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Dynamic Kinetic Resolution over *Cinchona*-Modified Platinum Catalyst: Hydrogenation of Racemic Ethyl 2-Fluoroacetoacetate

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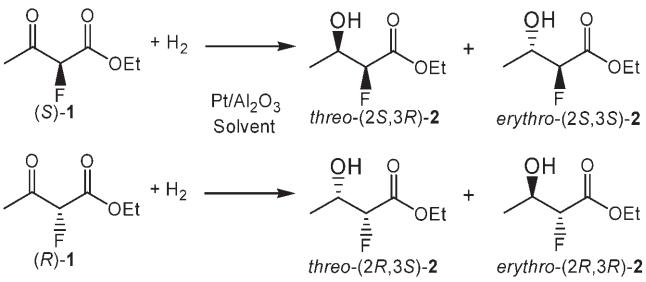
Abstract: The enantioselective hydrogenation over a *Cinchona* alkaloid-modified supported platinum catalyst and parallel spontaneous racemization under the reaction conditions of the unreacted enantiomer of ethyl 2-fluoroacetoacetate are described. Using the appropriate reaction conditions an 82% enantiomeric excess in favor of the (2*S*,3*R*)-ethyl 2-fluoro-3-hydroxybutanoate and a 99/1 *threo*/*erythro* ratio were obtained. This novel method for producing optically enriched α-fluoro-β-hydroxy esters is the first example of dynamic kinetic resolution of a chirally labile racemic fluorinated compound over a modified heterogeneous metal catalyst carried out without using supplementary additives except the chiral modifier. The hydrogenation described here shows that the activation of the keto group of acetoacetates by one fluorine atom in the α position is also sufficient for obtaining high enantiomeric excess in the Orito reaction.

Keywords: *Cinchona* alkaloids; dynamic kinetic resolution; enantioselectivity; heterogeneous catalysis; hydrogenation

Introduction

The unique chemical and pharmacological properties of fluorinated chiral molecules have raised wide interest in developing asymmetric catalytic methods for their production.[1,2] Among these, the enantioselective hydrogenations of fluorinated ketones using chiral metal complexes are simple methods for obtaining chiral fluorinated alcohols.[3–5] Since the discovery of the enantioselective hydrogenation of α-keto esters over *Cinchona* alkaloid-modified, supported Pt catalysts by Orito et al.[6] the scope of the reaction has been extended to other types of activated ketones,[7–9] due to the simplicity of this heterogeneous catalytic method. Activation by a trifluoromethyl moiety next to the keto group resulted in the enantioselective formation of the corresponding alcohols.[10,11] The optical purities of the products were highly dependent on the substrate structure,[12] high enantiomeric excesses (ee) were obtained only in limited cases.[13–15]

Recently, special interest was given to asymmetric reactions leading to the formation of optically enriched compounds in which fluorine is attached to a chiral center.[16,17] Among these, optically active α-fluoro alcohols are widely used chiral building blocks. A convenient method for obtaining these compounds is the enantioselective hydrogenation of α-fluorinated ketones. However, using a chiral Rh complex as catalyst resulted in disappointingly low ees in the hydrogenation of α-fluoro- and α,α-difluoromethyl ketones, although the same complex gave excellent ee when used for the hydrogenation of the corresponding trifluoromethyl ketone.[4] High optical purities were observed only in the hydrogenations of 2,2-difluoro-3-oxocarboxylates.[5] In spite of the well known advantages of the heterogeneous catalysts, i.e., easy handling, separation and reuse of the catalyst, such catalytic systems have not been tested yet in the hydrogenation of α-monofluoro ketones. Thus, we have decided to investigate the hydrogenation of racemic ethyl 2-fluoroacetoacetate (**1**), using the *Cinchona* alkaloid-modified Pt catalyst which, as mentioned



Scheme 1. General scheme of the hydrogenation of racemic ethyl 2-fluoroacetoacetate.

above, was applied successfully in the enantioselective hydrogenation of several α,α,α-trifluoromethyl ketone. The hydrogenation of racemic **1** may lead to the four ethyl 2-fluoro-3-hydroxybutanoate (**2**) stereomers as shown in Scheme 1.

Results and Discussion

Enantioselective Hydrogenation of 1

Results obtained in the hydrogenation of **1** over Pt/Al_2O_3 in the absence and presence of cinchonidine (**3**) in different solvents are collected in Table 1.

The hydrogenation of **1** resulted in the formation of **2** and ethyl acetoacetate (**4**) as major side product formed by hydrogenolysis of the C–F bond. The hydrogenation of the C=O group was diastereoselective, even in the absence of a chiral modifier the *threo* isomers ((2*S*,3*R*)-**2** and (2*R*,3*S*)-**2**) were formed in excess. In the presence of **3** both the hydrogenation selectivity (SelH) and the diastereomeric excess (de) increased. Moderate ees were obtained in THF or AcOEt (entries 4 and 6) with the formation of the *threo*-(2*S*,3*R*)-**2** enantiomer in excess (for determination of the absolute configuration of the product see Experimental Section). Interestingly, after each reaction the unreacted **1** was a racemic mixture as determined by gas chromatographic analysis, while the yields of (2*S*,3*R*)-**2** in THF and AcOEt were 59% and 61%, respectively. Considering that the conversion and SelH in THF were 91% and 99% (see Table 1) and the *erythro* isomers were obtained in 14% ee to the *erythro*-(2*R*,3*R*)-**2** enantiomer, a stereochemical balance shows that compounds having the 2*S* configuration [(*S*)-**1**, (2*S*,3*R*)-**2** and (2*S*,3*S*)-**2**] are in excess in the final mixture, the ratio of compounds 2*S*/2*R* was 70/30. Accordingly, racemization of the (*R*)-**1** took place which, in the presence of **3**, was hydrogenated with a lower rate than (*S*)-**1**. We also observed that in the case of both *threo* and *erythro* isomers the 3*R* products are formed in excess, i.e., *threo*-(2*S*,3*R*)-**2** and *erythro*-(2*R*,3*R*)-**2**, thus in the presence of **3** the hydrogenation of the C=O group is enantioselective and irrespective of the absolute configuration of the C-2 chiral center the configuration of the resultant C-3 center is *R*. The racemization of the unreacted (*R*)-**1** was possible due to the fast equilibration of the keto and enol forms of **1**, these latter species (**5**) could be stabilized by intramolecular hydrogen bonds, similarly as described for the 4,4,4-trifluoroacetoacetates.[11] The concentration of the keto species in different solvents, calculated from the ^{1}H NMR spectra of **1**, was found to be 70±2% in equilibrium with ~30% enol form (see Experimental Section). It has been shown by von Arx et al. that, in the hydrogenation of 4,4,4-trifluoroacetoacetates, the enolic forms are only spectator species.[11] On the contrary, during the hydrogenation of **1** the enolization has an important role in increasing the ee, due to racemization of the unreacted (*R*)-**1**, thus being transformed partially to (*S*)-**1** *via* the enol **5**, which is hydrogenated enantioselectively to *threo*-(2*S*,3*R*)-**2**. It should be mentioned that, similarly to the hydrogenation of 4,4,4-trifluoroacetoacetates, the enolic species of the substrate are not hydrogenated during the reaction. This was demonstrated by the reaction over Pd/Al_2O_3, when no transformation occurred after 2 h (entry 9), explained by the negligible activity of supported Pd catalysts in the hydrogenation of aliphatic ketones.[18]

The above presented enantioselective hydrogenation over chirally modified Pt and parallel racemization of the unreacted substrate is the first dynamic kinetic reso-

Table 1. Hydrogenation of **1** over Pt/Al_2O_3 in different solvents.[a]

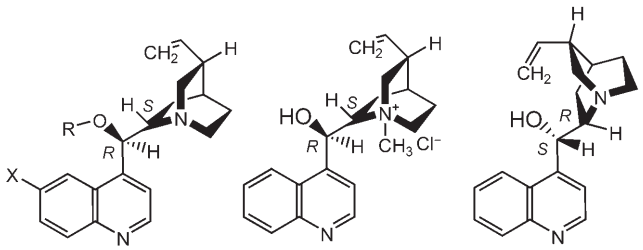
Entry	Solvent[b]	Modifier	Conv.[c] [%]	SelH[d] [%]	de[e] [%]	ee[e] [%]
1	Toluene	–	41	79	52	–
2		**3**	11	83	66	33
3	THF	–	96	97	45	–
4		**3**	91	99	71	53
5	AcOEt	–	98	96	42	–
6		**3**	100	98	66	50
7	MeOH	–	34	78	44	–
8		**3**	99	98	75	24
9		**3**[f]	0	–	–	–
10	AcOH	–	37	66	37	–
11		**3**	78	93	80	24

[a] *Reaction conditions:* 50 mg 5% Pt/Al_2O_3, 3 mL solvent, 17 μmol **3**, 0.8 mmol **1**, pH_2 3 MPa, *T* 297 K, 2 h.
[b] Solvent abbreviations: tetrahydrofuran (THF), ethyl acetate (AcOEt), methanol (MeOH), acetic acid (AcOH).
[c] Conversion of **1**.
[d] C=O group hydrogenation selectivity.
[e] Determined by gas chromatography.
[f] Reaction over 50 mg 5% Pd/Al_2O_3.

lution over a heterogeneous catalyst of a fluorine-containing compound described until now. Only few examples of dynamic kinetic resolution over heterogeneous catalysts have been reported. This type of reaction has been observed in hydrogenations using homogeneous catalysts during the hydrogenation of α-substituted β-keto esters.[19] Since then, the dynamic kinetic resolution of several chirally labile racemic compound has been reported by hydrogenation over homogeneous metal complexes.[20] The high importance of dynamic kinetic resolutions is well illustrated by the recently published examples which make use of enzymes and/or metal complexes; however, in all cases the use of high amounts of base additives were necessary.[21] The first dynamic kinetic resolution over a heterogeneous catalyst was reported by Tai et al. in the enantioselective hydrogenation of α-alkyl-β-keto esters over (*R*,*R*)-tartaric acid-modified Ni catalysts.[22] In a recent report Blaser et al. described the kinetic resolution of racemic α-keto ethers by hydrogenation over Pt modified by *Cinchona* derivatives.[23] High ee was obtained up to 50% conversion, due to faster hydrogenation of the *S* enantiomers. Dynamic kinetic resolution of the substrates could be accomplished if an additional solid base, able to racemize the unreacted enantiomers, was used. Thus, here we report the first example of dynamic kinetic resolution of an α-fluoro-β-keto ester by enantioselective hydrogenation over a chirally modified heterogeneous catalyst coupled with spontaneous racemization of the unreacted substrate. Due to the well known advantages of heterogeneous catalytic systems, this new method could be an easy, economic way for obtaining optically enriched α-fluoro-β-hydroxy esters.

Effect of the Reaction Parameters

In our attempt to increase the ee in the hydrogenation of **1** we carried out a limited study on the effect of modifier structure (see Scheme 2) and reaction parameters (see Table 2) which were found to have crucial influence on the enantioselective hydrogenation of 4,4,4-trifluoroacetoacetates.[11] We note that, in all these reactions, the unreacted **1** was a racemic mixture, special care has been taken to analyze the products immediately after sampling and using various chromatographic conditions (i.e,. injector and column temperature).



Scheme 2. Structure of *Cinchona* derivatives used as modifiers in the hydrogenation of **1**.

Decreasing the H_2 pressure in THF had little effect on the ee (entries 1 and 2). In AcOH the ee increased at low H_2 pressure, however, in this solvent a significant decrease of the initially high (61%) ee was obtained as a function of conversion. No significant changes were observed in the de and ee values over catalyst prereduced in H_2 at 673 K (compare entries 5 and 6) while both conversion and SelH decreased. Thus, we have continued to use the catalyst as received, pretreating it only in liquid phase. Using a 1/1 AcOH/THF solvent mixture resulted in higher de than in the pure solvents and no significant loss of ee was observed during the reaction at 297 K (entries 12 and 13). The ee was increased by decreasing the reaction temperature to 273 K. Under these conditions the *threo*/*erythro* ratio was 97/3 (de 94%) and the *threo* isomers were obtained in 76% ee after 0.5 h reaction (entry 14).

The effect of the modifier structure was investigated using the *Cinchona* derivatives presented in Scheme 2. Cinchonine (**9**), similarly to α-keto esters,[24] gave lower ee and the excess product had the opposite configuration at both chiral centers of **2** as compared with that obtained when **3** was used (entry 10). Thus, in the presence of **9** from the two substrate enantiomers the hydrogenation of (*R*)-**1** was faster and the unreacted (*S*)-**1** was racemized parallel with the hydrogenation. Furthermore, in the case of both isomer pairs (again excess of *threo* was obtained in an 87.5/12.5 ratio) the enantiomers having the 3*S* configuration, i.e., *threo*-(2*R*,3*S*)-**2** and *erythro*-(2*S*,3*S*)-**2**, were formed in excess (the latter in 17% ee, not included in Table 2). Quinine (**6**) surprisingly gave somewhat higher de and ee than **3** (entry 16), as a result of the effect of the methoxy group bonded to C-6 of the quinoline moiety. The highest ee values were obtained by using *O*-methylcinchonidine (**7**) as modifier, both in AcOH and 1/1 AcOH/THF, similar to the hydrogenation of 4,4,4-trifluoroacetoacetates.[11] In the latter solvent mixture an ee of 78% could be obtained at low conversion, which decreased to 65% when the transformation of **1** exceeded 80% (entries 17–19). Very low conversion and close to racemic product was obtained by using *N*-methylcinchonidinium chloride (**8**, entry 20), showing that the interaction of the tertiary nitrogen of the *Cinchona* derivatives with the substrate during the hydrogenation is crucial to obtain enantioselection.

According to these results the best ees were obtained in the 1/1 AcOH/THF mixture using **7** as chiral modifier, however, the ee decreased at higher conversions. In the reactions carried out in THF constant ee values were obtained up to over 90% transformation of **1**. Thus, we initiated a study on the effect of the amount of AcOH in THF aimed to find the best solvent composition.

Table 2. Effect of reaction conditions and modifier structure on the hydrogenation of **1**.[a]

Entry	Solvent	Modifier	p [MPa]	T [K]	Conv.[c] [%]	SelH[d] [%]	de[e] [%]	ee[e] [%]
1	THF	**3**	3	297	91	99	71	53
2		**3**	0.1	297	95	99	72	51
3		**7**	0.1	297	79	99	65	42
4	AcOH	**3**	6	297	81	93	75	23
5		**3**	3	297	78	93	80	24
6		**3**	3[f]	297	51	84	79	25
7		**3**	1	297	76	94	75	32
8		**3**	0.1[g]	297	43	92	83	61
9		**3**	0.1	297	67	91	79	49
10		**9**	0.1	297	64	91	75	28[i]
11		**7**	0.1	297	69	89	76	54
12	AcOH/THF 1/1	**3**	0.1[g]	297	22	97	89	58
13		**3**	0.1	297	53	98	86	57
14		**3**	0.1[g]	273	22	100	94	76
15		**3**	0.1	273	48	100	92	61
16		**6**	0.1	273	48	99	96	68
17		**7**	0.1[g]	273	13	100	97	78
18		**7**	0.1	273	41	99	94	72
19		**7**	0.1[h]	273	84	95	92	65
20		**8**	0.1	273	5	93	45	5[i]

[a] *Reaction conditions:* 50 mg 5% Pt/Al_2O_3, 3 mL solvent, 17 μmol modifier, 0.8 mmol **1**, 2 h.
[b] Conversion of **1**.
[c] C=O group hydrogenation selectivity.
[d] The *threo* isomers were formed in excess.
[e] Configuration of the excess enantiomer was 2*S*,3*R* unless otherwise stated.
[f] Reaction over catalyst prereduced in flowing hydrogen at 673 K.
[g] Sample after 0.5 h reaction.
[h] Reaction time 8 h.
[i] Configuration of the excess enantiomer was 2*R*,3*S*.

The ee in the samples withdrawn after 0.5 h increased with increasing amount of AcOH reaching 82% in 5/1 AcOH/THF (83 vol % AcOH, see Figure 1). However, after 2 h reaction the ee reached a maximum in the solvent with 1/1 AcOH/THF composition, further increases in the amount of AcOH led to decreases in the ee. We note that the amount of the AcOH had less influence on the conversions obtained after 0.5 h than after 2 h reaction. In this latter case the use of small amounts of AcOH (1/5 and 1/2 AcOH/THF) resulted in large decreases in the conversions, while after further increases of the AcOH amount conversion remained practically constant. The decrease with time in the ee values accentuated by inceasing amounts of AcOH may be caused by several processes demonstrated to take place during the hydrogenations in the *Cinchona*-modified Pt catalytic systems. The hydrogenation of the quinoline moiety of the chiral modifier, that causes a decrease in the ee in the hydrogenation of ethyl pyruvate[25] or the formation of the hydrate of the α-fluoro carbonyl compound and its hydrogenolysis to the α-fluoro alcohol, demonstrated to cause drops in the ee in the hydrogenation of 4,4,4-trifluoroacetoacetates,[11] are the most probable causes of the drops in the ee observed in this system, too.

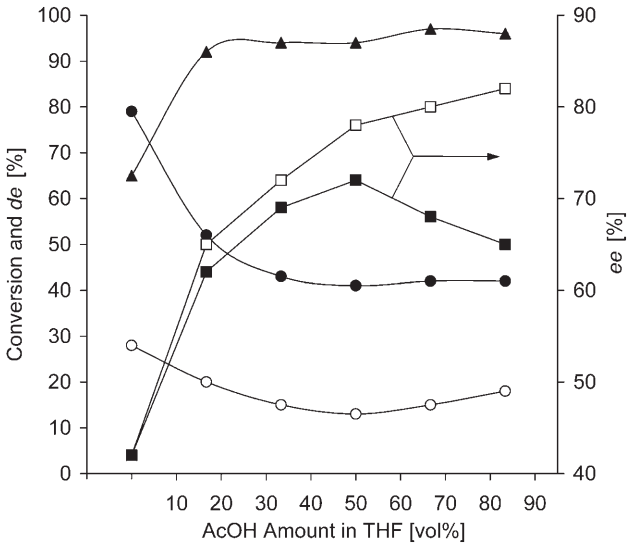


Figure 1. Effect of solvent composition on the hydrogenation of **1**. *Reaction conditions:* 50 mg Pt/Al_2O_3, 3 mL solvent, 0.8 mmol **1**, 17 μmol **7**, pH_2 0.1 MPa, T 273 K; conversion at 0.5 h (○) and 2 h (●); de at 2 h (▲); and ee at 0.5 h (□) and 2 h (■) reaction.

According to the above findings the time dependence of the product distribution was studied in the solvent mixture 1/1 AcOH/THF, under 0.1 MPa H_2 pressure, at 273 K using **7** as modifier. The results are presented in Figure 2a and the calculated conversion, SelH, de and ees are plotted in Figure 2b.

The *threo*-(2*S*,3*R*)-**2** isomer was in excess in the reaction mixture at any time, the selectivity of the hydrogenation was over 95%, the de over 90%, however the ee in the *threo* isomers decreased from 80% to 64% after 8 h reaction. From the *erythro* isomers formed in small amounts, (2*R*,3*R*)-**2** was in excess and in this case the ee increased from an initial low value up to 53% at 8 h. We stress out that the ratio of the excess *threo* and

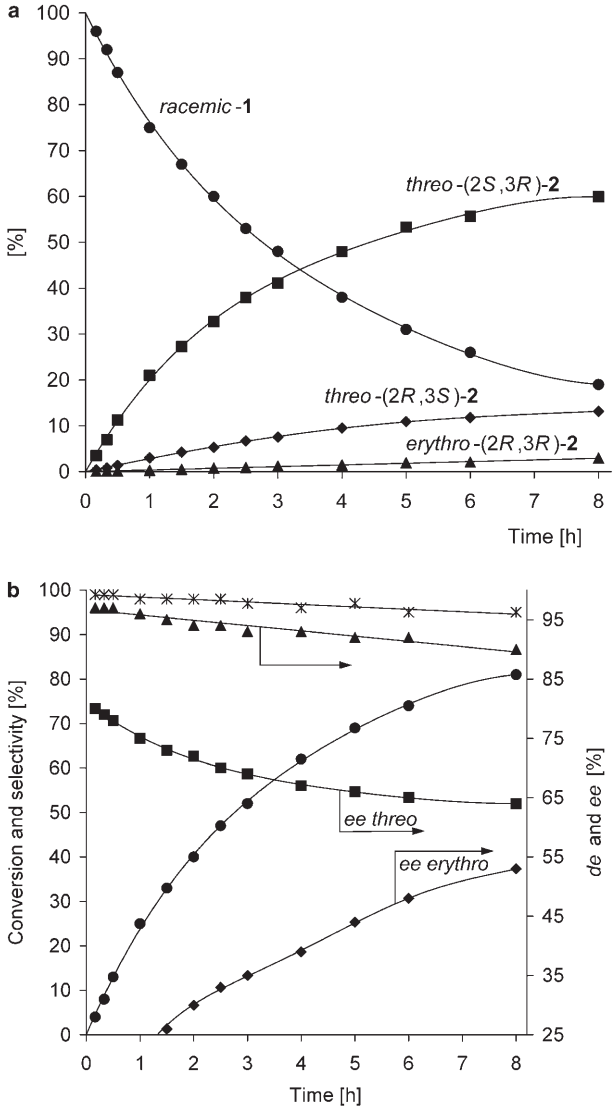


Figure 2. Hydrogenation of **1** in the presence of **7**. *Reaction conditions:* 50 mg Pt/Al_2O_3, 3 mL 1/1 AcOH/THF, 0.8 mmol **1**, 17 μmol **7**, pH_2 0.1 MPa, *T* 273 K. **a**) Reaction mixture composition. **b**) Conversion (●), hydrogenation selectivity (∗), de (▲), ee in the *threo* isomers (■) and ee in the *erythro* isomers (◆).

erythro enantiomers, i.e., (2*S*,3*R*)-**2** and (2*R*,3*R*)-**2** was high (over 20). This shows unambiguously that the rate of (*S*)-**1** hydrogenation is significantly higher than that of (*R*)-**1**, however the latter was not accumulated in the reaction mixture due to its racemization *via* **5**. This racemization led to partial transformation of the unreacted (*R*)-**1** to (*S*)-**1** the latter being hydrogenated enantioselectively with a high rate. The formation of (*S*)-**1** from (*R*)-**1** by racemization led to increase in the yield of the product having the *S* configuration of the C-2 chiral center. It is also important to note that the stereoselectivity of the hydrogenation of (*S*)-**1**, shown by the ratio of the (2*S*,3*R*)-**2** and (2*S*,3*S*)-**2** isomers, was even higher (over 66), reaching a stereoselectivity of 97% after 8 h reaction, calculated according to the formula: $100 \times ([(2S,3R)\text{-}\mathbf{2}] - [(2S,3S)\text{-}\mathbf{2}])/([(2S,3R)\text{-}\mathbf{2}] + [(2S,3S)\text{-}\mathbf{2}])$. Thus, the stereoselectivity of the hydrogenation of the enantiomer hydrogenated with a high rate is about as high as the best results obtained in the hydrogenation of other fluorinated α-ketones,[13–15] although in our case the carbonyl group is activated by only one fluorine atom.

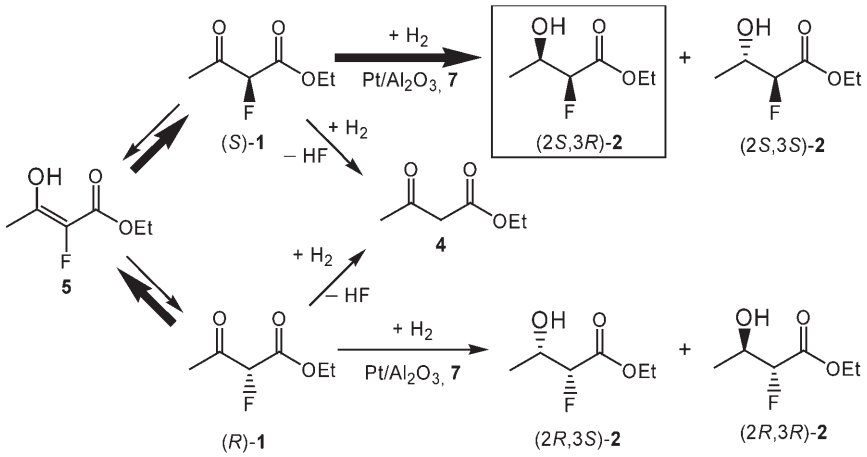
It is well known that in the classical Orito reaction a very low concentration of the *Cinchona* alkaloid used as chiral modifier can lead to maximal ee.[26] To verify this in the case of the enantioselective hydrogenation of **1** we have studied the effect of the amount of modifier **7** on this reaction, the results are presented in Figure 3.

Similarly, with the hydrogenation of α-keto esters, high ee values were obtained even in the presence of a small amount of **7** (0.034 μmol). A significant decrease in the de and ee was observed only by reducing the modifier amount to 0.0034 μmol. It is also a common feature of the enantioselective hydrogenation of α-keto esters over *Cinchona*-modified Pt catalysts that at high concentrations of modifier the reaction rate decreases.[7,26] This was also observed in the hydrogenation of **1**, and could be interpreted by a change in the adsorption mode of the modifier as a function of its concentration, similar to the hydrogenation of α-keto esters.[27] The decrease in the ee by conversion was not significantly influenced by the amount of modifier used, except at high values (17 and 34 μmol). Accordingly, the hydrogenation of the modifier may not be the main reason of the decrease in the ee during the reaction.

Finally, according to the observations discussed above, the reaction pathway of hydrogenation of racemic **1** may be sketched as on Scheme 3.

Conclusion

In conclusion we report here the first example of heterogeneous enantioselective hydrogenation of an α-fluoro-β-keto ester. It is known that hydrogenation of β-keto esters activated by a trifluoromethyl group over *Cinchona*-modified Pt catalyst results in enantioselec-



Scheme 3. Dynamic kinetic resolution and side-reactions in the hydrogenation of **1**.

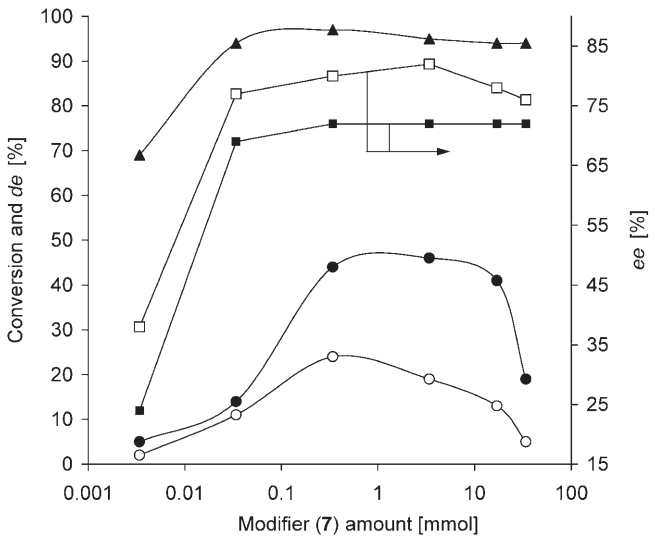


Figure 3. Effect of the amount of modifier **7** on the hydrogenation of **1**. *Reaction conditions:* 50 mg Pt/Al_2O_3, 3 mL 1/1 AcOH/THF, 0.8 mmol **1**, pH_2 0.1 MPa, *T* 273 K; conversion at 0.5 h (○) and 2 h (●); de at 2 h (▲); and ee at 0.5 h (□) and 2 h (■) reaction.

tive formation of fluorinated β-hydroxy esters[11,14] and the hydrogenation of ethyl acetoacetate in the same catalytic system leads to almost racemic product.[10] We have shown that activation of the keto group by only one fluorine atom is sufficient to obtain high enantioselectivities in the hydrogenation of acetoacetates over *Cinchona*-modified Pt catalyst. Using racemic 2-fluoroacetoacetate, parallel with the enantioselective hydrogenation, the spontaneous racemization of the unreacted enantiomer of the substrate led to dynamic kinetic resolution without addition of a base additive except the chiral modifier. We stress that the stereoselectivity of the hydrogenation of the (*S*)-**1** enantiomer, which reacts over 20 times faster than the (*R*)-**1** in presence of *O*-methylcinchonidine was 97%. This novel method provides a viable alternative to the asymmetric fluorinations for obtaining optically enriched fluoro alcohols. It is applicable to the enantioselective production of α-fluoro-β-hydroxy esters starting from stereochemically unstable racemic α-fluorinated-β-keto esters. Due to the fast racemization of the α-fluoro-β-keto esters the dynamic kinetic resolution of the starting material took place in our catalytic system, making it possible to obtain high enantioselectivities. The stereochemical lability of the substrate made the use of other basic additives unnecessary – except the chiral modifier which could be used in very small amounts.

Experimental Section

Materials

The substrate, ethyl 2-fluoroacetoacetate (**1**, Aldrich) was used as received. The modifiers: cinchonidine (**3**, ⩾98%, Fluka), cinchonine (**9**, ⩾98%, Fluka) and quinine (**6**, ⩾98%, Fluka) were commercial products and used without further purification. *O*-Methylcinchonidine (**7**), and *N*-methylcinchonidinium chloride (**8**) were prepared by known procedures.[28] Commercial 5% Pt/Al_2O_3 Engelhard E 4759, frequently used in the enantioselective hydrogenation of α-keto esters, having 38% Pt dispersion (as received), specific surface area 168 m^2/g, mean pore radius 2 nm, pore volume 0.27 cm^3/g was used as received.[26,29] The Pd catalyst used was Pd/Al_2O_3 5% Engelhard 40692, 21% Pd dispersion, specific surface area 200 m^2/g.[28,30] Commercial high purity solvents were used without purification.

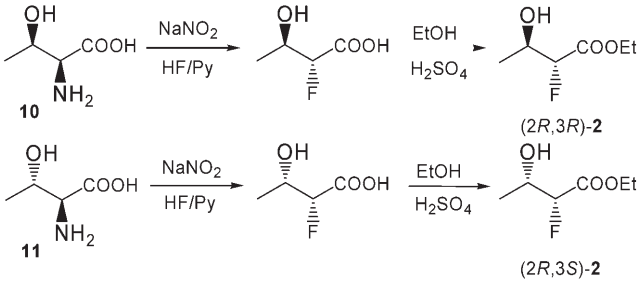
Catalytic Hydrogenations, General Procedure and Product Analysis

50 mg 5% Pt/Al_2O_3 catalyst (unless otherwise mentioned) were suspended in 3 mL solvent and pretreated by stirring the suspension under H_2 for 0.5 h. Then the modifier and the substrate were introduced. Samples were withdrawn by a gas

tight syringe at given times. The hydrogenation was stopped after 2 h or after the time specified, the catalyst filtered and the liquid analyzed. Products were identified by GC-MS (Agilent Techn. 6890N GC-5973 MSD) and ^{1}H NMR (Bruker AVANCE DRX-500 spectrometer) analysis. Conversion, hydrogenation selectivity (SelH) and stereoselectivity (de and ee) were determined by gas chromatographic analysis using an HP-5890 II GC-FID equipped with a CycloSil B (30 m × 0.2, J & W Scientific Inc.) chiral capillary column. The diastereomeric excess was calculated with the formula: de (%) = 100 × ([*threo*] – [*erythro*])/([*threo*] + [*erythro*]), where [*threo*] and [*erythro*] are the concentrations of the *threo* and *erythro* stereomers. The enantiomeric excess of the *threo* enantiomers was calculated by the formula: ee (%) = 100 × |[(2*S*,3*R*)-**2**] – [(2*R*,3*S*)-**2**]|/([(2*S*,3*R*)-**2**] + [(2*R*,3*S*)-**2**]), where [(2*S*,3*R*)-**2**] and [(2*R*,3*S*)-**2**] are the concentrations of (2*S*,3*R*)-**2** and (2*R*,3*S*)-**2**. The keto form concentration of **1** in different solvents was calculated from its ^{1}H NMR spectra based on the intensity of H_α (doublet, δ = 5.20, 5.34 and 5.32 ppm; J(F-H_α) = 49.5, 48.6 and 48.1 Hz in $CDCl_3$, THF-d_8 and 1/1 THF-d_8/AcOH-d_4) and of the ethyl CH_3 group (triplet, δ = 1.33, 1.27 and 1.21 ppm in $CDCl_3$, THF-d_8 and 1/1 THF-d_8/AcOH-d_4).

Identification of 2 Isomers and Determination of their Absolute Configurations

Diastereomers of **2** were identified by ^{1}H NMR spectroscopy on the basis of the chemical shifts and coupling constants (in $CDCl_3$) of H_α: double doublets, *threo*: δ = 4.83 ppm, J(F-H_α) = 48.6 Hz and J(H_α-H_β) = 3.66 Hz; *erythro*: δ = 4.75 ppm, J(F-H_α) = 48.1 Hz and J(H_α-H_β) = 3.2 Hz, and comparison with published data.[31] The absolute configuration of the **2** enantiomers were determined by synthesis of **2** isomers with known configurations from L-threonine (**10**, = 98%, Aldrich) and L-*allo*-threonine (**11**, 99%, Aldrich) by the method described by Olah et al. (Scheme 4)[32] and comparison of their retention times with those of the hydrogenated products. Reaction of these α-amino acids in pyridine/HF with excess $NaNO_2$ led, *via in situ* diazotization followed by bimolecular nucleophilic substitution, to the formation of the α-fluorocarboxylic acids with inversion of the absolute configuration at C-2. Subsequent esterification led to the products also obtained in the hydrogenation reactions shown in Scheme 4.



Scheme 4. Preparation of **2** with known absolute configuration.

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