Diastereoselective hydrogenation of *o*-toluic acid derivatives over supported rhodium and ruthenium heterogeneous catalysts

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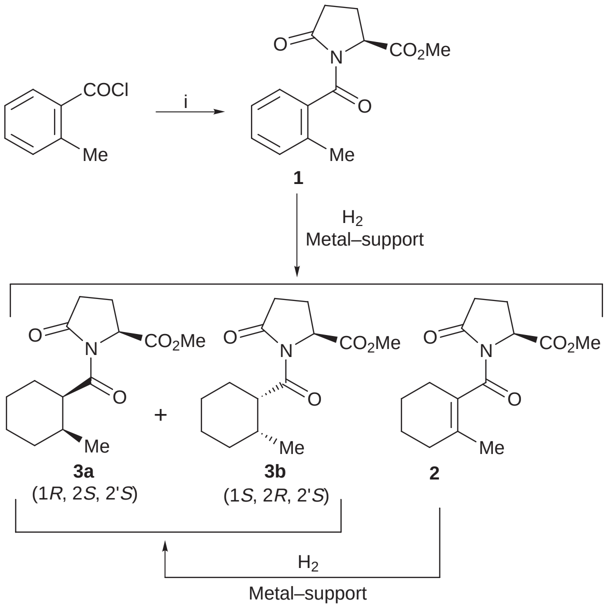
Asymmetric hydrogenation of an *o*-toluic acid derivative to 2-methylcyclohexanoic acid with high optical selectivity (up to 95%) was performed by using (*S*)-pyroglutamic acid methyl ester as a chiral auxiliary and Rh–Al_2O_3 as the catalyst.

Diastereoselective catalytic hydrogenation with heterogeneous metal catalysts has been applied for the reduction of C=C, C=O or C=N bonds.[1,2] Modest to high diastereoselectivities were obtained, depending on the chiral auxiliary used and the nature of the heterogeneous catalyst. Recently, this method was proposed to hydrogenate aromatic rings.[3,4] Thus, (*S*)-*N*-(2-methylbenzoyl)proline methyl ester was hydrogenated quantitatively on pretreated Rh–Al_2O_3 in the presence of a bulky amine (ethyldicyclohexylamine = EDCA); the *cis* isomer was obtained preferentially (yield > 97%) with diastereoisomeric excess (de) values reaching 67%.[5] We now report on the use of a pyroglutamic acid derivative as a chiral auxiliary which permits the diastereoselective reduction of aromatic moities with higher than 90% de.

Substrate **1** was synthesized with a 82% yield, after purification, by coupling under mild conditions *o*-toluoyl chloride with pyroglutamic acid methyl ester (Scheme 1).[6]‡ The hydrogenation was carried out in a stirred autoclave at a hydrogen pressure of 5 MPa at room temperature. The substrate was dissolved in EtOH and supported rhodium or ruthenium catalysts (2–5 mol%) were added. EDCA (2–3 equiv. with respect to metal) was optionally added. The typical product distribution as a function of time (entry 5) is given in Fig. 1 for a hydrogenation performed over Ru–C catalyst. The aromatic substrate was hydrogenated to **3a** and **b** with a constant de; some cyclohexenic compound **2** was formed transiently and consecutively hydrogenated to **3**. An overview of the most significant catalytic results is summarized in Table 1.



Scheme 1 *Reagents and conditions*: i, (*S*)-pyroglutamic acid methyl ester, toluene, 80 °C, N_2

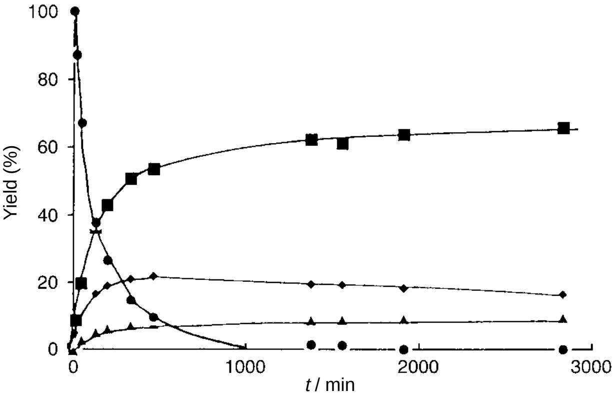


Fig. 1 Distribution of products *versus* time for hydrogenation of **1** over Ru–C (entry 5, Table 1). Reaction conditions: 2.26 mmol **1**, 0.063 mmol Ru, 130 ml EtOH, room temp., 5 MPa H_2. Less than 3% of the *trans* compound was detected. (●) **1**, (◆) **2**, (■) **3a** and (▲) **3b**.

In all reactions, only small amounts of *trans*-cyclohexane derivative were found (< 3%) and the absolute configuration of the major *cis* product was *(1S,2R,2′S)*. Hydrogenation of (*S*)-*N*-(2-methylbenzoyl) pyroglutamic acid methyl ester **1** in the presence of Rh–C catalyst resulted in 35% de, whereas on Rh–Al_2O_3 the conversion was slightly lower, although the diastereoselectivity was 90%. Addition of a bulky amine (EDCA) to the reaction medium lowered the reaction rate in both cases, but excellent diastereoisomeric excesses were observed, both on carbon (90% de) and on alumina (95% de). Compound **2** was detected in significant amounts only in the case of Rh–C; its hydrogenation gave preferentially **3b** and lowered the de.

In the case of the ruthenium catalyst, high diastereoselectivities were achieved without amine, irrespective of the support (74 and 85% de on carbon and alumina, respectively). However, it was found that the reaction was slower on the alumina-supported catalyst. The semi-hydrogenated compound **2** was

Table 1 Results for hydrogenation of *o*-toluic acid derivatives **1**

Entry	Metal–support	EDCA : metal[a]	Conversion (%)[b] after 24 h	Yield **2** (%)[b]	De (%)[b,c]
1	Rh–C (Aldrich, 3.6%)	—	100[d]	13	35
2	Rh–Al_2O_3 (Degussa, 3.7%)	—	89	5	90
3	Rh–C (Aldrich, 3.6%)	2	49	3.5	90
4	Rh–Al_2O_3 (Degussa, 3.7%)	3	49	2	95
5	Ru–C (Aldrich, 5%)[e]	—	99	19	74
6	Ru–Al_2O_3 (Degussa, 3.7%)[e]	—	61	11	85
7	Ru–C (Aldrich, 5%)[e]	3	61	10	83

[a] Molar ratio. [b] Determined by GC analysis (DB 1701). [c] The determination of the major configuration (1*S*,2*R*,2′*S*) was carried out by measuring the optical purity of the hydrolyzed product. [d] The conversion was complete after 100 min reaction. [e] Pretreated under H_2 at 300 °C for 2 h.

present in up to 19%, and due to steric constraints, it was hydrogenated with reduced de. The diastereoselectivity was increased from 74 to 83% when EDCA was added to the Ru–C catalyst.

These results clearly show that (*S*)-pyroglutamic acid methyl ester exerts much stronger chiral induction than (*S*)-proline derivatives since the de increased to 95% from 67%. This is probably due to the presence of the ketone group in the auxiliary, which plays a crucial role by interacting with the catalyst surface and blocking one of the faces of the aromatic ring.

Notes and References

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‡ *Selected data* for **1** : white crystals; mp 108 °C; $[\alpha]_D^{25}$ −28.9 (*c* 1, $CHCl_3$); δ_H ($CDCl_3$) 7.25 (m, 4 H), 4.96 (dd, 1 H, *J* 3.4, 5.8), 3.83 (s, 3 H), 2.74–2.07 (m, 4 H), 2.36 (s, 3 H); δ_C ($CDCl_3$) 173.0 (C), 171.5 (C), 170.4 (C), 135.5 (C), 135.0 (C), 130.4 (CH), 130.2 (CH), 126.9 (CH), 125.3 (CH), 57.9 (CH), 52.8 (CH_3), 31.7 (CH_2), 21.6 (CH_2), 19.2 (CH_3); ν (KBr) cm^{-1} 2928, 1751, 1679, 1304, 1218 [C, 64.62 (64.34); H, 5.77 (5.74); N, 5.32 (5.36); O, 24.07% (24.50)].

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