Hydrogenation of butane-2,3-dione with heterogeneous cinchona modified platinum catalysts: a combination of an enantioselective reaction and kinetic resolution

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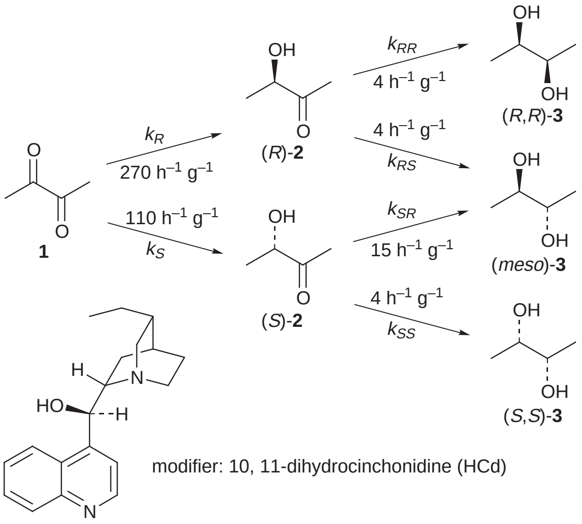
(*R*)-3-Hydroxybutan-2-one was obtained with 85–90% ee albeit in low yield by the Pt/Al_2O_3 cinchona catalyzed hydrogenation of butane-2,3-dione by a combination of enantioselective hydrogenation and kinetic resolution.

Modified heterogeneous catalysts for enantioselective hydrogenation are of interest, both from a theoretical and practical point of view.[1] Up to now only two efficient catalyst systems are known and only a few substrate types can be hydrogenated with enantioselectivities of 90% or higher. Most notable is the tartrate modified Raney-nickel catalyst with an ee of up to 98% for β-keto esters and β-diketones,[2–4] and the cinchona modified Pt catalysts for the hydrogenation of α-keto esters with 95% ee.[5] Even though some progress in expanding the scope of the latter was reported recently,[6–8] none of the new systems had an ee > 60%. Here we describe the enantioselective hydrogenation of butane-2,3-dione **1**, where we obtained (*R*)-3-hydroxybutan-2-one (*R*)-**2** in up to 90% ee by a combination of enantioselective hydrogenation and kinetic resolution using a Pt/Al_2O_3 catalyst modified with 10,11-dihydrocinchonidine (HCd).

Vermeer *et al.*[6] investigated the enantioselective hydrogenation of **1** to **2** and found an ee of 38% when using a 6.3% Pt/silica catalyst modified with cinchonidine in CH_2Cl_2 at 0 °C. We decided to re-investigate this substrate using a catalyst that gave the highest enantioselectivities so far reported for several α-keto esters (5% Pt/Al_2O_3, JMC type 94, pretreated for 2 h at 400 °C with H_2).[5] First, we investigated the effect of several reaction parameters.[9] Modifier type and concentration, as well as the solvent, had a very strong effect on the enantioselectivity, while the influence of H_2 pressure (25–135 bar) and temperature (0–25 °C) were found to be negligible. The best results were obtained with HCd in toluene (ee ≈ 50%). During the course of this investigation we noticed that at conversions > 80% the ee started to rise and the reaction did not stop at **2** but slowly continued to give the corresponding diols **3** (Scheme 1), a fact not described by Vermeer *et al.*[6]

These findings prompted us to investigate the two consecutive hydrogenation steps in more detail. The first step was carried out by hydrogenating 5 ml **1** with 50 mg catalyst, 10 mg HCd and 20 ml toluene in a 50 ml autoclave at 107 bar, stopping the reaction at the time given in Table 1. Because the reaction of **2** to **3** was considerably slower, the second step was carried out by hydrogenating the filtrate of the above described reaction mixture (after 15 min reaction time) with 125 mg catalyst and 25 mg HCd at 107 bar. Again, the reaction was stopped after the time given in Table 2, Figs. 1 and 2.

These results show that as the concentration of **2** declined, the ee of **2** increased from 50 to 85–90%, albeit with a rather low chemical yield of < 30%. We analyzed our data on the basis of the reaction network shown in Scheme 1. For the calculations we assumed that the reactions of **1** or **2** were first order in substrate and in catalyst, leading to equations of the type $d[(R)\text{-}\mathbf{2}]/dt = [cat]\{k_R'[\mathbf{1}] - (k_{RR}' + k_{RS}')[(R)\text{-}\mathbf{2}]\}$ at constant hydrogen pressure. The time dependent concentration of all species was calculated by numerically integrating these equations. The apparent rate constants k_i' at 107 bar H_2 were obtained by minimizing the difference between measured and calculated data points (least-squares, MS EXCEL 7.0 Solver subroutine). The reported k_i values are $k_i = k_i'/[cat]$. In the absence of modifier, the following values were found: $k_R = k_S = 17\ h^{-1}\ g^{-1}$, $k_{SR} = k_{RS} = 3\ h^{-1}\ g^{-1}$, $k_{RR} = k_{SS} = 4$



Scheme 1 Reaction scheme, modifier structure and calculated apparent rate constants

Table 1 Analytical results of the first step (**1** → **2**) [GLC area%, β-Dex 100 (Supelco 2-4301), 1 = 30 m, ø = 0.25 mm, 50 °C]

t/min	[**1**] (%)	[**2**] (%)	Ee of [**2**] (%)	[**3**][a] (%)
1	85	13	44	0
2	69	29	47	0
3	19	75	46	1
10	3	85	47	7
15	3	81	50	10

[a] All isomers.

Table 2 Analytical results of the second step (**2** → **3**) (GLC, as above)

t/ min	[**2**] (%)	Ee of **2** (%)	(Chiral)-[**3**] (%)	Ee [**3**] (%)	(*meso*)-[**3**] (%)	[**3**] total (%)	(chiral)-**3** : (*meso*)-**3**
0	82	50	3	29	6	9	0.5
30	45	74	16	43	31	47	0.5
60	27	85	23	54	41	64	0.6
75	20	85	28	63	44	71	0.6
90	13	86	30	60	49	79	0.6
100	9	90	33	65	50	83	0.7

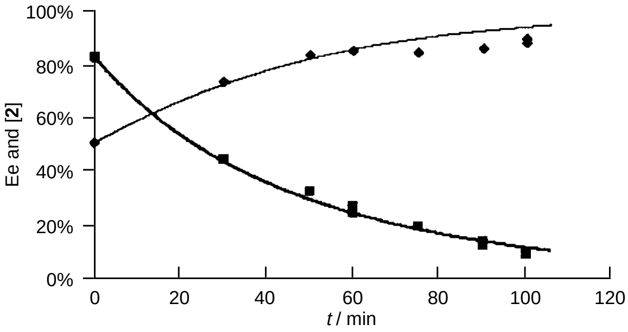


Fig. 1 Concentration and ee of **2** during step 2. (◆) ee **2** measured; (—) ee **2** calc.; (■) [**2**] measured; [**2**] calc.

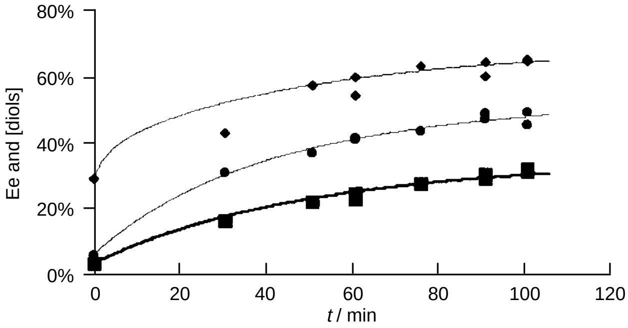


Fig. 2 Concentration and ee of **3** during step 2. (◆) ee chiral **3** measured; (—) ee chiral **3** calc.; (●) [*meso*-**3**] measured; (—) [*meso*-**3**] calc.; (■) [chiral **3**] measured; (—) [chiral **3**] calc.

$\mathrm{h}^{-1}\,\mathrm{g}^{-1}$. For the modified system, we obtained: $k_R = 270\ \mathrm{h}^{-1}\,\mathrm{g}^{-1}$, $k_S = 110\ \mathrm{h}^{-1}\,\mathrm{g}^{-1}$, $k_{SR} = 15\ \mathrm{h}^{-1}\,\mathrm{g}^{-1}$, $k_{RS} = k_{RR} = k_{SS} = 4\ \mathrm{h}^{-1}\,\mathrm{g}^{-1}$. Three points are important. First, our model describes the measured data well. Secondly, we confirmed the observation of Vermeer *et al.*[6] that the hydrogenation of **1** is a 'ligand accelerated' reaction as observed for several α-keto acid derivatives.[1] Unfortunately, the enantiodiscrimination is modest, leading to only 50% ee. Thirdly, the increase in the ee of **2** during the second step is due to kinetic resolution because k_{RS} is significantly larger for the modified than for unmodified catalyst, while k_{RS}, k_{RR} and k_{SS} remain virtually unchanged. This leads to a fast disappearance of (*S*)-**2**, and to a predominance of the *meso*-diol **3**. Another consequence is a gradual increase in the ee of the two chiral **3** molecules in favor of the (*R*,*R*)-**3**.

To the best of our knowledge, only two analogous investigations of the enantioselective reduction of diketones were reported. Kitamura *et al.*[10] and Fan *et al.*[11] investigated the hydrogenation of **1** using a homogeneous Ru$^{\mathrm{II}}$–(*S*)-BINAP catalyst. Tai *et al.*[3] and Brunner *et al.*[12] reported results on the hydrogenation of acetylacetone, a 1,3-dione, with a heterogeneous tartrate modified nickel catalyst. The results for both systems are quite different from ours: in both cases, enrichment was found for the diols but not for the intermediate hydroxy ketone. Unfortunately, no enantioselectivities were reported for **2** in refs. 10 and 11. For (*R*,*R*)- and (*S*,*S*)-**3**, both found an ee approaching 100% in favor of (*S*,*S*)-**3**, but a rather high *meso* : chiral ratio of 3. This can be explained assuming a very high enantioselectivity for the first step ($k_S \gg k_R$), and $k_{SR} \cong 3k_{SS}$. Similar to our results, Tai *et al.* found a modest ee of 74% in the first step with acetylacetone as substrate.[3] However, when 70% of the corresponding hydroxy ketone was converted, they obtained an ee of 98% for the chiral diols with the (*R*,*R*)-diol in excess (and only 8% of the *meso* form). They showed that this was due to a high k_{RR} value. The major difference between the two heterogeneous systems is that in the case of the 1,3-dione, the diastereoselective reaction of the major intermediate is faster, leading to enriched diol, whereas in our case the minor intermediate reacts preferentially, leading to an enriched hydroxyketone.

V. O. thanks the Foundation for Research Development, South Africa, and Andrew W. Mellon Foundation, USA, for financial support.

Notes and References

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1 H. U. Blaser, H. P. Jalett, M. Müller and M. Studer, *Catal. Today*, 1997, **37**, 441.
2 S. Nakagawa, T. Sugimura and A. Tai, *Chem. Lett.*, 1997, 589.
3 A. Tai, K. Ito and T. Harada, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 223.
4 A. Tai, T. Kikukawa, T. Sugimura, Y. Inoue, S. Abe, T. Osawa, S. Fujii and T. Harada, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 2473.
5 H. U. Blaser, H. P. Jalett and J. Wiehl, *J. Mol. Catal.*, 1991, **68**, 215.
6 W. A. H. Vermeer, A. Fulford, P. Johnston and P. B. Wells, *J. Chem. Soc., Chem. Commun.*, 1993, 1053.
7 T. Mallat, M. Bodmer and A. Baiker, *Catal. Lett.*, 1997, **44**, 95.
8 G. Z. Wang, T. Mallat and A. Baiker, *Tetrahedron: Asymmetry*, 1997, **8**, 2133.
9 V. Okafor, H.-U. Blaser and M. Studer, unpublished results.
10 M. Kitamura, T. Ohkuma, S.Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya and R. Noyori, *J. Am. Chem. Soc.*, 1988, **110**, 629.
11 Q.-h. Fan, C.-h. Yeung and A. S. C. Chan, *Tetrahedron: Asymmetry*, 1997, **8**, 4041.
12 H. Brunner, T. Amberger and J. Wiehl, *Bull. Soc. Chem. Belg.*, 1991, **100**, 571.

Received in Cambridge, UK, 18th February 1998; 8/01390J

Typeset and printed by Black Bear Press Limited, Cambridge, England