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Chemo- and enantioselective hydrogenation of the activated keto group of fluorinated β-diketones

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Abstract—Asymmetric hydrogenation of the activated carbonyl group of 1,1,1-trifluoro-2,4-diketones was studied over Pt/Al_2O_3 modified by various chiral 1,2-aminoalcohols and amines. The best chiral modifiers were cinchonidine and *O*-methyl-cinchonidine, which enhanced the chemoselectivity above 99%. The ee varied in the range of 22–86% depending on the steric hindrance around the nonactivated carbonyl group of the substrate. In one case the ee inverted from (*S*)- to the (*R*)-enantiomer by simply increasing the solvent polarity. The different reactivities of the substrates are correlated with their adsorption strength and the keto–enol equilibration, as only the keto form of the 2-carbonyl group is assumed to react on the chirally modified Pt surface.

1. Introduction

Compared to the number of highly selective homogeneous asymmetric catalysts, the variety and application range of heterogeneous asymmetric catalysts are limited. The most effective solid catalysts, the Ni-tartaric acid,[1–4] the Pt–cinchona,[5–8] and the Pd–cinchona alkaloid systems,[9–12] afford in some cases over 90% ee in the hydrogenation of C=O and C=C bonds. The obvious advantages of heterogeneous catalysts in handling and separation make the easily available catalyst systems interesting for practical applications.

Supported Pt, chirally modified by the simple addition of a strongly adsorbing cinchona alkaloid, is the best heterogeneous catalyst for the enantioselective hydrogenation of α,α,α-trifluoromethyl ketones. To our knowledge, the 96% ee and 1850 h^{-1} average TOF achieved under mild conditions (10 bar, room temperature) in the hydrogenation of ethyl 4,4,4-trifluoroacetoacetate to the corresponding chiral trifluoromethyl alcohol represent the highest values reported for the catalytic synthesis of this chiral building block.[13–15] In this reaction the most effective modifier of Pt is *O*-methyl-cinchonidine in AcOH/THF mixtures. The reaction can also be carried out in a continuous flow reactor for industrial application.[16] Hydrogenation of aromatic trifluoromethyl ketones afforded up to 92% ee (trifluoroacetophenone[17]) though the enantioselectivity varied in a broad range depending on the structure of the substrate.[18–21]

A few homogeneous transition metal catalysts have already been tested in the hydrogenation of trifluoromethyl ketones.[22,23] A rhodium–amidephosphine–phosphinite complex afforded excellent yields and up to 97% ee in a slow reaction.[24]

Herein we report the structural effects in the hydrogenation of trifluoromethyl diketones in which the steric hindrance around the nonactivated carbonyl group is varied (Fig. 1). The catalyst system consists of Pt/Al_2O_3 and various chiral 1,2-aminoalcohols and aminoether type modifiers, which possess an aromatic ring to favor adsorption on Pt.

2. Results and discussion

2.1. Chemoselectivity

Without modifiers, hydrogenation of **1a**–**3a** was moderately selective (79–83%) on Pt/Al_2O_3. The main products **1b**–**3b** always formed by hydrogenation of the 2-keto-carbonyl group activated by the trifluoromethyl group (Scheme 1). The chemoselectivity was diminished by the reduction of the 4-keto group and saturation of

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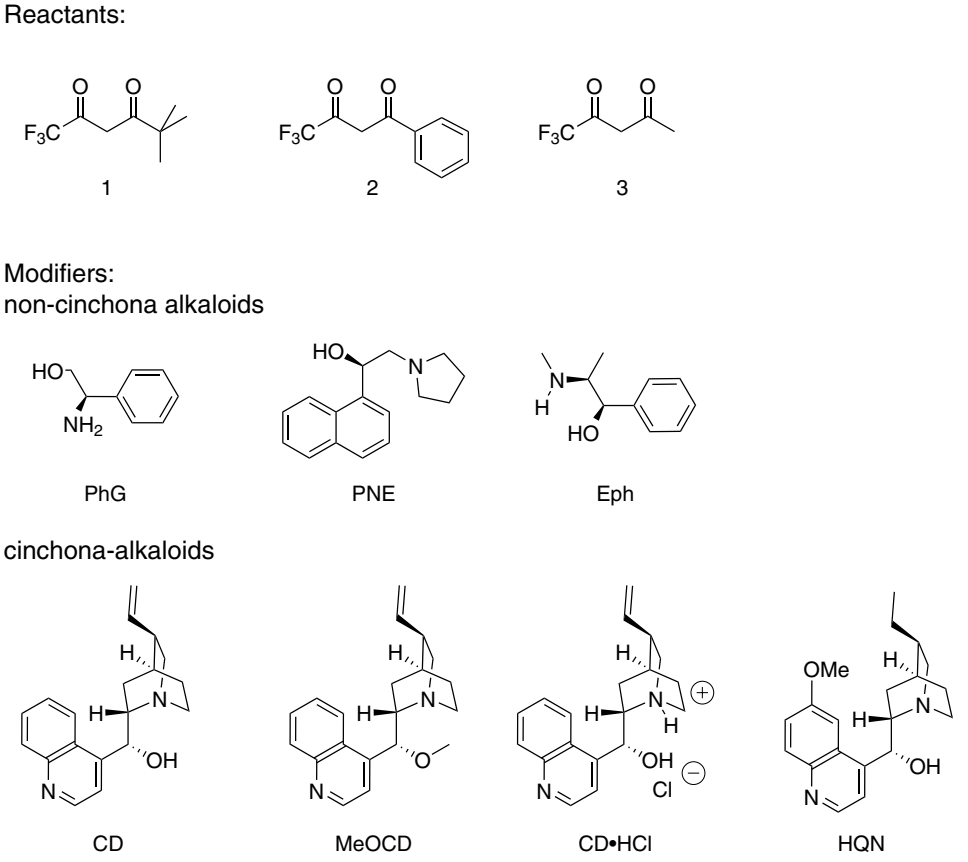
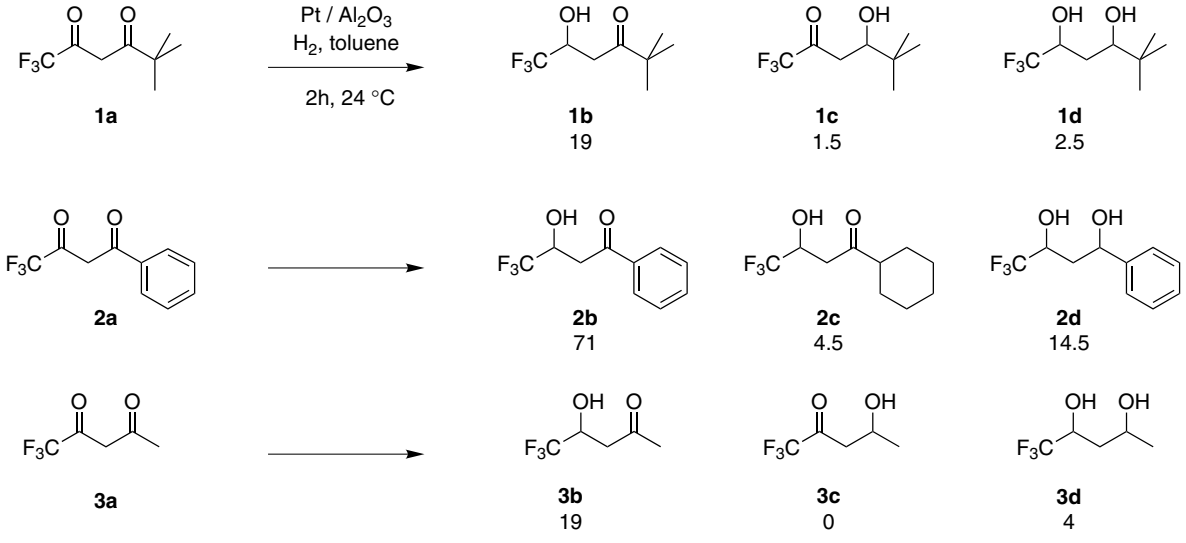


Figure 1. Structure of the substrates and chiral modifiers.



Scheme 1. Products and yields (%) identified in the hydrogenation of **1a**–**3a** on Pt/Al_2O_3 in the absence of chiral modifier.

the aromatic ring **2c**. Addition of the chiral 1,2-amino-alcohol and aminoether type modifiers (Fig. 1) suppressed these side reactions and in the best cases (CD, MeOCD, HQN) gave a chemoselectivity higher than 99%. This effect was attributed to the basic amine function of the modifiers, and also partly to site blocking, that is, the coverage of a considerable fraction of surface Pt sites by the strongly adsorbing modifiers. A general feature of heterogeneous catalytic hydrogenations is the improved chemoselectivity when decreasing the active site/substrate ratio.[25]

2.2. Influence of catalyst pretreatment

It was early recognized[5,26] that a reductive catalyst preconditioning at elevated temperatures enhanced the enantioselectivity of cinchona-modified Pt. Treatment in

Table 1. Influence of catalyst pre-treatment (H_2, 400 °C) on the reaction rate (TOF) and enantioselectivity in the hydrogenation of **1a** and **3a**; standard conditions, toluene

Pre-reduction	1a		3a	
	TOF (h^{-1})	Ee (%)	TOF (h^{-1})	Ee (%)
No	25	11	66	17
Yes	70	19.2	88	35

flowing hydrogen at 400 °C (almost) doubled the ee of the hydrogenation of **1a** and **3a** (Table 1). Probable explanations for this effect are a change of morphology of Pt particles, as indicated by TEM measurements,[27] and the removal of surface impurities.

Besides catalyst pre-reduction in the gas phase, the effect of some liquid phase treatments has also been tested. In these procedures the catalyst was stirred together with some of the reaction components for 10 min before hydrogenation. Though the ee varied significantly, no clear correlation could be established as the direction and size of the effect also depended on the solvent and substrate.

2.3. Test of different modifiers

Hydrogenation of **1a**–**3a** on Pt/Al_2O_3, previously modified by seven different chiral amines and 1,2-amino-alcohols, revealed strong structural effects (Table 2). In general, hydrogenation of the sterically less demanding substrate **3a** proved to be the most selective while that of the bulkiest, **2a**, proved to be the least selective (ee = 8%).

In the hydrogenation of **1a** and **3a**, CD and MeOCD were the best modifiers. The strikingly different effects of methylation of CD to MeOCD in the two reactions are most likely due to steric effects, as the OH group of CD is assumed not to be involved in the CD–substrate interaction in the hydrogenation of activated ketones.[28] Another interesting observation is that in the hydrogenation of **1a** and **3a**, the ee dropped close to zero on replacement of CD with the 6′-methoxy derivative HQN (hydrogenation of the C=C bond of cinchona alkaloids present in CD but absent in HQN is a fast side reaction and has practically no influence on the enantioselection[29]). For comparison, all cinchona alkaloids gave very similar ee's in the hydrogenation of α-ketoesters on Pt/Al_2O_3.[26] These two steric effects may be useful hints for understanding the substrate–modifier interaction on the Pt surface. Protonation of CD (in CD·HCl) diminished the ee but did not hinder the enantiodifferentiation.

It has been shown for the hydrogenation of another activated ketone, ethyl pyruvate, that PNE is a structurally simple analogue of CD.[30,31] Similar ee values achieved with the two modifiers in the hydrogenation of **3a** (33–35%) are in line with this conclusion.

PhG and Eph were barely effective modifiers, though it must be noted that Eph afforded the highest ee (8%) to (*R*)-**2b**. Their low efficiency is probably connected with the size of the aromatic ring: The single aromatic ring in PhG and Eph adsorbs less strongly on Pt than the naphthalene or quinoline rings of the other modifiers and the steric hindrance against the formation of the minor enantiomer is expected to be smaller.

Yields achieved in 2 h (8–80%) under standard conditions in toluene show that the reaction rates varied in a broad range depending on the substrate and modifier. A comparison of the data in Scheme 1 (unmodified Pt) and Table 2 (modified Pt) reveals that the addition of a modifier either increased or decreased the reaction rate. Fortunately, with the good modifiers always rate acceleration was observed when compared to the unmodified reaction. In our best case, the hydrogenation of **3a** over MeOCD-modified Pt, the yield to **3b** was more than tripled due to the substrate–modifier interaction. Not considering this reaction, the hydrogenation of **2a** proved to be the fastest on all chirally modified and unmodified Pt/Al_2O_3. A feasible explanation may be the stronger adsorption of **2a** on Pt due to the aromatic substituent, resulting in a higher surface concentration and thus faster reaction. Support for this assumption could be the saturation of the phenyl ring and the formation of a significant amount of **2c** (Scheme 1)—a reaction in which Pt is usually poorly active.[25] Another possible reason for the different reactivities of **1a**–**3a** is connected with the keto–enol equilibration, as discussed below.

2.4. Solvent effect

Figure 2 shows the influence of solvents on the enantioselectivity in the hydrogenation of **1a** under standard conditions, testing only the three good modifiers: CD,

Table 2. Enantioselective hydrogenation of **1a**–**3a** on Pt/Al_2O_3 with different modifiers under standard conditions, in toluene

Modifier	1a		2a		3a	
	Yield (%)	Ee (%)	Yield (%)	Ee (%)	Yield (%)	Ee (%)
CD	22	19	80	5	28	35
CD·HCl	11	10	68	4	15	32
MeOCD	30	3	60	2	66	64
HQN	8	<1	40	<1	21	3
PNE	—	—	—	—	23	33
PhG	23	4*	56	6	16	1
Eph	13	2	51	8*	15	5

The (*S*)-enantiomer of **1b**–**3b** is formed in excess, except when indicated by a (*).

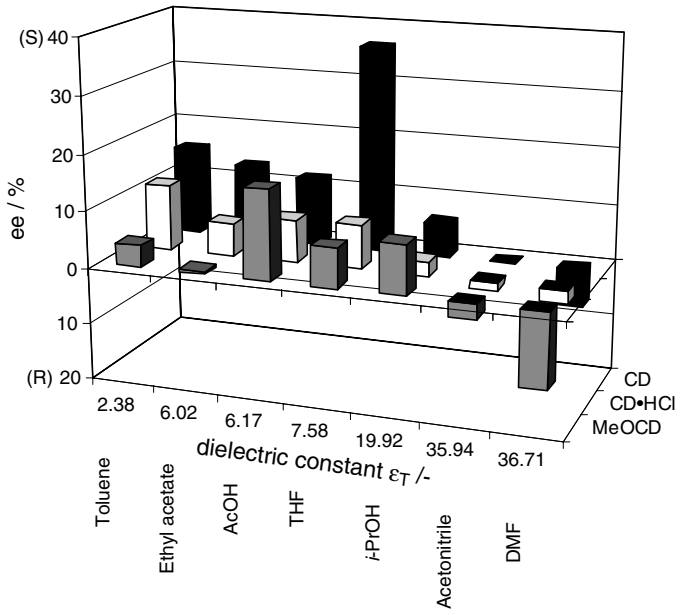


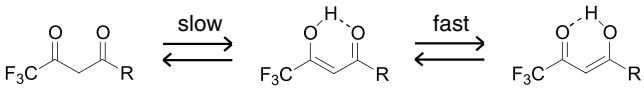
Figure 2. Solvent effect in the hydrogenation of **1a** using different modifiers under standard conditions.

MeOCD, and CD·HCl. The solvents are characterized by their relative permittivity (dielectric constant, ε_T). Generally, weakly polar solvents favor enantioselection. An inversion of the absolute configuration of the major enantiomer was observed in the polar, aprotic solvents acetonitrile and DMF. The most extreme values are 36% ee to (*S*)-**1b** in THF with CD and 13% ee to (*R*)-**1b** with MeOCD in DMF. Similar effects of solvent polarity have also been observed in the hydrogenation of other activated ketones on chirally modified Pt.[32,33]

The solvent effect in the hydrogenation of **3a** under standard conditions is shown in Table 3. Here, no clear correlation between the solvent polarity and the ee could be established. THF and MeOCD were the best solvent and modifier: 76.5% ee and 78.5% yield were achieved in only 2 h.

In acetonitrile the yields were higher than 90% for all three modifiers (Table 3). A feasible explanation for the high reaction rate in acetonitrile can be found in Table 4. The keto–enol equilibration of **1a**–**3a** was measured by ^{1}H NMR in different solvents. In these solvents the trifluoromethyl derivatives **1a**–**3a** mainly exist in their enol form.[34–36] The low keto content for **2a** can be attributed to the presence of the phenyl ring.[37,38] For all the reactants, the fraction of the keto form was the highest in acetonitrile. It has been proposed for the enantioselective hydrogenation of ethyl 4,4,4-trifluoroacetoacetate[39] that the C=O bond in the keto form is hydrogenated on Pt and not the C=C bond in the enol form. Thus, the enol form is only a spectator species that equilibrates to the keto form before hydrogenation. This model is in accordance with all mechanistic models suggested for the enantioselective hydrogenation of activated ketones on cinchona-modified Pt.[7,8,28,40,41] The

Table 4. Keto–enol equilibrium and the fraction of the keto form of **1a**–**3a** in different solvents



keto enol-1 enol-2

Solvent	Keto form (%)		
	1a	**2a**	**3a**
Toluene	3	1	2
THF	3	3	5
Acetonitrile	9	6	10

Table 3. Solvent effect in the hydrogenation of **3a** to (*S*)-**3b** using different modifiers under standard conditions

Solvent	ε_T	CD		CD·HCl		MeOCD	
		Yield (%)	Ee (%)	Yield (%)	Ee (%)	Yield (%)	Ee (%)
Toluene	2.4	28	35	15	32	66	64
Ethyl acetate	6.0	52	21.5	14.5	10	94	65.5
AcOH	6.2	31	15.5	18	3	55.5	58.5
THF	7.6	52	30.5	16	10	78.5	76.5
^{i}PrOH	19.9	<1	—	53.5	13.5	<1	—
Acetonitrile	35.9	93	8	95.5	3	95.5	27.5
DMF	36.7	—	—	9	4.5	23	53.5

high rates (yields) achieved in acetonitrile are in good agreement with this model.

In 1,3-diketones the situation is more complex because the enol-2 form also possesses the activated keto-carbonyl group in the keto form. It is very likely that the enol-2 species are reactive species on Pt. On the basis of the electronic effects of the substituents it is expected that not only the keto/enol but also the enol-2/enol-1 ratio is highest in substrate **2a**.[37,38] This ratio, however, cannot be determined by NMR.

2.5. The influence of reaction conditions

The effect of some reaction parameters has been investigated for the most selective reaction, the hydrogenation of **3a**. Working at higher pressures (higher surface hydrogen concentration) increased the reaction rate as expected but slightly diminished the enantioselectivity (Fig. 3). A similar influence of surface hydrogen concentration was found in the Pt-catalyzed enantioselective hydrogenation of acetophenone,[42] 2,2,2-trifluoroacetophenone,[13,41] and ring-substituted acetophenones.[43] This correlation is opposite to the typical behavior of the Pt–cinchona system in the hydrogenation of α-ketoesters and other activated ketones.[44] The surface hydrogen concentration may influence the adsorption of reactant or modifier and thus the enantioselection. It has recently been shown[45] that the adsorption geometry of methyl pyruvate on Pt changes from perpendicular to a tilted position due to co-adsorption of hydrogen. This competition of hydrogen with the substrate and modifier for surface Pt sites could be an explanation for the negative pressure effect as shown in Figure 3. In addition, high surface hydrogen concentration may accelerate the hydrogenation of the quinoline ring of MeOCD, leading to weaker adsorption of the partially saturated modifier.[10,46]

Reaction temperatures above room temperature diminished the enantioselectivity (Fig. 4), which is a general feature of hydrogenations over cinchona-modified Pt.[44] A feasible explanation could be the change in adsorption mode of the substrate and modifier, though recent NEXAFS studies with quinoline and dihydrocinchonidine do not support this assumption.[47,48] Another likely explanation is the faster hydrogenation of the quinoline ring of MeOCD at higher temperature.

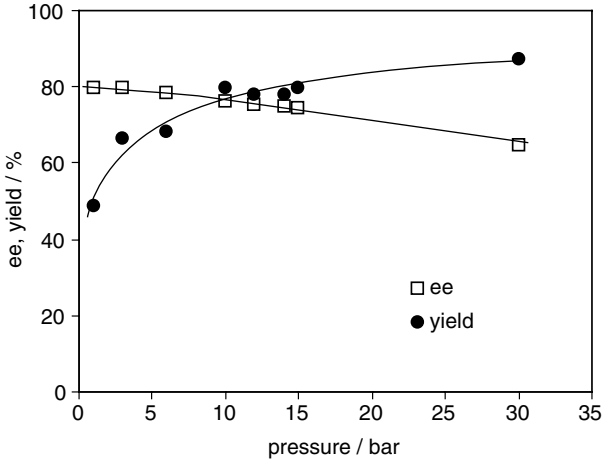


Figure 3. Influence of pressure on the yield and ee in the hydrogenation of **3a** to **3b** (THF, MeOCD, standard conditions).

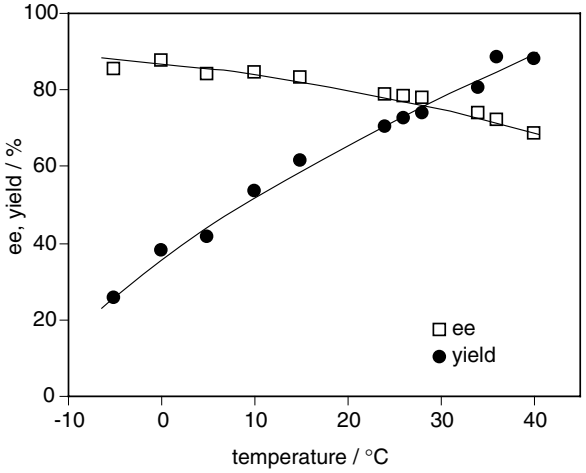


Figure 4. Effect of temperature in the hydrogenation of **3a** to **3b** (THF, MeOCD, standard conditions).

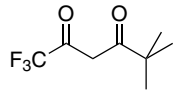
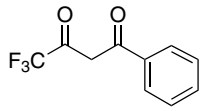
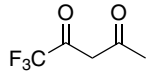
Around the optimum value, the substrate/modifier (MeOCD) molar ratio could be varied in a broad range without a significant effect on the ee. For example, at a substrate/modifier molar ratio of 270 and 2950 the ee's were 75% and 74%, respectively, under otherwise standard conditions in THF.

The best ee of 86%, measured for the hydrogenation of **3a** in this limited parameter study, was achieved at 0 °C and 3 bar (Table 5). Hydrogenation of **1a** and **2a** was far less selective, due to steric effects on the substrate–modifier interaction.

3. Conclusions

Herein we have shown that the Pt–cinchona system affords an excellent chemoselectivity in the hydrogenation of the 2-keto group of 1,1,1-trifluoro-2,4-diketones. The enantioselectivity is good but only in the absence of a bulky substituent at the 5-position. The ee dropped from 86% to 36% and 22% when replacing the methyl group in **3a** to *tert*-butyl and phenyl groups in **1a** and **2a**, respectively. Another interesting steric effect is the almost complete loss of enantioselectivity when replacing CD with its 6′-methoxy derivative HQN. These steric effects, together with the inversion of ee by replacing weak polar solvents with strong polar solvents may be a useful starting point for future mechanistic studies.

Table 5. Pt-catalyzed enantioselective hydrogenation of fluorinated diketones

Reactant	Modifier	Conditions (solvent, *p*, *T*)	TOF (h^{-1})	Yield (%)	Ee (%)
	CD	THF, 10 bar, 24 °C	35	11.1	36.3
	MeOCD	AcOH, 10 bar, 24 °C	150	47.4	22.2*
	MeOCD	THF, 3 bar, 0 °C	128	39.4	86.2

The (*S*)-enantiomer always formed in excess, except when indicated by a (*).

4. Experimental

4.1. Materials

1,1,1-Trifluoro-5,5-dimethyl-2,4-hexanedione **1a** (Acros), benzoyl-1,1,1-trifluoroacetone **2a** (Acros), 1,1,1-trifluoro-2,4-pentanedione **3a** (Acros), cinchonidine (CD, Fluka), cinchonidine hydrochloride (CD·HCl, Sigma), hydroquinine (HQN, Fluka), (1*R*,2*S*)-(−)-ephedrine (Eph, Fluka), and (*R*)-(−)-2-phenylglycinol (PhG, Fluka) were used as received. Methoxycinchonidine (MeOCD)[11] and (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol (PNE)[30] were prepared according to known methods. Elemental analysis and NMR data were in good agreement with the structure of the modifiers. ^{1}H and ^{13}C NMR spectra were measured using a DPX 300 spectrometer.

4.2. Catalytic hydrogenation

According to standard procedure, the 5 wt% Pt/Al_2O_3 catalyst (Engelhard 4759) 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 H_2 for 90 min at the same temperature. After cooling to room temperature in hydrogen, the catalyst was immediately transferred to the reactor.

Hydrogenations were carried out in the parallel pressure reactor system Endeavor (Argonaut Technologies), with eight mechanically stirred 15 ml stainless steel reactors equipped with glass liners. Controlled experiments using different amounts of catalyst and varying the stirring frequency (500–1000 rpm) did not indicate any mass transport limitation. Under standard conditions 42 ± 2 mg catalyst, 1.84 mmol substrate, 6.8 μmol modifier, and 5 ml solvent were stirred (500 rpm) at 10 bar at room temperature (23–25 °C) for 2 h. Deviations from these conditions are indicated in the Tables.

Conversion of **1a** and **3a**, and ee's of **1b** and **3b** (Scheme 1), were determined on an HP 6890 gas chromatograph equipped with a chiral capillary column (WCOT fused silica 25 m × 0.25 mm, coating CP-Chirasil-Dex CB, Chrompack), and the products were identified by GC/MS (HP 5973 mass spectrometer). Reproducibility of the ee's was within ±0.5%. The products in the hydrogenation of **2a** were analyzed by a Merck Hitachi D-7000 HPLC with Chiralcel OB column (diameter 4.6 mm, particle size 10 μm). The enantiomers were identified by comparing the sign of their specific rotation (Perkin Elmer 241 Polarimeter) with literature data.[49,50]

The average reaction rate is expressed as a turnover frequency (TOF, h^{-1}), that is, the molar amount of substrate converted by one mole of surface Pt atoms in 1 h.

NMR spectra were recorded on a Bruker DPX 500 spectrometer. Keto and enol forms were identified by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy. The relative amounts of the different compounds were calculated by the integration of the peak areas in the ^{1}H spectra.

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