DOI: 10.1002/adsc.200800458

Up to 96% Enantioselectivities in the Hydrogenation of Fluorine Substituted (*E*)-2,3-Diphenylpropenoic Acids over Cinchonidine-Modified Palladium Catalyst

György Szőllősi,[a,*] Beáta Hermán,[a,b] Károly Felföldi,[c] Ferenc Fülöp,[a,b] and Mihály Bartók[a,c]

[a] Research Group of Stereochemistry of the Hungarian Academy of Sciences, University of Szeged, H-6720 Szeged, Dóm tér 8, Hungary
Fax: (+36)-62-544-200; e-mail: szollosi@chem.u-szeged.hu
[b] Institute of Pharmaceutical Chemistry, University of Szeged, H-6720 Szeged, Eötvös utca 6, Hungary
[c] Department of Organic Chemistry, University of Szeged, H-6720 Szeged, Dóm tér 8, Hungary

Received: July 24, 2008; Revised: October 20, 2008; Published online: November 17, 2008

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800458.

Abstract: The enantioselective hydrogenation of methoxy- and fluorine-substituted (*E*)-2,3-diphenylpropenoic acid derivatives was studied over cinchonidine-modified, supported palladium catalysts in the absence and presence of benzylamine as additive. The fluorine substituent in the appropriate position was even more efficient than the methoxy group in increasing the optical purity of the saturated product. High enantioselectivities, up to 96%, were obtained in the hydrogenation of some disubstituted derivatives, unprecedented in the hydrogenation of prochiral unsaturated carboxylic acids over modified heterogeneous catalyst. The best optical purities were reached in the hydrogenation of derivates bearing a *para*-substituent on the β phenyl and an *ortho*-substituent on the α phenyl ring, respectively. The influence of the substituent on the β phenyl ring was attributed to the increase in the efficiency of the modifier-substrate interaction by electronic effects or to a decrease in the adsorption strength of the substituted acid over modified surface sites. The beneficial effect of the *ortho*-substituent on the α phenyl ring was assumed to be due to the additional interaction of this substituent with the modifier on the surface, its steric hindrance contributing only in a small part to the observed effect. These suggestions were supported by results obtained in the hydrogenations of some methyl-substituted derivatives.

Keywords: asymmetric hydrogenation; cinchonidine; diphenylpropenoic acid; fluorine; palladium; substituent effect

Introduction

Optically pure carboxylic acids are valuable pharmaceuticals or chiral building blocks used in the preparation of biologically active compounds.[1] Among the simplest methods for the production of optically enriched chiral carboxylic acids and their derivatives are the enantioselective catalytic hydrogenations of the corresponding prochiral unsaturated carboxylic acids.[2] The most widely used catalysts for these purposes are chiral homogeneous metal complexes.[2,3] Due to the advantages of the heterogeneous catalytic systems, metal catalysts modified on the surface by optically pure compounds are attractive potential alternatives of the highly selective soluble complexes.[4]

Following the exceptional results obtained in the enantioselective hydrogenation of β-keto esters and activated ketones over tartaric acid-modified Raney-Ni[4,5] and *Cinchona* alkaloid-modified, supported Pt catalysts,[4,6] *Cinchona* alkaloid-modified Pd catalysts were developed for the enantioselective hydrogenation of prochiral olefinic compounds, particularly α,β-unsaturated carboxylic acids[7,8] and 2-pyrone derivatives.[9] The hydrogenation of α,β-unsaturated carboxylic acids over cinchonidine (**1**)-modified Pd catalyst was found to be highly substrate sensitive. The best enantioselectivities were obtained in the hydrogenation of α-phenylcinnamic acid and its methoxy-substituted derivatives.[10,11] As a result of the extended efforts of Nitta and co-workers up to 92% enantiomeric excess (*ee*) was obtained in the hydrogenation of (*E*)-

2,3-di(4-methoxyphenyl)propenoic acid in the presence of benzylamine (**2**) as additive.[10d] The excellent *ee* values obtained in the hydrogenation of the *para*-methoxy-substituted derivatives were explained by the enhanced modifier-acid interaction due to the strong electron-releasing effect of the *para*-methoxy substituents.

Recently, we reported that (*E*)-2-(2-methoxyphenyl)-3-(4-methoxyphenyl)propenoic acid is hydrogenated in even higher *ee* then the di-*para*-methoxy-substituted derivative.[11] We supposed that the favourable effect of the methoxy substituents in the *ortho*-position on the α phenyl ring was due to its steric effect. Moreover, beside substitution in the *para*-position the *meta*-methoxy-substituent on the β phenyl ring also increased the enantioselectivity. It was suggested that either the steric effect of the methoxy substituent or an additional interaction with the modifier on the catalyst surface could be the reason of the observed substituent effect. The hydrogen bond acceptor ability of the methoxy group may further increase the strength of the modifier-acid interaction by additional hydrogen bonding.[11] The effect of the substituent on the adsorption on the metal surface of the phenyl-substituted olefins[12] and consequently on the hydrogenation rate of the acid or the **1**-acid intermediate may also have an effect on the *ee*. Accordingly, we continued our investigation on the effect of substituents in different positions on both α and β phenyl rings in order to explore the reason for the *ee* increase observed in the hydrogenation of methoxy-substituted derivatives, also attempting the extension of the scope of this highly effective heterogeneous asymmetric catalytic system.

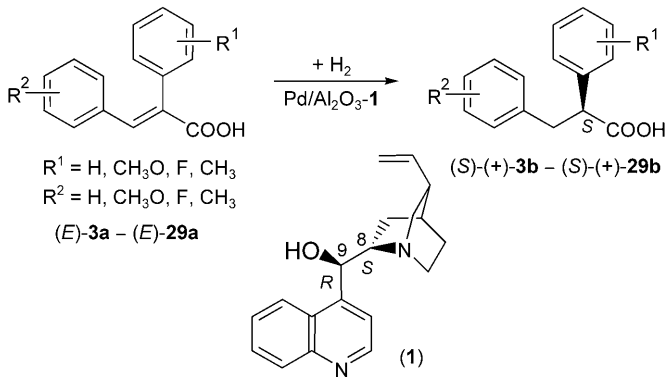
Based on the above considerations, we chose to study the effect of fluorine substituents. Fluorine exerts smaller steric hindrance and has a stronger inductive electron-withdrawing coupled with a weaker resonance electron-releasing effect as compared with the methoxy group. As a consequence the effect of the fluorine substituents on the *ee* may lead to new insights into the interaction mode of the modifier with the unsaturated acid on the catalyst surface. Moreover, the hydrogen-bond forming ability of fluorine is weaker than that of oxygen. Although it was found that covalently bonded fluorine hardly ever accepts hydrogen bonds,[13] C–F···H–C weak contacts are more frequent and these may also contribute to the enantiodiscrimination.[13a] Furthermore, the effect of the additive **2** on the *ee* and initial rate may also provide useful information on the substrate-modifier interaction.

Beside the expected mechanistic findings, the optically enriched fluorinated products are of high practical importance. The exceptional chemical and pharmaceutical properties of fluorinated compounds promoted the development of asymmetric methods for the preparation of fluorine-containing, optically pure chiral building blocks.[14] Among these are the enantioselective hydrogenations of fluorinated prochiral substrates.[15] Chiral heterogeneous catalysts, such as Pt modified by *Cinchona* derivatives, were found to be efficient in the enantioselective hydrogenation of trifluoromethyl ketones[16,17] and even some α-fluoro ketones.[18] The attempts on the hydrogenation of fluorine-containing, aliphatic α,β-unsaturated carboxylic acids over Pd catalysts in the presence of **1** resulted in low optical yields,[7e,19] while the enantioselective hydrogenation of prochiral cinnamic acid derivatives substituted with fluorine on the aromatic ring has not yet been attempted.

In the present study we investigated the effect of fluorine and mixed fluorine and methoxy substitution on both phenyl rings in (*E*)-2,3-diphenylpropenoic acid in comparison with the unsubstituted form and some relevant methoxy-substituted derivatives. Beside the fluorine- and methoxy-substituted compounds, the effect of the methyl substituent in certain positions was also examined to ascertain the role of the electronic and steric effects of the substituents.

Results and Discussion

The hydrogenation of (*E*)-2,3-diphenylpropenoic acid [(*E*)-**3a**] and its substituted derivatives over supported Pd results in the formation of the corresponding 2,3-diphenylpropionic acid derivatives. The solvent (DMF with 2.5 vol% water) was selected according to previous studies.[10,11] Commercial 5% Pd/Al_2O_3 (Engelhard 40692) was chosen from a range of catalysts and was prereduced in flow of H_2 at 523 K.[11] Complete conversions were reached in 1–4 h under 0.1 MPa H_2 pressure at room temperature. In the presence of the chiral modifier **1** (5 mol%) under the same conditions the hydrogenations took 6–8 h (over 99% conversions) and (*S*)-2,3-diphenylpropionic acid derivatives were formed in excess, as shown by the identical sense of rotation of the excess enantiomers (see Scheme 1). The enantioselective hydrogenations were carried out both in the absence and the presence of 1 equivalent of **2**. This achiral additive increased the *ee* in the hydrogenation of α-phenyl- and α-alkylcinnamic acid derivatives[10,11] and aliphatic and cycloaliphatic unsaturated carboxylic acids.[8,19] Although the increase in the *ee* seems to be a common feature of the hydrogenations of prochiral carboxylic acids, the effect of **2** on the initial rates showed that the influence of this additive varies as a function of the substrate structure. The initial rate and *ee* increase obtained in the hydrogenation of (*E*)-**3a** in the presence of **2** was attributed to acceleration of the desorption of the saturated product from the modified sites of the catalyst, where the adsorbed (*S*)-**3b** interacts with



Scheme 1. The enantioselective hydrogenation of substituted (*E*)-2,3-diphenylpropenoic acid derivatives over **1** modified Pd/Al_2O_3.

1. This indicated that the rate-determining step over modified catalyst is the product desorption.[10b]

Hydrogenation of Methoxy- or Fluorine-Monosubstituted Derivatives

The hydrogenations of (*E*)-2,3-diphenylpropenoic acids substituted on the α phenyl ring in the *ortho*-position or on the β phenyl ring in the *ortho*- or *para*-position either with a methoxy group or with fluorine was compared with that of the unsubstituted acid in Table 1. In line with the small effect of the substituents on the hydrogenation of phenyl-substituted olefins described by Kieboom and van Bekkum,[12] the initial rate over unmodified catalyst (R_u) decreased only slightly and in a similar extent as the effect of both substituents in a given position on the β phenyl ring. The decrease is the consequence of the reduced adsorption strength and accordingly the lower surface concentration of the reaction intermediates formed from the substituted acids as compared with (*E*)-**3a**. Similar phenomenon was described in the hydrogenation of substituted anisole derivatives,[20] although, in the present study the effect is smaller, as the substituted rings are not hydrogenated, but rather an adjacent olefinic bond. A larger R_u decrease was observed in the hydrogenation of the compounds substituted on the α phenyl ring in the *ortho*-position, due to the orientation of this ring.[11,21] The tilted arrangement of this phenyl group with respect to the acrylic acid moiety results in stronger hindering of the adsorption on the C=C group by both the *ortho*-methoxy and the *ortho*-fluorine substituent.

The initial rates in presence of **1** (R_m) decreased in all these reactions as compared with the racemic hydrogenations. Higher *ee*s were obtained in the reactions of the acids substituted in the *para*-position on the β phenyl ring [(*E*)-**4a** and (*E*)-**5a**)] and in the *ortho*-position on the α phenyl ring [(*E*)-**8a** and (*E*)-**9a**)] with respect to (*E*)-**3a**. On the other hand, the R_m values decreased in the hydrogenation of the methoxy-substituted compounds (*E*)-**4a** and (*E*)-**8a**, while a surprising increase in R_m was observed as the effect of fluorine in the same positions as compared with (*E*)-**3a**. Substitution in the *ortho*-position on the β phenyl ring [(*E*)-**6a** and (*E*)-**7a**)] decreased both the R_m and *ee*, with the fluorine substituent affecting both values less than the methoxy group.

The higher *ee* obtained in the hydrogenation of (*E*)-**4a** as compared with (*E*)-**3a** was attributed to the electron-releasing resonance effect of the methoxy substituents in the *para*-position.[10c,11] However, the fluorine substituent in this position has an opposite, electron-withdrawing effect, as indicated by the sign of the Hammett parameters (σ *para*-$CH_3O = -0.27$ or -0.17; σ *para*-$F = +0.06$ or $+0.15$)[22,23] and also by the acidities of cinnamic acid and its fluorine-substituted derivative (cinnamic acid $pK_a = 4.44$; *para*-fluorocinnamic acid $pK_a = 4.21$),[24] thus, will not increase the interaction strength with **1**. Furthermore, over un-

Table 1. Hydrogenation of monomethoxy- or fluorine-substituted (*E*)-2,3-diphenylpropenoic acids.[a]

Substrate	Substituent		R_u[b]	R_m[b]	*ee* [%]	R_A[c]	ee_A[d] [%]	R_A/X[e]	ee_A[e] [%]
	R^1	R^2							
(*E*)-**3a**[11]	H	H	50.8	8.6	70	12.4	73	2.7/99	80
(*E*)-**4a**[11]	H	4-OCH_3	41.7	6.2	83	17.8	89	2.9/76	89
(*E*)-**5a**	H	4-F	41.8	11.0	73	18.8	84	3.2/99	86
(*E*)-**6a**[11]	H	2-OCH_3	49.2	2.2	13	3.1	10	1.0/43	10
(*E*)-**7a**	H	2-F	49.5	8.5	27	6.8	22	2.1/82	16
(*E*)-**8a**[11]	2-OCH_3	H	22.9	5.7	76	11.1	85	1.9/42	86
(*E*)-**9a**	2-F	H	20.1	11.0	80	14.4	84	3.7/99	85

[a] *Reaction conditions*: 25 mg 5% Pd/Al_2O_3, 5 mL DMF + 2.5 vol% H_2O, 0.025 mmol **1**, 0.5 mmol substrate, 0.1 MPa H_2, 294 K, conversions of 98–100% in 2–8 h.
[b] Inital rates [$mmol\,h^{-1}\,g^{-1}$] obtained in the absence (R_u) and the presence of **1** (R_m).
[c] Inital rates [$mmol\,h^{-1}\,g^{-1}$] obtained in the presence of **1** and 0.5 mmol **2**.
[d] *ee* values obtained in the presence of **1** and 0.5 mmol **2**.
[e] Hydrogenation at 273 K in the presence of **1** and 0.5 mmol **2**; X = conversion [mol%] reached in 8 h.

modified catalyst the two substituents had similar effects on the initial rate, while in the presence of **1** these substituents had opposite effects on R_m.

The *ee* value obtained over a heterogeneous catalyst is influenced by the fraction of the chiral surface sites, the intrinsic enantiodifferentiating ability of a surface chiral site and the ratio of the turnover frequencies on modified and unmodified sites (if the fraction modified sites/total active sites <1). In the reaction studied the fraction of the chiral sites is not influenced significantly by the substitution of the acids. The enantiodifferentiating ability of a chiral site was improved by the methoxy substituents due to increase in the strength of the substrate-modifier interaction,[10c] but not by the *para*-fluorine substituent. On the other hand, the rate-determining step over modified catalyst was shown to be the product desorption.[10b] In this step the olefinic bond is already hydrogenated.[12] Lacking the extended conjugated system the product interacts with the surface only *via* the β-phenyl moiety and with **1** *via* the carboxylic group. Accordingly, the fluorine substituent in the *para*-position on the β phenyl ring instead of enhancing the interaction with the modifier, decreased the adsorption strength on the Pd surface leading to an increase in the turnover frequency on the modified sites and consequently to a small increase in the *ee*. Using **2** as additive resulted in an increase in *ee* and initial rate (R_A) in the hydrogenations of both (*E*)-**4a** and (*E*)-**5a**. Thus, the amine additive accelerated the desorption as suggested by Nitta of both saturated acids.[10b]

The drastic *ee* and R_m decrease observed in the hydrogenation of the *ortho*-methoxy-substituted (*E*)-**6a** was explained by the substituent steric effect.[11] This was confirmed by the results obtained with (*E*)-**7a**. The steric hindrance of the *ortho*-fluorine substituent on the β phenyl ring is much smaller than that of the methoxy group, thus it is reasonable to obtain a higher *ee* in the hydrogenation of (*E*)-**7a** than in that of (*E*)-**6a**. The *ortho* substituents had a similar effect in the enantioselective hydrogenation of ring-substituted acetophenones over **1** modified Pt catalyst.[23]

The higher *ee* obtained in the hydrogenation of the fluorine-substituted (*E*)-**9a** as compared with (*E*)-**8a** was surprising, as we supposed that the *ee* increase observed in the hydrogenation of (*E*)-**8a** was mostly due to steric effects of the substituent.[11] Moreover, the R_m value obtained in the hydrogenation of (*E*)-**9a** was higher as compared with (*E*)-**3a**. The electronic effect of the substituents may be disregarded as a plausible cause, as fluorine has an opposite electronic effect than the methoxy group and the electronic effect of the substituents can be hardly felt due to the tilt of the α phenyl ring.[21]

As fluorine increased significantly both the *ee* [higher than in the hydrogenations of (*E*)-**5a** and (*E*)-**8a**] and R_m, according to the train of thoughts presented before, this substituent increased the strength of the modifier-acid interaction and decreased the adsorption strength on the surface. While the methoxy group in this position had an anchoring effect of the phenyl ring, fluorine impeded the strong contact with the surface. However, this effect cannot explain the lower *ee* obtained with (*E*)-**8a** as compared with (*E*)-**9a**. The combination of the aforementioned effect with the formation of an additional interaction of the substituents in the *ortho* position on the α phenyl ring with adsorbed **1** *via* formation of a hydrogen bond could be the cause of the observed results. Although covalently bonded F is a weak hydrogen bond acceptor,[13] it was shown that it is able to form hydrogen bond during hydrogenation leading to stabilization of a compound which had a crucial role on the outcome of the reaction.[17] Moreover, recently it was suggested that in the enantioselective hydrogenation of 2,2,2-trifluoroacetophenone over Pt the modifier interacts with the substrate through a C–F···H–N^+(**1**) hydrogen bond.[25] Although, in the hydrogenation of the unsaturated acids **1** is protonated by the substrate,[7,8] an additional interaction of the substituent in the *ortho* position on the α phenyl ring either with the H–N^+(**1**) or with a H–C(**1**) may explain the effect of these substituents. Another possible explanation could be the influence of these substituents on the dipole moment (the orientation of the vector of the dipole moment) of the acid molecule leading to a favourable effect on the modifier-acid interaction, as was suggested in the hydrogenation of trifluoromethyl ketones over Pt.[13c] Thus, further studies are needed to reveal the mode of the interaction of **1** with the *ortho*-substituted compounds on the α phenyl ring.

A decrease in the hydrogenation temperature has a beneficial effect on the *ee* in the hydrogenation of various unsaturated carboxylic acids.[7,8,11] Increases in the *ee* were observed in the hydrogenations of both methoxy- and fluorine-substituted compounds, except (*E*)-**6a** and (*E*)-**7a** (see Table 1). At low temperature the initial rates decreased, however, the tendencies observed at room temperature were kept. Under these reaction conditions the *ee* obtained in the hydrogenations of the two *ortho*-substituted compounds (*E*)-**8a** and (*E*)-**9a** were almost identical, while significant *ee* difference was observed in the hydrogenation of (*E*)-**4a** and (*E*)-**5a** in favour of the methoxy-substituted acid. These observations seem to confirm the above suggestions on the role of these substituents.

Hydrogenation of Methoxy and Fluorine Disubstituted Derivatives

The hydrogenations of (*E*)-2,3-diphenylpropenoic acids substituted on both phenyl rings with two me-

Table 2. Hydrogenation of disubstituted (*E*)-2,3-diphenylpropenoic acids bearing two methoxy or methoxy and fluorine substituents.[a]

Substrate	Substituent		R_u[b]	R_m[b]	*ee* [%]	R_A[c]	ee_A[d] [%]
	R^1	R^2					
(*E*)-**10a**[11]	4-OCH_3	4-OCH_3	28.9	4.0	86	7.5	89
(*E*)-**11a**	4-OCH_3	4-F	15.9	4.1	74	10.4	82
(*E*)-**12a**	4-F	4-OCH_3	28.4	8.2	83	11.7	88
(*E*)-**13a**	4-F	2-OCH_3	70.8	3.4	24	3.3	20
(*E*)-**14a**[11]	2-OCH_3	4-OCH_3	8.2	3.7	83	3.8	90
(*E*)-**15a**	2-F	4-OCH_3	10.5	4.5	85	8.5	92
(*E*)-**16a**	2-OCH_3	4-F	7.1	2.9	86	5.4	93
(*E*)-**17a**	2-OCH_3	3-F	14.9	4.1	87	6.8	91
(*E*)-**18a**	2-OCH_3	2-F	17.6	2.1	20	5.5	29

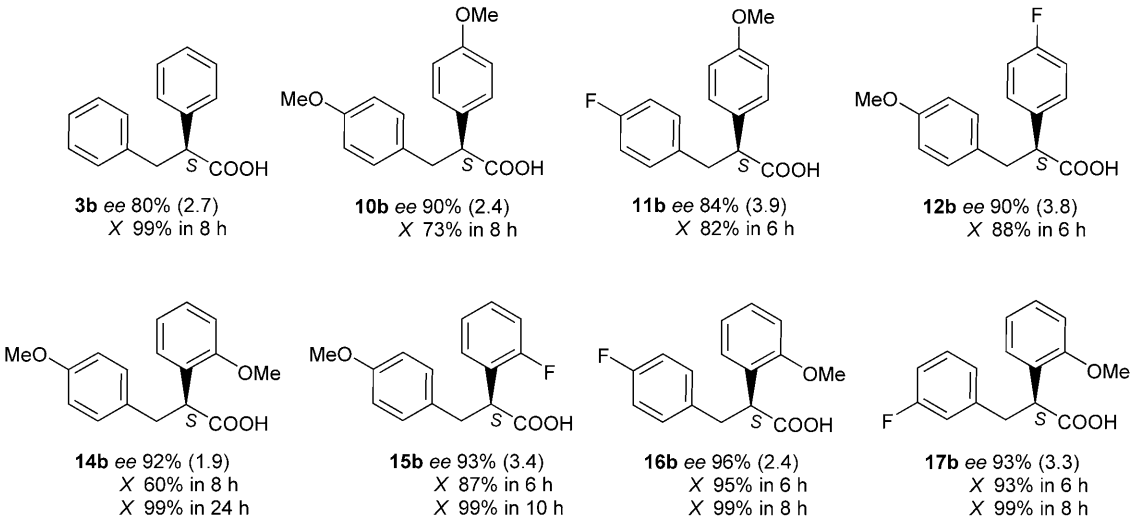
[a] *Reaction conditions*: 25 mg 5% Pd/Al_2O_3, 5 mL DMF + 2.5 vol% H_2O, 0.025 mmol **1**, 0.5 mmol substrate, 0.1 MPa H_2, 294 K, conversions of 98–100% in 2–8 h.
[b] Inital rates [mmol h^{-1} g^{-1}] obtained in the absence (R_u) and the presence of **1** (R_m).
[c] Inital rates [mmol h^{-1} g^{-1}] obtained in the presence of **1** and 0.5 mmol **2**.
[d] *ee* values obtained in the presence of **1** and 0.5 mmol **2**.

thoxy groups resulted in lower R_u and R_m, but higher *ee* than the monosubstituted derivatives, except when the β phenyl ring was substituted in the *ortho* position.[10c,11] Next we examined the effect of replacement of one of the methoxy substituents with fluorine. The results obtained at room temperature are summarized in Table 2 and compared with two dimethoxy-substituted compounds, (*E*)-**10a** and (*E*)-**14a**.

In the hydrogenations of the compounds substituted in both *para* positions the replacement of the electron-releasing methoxy substituent on the β phenyl ring with fluorine [(*E*)-**11a**] decreased the *ee* as compared with the dimethoxy-substituted acid (*E*)-**10a**, while in the hydrogenation of (*E*)-**12a** having the *para*-fluorine on the α phenyl ring similar *ee*s were obtained as with (*E*)-**10a**. Accordingly, strong electron-releasing groups are necessary in the *para* position on the β phenyl ring in order to obtain high *ee*, while the effect of the *para* substituent on the α phenyl ring is smaller. This confirmed the proposed electronic effect of the substituent on the β phenyl ring due to the influence on the electron distribution along the conjugated system, while the substituents on the α phenyl ring barely have any effect. The shift of the methoxy substituent on the β phenyl ring to the *ortho* position [(*E*)-**13a**] decreased the *ee* and R_m, similarly with the hydrogenation of all the compounds substituted either with methoxy group or with fluorine in this position, such as (*E*)-**6a**, (*E*)-**7a** and (*E*)-**18a**, irrespective of absence or presence of other substituents on the α phenyl ring.

The best *ee* in our recent study was obtained in the hydrogenation of (*E*)-**14a** bearing a methoxy substituent in the *ortho* position on the α phenyl ring.[11] Replacement of the methoxy group in this position with fluorine [(*E*)-**15a**] further increased the *ee* in accordance with the hydrogenation of the monosubstituted derivatives (*E*)-**8a** and (*E*)-**9a**. Thus, 92% *ee* was obtained even at room temperature in the presence of **2**. These results confirmed the beneficial effect of the fluorine substituent in the *ortho* position on the α phenyl. As discussed above the results may be explained by a combination of decreasing the adsorption strength by fluorine and the interaction of this substituent with the adsorbed **1**.

Even higher *ee* values were obtained when the *para*-methoxy group on the β phenyl ring in (*E*)-**14a** was replaced with fluorine [(*E*)-**16a**]. Thus, the effect of fluorine in the *para* position was enough to reach high *ee* when an *ortho* substituent on the α phenyl ring also enhanced the interaction of the acid with the modifier. Moreover, similar results were obtained in the hydrogenation of (*E*)-**17a** with fluorine in the *meta* position on the β phenyl ring. The surprisingly beneficial effect of both methoxy[11] and fluorine in this position is in contrast with the electronic effect of these substituents. Both *meta* substituents have positive Hammett parameters (σ *meta*-$CH_3O = +0.15$; σ *meta*-$F = +0.35$)[22,23] and lead to increased acidities as indicated by the pK_a values of cinnamic acid and its *meta*-substituted derivatives (cinnamic acid $pK_a = 5.68$; *meta*-metoxycinnamic acid $pK_a = 5.62$; *meta*-fluorocinnamic acid $pK_a = 5.44$).[26] Thus, the electronic effect of the substituents in the *meta* position would not increase the interaction strength with the modifier. Although further studies are necessary to find the explanation for the increased *ee* obtained in the reaction of (*E*)-**17a**, we note that the higher initial rate obtained in this hydrogenation as compared with (*E*)-**16a** may indicate that the substituents in the *meta* position hinder to some extent the adsorption of these acids. This could lead to a higher rate over modified sites increasing the *ee*. This suggestion correlates with the smaller increase obtained in the presence of **2** in



Scheme 2. Products obtained in the hydrogenation of selected methoxy- and fluorine-disubstituted (*E*)-2,3-diphenylpropenoic acids in comparison with (*E*)-**3a** at 273 K in presence of 0.025 mmol **1** and 0.5 mmol **2**. *Reaction conditions*: see Table 2; initial rates [mmol h^{-1} g^{-1}] are shown in parenthesis; conversions (*X*) and the reaction times necessary to reach these are given below the structures.

the hydrogenation of (*E*)-**17a** as compared with (*E*)-**16a**. We stress that both the *meta* and *para* substituents on the β phenyl ring led to excellent *ee* only when their effect was complemented with the effect of the *ortho* substituent on the α phenyl ring. As mentioned before it is also possible that these substituents affected the dipole moments of the unsaturated acids, thus, both the *meta* and *para* substituents leading to increase in the efficiency of the **1**-acid interaction.

According to these results high enantioselectivities can be obtained in the hydrogenations of disubstituted compounds bearing methoxy and fluorine substituents in appropriate positions. The *ee* values increased a few percent by decreasing the reaction temperature (see Scheme 2). Although, under these reaction conditions, the initial rates were low, full conversions could be obtained by extending the hydrogenation time without altering the stereochemical outcome of the reactions. Under these conditions the saturated products could be prepared in excellent, up to 93–96%, optical purities [see Scheme 2, (*S*)-**13b**, (*S*)-**14b** and (*S*)-**15b**], unprecedented in the enantioselective hydrogenation of prochiral carboxylic acids over modified heterogeneous catalyst.

Hydrogenation of Difluorine Derivatives

Comparison of the results obtained in the hydrogenation of the derivatives disubstituted with both fluorine and methoxy groups with those obtained in the reaction of the corresponding dimethoxy derivatives indicated that the fluorine substituent in certain compounds is even more efficient in increasing the *ee* than the methoxy group. This observation led us to investigate the hydrogenations of some difluorine-substituted derivatives (see Table 3).

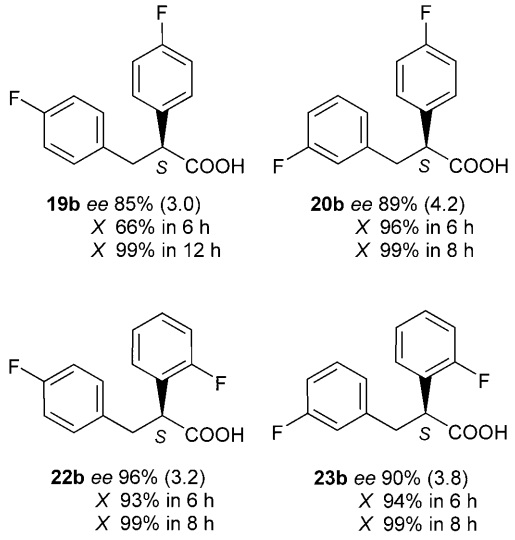
The enantioselective hydrogenation of the di-*para*-fluorine substituted compound (*E*)-**19a** resulted in *ee* values close to that obtained in the reaction of (*E*)-**11a**, lower than in the reaction of (*E*)-**10a** or (*E*)-**12a**. This confirmed our previous observation that the *para*-fluorine substituent on the β phenyl ring is less efficient in enhancing the modifier-acid interaction than the methoxy group, also supporting our interpretation of the effect of the substituents in this position. Similar, but slightly higher *ee* values were obtained in the hydrogenation of (*E*)-**20a**, with the substituent in the *meta* position, accompanied with much higher R_m and R_A, as compared with (*E*)-**19a**, similarly as in the hydrogenation of (*E*)-**17a** in comparison with that of (*E*)-**16a**. This demonstrated that the effect of the *meta* substituent on the β phenyl ring is general and independent from the position of the substituent on the α phenyl ring. In light of the findings described in the previous subsections the low *ee* obtained in the reaction of (*E*)-**21a** as an effect of the *ortho* position of the fluorine on the β phenyl ring could be anticipated.

Higher *ee* values were obtained when the position of the fluorine was changed to *ortho* on the α phenyl ring [(*E*)-**22a** and (*E*)-**23a**]. Similar results were obtained as in the hydrogenations of (*E*)-**16a** and (*E*)-**17a**, although, in the hydrogenation of the difluorine substituted compounds the *para*-fluorine substituent was also more efficient in the absence of **2**. The favourable effect of the fluorine substituent was evidenced even more by the results obtained at lower temperature (see Scheme 3). Thus, in the hydrogena-

Table 3. Hydrogenation of disubstituted (*E*)-2,3-diphenylpropenoic acids bearing fluorine substituents on both phenyl rings.[a]

Substrate	Substituent		R_u[b]	R_m[b]	*ee* [%]	R_A[c]	ee_A[d] [%]
	R^1	R^2					
(*E*)-**19a**	4-F	4-F	14.4	4.8	73	8.5	84
(*E*)-**20a**	4-F	3-F	24.1	14.0	78	26.7	85
(*E*)-**21a**	4-F	2-F	33.5	6.9	27	5.9	25
(*E*)-**22a**	2-F	4-F	8.9	4.8	86	10.5	91
(*E*)-**23a**	2-F	3-F	16.5	10.2	84	11.9	87

[a] *Reaction conditions*: 25 mg 5% Pd/Al_2O_3, 5 mL DMF + 2.5 vol% H_2O, 0.025 mmol **1**, 0.5 mmol substrate, 0.1 MPa H_2, 294 K, conversions of 98–100% in 2–8 h.
[b] Inital rates [mmol h^{-1} g^{-1}] obtained in the absence (R_u) and the presence of **1** (R_m).
[c] Inital rates [mmol h^{-1} g^{-1}] obtained in the presence of **1** and 0.5 mmol **2**.
[d] *ee* values obtained in the presence of **1** and 0.5 mmol **2**.



Scheme 3. Products obtained in the hydrogenation of selected difluorine-substituted (*E*)-2,3-diphenylpropenoic acids at 273 K in the presence of 0.025 mmol **1** and 0.5 mmol **2**. *Reaction conditions*: see Table 3; initial rates [mmol h^{-1} g^{-1}] are shown in parenthesis; conversions (*X*) and the reaction times necessary to reach these are given below the structures.

tion of (*E*)-**22a** a similarly high *ee* (96%) was obtained under these reaction conditions as in that of (*E*)-**16a**, the highest value reached up to now in this reaction. The initial rates usually exceeded those obtained in the hydrogenations of the methoxy-substituted derivatives, even at decreased temperature, in accordance with the weaker adsorption of the fluorine-substituted compounds. We note that the hydrogenation of the difluorine derivatives evidenced even more the higher efficiency of the *ortho* substituents on the α phenyl ring in increasing the *ee* in comparison with the substituents in the *para* position on the same ring.

According to these results similarly high or even higher *ee* values may be obtained in the hydrogenation of fluorine-substituted (*E*)-2,3-diphenylpropenoic acids as in the reaction of the methoxy-substituted derivatives. This is surprising considering the small steric hindrances and the electron-withdrawing effect of fluorine, however, the additional interactions of this substituent in some position either with the modifier or the surface increased the *ee*. Confirmation of the suggestions explaining the substituent effects was sought for by continuing our study with examining the effect of a substituent having a different character as those examined.

Hydrogenation of Methyl-Substituted Derivatives

The methyl group has an electron-releasing inductive effect, practically no hydrogen bonding ability and an intermediate steric effect between the methoxy group and fluorine. The methyl group in the *para* position on the β phenyl ring [(*E*)-**24a**] having a negative Hammett parameter (σ *para*-$CH_3 = -0.13$)[22] and slightly increasing the acidity [(*E*)-**3a** $pK_a = 7.00$; (*E*)-**24a** $pK_a = 6.99$],[27] increased the *ee* both in the absence and in the presence of **2** as compared with (*E*)-**3a**, although this increase was much smaller than that in the reaction of (*E*)-**4a** (see Table 4). Extremely informative are the initial rates obtained in the reactions of (*E*)-**24a**. The identical R_u with (*E*)-**4a** and (*E*)-**5a** and the higher R_m as compared even with the fluorine-substituted acid supported our previous suggestions. Thus, it became unambiguous that the electronic effect of the *para* substituent on the β phenyl ring is of paramount importance for increasing the efficiency of the interaction with **1** and obtaining good *ee*. Furthermore, the steric effect of the substituent caused the weaker adsorption of (*E*)-**24a** on modified sites leading to increased R_m and contributing to the increase in the *ee*.

The methyl group in the *ortho* position on the α phenyl ring [(*E*)-**25a**] did not lead to significant *ee*

Table 4. Effect of the methyl substituent on the hydrogenation of (*E*)-2,3-diphenylpropenoic acids.[a]

Substrate	Substituent		R_u[b]	R_m[b]	*ee* [%]	R_A[c]	ee_A[d] [%]	R_A/X[e]	ee_A[e] [%]
	R^1	R^2							
(*E*)-**24a**	H	4-CH_3	41.9	15.9	74	20.4	76	3.3/84	80
(*E*)-**25a**	2-CH_3	H	16.8	7.4	71	13.6	75	2.5/83	81
(*E*)-**26a**	2-CH_3	4-CH_3	6.6	3.0	76	2.5	77	0.8/40	83
(*E*)-**27a**	2-CH_3	4-F	5.8	2.8	75	5.2	84	1.7/85	84
(*E*)-**28a**	2-F	4-CH_3	13.3	8.1	81	6.9	84	1.8/87	85
(*E*)-**29a**	2-OCH_3	4-CH_3	11.1	4.8	77	2.8	89	1.1/62	89

[a] *Reaction conditions*: 25 mg 5% Pd/Al_2O_3, 5 mL DMF + 2.5 vol% H_2O, 0.025 mmol **1**, 0.5 mmol substrate, 0.1 MPa H_2, 294 K, conversions > 95% in 2–8 h.
[b] Inital rates [mmol h^{-1} g^{-1}] obtained in the absence (R_u) and the presence of **1** (R_m).
[c] Inital rates [mmol h^{-1} g^{-1}] obtained in the presence of **1** and 0.5 mmol **2**.
[d] *ee* values obtained in the presence of **1** and 0.5 mmol **2**.
[e] Hydrogenation at 273 K in the presence of **1** and 0.5 mmol **2**; X = conversion [mol%] reached in 8 h.

and initial rate increase as compared with (*E*)-**3a**. This confirmed that neither the electronic nor the steric effects of the substituents in this position were decisive, but the formation of an additional interaction between the *ortho* substituents having lone electron pairs and the modifier is responsible for obtaining an *ee* increase in the hydrogenation of the compounds substituted in this position. Similar conclusion may be drawn from the *ee* obtained in the hydrogenation of (*E*)-**26a** and (*E*)-**27a**, the former giving only slightly higher *ee* than (*E*)-**24a** and the latter having a similar behaviour as (*E*)-**5a**. On the contrary, when fluorine or methoxy group was situated in the *ortho* position on the α phenyl ring in the presence of a *para*-methyl group on the β phenyl ring [(*E*)-**28a** and (*E*)-**29a**] the *ee* increased significantly, reaching slightly higher values than in the hydrogenation of (*E*)-**8a** and (*E*)-**9a** and significantly increased *ee*s as compared with (*E*)-**24a**. These observation supported again the rationalization of the effects of the methoxy and fluorine substituents.

Conclusions

We have studied the enantioselective hydrogenation of methoxy- and fluorine-substituted (*E*)-2,3-diphenylpropenoic acid derivatives over cinchonidine-modified, supported Pd catalyst in the absence and presence of benzylamine as additive. The results showed that a fluorine substituent in some positions may be as efficient or even more efficient than the methoxy group in increasing the optical purity of the resultant saturated products. Enantioselectivities up to 96% were obtained in the hydrogenation of some methoxy- and fluorine-disubstituted or difluorine-substituted derivatives, unprecedented in the hydrogenation of prochiral unsaturated carboxylic acids over modified heterogeneous catalysts. The highest enantioselectivities were reached in the hydrogenation of derivatives bearing a *para* substituent on the β phenyl and an *ortho* substituent on the α phenyl ring, respectively.

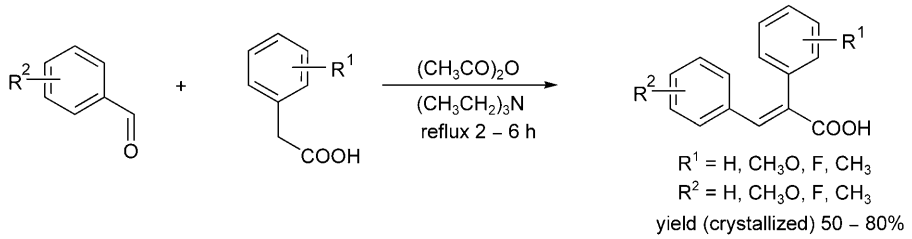
It was suggested that the substituent on the β phenyl ring influenced the *ee* by its electronic effect and by its effect on the adsorption strength on the Pd surface. Thus, an electron-releasing substituent decreased the acidity of the substrate and consequently increased the interaction efficiency with the modifier. A substituent in this position which decreases the adsorption strength of the acid may also lead to an increase in *ee* by increasing the rate on the modified sites. The two effects may act in opposite directions as in the case of both methoxy and fluorine substituents. The beneficial effect of the *ortho* substituent on the α phenyl ring was not related to its electronic and only in small part to its steric effect. We assumed that the increased enantioselectivity was due to the ability of the methoxy or fluorine substituents to form additional interactions with the modifier on the surface. These suggestions were supported by results obtained in the hydrogenations of several methyl-substituted derivatives.

Most important, the present study is the first reporting enantioselectivities up to 96% in the hydrogenation of unsaturated carboxylic acid derivatives over a heterogeneous catalyst in presence of chiral modifiers. The pharmaceutical importance of the optically pure carboxylic acids and the increased interest in the preparation of fluorinated chiral compounds may lead to practical applications of this convenient, highly enantioselective procedure.

Experimental Section

Materials

The 5% Pd/Al_2O_3 was purchased from Engelhard (40692) and used after reducing in a 30 cm^3 min^{-1} H_2 flow at 523 K for 100 min as in our previous study.[11] Cinchonidine (≥



Scheme 4. Preparation of substituted (*E*)-2,3-diphenylpropenoic acid derivatives.

98%) and benzylamine (≥99.5%) were commercial products (Fluka) and were used as received. (*E*)-2,3-Diphenylpropenoic acid (Aldrich, ≥97%) was purified by crystallization in acetone-water, *N*,*N*-dimethylformamide (Scharlau, Multisolvent, HPLC grade) was used without purification. The benzaldehyde and phenylacetic acid derivatives, acetic anhydride and triethylamine used in the preparation of the (*E*)-2,3-diphenylpropenoic acid derivatives were purchased from Aldrich or Fluka and used as received.

Preparation of the Substituted (*E*)-2,3-Diphenylpropenoic Acids

The substituted (*E*)-2,3-diphenylpropenoic acid derivatives were prepared by Perkin condensation as previously described using the corresponding benzaldehydes and arylacetic acids (see Scheme 4).[11,28] A stirred mixture of arylacetic acid (40 mmol) and aromatic aldehyde (40 mmol) in 4 cm^3 triethylamine and 8 cm^3 acetic anhydride was refluxed for 2–6 h. To the cooled mixture 9 cm^3 concentated HCl solution and 30–40 cm^3 water were added, the precipitate was filtered and washed with cold water. After drying the solid was dissolved in 1% NaOH aqueous solution and the alkaline solution was stirred with charcoal in an ice bath and filtered. For the separation of isomer acids the alkaline solution was gradually acidified with 1/1 concentrated HCl/water solution. If the reaction product after acidification was semisolid or oil, it was dissolved in diethyl ether (200–250 cm^3). The ethereal solution was extracted with 1% NaOH solution and the alkaline solution was treated as above. The isomer acids were further purified by crystallization in ethanol or ethanol-water. The isomer distribution of the crude reaction products and the purity of the prepared acids were monitored by analytical TLC (Fluka silica gel/TLC cards, eluent hexane-acetone) and GC-MS analysis (as methyl esters prepared using CH_2N_2 ethereal solution, GC-MS: Agilent Techn. 6890N GC-5973 MSD, HP-1MS, 60 m capillary column). The purities of the acids (>98%) were checked by ^1H- and ^{13}C NMR spectroscopy using a Bruker Avance DRX 500 NMR instrument (^1H at 500 MHz, ^{13}C at 125 MHz) in $(CD_3)_2SO$ solution.

Catalytic Hydrogenations and Product Analysis

The hydrogenations were carried out in batch reactors under atmospheric H_2 pressure in a glass hydrogenation apparatus using magnetic stirring. The H_2 consumption up to 25% of the total H_2 uptake was used for calculations of the initial rates taking into account the fast hydrogenation of the vinyl group of **1**. In a typical run 0.025 g reduced catalyst and 3 cm^3 DMF containing 2.5 vol% water were introduced into the reactor, the apparatus was flushed with H_2 and the catalyst was pretreated *in situ* by stirring (1000 rpm) for 0.5 h. After pretreatment 0.025 mmol **1**, 0.5 mmol unsaturated acid, 0.5 mmol **2** (when used) and another 2 cm^3 solvent were added, the system was flushed again with H_2 and the reaction was started by turning on the stirring. Unless otherwise noted over 98% conversions were obtained in 1–4 h during hydrogenations in the absence of modifier and in 6–8 h over modified catalyst.

After the H_2 uptake ceased the precipitated products (when formed) were dissolved by addition of 5 cm^3 methanol, the catalyst was filtered, washed with another 2 portions of methanol and the combined filtrates were concentrated under reduced pressure. Small portions of these products were transformed into methyl esters using concentated H_2SO_4 in methanol and/or CH_2N_2 ethereal solution. The resulting compounds were identified by GC-MS analysis. Conversions and enantiomeric excesses (*ee*) were determined by GC analysis using a HP 5890 II GC-FID and a 30 m chiral capillary column (Cyclosil-B). The enantiomeric excess (*ee*%) was calculated with the formulae $ee\% = 100 \times |[S]-[R]|/([S]+[R])$, where $[S]$ and $[R]$ are the concentrations of the product enantiomers. In cases where the separation of the methyl ester enantiomers was incomplete (few compounds), samples of the products were transformed into (*R*)-2-butyl and (*S*)-2-butyl esters using (*R*)-2-butanol and (*S*)-2-butanol (Fluka, ≥98%), respectively and the *ee* was calculated after separation of the diastereomers using the same chiral capillary column. Repeated experiments gave *ee* values reproducible within ±1%.

The remaining products were taken up in 1 cm^3 10% HCl solution in 9 cm^3 water, the crude acids were extracted with 3 portions of 5 cm^3 diethyl ether or $CHCl_3$, the combined organic layers were dried over Na_2SO_4 and the solvent was evaporated to give the crude saturated acids in over 90% yields as pale yellow oils or solids in ≥98% purity as determined by GC-MS and GC analysis of their methyl esters. The optical purity of these crude products was the same as determined for the corresponding samples analyzed before work-up. The absolute configurations of the excess enantiomers of unsubstituted and methoxy-substituted 2,3-diphenylpropionic acids were assigned in previous studies to be *S*.[10] The configuration of the excess enantiomers resulting in the hydrogenation of the other compounds has not yet been determined, however, based on the same rotation sign and similar chromatographic behaviour, we assume that also the *S* enantiomers were formed in excess. Optical rotation measurements using a Polamat A polarimeter showed that all products contained the dextrogir enantiomers in excess.

Supporting Information

Spectroscopic and analytical data of the unsaturated acids and their methyl esters, the analytical data of the saturated products are available in the Supporting Information.

Acknowledgements

Financial support by the Hungarian National Science Foundation (OTKA Grants T 048764 and K 72065) is highly appreciated. Gy. Sz. is grateful for the financial support of HAS through Bolyai János Research grant.

References

[1] a) E. Francotte, W. Lindner (Eds.), *Chirality in Drug Research*, Wiley-VCH, Weinheim, **2006**; b) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer, T. Zelinski, *Angew. Chem.* **2004**, *116*, 806–843; *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824.

[2] a) T. Ohkuma, M. Kitamura, R. Noyori, in: *Catalytic Asymmetric Synthesis* 2nd edn., (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**, Chapt. 1, pp 1–110; b) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103–151; c) H.-U. Blaser, E. Schmidt (Eds.), *Asymmetric Catalysis on Industrial Scale. Challenges, Approaches and Solutions*, Wiley-VCH, Weinheim, **2004**; d) H.-U. Blaser, B. Pugin, F. Spindler, *J. Mol. Catal. A: Chem.* **2005**, *231*, 1–20.

[3] a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3069; b) C. Jäkel, R. Paciello, *Chem. Rev.* **2006**, *106*, 2912–2942; c) J. A. F. Boogers, U. Felfer, M. Kotthaus, G. Steinbauer, A. H. M. de Vries, J. G. de Vries, *Org. Proc. Res. Dev.* **2007**, *11*, 585–591; d) H.-U. Blaser, B. Pugin, F. Spindler, M. Thommen, *Acc. Chem. Res.* **2007**, *40*, 1240–1250; e) A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc. Chem. Res.* **2007**, *40*, 1267–1277.

[4] a) D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs (Eds.), *Chiral Catalyst Immobilization and Recycling*, Wiley-VCH, Weinheim, **2000**; b) M. Studer, H.-U. Blaser, C. Exner, *Adv. Synth. Catal.* **2003**, *345*, 45–65; c) D. Yu. Murzin, P. Mäki-Arvela, E. Toukoniitty, T. Salmi, *Catal. Rev. Sci. Eng.* **2005**, *47*, 175–256; d) M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem.* **2006**, *118*, 4850–4881; *Angew. Chem. Int. Ed.* **2006**, *45*, 4732–4762; e) T. Mallat, E. Orglmeister, A. Baiker, *Chem. Rev.* **2007**, *107*, 4863–4890.

[5] a) A. Tai, T. Kikukawa, T. Sugimura, Y. Inoue, T. Osawa, A. Fujii, *J. Chem. Soc. Chem. Commun.* **1991**, 795–796; b) T. Sugimura, S. Nakagawa, A. Tai, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 355–363; c) T. Osawa, T. Harada, O. Takayasu, *Curr. Org. Chem.* **2006**, *10*, 1513–1531.

[6] a) Y. Orito, S. Imai, S. Niwa, *J. Chem. Soc. Jpn.* **1979**, 1118–1120; b) Y. Orito, S. Imai, S. Niwa, *J. Chem. Soc. Jpn.* **1980**, 670–672; c) M. von Arx, T. Mallat, A. Baiker, *Top. Catal.* **2002**, *19*, 75–87; d) C. Exner, A. Pfaltz, M. Studer, H.-U. Blaser, *Adv. Synth. Catal.* **2003**, *345*, 1253–1260; e) M. Bartók, *Curr. Org. Chem.* **2006**, *10*, 1533–1567.

[7] a) J. R. G. Perez, J. Malthête, J. Jacques, *C. R. Acad. Sc. Paris Série II* **1985**, *300*, 169–172; b) M. Bartók, Gy. Wittmann, Gy. Göndös, G. V. Smith, *J. Org. Chem.* **1987**, *52*, 1139–1141; c) Y. Nitta, Y. Ueda, T. Imanaka, *Chem. Lett.* **1994**, *23*, 1095–1098; d) Y. Nitta, K. Kobiro, *Chem. Lett.* **1996**, *25*, 897–898; e) T. J. Hall, P. Johnston, W. A. H. Vermeer, S. R. Watson, P. B. Wells, *Stud. Surf. Sci. Catal.* **1996**, *101*, 221–230; f) K. Borszeky, T. Mallat, A. Baiker, *Catal. Lett.* **1996**, *41*, 199–202; g) K. Borszeky, T. Mallat, A. Baiker, *Tetrahedron: Asymmetry* **1997**, *8*, 3745–3753; h) K. Borszeky, T. Bürgi, Z. Zhaohui, T. Mallat, A. Baiker, *J. Catal.* **1999**, *187*, 160–166; i) M. Maris, W.-R. Huck, T. Mallat, A. Baiker, *J. Catal.* **2003**, *219*, 52–58; j) A. Solladié-Cavallo, F. Hoernel, M. Schmitt, F. Garin, *J. Mol. Catal. A: Chem.* **2003**, *195*, 181–188; k) Y. Nitta, T. Kubota, Y. Okamoto, *J. Mol. Catal. A: Chem.* **2004**, *212*, 155–159; l) M. Casagrande, S. Franceschini, M. Lenarda, O. Piccolo, A. Vaccari, *J. Mol. Catal. A: Chem.* **2006**, *246*, 263–267; m) A. Tungler, É. Sípos, V. Háda, *Curr. Org. Chem.* **2006**, *10*, 1569–1583.

[8] a) I. Kun, B. Török, K. Felföldi, M. Bartók, *Appl. Catal. A: Gen.* **2000**, *203*, 71–79; b) Gy. Szőllősi, S. Niwa, T. Hanaoka, F. Mizukami, *J. Mol. Catal. A: Chem.* **2005**, *230*, 91–95; c) Gy. Szőllősi, T. Hanaoka, S. Niwa, F. Mizukami, M. Bartók, *J. Catal.* **2005**, *231*, 480–483; d) K. Szőri, Gy. Szőllősi, K. Felföldi, M. Bartók, *React. Kinet. Catal. Lett.* **2005**, *84*, 151–156; e) Gy. Szőllősi, E. Szabó, M. Bartók, *Adv. Synth. Catal.* **2007**, *349*, 405–410; f) Gy. Szőllősi, K. Balázsik, M. Bartók, *Appl. Catal. A: Gen.* **2007**, *319*, 193–201; g) B. Hermán, Gy. Szőllősi, F. Fülöp, M. Bartók, *Appl. Catal. A: Gen.* **2007**, *331*, 39–43; h) Gy. Szőllősi, *Magy. Kém. Foly.* **2007**, *113*, 146–153; i) Gy. Szőllősi, K. Szőri, M. Bartók, *J. Catal.* **2008**, *256*, 349–352; j) K. Szőri, Gy. Szőllősi, M. Bartók, *New J. Chem.* **2008**, *32*, 1354–1358.

[9] a) W.-R. Huck, T. Mallat, A. Baiker, *J. Catal.* **2000**, *193*, 1–4; b) W.-R. Huck, T. Bürgi, T. Mallat, A. Baiker, *J. Catal.* **2001**, *200*, 171–180; c) W.-R. Huck, T. Mallat, A. Baiker, *New J. Chem.* **2002**, *26*, 6–8; d) W.-R. Huck, T. Bürgi, T. Mallat, A. Baiker, *J. Catal.* **2003**, *219*, 41–51; e) W.-R. Huck, T. Mallat, A. Baiker, *Adv. Synth. Catal.* **2003**, *345*, 255–260.

[10] a) Y. Nitta, *Chem. Lett.* **1999**, *28*, 635–636; b) Y. Nitta, *Top. Catal.* **2000**, *13*, 179–185; c) T. Sugimura, J. Watanabe, T. Okuyama, Y. Nitta, *Tetrahedron: Asymmetry* **2005**, *16*, 1573–1575; d) Y. Nitta, J. Watanabe, T. Okuyama, T. Sugimura, *J. Catal.* **2005**, *236*, 164–167; e) T. Sugimura, J. Watanabe, T. Uchida, Y. Nitta, T. Okuyama, *Catal. Lett.* **2006**, *112*, 27–30.

[11] Gy. Szőllősi, B. Hermán, K. Felföldi, F. Fülöp, M. Bartók, *J. Mol. Catal. A: Chem.* **2008**, *290*, 54–59.

[12] A. P. G. Kieboom, H. van Bekkum, *J. Catal.* **1972**, *25*, 342–349.

[13] a) J. A. K. Howard, V. J. Hoy, D. O'Hagan, G. T. Smith, *Tetrahedron* **1996**, *52*, 12613–12622; b) J. D. Dunitz, R. Taylor, *Chem. Eur. J.* **1997**, *3*, 89–98; c) A. Vargas, F. Hoxha, N. Bonalumi, T. Mallat, A. Baiker, *J. Catal.* **2006**, *240*, 203–212.

[14] a) K. Mikami, Y. Itoh, M. Yamanaka, *Chem. Rev.* **2004**, *104*, 1–16; b) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119–6146; c) H. Ibrahim, A. Togni, *Chem. Commun.* **2004**, 1147–1155; d) M. Oestreich, *Angew. Chem.* **2005**, *117*, 2376–2379; *Angew. Chem. Int. Ed.* **2005**, *44*, 2324–2327.

[15] a) T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 13529–13529; b) Y. Kuroki, D. Asada, K. Iseki, *Tetrahedron Lett.* **2000**, *41*, 9853–9858; c) Y. Kuroki, Y. Sakamaki, K. Iseki, *Org. Lett.* **2001**, *3*, 457–459; d) M. Berthod, G. Mignani, M. Lemaire, *J. Mol. Catal. A: Chem.* **2005**, *233*, 105–110.

[16] a) T. Mallat, M. Bodmer, A. Baiker, *Catal. Lett.* **1997**, *44*, 95–99; b) B. Török, K. Balázsik, Gy. Szöllősi, K. Felföldi, M. Bartók, *Chirality* **1999**, *11*, 470–474; c) K. Balázsik, B. Török, K. Felföldi, M. Bartók, *Ultrasonics Sonochem.* **1999**, *5*, 149–155; d) M. von Arx, T. Mallat, A. Baiker, *J. Catal.* **2000**, *193*, 161–164; e) M. von Arx, T. Mallat, A. Baiker, *Tetrahedron: Asymmetry* **2001**, *12*, 3089–3094; f) M. von Arx, T. Mallat, A. Baiker, *Catal. Lett.* **2002**, *78*, 267–271; g) R. Hess, S. Diezi, T. Mallat, A. Baiker, *Tetrahedron: Asymmetry* **2004**, *15*, 251–257; h) T. Varga, K. Felföldi, P. Forgó, M. Bartók, *J. Mol. Catal. A: Chem.* **2004**, *216*, 181–187; i) S. Diezi, M. Hess, E. Orglmeister, T. Mallat, A. Baiker, *Catal. Lett.* **2005**, *102*, 121–125; j) S. Diezi, M. Hess, E. Orglmeister, T. Mallat, A. Baiker, *Catal. Lett.* **2005**, *239*, 49–56.

[17] M. von Arx, T. Mallat, A. Baiker, *Angew. Chem.* **2001**, *113*, 2369–2372; *Angew. Chem. Int. Ed.* **2001**, *40*, 2302–2305.

[18] a) K. Szőri, Gy. Szőllősi, M. Bartók, *Adv. Synth. Catal.* **2006**, *348*, 515–522; b) K. Szőri, Gy. Szőllősi, M. Bartók, *J. Catal.* **2006**, *244*, 255–259.

[19] Gy. Szőllősi, T. Varga, K. Felföldi, Sz. Cserényi, M. Bartók, *Catal. Commun.* **2008**, *9*, 421–424.

[20] N. Bonalumi, A. Vargas, D. Ferri, A. Baiker, *J. Phys. Chem. B* **2006**, *110*, 9956–9965.

[21] a) I. Pálinkó, A. Burrichter, G. Rasul, B. Török, G. K. S. Prakash, G. A. Olah, *J. Chem. Soc. Perkin Trans. 2* **1998**, 379–385; b) J. T. Kiss, K. Felföldi, I. Hannus, I. Pálinkó, *J. Mol. Struct.* **2001**, *565–566*, 463–468; c) T. M. Babar, N. H. Rama, G. Qadeer, G. S. Khan, W.-Y. Wong, *Acta Crystallogr. Sect. E* **2006**, *E62*, o4082-o4083.

[22] a) R. W. Taft Jr. , *J. Am. Chem. Soc.* **1957**, *79*, 1045–1049; b) R. W. Taft Jr. , *J. Phys. Chem.* **1960**, *64*, 1805–1815; c) J. Hine, *J. Am. Chem. Soc.* **1960**, *82*, 4877–4880.

[23] R. Hess, T. Mallat, A. Baiker, *J. Catal.* **2003**, *218*, 453–456.

[24] S. E. Boiadjiev, D. A. Lightner, *J. Phys. Org. Chem.* **1999**, *12*, 751–757.

[25] a) S. Lavoie, M.-A. Laliberté, I. Temprano, P. H. McBreen, *J. Am. Chem. Soc.* **2006**, *128*, 7588–7593; b) M.-A. Laliberté, S. Lavoie, B. Hammer, G. Mahieu, P. H. McBreen, *J. Am. Chem. Soc.* **2008**, *130*, 5386–5387.

[26] R. Fuchs, J. J. Bloomfield, *J. Org. Chem.* **1966**, *31*, 3423–3425.

[27] K. Bowden, D. C. Parkin, *Can. J. Chem.* **1968**, *46*, 3909–3914.

[28] K. Felföldi, M. Sutyinszky, N. Nagy, I. Pálinkó, *Synth. Commun.* **2000**, *30*, 1543–1553.

