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Chemo and enantioselective hydrogenation of fluorinated ketones on platinum modified with (*R*)-1-(1-naphthyl)ethylamine derivatives

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Abstract

The application range of platinum modified by new synthetic chiral amines was investigated in the enantioselective hydrogenation of α,α,α-trifluoromethyl ketones to the corresponding chiral alcohols. High-throughput screening was used to study the transformation of eight different substrates over a 5 wt.% Pt/Al_2O_3 catalyst chirally modified by eight derivatives of (*R*)-1-(1-naphthyl)ethylamine. The chiral modifiers possessed the same anchoring moiety (naphthalene ring) that allows strong adsorption on the Pt surface and the surroundings of the basic N atom was varied systematically. All modifiers improved the chemoselectivity to hydrogenation of the activated carbonyl group. The yield achieved in 2 h varied in a broad range (2–100%) and the modifiers had no clear positive or negative influence on the rate of the unmodified reaction. The best modifier pantoyl-naphthylethylamine (**H**) afforded better than 99% chemoselectivity and 90% enantiomeric excess (ee) (at 5% conversion in 2 h) in the hydrogenation of 1,1,1-trifluoro-5,5-dimethyl-2,4-hexanedione (**1**). Critical parameters of the reactions were the nature of solvent and catalyst pretreatments. This new catalyst system provided far better enantioselectivities than the commonly used cinchonidine-modified Pt.

Keywords: Heterogeneous asymmetric catalysis; Hydrogenation; Naphthylethylamine derivatives; α,α,α-Trifluoromethyl ketones; High-throughput screening

1. Introduction

Enantioselective hydrogenation of C=O and C=C bonds has been one of the most intensively studied areas in asymmetric catalysis [1]. Significant progress has been achieved in the past decades with homogeneous enantioselective catalysis, as reflected by the Nobel prizes in 2001 awarded to K.B. Sharpless for enantioselective oxidation and R. Noyori and W.S. Knowles for enantioselective hydrogenation [2–4]. Compared to the number of highly selective homogeneous catalysts, the application range of heterogeneous enantioselective catalysts is still limited.

In heterogeneous catalysis, the Ni-tartaric acid [5–8], the Pt-cinchona [9–12] and the Pd-cinchona alkaloid systems [13–16] afforded over 90% enantiomeric excess (ee) in the hydrogenation of C=O and C=C bonds. Development of new catalyst systems is commonly based on the empirical study of the modifier structure–selectivity relationship [17,18]. This approach has been extensively used in the hydrogenation of pyruvate esters on Pt [19–32].

The enantioselective hydrogenation of trifluoromethyl ketones represents a direct and viable route to chiral trifluoromethyl alcohols that have attracted increasing attention in the past years in pharmaceutical chemistry and agrochemistry. Some soluble chiral transition metal catalysts afforded excellent ees (up to 98% [33,34]). The efficiency of cinchonidine (CD)-modified Pt is highly substrate specific. At best 92% ee was achieved in the hydrogenation of 2,2,2-trifluoroacetophenone [35] and 96% ee in the hydrogenation of ethyl-4,4,4-trifluoroacetoacetate [36] but in the hydrogenation of several other aliphatic fluorinated ketones the enantioselectivity was poor [37–39].

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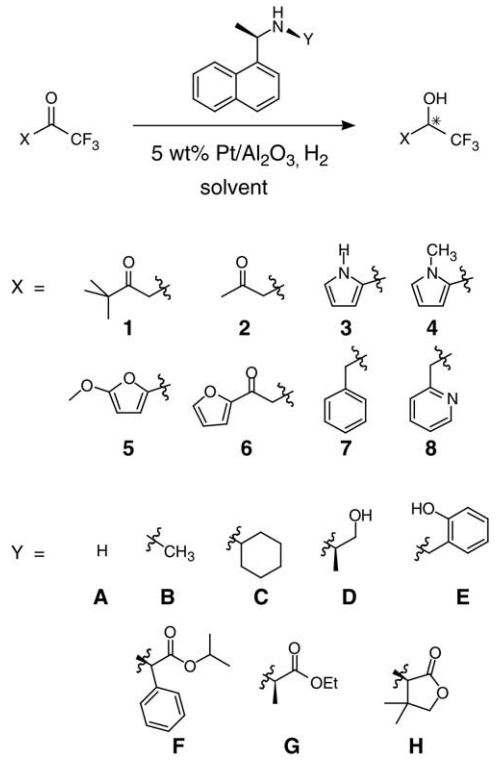


Scheme 1. Enantioselective hydrogenation of trifluoromethyl ketones **1–8** over Pt/Al_2O_3 chirally modified by naphthylethylamine derivatives **A–H**.

Pantoyl-naphthylethylamine (**H**, Scheme 1) has been found recently to be an efficient synthetic chiral modifier for Pt/Al_2O_3 in the enantioselective hydrogenation of ketopantolactone (79% ee [18]) and a fluorinated β-diketone **2** (93% ee [40]). Here, we present a structure–selectivity study aimed at extending the application range of Pt modified by naphthylethylamine derivatives. Pt/Al_2O_3 in combination with eight different modifiers **A–H** was tested in the enantioselective hydrogenation of α,α,α-trifluoromethyl ketones **1–8** as shown in Scheme 1. All modifiers contain the same naphthalene ring as the "anchoring" group, i.e. a fragment of the molecule responsible for the strong adsorption on the metal surface, and a primary or secondary amino group for interacting with the ketone substrate. The surroundings of the N atom of naphthylethylamine was varied by introducing alkyl, cycloalkyl, hydroxyalkyl and hydroxybenzyl groups or by an ester group in α-position to the N. The fluorinated β-diketones **1** and **2** have already been hydrogenated on Pt modified by cinchonidine and *O*-methyl-cinchonidine and the ees varied in the range 36–86% [41].

2. Experimental

2.1. Materials

1,1,1-Trifluoro-5,5-dimethyl-2,4-hexanedione **1** (Acros, Lancaster), 1,1,1-trifluoro-2,4-pentanedione **2** (Acros), 2-(trifluoroacetyl)pyrrole **3** (Aldrich), 4,4,4-trifluoro-1-(2-furyl)-1,3-butanedione **6** (ABCR, Acros) and 3-phenyl-1,1,1-trifluoropropane-2-on **7** (Aldrich) were used as received. 2-(Trifluoroacetyl)-*N*-methyl-pyrrole **4** [42], 2-trifluoroacetyl-5-methoxy-furan **5** [42], 1,1,1-trifluoro-3-pyridine-2-ylacetone **8** [43] and all modifiers [18,26] except **A** (Acros) and **B** (Aldrich) were prepared according to published methods. Toluene (J.T. Baker) was dried and stored over activated molecular sieve and THF (Fluka) was dried over potassium before use.

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 [44].

2.2. Catalytic hydrogenations

The high-throughput screening experiments were carried out in a parallel pressure reactor system Endeavor (Argonaut Technologies), with eight mechanically stirred stainless steel reactors equipped with glass liners, or in a magnetically stirred stainless steel autoclave controlled by a computerized constant–volume constant–pressure equipment (Büchi BPC 9901). According to the standard procedure, the 5 wt.% Pt/Al_2O_3 catalyst was pre-reduced before use in a fixed-bed reactor by flushing with N_2 at 400 °C for 30 min, followed by reductive treatment in flowing 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, 6.8 μmol modifier and 5 ml solvent were stirred (1000 rpm) at 10 bar and room temperature (23–25 °C). The reaction time was fixed to 2 h in all experiments to obtain some qualitative data on the reaction rate.

A multi-ultrasonic bath (Elma TI-H-5) was used for catalyst presonication 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. Ultrasonic pretreatment was used for final optimization.

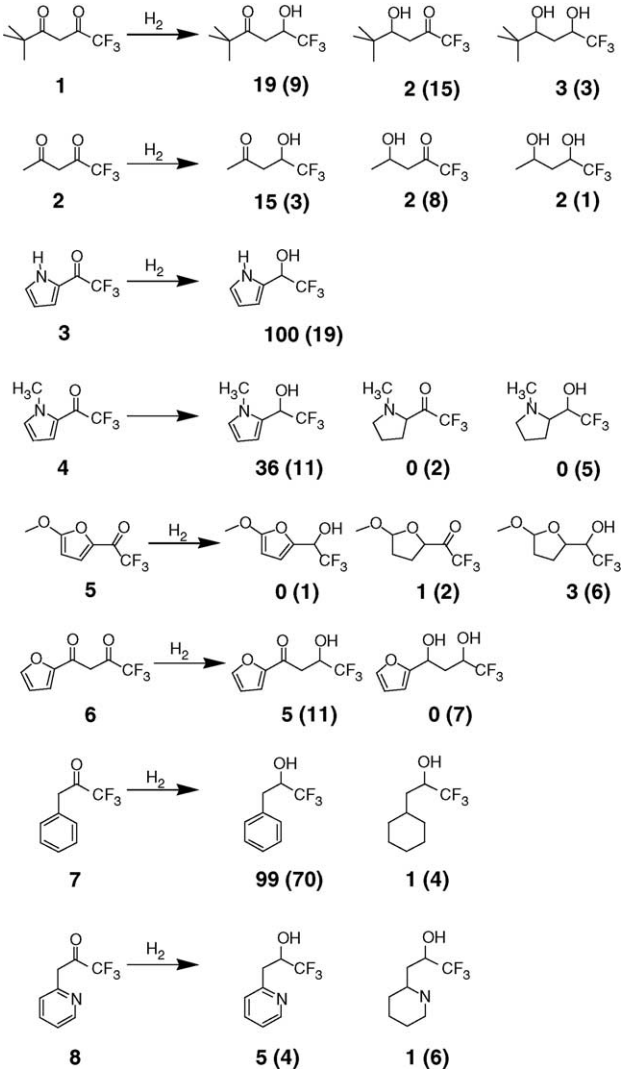
Conversion and enantioselectivity were determined by gas chromatography using a Chirasil-DEX CB capillary column (Chrompack). Some experiments have been repeated several times and the reproducibility of the yields and ees was always better than ±1%. Products were identified by GC/MS (HP 5973 mass spectrometer) and by ^{1}H- and ^{13}C-NMR spectra (Bruker DPX 500 spectrometer). The enantiomers of **1**, **2**, **5** and **6** were identified by comparing the sign of their specific rotation (Perkin-Elmer 241 Polarimeter) with literature data [45].

3. Results and discussion

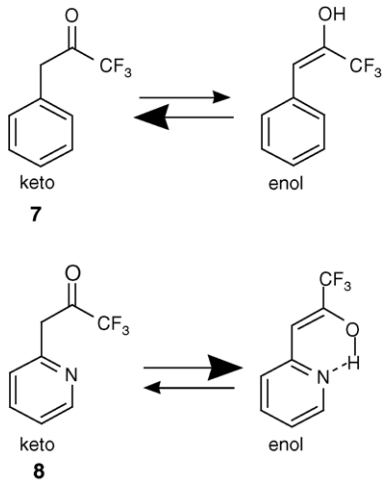
3.1. Chemoselectivity

Hydrogenation of the fluorinated ketones **1–8** in toluene or acetic acid over unmodified Pt/Al_2O_3 was moderately selective. The chemoselectivity was diminished by reduction of the second (non-activated) keto group or by saturation of the (hetero)aromatic ring (Scheme 2). An exception was the pyrrole derivative **3**; in this reaction quantitative transformation to the corresponding alcohol was achieved in toluene within 2 h. In general, the chemoselectivity decreased in acetic acid because the rate of the side reactions increased and the rate of the target reaction decreased (with the exception of **6**).

Interestingly, the β-diketone **1** possessing a bulky ^{t}butyl group was more reactive than the analogous methyl derivative **2**. A comparison of the hydrogenation of **3** and **4** reveals that



Scheme 2. Products and yields (%) in the hydrogenation of **1–8** on Pt/Al_2O_3 in the absence of chiral modifier in toluene under standard conditions. Values in acetic acid are presented in brackets.



Scheme 3. Possible keto-enol structures for the trifluoromethyl ketones **7** and **8**.

N-methylation decreased the rate of ketone reduction, probably due to steric effects, and diminished the chemoselectivity in acidic medium. In toluene, substitution of the phenyl ring in **7** by a 2-pyridyl ring in **8** resulted in a drop in the yield of the trifluoromethyl alcohol from 99 to only 5%. The likely explanation is that **8** is mainly present in the enol form due to stabilization via an internal hydrogen bridge (Scheme 3). This stable H-bond and the resulting rigid structure is expected to strongly influence the adsorption and reactivity of this compound.

When the hydrogenations were carried out on Pt/Al_2O_3 modified by the naphthylethylamine derivatives **A–H**, the fraction of byproducts was suppressed to below 2% for all substrates. No byproducts could be detected in the hydrogenation of **1** and **2** when Pt was modified by **H**. Cinchonidine had a similar effect on the chemoselectivity in the hydrogenation of some fluorinated ketones [41]. We attribute the dramatic improvement in chemoselectivity to the basic amine function of the modifiers, and partly to the site blocking effect, that is, the coverage of a considerable fraction of surface Pt sites by the strongly adsorbing modifiers. It is frequently observed in heterogeneous catalytic hydrogenations that chemoselectivity is improved by decreasing the active site/substrate ratio [46].

3.2. High-throughput screening

It has been shown earlier [41] that in the hydrogenation of trifluoromethyl ketones (and also other activated ketones), the most important parameters that control the performance of a catalyst system are the solvent and catalyst pretreatment methods, assuming that there is sufficient amount of chiral modifier in the system to cover a large fraction of Pt surface sites. Accordingly, at the first stage of screening of the substrates and modifiers only the solvent was varied and the other parameters were fixed at values frequently applied in Pt-catalyzed hydrogenation of ketones. The reaction time was

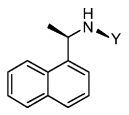
also fixed to 2 h to obtain some information on the rate of the hydrogenation reactions.

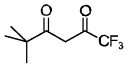
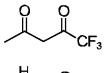
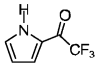
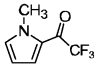
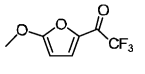
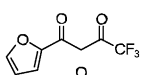
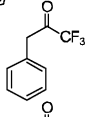
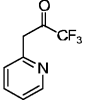
The yields and enantioselectivities achieved in the weakly polar and aprotic toluene (Table 1), and the more polar and protic acetic acid (Table 2) revealed strong structural effects that are difficult to generalize. For example, in the hydrogenation of **1** in toluene the yields varied between 4 and 44% depending on the modifier. Since the unmodified Pt/Al_2O_3 gave 19% yield in this reaction (Scheme 2), apparently some modifiers induced rate acceleration while others reduced the catalyst activity considerably. Note that an unknown fraction of the Pt surface is covered by the modifier and, thus, a real evaluation of the rate acceleration or deceleration is not possible.

Alkylation of naphthylethylamine (**A**) with increasing bulkiness of the substituent (**B** and **C**) resulted in a significant improvement in enantioselectivity in the hydrogenation of **1** and **6** in toluene but this transformation of the modifier had no or even negative effect in some other reactions in toluene and acetic acid. In most reactions, the modifiers possessing a phenolic OH (**E**) or an ester group (**F–H**) outperformed the other derivatives. The latter group was particularly effective in acidic medium which difference is attributed to the formation of an intramolecular H-bond between the protonated N atom and the ester carbonyl O atom, leading to a more rigid conformation of the modifier [47].

An analysis of the role of substrate structure reveals that the best selectivities were obtained in the hydrogenation of the β-diketones **1**, **2** and **6**, and the furan derivative **5**. The lower ees in the hydrogenation of the pyrrole derivatives **3** and **4** may be due to additional (undesired) interactions involving the basic N atom. None of the modifiers were effective in the hydrogenation of the "benzylic" ketones **7** and **8**. The poor ees in the hydrogenation of **7** can be explained by the methylene unit that separates the carbonyl group and the aromatic ring and allows additional flexibility during adsorption of the substrate. Note the similarity to the Pt-cinchona system that affords high ee in the hydrogenation of 1,1,1-trifluoroacetophenone and derivatives thereof but only very low ee in the hydrogenation of **7** [35,39,48]. Interestingly, the latter reaction was very fast and (almost) quantitative transformation was achieved with all modifiers in both solvents. Unfortunately, those substrates that could be hydrogenated with reasonable enantioselectivity were much less reactive.

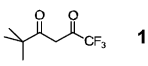
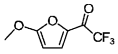
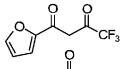
Table 1
The efficiency of naphthylethylamine derivatives used as chiral modifiers of Pt/Al_2O_3 in the hydrogenation of fluorinated ketones in toluene (standard conditions)



substrate		A ee (%) [yield]	B ee (%) [yield]	C ee (%) [yield]	D ee (%) [yield]	E ee (%) [yield]	F ee (%) [yield]	G ee (%) [yield]	H ee (%) [yield]
	**1**	0 [8]	15 (***S***) [6]	30 (***S***) [12]	15 (***S***) [4]	33 (***S***) [4]	25 (***S***) [44]	27 (***S***) [9]	27 (***S***) [10]
	**2**	- [-]	- [-]	- [-]	- [-]	- [-]	- [-]	22 (***S***) [10]	26 (***S***) [12]
	**3**	15 [89]	11 [87]	11 [98]	15 [91]	9 [85]	9 [99]	9 [99]	8 [98]
	**4**	8 [46]	9 [53]	10 [35]	7 [17]	2 [29]	3 [34]	0 [30]	0 [26]
	**5**	4 (***R***) [10]	1 (***R***) [8]	2 (***R***) [13]	6 (***R***) [2]	13 (***R***) [5]	5 (***R***) [4]	18 (***R***) [5]	38 (***R***) [5]
	**6**	0 [20]	8 (***S***) [19]	19 (***S***) [8]	10 (***S***) [6]	27 (***S***) [15]	28 (***S***) [7]	41 (***S***) [8]	18 (***S***) [4]
	**7**	18 [100]	1 [99]	7* [100]	5* [100]	3* [100]	6 [100]	9* [100]	0 [100]
	**8**	- [-]	- [-]	- [-]	- [-]	- [-]	- [-]	8 [9]	5 [8]

*Opposite enantiomer formed in excess.

Table 2
The efficiency of naphthylethylamine derivatives used as chiral modifiers of Pt/Al_2O_3 in the hydrogenation of fluorinated ketones in acetic acid (standard conditions)

substrate		Y = A: H	B: CH_3	C: cyclohexyl	D: OH	E: HO	F: O	G: OEt	H: O
		ee (%) [yield]	ee (%) [yield]	ee (%) [yield]	ee (%) [yield]	ee (%) [yield]	ee (%) [yield]	ee (%) [yield]	ee (%) [yield]
	1	18 (***S***) [12]	11 (***S***) [8]	16 (***S***) [7]	13 (***S***) [6]	16 (***S***) [4]	34 (***S***) [5]	23 (***S***) [6]	62 (***S***) [14]
	2	- [-]	- [-]	- [-]	- [-]	- [-]	- [-]	19 (***S***) [12]	60 (***S***) [10]
	3	4 [10]	3 [12]	5 [17]	4 [16]	3 [13]	5 [14]	5 [17]	4 [17]
	4	4 [9]	4 [7]	0 [9]	0 [8]	0 [9]	- [-]	0 [10]	0 [10]
	5	5 (***R***) [12]	3 (***R***) [6]	4 (***R***) [8]	6 (***R***) [5]	8 (***R***) [5]	4 (***R***) [3]	9 (***R***) [7]	20 (***R***) [1]
	6	39 (***S***) [21]	31 (***S***) [12]	23 (***S***) [5]	17 (***S***) [5]	28 (***S***) [12]	- [-]	43 (***S***) [9]	44 (***S***) [7]
	7	0 [99]	4* [100]	0 [97]	2 [98]	2 [99]	4* [97]	11 [100]	24 [100]
	8	- [-]	- [-]	- [-]	- [-]	- [-]	- [-]	5 [13]	6 [9]

*Opposite enantiomer formed in excess.

To sum up, the best modifier in this series was the α-amino ester type modifier **H** in acidic medium and the highest enantioselectivities were obtained in the hydrogenation of **1** (63% ee) and **2** (60% ee).

3.3. Solvent effect

Next, the role of solvent was investigated in the hydrogenation of **1** and **5**, using only the most promising catalyst system: Pt/Al_2O_3 modified by **H**. It is clear from Tables 3 and 4, that there is no correlation between the solvent polarity, characterized by the relative permittivity (ε_r) and the empirical solvent parameter (E_T^N) [49], and the enantioselectivity. In both hydrogenation reactions, the highest enantioselectivities were obtained in halogenated solvents, particularly in dichloromethane. The reactions were the fastest in acetonitrile, without any significant enantioselection in this medium.

Table 3
Solvent effect in the hydrogenation of **1** using Pt/Al_2O_3 modified by **H** (standard conditions)

Solvent	ε_r	E_T^N	Yield (%)	ee (%)
Toluene	2.38	0.099	10	27
Ethyl acetate	6.02	0.228	11	47
Acetic acid	6.17	0.648	14	62
THF	7.58	0.270	2	2
2-Propanol	19.92	0.546	18	59
Acetonitrile	35.94	0.460	33	<1
α,α,α-Trifluorotoluene	–	–	6	83
1,2-Dichlorobenzene	9.93	0.225	13	82
1,2-Dichloroethane	10.37	10.37	23	84
Dichloro methane	8.93	0.309	32	85

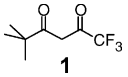
ε_r, Relative permittivity; E_T^N, empirical solvent parameter [49].

Excluding the halogenated solvents, the best ees were achieved in acetic acid which observation is not unusual in the enantioselective hydrogenation of α-fluorinated ketones [35,36,38,50,51]. The influence of acid on the hydrogenation of **1** and **5** has been further investigated by repeating some reactions in the presence of 10 molar equivalent of trifluoroacetic acid (TFA) related to the amount of modifier. Slightly better enantioselectivities were achieved in the hydrogenation of **5** in toluene, THF and dichloromethane but the yields decreased (Table 4). No improvement of ee could be achieved in the hydrogenation of **1**. In the hydrogenations of α-ketoesters, α-ketolactones and pyrrolidine triones, the effect of improved enantioselectivities by using acetic acid as solvent or small amounts of an acid (TFA) in toluene were attributed mainly to protonation of the basic N atom of cinchonidine [52–55] and **H** [18].

Table 4
Effect of solvent and trifluoroacetic acid (TFA) additive on the enantioselection in the hydrogenation of **5** using Pt/Al_2O_3 modified by **H** (10 molar equivalent of TFA compared to modifier, standard conditions)

Solvent	ε_r	E_T^N	Without TFA		With TFA	
			Yield (%)	ee (%)	Yield (%)	ee (%)
Toluene	2.38	0.099	8	39	7	7
Ethyl acetate	6.02	0.228	5	30	–	–
Acetic acid	6.17	0.648	10	46	12	12
THF	7.58	0.270	4	11	3	19
2-Propanol	19.92	0.546	19	19	–	–
Acetonitrile	35.94	0.460	53	<1	–	–
DMF	–	–	2	1	–	–
1,2-Dichlorobenzene	9.93	0.225	10	10	–	–
1,2-Dichloroethane	10.37	10.37	21	21	–	–
Dichloromethane	8.93	0.309	19	52	11	55

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

Substrate	Modifier	Toluene		Acetic acid		Dichloromethane	
		Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)
 **1**	–	19	–	9	–	20	–
	H	10	27	6	63	32	85
	CD	22	19	3	2	9	10

In the above screening study, hydrogenation of **1** in dichloromethane over Pt/Al_2O_3 modified by **H** provided the highest ee (85%, Table 3). The performance of **H** is compared to that of cinchonidine in Table 5. Clearly, in this reaction, **H** is a far more effective chiral modifier of Pt than cinchonidine, except in the apolar solvent toluene. It is also interesting that rate acceleration related to the unmodified reaction is not a typical feature of the hydrogenation of **1**, independent of the modifier.

3.4. Influence of catalyst pretreatments

In the final stage of this limited optimization study, we investigated the effect of various catalyst pretreatment methods on the activity and selectivity of **H**-modified Pt/Al_2O_3 in the hydrogenation of **1**. It is well known since the early work of Orito et al. that a reductive catalyst preconditioning at elevated temperatures enhances considerably the enantioselectivity of cinchona-modified Pt/Al_2O_3 [56]. The same effect was observed in our study. A comparison of entries 2 and 4 in Table 6 shows that the heat treatment of Pt/Al_2O_3 at 400 °C in flowing H_2 improved the ee by 38%. This improvement in enantioselectivity can probably be ascribed to changes in the Pt particle size and morphology, or to removal of surface impurities [57]. Also significant is the more than three-fold higher reaction rate after heat treatment although the metal dispersion decreased from 0.32 to 0.20.

Sonochemical pretreatment of Pt/Al_2O_3 can also have a beneficial effect on the enantioselectivity presumably due to restructuring (and cleaning) of the metal particles [58,59]. Similarly to the earlier findings, the positive effect of ultrasonication on the ee and yield reached its optima at 25–35 kHz and at a sonication time of 50 min. Furthermore, it was important to carry out the sonication in a solution containing the modifier and under hydrogen. Even under these conditions the impact of sonication was minor compared to that of reductive heat treatment. Fortunately, the two positive effects were additive (Table 6, entry 6). Some small changes in the catalyst and solvent amount finally afforded 90% ee, albeit on the expense of the reaction rate.

Table 6
Enantioselective hydrogenation of **1** over the Pt/Al_2O_3 modified by **H**: influence of catalyst pretreatment (standard conditions, magnetically stirred autoclave)

Entry	Modifier added	Catal. amount (mg)	Solvent amount (ml)	Prereduction at 400 °C	Ultrasonication at r.t.	Yield (%)	ee (%)
1	–	42	5	–	–	16	0
2	+	42	5	–	–	6	47
3	+	42	5	–	+	9	49
4	+	42	5	+	–	22	85
5	+	21	10	+	–	5	88
6	+	21	10	+	+	5	90

4. Conclusions

With a few exceptions, the known chirally modified metal catalysts are highly substrate specific and determination of the application range of a new catalyst system is troublesome. A further difficulty is that some critical parameters, such as the chemical nature of the solvent or the catalyst preconditioning are so-called "qualitative" parameters that cannot easily be optimized with the usual techniques. High-throughput screening is a helpful approach to accelerate such structure–performance studies.

The present work revealed that already small structural changes in the substrate or the chiral modifier of Pt can strongly alter the reaction rate and enantioselectivity. Though the yields and enantioselectivities were moderate in most cases, a limited optimization of a few parameters afforded 90% ee in the hydrogenation of **1** over Pt/Al_2O_3 in the presence of the new modifier pantoyl-naphthylethylamine **H**. A further advantage is that addition of **H** suppresses the side reactions on Pt and improves the chemoselectivity above 99%.

Hydrogenation of **1** is already the second highly enantioselective reaction with the Pt/Al_2O_3-**H** catalyst system. In a preliminary work we have reached recently 93% ee in the hydrogenation of **2** under partly similar conditions [40]. It seems likely that in both reactions the enantioselectivities can be further improved by applying a more extended optimization strategy. Final assessment of the synthetic potential of the Pt/Al_2O_3-**H** catalyst system will need further extension of the scope of substrates.

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