New synthesis of a useful C3 chiral building block by a heterogeneous method: enantioselective hydrogenation of pyruvaldehyde dimethyl acetal over cinchona modified Pt/Al_2O_3 catalysts

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The first satisfactory application of the heterogeneous cinchona-modified Pt catalyst system for the synthesis of a C3 chiral building, namely, the highly enantioselective (up to 96.5% ee) hydrogenation of pyruvaldehyde dimethyl acetal to lactaldehyde dimethyl acetal is described.

The increasing use of chiral compounds has raised the profile of asymmetric synthesis, in particular the environmentally more friendly heterogeneous enantioselective hydrogenations.[1] One of them, the cinchona alkaloid-modified platinum catalyst system, was found to be effective in the hydrogenation of α-keto esters and keto acids.[1] The chiral hydrogenation of ethyl pyruvate provides excellent (up to 97% ee) enantioselectivity using presonicated cinchonidine–Pt/Al_2O_3 catalysts under mild hydrogen pressure.[2] In recent years new substrates have also been studied such as unsaturated carboxylic acids,[3–5] ketoamides,[6] pyruvic acid oxime,[7] ethyl nicotinate[8] and trifluoromethyl ketones.[9] Unfortunately, the optical yields in these latter cases are far from excellent.

The major thrust of our work was to widen the type of substrates in the Pt–cinchona catalyzed hydrogenations. Here, we report a new successful enantioselective ketone hydrogenation over cinchona-modified Pt/Al_2O_3 catalyst, namely, the asymmetric hydrogenation of pyruvaldehyde dimethyl acetal. This compound is a very frequently used synthon equivalent in synthetic organic chemistry for the preparation of chiral *O*-protected α-hydroxy aldehydes.[10] The enantioselective hydrogenation of the target compound and its further transformation to a valuable synthon are shown in Scheme 1.

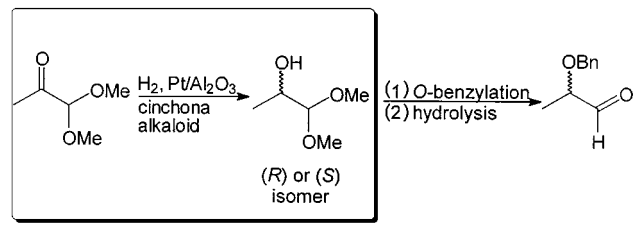
Pyruvaldehyde dimethyl acetal itself has already been reduced to the corresponding hydroxy derivatives by rhodium complexes,[11] boranes[12] or by enzymatic methods.[13] Although each method is satisfactory, in cost or simplicity they cannot be compared to the cinchona modified Pt-catalyzed hydrogenations.

In this study two Pt/Al_2O_3 catalysts (Engelhard 4759 and 40655) were used while the modifiers [cinchonidine (CD) and cinchonine (CN)] and the substrate [Pyruvaldehyde dimethyl acetal (PDA)] were all Fluka products. The hydrogenations were performed in an atmospheric batch reactor or in a Berghof Bar 45 autoclave at 20 °C as described previously.[2] Product identification was carried out by GC-MS (HP5890 GC-HP5970MSD) and ^{1}H NMR spectroscopy (Bruker AM400), while the enantiomeric excesses (ee (%) = ($|[R] - [S]|$) × 100/($[R] + [S]$)] were monitored by chiral gas chromatography (HP 5890 GC-FID, 30 m long Lipodex-A capillary column). The ee values were reproducible to within 1%.

According to our recent observations[2] two catalysts, the well-known reference catalyst E4759 and a second 5% Pt/Al_2O_3 catalyst (E40655), which was highly efficient in the enantioselective hydrogenation of ethyl pyruvate, were tested in the hydrogenation of PDA. Taking into account the fact that in the literature many solvents have been applied, some common solvents were tested in an atmospheric system to find the most suitable medium for the hydrogenation of PDA. Although in toluene or EtOH the enantioselectivity is only moderate (up to 66% with CD and 25% with CN), using AcOH as solvent the results are comparable to those obtained with ethyl pyruvate[1,2] using both modifiers. The results obtained in AcOH including reaction rates and optical yields are summarized in Table 1.

Since the ethyl pyruvate hydrogenation produces higher optical yields under elevated hydrogen pressures the effect of hydrogen pressure on the present system was also studied. The optical yields obtained in different solvents are plotted as a function of the hydrogen pressure in Fig. 1.

According to the ee data the enantioselectivity seems to be strongly solvent dependent. It was found that the application of



Scheme 1

Table 1 Enantioselective hydrogenation of pyruvaldehyde dimethyl acetal over 5% Pt/Al_2O_3 catalysts (E4759, E40655) under 1 bar hydrogen pressure and at 20 °C in AcOH

Entry	Substrate/ml	Catalyst	Modifier[a]	Rate/mol g^{-1} min^{-1}	Configuration	Ee (%)
1	0.27	E4759	CD	0.79	*R*	93.2[b]
2	0.27	E4759	CN	0.61	*S*	88
3	0.27	E40655	CD	0.81	*R*	96.5[b]
4	0.27	E40655	CN	0.72	*S*	88
5	1.35	E40655	CD	0.77	*R*	93
6	2.70	E40655	CD	0.75	*R*	93
7	0.27	E4759	—	0.20	racemic	0

[a] CD = cinchonidine, CN = cinchonine. [b] Average of three experiments.

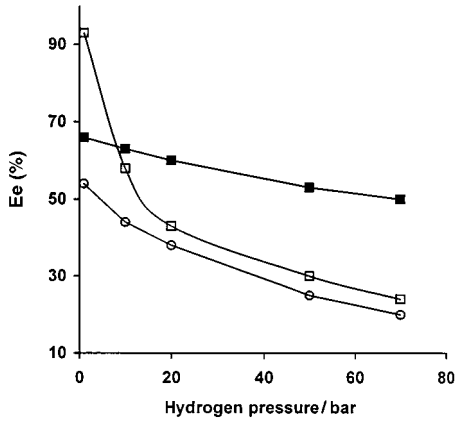


Fig. 1 Enantiomeric excess *vs.* hydrogen pressure for the enantioselective hydrogenation of pyruvaldehyde dimethyl acetal over a 5% Pt/Al_2O_3 (E4759)–cinchonidine catalyst system in different solvents at 20 °C: (□) AcOH, (■) EtOH and (○) toluene.

both CD and CN provides the best optical yields in AcOH at low hydrogen pressures. In our opinion this significant solvent dependence is a result of the weaker adsorption of PDA in the case of toluene (6π electrons *versus* 2π electrons), while using EtOH the substrate can form a semi-acetal with the solvent as pointed out for ethyl pyruvate.[1] As the data show, the increase in hydrogen pressure resulted in monotonically decreasing enantioselectivities in each solvent. However, this decrease is more pronounced in AcOH and toluene than in EtOH, for which only a slight decrease was observed.

Although E4759 provided excellent results [93% for the (*R*)-isomer], however, the other catalyst (E40655) produced even higher enantioselectivity; the highest ee obtained is 96.5% for the (*R*)-isomer. The (*S*)-isomer can be prepared in 88% optical purity in the presence of the E4759 catalyst. In this way, both enantiomers can be prepared in excellent optical purity, and no further optimization is needed. Although this work is basically of an experimental nature, the kinetic data indicate that the mechanism is most likely similar to that proposed in the case of ethyl pyruvate. The modified reactions all take place at higher rates than the nonmodified one (Table 1, compare all entries to entry 7), indicating a ligand accelerated mechanism. As a result, the highest enantioselectivity was obtained at the highest reaction rate (entry 3), however, explaining the roles of geometrical and electronic factors is not possible at this level of the study.

It should be mentioned that the above listed results were obtained on a microscale level. Taking into account the potential of the optically active product the scale up the reaction was also studied in order to isolate the hydroxy acetal. The results of the scale up experiments are also shown in Table 1 (compare entries 3, 5 and 6). After the hydrogenation was complete (see entry 6), the product mixture was poured into NaOH solution and the hydroxy acetal was extracted with Et_2O. After solvent evaporation, 2.1 g (78% yield) of the (*R*)-product was isolated. Further purification by distillation resulted in a product of 99.9% chemical (GC) and 93% optical purity [(*R*)-enantiomer]. The (*S*)-isomer can also be isolated in the same way.

The present study provides the first experimental proof that species other than α-keto acids and α-keto esters (including the cyclic ketopantolactone) can be hydrogenated with excellent optical yields over cinchona-modified platinum catalysts. Since the synthetic importance of chiral hydroxy aldehydes as useful chiral building blocks is well-known this new, environmentally friendly method for their preparation may even widen their applications.

In conclusion, the cinchona-modified Pt/Al_2O_3 catalytic system was found to be effective in the enantioselective hydrogenation of a 2-keto aldehyde derivative, providing the opportunity to still widen the practical applications and potential of this unique and important catalytic system.

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