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Asymmetric synthesis of alkyl 5-oxotetrahydrofuran-2-carboxylates by enantioselective hydrogenation of dialkyl 2-oxoglutarates over cinchona modified Pt/Al_2O_3 catalysts

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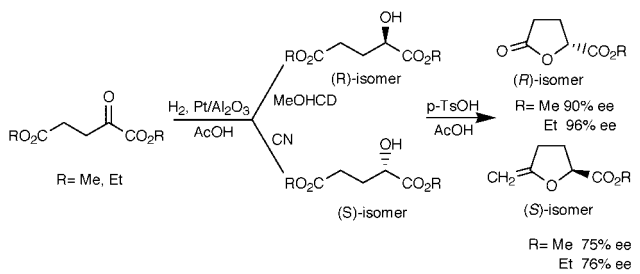
The first direct asymmetric synthesis of chiral alkyl 5-oxotetrahydrofuran-2-carboxylates (up to 96% ee), which are important building blocks in the synthesis of natural products by heterogeneous cinchona-modified Pt-catalyzed hydrogenation of α-ketoglutaric acid esters and subsequent cyclization of hydroxy esters is described.

The growing interest in the synthesis of important chiral compounds provides significant impetus for asymmetric synthesis. Owing to the recent environmental considerations and safety concerns, the use of heterogeneous asymmetric methods such as enantioselective hydrogenation are especially preferable.[1] One of those, the cinchona alkaloid-modified platinum catalyst system, was found to be especially effective in the hydrogenation of α-ketoesters and ketoacids[1] and ketoacetals.[2] The most prominent substrates are ethyl pyruvate,[3] pyruvaldehyde dimethyl acetal,[2] ketopantolactone[4] and 1-ethyl-4,4-dimethylpirrolidine-2,3,5-trione,[5] which can all be hydrogenated with excellent enantioselectivity (91–98%) over cinchona-modified Pt/Al_2O_3 catalysts.

Here, we report a new successful enantioselective synthesis of alkyl (*R*)-5-oxotetrahydrofuran-2-carboxylates, *via* the asymmetric hydrogenation of α-ketoglutaric acid esters over cinchona-modified Pt/Al_2O_3 catalyst.

The target chiral esters are very frequently used synthons in the synthesis of natural products.[6] In addition, their utilization in the free acid form as chiral derivatizing agents[7] or as a template for acyclic stereoselection through asymmetric synthesis[8] is also well known. The enantioselective hydrogenation of dialkyl 2-ketoglutarates and the subsequent cyclization to alkyl 5-oxotetrahydrofuran-2-carboxylates are shown in Scheme 1.

The existing process for the preparation of the target compounds is a template synthesis based on the deamination of enantiopure glutamic acid.[9] Asymmetric pathways to their perparation are enzymatic resolution of the racemic mixtures or direct bioreduction of ketoglutaric acid esters.[10] The former process provides high enantiomeric excess, however, the yield is obviously does not exceed 50% in the best case. The bioreduction, however, is not an efficient method for the preparation of enantiomers of high purity, since the ee values (up to 67%) vary considerably and significant decarboxylation and byproduct formation may be observed. Heterogeneous hydrogenation carried out on camphor-modified Raney Ni was also inefficient (24% ee).[11] As a consequence, to the best of our knowledge, no satisfactory enantioselective reduction of α-ketoglutaric acid derivatives has been developed.



Scheme 1

In this study two well known Pt/Al_2O_3 reference catalysts (Engelhard 4759, denoted E4759 and Johnson Matthey 94, denoted JMC94) were used while the two modifiers [cinchonidine (CD) and cinchonine (CN)] and 2-ketoglutaric acid were all Fluka products. 9-Methoxy-10,11-dihydrocinchonidine (MeOHCD) was kindly donated by Dr Martin Studer (Novartis, Basel, Switzerland). The dimethyl and diethyl α-ketoglutaric acid esters were prepared on the basis of a literature procedure.[10] The hydrogenations were performed in an atmospheric batch reactor or in a Berghof Bar 45 autoclave at 20 °C as described previously.[2,3] After hydrogenation, the hydroxyester obtained was subjected to a cyclization reaction with *p*-toluenesulfonic acid according to the literature procedure.[10] During the reaction no racemization or inversion occured, as a result the ee of the cyclic products corresponded to that of the open chain hydroxy esters. Product identification was carried out by GC–MS (HP5890 GC-HP5970 MSD) and ^{1}H NMR spectroscopy (Bruker AM500), while the enantiomeric excesses $\{ee\% (|[R] - [S]|) \times 100/([R] + [S])\}$ were monitored by chiral gas chromatography [HP 5890 GC-FID, 30 m long Cyclodex-B (J&W Scientific) capillary column, carrier gas: He, 15 psi, 125 °C, retention time for (*S*)-isomer: 31.8 min, for (*R*)-isomer: 32.5 min]. The ee values were reproducible within 2%.

According to earlier findings[1–5] two well known 5% Pt/Al_2O_3 references catalysts (E4759 and JMC94) were highly efficient in the enantioselective hydrogenation of activated α-oxo-compounds. As a result, these samples were selected for the enantioselective hydrogenation of diethyl α-ketoglutarate. Taking into account that in the literature, toluene and acetic acid have mainly been applied as solvents in these systems, both of them were tested first to find the most suitable medium, catalyst and modifier for the hydrogenation. Although the enantioselectivity in toluene is only moderate (up to 63% ee), using acetic acid as solvent, the results are excellent (up to 93% ee) and comparable or even slightly higher than those obtained with ethyl pyruvate.[1,2] As generally found,[12] the ee was always higher with the CD modifier than with the CN modifier. The results obtained in the two solvents, including reaction rates and optical yields, are tabulated in Table 1.

In the light of the results shown in Table 1 it can be concluded that the JMC catalyst exhibited a slight but clear increase in both reaction rates and optical yields (5–6% ee increase) compared to E4759. It seems also clear that MeOHCD is the best modifier for the reaction, the ee values obtained mostly exceed by *ca.* 10% those achieved with cinchonidine.

Since the enantioselective hydrogenation of α-ketoesters over the Pt-cinchona catalyst system generally shows better performance (higher reaction rates and optical yields) under elevated hydrogen pressures, the effect of hydrogen pressure, on the present system was also studied. According to the literature[1] a wide hydrogen pressure (1–100 bar) was studied with acetic acid as solvent using the JMC94 catalyst and MeOHCD modifier.

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Table 1 Enantioselective hydrogenation (and subsequent cyclization) of diethyl α-ketoglutarate to ethyl 5-oxotetrahydrofuran-2-carboxylate over 5% Pt/Al_2O_3 catalysts (E4759, JMC94) under 1 bar hydrogen pressure and at 20 °C (values are the average of three experiments)

Entry	Solvent	Catalyst	Modifier[a]	*r*/mmol $min^{-1}g_{cat}^{-1}$	Product configuration	ee (%)
1	Toluene	E4759	CD	0.51	(*R*)	53
2	Toluene	E4759	CN	0.34	(*S*)	25
3	Toluene	E4759	MeOHCD	0.53	(*R*)	47
4	Toluene	E4759	—	0.49	Racemic	—
5	AcOH	E4759	CD	0.50	(*R*)	78
6	AcOH	E4759	CN	0.37	(*S*)	60
7	AcOH	E4759	MeOHCD	0.55	(*R*)	87
8	AcOH	E4759	—	0.12	Racemic	—
9	AcOH	JMC94	CD	0.75	(*R*)	83
10	AcOH	JMC94	CN	0.46	(*S*)	66
11	AcOH	JMC94	MeOHCD	1.41	(*R*)	93
12	AcOH	JMC94	—	0.34	Racemic	—
13	Toluene	JMC94	MeOHCD	0.75	(*R*)	63

[a] CD = cinchonidine, CN = cinchonine, MeOHCD = 9-methoxy-10,11-dihydrocinchonidine.

The ee data indicate that the enantioselectivity of the reaction shows a slight hydrogen pressure dependence. Starting from 93% ee (1 bar H_2) the optical yields increased as a function of hydrogen pressure up to 96% ee. However, at 20 bar hydrogen pressure the enantiomeric excess seems to reach its maximum, and any further increase in hydrogen pressure does not result in higher optical yields. Under the same conditions (JMC94, MeOHCD, 20 bar) using dimethyl ester, the product was obtained in 90% ee. The (*S*)-isomer can also be prepared in 76% optical purity in the presence of CN-modified JMC94 catalyst at elevated hydrogen pressures (20–40 bar). Although the study currently is of an experimental nature, the kinetic data (Table 1)indicate that the mechanism is most likely similar to that proposed for ethyl pyruvate and other α-ketoesters. The cinchona-modified reactions all take place at higher rates than the modifier-free runs, resulting in a racemic product mixture. This phenomenon unambiguously indicates a ligand accelerated mechanism.[13] As a result, the highest enantioselectivity was obtained at the highest reaction rate (entry 11, Table 1).

Taking into account the practical importance of the products, one of them was prepared and isolated in preparative scale. Starting from 1.5 g of diethyl 2-ketoglutarate after the hydrogenation (20 bar) and cyclization, ethyl (*R*)-5-oxotetrahydrofuran-2-carboxylate was isolated in 80% yield and 94% ee optical purity.

In conclusion, the cinchona-modified Pt/Al_2O_3 catalytic system was found to be effective in the highly enantioselective hydrogenation of α-ketoglutaric acid esters providing the first satisfactory asymmetric synthetic route for the preparation of chiral alkyl 5-oxotetrahydrofuran-2-carboxylates which are frequently used as chiral building blocks. In addition, this work provides an opportunity to widen further the practical applications and potential of the Pt–cinchona catalytic system.

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