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Diastereoselective heterogeneous catalytic hydrogenation of 2-methyl nicotinic acid using pyroglutamate chiral auxiliary

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Abstract—The diastereoselective hydrogenation of 2-methyl nicotinic acid covalently bound to proline ester or pyroglutamic ester over supported metallic catalyst yielded moderate diastereoselectivity (26%). The hydrogenation of the corresponding pyridinium salt was studied and similar de's were achieved.

Optically active substituted piperidines derivatives are attractive molecules because their structure is present in several natural compounds or drugs.[1] Different strategies were described for the stereoselective synthesis of substituted piperidines such as aza Diels–Alder,[2] Sharpless dihydroxylation,[3] or intramolecular Mannich reaction.[4] Recently, several groups have investigated the catalytic asymmetric hydrogenation of nicotinic acid derivatives. Ethyl nipecotinate was obtained in a two-step synthesis by Studer et al. with a moderate ee (24%).[5] The tetrahydroderivative obtained in the first step was further hydrogenated with palladium-supported catalyst modified with 10,11-dihydrocinchonidine. This group performed also the homogeneous enantioselective hydrogenation of nicotinic and picolinic acids catalyzed by diphosphine–Rh complexes and ee as high as 27% was achieved.[6] Parallelly, Raynor et al.[7] published the direct enantioselective hydrogenation of ethylnicotinate using a chiral ferrocenyl-palladium catalyst anchored within MCM-41 mesoporous material with 17% ee. The diastereoselective route is an alternative approach which has been investigated. Tungler et al described diastereoselective hydrogenation of picolinic acid derivatives with 79% de.[8] In our previous studies, (*S*)-proline and (*S*)-pyroglutamic esters were used as chiral auxiliaries for the diastereoselective hydrogenation of *o*-toluic acid, resulting in moderate to high de.[8–11] We used the same procedure for the hydrogenation of 2-methyl nicotinic acid.[12] The influence of different parameters such as the nature of catalytic metal, the support, the solvent were investigated in the (*S*)-proline derivative, but it resulted in low diastereoselectivities (26% in the presence of Rh/Al_2O_3 catalyst). We also tested other chiral auxiliaries, in particular pyroglutamate methyl which had been found to induce high asymmetry (de >95%) during hydrogenation of aromatic ring.[10] However, this synthon yielded only 28% de for the hydrogenation of pyridine ring in ethanol in presence of Rh/C.

The present paper describes the attempts to improve the selectivity in hydrogenation of **1**, including hydrogenation of a pyridinium derivative **3** (Fig. 1).

The asymmetric hydrogenation of **1** formed mainly the two *cis* isomers **4a** and **4b**.[13] The influence of the catalytic metal and the temperature on the initial reaction rate and the diastereoselectivity in the hydrogenation of **1** is summarized in Table 1. For comparison, results achieved with derivative **2** (proline methyl ester derivative) are reported in brackets.[12]

Compound **1** exhibited similar behaviors as derivative **2**: in both cases, no partially hydrogenated compound was detected and the de was dependent on the nature of the metal and the support of the catalyst. Except over Pd/C for which the reactions were very slow, the methyl pyroglutamate as chiral auxiliary yielded higher initial reaction rates compared to methyl proline (respectively 17 and 7.4 mol h^{-1}. mol_{Me}^{-1} at 50°C). Moreover, these results illustrated the difficulties to predict the influence of the different parameters studied on the stereoselectivity of a selected reaction: while the carbon supported

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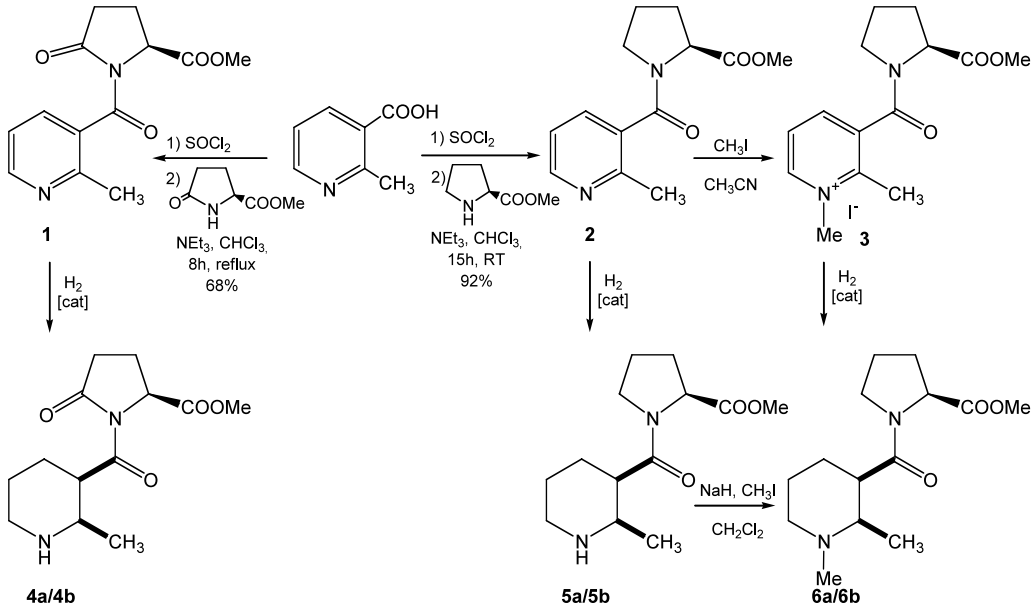

Figure 1. Synthesis of piperidine derivatives.

rhodium catalyst was more selective in hydrogenation of **1**, the best de was achieved using alumina supported rhodium catalyst for **2**. As expected, lowering the temperature of the reaction, decreased the reaction rate. Simultaneously, a small improvement of the de was observed, however, due to the low reaction rate at room temperature, it was not further possible to study the transformation at lower temperature.

Whatever the catalyst, moderate de was achieved using these two chiral auxiliaries, while they yielded very good selectivity in the case of the reduction of an aromatic ring.[10] In the latter case, the very high diastereoselectivity was attributed to the existence in solution of one preferred conformer which was supposed to be adsorbed on the metallic surface via the less hindered face.[11] Recent DFT calculations confirm this hypothesis, i.e. a flat adsorption of the benzene ring.[14] On the other hand, the presence of the lone pair of electrons on the nitrogen atom in the pyridine ring modifies the adsorption on the surface. DFT calculations showed that the structure in which the unshared pair of electrons of the nitrogen atom of the pyridine interacts vertically with the metallic surface is also stable. So, the hydrogenation through the two faces of the aromatic should be less differentiated yielding lower selectivity.

To avoid this possible interaction and force the pyridine ring to interact flat with the surface, we studied the hydrogenation of the corresponding pyridinium salts. The methyl pyridinium compound **3** was prepared by alkylation with methyl iodide in good yield (Fig. 1).

The hydrogenation was performed as previously, however the substrate was not detected by GC analysis and only the formation of the products was followed. To identify the hydrogenation products, **2** was hydrogenated to **5a** and **5b** and directly alkylated to **6a** and **6b**. To assure the total conversion of the substrate, the catalytic hydrogenation was stopped after 24 h. No aromatic proton could then be detected by NMR.

The influence of catalyst, solvent, temperature and pressure on the diastereoselectivity was studied and the main results are reported in Figure 2.

Whatever the catalyst, the de's achieved with the pyridinium salts were slightly lower than with the corresponding pyridine substrate. Since the pyridinium compound is much more reactive towards hydrogenation than the pyridine, milder reaction conditions (temperature and pressure) were tested. But even so, the diastereoselectivity was not improved as would have been expected. No improvement was achieved using palladium based catalyst.

In conclusion, the asymmetric hydrogenation of pyridine derivatives still remains challenging. The presence of the nitrogen atom in the ring affects deeply the

Table 1. Influence of the nature of the catalyst on the initial reaction rate and the diastereoselectivity of the hydrogenation of **1** (reaction conditions: ethanol, P = 50 bar)[a]

Catalyst	T (°)	ri (mol h^{-1}·mol_M^{-1})	de (*cis*) (%)
4.2% Rh/C	50	17 (7.4)	11 (14)
4.2% Rh/C	rt	9 (3.6)	28 (18)
3.8% Rh/Al_2O_3	50	9.3 (7.2)	17 (26)
4.6% Ru/C	50	3.6 (1.8)	20 (25)
4.9% Pd/C	50	0.2 (0.5)	11 (11)

[a] The catalysts used for hydrogenation were 4.2% Rh/C (Aldrich, ref 20,616-4), 3.8% Rh/Al_2O_3 (Aldrich, ref 21,285-7), 4.6% Ru/C (Aldrich, ref 20,618-0), 4.9% Pd/C (Aldrich, ref 20,568-0). High-resolution transmission electron microscopy showed that most of the metallic particles in the catalysts were in the size range 1–4 nm.

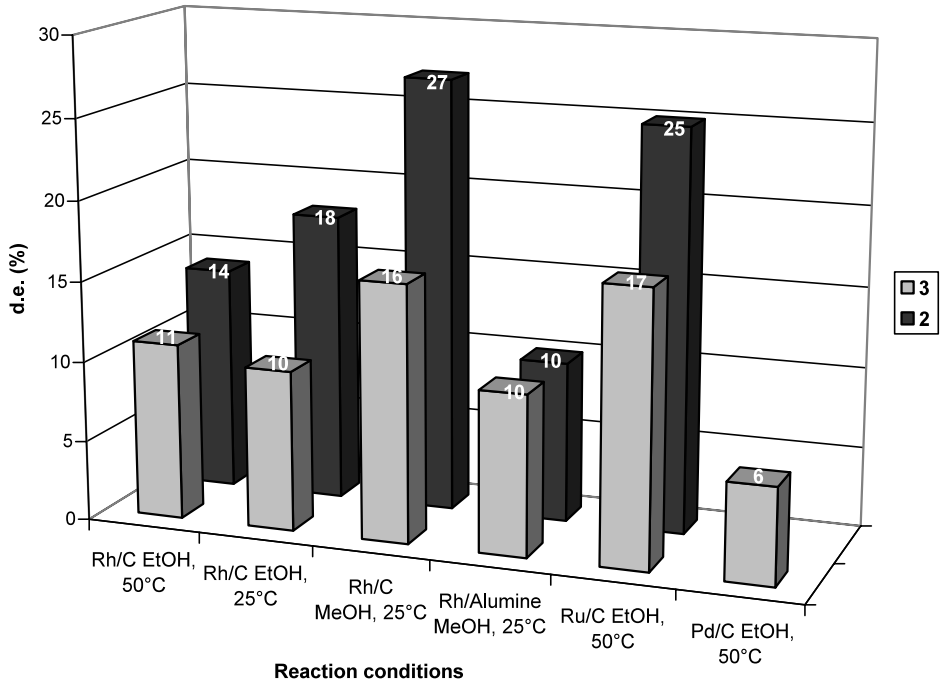

Figure 2. Diastereoselectivity for pyridine **2** and pyridinium **3** derivatives hydrogenation. ($P_{H2}=50$ bar except for Pd/C, 10 bar).

process of the hydrogenation probably by modifying the adsorption mode on the metallic surface. Up to now we did not succeed to obtain high de. Further works should be performed on hydrogenation of pyrazine to establish the influence of a second nitrogen atom in the ring.

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