Diastereoselective hydrogenation of 2-methylnicotinic acid derivatives with supported metallic catalysts

Najiba Douja, Michèle Besson*, Pierre Gallezot, Catherine Pinel

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

Abstract

The diastereoselective hydrogenation of 2-methylnicotinic acid covalently bound to different chiral auxiliaries was performed on Pd, Rh and Ru supported catalysts. The *cis* isomers were formed predominantly with a diastereoselectivity influenced by the structure of the chiral inductor and the nature of the catalyst. The best diastereoselectivity (35%) was obtained when pantolactone was used as chiral auxiliary. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Diastereoselection; Hydrogenation; Pyridine; Piperidine; Catalysts

1. Introduction

The stereoselective synthesis of chiral substituted piperidines is of great interest due to their presence in many natural products and pharmacologically active compounds [1]. Different routes were proposed for the asymmetric synthesis of such ring systems and significant results were reported in different reviews [2–4]. Few of them concerned the preparation of optically active piperidine rings starting from the corresponding substituted pyridine substrates. During the last 2 years several groups focussed on the asymmetric hydrogenation of nicotinic acid derivatives. Studer and co-workers [5] performed a two steps synthesis of ethyl nipecotinate: ethyl tetrahydronicotinate was first isolated, then the last C=C double bond was hydrogenated using dihydrocinchonidine/Pd catalyst. Moderate ee of up to 24% was achieved at low conversion. The same group performed the enantioselective,

homogeneous hydrogenation of nicotinic and picolinic acids and of the corresponding esters catalysed by diphosphine–Rh complexes. None of the nine tested ligands yielded more than 27% ee [6]. At the same time, Raynor et al. [7] described the direct enantioselective hydrogenation of ethyl nicotinate with a chiral ferrocenyl-palladium catalyst anchored within MCM-41 mesoporous material. While the use of the corresponding homogeneous catalyst resulted in the production of racemic compound, the confined catalyst yielded 17% ee. Recently, we developed the synthesis of optically active cyclohexane derivatives from the corresponding aromatic rings. The diastereoisomeric route was adopted, since the direct enantioselective approach was unsuccessful [8,9]. Thus, the hydrogenation of *o*-toluic acid coupled with proline ester or pyroglutamic ester was performed with Rh/Al$_2$O$_3$ and the corresponding cyclohexanoic compound was obtained with de (diastereoisomeric excess) up to 95% [10,11]. It was checked that hydrolysis occurred without epimerization by comparing the ee of the acid with the de of the reaction. Encouraged by these results, we adopted this approach for

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* Corresponding author. Tel.: +33-4-7244-5358;
fax: +33-4-7244-5399.
E-mail address: mbesson@catalyse.univ-lyon1.fr (M. Besson).

the synthesis of optically active substituted piperidine derivatives. In the present work, 2-methylnicotinic acid was used as model compound. The diastereoselective hydrogenation of this type of compounds has been recently published by Hegedus et al. [12] who described the hydrogenation of nicotinic acid grafted to proline over supported metallic catalysts. They claimed de up to 94% but in our hands, we could not reproduce these results. After discussion with the authors, they agreed that this de was not reproducible and the maximum de they can reach was 30% [13].

2. Experimental section

NMR ^{1}H and ^{13}C spectra were recorded on AC 250 Bruker spectrometers using residual solvent as reference (CDCl$_3$: δH: 7.24 ppm, δC: 77 ppm). FT-IR spectra were recorded on a Bruker Vector 22 apparatus. Elemental analyses were performed at the "Service Central d'Analyse" of CNRS.

2.1. Methyl-2-nicotinic acid chloride

To a stirred solution of 2-methylnicotinic acid (2 g) under nitrogen at 0 °C was added thionyl chloride (16 ml, 15 equiv.). The solution was stirred at 50 °C for 5 h and concentrated. The brown solid was washed twice with ether (2 × 30 ml) then dried to give 1.9 g of a beige solid (yield: 85%). ^{1}H RMN (D$_2$O, 250 MHz): δ (ppm) 8.90 (dd, 8.1 Hz, 1.5 Hz, 1H); 8.66 (dd, 6 Hz, 1.5 Hz, 1H); 7.89 (dd, 6 Hz, 8.1 Hz, 1H); 2.90 (s, 3H). ^{13}C RMN (D$_2$O, 63 MHz): δ (ppm) 150.1; 147.3; 142.3; 127; 124.2; 19.2. IR (cm^{-1}): 3425; 3059–3096; 2929–3096; 1599; 1576; 1092.

2.2. Methyl (S) (2-methylnicotinyl) prolinate (Pypro)

To a stirred solution of 2-methylnicotinic acid chloride (5 g) in chloroform (50 ml) under argon at 0 °C were added successively, methyl prolinate (5.3 g, 1 equiv.) and triethylamine (13.4 ml, 3 equiv.) and stirring continued overnight at room temperature. The organic layer was washed with water, dried (MgSO$_4$) and concentrated to give a brown oil. Purification on silica gave 7.3 g of a slightly yellow oil (92%). ^{1}H RMN (CDCl$_3$, 250 MHz): δ (ppm) 8.5 (dd, 5.2 Hz,

1.7 Hz, 1H); 7.55 (dd, 7.7 Hz, 1.7 Hz, 1H); 7.15 (dd, 7.75 Hz, 5.25 Hz, 1H); 4.5 (dd, 8 Hz, 3.7 Hz, 1H); 3.75 (s, 3H); 3.1–3.4 (m, 2H); 2.55 (s, 3H); 1.7–2.5 (m, 4H); ^{13}C RMN (CDCl$_3$, 63 MHz): δ (ppm) 172.3; 168.2; 154.8; 149.7; 133.8; 132.0; 120.8; 58.8; 52.3; 48.7; 29.5; 24.8; 22.1; M/S: *m/z* 65, 92, 120 (100%), 189, 248 (M); IR (cm^{-1}): 3050; 3000; 2881; 2960; 1744; 1638; 1584; 1412; 1281; 1198; $[\alpha]_D^{20}$: −84 (*c* = 1, CHCl$_3$); Anal. calcd for C$_{13}$H$_{16}$·N$_2$O$_3$: C, 62.9; H, 6,5; N, 11.3; found: C, 61.7; H, 6.6; N, 11.0.

2.3. Methyl (S) (2-methylnicotinyl) pyroglutamate (Pypyro)

To a stirred solution of 2-methylnicotinic acid chloride (5.8 g) in chloroform (50 ml) under argon at 0 °C were added successively, methyl pyroglutamate (5.3 g, 1 equiv.) and triethylamine (15.6 ml, 3 equiv.) and stirring continued for 8 h at reflux. The organic layer was washed with water, dried (MgSO$_4$) and concentrated to give a brown oil. Purification on silica gave 6.7 g of a slightly yellow oil (68%). ^{1}H RMN (CDCl$_3$, 250 MHz): δ (ppm) 8.6 (dd, 4.9 Hz, 1.7 Hz, 1H); 7.5 (dd, 7.6 Hz, 1.7 Hz, 1H); 7.15 (dd, 7.6 Hz, 4.9 Hz, 1H); 5.0 (dd, 9 Hz, 3.1 Hz, 1H); 3.8 (s, 3H); 2.55 (s, 3H); 1.4–1.9 (m, 4H); ^{13}C RMN (CDCl$_3$, 63 MHz): δ (ppm) 173.1; 171.2; 168.8; 155.3; 150.2; 134.8; 130.7; 120.2; 60.3; 57.7; 31.4; 22.8; 21.5; M/S: *m/z* 65, 92, 120(100%), 203, 247, 262(M); IR (cm^{-1}): 3050; 2882; 2960; 1744; 1637; 1571; 1444; 1198; $[\alpha]_D^{20}$: −90 (*c* = 1, CHCl$_3$); Anal. calcd for C$_{13}$H$_{14}$N$_2$O$_4$: C, 62.9; H, 5.4; N, 10.7; found: C, 59.2; H, 6.0; N, 10.5.

2.4. Methyl (R) (2-methylnicotinyl) pantolactone (Pypanto)

To a stirred solution of 2-methylnicotinic acid chloride (2.1 g) in chloroform (15 ml) under argon at 0 °C were added successively, pantolactone (3.2 g, 1 equiv.) in 15 ml chloroform and triethylamine (5.5 ml, 3 equiv.) and stirring continued for 8 h at 60 °C. The organic layer was washed with water (3 × 30 ml), dried (MgSO$_4$) and concentrated to give a brown oil. Purification on alumina gave 1.2 g of a beige powder (38%). ^{1}H RMN (CDCl$_3$, 250 MHz): δ (ppm) 8.65 (dd, 4.8 Hz, 1.8 Hz, 1H); 8.26 (dd, 7.9 Hz, 1.8 Hz, 1H); 7.23 (dd, 7.9 Hz, 4.8 Hz, 1H); 5.6 (s, 1H); 4.1 (s, 2H); 2.85 (s, 3H); 1.3 (s, 3H); 1.2 (s,

3H); ^{13}C RMN (CDCl$_3$, 63 MHz): δ (ppm) 172.1; 165.2; 160.6; 152.6; 138.8; 124.1; 121.2; 76.3; 75.8; 40.5; 25.1; 23.2; 20.2; M/S: m/z 65, 92, 120(100%), 249 (M); IR (cm^{-1}): 3050; 2960; 2881; 1782; 1726; 1585; 1469; 1291; 1133; $[\alpha]_D^{20}$: +8 ($c = 1$, CHCl$_3$); mp = 100–101; Anal. calcd for C$_{13}$H$_{15}$NO$_4$: C, 62.6; H, 6.0; N, 5.6; found: C, 62.2; H, 6.1; N, 5.6.

2.5. Methyl (S)-N-(2-methylnicotinyl) prolinol (Pyprolynol)

To a stirred solution of 2-methylnicotinic acid chloride (2.1 g) in chloroform (15 ml) under argon at 0 °C were added successively, 2-pyrrolidinemethanol (1.3 g, 1 equiv.) in 15 ml chloroform and triethylamine (5.5 ml, 3 equiv.) and stirring continued for 24 h at room temperature. The organic layer was washed with water (3 × 30 ml), dried (MgSO$_4$) and concentrated. Purification on alumina gave 560 mg of a slightly brown oil (20%). ^{1}H RMN (CDCl$_3$, 250 MHz): δ (ppm) 8.52 (dd, 4.9 Hz, 1.7 Hz, 1H); 7.53 (dd, 7.6 Hz, 1.7 Hz, 1H); 7.23 (dd, 7.6 Hz, 4.9 Hz, 1H); 4.4 (m, 1H); 3.8 (d, 3.6 Hz, 2H); 3.2 (dd, 7.4 Hz, 6 Hz, 2H); 2.54 (s, 3H); 1.7–2.3 (m, 4H); ^{13}C RMN (CDCl$_3$, 63 MHz): δ (ppm) 170.3; 154.0; 149.7; 133.7; 132.5; 121.0; 66.4; 61.1; 49.8; 28.4; 24.6; 22.1; M/S: m/z 65, 92, 120(100%), 189, 202, 220 (M); IR (cm^{-1}): 3370; 3050; 2960; 2900; 1618; 1420; 1053; $[\alpha]_D^{20}$: −20 ($c = 1$, CHCl$_3$).

2.6. Methyl (S) (2-methylnicotinyl) methoxymethylpyrrolidine (Pmmp)

To a stirred solution of 2-methylnicotinic acid chloride (500 mg) in chloroform (15 ml) under argon at 0 °C were added successively, 2-methoxymethylpyrrolidine (370 mg, 1 equiv.) in 5 ml chloroform and triethylamine (1.3 ml, 3 equiv.) and stirring continued for 24 h at room temperature. The organic layer was washed with water (3 × 30 ml), dried (MgSO$_4$) and concentrated. Purification on alumina gave 243 mg of a yellow oil (40%). ^{1}H RMN (CDCl$_3$, 250 MHz): δ (ppm) 8.55 (dd, 4.9 Hz, 1.9 Hz, 1H); 7.5 (dd, 7.6 Hz, 1.9 Hz, 1H); 7.1 (dd, 7.6 Hz, 4.9 Hz, 1H); 4.37 (m, 1H); 3.70 (dd, 9.4 Hz, 5.6 Hz, 1H); 3.57 (dd, 9.4 Hz, 3.4 Hz, 1H); 3.35 (s, 3H); 2.9–3.2 (m, 2H); 2.5 (s, 3H); 1.8–2.1 (m, 4H); ^{13}C RMN (CDCl$_3$, 63 MHz): δ (ppm) 168.2; 154.3; 149.4; 133.7; 133.1; 120.9; 72.2; 59.1; 56.5;

49.3; 27.8; 24.6; 22.2; M/S: m/z 65, 92, 120(100%), 189, 202, 234 (M); IR (cm^{-1}): 3050; 2950; 2820; 1637; 1411; 1153; $[\alpha]_D^{20}$: +198 ($c = 1$, CHCl$_3$).

2.7. Catalysts

The catalysts used for hydrogenation were 4.2% Rh/C (Aldrich, ref 20,616-4), 3.8% Rh/Al$_2$O$_3$ (Aldrich, ref 21,285-7), 4.6% Ru/C (Aldrich, ref 20,618-0), 4.9% Pd/C (Aldrich, ref 20,568-0), 0.7% Rh–3.3% Pd/C (Hereaus, ref K-0234). High-resolution transmission electron microscopy showed that most of the metallic particles in the catalysts were in the size range 1–4 nm.

2.8. Typical hydrogenation reaction and analysis

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 the presence of 10–12 mol% of metal as the catalyst. Sampling of the mixture, to follow reaction progress, was possible and the conversion and selectivity were determined from gas chromatography (GC) analyses which were performed using a Shimadzu GC14A apparatus with a J&W DB1701 column. The reaction products were identified by GC–MS analysis using a Fisons GC 8000 apparatus.

3. Results and discussions

The asymmetric hydrogenation of substrate **1** led to the formation of the two *cis* isomers **2** and **3** and the two *trans* isomers **4** and **5** (Fig. 1). In order to determine the relative configuration of the product, the hydrogenation of the 2-methylnicotinic acid was performed with 4.2% Rh/C catalyst. GC analysis of the mixture indicated the formation of two compounds with a ratio 80/20. The NMR analysis of the crude mixture was performed and the chemical shifts were compared with literature data [14]. This allowed us to attribute the main compound to the *cis* isomer. After coupling with methyl prolinate, the four diastereoisomers were obtained and separated by GC analysis. The respective integrals of the signals were 40/40/10/10,
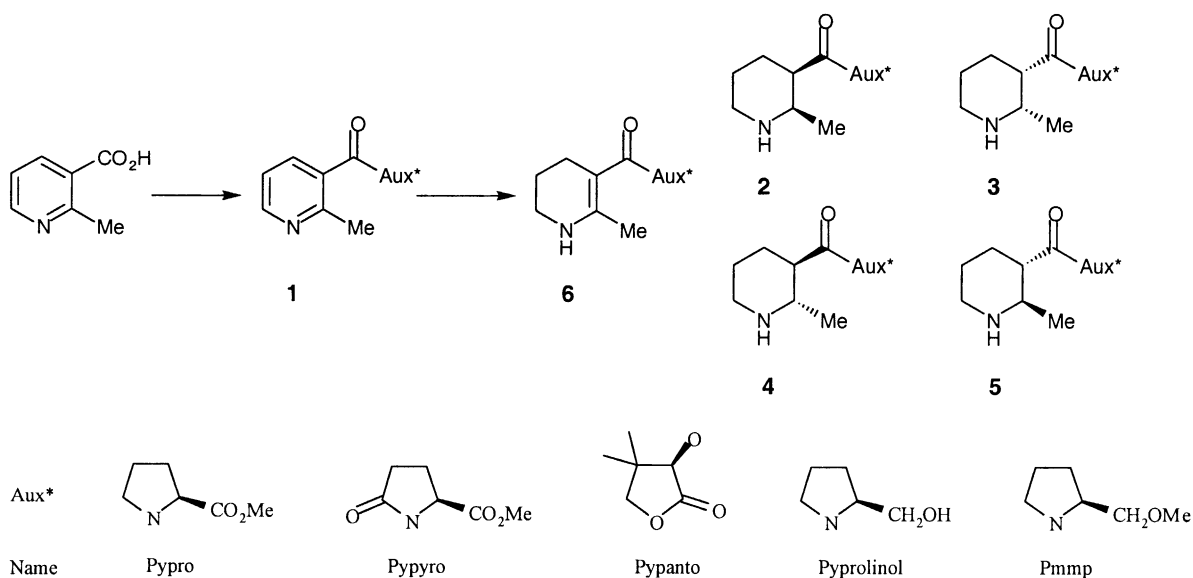
Fig. 1. Diastereoselective hydrogenation of nicotinic derivatives.

the two first corresponding to the *cis* isomers, while the two latter were the *trans* ones. The absolute configuration of the diastereoisomers was not established. Upon reduction, the two *cis*-hydrogenated isomers predominated under all conditions and the de of the *cis* isomers was defined as

$$de\,(\%) = \left|\frac{\mathbf{2}-\mathbf{3}}{\mathbf{2}+\mathbf{3}}\right| \times 100$$

In addition, an intermediate product was detected in some cases and it was identified as the enamine **6**.

3.1. Hydrogenation of Pypro

We first focussed on proline which was shown to be an efficient chiral auxiliary in the hydrogenation of the *o*-toluic derivatives (de up to 68%). The hydrogenation of methyl (*S*) (2-methylnicotinyl) prolinate (Pypro) over metallic heterogeneous catalysts was studied. Whatever the reaction conditions less than 3% of *trans* product were obtained and surprisingly no enamine was detected with that substrate.

3.2. Effect of metal catalyst

The influence of the catalytic metal on the initial reaction rate and the diastereoselectivity in the

hydrogenation of Pypro is summarised in Table 1. For comparison, all reactions were carried out at 50 °C. Hydrogenation was effective using rhodium, ruthenium or palladium catalysts, but the initial reaction rate was largely affected by the nature of the metal. While rhodium based catalysts exhibited high activity (7 and 7.2 mol h^{-1} mol$_{metal}$$^{-1}$ on carbon and alumina, respectively), ruthenium and, even more, palladium catalyst hydrogenated the substrate at much lower reaction rate. The highest de was measured for the Rh/Al$_2$O$_3$ catalyst which was also the most stereoselective for the hydrogenation of aromatic ring [10,11]. This was attributed to a flat morphology of the

Table 1
Influence of the catalyst on the initial reaction rate and the diastereoselectivity of hydrogenation of Pypro (reaction conditions: Pypro $\approx$ 0.02 M, catalyst/substrate = 10–12%, EtOH, 50 °C, 50 bar)

Catalyst	Conversion (12 h) (%)	r_i (mol h^{-1} mol$_{Rh}$$^{-1}$)	de (*cis*) (%)
Rh/C (4.2%)	100	7	14
Rh/Al$_2$O$_3$ (3.8%)	100	7.2	26
Ru/C (4.6%)	100	1.8	25
Pd/C (4.9%)	90	0.5	11
Rh (0.7%)–Pd (3.2%)/C[a]	27 (48 h)	<0.1	10

[a] Reaction was performed at 75 °C.

Rh-particles supported on alumina compared to those supported on carbon as suggested by TEM analysis showing that the contrast of alumina-supported particles was lower than that of carbon-supported metallic catalyst [15]. A bimetallic catalyst Pd–Rh/C, known to be more efficient than Rh catalysts for the hydrogenation of substituted aromatic ring [16], exhibited both very low diastereoselectivity (10%) and activity ($< 0.1 \, \text{mol h}^{-1} \, \text{mol}_{\text{metal}}^{-1}$) for the hydrogenation of Pypro even at 75 °C.

3.3. Effect of temperature

The effect of the temperature on the activity of the catalyst and on the de was investigated in the presence of Rh/C and Rh/Al$_2$O$_3$ catalysts which were the most active. As expected, the reaction rate increased with temperature (Table 2). No by-products were observed even at 100 °C. The influence on the diastereoselectivity was much pronounced in the case of the carbon-supported catalyst, since the optical yield decreased from 18 to 10% when the temperature increased from 25 to 100 °C. On the contrary, the de was not affected by the temperature when the reaction was performed in the presence of alumina-supported catalyst (26–28% de).

3.4. Effect of solvent

Then, the reaction was performed at room temperature in various solvents (Table 3). The initial reaction rate was strongly dependent on the nature of the solvent: the less polar the solvent, the lower the reaction rate. Moreover, as far as the alcoholic solvents were concerned, the reaction rate and the acidity of the solvent varied in a similar way ($pK_{a, \text{MeOH}} >$

Table 2

Influence of the temperature on the initial reaction rate and diastereoselectivity of hydrogenation of Pypro (reaction conditions: Pypro, Rh/C = 12%, ethanol, 50 bar)

Temperature (°C)	4.2% Rh/C		3.8% Rh/Al$_2$O$_3$	
	r_i (mol h^{-1} mol$_{\text{Rh}}^{-1}$)	de (%)	r_i (mol h^{-1} mol$_{\text{Rh}}^{-1}$)	de (%)
25	3.6	18	1.5	28
50	7.4	14	7.2	26
100	17.9	10		

Table 3

Influence of the solvent on initial reaction rate and diastereoselectivity of hydrogenation of Pypro (reaction conditions: Pypro ≈ 0.02 M, Rh/C = 12%, 50 bar, RT)

Solvent	Dielectric constant [20]	r_i (mol h^{-1} mol$_{\text{Rh}}^{-1}$)	de (%)
MeOH	32.70	3.8	19
EtOH	24.55	3.6	18
iPrOH	19.92	1.4	5
CH$_2$Cl$_2$	8.93	1.4	18
AcOEt	6.02	0.4	15

$pK_{a, \text{EtOH}} > pK_{a, i\text{PrOH}}$). The evolution of the initial reaction rate is not directly correlated to one of these two characteristics of the solvents, but more probably to a combination of many parameters. Concerning the diastereoselectivity, a small effect of the solvent was observed and moderate de up to 15–19% was achieved except in iPrOH, in which almost racemic piperidine was produced.

It is well known that, hydrogenation of pyridine derivatives occurs readily in acidic media [17]. The results of the catalytic hydrogenation of Pypro in the presence of acid, over carbon-supported rhodium, are summarised in Table 4. As expected, the reaction rate increased in acetic acid compared to ethanol (7 and 3.6 mol h^{-1} mol$_{\text{Rh}}^{-1}$, respectively). A similar effect was achieved when 0.9 equiv. of HCl was added to ethanol. In the presence of one equivalent of tartaric acid ((D)-TA or racemic-TA) a strong enhancement of the initial reaction rate was observed. Actually, upon hydrogenation, basic piperidine is produced, which may poison the catalyst by its strong adsorption on the surface; in the protonated form this adsorption is less important. Moreover, formation of pyridinium ions is also thought to change the nature of the adsorption

Table 4

Influence of acid on the initial reaction rate and diastereoselectivity of hydrogenation of Pypro (reaction conditions: Pypro, Rh/C = 12%, 50 bar, RT)

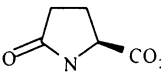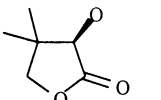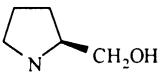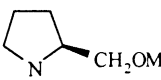| Solvent	r_i (mol h^{-1} mol$_{\text{Rh}}^{-1}$)	de (%)
EtOH	3.6	18
AcOH	7	5
EtOH + HCl	5	19
EtOH + (D)-tartaric Acid	15.9	15
EtOH + racemic-tartaric acid	13.4	15
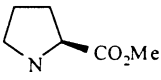
mode of the substrate from edgewise to flat. The flat adsorption is also supposed to improve the diastereoselectivity of the reaction because of a larger differentiation of the two faces of the heteroaromatic. However, no positive effect of the acidic medium on the optical yield was observed. Even worse, the product was almost racemic in acetic acid. Tartaric acid is an efficient modifier for the hydrogenation of a-ketoesters over nickel catalyst [18]. The addition of optically pure (D)-tartaric acid had no effect on the de, compared to the addition of racemic-tartaric acid. That means, that no significant interaction between tartaric acid and substrate occurred during the hydrogenation step.

3.5. Hydrogenation of methyl-2-nicotinic acid coupled with other chiral inductors

Considering the influence of the nature of the chiral auxiliary on the diastereoselective hydrogenation of aromatic compounds [19], we tested other chiral inductors such as methyl (S)-pyroglutamate (Pypyro), which led to an outstanding diastereoselectivity during the hydrogenation of aromatic derivatives [11]. To establish the parameters which can influence the diastereoselectivity, some other auxiliaries, even more expensive, such as (S)-prolinol (Pyrolinol), (S)-methylmethoxypyrrolidine (Pmmp) and (R)-pantolactone (Pypanto) were studied. The

Table 5
Influence of the nature of the chiral auxiliary on diastereoselectivity and initial reaction rate (reaction conditions: substrate ≈ 0.02 M, Rh/C = 12%, 50 bar, RT)

Auxiliary	Acronym	r_i (mol h^{-1} mol$_{Rh}^{-1}$)	de (%)
CO$_2$Me	Pypro	3.6	18
CO$_2$Me	Pypyro	9	28
(pantolactone structure)	Pypanto	15.2	31
CH$_2$OH	Pyrolinol	ε[a]	–
CH$_2$OMe	Pmmp	0.3[a]	<5

[a] Reaction performed at 50 °C.

reactions were performed over carbon-supported rhodium catalyst and the main results achieved in the hydrogenation of the different substrates are reported in Table 5.

A higher initial reaction rate was observed when pyroglutamic ester was used as chiral auxiliary instead
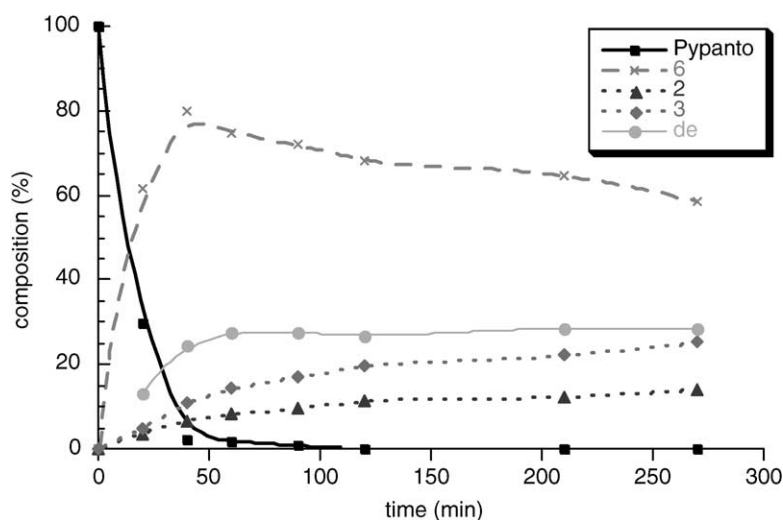

Fig. 2. Distribution of products versus time for hydrogenation of Pypanto over Rh/C. Reaction conditions: see Table 5.

of the proline ester (9 and $3.6 \, mol \, h^{-1} \, mol_{Rh}^{-1}$, respectively). No intermediate **6** was detected and less than 3% of *trans* compounds were produced. However, the diastereoselectivity was not as high as expected and reached only 28%. None of the other supported metallic catalysts led to an improvement of the de during hydrogenation of Pypyro. Concerning the Pyprolinol and the Pmmp substrates, the hydrogenation proceeded at very low reaction rate even at $50\,°C$ and the products were obtained in a racemic form.

Interesting results were achieved when (*R*)-pantolactone was bonded to methyl-2-nicotinic acid. The typical product distribution as a function of time is shown in Fig. 2. The Pypanto substrate disappeared rapidly to yield mainly the tetrahydrogenated intermediate **6** (up to 80% at 100% conversion of **1**). Simultaneously the two *cis* isomers **2** and **3** were formed. The intermediate **6** was further hydrogenated; this transformation was very slow and after 24 h reaction time, 30% of **6** were still present. The de was nearly constant as a function of conversion and slightly higher diastereoselectivity in the *cis* isomers of 31% was achieved. The hydrogenation of Pypanto was studied over several supported metallic catalysts (Rh/Al_2O_3, Ru/C, Ru/Al_2O_3, Pd/C, Rh–Pd/C). Whatever the catalyst, large amount of intermediate 6 was detected and de from 17 to 35% were obtained.

4. Conclusion

The diastereoselective hydrogenation of methyl-2-nicotinic acid bonded to several optically pure auxiliaries was studied in the presence of supported metallic catalysts. Moderate diastereoselectivities (up to 35%) were achieved whatever the substrate or the catalytic system. The diastereoselective approach in that case was not as efficient as in the hydrogenation of the *o*-toluic derivatives and only a slight improvement of the selectivity was achieved compared to the enantioselective route [5–7]. The presence of the nitrogen atom in the aromatic ring modified deeply the mechanism of hydrogenation and probably due to electronic effects, the selectivity of the transformation was lowered. The structure of the chiral auxiliary has a lower effect on the diastereoselectivity than with the *o*-toluic derivatives. Theoretical studies of the adsorption of the nicotinic derivatives on Rh surface atoms are under progress to model the reaction pathway.

References

[1] M. Rubiralta, E. Giralt, A. Diez, Piperidines, Structure, Preparation, Reactivity and Synthetic Applications of Piperidines and its Derivatives, Elsevier, Amsterdam, 1991.
[2] P. Hammann, Org. Synth. Highlights 2 (1995) 323.
[3] P.D. Bailey, P.A. Millwood, P.D. Smith, Chem. Commun. (1998) 633.
[4] I. Ojima, D.M. Iula, Alkaloids: Chem. Biol. Persp. 13 (1999) 372.
[5] H.-U. Blaser, H. Hönig, M. Studer, C. Wedemeyer-Exl, J. Mol. Catal. 139 (1999) 253.
[6] M. Studer, C. Wedemeyer-Exl, F. Spindler, H.-U. Blaser, Monatshefte für Chemie 131 (2000) 1335.
[7] S.A. Raynor, J.M. Thomas, R. Raja, B.F.G. Johnson, R.G. Bell, M.D. Mantle, Chem. Commun. (2000) 1925.
[8] K. Nasar, F. Fache, M. Lemaire, J.-C. Beziat, M. Besson, P. Gallezot, J. Mol. Catal. 87 (1994) 107.
[9] C. Exl, E. Ferstl, H. Hönig, R. Rogi-Kohlenprath, Chirality 7 (1995) 211.
[10] M. Besson, B. Blanc, M. Champelet, P. Gallezot, K. Nasar, C. Pinel, J. Catal. 170 (1997) 254.
[11] M. Besson, P. Gallezot, S. Neto, C. Pinel, Chem. Commun. (1998) 1431.
[12] L. Hegedus, V. Hada, A. Tungler, T. Mathe, L. Szepesy, Appl. Catal. A 201 (2000) 107.
[13] A. Tungler, Personal communication.
[14] G. Lapuyade, G. Schlewer, C.G. Wermuth, Bull. Soc. Chim. Fr. 4 (1986) 663.
[15] M. Besson, P. Gallezot, C. Pinel, S. Neto, in: H.U. Blaser, A. Baiker, R. Prins (Eds.), Studies in Surface Science and Catalysi, Heterogeneou Catalysis and Fine Chemicals, Vol. 108, Elsevier, Amsterdam, 1997, p. 215.
[16] H. Steiner, P. Giannousis, A. Pische-Jacques, H.U. Blaser, Top. Catal. 13 (2000) 191.
[17] P.N. Rylander, Hydrogenation Methods, Academic Press, New Press, 1985, p. 135.
[18] Y. Izumi, Adv. Catal. 32 (1983) 215.
[19] M. Besson, P. Gallezot, S. Neto, C. Pinel, Tetrahedron: Asymmetry 11 (2000) 1809.
[20] C. Reichart, Solvents and Solvent Effects in Organic Chemistry, VCH, Weinheim, 1990, p. 408.