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Steric and electronic effects in enantioselective hydrogenation of ketones on platinum modified by cinchonidine: Directing effect of the trifluoromethyl group

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Abstract

The directing effect of the CF_3 group on Pt/alumina modified by cinchonidine in the enantioselective hydrogenation of activated ketones was studied experimentally and theoretically using aliphatic α,α,α-trifluoromethyl ketones as model compounds. α,α,α-Trifluoromethyl ketones with varying steric hindrances of the groups on the two sides of the keto group (methyl-trifluoromethyl ketone **1a**, adamantyl-trifluoromethyl ketone **2a**, and *tert*-butyl-trifluoromethyl ketone **3a**) were examined. The catalytic results show that in weakly polar solvents, in which the interaction of the solvent with the substrate, modifier, and Pt is less important, the three alcohols **1b**, **2b**, and **3b** have the same absolute configuration (*R*). This indicates that enantioselectivity is guided by the trifluoromethyl substitution rather than by the relative bulkiness of the substituents at the two sides of the carbonyl group. The fluorinated substrate has a preferential interaction on the side of the α,α,α-trifluoromethyl group, as corroborated by the calculation of hydrogen–bonding interactions. When this interaction mode is calculated for the system alkaloid–trifluoroacetone, an energy difference between the Pro(*R*) and the Pro(*S*) configurations is found. Our findings suggest that electronic effects give a bias toward the formation of the (*R*)-enantiomer.

Keywords: Activated ketones; α,α,α-Trifluoromethyl ketones; Enantioselective hydrogenation; Pt/alumina; Cinchonidine; Steric and electronic effects

1. Introduction

Over the past two decades, the synthesis of enantiopure compounds by asymmetric catalysis has established its position as a frontier in chemical technology [1]. The most striking results have been obtained in homogeneous catalysis, but the intrinsic technical advantages of heterogeneous catalysis have also stimulated research in this field [2]. Promising results were achieved by chiral modification of metals, particularly using supported platinum modified with alkaloids of the cinchona series. Its remarkable versatility was shown by the asymmetric hydrogenation of various α-functionalized (activated) ketones, including α,α,α-trifluoromethyl ketones [3–12]. Several reviews offer a panorama of the state of the art in this field [13–17]. Nevertheless, a complete mechanistic insight has not yet been achieved, and several questions still puzzle researchers attempting to rationally design new catalysts based on this approach.

Reducing the debate to its basic issues, we can state that there is wide agreement that the alkaloid generates chiral sites by chemisorption on an otherwise achiral surface, and that enantiodiscrimination occurs through a 1:1 interaction between adsorbed substrate and modifier, whereas several proposals have been advanced concerning the interaction mode between substrate and modifier that leads to selectivity. We recently proposed [18] that on cinchona-modified Pt, adsorption of an α-ketoester on the *si*-side is directed by the position of the ester group, independent of the steric bulkiness on any side of the keto-carbonyl group. Some indications in this direction had already emerged in a previous study [19]. In other words, the activating function (an ester, carbonyl, acetal, or amido group) not only increases the reactivity of the ketone, but also directs its adsorption in the chiral environment generated by adsorption

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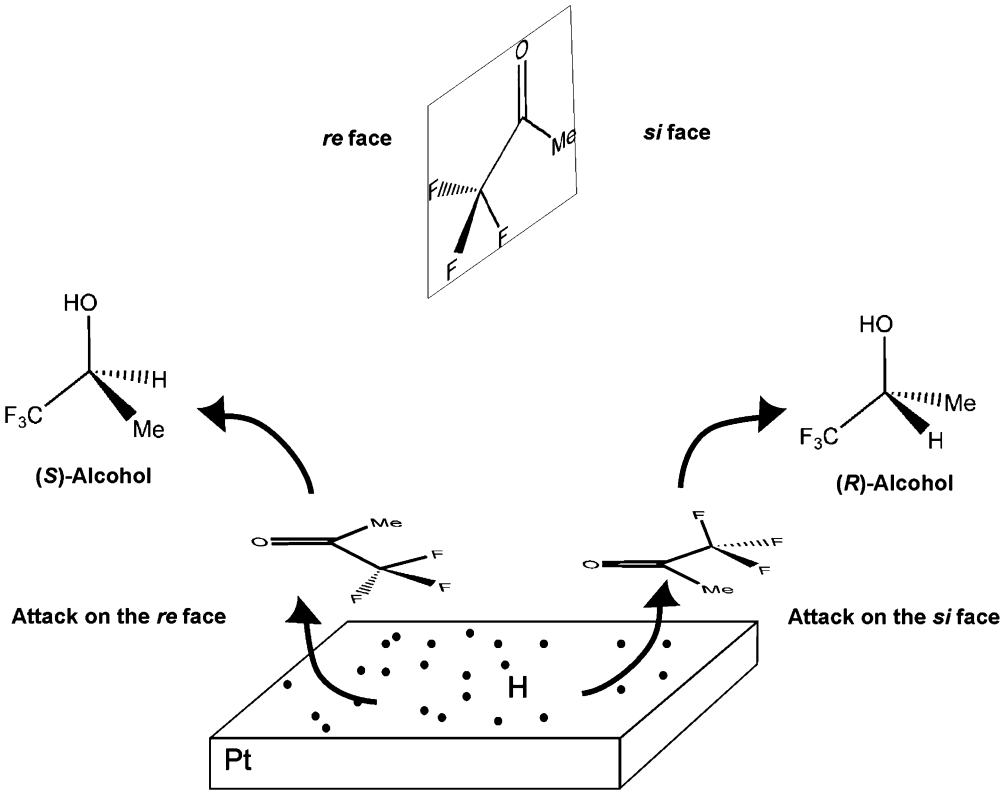


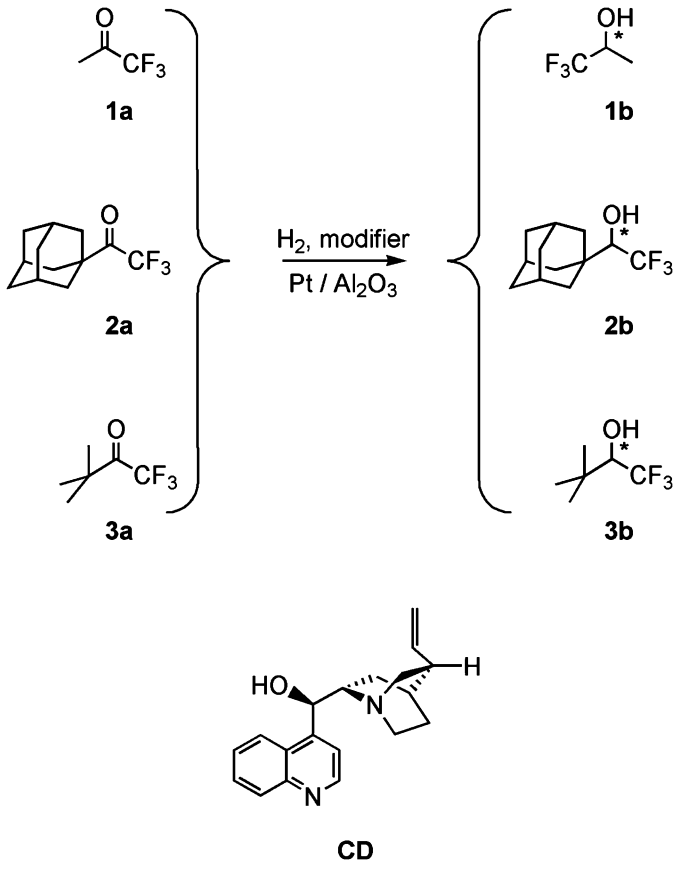
Scheme 1. Scheme of the hydrogen uptake by trifluoroacetone on a metal surface. Enantioselectivity occurs if one of the faces of the ketone is preferentially exposed to the adsorbed hydrogen.

of the alkaloid. In the present work, the enantioselective hydrogenation of aliphatic α,α,α-trifluoromethyl ketones is examined.

On hydrogenation, prochiral ketones generate either the (R)- or the (S)-alcohol according to the prochiral face that is attacked. In a racemic hydrogenation, addition at both the *re* and *si* faces occurs at equal amounts, and the racemate is obtained, but if the reaction is performed enantioselectively, then a chiral auxiliary is able to bias the hydrogenation selectively via a single face [20,21]. In reactions on metal surfaces, the activated hydrogen is added from the metal, and thus the selectivity occurs according to which face of the ketone is preferentially exposed to the surface. Scheme 1 shows the case of trifluoroacetone. When the metal is chirally modified, the chiral site generated can bias the hydrogen uptake selectively from one face. This can occur if the modifier interacts differently with the Pro(R) and the Pro(S) adsorbed ketones. In this work the nature of this interaction is investigated.

A widely accepted model for the enantioselective hydrogenation of activated ketones on cinchona-modified platinum is based on a hydrogen bonding interaction between the protonated alkaloid and the adsorbed substrate [15,22], which is supported by an in situ experimental evidence [23]. This 1:1 interaction model has been extensively described and discussed in the literature [13,15,17]; here we take only the basic assumption that a hydrogen bonding interaction is present in the chiral site and that the reaction at the molecular level is accelerated by the modifier (although this may not be reflected by the rate of hydrogen uptake, due to the coverage of a fraction of active sites by the modifier). Discrimination within a chiral site may occur because of the different steric requirements of the substituents at the two sides of the keto-carbonyl group. In this case the enantioselectivity would depend on the relative steric hindrance. The face of the prochiral ketone that better fits the chiral pocket is more stable and thus has a higher fractional coverage; furthermore, the best fit within the chiral space also determines a stronger hydrogen bond, and kinetic resolution can occur [24]. Note that in this case, only one attractive interaction occurs between the hydrogen donor and the ketone, whereas repulsive (steric) interactions determine the best fit in the chiral space.

On the other hand, enantiodiscrimination could also result from a guiding effect of the activating group of the ketone, due to a second interaction with the activating substituent. In this case, the relative interaction energy between the bifurcated bonds, involving two hydrogen acceptors, would determine the selectivity. Steric requirements also play a role in such an interaction, but these are restricted to the nonactivating substituent of the ketone. The most widely studied reaction on platinum is the hydrogenation of α-ketoesters, but this reaction is complicated by numerous side reactions [25–28]. To minimize this influence, we address enantioselection in the hydrogenation of α,α,α-trifluoromethyl ketones. In particular, we chose ketones for which the relative steric hindrance of the substituents is inverted but the (possible) directing effects due to the activating moiety are maintained. The analysis of the absolute configuration of the final products should then reveal which of the effects have driven enantioselection. The energies of the interaction



Scheme 2. Hydrogenation of fluorinated ketones on Pt/Al_2O_3 modified by cinchonidine (CD).

between modifier and reactant, and also the model hydrogen bonding interactions, are evaluated by ab initio computations.

2. Strategy

2.1. Choice of ketones: relative steric requirements of substituents

For this work, α,α,α-trifluoromethyl ketones for which the steric hindrance of the groups on the two sides of the keto group is inverted should be studied. Thus, we decided to use methyl-trifluoromethyl ketone **1a**, adamantyl-trifluoromethyl ketone **2a**, and *tert*-butyl-trifluoromethyl ketone **3a** (Scheme 2). The van der Waals surfaces are depicted in Fig. 1. In ketone **1a**, the CF_3 moiety has a larger van der Waals radius than the methyl substituent. Approximating the two groups with a sphere, their relative size is $CH_3 < CF_3 <$ *tert*-butyl (Fig. 1). In other words, whereas in ketone **1a** the trifluoromethyl group is more sterically demanding than the methyl group, the opposite holds for ketone **3a**. On the other hand, ketone **2a** has similar steric relationships as ketone **3a**, but more pronounced. If enantioselectivity on CD-modified Pt were guided by the relative hindrance of the alkyl substituents, then enantioselective hydrogenation of ketone **1a** would be expected to give an alcohol of opposite absolute configuration to the alcohols obtained in the hydrogenation of ketones **2a** and **3a**.

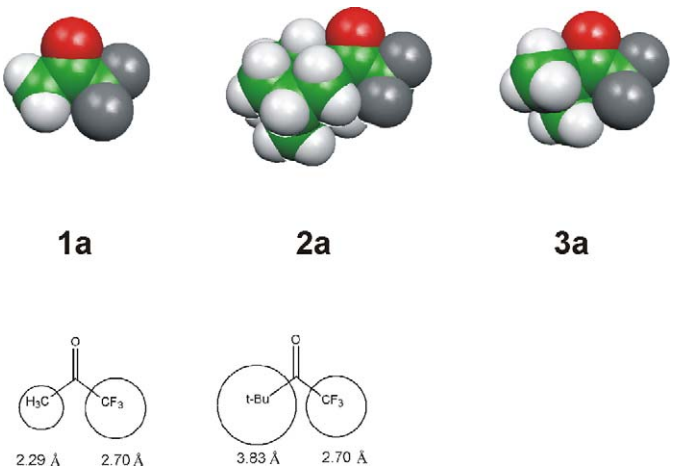


Fig. 1. van der Waals spheres of the fluorinated ketones **1a**–**3a**. **2a** and **3a** have inverted sterical requirements with respect to **1a**, because the *tert*-butyl and adamantyl substituents are sterically more demanding while the methyl group is sterically less demanding than the trifluoromethyl group. The adamantil moiety has approximately the same van der Waals radius as the *tert*-butyl moiety, only the center of the sphere is more distant from the carbonyl C.

2.2. Guiding effect of the activating group

According to the 1:1 model proposed by our group, the chiral modifier (cinchona alkaloid) forms a hydrogen bond between the quinuclidine moiety and the keto-carbonyl moiety of the ketone in the critical step leading to enantiodiscrimination. In principle, the hydrogen bond also could be biased by the trifluoromethyl moiety neighboring the keto-carbonyl moiety, and this bias could generate preferential interactions leading to enantiodiscrimination. If this were the case, then all three ketones in this study would be expected to give the same enantiomer on hydrogenation.

In the literature, the hydrogen bond in which organic fluorine is the hydrogen acceptor is described as a very weak interaction that seldom constitutes a bias to chemical structures. Duniz and Taylor [29], as well as Howard et al. [30], have concluded that covalently bonded fluorine hardly ever acts as a H-bond acceptor. Buemi [31] estimated the value of the OH–F internal hydrogen bond in trifluoro-acetylacetone to be ca. 2 kcal/mol. To determine whether such an interaction might play a role in the system under study, the energy involved was calculated with ab initio methods for some model hydrogen bonds involving fluorine. These structures are shown in Fig. 2. The methanol-trifluoromethane (Fig. 2a), methanol-trifluoroacetone (Figs. 2b and c), trimethylammonium-trifluoromethane (Fig. 2e), and trimethylammonium-trifluoroacetone (Fig. 2f) hydrogen bonding interactions were calculated. For comparison, the interactions between methanol and acetone (Fig. 2d) and trimethylammonium and acetone (Fig. 2g) were also calculated.

3. Methods

3.1. Computational

Calculations were performed using the Gaussian 98 program package [32]. The hydrogen bonding energies were per-

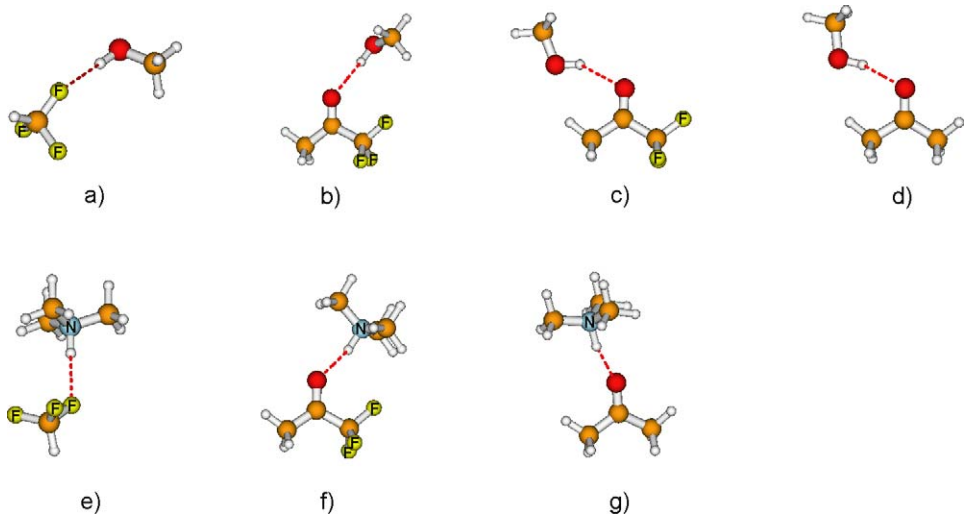


Fig. 2. Hydrogen bonding interactions involving organic fluorine atoms: (a) methanol and trifluoromethane; (b) methanol and trifluoroacetone (side of CF_3); (c) methanol and trifluoroacetone (side of CH_3); (d) methanol and acetone; (e) trimethylammonium ion and trifluoromethane; (f) trimethylammonium ion and trifluoroacetone; (g) trimethylammonium ion and acetone.

formed using density functional theory (DFT) and second-order Møller–Plesset perturbation theory (MP2), as implemented in the Gaussian 98 program package [32]. For the DFT method, the hybrid HF/DFT Becke three-parameter functional [33], in combination with the nonlocal correlation corrections of Lee, Yang, and Parr (B3LYP) [34] and the 6-31G basis set of Pople and coworkers [35–39], with the addition of single polarization functions and diffuse functions on hydrogen and second row elements [6-31G++(d,p)], was used [40]. For the MP2, a Dunning correlation-consistent basis set (Aug-cc-pVDZ) [41] was used. Basis set superposition errors were calculated using the counterpoise correction of Boys and Bernardi [42], taking into account the distortion of the single components within the hydrogen-bonded species. All degrees of freedom were optimized. The Pro(R) and Pro(S) interaction complexes between CD and trifluoroacetone were calculated using the DFT method described above, also with a 6-31G(d,p) basis set. For these calculations, surface constraints were set to have the C–O axis of the keto-carbonyl moiety in the same plane as the quinoline moiety of the alkaloid, as described previously [24,43–46]. Molden [47] and Molekel [48] were used as graphical interfaces.

Rotational and dipole strengths associated with the normal modes were calculated to simulate adsorption and vibrational circular dichroism (VCD) spectra [49]. For this scope, the implementation on Gaussian 98 [32] was used, at the B3LYP-6-31G(dp) level of theory.

3.2. Materials

All chemicals were used as received: toluene (Fluka, >99.7%), ethyl acetate (Merck p.a.), isobutyl acetate (Acros, 98%), dichlorobenzene (Fluka, >99%), dichloromethane (J.T. Baker, >99.5%), chloroform (Merck, ⩾99.8), 2-propanol (Acros, extra dry, water <50 ppm), methanol (J.T. Baker, >99,8%), acetic acid (Fluka, p.a.), 1,1,1-trifluoroacetic acid (TFA; Fluka, >98%), diethyl ether (Fluka, ⩾99.8%), acetic anhydride (Acros, >98%), 4-nitrobenzoylchloride (Fluka, ⩾99%), 4-dimethylaminopyridine (Fluka, ⩾99%), cinchonidine (CD; Fluka, 98% alkaloid), 1,1,1-trifluoroacetone (**1a**, Acros, >98%), 1,1,1-trifluoro-3,3-dimethyl-butan-2-one (**3a**, Hansa Fine Chemicals, 95%), (S)-1,1,1-trifluoro-2,3-epoxypropane (Wako-Chemicals, 98%), and molecular sieve (Zeochem, Z4-01, 2–3 mm).

1-Adamantan-1-yl-2,2,2-trifluoro-ethanone (**2a**) was synthesized by reacting trifluoroacetyl chloride with 1-adamantylmagnesium bromide [50–52]. After purification on silicagel and distillation under reduced pressure, the yield of the ketone **2a** was 50%. ^{1}H nuclear magnetic resonance (NMR) (500 MHz): δ 1.69 (m, 6 H), 1.96 (m, 6H), 2.09 (m, 3 H). ^{13}C NMR (500 MHz): δ 27.9, 36.5, 37.5, 45.4, 116.8 (q, J = 295 Hz), 195.4 (q, J = 31 Hz). ^{19}F NMR (200 MHz): 3.65 (s, CF_3). Chemical shifts are expressed in (ppm) downfield from TMS (^{1}H), CF_3COOH (^{19}F), and $CDCl_3$ (^{13}C) as standards. MS: m/z (relative intensity, %) 232 (M^+ 0.3), 213 (0.1), 163 (0.5), 135 (100), 107 (8.4), 93 (17.6), 79 (17.8), 67 (7.0), 55 (3.8). Elemental analysis: calculated for $C_{12}H_{15}F_3O$: C 62.06%, H 6.51%, O 6.89%, F 24.54%; found C 62.13%, H 6.59%, F 24.27%.

1,1,1-Trifluoro-2-propanol (**1b**) was the product of hydrogenation of **1a** on Pt/Al_2O_3. ^{1}H NMR (500 MHz): δ 1.37 (d, 3 H), 2.46 (d, 1H), 4.12 (m, 1 H). ^{13}C NMR (500 MHz): δ 15.3, 66.7 (q, J = 32 Hz), 125.2 (q, J = 281 Hz). Chemical shifts are expressed in (ppm) downfield from TMS (^{1}H) and $CDCl_3$ (^{13}C) as standards. The ^{1}H NMR and ^{13}C NMR spectra were similar to those from the Spectral Database for Organic Compounds (SDBS no. 19808).

1-Adamantan-1-yl-2,2,2-trifluoro-ethanol (**2b**) was the product of hydrogenation of **2a**. ^{1}H NMR (500 MHz): δ 1.72–1.51 (m, broad, 12H), 1.93 (m, 3H), 2.10 (OH), 3.40 (m, 1H). ^{13}C NMR (500 MHz): δ 27.1, 34.8, 35.8, 36.7, 76.6 (q, J = 28 Hz), 124.6 (q, J = 285 Hz). ^{19}F NMR (200 MHz): 5.10 (d, $J_{H–F}$ = 7.5 Hz). Chemical shifts are expressed in (ppm)

downfield from TMS (^{1}H), CF_3COOH (^{19}F), and $CDCl_3$ (^{13}C) as standards.

1,1,1-Trifluoro-3,3-dimethyl-butan-2-ol (**3b**) was the product of hydrogenation of **3a**. ^{1}H NMR (500 MHz): δ 1.07 (s, 9 H), 1.7 (OH), 3.63 (q, 1 H). Chemical shifts are expressed in (ppm) downfield from TMS as standards. MS: m/z (relative intensity, %) 139 (M−17, 8), 57 (100). The ^{1}H NMR and MS spectra correspond well to spectra reported previously [53].

(*S*)-1,1,1-Trifluoro-2-propanol (**1b**) was synthesized (with 75% *ee*) by the reaction of (*S*)-1,1,1-trifluoro-2,3-epoxypropane with $LiAlH_4$ according to a known method [54]. The ^{1}H NMR spectra and ^{13}C NMR were identical to those of the product obtained from the hydrogenation of **1a**.

3.3. Catalytic hydrogenation

The 5 wt% Pt/Al_2O_3 catalyst (Engelhard 4759) was prereduced at 400 °C for 90 min in flowing hydrogen. After cooling to room temperature in hydrogen, the catalyst was transferred to the reactor (under solvent) without exposure to air. The metal dispersion after heat treatment was 0.27, as determined by transmission electron microscopy.

Hydrogenation of **1a** was carried out in a magnetically stirred 100-mL stainless steel autoclave equipped with a 50-mL glass liner and a PTFE cover. Under standard conditions, 42 mg of catalyst, 1.84 mmol of substrate, 6.8 μmol of modifier, and 5 mL of solvent were stirred magnetically (at 500 rpm) at 10 bar for 2–6 h in a Büchi reactor system (model BPC 9901). After the reaction, hydrogen uptake was monitored. Because of the low boiling point and volatility of the substrate, all experiments were carried out at 0 °C. The product (**1b**) was identified by NMR spectroscopy. NMR spectra were measured at 200 and 500 MHz using DPX 200 and DPX 500 spectrometers, respectively. The conversions and *ee*'s were determined by gas chromatography analysis of the reaction mixture, using a HP 6890 gas chromatograph and a Chirasil-DEX CB (Chrompack 7502; 25 m × 0.25 mm × 0.25 μm) capillary column. Enantioselectivity was determined after derivatization of **1b** with acetic anhydride in the presence of 4-dimethylamino pyridine. All experiments were carried out at least twice; the estimated standard deviation of *ee* was about ±0.5% (±1% at <5% *ee*).

Hydrogenation of **2a** and **3a** was carried out in an Endeavor parallel pressure reactor system (Argonaut Technologies). This multiple reactor system contains eight mechanically stirred, 15-mL stainless steel pressure, glass-lined reactors. Under standard conditions, 42 mg of catalyst, 0.61 mmol of substrate, 6.8 μmol of CD, and 5 mL of solvent were stirred (at 1000 rpm) at room temperature and 10 bar pressure for 5 h (**2a**) or 6 h (**3a**). Deviations from the standard procedure (amount of CD) are indicated in Table 2. The products were identified by NMR spectroscopy. The conversions for both **2b** and **3b** and *ee* for **3b** were determined by gas chromatography (see above).

The *ee* of **2b** was determined using a Merck LaChrom HPLC-system and a Chiralpak AS column. The measurements were carried out at 15 °C with the ultraviolet detector set at 254 nm (eluent: hexane/*i*PrOH = 75/15; liquid flow rate, 0.2 mL/min; retention times, 26.5 and 28.2 min for the two enantiomers). **2b** was transformed before high-pressure liquid chromatography analysis with 4-nitrobenzoyl chloride in the presence of 4-dimethylamino pyridine to the corresponding ester. The estimated standard deviation of the determination of *ee* was about ±1% (±2% at <5% *ee*).

3.4. VCD spectroscopy

VCD spectra of the product alcohols **1b**, **2b**, and **3b** were measured using a Bruker PMA 37 accessory coupled to a Vector 33 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90) set at $l/4$ retardation was used to modulate the handedness of the circular polarized light, and demodulation was performed by a lock-in amplifier (SR830 DSP). To enhance the signal-to-noise ratio, an optical low-pass filter (<1800 cm^{-1}) was placed before the photoelastic modulator. A transmission cell equipped with CaF_2 windows and a 0.5-mm Teflon spacer was used. A single-beam spectrum of the neat solvent served as the reference for the absorption spectrum, and a spectrum of the neat solvent recorded in VCD mode was subtracted from the VCD spectrum of the dissolved molecules. The data are presented without smoothing or further data processing.

4. Results

4.1. Catalytic hydrogenation

Chemoselectivity was excellent in the hydrogenation of **1a**, **2a**, and **3a** on the Pt–CD system; no other products beside the corresponding alcohols were detected. Preliminary studies indicated that the most influential parameter of all three reactions was the reaction medium including the solvent, the presence of water, and a strong acid additive. Note that in this limited parameter study, optimization of the conditions to achieve the highest *ee* was not attempted. The objective of the catalytic investigation was to find the appropriate conditions to achieve sufficiently high *ee*'s at high yields to allow reliable identification of the major enantiomers by VCD spectroscopy.

The role of the reaction medium in the hydrogenation of **1a** is summarized in Table 1. The solvent polarity is characterized by the relative permittivity (dielectric constant, ε_T). No clear correlation between the solvent polarity and *ee* could be established, and the correlation was no better when the relative permittivity was replaced by the empirical solvent parameter E_N^T [55]. The best *ee*'s were achieved in halogenated solvents and toluene (entries 1, 6, 8, and 9).

The reaction was very sensitive to the presence of water. In response to the addition of water to 1,2-dichlorobenzene, the *ee* dropped and the reaction time necessary to achieve full conversion more than doubled (entries 9 and 11). In a control experiment, slightly higher *ee* was obtained after even traces of water were eliminated by adding an activated molecular sieve to the reaction mixture (entry 12). The negative effect of water is probably related to rapid hydration of the activated ketone, as was reported for the enantioselective hydrogenation of ethyl 4,4,4-trifluoroacetoacetate [56]. Note that a small amount of

Table 1
Enantioselective hydrogenation of **1a** to **1b** on CD-modified Pt/Al_2O_3

Entry	Solvent	ε_T	Time (h)	Yield (%)	*ee* (%)
1	Toluene + 40 mg mol. sieve	2.4	2	100	18
2	Diethyl ether	4.2	2	100	8
3	Isobutyl acetate	5.6	2	100	9
4	Ethyl acetate	6.0	2	100	5.5
5	Acetic acid	6.2	2	65	5.5
6	Dichloromethane	8.9	2	100	16.5
7	Dichloromethane + 10 μL TFA	–	6	95	17.5
8	α,α,α-Trifluorotoluene	9.2	2	100	19.5
9	1,2-Dichlorobenzene	9.9	2	100	22
10	1,2-Dichlorobenzene + 5 μL TFA	–	4	4	–
11	1,2-Dichlorobenzene + 25 μL H_2O	–	4	98	5
12	1,2-Dichlorobenzene + 40 mg mol. sieve	–	2	100	23.5
13	2-Propanol	19.9	2	100	7

Standard conditions. Always the *R*-enantiomer was formed in excess.

Table 2
Enantioselective hydrogenation of **2a** to **2b** on Pt/Al_2O_3 modified by CD

Entry	Solvent	ε_T	CD (μmol)	Yield (%)	*ee* (%)
1	Toluene	2.4	13.6	100	2 (*R*)
2	Toluene + 5 μL TFA	–	13.6	36	36 (*R*)
3	Ethyl acetate	6.0	13.6	100	2 (*S*)
4	THF	7.6	6.8	100	5 (*S*)
5	THF + 5 μL TFA	–	6.8	98	4 (*R*)
6	Acetic acid	6.2	13.6	100	2 (*R*)
7	Dichloromethane	8.9	6.8	99	3 (*R*)
8	Dichloromethane + 10 μL TFA	–	6.8	83	44 (*R*)
9	Dichlorobenzene	9.2	13.6	96	11 (*R*)
10	2-Propanol	19.9	6.8	100	15 (*S*)
11	2-Propanol + 5 μL TFA	–	6.8	100	10 (*R*)
12	methanol	32.6	13.6	100	22 (*R*)

Standard conditions.

water is inevitably produced at the Pt surface during reduction of the surface oxides (present on the catalyst exposed to open air) by introducing hydrogen into the reactor.

The addition of a strong acid (TFA) decreased the reaction rate (compare entries 6 and 7, and particularly entries 9 and 10), but barely affected enantioselectivity. The major enantiomer remained the same.

The characteristics of the hydrogenation of **2a** differ significantly, as shown in Table 2. In most solvents (i.e., toluene, ethyl acetate, acetic acid, dichloromethane), enantioselection was poor, and the *ee* was close to zero. In weakly polar solvents, the best *ee* was achieved in dichlorobenzene (entry 9). In the more polar and protic solvents (i.e., 2-propanol and methanol), the *ee* was higher, and the opposite enantiomer formed in excess. A similar inversion of *ee* was recently reported for the hydrogenation of trilfluoromethylcyclohexyl ketone in toluene and ethanol [9]. The probable reason for this inversion is additional H-bonding interactions with the solvent.

The addition of TFA had a dramatic effect on enantioselection. In weakly polar solvents, *ee*'s up to 44% were attained, whereas in 2-propanol, the *ee* was inverted; that is, in the presence of the strong acid, the same enantiomer (*R*) was formed in excess in all solvents. The effect of the amount of TFA in dichloromethane is shown in Fig. 3. Twenty molar equivalents of TFA related to CD were needed to achieve the highest *ee* of 44%, although protonation of the quinuclidine N of CD requires only one equivalent of TFA [57]. The probable explanation for this finding is the strong adsorption of TFA on the basic sites of alumina, the support of Pt.

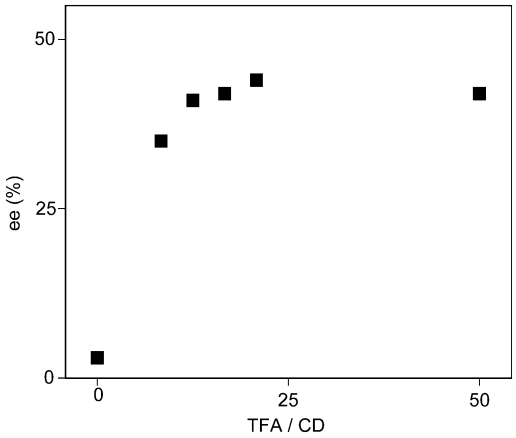


Fig. 3. Influence of TFA additive on the enantioselectivity in the hydrogenation of **2a**. Standard conditions but 0.61 mmol reactant; the yield varied in the range 72–99%.

Table 3
Enantioselective hydrogenation of **3a** to **3b** on Pt/Al_2O_3 modified by CD

Entry	Solvent	ε_T	Yield (%)	*ee* (%)
1	Dichloromethane	8.9	95	0
2	Dichloromethane + 10 μL TFA	–	80	42 (*R*)
3	Dichlorobenzene	9.2	98	7 (*R*)
4	2-Propanol	19.9	100	11 (*S*)
5	Acetic acid	6.2	100	2 (*R*)

Standard conditions, 6 h reaction time.

The solvent effect in the hydrogenation of **3a** was similar to that in the hydrogenation of **2a**, indicating some structural similarity. Here again the *ee* was inverted in 2-propanol (entry 4), and the addition of TFA significantly increased the *ee* (entries 1 and 2) and enabled determination of the major enantiomer by VCD spectroscopy.

To sum up, in the hydrogenation of all three aliphatic ketones, the (*R*) enantiomer was formed in excess in weakly polar solvents both with and without a strong acid additive. These findings will be used in the subsequent mechanistic considerations, because solvent effects are of the least importance in weakly polar solvents.

4.2. Determination of the absolute configuration of the products

Determination of the absolute configuration of the enantiomer produced in excess in an enantioselective reaction is demanding when reference data on the enantiomer are not available. Here the absolute configurations of the enantiomers of **1b**, **2b**, and **3b** were determined by comparing the calculated VCD spectrum of one enantiomer with the experimental VCD spectrum of the product of the asymmetric reaction [58–60]. When using this technique, one should bear in mind that the

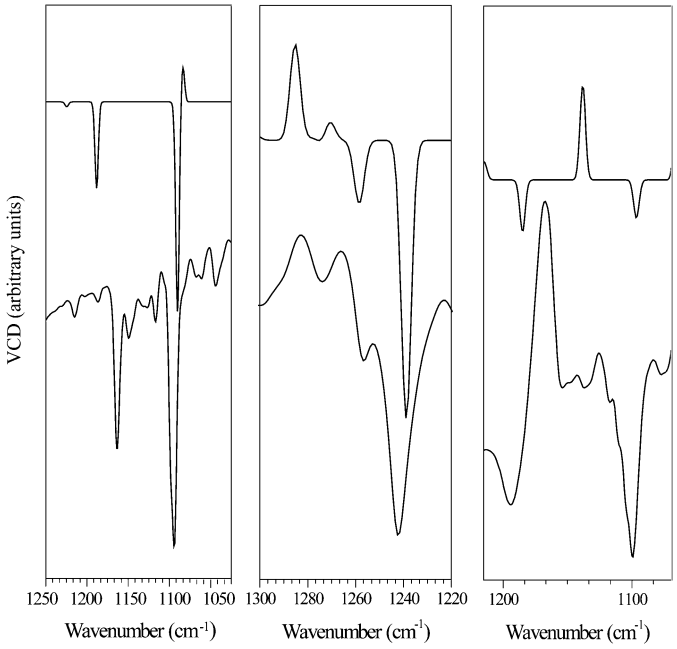


Fig. 4. Measured VCD spectra (bottom) of the alcohols **1b**, **2b**, and **3b** (from left to right) obtained by hydrogenation of **1a**, **2a**, and **3a**. The concentrations of the alcohols in the samples were 22, 48, and 60 mM, respectively. The calculated VCD spectra of the (*R*)-enantiomers (top) of the alcohols are provided for comparison.

VCD signal is about three orders of magnitude less intensive than the corresponding signal in the ordinary transmission spectrum. This situation makes the concentration and *ee*'s of the sample critical factors; a relatively small *ee* requires a more concentrated sample, whereas saturation of the signals must be avoided to prevent the formation of artificial spectral bands. Furthermore, in our case the characteristic high extinction coefficients of the ν(C–F) and σ(C–F) vibrations require further dilution to avoid signal saturation. Because of these limitations, the absolute configuration of **1b** (rather low *ee*) was confirmed independently by synthesizing the (*S*)-alcohol from the chiral epoxide (see the Experimental section).

Fig. 4 shows the theoretical and measured VCD spectra for **1b**, **2b**, and **3b**. The (*R*) absolute configuration was thus assigned to all three enantiomers produced in excess on CD-modified Pt.

4.3. Computation of hydrogen-bonded systems

The interaction energies between some hydrogen donors and some hydrogen acceptors of interest for the present study, calculated at the B3LYP/6-31G(dp) level of theory, are reported in Table 4, corrected for basis set superposition errors. Some interaction energies were also calculated at the MP2 level of theory, with a correlation-consistent basis set for comparison; good agreement was found. Methanol interacts rather weakly with organic fluorine (trifluoromethanol in the case of Fig. 2a), in agreement with the observation that such interactions are in general not very important in biasing chemical structures [29,30]. The hydrogen bonding interaction between methanol and α,α,α-trifluoromethyl ketones is stronger and depends on the position of the hydrogen donor, with a smaller interaction energy for the position in which methanol is located on the side of the fluorine substitution (Fig. 2b) and a larger one in the position in which methanol is located on the side of the methyl group (Fig. 2c). In each case, the principal hydrogen bond acceptor is oxygen, but fluorine provides a bias for the interaction. For comparison, the hydrogen bonding interaction between methanol and acetone was also calculated (Fig. 2d), and the interaction was found to be stronger than in the case in which the ketone is fluorinated. This weakening was previously reported for the intramolecular hydrogen bond in trifluoro-acetoacetone and is due to the electron-withdrawing properties of the fluorine atoms, which weaken the hydrogen acceptor capability of the neighboring keto-carbonyl oxygen [31].

In hydrogenation on cinchona-modified platinum, the hydrogen donor is supposed to be the protonated quinuclidine moiety [22]. A long-debated question is whether such a model can explain the reactivity only when the reaction is performed in an acidic solvent, such as acetic acid, where enantioselectivity in the hydrogenation of methyl pyruvate is optimal, and is not appropriate for rationalizing the reaction mechanism when aprotic solvents (such as toluene) are used. A computational study has recently shown that in principle, CD can extract a proton from chemisorbed hydrogen, thus accounting for the protonation of the alkaloid in aprotic solvents as well. Furthermore, Lee and Masel [61], using electron energy loss spectroscopy, found evidence that a pyridinium cation can be formed during coadsorption of pyridine and hydrogen on platinum. These results demonstrate that admitting the relevance of protonated CD in the mechanism of enantioselective hydrogenation of ketones on cinchona-modified platinum is very likely a more general concept, applicable to aprotic solvents as well. For this reason also, the interaction energy between the trimethylammonium ion and trifluoromethane was calculated (Table 4e). In this case, charge–dipole interactions come into play, and the energy associated with the H bonding is more effective than in the previous cases. The calculated interaction energy between trimethylammonium ion and trifluoroacetone (Table 4f) was almost three times greater than the corresponding interaction energy between methanol and trifluoroacetone (Table 4b). It was also found that the protonated amine adjusts on the side of the fluorine substitution, whereas no minimum

Table 4
Interaction energies (kcal/mol) in the hydrogen bonded species in Fig. 2

	a	*b*	*c*	*d*	*e*	*f*	*g*
B3LYP 6-31++Gdp	0.8 (0.2)	2.7 (0.4)	4.6 (0.3)	5.8 (0.4)	6.3 (0.3)	15.1 (0.5)	20.6 (0.6)
MP2 Aug-cc-pVDZ		3.4 (1.5)	4.3 (2.0)		7.7 (2.6)		

In parentheses is the basis set superposition error calculated with the counterpoise correction.

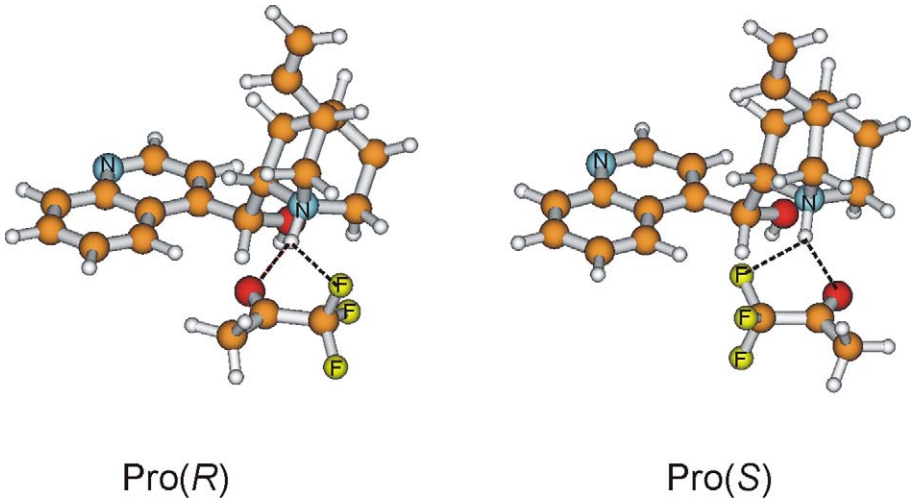


Fig. 5. Interaction model between cinchonidine and trifluoroacetone using surface constraints to force the quinoline ring and the ketone to be coplanar.

energy structure is found for the other (unsubstituted) side. In other words, the trifluoromethyl group biases the interaction between a protonated amine and trifluoroacetone. For comparison, the interaction energy between the trimethylammonium ion and acetone was also calculated (Table 4g) and was found to give a higher interaction energy compared with that of the fluoro-substituted analog. Again, the presence of the fluorine weakens the hydrogen-acceptor capability of the ketone.

To better understand CD's ability to differentiate the Pro(R) and Pro(S) faces of a trifluoromethyl ketone, the interaction of ketone **1a** with CD in the Open(3) conformation was also calculated, using surface constraints that force the substrate to be in the same plane as the quinoline ring (anchoring group). This approach has already been used to model the interaction between prochiral ketones and cinchona alkaloids, and although not explicitly including the metal surface, it has proven to be a useful approximation for the study of the reactant modifier–modifier interaction [43,44]. Fig. 5 shows the Pro(R) and the Pro(S) interactions. The Pro(R) interaction resulted in more stable interaction, by ca. 0.5 kcal/mol. This result should be considered only a qualitative indication of a bias toward the formation of the (R)-enantiomer rather than a quantitative prediction of the *ee*. This difference in energy is likely due to the difference between charge–dipole interactions of differently oriented substrates with the protonated alkaloid.

5. Discussion

As mentioned in the Introduction, the enantioselectivity in the hydrogenation of fluorinated ketones on cinchona-modified platinum could in principle originate from differences of steric hindrance between the substituents of the ketone, or from the bias set by the strongly polarizing trifluoromethyl group. If steric effects alone guide the selectivity of the substrate–modifier interaction, then ketone **1a** would be expected to give an alcohol having the opposite absolute configuration to that obtained by enantioselective hydrogenation of ketones **2a** and **3a**, compounds for which the relative hindrance of the substitutents is opposite to that of **1a**. On the other hand, if the trifluoromethyl group guides the interaction, then the three ketones should generate alcohols with identical absolute configuration. The catalytic result show that with weakly polar solvents, in which the interaction of the solvent with the substrate, modifier and Pt is less important, the three alcohols **1b**, **2b**, and **3b** have the same absolute configuration (R). This is a clear indication that in such solvents, enantioselectivity is guided by the trifluoromethyl substitution rather than by the relative bulkiness of the substituents at the two sides of the carbonyl group. The fluorinated substrate has a preferential interaction on the side of the α,α,α-trifluoromethyl group, as shown by the calculation of hydrogen bonding interactions (Fig. 2; Table 4). When this interaction mode is calculated for the system alkaloid–trifluoroacetone, an energy difference between the Pro(R) and the Pro(S) configurations (Fig. 5) can be detected. In conclusion, electronic effects theoretically give a bias toward the formation of the (R)-enantiomer, in accordance with the experimental data available.

When the reaction is performed in an alcohol (2-propanol), only the ketone **1a** gives the (R)-enantiomer in excess, whereas in the hydrogenation of **2a** and **3a**, the (S)-enantiomer is produced as the major enantiomer. Although it is not yet clear how the alcohols affect enantioselectivity, it is interesting to note that this inversion occurs in solvents for which direct interactions can occur between solvent and substrate molecules, whereas no inversion occurs in noninteracting solvents. Calculations (Table 4) have shown that alcohols bind to ketones less strongly than protonated amines, but the large excess of solvent molecules may lead to the formation of stable aggregates that may show different interaction modes with the chiral modifier, leading to a change in selectivity. The effect of the TFA additive in enhancing the enantioselectivity of the hydrogenation of **2a** and **3a**, when toluene is used as solvent, also is not clear. When dichloromethane is used as solvent, an increase in *ee* is observed only for the hydrogenation of **2a**, whereas in the hydrogenation of **1a**, the *ee* remains almost constant after the addition of TFA. The presence of a proton donor is not a sufficient explanation for this, because in the hydrogenation of **2a** in acetic acid, almost no enantioselectivity is observed. Adding

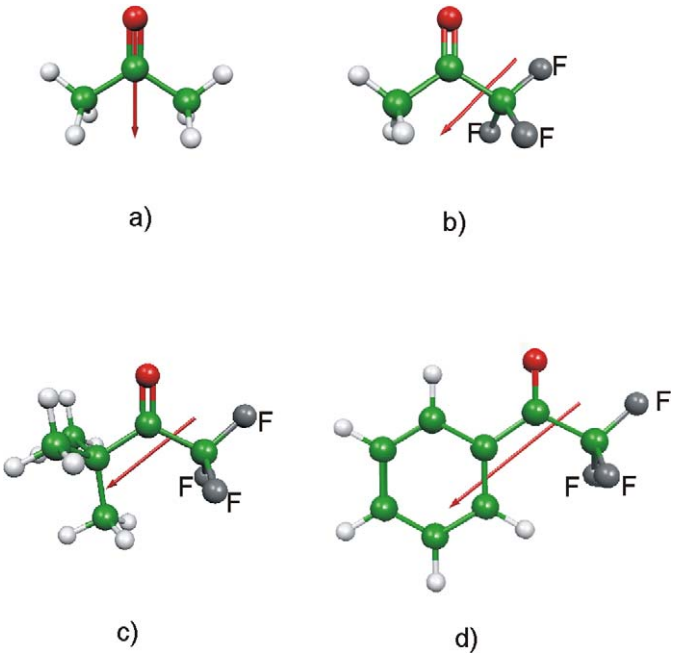


Fig. 6. Calculated dipole moments (vectors) of ketones **1a**, **2a**, and **3a** and of trifluoroacetophenone. In prochiral fluorinated ketones the vector of the dipole moment strongly deviates from the axis of the keto-carbonyl group.

TFA to 2-propanol leads to inversion of the enantioselectivity in the hydrogenation of **2a**, and thus to excess formation of the (*R*)-enantiomer. Direct solvent interactions and the presence of a strong proton donor, such as TFA, add complexity to the system, possibly by binding to the chiral modifier, as suggested in previous studies [62,63], or by binding to the substrate.

In the simpler situation in which noninteracting solvents are used, the activating group not only plays a role by accelerating the hydrogenation (activation of the substrate), and thus by enhancing enantioselectivity through kinetic resolution, but also is able to guide enantioselectivity by controlling the interaction mode with the chiral auxiliary. Interestingly, aromatic fluorinated ketones (α,α,α-trifluoroacetophenones) almost invariably give the (*R*)-enantiomer in enantioselective hydrogenation on CD-modified platinum [3,6,9,11]. This demonstrates that the directing effect of CF_3 also likely plays a role in aromatic ketones, in whose substrates adsorption is guided by the aryl substituent. Fig. 6 shows the dipole moments of acetone, trifluoroacetone, *tert*-butyl-trifluoromethyl ketone, and trifluoro acetophenone. In acetone, the vector of dipole moment lies on the C–O axis, whereas in the other fluorinated substrates, it deviates significantly from this axis. This loss of symmetry of the electron distribution due to the strongly polarizing trifluoromethyl substituent may be the origin of the energy differences in the interactions depicted in Fig. 5.

A recent study also demonstrated that similar guiding effects due to the activating moiety of a ketone are present for α-ketoesters [18], for which the (*R*)-enantiomer was also always found when CD was used as chiral modifier, as well as the (*S*)-enantiomer when *O*-phenyl-cinchonidine was used. This leads to the possible formulation of a rather general statement on the enantioselectivity of activated ketones on cinchona-modified platinum, according to which, independent of the substitution, in the hydrogenation of activated ketones cinchonidine gives the (*R*)-enantiomer and cinchonine and *O*-phenyl-cinchonidine give the (*S*)-enantiomer. Tuning of selectivity can then be achieved by additives, using a solvent system able to directly interact with the substrate or the modifier.

6. Conclusion

To better understand the nature of the crucial interactions between modifier and substrate in the enantioselective hydrogenation of α,α,α-trifluoromethyl ketones on cinchona-modified platinum, three fluorinated ketones with differing steric relationships between substituents have been studied by analyzing their reactivity in relation with the 1:1 interaction model with the protonated alkaloid. Our findings reveal that the electronic effects due to the trifluoromethyl group can play a role in determining the absolute configuration of the product alcohol. This demonstrates that the chiral environment generated by the alkaloid on the platinum surface has both sterical and electronic biases that can induce preferential hydrogen uptake on one of the prochiral faces of an activated ketone. Considering these findings together with analogous results obtained for α-ketoesters, it is tempting to propose a general statement according to which activated ketones give the same enantiomer, independent of the substituents and depending only on the chiral modifier used. Modulation of reactivity can then be achieved by using additives, such as strong proton donors, or using solvents that can directly interact with either the substrate or the modifier.

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