$ (2 × 10 mL) then NaCl (2 × 10 mL), dried ($MgSO_4$) and concentrated under vacuum to yield 2 g of a brownish oil. The GC/MS analysis of the crude product showed 3 signals (t_R = 13.2, 13.7, 14.3 min, respective integration: 11:50:39). Recrystallisation from cyclohexane yielded enriched *cis* isomer (respective integration: 7:87:6). Selected data of the main compound [**3b** (R = Me)]: ^{1}H NMR (100 MHz, $CDCl_3$): δ = 4.68 (dd, ^3J(H,H) = 2.4 Hz, 9.3 Hz, 1H; C*H*COO), 3.74 (s, 3H; COOCH_3), 2.8–1.3 (m, 14H), 0.83 (d, ^3J(H,H) = 7.1 Hz, 3H; CH_3); ^{13}C NMR (25 MHz, $CDCl_3$): δ = 176.4 (C), 173.8 (C), 171.9 (C), 135.4 (C), 58.3 (CH), 52.6 (CH_3), 32.3 (CH_2), 31.9 (CH_2), 30.8 (CH), 24.2 (CH_2), 23.4 (CH_2), 21.6 (CH_2), 21.2 (CH_2), 15.2 (CH_3); MS (70 eV, EI): m/z (%): 124, 144 (100), 185, 198, 208, 267 [M^+].

Catalysts: The catalysts used in the hydrogenation were 3.6% Rh/C (Aldrich 20,616-4), 3.7% Rh/Al_2O_3 (Aldrich 37,971-9), 5% Ru/C (Aldrich 28,147-6) and 3.5% Ru/Al_2O_3 (Aldrich 22,853-2). 2.8% Ru/TiO_2 was supplied by Engelhard (Q500-069D). High-resolution electron microscopy showed that most of the rhodium and ruthenium particles in the catalysts were in the size range 1–4 nm and homogeneously distributed inside the grains. The ruthenium catalysts were pre-treated at 300 °C under hydrogen atmosphere and transferred to the reactor without exposure to air.

Hydrogenation experiments: The hydrogenation of substrate **1** was carried out in a stainless steel autoclave equipped with a magnetically driven turbine stirrer under 50 MPa and at room temperature. Standard experiments used 2.25 mmol of substrate dissolved in 130 ml ethanol. In order to improve the selectivity, some experiments were carried out with the addition of EDCA (ethyldicyclohexylamine). The conversions and selectivities were determined from GC data.

Molecular-modelling calculations: Molecular-modelling calculations were performed using Sybil software. Initial conformational structure for the diastereoisomer was constructed and the geometries were minimised with the MM2 force field. The Cartesian coordinates that were generated were converted to graphics to allow examination from alternative perspectives.

Acknowledgements

The authors thank Prof. René Faure (University Claude Bernard-Lyon 1) for the X-ray structure determination. The Ministry of National Education and Research is acknowledged for a grant (SN).

[1] *The Merck Index*, 12th ed., Merck Research Lab, Merck, **1996**.
[2] S. Hanessian, *Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon, Oxford, **1984**, p. 163.
[3] J. K. Whitesell, *Chem. Rev.* **1992**, *92*, 953.
[4] P. Thom, P. Kocienski, K. Jarowicki, *Synthesis*, **1992**, 475.
[5] R. L. Gu, C. J. Sih, *Tetrahedron Lett.* **1990**, *31*, 3287.
[6] Y. Izumi, *Adv. Catal.* **1983**, *32*, 215; T. Ozawa, T. Harada, A. Tai, *Catal. Today* **1997**, *37*, 465.
[7] H. U. Blaser, H. P. Jalett, M. Müller, M. Studer, *Catal. Today* **1997**, *37*, 441; A. Baiker, *Stud. Surf. Sci. Catal.* **1996**, *101*, 51; A. Baiker, H. U. Blaser, in *Handbook of Catalysis, Vol. 5* (Eds.: G. Ertl, H. Knözinger, J. Weitkamp), VCH, Weinheim, **1997**, p. 2442; M. Schürch, T. Heinz, R. Aeschimann, T. Mallat, A. Pfaltz, A. Baiker, *J. Catal.* **1998**, *173*, 187; R. L. Augustine, S. K. Tanielyan, L. K. Doyle, *Tetrahedron: Asymmetry* **1993**, *4*, 1803; J. L. Margitfalvi, E. Tfirst, *J. Mol. Catal.* **1999**, *139*, 81.
[8] K. Harada, *Asymmetric Synthesis*, *Vol. 5*, *Chiral Catalysis*, Academic Press, Orlando, **1985**, p. 345.
[9] M. Besson, C. Pinel, *Topics in Catalysis* **1998**, *5*, 25.
[10] K. Nasar, M. Besson, P. Gallezot, F. Fache, M. Lemaire, in *Chiral Reactions in Heterogeneous Catalysis* (Eds.: G. Jannes, V. Dubois), Plenum, New York, **1995**, p. 141.
[11] C. Exl, E. Ferstl, H. Hönig, R. Rogo-Kohlenprath, *Chirality*, **1995**, *7*, 211.
[12] M. Besson, B. Blanc, M. Champelet, P. Gallezot, K. Nasar, C. Pinel, *J. Catal*. **1997**, *170*, 254.
[13] V. S. Ranade, G. Consiglio, R. Prins, *Catal. Lett.* **1999**, *58*, 71.
[14] V. S. Ranade, R. Prins, *J. Catal.* **1999**, *185*, 479.
[15] A. Tungler, Z. P. Karancsi, V. Háda, L. Hegedus, T. Máthé, L. Szepessy, *Poster 14*, 5th International Symposium On Heterogeneous Catalysis and Fine Chemicals, Lyon (France), **1999**.
[16] M. Besson, C. Pinel, S. Neto, F. Delbecq, N. Douja, P. Gallezot, *Poster 2*, 5th International Symposium On Heterogeneous Catalysis and Fine Chemicals, Lyon (France), **1999**.
[17] M. Besson, P. Gallezot, S. Neto, C. Pinel, unpublished results.
[18] M. Besson, P. Gallezot, S. Neto, C. Pinel, *Chem. Commun.* **1998**, 1431.
[19] J. Buckingham, S. M. Donaghy, in *Dictionary of Organic Compounds*, 5th ed., Chapman and Hall, New York, **1982**.
[20] A mixture of the isomers was synthesised from commercial 2-methyl cyclohexane carboxylic acid (*cis*:*trans* = 85:15). The GC analysis showed three peaks at t_1, t_2 and t_3, with relative surface areas of 11, 50 and 39%, respectively. It is quite reasonable to propose the following assignment: the peak at t_1 is *trans*-1 (the first *trans* isomer off the column), that at t_2 is *cis*-1 + *trans*-2 and at t_3 it is *cis*-2, namely there is a superimposition of one of the *cis* isomers and one of the *trans* isomers. Furthermore, the reaction medium after hydrogenation of **1** (R = Me), which gave three peaks of relative surface areas 5, 65 and 30%, was hydrolysed in HCl (6N). After extraction with ethyl acetate, the analysis of the 2-methyl cyclohexane carboxylic acid thus formed, yielded a *cis*:*trans* ratio of 96:4, which demonstrates that the concentration of the *trans* isomers in the reaction medium was very low (always < 5%). The uncertainty, which would result regarding the intensity of peak for *cis*-1, would therefore be negligible. Finally, the

hydrolysis of a hydrogenation medium, in which no peak with retention time t_1 was detected, allowed us to verify that there was actually no *trans*-2-methyl cyclohexane carboxylic acid produced.

[21] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-125671. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[22] M. Besson, P. Gallezot, C. Pinel, S. Neto, in *Studies in Surface Science and Catalysis*, *Heterogeneous Catalysis and Fine Chemicals*, *Vol. 108* (Eds.: H. U. Blaser, A. Baiker, R. Prins), Elsevier, Amsterdam, **1997**, p. 215.

[23] Prepared according to F. W. Sum, L. Weiler, *Can. J. Chem.* **1979**, *57*, 1431.

Received: June 16, 1999 [F1854]

0947-6539/00/0606-0958 $ 17.50+.50/0