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Diastereoselective Hydrogenation of (*S*)-Proline-2-methylanilide

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The diastereoselective hydrogenation of *o*-toluidine covalently linked to the chiral auxiliary (*S*)-proline has been studied. The hydrogenation of (*S*)-proline-2-methylanilide on supported noble metal catalysts yielded both the *cis* and the *trans* isomers of (*S*)-proline-2-methylcyclohexylamide. Rhodium and ruthenium were found to be the most active catalysts, rhodium being more selective than ruthenium. With (*S*)-proline as the chiral auxiliary, the 1*R*,2*S cis*-cyclohexanediyl isomer formed preferentially and with (*R*)-proline the 1*S*,2*R cis*-cyclohexanediyl isomer formed. No diastereoselectivity was obtained for the *trans* isomers. The activity of rhodium catalysts was dependent on the rhodium salt used as a precursor in catalyst preparation and on the support and the process conditions, while the *cis*–*trans* selectivity was independent of these parameters. The diastereoselectivity was dependent only on the nature of the noble metal. Prereduced and reused rhodium catalysts were less active than fresh ones. EXAFS and XANES showed that the catalyst was in an incompletely reduced state during the reaction.

Key Words: **stereoselective hydrogenation; auxiliary-aided hydrogenation; noble metal catalysts; proline auxiliary; toluidine hydrogenation.**

INTRODUCTION

The chiral element necessary for a stereoselective reaction has to be incorporated either in the substrate (diastereoselective reaction) or in the catalyst (enantioselective reaction). In the latter case spectacular results have been achieved with homogeneous catalysts in which the metal atom is surrounded by chiral ligand(s) (1, 2). In the case of heterogeneous catalysis, noteworthy results have been obtained only with a limited number of reactions like hydrogenation of α-keto compounds on cinchona-modified platinum catalysts (3) and hydrogenation of β-keto compounds on tartaric acid-modified nickel catalysts (4). The former approach, in which the chiral element is incorporated in the substrate has received less attention, partly due to the success of chiral homogeneous catalysts and partly because the chiral element has to be introduced stoichiometrically.

A substituted cyclohexane ring is a constituent of several biologically active molecules like terpenoids, steroids, and alkaloids. It can be formed by hydrogenation of the corresponding substituted aromatic compound. There are two very important advantages in using a substituted aromatic compound as a precursor for substituted cyclohexane compounds. One is the ease of introducing various functional groups into the aromatic ring via electrophilic and nucleophilic substitution, and the other is the availability of a considerable amount of literature on the hydrogenation of substituted aromatic compounds using heterogeneous catalysts (5–7). Thus, stereoselective hydrogenation of aromatic rings should be of potential interest. Although there are several reports regarding the influence of process conditions and the nature of the catalyst on the *cis*–*trans* selectivity in the hydrogenation of substituted aromatics using heterogeneous catalysts (8), there are very few examples illustrating diastereoselective hydrogenation of aromatics (9), using either homogeneous or heterogeneous catalysts (10, 11). Good results, however, have been obtained by noncatalytic means (12, 13).

In this paper we present the use of *(S)*-proline auxiliary-aided diastereoselective hydrogenation of *o*-toluidine, using supported noble metal catalysts. Besson *et al*. have already reported the diastereoselective hydrogenation of *o*-toluic acid using the same auxiliary (10, 14, 15); moderate diastereoselectivity and a good *cis* to *trans* selectivity were reported. In a recent article, they reported excellent diastereoselectivity with pyroglutamic acid as the chiral auxiliary (11). Our aim was to extend the approach of diastereoselective hydrogenation from aromatic carboxylic acids to aromatic amines. Although noble metal catalysts are frequently employed in hydrogenation reactions in organic syntheses, very little data are available regarding the nature of the active site in these kinds of reactions. We have also attempted to delineate the changes in the nature of a rhodium catalyst during the hydrogenation reaction.

EXPERIMENTAL

Synthesis of Substrate and Reference Compounds

All organic chemicals, except 2-methylcyclohexylamine (Aldrich), were supplied by Fluka. *(S)*-proline-2-methylanilide was synthesized by coupling the carboxylic acid

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group of a butyloxycarbonyl (BOC) protected *(S)*-proline molecule with the amine group of *o*-toluidine, according to the following procedure. BOC-(*S*)-proline (20 g (93 mmol)) was dissolved in 150 ml THF and 13.0 ml (93 mmol) of triethylamine (TEA) was added to the solution. The mixture was cooled to −15°C and 13.3 ml (102 mmol) of isobutylchloroformate was added dropwise with stirring followed by 20 ml (187 mmol) of *o*-toluidine after 5 min. The mixture was allowed to reach room temperature and stirred for a couple of hours. The solution was concentrated *in vacuo* to about 50 ml and then poured into 300 ml of a 1 N HCl solution. This solution was extracted twice with 300 ml diethyl ether. The diethyl ether extracts were pooled together and washed twice successively with a sodium bicarbonate solution and water and then dried over sodium sulfate. The solvent was removed *in vacuo* to give 22.5 g of solid BOC-(*S*)-proline-2-methylanilide (yield, 80%), which was purified by recrystallization from hexane.

Deprotection of proline was achieved by adding the purified BOC-(*S*)-proline-2-methylanilide to pure trifluoroacetic acid at 0°C, with stirring. The stirring was then continued for a couple of hours at room temperature. The excess of trifluoroacetic acid was removed *in vacuo* and sodium hydroxide solution was added till the pH was 13. The aqueous solution was extracted twice with diethyl ether and the extracts were treated as in the previous case. Recrystallization from hexane afforded 6 g pure (>98%) (*S*)-proline-2-methylanilide (yield, 40%). The scheme of the preparation of the substrate is shown in Fig. 1. The NMR

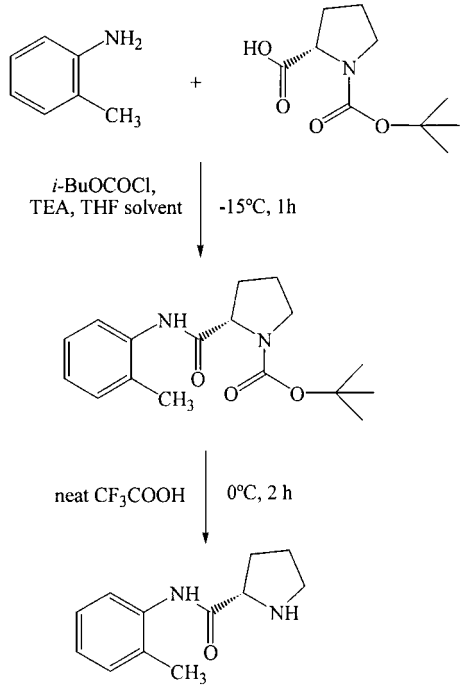

FIG. 1. Synthesis of (*S*)-proline-2-methylanilide.

TABLE 1

Catalyst Precursors and Solvents Used in Preparation of Rhodium and Platinum Catalysts by the Incipient Wetness Technique

Catalyst	Precursor	Solvent	H/M
Rh/c	na.	—	0.29
Rh/Al_2O_3 I	$Rh(C_5H_8O_2)_3$	Acetone	0.27
Rh/Al_2O_3 II	$Rh(NO_3)_3 \cdot 2H_2O$	Water	0.74
Rh/Al_2O_3 III	$RhCI_3 \cdot 3H_2O$	Water	0.67–0.70
Rh/TiO_2	$Rh(C_5H_8O_2)_3$	Acetone	0.27
Rh/ZrO_2	$Rh(C_5H_8O_2)_3$	Acetone	0.19
Pt/Al_2O_3	$PtCl_4$	Water	Not determined

spectral data for (*S*)-proline-2-methylanilide are given in the appendix.

Identification of the absolute configuration was done by preparing a reference racemic mixture and the 1*R*,2*S* optically pure *cis* isomer (through synthetic route). The experimental details of preparation of the reference compounds are given in the appendix.

Catalyst Preparation and Characterization

Rh/C (5 wt%) (Aldrich, 20,616-4), 5 wt% Ru/C (Fluka, 84031), and 10 wt% Pd/C (Fluka, 75990) were used as supplied. Several other catalysts were made by the incipient wetness technique using various supports (Al_2O_3, TiO_2, and ZrO_2) and precursors as shown in Table 1. TiO_2 (anatase; BET area, 54 m^2/g) and ZrO_2 (BET area, 54 m^2/g) were used as obtained from Degussa. Al_2O_3 granules from Condea were crushed to particles smaller than 60 μm (BET area, 230 m^2/g). All rhodium salt precursors were supplied by Johnson Matthey and the platinum salt was supplied by Fluka. The catalysts were prepared with a metal loading of 5 wt% and were dried in an oven at 120°C and then calcined in air at 350°C for 3 h after impregnation. These calcined catalysts were used for the hydrogenation experiments in the autoclave. In order to quantify the active surface area of the catalyst, hydrogen chemisorption was used. The catalysts were first reduced at 300°C for 1 h in hydrogen and outgassed under vacuum at the same temperature for the same period of time. The desorption isotherms were measured at 20°C and the H/M value was determined by extrapolating the part of the isotherm between 10 and 50 kPa to zero hydrogen pressure. Table 1 lists the H/M values for various rhodium catalysts. In the case of the Rh/Al_2O_3 III catalyst, three batches of catalyst were prepared with dispersions ranging from 0.67 to 0.70.

Catalytic Hydrogenation

Experiments were conducted in a 200-ml stainless steel autoclave at a total pressure of 4.0 MPa and a temperature of 70°C. In a typical experiment 400 mg of (*S*)-proline-2-

methylanilide was dissolved in 60 ml ethanol. To this solution, 200 mg of supported metal catalyst added in the oxidic form and the slurry was transferred to the autoclave. The autoclave was closed and flushed three times with nitrogen and subsequently three times with hydrogen. The hydrogen pressure was then increased to 3.7 MPa and stirring (1000 rpm) was started. The subsequent heating of the autoclave to 70°C resulted in a total pressure of about 4.0 ± 0.2 MPa. Changing the stirring speed to 800 and 1200 rpm did not change the rate of the reaction, establishing the absence of diffusion limitations. All subsequent reactions were conducted with a stirring speed of 1000 rpm. Since the autoclave was being heated to 70°C during the first few minutes of reaction, it was not possible to obtain reliable initial reaction rate values. The activities (ACT) are therefore reported as reciprocal of the time required for 50% conversion of the substrate ($ACT = 1/t_{50\%}$).

The autoclave was equipped with a sampling tube, enabling periodic sampling of the liquid phase (sample volume, 0.5–1 ml). The samples were analyzed using a GC equipped with a γ-cyclodextrin column and a FID detector. The response factor was assumed to be 1 for the substrate and the hydrogenated products. In a typical chromatogram all the diasteromers of (*S*)-proline-2-methylcyclohexylamide were separated from each other as well as from the intermediate cyclohexene derivative (identified by GC-MS) and the reactant. The position of the double bond in the cyclohexene intermediate could not be identified.

X-ray Absorption Experiments

X-ray absorption spectra of the catalysts at the Rh–K edge were measured in the transmission mode at the synchrotron facility at the Swiss–Norwegian Beamline (SNBL) at ESRF, Grenoble. The catalyst samples were prepared by reduction and/or reaction in the autoclave at 4 MPa hydrogen pressure and 70°C. After reduction and/or reaction and after filtering off the solvent, the catalysts were transferred to the sample cells in a nitrogen environment. The sample cell was then closed and the measurements were performed at room temperature without exposure to the atmosphere. Reference measurements were made on the calcined catalyst and a rhodium foil.

RESULTS

Two *cis* and two *trans* hydrogenated products as well as a cyclohexene intermediate were obtained in the hydrogenation of (*S*)-proline-2-methylanilide (Fig. 2). The *cis* to *trans* ratio was between 4 and 5 for all the experiments. The two *trans* isomers were formed without any selectivity. In the case of the *cis* isomers, the 1*R*,2*S* isomer was always obtained in excess when (*S*)-proline was used as the chiral

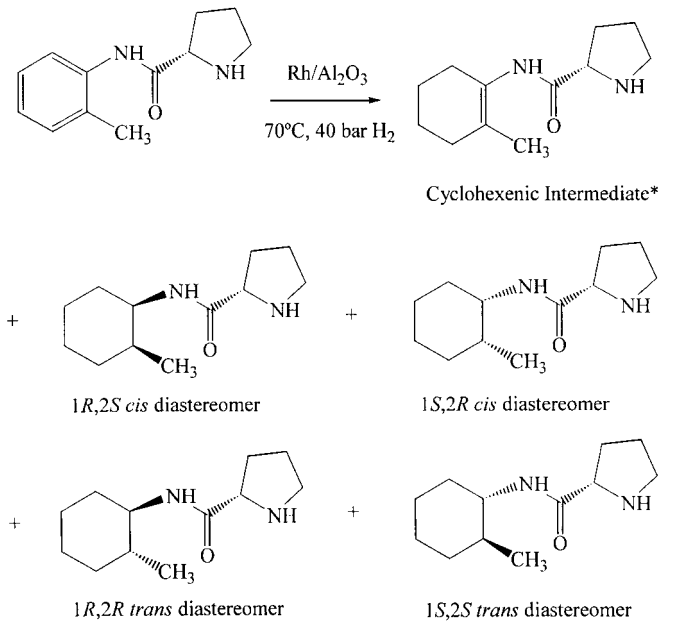

FIG. 2. Hydrogenation of (*S*)-proline-2-methylanilide (*position of double bond in the cyclohexenic intermediate is not known).

auxiliary. The selectivity between the *cis* isomers is reported as the d.e. (diastereomeric excess), where d.e. is defined as

$$\text{d.e} = \frac{[1R,2S\,\text{isomer}] - [1S,2R\,\text{isomer}]}{[1R,2S\,\text{isomer}] + [1S,2R\,\text{isomer}]}.$$

Typically, the d.e. was about 45% for the rhodium catalysts and increased slightly with the conversion of the substrate. The reproducibility of the diastereoselectivity was about ±2%. The concentration of the intermediate went through a maximum during the reaction. Kinetic data of the reaction indicated that the cyclohexene intermediate was hydrogenated simultaneously with the substrate and, in standard experiments, it reached a maximum concentration between 4 and 8% of the initial reactant concentration.

Comparison of Different Catalysts

The results of the hydrogenation reaction with various noble metal catalysts are summarized in Table 2. All

TABLE 2

Activity and Selectivity of Different Noble Metal Catalysts in the Hydrogenation of (*S*)-Proline-2-methylanilide at 70°C and 4.0 MPa in Ethanol

Catalyst	ACT (h^{-1})	d.e. (%)
Rh/Al_2O_3 I	0.50	55
Rh/C	0.75	41
Ru/C	0.47	11
Pt/Al_2O_3	Negligible	
Pd/C	Negligible	

TABLE 3

Activity and Selectivity of Different Rhodium Catalysts in Hydrogenation of (*S*)-Proline-2-methylanilide at 70°C and 4.0 MPa in Ethanol

Catalyst	BET area (m^2/g)	H/M	ACT (h^{-1})	d.e. (%)
Rh/TiO_2	54	0.27	0.75	56
Rh/C	944	0.29	0.75	41
Rh/ZrO_2	54	0.19	0.27	57
Rh/Al_2O_3 I	227	0.27	0.50	55
Rh/Al_2O_3 II	227	0.74	1.20	49
Rh/Al_2O_3 III	227	0.67	1.50	46

reactions were conducted at 70°C and 4.0 MPa, using ethanol as the solvent. At higher conversion considerable amounts of side products were obtained over the ruthenium catalyst.

Because of the lower activity of the palladium and platinum catalysts and the low selectivity of the ruthenium catalyst, rhodium metal catalysts were chosen for further studies. With rhodium acetylacetonate as the salt precursor, a series of rhodium catalysts were prepared on different supports (viz. Rh/TiO_2, Rh/ZrO_2, and Rh/Al_2O_3 I). The activities of these catalysts differed widely (Table 3) but they had an identical diastereoselectivity. With the same Al_2O_3 as the support, three rhodium catalysts were prepared using different metal precursors, as indicated in Table 1. The activity and to some extent the diastereoselectivity of these catalysts depended on the rhodium salt used in their preparation (Table 3).

Influence of Process Conditions: Temperature, Pressure, and Solvent

The reaction temperature had a considerable influence on the activity of the catalyst. Thus, after about 500 min of reaction time, only 40% conversion of the reactant was obtained when the reaction was carried out at 50°C with the Rh/Al_2O3 III catalyst, while at 70°C complete conversion was obtained. With the Rh/Al_2O_3 III catalyst, the reaction rate as well as the selectivity remained almost unaffected on increasing the reaction pressure from 4.0 to 6.0 MPa.

Solvents are known to play a significant role in determining the stereoselectivity in hydrogenation reactions. Besides ethanol, which was used as the standard solvent, the use of tetrahydrofuran, ethyl acetate, and chloroform was investigated. In the case of chloroform, the reactant was slowly converted to an unidentified product without any selectivity toward the ring hydrogenation product. The activity in tetrahydrofuran and ethyl acetate was much lower than that in ethanol but a slightly higher diastereoselectivity was obtained (Table 4).

Influence of Prereduction, Reuse of Catalyst, and Addition of Diethylamine

As described in the experimental section, the catalyst was introduced in the oxidic form in the autoclave along with the substrate and the solvent. Reduction of the catalyst took place on introducing hydrogen and subsequent heating of the autoclave to 70°C. This procedure gave relatively good activities for the rhodium catalysts. Prereduction of the Rh/C catalyst under hydrogen (before or after introduction into the autoclave in the absence of ethanol) led to a drastic reduction in the rate of the reaction. Prereduction of the catalyst in the solvent under hydrogen pressure led to an even lower rate and d.e. Similar results were obtained with the Rh/Al_2O_3 III catalyst.

After a standard experiment with the Rh/Al_2O_3 III catalyst, the reaction mixture was decanted to remove most of the solvent and substrate and the catalyst was repeatedly washed in ethanol, until the ethanol was almost free of product (as detected by GC analysis). The catalyst was then used again for another hydrogenation reaction. This reused catalyst exhibited a much lower activity and the reaction almost stopped at about 50% conversion of the substrate.

In a separate experiment, one equivalent of diethylamine was added to the reaction mixture before it was pressurized under hydrogen. Diethylamine was used as the additive because its basicity is comparable to that of the secondary amine group present in the substrate. The addition of diethylamine resulted in a marginal increase in the diastereoselectivity, but in a large reduction in the reaction rate.

EXAFS and XANES Studies on the Catalyst

EXAFS measurements and analyses were performed on the Rh/Al_2O_3 III catalyst to obtain information about the change in the oxidation state of rhodium during reaction. The EXAFS data were fitted using the k^1 weighted Fourier transformed $\chi(k)$ function. Details of the analyses and interpretation of the spectra can be found elsewhere (16). The coordination numbers obtained from the EXAFS analysis and the percentage of reduced rhodium obtained from the XANES data are reported for various samples in Table 5. The data indicate that the reduction of rhodium metal is

TABLE 4

Effect of Solvent on the Selectivity in the Hydrogenation of (*S*)-Proline-2-methylanilide with Rh/Al_2O_3 III Catalyst at 70°C and 4.0 MPa

Solvent	ACT (h^{-1})	d.e. (%)
Ethanol	1.50	46
Tetrahydrofuran	0.50	56
Ethyl acetate	0.11	52
Chloroform	—	

TABLE 5

EXAFS and XANES Results for the Rh/Al_2O_3 III Catalyst

	Coordination number[a]		Percentage of reduced Rh[b]
	Rh–Rh	Rh–O	
Catalyst after reduction in EtOH	6.1	1.2	69
Catalyst after reaction in EtOH	5.3	1.4	53
Catalyst as calcined	0.0	5.3	0

[a] Obtained from EXAFS.
[b] Obtained from XANES.

incomplete during the reduction or reaction, under the typical process conditions. The catalyst is reduced to a lesser extent during reaction (53%) than during reduction (69%).

DISCUSSION

The 1*R*,2*S* *cis* diastereomer was formed in excess when (*S*)-proline was used as the chiral auxiliary, while on hydrogenating a substrate made by coupling of *o*-toluidine with (*R*)-proline instead of (*S*)-proline, the 1*S*,2*R* diastereomer was formed in excess. This demonstrates that the proline auxiliary is responsible for the chiral induction in the hydrogenation reaction. The values of d.e. obtained with (*S*)-proline and (*R*)-proline were approximately equal but opposite in sign. Thus we can think of the following two speculative structures of the substrate on the rhodium surface for (*R*)-proline-2-methylanilide and for (*S*)-proline-2-methylanilide (top two structures in Fig. 3) which result in the formation of the *R*′,1*S*,2*R* and the *S*′,1*R*,2*S* diastereomers, respectively, on addition of hydrogen from the metal face of the rhodium catalyst. In these two structures, the nitrogen atom of the proline ring and the aromatic ring lie in the same plane on the catalyst surface and the amide bond is approximately parallel to the surface of the catalyst. The other *cis* diastereomer is formed from these substrates when the adsorption through the benzene ring takes place by its opposite face (bottom two structures in Fig. 3). However, this configuration leads to more steric crowding because of the interaction of the methyl group with the carbonyl group and hence is the less preferred structure.

Partial hydrogenation of a substituted aromatic ring leads to the formation of cyclohexene and cyclohexadiene derivatives. Intermediate cyclohexadiene species have rarely been observed in hydrogenation of aromatic compounds (17), but cyclohexene species have often been detected. Hydrogenation of these cyclohexene species is responsible for the formation of *trans* isomers. Although many different cyclohexene intermediates can be formed, only the five species shown in Fig. 4 are relevant in the present reaction for the formation of *trans* isomers. In the case of intermediate I, *trans* formation can result only if the addition of the two

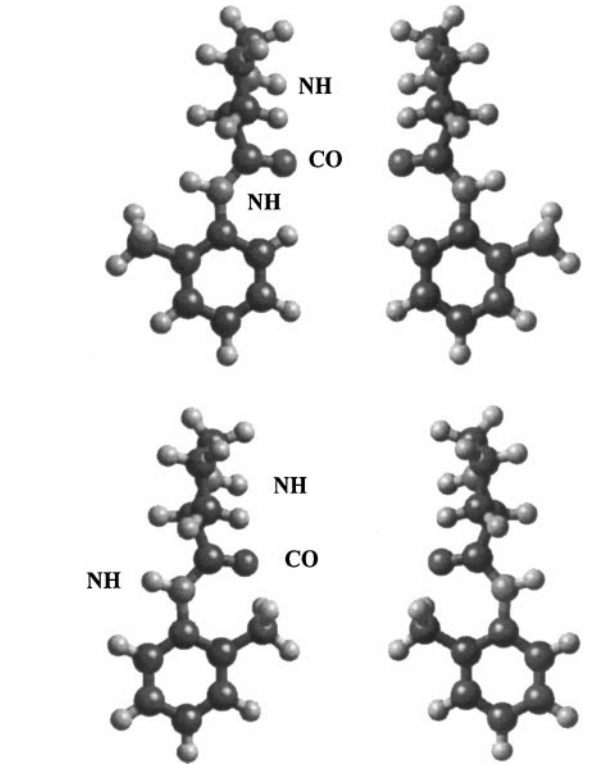

FIG. 3. Top views of the adsorption-structure of proline-2-methylanilide. From top left clockwise, formation of *R*′,1*S*,2*R*; *S*′,1*R*,2*S*; *S*′,1*S*,2*R*, and *R*′,1*R*,2*S* isomers.

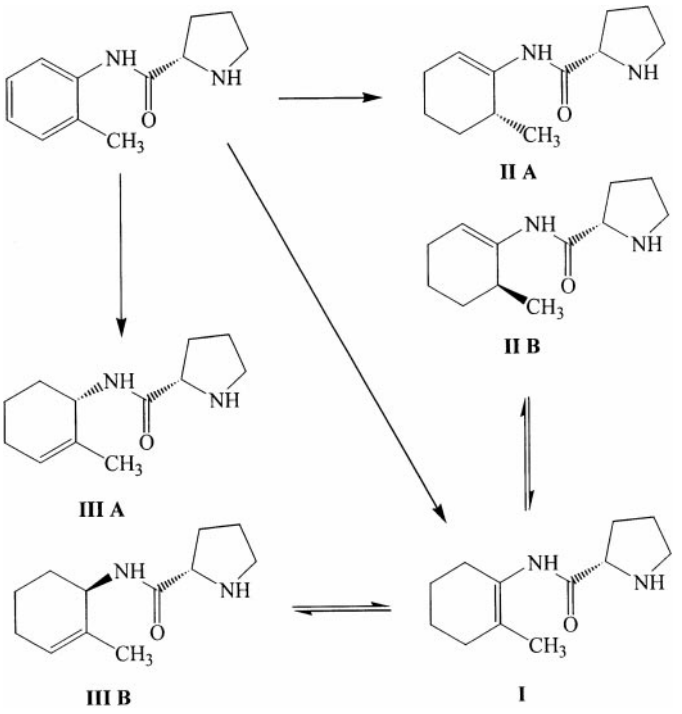

FIG. 4. Formation and interconversion of cyclohexenic intermediates.

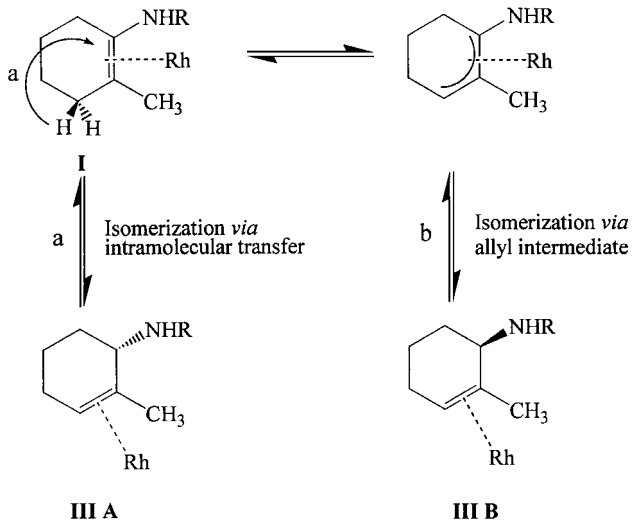

FIG. 5. Example of the mechanisms for interconversion of the cyclohexenic intermediates (*R*, -pyrrolidine-2-carboxyl).

hydrogen atoms takes place from the opposite faces on the aromatic ring. This is possible if the catalyst has a stepped surface or if the hydrogen atom comes from the solvent (in the case of protic solvents or acidic conditions) (18). Since the *cis* to *trans* ratio was independent of the solvent and the metal dispersion, these possibilities do not seem likely. The maximum concentration of the intermediate detected in the solution phase (~6%) cannot be correlated with the amount of *trans* products (20%) because the intermediate and the reactant are hydrogenated simultaneously. Thus the formation of *trans* isomers exclusively from the intermediate I via its conversion, on the surface of the catalyst by a π-allyl mechanism or intramolecular hydrogen transfer, to the intermediates II and III is a possibility (Fig. 5). In addition, the *trans* products could be formed directly through the hydrogenation of intermediates II and III or by intramolecular hydrogen transfer followed by hydrogenation (8, 19). The slow hydrogenation of the substrate probably allows equilibrium to be reached between various hydrogenation and isomerization processes of the intermediate(s). This accounts for the independence of the *cis* to *trans* ratio from either the process parameters or the catalyst preparation. The d.e. is strongly dependent only on the nature of the noble metal and fairly independent of the process conditions. A relatively small dependence of the diastereoselectivity on the process parameters but a strong dependence on the molecular structure has been observed in other (nonaromatic) diastereoselective hydrogenations (20).

As has been reported earlier for different kinds of aromatic substrates (9), ruthenium and rhodium were the most active catalysts for the present hydrogenation reaction. The platinum and palladium catalysts were almost inactive probably because of strong adsorption of the amine group on those catalysts (5).

All the catalysts prepared from the same rhodium precursor but with different oxide supports give similar results in terms of diastereoselectivity (viz. Rh/TiO_2, Rh/ZrO_2, and Rh/Al_2O_3 I, Table 3). The difference in diastereoselectivity between the oxide-supported catalysts and carbon-supported catalyst could be due to the difference in the nature of the surface of the two supports. However, this difference in selectivity may also be due to the different precursor, which has been used in the preparation of the catalysts. (Since the Rh/C catalyst was purchased from Aldrich, the rhodium salt precursor is not known for this catalyst). For the three catalysts prepared on the same Al_2O_3 support but from different precursors (viz. Rh/Al_2O_3 I, Rh/Al_2O_3 II, and Rh/Al_2O_3 III), no clear correlation is observed between the activity of the catalysts and their dispersion (Table 3). In general a higher activity is obtained at higher dispersion. The EXAFS data on the calcined Rh/Al_2O_3 III catalyst indicated that the chlorine originating from the rhodium chloride precursor was probably not completely removed during the calcination step. Thus the possibility of residual chlorine influencing the activity of this catalyst cannot be excluded. The Rh/Al_2O_3 II catalyst was, however, free of nitrate as confirmed by FT-IR measurements on the impregnated and the calcined catalyst samples.

Rhodium is a very good catalyst for hydrogenation of aromatic compounds since it can catalyze these reactions at relatively mild process conditions as compared to other catalysts. However, the present substrate hydrogenated very slowly at room temperature. Hence, the reaction was conducted at 70°C in order to get a reasonable activity. The relatively strong dependence of the rate of reaction on temperature is indicative of a strong adsorption of the substrate on the catalyst. The substrate molecule is most probably preferentially adsorbed through the secondary amine group on the proline ring, as is evident from the experiments in which diethylamine is added to the reaction mixture. The product of the hydrogenation reaction is also an amine and hence the total concentration of amine groups remains constant in the reaction mixture. A negligible effect of the hydrogen pressure on the reaction rate suggests that the reaction is product-desorption controlled. In the diastereoselective hydrogenation of (*S*)-proline modified *o*-toluic acid, Besson *et al.* (15) have reported enhancement of the diastereoselectivity and a decrease in the reaction rate on the addition of an amine. In the present case no big enhancement in the diastereoselectivity was observed because the reaction mixture already contained a significantly high concentration of amine groups.

Use of aprotic solvents like tetrahydrofuran and ethyl acetate resulted in a marginally higher d.e. (Table 4). As observed before in the hydrogenation of other aromatic substrates, the rate was fastest in the alcoholic solvent (6). The reason for a 14-fold higher activity in ethanol than in ethyl acetate is unclear. The hydrogenation failed when

chloroform was used as the solvent, probably because of poisoning of the active sites by chloride resulting from chloroform (5).

The catalyst is not reduced completely during either prereduction or reaction as indicated in Table 5. As the catalyst becomes reduced, it loses its activity as shown by experiments in which the catalyst is prereduced. Accordingly a reused catalyst also exhibits lower activity than a fresh one. The loss in activity occurs irrespective of whether carbon or alumina is used as the support. The EXAFS data reported for catalyst Rh/Al_2O_3 III in Table 5 indicate that the particle size remains unchanged during the reduction of the catalyst. Therefore sintering of small metal particles during reaction can be excluded as an explanation for the loss in catalyst activity. The loss in activity is therefore probably due to loss of the active sites, either due to a change in the morphology of the rhodium particles or due to a change in the oxidation state of the rhodium.

CONCLUSIONS

Ruthenium and rhodium are the most active metal catalysts for the hydrogenation of the (*S*)-proline-2-methylanilide among the noble metal catalysts investigated. The selectivity is strongly dependent on the substrate structure since relatively small differences are observed between the different rhodium catalysts. This has also been observed in other diastereoselective heterogeneous catalytic hydrogenations. The hydrogenation activity is dependent on the temperature, the catalyst precursor and support, and the solvent. The substrate adsorbs preferentially through the amine group and the diastereoselectivity arises from adsorption of the substrate on a rhodium surface preferentially through one of the two diastereotopic faces of the aromatic ring. ZrO_2, TiO_2, and Al_2O_3 yield comparable results in terms of the selectivity in the case of rhodium catalysts. The catalyst deactivates as it is reduced during the reaction. EXAFS and XANES experiments indicate that only a part of the rhodium in the catalyst is reduced under reaction conditions. A partly reduced catalyst is thus more active than a fully reduced catalyst.

APPENDIX

Spectral Data of (S)-Proline-2-methylanilide

The NMR spectra were recorded on a Bruker AMX 500 instrument at room temperature, using $CDCl_3$ as the solvent.

^{1}H NMR δ: 9.83(br, 1H), 8.12 (d, 1H, $J = 7.8$), 7.20 (t, 1H, $J = 7.7$), 7.15 (d, 1H, $J = 7.4$), 7.02 (td, 1H, $J = 7.5$, 1.1), 3.90 (dd, 1H, $J = 9.2$, 4.9), 3.10 (m, 1H), 3.00 (m, 1H), 2.29 (s, 3H), 2.19 (m, 1H), 2.07 (m, 1H), 1.78 (m, 2H); ^{13}C NMR δ: 173.1, 136.0, 130.2, 127.4, 126.8, 124.1, 120.8, 61.3, 47.4, 30.8, 26.3, 17.6; GC-MS: $M^+ = 204$.

Preparation of Racemic cis- and Racemic trans-(S)-Proline-2-Methylcyclohexylamide (as Reference Compounds)

A small amount of BOC-proline was dissolved in 40 ml chloroform and the solution cooled to 0°C under nitrogen. Triethylamine (3 eq.), 1.2 eq. hydroxybenzotriazole, 1 eq. 2-methylcyclohexylamine (*cis* : *trans* = 1 : 3), and 1.2 eq. *N*-(3-dimethylaminopropyl)-*N*′-ethyl-carbodiimide hydrochloride were added to the cooled solution in succession. The solution was allowed to warm to room temperature and was stirred overnight under nitrogen. After washing the solution three times with 1 N HCl and twice with saturated sodium bicarbonate solution and finally with a saturated salt solution, the solvent was removed *in vacuo* to yield racemic *cis*- and racemic *trans*-BOC-(*S*)-proline-2-methylcyclohexylamide with a *cis–trans* ratio of 1 : 3. Deprotection of the racemic amides was carried out in autoclavable sample bottles using a solution of dry HCl in dioxane. Thus, racemic *cis*- and racemic *trans*-(*S*)-proline-2-methylcyclohexylamide with a *cis* to *trans* ratio of 1 : 3 were obtained. The dioxane was then evaporated in a stream of air and about 0.5 ml of dichloromethane and 0.05 ml of perfluoropropionic anhydride were added. The mixture was heated to 110°C for 5 min after sealing the sample bottle. The excess anhydride was evaporated in a stream of air along with dichloromethane and the contents of the sample bottle were dissolved in fresh dichloromethane. The perfluoropropionic acid derivatives of the racemic *cis*- and *trans*-(*S*)-proline-2-methylcyclohexylamide were then injected into a GC equipped with a RTX-200 capillary column. The isolated product of catalytic hydrogenation was derivatized similarly. Comparison of the chromatogram and mass spectra of the derivatized racemic mixture to those of the derivatized product of catalytic hydrogenation confirmed that the *cis* products were obtained in excess during catalytic hydrogenation.

Preparation of (S)-Proline-(1R, 2S)-2-methylcyclohexylamide (as Reference Compound)

The optically active BOC-(*S*)-proline-(1*R*,2*S*)-2-methylcyclohexylamide *cis* isomer was synthesized as described above except that the optically active (1*R*,2*S*)-2-methylcyclohexylamine hydrochloride (synthesized using the procedure reported by Knupp and Frahm (21)) was used instead of racemic 2-methylcyclohexylamine. Deprotection of BOC-(*S*)-proline-(1*R*,2*S*)-2-methylcyclohexylamide and subsequent derivatization of the optically pure (*S*)-proline-(1*R*,2*S*)-2-methylcyclohexylamide isomer was carried out as reported above for the racemic product. Comparison of the chromatogram and the mass spectrum of the derivatized optically pure product to those of derivatized product of catalytic hydrogenation, as for the racemic mixture, revealed the absolute configuration of the *cis* products.

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