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Influence of the nature of chiral auxiliaries on the diastereoselective hydrogenation of *ortho*-substituted benzoic acid derivatives

Michèle Besson,* Pierre Gallezot, Samuel Neto and Catherine Pinel

Institut de Recherches sur la Catalyse-CNRS, 2, Avenue Albert Einstein, 69626 Villeurbanne Cedex, France

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Abstract

The diastereoselective hydrogenation of *o*-toluic acid or *o*-methoxy benzoic acid covalently bound to different chiral auxiliaries was performed on Rh and Ru supported catalysts. The *cis*-isomers were formed predominantly, with a diastereoselectivity largely influenced by the structure of the chiral inductor and the steric hindrance brought for the preferential adsorption of one face of the aromatic substrate. The effect of the functional group on the proline auxiliary (alcohol or ester groups susceptible to modify the anchoring of the aromatic substrate) was weak. Hydrogenolysis occurred rather extensively with the methoxy benzoic acid and constituted the most important hydrogenation pathway on Rh/C. The presence of the C=O group in the pyroglutamic acid methyl ester is a determining factor for obtaining good diastereoselectivity.

1. Introduction

Selective synthesis of optically active alicyclic compounds is of interest to the pharmaceutical and agrochemical industries, because these compounds are constituents of biologically active molecules.[1] One attractive way to access these molecules is the asymmetric catalytic hydrogenation of the corresponding prochiral aromatic compound. Among the possible different methods to achieve this, the diastereoselective hydrogenation of disubstituted aromatic rings over heterogeneous catalysts has attracted some attention in recent years.[2–7] In this strategy, the substrate is temporarily covalently attached to a chiral auxiliary, before the hydrogenation over supported metallic catalysts to the pairs of *cis*- and *trans*-isomers. The bulkiness of the chiral auxiliary causes the molecule to approach the surface of the catalyst, with the face which produces the least steric hindrance toward the catalyst surface.[8]

* Corresponding author. Fax: (+33) (0)4 72 44 53 99; e-mail: mbesson@catalyse.univ-lyon1.fr

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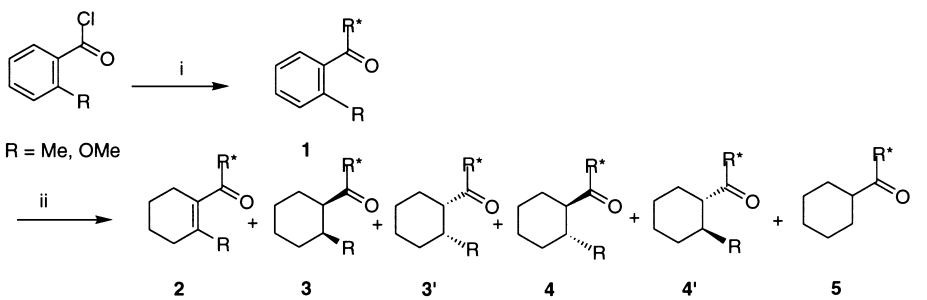
We have reported recently[2,3] on the diastereoselective hydrogenation of *o*-toluic acid, chosen as a model of disubstituted aromatic compounds. We have shown that, using supported metals, the hydrogenation yielded the corresponding *cis*-cyclohexane derivatives with high yield and enantiomeric excess. The diastereoselectivity of the reaction was largely influenced by the nature of the chiral auxiliary. Whereas d.e.s up to 68% were achieved using proline esters as the chiral auxiliary,[2] improvement up to 95% was observed with pyroglutamic acid esters.[3] The importance of the aromatic compound-auxiliary moiety was also found to be an important factor by Hönig et al.[5] in the hydrogenation of vanillic acid. After modification of either the carboxylic acid function with (*S*)-proline or (−)-menthol, or the hydroxyl group with *N*-acetyl-(*S*)-proline, only low diastereoisomeric excesses for the *cis*-products were obtained (<6%). By making the structure more rigid, with the attachment of the chiral auxiliary to both the hydroxy and methoxy groups, an increase in d.e. to 25% over an Ru/C catalyst was found. In the group of Prins,[6,7] (*S*)-proline-modified anthranilic acid was hydrogenated on Rh and Ru catalysts with moderate selectivity to the *cis*-isomers, but with high diastereoselectivity (up to 96%), probably due to the rigidity of the system. On the other hand, hydrogenation of (*S*)-proline-modified *o*-toluidine yielded the *cis*-isomers (*cis* to *trans* ratio of 4–5) with d.e. = 41–57% on different rhodium catalysts.

Considering the dramatic influence of the nature of the chiral auxiliary on the diastereoselectivity, we tested other chiral inductors for the hydrogenation of *o*-toluic acid. The use of prolinol allowed us to study the influence of the ester group compared to that of alcohol in the chiral auxiliary. (*S*)-(2-Pyrrolidinylmethyl)pyrrolidine is a very bulky chiral ligand which should modify the selectivity. Finally, (*R*)-pantolactone has often been used in diastereoselective reactions because of the easy esterification of the alcohol function.[9] The influence of the *ortho*-substitutent group in the benzoic substrate was also studied (methoxy group in place of methyl group).

2. Results and discussion

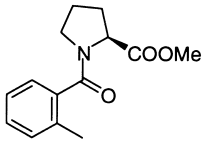
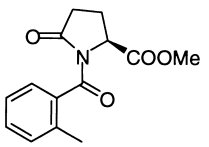
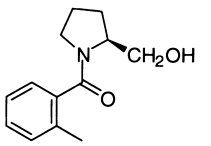
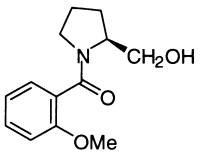
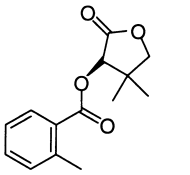
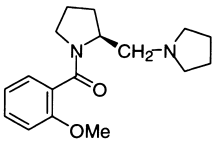
2.1. Synthesis of substrates *1* and identification of hydrogenation products

The substrates **1c**, **e**, **f** (Table 1) were synthesized in good yields (65–87%) from *o*-toluoyl chloride and the corresponding auxiliaries according to Scheme 1. (*S*)-*N*-(2-Methoxybenzoyl)-prolinol **1d** was commercially available (Aldrich) and used without further purification.



Scheme 1. (i) R*H, NEt_3, $CHCl_3$; (ii) catalyst, EtOH, 5 MPa hydrogen, room temperature

Table 1
Influence of the nature of the chiral auxiliary on the diastereoselectivity and the initial reaction rate of the hydrogenation

substrate	catalyst	initial reaction rate [a] ($mol.h^{-1}.mol^{-1}_{met}$)	d.e. at 100% conversion [a, b] (%)	max **2** (%)	Remarks
 **1a**	Rh/C	15 (5.5)	0-17 (41)	25	
	Ru/C	33 (14)	23-31	36	
	Rh/Al_2O_3	5 (4.5)	50 (67)	< 10	
 **1b**	Rh/C	23 (4)	50-35 (91)	27	Auxiliary cleavage ≈8%
	Ru/C	14 (5)	74 (80)	21	≈6%
	Rh/Al_2O_3	3 (2)	90 (94)	< 5	≈6%
 **1c**	Rh/C	2	10-17	35	*Trans* ≈10%
	Ru/C	9.5	9-19	47	≈5%
 **1d**	Rh/C	12 (0)	28	5	OMe hydrogenolysis ≈52%
	Ru/C	2	33	5	≈22%
	Rh/Al_2O_3	2	30	5	≈22%
 **1e**	Rh/C	12 (0.3)	5 (n.d.)	3	*Trans* ≈8%
	Ru/C	73 (31)	17 (17)	3	≈8%
	Rh/Al_2O_3	17 (11)	20 (18)	3	11-12%
 **1f**	Rh/C				no reaction
	Ru/C				no reaction
	Rh/Al_2O_3				no reaction

[a] in parenthesis are given the results achieved in the presence of an amine N-ethyldicyclohexylamine EDCA (molar EDCA/metal ratio = 3-5) ;
[b] when a large amount of **2** was formed, d.e. is given at total conversion of **1** then at maximum conversion of **2**.

Typically, the asymmetric hydrogenation of the aromatic substrates **1** was performed in ethanol at room temperature and under 5 MPa hydrogen pressure. Rhodium and ruthenium catalysts, known as the most active catalysts for hydrogenation of aromatic substrates and able to catalyze these reactions at mild process conditions, were used.

The hydrogenation resulted in the formation of four cyclohexane diastereoisomers, the pair of *cis*-isomers **3** and **3′** and the pair of *trans*-isomers **4** and **4′**. All hydrogenation reactions of the different substrates yielded predominantly the two *cis*-diastereoisomers with a *cis* to *trans* ratio higher than 7.5. The diastereoisomeric excess was then reported for the *cis*-isomers and defined as d.e. = (%**3**−%**3′**)/(%**3**+%**3′**)×100; usually, the d.e. did not vary with the conversion of **1**. During the course of the reaction variable amounts of cyclohexene intermediate **2** were also detected. The position of the double bond in **2** was verified by DEPT ^{13}C NMR spectroscopy for the proline methyl ester auxiliary.[2] The concentration of **2** went through a maximum during the reaction, the amount of which depended on the substrate. In some cases (R = OMe), hydrogenation was accompanied by extensive hydrogenolysis and significant amounts of the hydrogenolysis–hydrogenation compound **5** were detected.

The main results achieved in the hydrogenation of these substrates, with different metal supported catalysts, are reported in Table 1. For comparison, data corresponding to the substrates **1a** and **b** with the proline and pyroglutamic acid auxiliaries described in previous studies are also mentioned.[2–4]

2.2. *Hydrogenation of* (S)-N-*(2-methylbenzoyl)-prolinol* **1c**

Hydrogenation of (*S*)-*N*-(2-methylbenzoyl)-prolinol **1c** resulted in the formation of five compounds analyzed by gas chromatography and identified by GC–MS as **2**, **3** and **3′**, **4** and **4′**. The absolute configuration of the hydrogenated diastereoisomers was not identified directly, but attributed by analogy with the hydrogenated products of (*S*)-*N*-(2-methylbenzoyl)proline methyl ester **1a**. The comparison of the initial reaction rates (Table 1) shows that the replacement of the methyl ester group in the proline auxiliary by a CH_2OH group resulted in a reaction which proceeded more slowly. The initial reaction rates are 2 mol h^{-1} mol_{Rh} and 9.5 mol h^{-1} mol_{Ru} for hydrogenation of **1c**, compared to 15 mol h^{-1} mol_{Rh} and 33 mol h^{-1} mol_{Ru} for hydrogenation of **1a**. A better availability of the oxygen lone pairs of the proline ester for stronger interactions between the substrate and the metallic surface may explain these differences.

Fig. 1 gives the composition of the reaction medium versus time, when the reaction was performed on Ru/C. The pathway was very close to that observed with substrate **1a**.[2] The aromatic ring was mainly hydrogenated to the two *cis*-isomers with a low and constant d.e. = 10% in favor of diastereoisomer **3**. The cyclohexenic compound accumulated and reached a maximum yield of 47%. When the amount of unreacted **1c** approached zero, the accumulated intermediate was hydrogenated slowly to give the *cis*-isomers as main products. However, the diastereoselectivity of hydrogenation was higher than that resulting from the hydrogenation of the parent aromatic compound, as indicated by the slight increase of d.e. up to 19% at nearly complete conversion of **2**.

Very similar results were obtained on Rh/C catalyst, but at a lower rate. Upon hydrogenation of intermediate **2** (maximum yield 35%), the d.e. value, initially 9%, increased to 17% in favor of **3**.

If we compare the effect of the substituent at the stereogenic carbon on the pyrrolidine group, replacing an ester group by an alcoholic functional group does not seem to exert any supplementary orientating effect.

The influence of the addition of an amine, which was found to improve the diastereoselectivity in hydrogenation of **1a** and **b**, was not studied in detail, as this caused a significant decrease in the activity.

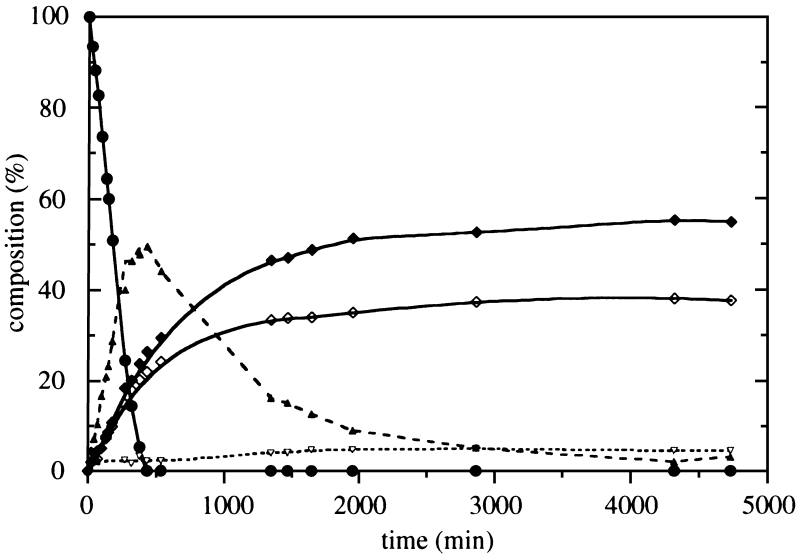


Figure 1. Distribution of products versus time for hydrogenation of **1c** over Ru/C. Reaction conditions: 2.27 mmol substrate, 0.06 mmol Ru, 130 ml ethanol, 25°C, 5 MPa hydrogen. ● **1c**, ▲ **2**, ◆ **3**, ◇ **3′**, ▽ **4+4′**

2.3. *Hydrogenation of* (S)-N-*(2-methoxybenzoyl)-prolinol* ***1d***

Catalytic hydrogenation of commercial (*S*)-*N*-(2-methoxybenzoyl)-prolinol **1d** over different catalysts resulted in four hydrogenated products. They were identified as the two *cis*-diastereoisomers **3** and **3′**, the cyclohexenic intermediate **2** and (*S*)-*N*-cyclohexane carbonyl prolinol, the saturated compound **5** in which the methoxy group has been eliminated. This latter compound was identified by GC–MS and the reference was also synthesized from cyclohexane carboxylic acid chloride and (*S*)-prolinol. No *trans*-isomers were observed.

The initial reaction rate was apparently much faster on Rh/C than on Rh/Al_2O_3 or Ru/C (for instance, 12 mol h^{-1} mol_{Rh}^{-1} on Rh/C compared to 2 mol h^{-1} mol_{Rh}^{-1} on Rh/Al_2O_3, Table 1). However, these initial reaction rates were measured from the disappearance of the aromatic substrate, and one must take into account that **1d** is converted either by hydrogenation or by hydrogenolysis of the methoxy group. The splitting of this group attached to the ring system is possible by cleavage of the C–O bond adjacent to the ring.[10,11] The proportion of hydrogenolysis was found to be dependent on the catalyst. While hydrogenolysis became even a major part of the reaction on Rh/C (52% of hydrogenolysis–hydrogenation product **5** detected), it occurred to a lesser extent on Rh/Al_2O_3 or Ru/C (22% of **5**). In all experiments, only small amounts of cyclohexenic compound were formed (5%) and the d.e. measured on the *cis*-derivatives remained moderate, in the range 28–33% (Table 1). However, one can note that these values are higher than those observed with *o*-toluic acid grafted to the same chiral inductor (substrate **1c**, d.e. in the range 9–19%). The methoxy substituent, by steric effect and additional electronic interactions with the metallic surface (haptophilicity), may contribute to the favorable adsorption of one face of the aromatic substrate and enhance the diastereodifferentiation. Such an interaction was already proposed[2] to explain the higher selectivity observed in hydrogenation of **1a** on ruthenium catalysts, whose affinity for oxygen groups in the substrate is higher than rhodium. Also, this haptophilic

effect was suggested in a recent work[12] dealing with hydrogenation of indane and tetraline substrates monosubstituted with hydroxyl, amino and methyl groups.

As shown by the d.e. results (Table 1), the effects of support and metal are negligible for substrate **1c**. The addition of an amine to the Rh/C catalyst drastically suppressed the reaction.

2.4. *Hydrogenation of (*R*)-pantolactone-methyl benzoate **1e***

When (*R*)-pantolactone is bonded to the *o*-toluic acid, the stereogenic center on the auxiliary is separated from the aromatic ring by an ester group instead of an amide group in the case of proline methyl ester or prolinol modified substrates. Hydrogenation of **1e** led to the simultaneous formation of mainly the *cis*-isomers, the *trans*-isomers and the semi-hydrogenated intermediate. The identity of the products was established by GC–MS and by synthesis of the authentic samples. However, determination of the absolute configurations was not performed.

In the absence of amine, the initial reaction rates varied greatly, depending on the nature of the metal and the support. The catalyst activity followed the same order as that observed during the hydrogenation of **1a**,[2] Ru/C being six times more active than Rh/C. A higher adsorption of the carboxylate functional group of pantolactone on oxophilic ruthenium may explain the higher activity of the ruthenium catalyst. The effect was lower on Rh/Al_2O_3 containing residual oxidized rhodium species. One can also note that the initial reaction rates were higher than in the case of **1a** or **b**, probably due to the presence of four oxygens which enhance the interactions between the substrate and the metal. Fig. 2 shows the composition of the reaction medium as a function of time for a reaction performed on Rh/Al_2O_3.

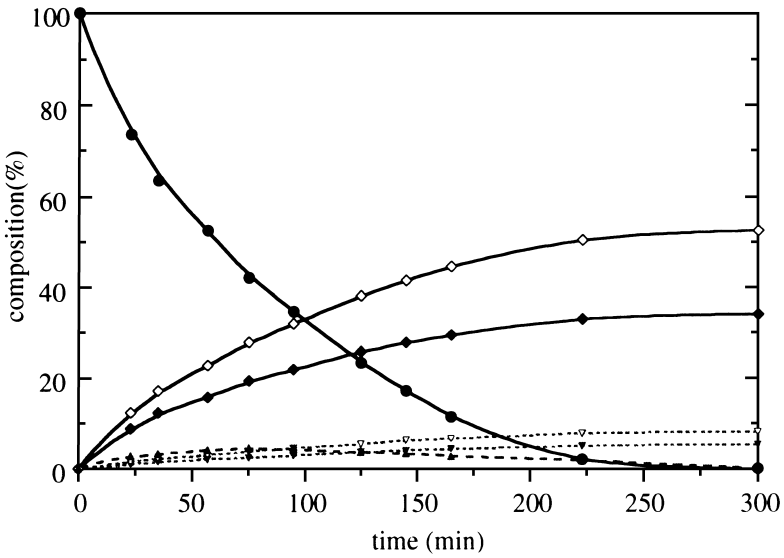


Figure 2. Distribution of products as a function of time for hydrogenation of **1e** on Rh/Al_2O_3. Reaction conditions: 2.04 mmol substrate, 0.05 mmol Rh, 130 ml ethanol, 5 MPa hydrogen. ● **1e**, ▲ **2**, ◆ *cis* **1**, ◇ *cis* **2**, ▼ *trans* **1**, ▽ *trans* **2**

With this chiral auxiliary, the amount of the *trans*-derivatives was significant and was in the range of 8–12% at the end of the reaction. In contrast with other substrates, the semi-hydrogenated compound **2** formed transiently (5–10%) did not accumulate and was hydrogenated

during the conversion of **1e**. Concerning the diastereoselectivity in the *cis*-isomers, Rh/C is poorly selective (5% d.e.), while slightly higher values were obtained on the other catalysts (ca. 20%). The aromatic ring is bound to the pantolactone auxiliary via an ester function which is less rigid than the amide present in the proline derivatives, and this could explain the low diastereoselectivities.

Previous experiments on **1a** revealed that better diastereoselectivity could be achieved if the Rh/Al_2O_3 catalyst was pre-treated at 100°C or 300°C under hydrogen flow.[13] However, using these pre-treated catalysts in the reduction of **1e** did not improve the diastereoselectivity of the reaction (de = 20–23%). Finally, amine addition decreased the reaction rate of the hydrogenation of **1e**, as already observed in the case of **1a** or **b**. However, no improvement of the diastereoselectivity could be achieved.

2.5. *Hydrogenation of* (S)-N-*(2-methylbenzoyl)-2-pyrrolidinylmethylpyrrolidine* ***1f***

The structure of this chiral auxiliary is close to that of prolinol, where the hydroxyl group is replaced by a second pyrrolidine group. Whatever the rhodium or ruthenium catalyst, no hydrogenation products were detected, even when the reaction was conducted at 90°C. This was attributed to the too high steric hindrance of the auxiliary which inhibited the adsorption of the substrate on the metallic surface.

3. Conclusion

The diastereoselective hydrogenation of *o*-toluic acid over Rh and Ru supported catalysts was studied using different chiral auxiliaries. Though the use of new chiral auxiliaries did not provide as high a diastereoselectivity as previously obtained with pyroglutamic acid esters, some observations can be summarized. The steric hindrance induced by the bonding of the different chiral auxiliaries facilitates the adsorption of one face of the aromatic substrate undergoing hydrogenation and results in some stereoinduction. The importance of the nature of the chiral moiety on diastereoselective induction is confirmed. Pyroglutamic acid esters are the most effective chiral auxiliaries in this type of asymmetric hydrogenation, probably due to the efficient steric and electronic effects introduced by the C=O group. The use of prolinol or pantolactone as chiral auxiliaries for *o*-toluic acid hydrogenation led to the formation of higher amounts of *trans*-derivatives compared to the proline ester moiety (10–12% compared to less than 3%). The substitution of the methyl ester on the proline by a CH_2OH group resulted in a decrease in the reaction rate, but with little influence on the diastereoselectivity. (*S*)-(2-Pyrrolidinylmethyl)pyrrolidine, containing a second nitrogen atom, was a too bulky ligand and the substrate could not be converted. The experiments performed with (*S*)-*N*-(2-methoxybenzoyl)prolinol yielded the *cis*-cyclohexyl compounds with 33% d.e. indicating that, in addition to steric effects of the substituent on the aromatic ring, this functional group can further interact with the metallic surface. However, on these catalysts, hydrogenation was accompanied by hydrogenolysis, which occurred extensively (52%) on Rh/C.

4. Experimental

Compounds **2e** and **5**, and the mixture of isomers (**3e+3′e+4e = 4′e**) were synthesized to authenticate the products formed during hydrogenation.

4.1. (S)-N-(2-Methylbenzoyl)-prolinol **1c**

To a stirred solution of (*S*)-(+)-prolinol (2 g) in chloroform (15 ml) under argon at 0°C were added successively dropwise triethylamine (5.5 ml, 2 equiv.) and *o*-toluoyl chloride (2.8 ml, 1.1 equiv.) and stirring continued overnight at room temperature. The mixture was treated with saturated $NaHCO_3$ (2×20 ml), NaCl (20 ml), dried ($MgSO_4$) and concentrated to give 3.5 g of a slightly yellow solid (81%), which was used for hydrogenation without further purification.

^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.0–7.2 (m, 4H); 5.1 (s, 1H); 4.3–4.5 (m, 1H); 3.8 (d, 5.5 Hz, 2H); 3.2 (t, 6 Hz, 2H); 2.3 (s, 3H); 1.7–2.2 (m, 4H); ^{13}C NMR ($CDCl_3$, 25 MHz): δ (ppm) 171.89 (C); 137.06 (C); 133.32 (C); 130.27–128.80–125.75–125.14 (4 CH); 66.32 (CH_2); 60.57 (CH); 49.58 (CH_2); 28.23 (CH_2); 24.30 (CH_2); 18.61 (CH_3). IR film (cm^{-1}): 3352; 3050; 2947–2877; 1616; 1447; 1251–1176; MS: *m*/*z* 77, 90 (100%), 119, 188, 201, 219 (M); mp = 76°C, $[\alpha]_D^{24}$ −81.3 (*c* = 1; $CHCl_3$). Anal. calcd for $C_{13}H_{14}NO_2$: C, 71.2; H, 7.8; N, 6.4. Found: C, 71.6; H, 7.6; N, 5.8.

4.2. (S)-N-Cyclohexane carbonyl prolinol **5**

To a stirred solution of (*S*)-prolinol (1.3 g) in chloroform (15 ml) under argon at 0°C were added successively dropwise triethylamine (3.3 ml, 2 equiv.) and cyclohexane carboxylic acid chloride (1.7 g). The mixture was treated with saturated $NaHCO_3$, NaCl, dried ($MgSO_4$) and concentrated to give 1.6 g of a yellow solid (66%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 5.3 (m, 1H); 3.9–4.3 (m, 1H); 3.3–3.7 (m, 2H); 1.0–2.5 (14H); ^{13}C NMR ($CDCl_3$, 25 MHz): δ (ppm) 178.0 (C); 67.83 (CH_2); 61.28 (CH); 47.99 (CH_2); 43.31 (CH); 29.55–28.78–28.47–26.04–25.70 (5 CH_2); 24.73 (CH_2). IR film (cm^{-1}): 3393; 2935–2872; 1611; 1437; MS: *m*/*z* 41, 55, 70 (100%), 83, 180, 193, 212 (M); mp = 76°C.

4.3. (R)-Pantolactone-o-toluoate **1e**

To a stirred solution of (*R*)-pantolactone (12 g) in chloroform (60 ml) under argon at 0°C were added successively dropwise triethylamine (14.3 ml, 2 equiv.) and *o*-toluoyl chloride (13.2 ml, 1.1 equiv.) and stirring continued overnight under reflux. The solution was cooled to room temperature and the organic layer was treated with saturated $NaHCO_3$ (2×20 ml), NaCl (20 ml), dried ($MgSO_4$) and concentrated to give a slightly yellow solid. The product was crystallized in cyclohexane to give 20 g of white needles (87%).

^{1}H NMR ($CDCl_3$, 100 MHz): δ (ppm) 8.0 (m, 1H); 7.2–7.4 (m, 3H); 5.6 (s, 1H); 4.1 (s, 2H); 2.6 (s, 3H); 1.2–1.3 (2s, 6H); ^{13}C NMR ($CDCl_3$, 25 MHz): δ (ppm) 172.87 (C); 166.27 (C); 141.28 (C); 133.13–132.18–131.34 (3 CH); 128.27 (C); 126.20 (CH); 76.55 (CH); 75.63 (CH_2); 40.71 (C); 22.23 (CH_3); 23.35–20.47 (2 CH_3). IR film (cm^{-1}): 3050; 2978–2958–2939; 1733–1740; 1256–1141–1099; MS: *m*/*z* 77, 83, 90 (100%), 113, 119, 135, 248 (M); mp = 65°C, $[\alpha]_D^{24}$ 0.6 (*c* = 1; $CHCl_3$). Anal. calcd for $C_{14}H_{16}O_4$: C, 67.7; H, 6.5. Found: C, 67.9; H, 6.5.

4.4. cis/trans (R)-N-(2-Methyl-cyclohexane carbonyl)-pantolactone (**3e+3e′+4e+4′e**)

To a solution of commercial mixture (*cis*/*trans*) of 2-methyl-cyclohexane carboxylic acid (2 g, 14 mmol) in $CHCl_3$ (10 ml) was added dropwise $SOCl_2$ (4 ml, 4 equiv.) at 0°C under argon, the stirring was maintained overnight at room temperature and the solvents were removed. The yellow

oil was used without purification in the following step. In a three-neck round-bottomed flask was placed (*R*)-pantolactone (1.66 g, 12.7 mmol) in $CHCl_3$ (30 ml). Triethylamine (1.5 ml, 1.1 equiv.) followed by crude acid chloride (2.3 g) were added dropwise and the mixture was stirred overnight under reflux. The solution was washed with $NaHCO_3$ (2×10 ml) then NaCl (2×10 ml), dried ($MgSO_4$) and concentrated under vacuum to give a brown oil. Purification on silica gave 540 mg of a white solid (17%), which was a mixture of the four stereoisomers.

Selected data of the main compound: ^{1}H NMR ($CDCl_3$, 100 MHz): δ (ppm) 5.35 (s, 1H); 4.0 (s, 2H); 2.6–2.7 (m, 1H); 2.0–2.4 (s, 1H); 0.9–1.8 (m, 8H); 1.1 (s, 6H); 0.93 (d, 4.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 25 MHz): δ (ppm) 174.03–172.72 (2C); 76.38 (CH_2); 74.68 (CH); 46.11 (CH); 40.39 (C); 31.87 (CH_2); 31.42 (CH); 24.53 (CH_2); 23.28–20.27 (2 CH_3); 21.67–21.62 (2 CH_2); 15.56 (CH_3); MS: *m*/*z* 96 (100%), 125, 131, 157, 172, 186, 254 (M).

4.5. (R)-N-(2-Methyl-1-cyclohex-2-ene carbonyl)-pantolactone **2e**

To a solution of 2-methyl-1-cyclohex-2-ene carboxylic acid[4] (100 mg, 7 mmol) in $CHCl_3$ (2 ml) was added $SOCl_2$ (0.2 ml, 4 equiv.) at 0°C under argon. The solution was stirred overnight and the solvents were removed under vacuum. The crude product was used in the following step without purification. In a three-neck round-bottomed flask was placed (*R*)-pantolactone (246 mg, 1.89 mmol) in CH_2Cl_2 (6 ml). Triethylamine (0.3 ml, 3 equiv.) followed by the crude acid chloride (300 mg) were added and the mixture was stirred for one night at 60°C. The solution was washed with $NaHCO_3$ (2×10 ml) then NaCl (2×20 ml), dried ($MgSO_4$) and concentrated under vacuum to yield 300 mg of a slightly brown oil (63%).

^{1}H NMR ($CDCl_3$, 100 MHz): δ (ppm) 5.4 (s, 1H); 4.0 (s, 2H); 2–2.3 (m, 4H); 1.5–1.7 (m, 4H); 1.2 (s, 3H); ^{13}C NMR ($CDCl_3$, 25 MHz): δ (ppm) 173.16 (C); 167.29 (C); 150.70 (C); 123.08 (C); 76.52 (CH_2); 74.80 (CH); 40.50 (C); 34.54–26.47–22.50–22.39 (4 CH_2); 22.70 (CH_3). IR film (cm^{-1}): 2935–2863–2824; 1792–1721; 1634; 1224–1203–1097; MS: *m*/*z* 94 (100%), 99, 113, 122, 139, 163, 194, 252 (M); $[\alpha]_D^{22}$ −3.9 (*c* = 0.51; $CHCl_3$).

4.6. (S)-N-(2-Methylbenzoyl)-(2-pyrrolidinylmethyl)-pyrrolidine **1f**

To a stirred solution of (*S*)-(pyrrolidinemethyl)pyrrolidine (3 g) in chloroform (30 ml) under argon at 0°C were added successively dropwise triethylamine (3 ml, 1.1 equiv.) and *o*-toluoyl chloride (3.3 g, 1.1 equiv.) and stirring continued overnight at room temperature. The mixture was treated with saturated $NaHCO_3$ (2×20 ml), NaCl (20 ml), dried ($MgSO_4$) and concentrated to give a brown oil which was distilled under vacuum to give 3.8 g of a slightly yellow oil (65%).

^{1}H NMR ($CDCl_3$, 100 MHz): δ (ppm) 7.1–7.3 (m, 4H); 4.3 (m, 1H); 3.47 (m, 2H); 2.8 (m, 2H); 2.5 (m, 4H); 2.1 (s, 3H); 1.4–2.0 (m, 8H); ^{13}C NMR ($CDCl_3$, 25 MHz): δ (ppm) 169.33 (C); 137.30 (C); 133.13 (C); 129.76–128.11–125.22–124.97 (4 CH); 57.13 (CH_2); 55.05 (CH); 53.78 (CH_2); 48.03–44.51 (2 CH_2); 28.48–23.61–23.00–22.76 (4 CH_2); 18.30 (CH_3). IR film (cm^{-1}): 3050; 2966; 2876; 2788; 1783; 1723; 1632; 1411; 1256; MS: *m*/*z* 84 (100%), 91, 110, 119, 137, 188, 202, 272 (M); bp = 160°C/2.7×10^{-2} mbar.

4.7. Catalysts

The catalysts used in hydrogenation were 3.6% Rh/C (Aldrich 20,616–4), 3.7% Rh/Al_2O_3 (Aldrich 37,971–9) and 5% Ru/C (Aldrich 28,147–6). 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 in the reactor without exposure to air.

4.8. Hydrogenation experiments

The hydrogenation of the substrates 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 gas chromatography analyses (GC) which were performed using a Shimadzu GC14A apparatus using a J&W DB1701 column. The products of the reaction were identified by GC–MS analysis using a Fisons GC 8000 apparatus and by synthesis of the references. The absolute configuration of the diastereoisomers was not established.

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