

# Enantioselective hydrogenation of $\alpha$ -keto acetals with cinchona modified Pt catalyst

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The enantioselective hydrogenation of a variety of  $\alpha$ -keto acetals to the corresponding  $\alpha$ -hydroxy acetals with Pt catalysts modified with cinchonidine derivatives is described with ees up to 97% and high reaction rates, and the influence of the substrate structure, the modifier and the reaction conditions (catalyst, solvent, temperature, pressure, modifier concentration) was investigated in some detail.

Modified heterogeneous catalysts for enantioselective hydrogenation are of interest, both from a theoretical and practical point of view.<sup>1</sup> Up to now only two efficient catalyst systems are known with enantioselectivities of 90% or higher. Most notable are the tartrate modified Raney nickel catalysts with ees of up to 98% for  $\beta$ -keto esters and for  $\beta$ -diketones<sup>2-4</sup> and the cinchona modified Pt catalysts for the hydrogenation of  $\alpha$ -keto esters with ees up to 98%.<sup>5-7</sup> Even though recently some progress in expanding the substrate scope of the Pt-cinchona catalysts has been reported,<sup>8-11</sup> only a few of the new substrates are hydrogenated with ees > 60% or are of synthetic relevance. Here we describe the enantioselective hydrogenation of  $\alpha$ -keto acetals to the corresponding  $\alpha$ -hydroxy acetals with cinchona modified Pt catalysts with ees up to 97% and high rates. The influence of substrate structure, the modifier, pressure and the reaction conditions (catalyst, solvent, temperature, pressure, modifier concentration) were investigated. While there are some literature reports of the enantioselective reduction of  $\alpha$ -keto acetals,<sup>12-15</sup> the Pt-cinchona catalysts shows clear advantages with respect to selectivity, activity and simplicity for the synthesis of interesting chiral synthons.

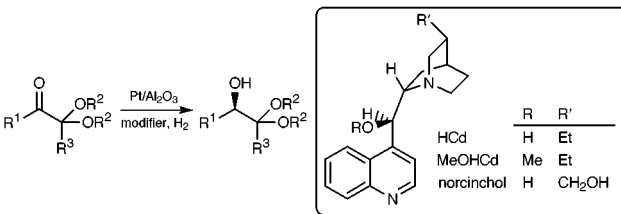
The results of a rather broad variation of the  $\alpha$ -keto acetal structure, using Pt/Al<sub>2</sub>O<sub>3</sub> in presence of 10,11-dihydrocinchonidine (HCd) in toluene or 9-methoxy-HCd (MeOHCd) in AcOH are summarized in Table 1. Obviously,  $\alpha$ -keto acetals are extraordinarily suitable substrates for the cinchona modified Pt catalysts with respect to both enantioselectivity and activity. The highest ee and rate values were obtained with two pyruvaldehyde acetals (entries 1 and 2). Compared to ethyl pyruvate, the ees were slightly higher (ee up to 96% for ethyl pyruvate), and the rates somewhat lower (up to 400 mmol g<sup>-1</sup> min<sup>-1</sup> for ethyl pyruvate). The addition of the modifier led to a rate acceleration of the order of ten, also comparable to ethyl pyruvate. Other aliphatic and aromatic  $\alpha$ -keto acetals with low bulkiness gave very high ees, but with significantly lower rates (entries 5,7,9-11). Significantly lower ees and very much lower rates were observed for keto acetals with more bulky R especially with larger R' moieties. Aromatic and aliphatic ethers as well as esters and amides are tolerated and do not affect the enantioselectivity very much (entries 10-13).  $\alpha$ -Keto ketals (entries 14,15) are hydrogenated very slowly and with negligible induction.

The effect of the modifier/solvent combination and of different Pt catalysts was studied for pyruvaldehyde dimethyl acetal and other substrates (for selected results see Table 2). The best results were always observed either with MeOHCd in AcOH or with HCd in toluene, while EtOH usually gave both lower enantioselectivities and rates. The reaction rates of the modified and the unmodified system were compared for HCd in EtOH. In most cases, ligand accelerated catalysis was observed.

The best catalyst was a 5% Pt/Al<sub>2</sub>O<sub>3</sub> catalyst, JMC 94 (Johnson Matthey), which in our hands also had the best performance with ethyl pyruvate. Several alumina and silica supported Pt catalysts from several catalyst manufacturers were compared; while the rates differed by a factor of up to 4, all catalysts gave ees of  $\geq$ 93% with pyruvaldehyde dimethyl acetal and MeOHCd in AcOH.

For the model reaction with pyruvaldehyde dimethyl acetal, the influence of hydrogen pressure, temperature and substrate and modifier concentration were investigated, with results similar to those obtained for ethyl pyruvate.<sup>16,17</sup> The most notable difference was the influence of the hydrogen pressure. In contrast to ethyl pyruvate, ees  $\geq$  94% were observed at 1 bar (increasing to 96% at pressures between 2 and 140 bar), and the rate showed a half order dependence on hydrogen pressure. The substrate concentration had only a small effect on the enantioselectivity (94% at 0.4 M, 96% at 2.8 M and 80% in neat substrate at 8 M) while the rate was affected very strongly: 25 mmol g<sup>-1</sup>

Table 1 Variation of ketone structure<sup>a</sup>



Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Ee (%)	Rate/mmol g <sup>-1</sup> min <sup>-1</sup>
1 <sup>b</sup>	Me	Me, Me	H	96	53
2 <sup>c</sup>	Me	(CH <sub>2</sub> ) <sub>3</sub>	H	97	42
3 <sup>d</sup>	Me	Et, Et	H	91	5.8
4 <sup>e</sup>	Me	Bu, Bu	H	85	1.8
5 <sup>f,g</sup>	Ph	Me, Me	H	89	1.5
6 <sup>b,g</sup>	Ph	Et, Et	H	81	0.5
7 <sup>h</sup>	Pr	Me, Me	H	93	4
8 <sup>g,c</sup>	Bu <sup>i</sup>	Me, Me	H	62	<0.1
9 <sup>h</sup>	PhCH <sub>2</sub> CH <sub>2</sub>	Me, Me	H	93	15
10 <sup>c</sup>	PhO(CH <sub>2</sub> ) <sub>3</sub>	Me, Me	H	93	5
11 <sup>c</sup>	EtO(CH <sub>2</sub> ) <sub>3</sub>	Me, Me	H	92	5
12 <sup>c,g,i</sup>	Me <sub>2</sub> NOC(CH <sub>2</sub> ) <sub>2</sub>	Me, Me	H	80	0.7
13 <sup>c,i</sup>	MeO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub>	Me, Me	H	50	<0.1
14 <sup>b</sup>	Me	Me, Me	Me	<10%	<0.1
15 <sup>b</sup>	Ph	Me, Me	Ph	<10%	<0.1

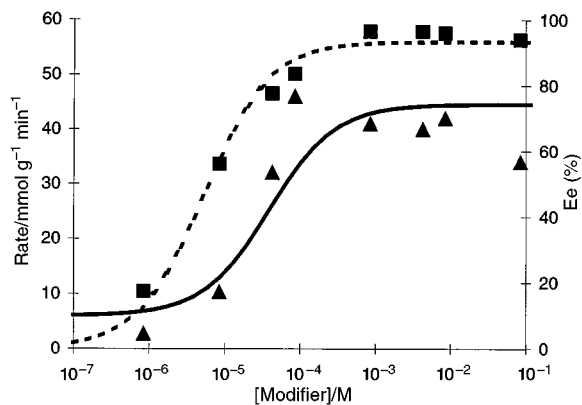
<sup>a</sup> Conditions: all hydrogenations were carried out as described in ref. 17. Typically, 1–2 g substrate, 5% Pt/Al<sub>2</sub>O<sub>3</sub> (JMC type 94, 2 h pretreated with H<sub>2</sub> at 400 °C), 5–50 mg MeOHCd, 15–20 ml AcOH, 60 bar, 25 °C. All ees and conversions were determined by GLC (Beta-dex 110, Supelco hydrogen carrier) or by HPLC (Chiracel OD, 95% hexane and 5% Pr<sup>i</sup>OH). All new substrates and products gave satisfactory analytical results (<sup>13</sup>C, <sup>1</sup>H, and MS). <sup>b</sup> Substrate from Fluka. <sup>c</sup> Substrate synthesized according to literature methods. <sup>d</sup> Substrate synthesized from substrate in entry 1 using H<sup>+</sup> and EtOH. <sup>e</sup> Substrate synthesized from substrate in entry 1 using H<sup>+</sup> and BuOH. <sup>f</sup> Substrate synthesized from substrate in entry 6 using H<sup>+</sup> and MeOH. <sup>g</sup> Reaction in toluene using HCd. <sup>h</sup> Ee estimated. <sup>i</sup> Substrate not very pure.

**Table 2** Effect of solvent, modifier structure and catalyst type (selected results)<sup>a</sup>

Solvent/modifier	Catalyst	Ee % (R)	Rate/mmol g <sup>-1</sup> min <sup>-1</sup>
AcOH/MeOHCd	1	96.5	41
AcOH/MeOHCd	2	96	23
AcOH/MeOHCd	3	94	12
AcOH/MeOHCd	4	93	33
Propanoic acid/MeOHCd	1	96	50
AcOH/norcinchol	1	83	26
AcOH/HCd	1	82	28
Toluene/HCd	1	79	5.7
EtOH/HCd	1	61	8.4
EtOH/MeOHCd	1	35	—
EtOH/none	1	-1.1	1.3

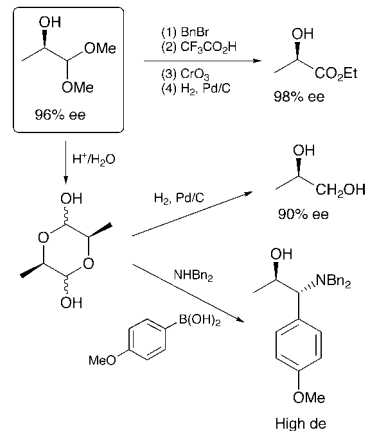
<sup>a</sup> Conditions: 2 ml pyruvaldehyde dimethyl acetal, 50 mg catalyst, 5 mg modifier, 25 °C, 60 bar, 20 ml solvent. Catalyst 1 was 5% Pt/Al<sub>2</sub>O<sub>3</sub>, JMC 94 (Johnson Matthey), catalyst 2 was 5% Pt/Al<sub>2</sub>O<sub>3</sub>, E 4759 (Engelhard), catalyst 3 was 5% Pt/Al<sub>2</sub>O<sub>3</sub>, F 213XR/D (Degussa), catalyst 4 was 5% Pt/SiO<sub>2</sub>, 98993 (Heräus), all 2 h pretreated with H<sub>2</sub> at 400 °C.

min<sup>-1</sup> at 0.4 M and 119 mmol g<sup>-1</sup> min<sup>-1</sup> at 2.8 M, decreasing to 36 mmol g<sup>-1</sup> min<sup>-1</sup> at 8 M. The dependence of ee and rate on the temperature was studied between 10 and 50 °C. While the ee was almost constant (97 and 96%), the rate strongly increased between 10–30 °C. At temperatures above 30 °C, a decrease in both ee and rate was observed. Most likely, the modifier is either desorbed from the catalyst surface or hydrogenated at higher temperature. Fig. 1 shows the dependence of ee and rate on the MeOHCd concentration. Both curves had a similar shape, as was observed for ethyl pyruvate in toluene,<sup>16</sup> and could be modeled with a simple kinetic model assuming reversible but strong adsorption of the modifier on the Pt surface. As expected, the ee values are rather low at low modifier concentration if the reaction is run to high conversion, most likely because the modifier is hydrogenated and thereby made ineffective during the course of the reaction.



**Fig. 1** Dependence of ee and rate on modifier concentration: (▲) observed rate, (—) calculated rate, (■) observed ee and (---) calculated ee. Calculated curves according to ref. 11. Pyruvaldehyde dimethyl acetal (2 ml), AcOH (18 ml), 5% Pt/Al<sub>2</sub>O<sub>3</sub> (50 mg) (JMC type 94, 2 h pretreated with H<sub>2</sub> at 400 °C), 25 °C, 60 bar.

Enantiomerically enriched  $\alpha$ -hydroxy acetals are interesting synthons and can be transformed into a variety of chiral building blocks (e.g. 1,2 diols,  $\alpha$ -hydroxy acids, 1,2 amino alcohols) as shown in Scheme 1. While the oxidation to (*R*)-ethyl lactate was rather difficult and required the protection of the OH group, the reduction could be easily accomplished after hydrolysis of the acetal. No significant racemisation was observed. With a boronic acid derivative and a secondary amine, it was also possible to synthesize amino alcohols with high diastereoselectivity according to ref. 18.



**Scheme 1**

From all the results presented above, we conclude that the Pt-cinchona catalyzed hydrogenation of  $\alpha$ -keto acetals is very similar to the well studied reaction of  $\alpha$ -keto acid derivatives:<sup>1</sup> the most likely mode of action is that the adsorbed ketone interacts with the N<sub>1</sub> atom of the adsorbed cinchona modifier, probably *via* a hydrogen bridge, resulting in both a rate acceleration and the preferential addition of hydrogen from the *si* side of the keto group to produce (*R*)- $\alpha$ -hydroxy acetals.<sup>17</sup> Concerning the requirements for a suitable substrate for this chiral catalyst system we in principle confirm the postulate of Mallat *et al.*<sup>9</sup> that an electron-withdrawing group  $\alpha$  to the C=O can lead to good ees. However, if we consider the results for methoxy acetone (best ee 12%), trifluoroacetophenone (56%) and the  $\alpha$ -hydroxy acetals (97%), it is obvious that there is no clear correlation between the electronic character of the carbon  $\alpha$  to the ketone and the enantioselectivity. The presence of either a second C=O or of a CH(OR)<sub>2</sub> group in the  $\alpha$ -position is especially beneficial to obtain both very high ees and acceptable reaction rates. For this fact there is as yet no convincing explanation available.

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