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An efficient synthetic chiral modifier for platinum

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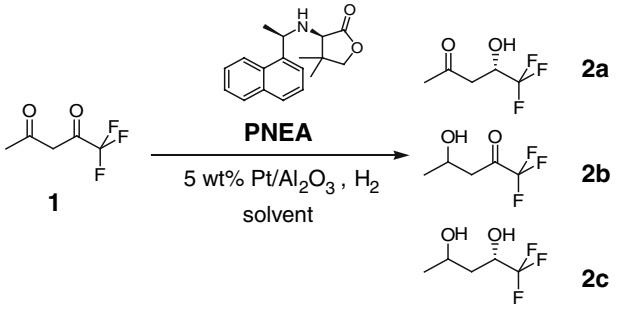
A new chiral modifier pantoyl-naphthylethylamine (PNEA) was synthesized by reductive alkylation of 1-(1-naphthyl)ethylamine with ketopantolactone. Platinum-on-alumina modified by PNEA afforded 93% *ee* and 100% chemoselectivity in the hydrogenation of the activated carbonyl group of 1,1,1-trifluoro-2,4-pentanedione. Reductive heat treatment and ultrasonication of the catalyst, and the use of chlorinated solvents under mild conditions (10 bar, 10 °C) enhanced the enantioselectivity. This is the first case in heterogeneous catalysis that a synthetic modifier gives more than 90% *ee*, better than the commonly used modifier of natural origin (cinchonidine or *O*-methyl-cinchonidine).

KEY WORDS: α,α,α-trifluoromethyl ketone, cinchonidine, enantioselective hydrogenation, pantoyl-naphthylethylamine, Pt/Al_2O_3, ultrasonication.

1. Introduction

Enantioselective hydrogenation of C=O and C=C bonds has been one of the most intensively studied areas in asymmetric catalysis [1]. Compared to the number of highly effective homogeneous asymmetric catalysts [2–4], the variety and application range of heterogeneous asymmetric catalysts are still limited. Nevertheless, heterogeneous catalysts have obvious advantages in handling and separation and even continuous process operation is feasible [5–7]. Metal hydrogenation catalysts modified by trace amounts of a strongly adsorbing chiral compound (modifier) offer a synthetically useful alternative to the homogeneous catalytic hydrogenation of ketones and olefins [8–13]. The best chiral modifiers are naturally occurring compounds. A thoroughly investigated catalyst system is cinchonidine (CD)-modified Pt that provides higher than 90% enantiomeric excess (*ee*) in the hydrogenation of various activated ketones [14]. Any effort to surpass the performance of cinchona alkaloids or their simple derivatives by using synthetic organic compounds has failed [15–21].

Chiral fluorinated compounds have attracted great attention in the past years in agro- and pharmaceutical chemistry [22,23]. A viable route to chiral α,α,α-trifluoromethyl alcohols is the enantioselective hydrogenation of trifluoromethyl ketones. Some chiral transition metal catalysts afforded excellent yields and *ee*s up to 98% [24,25]. The efficiency of the platinum–cinchona system in this reaction class is extremely substrate specific: at best 92–96% *ee* was achieved under mild reaction conditions [26,27] but for many substrates the enantioselectivities were medium to low or no reaction occurred at all [28–31]. Here we show that a new synthetic chiral modifier for Pt provides over 90% *ee* in the hydrogenation of 1,1,1-trifluoro-2,4-pentanedione **1** (Scheme 1) a reaction for which CD is less effective.



Scheme 1. Asymmetric hydrogenation of 1,1,1-trifluoro-2,4-pentanedione (**1**) over Pt/Al_2O_3 chirally modified by pantoyl-aphthylethylamine (PNEA).

2. Experimental

2.1. Materials

1,1,1-Trifluoro-2,4-pentanedione **1** (Acros), cinchonidine (CD, Fluka), dichloromethane (J.T. Baker), and acetic acid (Fluka) were used as received. Toluene (J.T. Baker) was dried and stored over activated molecular sieve. The new modifier (*R*,*R*)-pantoyl-naphthylethylamine (PNEA) was synthesized starting from (*R*)-1-(1-naphthyl)ethylamine (NEA) and ketopantolactone via reductive alkylation. The preferred method was formation of the imine in titanium(IV)isopropoxide and reduction with $NaBH_3CN$. The two diastereoisomers were separated

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by flash chromatography [32]. The 5 wt% Pt/Al_2O_3 (E4759) catalyst was purchased from Engelhard. The metal dispersion was 0.32 and 0.20 before and after reductive heat treatment, respectively, as calculated from the average particle size determined by TEM [33].

2.2. Ultrasonic pretreatment

A multi-ultrasonic bath (Elma TI-H-5) was used for this catalyst pretreatment at 20 °C. The 50 ml glass liner of the autoclave was equipped with a gas inlet and a rubber septum to enable the sonication under hydrogen. The slurry containing the solvent, catalyst, and modifier was sonicated for the required time (optimally 50 min); the substrate was injected to the reaction mixture only after sonication.

2.3. Catalytic hydrogenations

The hydrogenation reactions were carried out in a mechanically stirred eight parallel pressure reactor system (Argonaut Technologies) or in a magnetically stirred stainless steel autoclave controlled by a computerized constant-volume constant-pressure equipment (Büchi BPC 9901). Optimally, the 5 wt% Pt/Al_2O_3 catalyst was prereduced before use in a fixed-bed reactor by flushing with N_2 at 400 °C for 30 min, followed by reductive treatment in H_2 for 60 min at the same temperature. After cooling to room temperature in H_2 (30 min), the catalyst was used directly for hydrogenation or it was first sonicated before the hydrogenation reaction. Under standard conditions 42 mg catalyst, 1.84 mmol substrate, 6.8μmol modifier, and 5 ml solvent were stirred (1000 rpm) at 10 bar and room temperature (23–25 °C) for 2 h.

Conversion and *ee* were determined by gas chromatography using a Chirasil-DEX CB column (Chrompack). The product was identified by GC/MS (HP 5973 mass spectrometer) and by ^{1}H- and ^{13}C-NMR (Bruker DPX 500 spectrometer). The enantiomers were identified by comparing the sign of their optical rotation (Perkin Elmer 241 polarimeter) with literature data [34].

The reaction rate was characterized by the TOF value, that is the number of moles of **1** converted by one mole of surface Pt atoms in 1 h.

3. Results and discussion

3.1. Chemoselectivity

In the enantioselective hydrogenation of **1** over Pt/Al_2O_3 modified by PNEA the (*S*)-α,α,α-trifluoromethyl alcohol **2a** was produced in excess, similary to the reactions where CD was used as a modifier (Scheme 1). An interesting feature of the hydrogenation of this β-diketone is that in the absence of chiral modifier the chemoselectivity is poor due to competing hydrogenation of the non-activated keto group. For example, under standard conditions the target molecule **2a** formed with 79% chemoselectivity in toluene and with 33% chemoselectivity in acetic acid. But addition of even trace amounts of PNEA completely suppressed the side reactions and only the main product was formed by hydrogenation of the activated carbonyl group. The same effect was observed when CD was used as modifier [30]. The dramatic improvement in chemoselectivity is probably due to interactions with the basic amine function of the modifier. Another important effect may be the site blocking, i.e., the coverage of a considerable fraction of surface Pt sites by the strongly adsorbing modifier. By decreasing the active site/reactant ratio the chemoselectivity may improve, which is a general feature of heterogeneous catalytic hydrogenations [35].

3.2. Solvent effect and comparison to CD

In the preliminary experiments several parameters were varied to find the appropriate conditions. The solvent had a strong influence on the reaction rate and *ee* (Table 1). The highest enantioselectivities were obtained in halogenated solvents, in particular dichloromethane. In this solvent PNEA-modified Pt/Al_2O_3 afforded 81% *ee* and 52% yield to **2a** under standard conditions. Similar *ee*s but lower yields were achieved (in 2 h) in α,α,α-trifluorotoluene, 1,2-dichloromethane, and 1,2-dichlorobenzene. Both yields and enantioselectivities were lower in other solvents and there was no correlation between solvent polarity and *ee*. As illustrated in Table 1, PNEA was always a more effective chiral modifier than CD, independent of the solvent. Note, however, that in this reaction *O*-methyl-cinchonidine is more efficient than CD and gives 86% *ee* under optimized conditions [30].

Table 1
Enantioselective hydrogenation of **1** over a 5 wt.% Pt/Al_2O_3 catalyst in various solvents (2 h, standard conditions, parallel reactor system)

Modifier	Toluene			Acetic acid			Dichloromethane		
	TOF (h^{-1})	Yield (%)	*ee* (%)	TOF (h^{-1})	Yield (%)	*ee* (%)	TOF (h^{-1})	Yield (%)	*ee* (%)
–	101	19	0	114	12	0	155	13	0
PNEA	97	23	60	72	17	57	219	52	81
CD	118	28	35	130	31	16	84	20	21

The hydrogenation rate (TOF, Table 1) over the chirally modified catalysts was either higher or lower than in the absence of modifier. The rate depended on the solvent and the modifier (PNEA or CD). Clearly, rate acceleration induced by the modifier is not a typical feature of this reaction, in contrast to the hydrogenation of several activated ketones on cinchona-modified Pt [14].

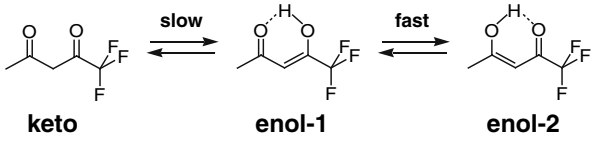
The influence of strong acid on the enantiodifferentiation was investigated using small amounts of trifluoroacetic acid (TFA). No selectivity enhancement could be achieved with TFA, in contrast to earlier studies with other α,α,α-trifluoromethyl ketones [27].

When discussing the solvent effect, we have to consider that the solvent has an influence also on the keto–enol equilibrium as depicted in Scheme 2. In weakly polar solvents, such as toluene and dichloromethane, the β-diketone mainly exists in its enol form [30]. For ethyl 4,4,4-trifluoroacetoacetate it has been proposed that the C=O bond of the keto form is hydrogenated on Pt and not the C=C bond of the enol form [36]. For the β-diketone **1** the situation is more complex because both the carbonyl group of the keto form and that of the enol-2 form may be the reactive species. It is also not clear yet how the keto–enol equilibrium is shifted by adsorption on Pt.

3.3. *Influence of catalyst pretreatments*

It was recognized early on that a reductive catalyst preconditioning at elevated temperature enhanced considerably the enantioselectivity of cinchona-modified Pt/Al_2O_3 [37]. A similar but smaller effect was observed in our case. A comparison of entries 2 and 4 in Table 2 reveals that the heat pretreatment of Pt/Al_2O_3 at 400 °C in flowing H_2 improved the *ee* by 18%. The enhanced enantioselectivity is probably due to changes in the Pt particle size and morphology, or to removal of surface impurities [38]. The importance of the latter is supported by the strikingly higher rate of conversion of **1** (TOF). Similarly, the yield to **2a** was 4-fold higher after heat treatment though the metal dispersion decreased from 0.32 to 0.20.

Sonochemical pretreatment of Pt/Al_2O_3 can also lead to restructuring (and cleaning) of the metal particles and to higher enantioselectivity [39,40]. The influence of sonication frequency on the reaction rate and enantioselectivity is plotted in figure 1. The positive effect of ultrasonication on the *ee* and yield reached optima at 25–35 kHz. Besides, there was an optimum in sonication time at 50 min (not shown). The best *ee* was achieved when ultrasonication was applied to the catalyst previously reduced at 400 °C (Table 2, entry 6). It was important to carry out the sonication under hydrogen and in the presence of modifier; otherwise even the rather small positive effect on *ee* (4–6%) was lost. Ultrasonication of the catalyst was a far less effective pretreatment than reduction at elevated temperature but – luckily – the two effects were additive.



solvent	keto form (%)
Toluene	2
Dichloromethane	7

Scheme 2. Keto–enol equilibrium and the fraction of the keto form of **1** in different solvents, according to literature data [30].

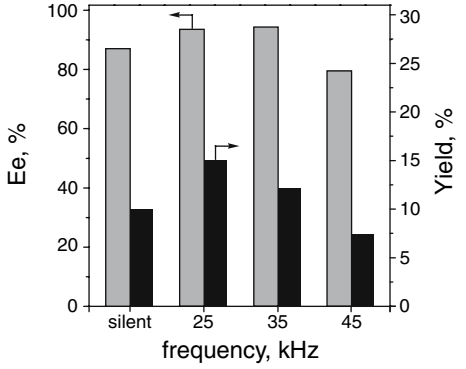


Figure 1. Influence of the ultrasonic frequency during catalyst pretreatment on the yield to **2a** and enantioselectivity; reaction conditions according to Table 2, entry 6.

Table 2
Enantioselective hydrogenation of **1** over the Pt/Al_2O_3-PNEA catalyst system: influence of catalyst pretreatment (2 h, 10 °C, standard conditions, magnetically stirred autoclave)

Entry	Modifier added	Catalyst amount (mg)	Solvent amount (ml)	Prereduction at 400 °C	Ultrasonic at r.t.	TOF (h^{-1})	Yield (%)	*ee* (%)
1	–	42	5	–	–	38	9	0
2	+	42	5	–	–	33	12	63
3	+	42	5	–	+	–[a]	15	67
4	+	42	5	+	–	219	51	81
5	+	21	10	+	–	42	10	87
6	+	21	10	+	+	–[a]	12	93

[a]Not determined.

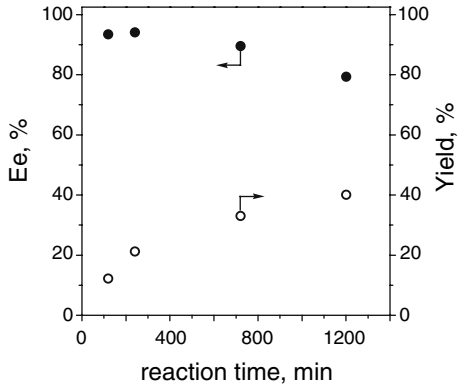


Figure 2. Variation of *ee* and the yield to **2a** with the reaction time in the hydrogenation of **1** over PNEA-modified Pt/Al_2O_3; reaction conditions according to Table 2, entry 6.

Some small variations in the catalyst and solvent amounts afforded 93% *ee* though the yield (in 2 h) decreased (Table 2, entries 5 and 6). Figure 2 shows the time dependence of the yield and enantioselectivity under the best conditions for achieving high *ee*. The monotonic decrease of *ee* after about 4 h reaction time is attributed to the competitive hydrogenation of the naphthyl ring of the modifier and to the resulting weaker adsorption on Pt. NMR analysis proved that after 2 h the degradation of the modifier was negligible except in acidic medium [32]. For comparison, saturation of the quinoline ring of CD during enantioselective hydrogenation and the resulting loss of *ee* due to weaker adsorption of the partially hydrogenated alkaloid on Pt and Pd have also been demonstrated [41–43].

4. Conclusions

The new chiral modifier for Pt, pantoyl-naphthylethylamine (PNEA) provides 93% *ee* in the hydrogenation of 1,1,1-trifluoro-2,4-pentanedione. This is the first case that a synthetic modifier surpasses the performance of a naturally occurring compound and gives >90% *ee*. For comparison, the best enantioselectivities achieved with CD and its simple derivative *O*-methyl-cinchonidine are 35 and 86% *ee*, respectively. The results confirm that proper tuning of the structure of chiral modifiers plays a key role in improving the efficiency and extending the application range of chirally modified metals in asymmetric catalysis.

Acknowledgments

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