Enantio- and chemoselective reduction of 2,4-diketo acid derivatives with cinchona modified Pt-catalyst—Synthesis of (*R*)-2-hydroxy-4-phenylbutyric acid ethyl ester

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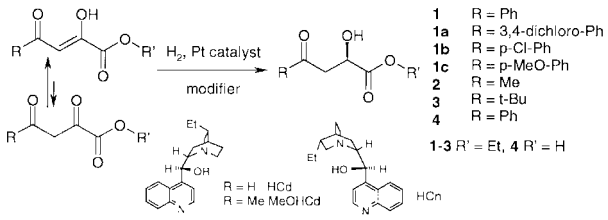
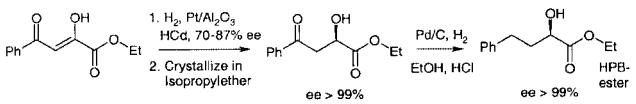
The enantio- and chemoselective hydrogenation of several 2,4-diketo acid derivatives to the corresponding 2-hydroxy compounds with cinchona modified Pt catalysts can be carried out with chemoselectivities of > 99% and enantioselectivities up to 86% (*R*) and 68% (*S*), respectively, and enrichment to > 98% ee was possible for several compounds by one crystallization, opening up an efficient technical synthesis of (*R*)-2-hydroxy-4-phenylbutyric acid ethyl ester, a building block for several ACE inhibitors.

Chiral 2-hydroxy-4-keto acid derivatives are interesting starting materials for the synthesis of a wide variety of intermediates and active substances.[1–3] Considering that many different 2,4-dioxo keto esters are easily synthesized *via* a Claisen condensation of methyl ketones with oxalate esters,[4] a chemo- and enantioselective reduction would give direct access to the desired compounds (Scheme 1). However, this enantioselective hydrogenation has not been reported until recently[2] due to the difficulty of discriminating between the two keto functions. The Pt–cinchona system is known to be very specific for the enantioselective hydrogenation of 2-keto esters[5] and a few other activated C=O bonds,[6–8] whereas unfunctionalized ketones are not suitable substrates. This high specificity is usually a disadvantage, but this paper shows that the underlying chemoselectivity can also be used to good advantage. Here, we report the hydrogenation of various 2,4-diketo acid derivatives with excellent chemoselectivity and medium to high ee's, and describe a new synthesis of enantiomerically pure (*R*)-2-hydroxy-4-phenylbutyric acid ethyl ester (HPB-ester), a building block for the synthesis of several commercially important ACE inhibitors[1] (Scheme 2).†



Scheme 1 Hydrogenation of 2,4-diketo acid derivatives, structure of substrates and modifiers.

Because **1** and **4** are cheap and easily accessible precursors for the HPB-ester,[4] their hydrogenation was investigated in some detail (selected results are summarized in Table 1). Based on our experience with the enantioselective hydrogenation of 2-keto acid derivatives,[5] heterogeneous Pt catalysts modified by 10,11-dihydrocinchonidine (HCd) and 10,11-dihydrocinchonine (HCn) were our favorites to obtain the (*R*)- and (*S*)-HPB-ester. With these modifiers, an extensive screening of the influence of catalyst type, solvent and reaction conditions was carried out. As hoped for, the chemoselectivity of all modified systems was always > 95% at 25 °C, regardless of catalyst type and solvent, provided that the reaction was stopped after the uptake of one mole of hydrogen. It is well known that for ethyl pyruvate or 4-phenyl-2-oxobutyric acid ethyl ester, by far the highest ee's are obtained with *O*-methyl-10,11-dihydrocinchonidine (MeOHCd) in AcOH.[5] In contrast, the highest ee for **1** of 86% (*R*) as well as the highest rate were observed in toluene with HCd and 5% Pt–Al_2O_3 catalysts. Pt on SiO_2 or other supports always gave lower ee's and most of the time lower rates. Other apolar or slightly polar solvents like benzene, xylene, cyclohexane, hexane, ethyl acetate, or diisopropyl ether led to ee's between 85 and 71%. In protic solvents like *t*-BuOH, AcOH or EtOH ee's between 40 and 61%, and in DMF an ee of



Scheme 2 Synthesis of (*R*)-2-hydroxy-4-phenyl butyric acid ethyl ester.

Table 1 Screening of support and solvents for the enantioselective hydrogenation of **1** and **4** with supported Pt catalysts modified with HCd, MeOHCd and HCn: effect on ee and rate

Entry	Substrate	Solvent	Catalyst	Pressure/bar	Modifier	Ee (%)	Rate/mmol g^{-1} min^{-1}
1	1	Toluene	JMC 94[a]	60	HCd	86 (*R*)	6.4
2	1	AcOH	JMC 94[a]	60	HCd	45 (*R*)	3.6
3	1	EtOH	JMC 94[a]	60	HCd	40 (*R*)	5.2
4	1	Toluene	E 4759[b]	60	HCd	86 (*R*)	3.4
5	1	Toluene	E 4759[b]	5	HCd	80 (*R*)	1.5
6	1	Toluene	E 4759[b]	135[d]	HCd	87 (*R*)	4.0
7	1	Toluene	F 340[c]	60	HCd	74 (*R*)	1.9
8	1	Toluene	E 4759[b]	60	HCn	59 (*S*)	0.9
9	1	AcOH	E 4759[b]	60	HCn	48 (S)	0.8
10	4	Toluene	JMC 94[a]	60	MeOHCd	23 (*R*)	0.2
11	4	EtOH	JMC 94[a]	60	MeOHCd	52 (*R*)	3.4
12	4	THF	JMC 94[a]	60	MeOHCd	56 (*R*)	0.9

Conditions: See experimental. [a] 5% Pt/Al_2O_3 (Johnson Matthey). [b] 5% Pt–Al_2O_3 (Engelhard). [c] 5% Pt–SiO_2 (Degussa). [d] 0 °C.

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25% were obtained. Temperature and pressure affected the results only slightly. The optimal modifier concentration was 5.3×10^{-4} M at a modifier to catalyst ratio of 1:10 (w/w), similar to the results obtained with ethyl pyruvate.[9] Analogous experiments were carried out with the pseudoenantiomeric HCn as modifier. All trends were similar, but the best ee's in toluene were always lower by about 20%. Furthermore, the reactions were always slower by a factor of about three and a doubling of the modifier concentration was necessary for the highest ee. Surprisingly, the ee's in AcOH were comparable, as described by LeBlond *et al.* for ethyl pyruvate.[10] Obviously the small difference between HCd and HCn (attachment point of the side chain in the quinuclidine unit) is quite important in toluene but not so much in AcOH. For the 2,4-diketo acid **4**, the ee's were significantly lower than for the corresponding ethyl ester **1**. More polar solvents gave better results as observed for mono keto acids, where the highest ee's were obtained in a EtOH–H_2O mixture.[11]

To obtain the HPB-ester with the desired ee of > 99%, further enrichment of the 2-hydroxy-4-keto ester was necessary. This worked remarkably well: a single crystallization from $^{i}Pr_2O$ brought the ee from > 72% to > 99% with a chemical yield of approx. 50–60%. Hydrogenolysis of the keto group with Pd–C in EtOH–HCl finally gave the desired HPB-ester in high yield with an ee of > 99% (overall yield starting from **1** approx. 50–60%).[12]

In order to expand the scope of this chemo- and enantioselective reaction, substrates **1a**–**c**, **2** and **3** were also tested (Table 2), and proved to be highly chemoselective. This is remarkable considering that only a few of the homogenous catalysts mentioned above showed high chemoselectivity for **2** and **3**, and even fewer both high chemo- and enantioselectivity.[2] As observed for **1**, the highest ee's (70–80%) were usually obtained in toluene. The only exception was **3**, where AcOH gave 74% and toluene 63% ee. For all esters investigated, the reactions in EtOH proceeded with the lowest ee's but often the highest rates. Comparing **1**, **1a**, **1b** and **1c**, it seems that electron withdrawing groups on the Ph groups give slightly higher ee's and rates. For all these substrates, HCn was also investigated as modifier to give the (*S*)-2-hydroxy-4-keto esters. The ee's were again lower by 20–30%. Enrichment by recrystallization to > 98% ee was possible for **1a**, **1b** and **1c** but not for **2** and **3** which are not crystalline at rt.

Table 2 Screening of solvents and modifiers for the enantioselective hydrogenation of various 2,4-diketo esters with Pt–Al_2O_3 catalysts: effect on ee and rate

Entry	Substrate	Solvent	Modifier	Ee/(%)	Rate/mmol g^{-1} min^{-1}
13	1a	Toluene	HCd	84 (*R*)	Nd
14	1a	Toluene	HCn	68 (*S*)	1.3
15	1b	Toluene	HCd	82 (*R*)	5.0
16	1b	Toluene	HCn	64 (*S*)	Nd
17	1c	Toluene	HCd	79 (*R*)	2.0
18	1c	Toluene	HCn	49 (*S*)	Nd
19	2	EtOH	—	0[a]	0.3
20	2	EtOH	HCd	56 (*R*)	13
21	2	Toluene	HCd	78 (*R*)[b]	3.5
22	2	Toluene	HCn	57 (*S*)	Nd
23	2	AcOH	MeOHCd	65 (*R*)	7.5
24	2	AcOH	HCn	63 (*S*)	Nd
25	3	EtOH	—	0[c]	0.1
26	3	EtOH	HCd	34 (*R*)	0.7
27	3	Toluene	HCd	63 (*R*)	0.5
28	3	Toluene	HCn	42 (*S*)	Nd
29	3	AcOH	MeOHCd	74 (*R*)	1.5
30	3	AcOH	HCn	54 (*S*)	Nd

Conditions see Experimental. Catalyst for **1a**—E 4759, for **2** and **3**—JMC 94, 60 bar, 25 °C. [a] 4% diol. [b] 5 °C. [c] Diol not detectable by NMR.

The hydrogenation of all 2,4-diketo esters with the unmodified Pt catalysts was slower than the modified systems, typically by a factor of 3–60 (ligand accelerated catalysis[5,10]). However, all rates were relatively low compared to ethyl pyruvate (rates up to 300 mmol g^{-1} min^{-1}) or 4-phenyl-2-oxobutyric acid ethyl ester (rates up to 40 mmol g^{-1} min^{-1}).[13] For ethyl pyruvate it was demonstrated by reaction with D_2 that hydrogenation occurs by addition across the C=O bond.[5] In contrast to mono keto esters where only the keto form is observed, diketo esters showed > 80% enol in the solvents used for the hydrogenation (NMR results). Therefore, one possible explanation for these rate differences between mono and diketo esters could be the different keto–enol ratio. Unfortunately, a reaction with D_2 was not conclusive due to a massive exchange of H/D in the starting material and product, and it is uncertain whether the keto or the enol form is hydrogenated. In addition, the modified catalyst gave significantly less 2,4-dihydroxy ester than unmodified catalyst. This improved chemoselectivity is mainly due to the acceleration of the hydrogenation of the 2-keto group, but there are also indications that the reaction of the 4-keto group is slowed down.

In conclusion, the scope of the cinchona modified Pt catalysts has been expanded to the enantio- and chemoselective hydrogenation of various 2,4-diketo ester derivatives. For a range of 2-hydroxy-4-keto esters enrichment to > 98% ee is possible by a simple crystallization thereby enabling an efficient technical access to enantiomerically pure building blocks for ACE inhibitors and related compounds.

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Notes and references

† Hydrogenations were carried out as described in ref. 6. Example for ethyl (*R*)-2,4-dioxo-4-phenylbutyrate **1**: 2.0 g diketo ester **1** in 30 ml toluene were hydrogenated at 25 °C and 60 bar H_2 pressure in a 50 ml stainless steel autoclave in the presence of 50 mg 5% Pt–Al_2O_3 (pretreated for 2 h in H_2 at 400 °C) and 5 mg HCd. After H_2 uptake had stopped (*ca.* 160 min), the catalyst was filtered and the solution was evaporated to dryness at reduced pressure. Yield: 1.97 g (98%), product content > 97% (NMR), ee 86% (HPLC, OD-H, hexane–EtOH 98.5:1.5, flow 0.7 ml min^{-1}; retention time: (*S*)-enantiomer 46.0 min, (*R*)-enantiomer 49.6 min).

The experiments with the other substrates were carried out in a similar manner. In cases with low activity, higher catalyst loadings were used (constant catalyst–modifier ratio). With HCn, a modifier–catalyst ratio of 1:5 was normally used. All new substrates and products gave satisfactory analytical results (^{13}C, ^{1}H, and MS).

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