PhD Thesis

Enantioselective hydrogenations of α,β-unsaturated carboxylic acids over a cinchonidine-modified palladium catalyst

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2011

A. INTRODUCTION AND AIMS

Optically pure carboxylic acids and their substituted derivatives are essential pharmaceuticals or chiral building blocks used in the preparation of biologically active compounds. The most convenient procedures for the preparation of chiral carboxylic acids include asymmetric hydrogenation of the corresponding prochiral unsaturated carboxylic acids. Following the development of a large variety of highly enantioselective chiral noble metal complexes, these reactions gained increased industrial importance. Replacement of these highly efficient soluble catalysts by heterogeneous catalytic systems results in various economic and technical advantages, provided the heterogeneous catalysts are competitive as concerns the activities and optical purities of the saturated products. The simplest approach for the development of enantioselective heterogeneous hydrogenation catalysts is surface modification of the conventional metal catalysts by chiral compounds. However, only a few efficient modified heterogeneous metal catalysts are known as yet for the enantioselective hydrogenation of prochiral unsaturated compounds. Among the known catalytic systems, a cinchonidine (CD)-modified Pd catalyst has been found to be substrate-sensitive in the hydrogenation of α,β-unsatured carboxylic acids. The best enantioselectivities were obtained in the hydrogenation of (*E*)-2,3-diphenylpropenoic acid and its methoxy-substituted derivatives. Excellent ee values were obtained in the hydrogenation of the *para*-methoxy-substituted derivatives. Since the exact structure of the intermediate complex is still unknown, it was difficult to predict the behaviour of the derivatives substituted in the *ortho* or *meta* position on either of the two phenyl rings and whether the steric effect of the methoxy substituent in a certain position would be favourable as concerns the enantiodifferentiation.

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, including enantioselective hydrogenations of fluorinated prochiral substrates. Chiral heterogeneous catalysts, such as Pt modified by cinchona derivatives, have proved efficient in the enantioselective hydrogenation of trifluoromethyl ketones, and particularly α-fluoro ketones. Attempts to hydrogenate fluorine-containing, aliphatic α,β-unsaturated carboxylic acids over Pd catalysts in the presence of CD resulted in low optical yields. The enantioselective hydrogenation of prochiral cinnamic acid derivatives substituted with fluoro on the aromatic ring has not yet been attempted.

The aims of our work were to examine the enantioselective hydrogenation of (*E*)-2,3-diphenylpropenoic acid substituted with a methoxy group or fluoro in different positions over a CD-

modified Pd catalyst and to investigate the effects of the position of the substituents on ee and the reaction rate. Besides the fluoro- and methoxy-substituted compounds, the effects of methyl substitution in certain positions were also examined in order to ascertain the roles of the electronic and steric effects of the substituents.

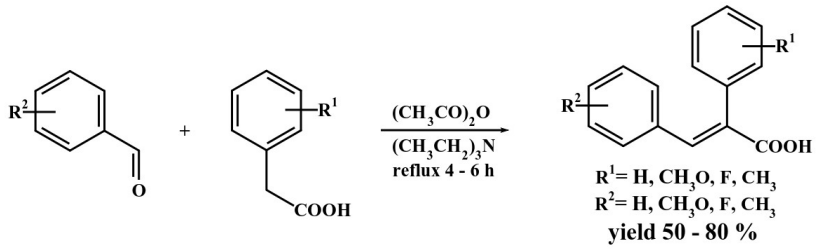
The presence of heteroaromatic rings in the α,β-unsaturated carboxylic acid may lead to versatile optically pure building blocks for the synthesis of biologically active compounds. In spite of the excellent enantioselectivities obtained in the reactions of (*E*)-2,3-diphenylpropenoic acid derivatives and the increased pharmaceutical importance of their heteroaromatic analogues, the hydrogenation of these compounds over heterogeneous catalysts has not yet been studied. Our aim was to extend the scope of the CD-Pd catalytic system to the enantioselective hydrogenation of propenoic acid derivatives bearing 2-furyl or 3-pyridyl moieties.

Industry prefers continuously operating methods. The large-scale production of certain optically pure compounds may lead to replacement of the widely applied discontinuously operated batch reactors with continuously operated reactor systems for the production of bulk chemicals. As heterogeneous catalysts are more suitable for use in continuous processes, chirally modified metal catalysts are the most promising alternatives for these purposes. The behaviour of prochiral α,β-unsaturated carboxylic acids over Pd catalysts in a continuous-flow system has not been reported previously. Consequently, we planned to examine the enantioselective hydrogenation of four α,β-unsaturated carboxylic acids over a Pd/Al_2O_3 catalyst in a continuous-flow system, using a fixed-bed reactor. We investigated whether these compounds may be efficiently hydrogenated in a continuously operated experimental set-up in order to produce optically enriched carboxylic acids.

B. MATERIALS AND METHODS

The substituted 2,3-diphenylpropenoic acid derivatives were prepared by Perkin condensation according to the Fieser method [1-3], using the corresponding aromatic aldehydes and arylacetic acids purchased from Fluka or Aldrich (Scheme 1).

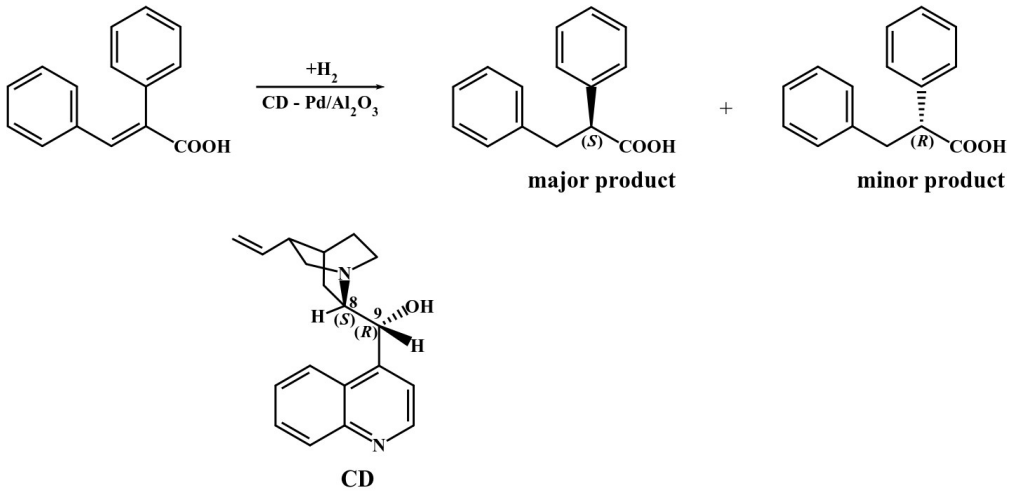
The hydrogenations were carried out over a Pd/Al_2O_3 catalyst after pretreatment (Scheme 2). As solvent, *N,N*-dimethylformamide containing 2.5 vol.% water was used. The hydrogenations were carried out in batch reactors under atmospheric H_2 pressure at room temperature (occasionally low temperature) in a glass hydrogenation apparatus, using magnetic stirring. In the hydrogenations, CD was used as chiral modifier and benzylamine (BA) as an achiral additive. The hydrogenations in the absence of modifier were carried out for 1-4 h, and those in the presence of CD for 6-8 h.



Scheme 1

The products were identified by GC-MS analysis as their methyl esters. Conversions (X %) and enantiomeric excesses (ee %) were determined by GC analysis. Ee was calculated from the formulae ee % = 100 × |[*S*] – [*R*]|/([*S*] + [*R*]), where [*S*] and [*R*] are the concentrations of the product enantiomers.

Continuous hydrogenations were carried in an H-Cube high-pressure continuous-flow system purchased from Thales Nanotechnology Inc. The reactant, modifier (CD) and achiral additive (BA) were dissolved in the desired solvent (methanol or toluene) and this solution was delivered to the hydrogenation system via a conventional HPLC pump, H_2 being mixed into the liquid flow under the desired pressure (0.1-5 MPa) in the mixer of the apparatus. Samples were collected at regular time intervals and analyzed. Products were identified by GC-MS analysis. Conversions and ee were determined by GC analysis. Ee was calculated with the above-mentioned formula.

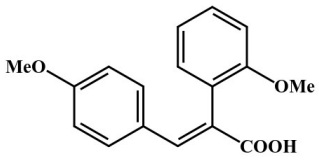


Scheme 2

C. RESULTS AND DISCUSSION

I. Enantioselective hydrogenations of methoxy-substituted (*E*)-diphenylpropenoic acid derivatives

We studied the effect of the position of the methoxy substituent on the initial rate and the enantioselectivity in the hydrogenations of mono- and dimethoxy-substituted 2,3-diphenylpropenoic acids over a CD-modified supported Pd catalyst in the absence and presence of BA as additive. The results obtained could not be interpreted solely in terms of the electronic effects of the substituents. Depending on the substituent position, the steric effects may become a dominant factor. This was indicated by the opposite effects on the initial rate and ee of the 2-methoxy substituent situated on the α- and β-phenyl rings, the former increasing, and the latter significantly decreasing the optical purity of the resulting saturated products. The highest ee-s, up to 92% were obtained in the hydrogenation of (*E*)-2-(2-methoxyphenyl)-3-(4-methoxyphenyl)propenoic acid (**1**) (Scheme 3), due to combined favourable steric and electronic effects of the substituent on the α- and β-phenyl rings.



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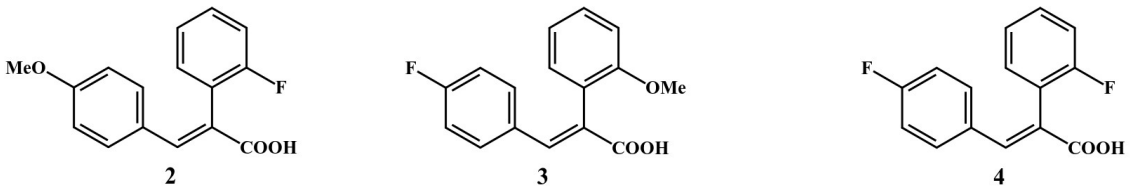
Scheme 3

II. Enantioselective hydrogenations of methoxy-, fluoro- and methyl-substituted (*E*)-2,3-diphenylpropenoic acid derivatives

The enantioselective hydrogenations of methoxy-, fluoro- and methyl-substituted (*E*)-2,3-diphenylpropenoic acid derivatives were investigated under the same reaction conditions. The results showed that a fluoro substituent in some positions may be as efficient or even more efficient than the methoxy group in increasing the optical purity of the saturated products. Ee-s up to 96% were obtained in the hydrogenations of prochiral unsaturated carboxylic acids over modified heterogeneous catalysts. The highest ee-s were attained in the hydrogenations of derivatives bearing a *para* substituent on the β-phenyl and an *ortho* substituent on the α-phenyl ring (**2, 3** and **4**) (Scheme 4).

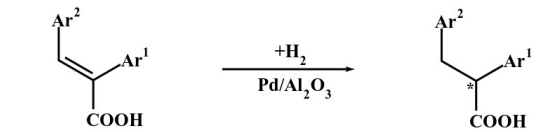


Scheme 4

The substituent on the β-phenyl ring influenced the ee through 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 also decreased the adsorption strength of the acid, leading to an increase in ee by increasing the rate over modifier sites. The two effects may act in opposite directions, as in the case of both methoxy and fluoro substituents. The beneficial effect of the *ortho* substituent on the α-phenyl ring was not related to its electronic effect, and only slightly to its steric effect. We assumed that the increased ee was due to the ability of the methoxy or fluoro substituents to form additional interactions with the modifier on the surface. These suggestions were supported by the results obtained in the hydrogenations of several methyl-substituted derivatives.

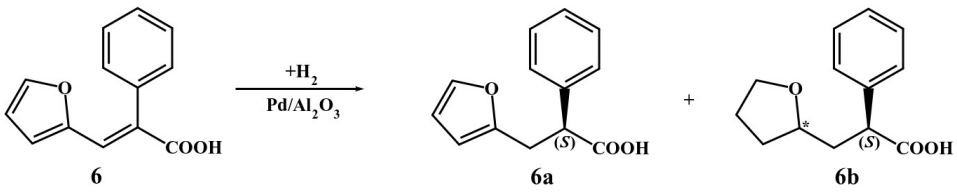
III. Enantioselective hydrogenations of propenoic acids bearing heteroaromatic substituents

The hydrogenations of 2,3-diarylpropenoic acid bearing heteroaromatic substituents (**5, 6** and **7**) over a CD-modified Pd catalyst resulted in enantioselective formation of the corresponding diarylpropionic acids (Scheme 5). The 2-furyl-substituted compound was selectively hydrogenated to 2-phenyl-3-(2-furly)propionic acid in the presence of modifier with up to 73% ee, whereas over the unmodified catalyst the furyl moiety was hydrogenated simultaneously with the olefinic double bond (Scheme 6). The hydrogenation of the acid bearing a 3-pyridyl substituent in the α position afforded a lower ee as compared with the phenyl substituent in the same position.



5: Ar^1: phenyl, Ar^2: phenyl
6: Ar^1: phenyl, Ar^2: 2-furyl
7: Ar^1: 3-pyridyl, Ar^2: phenyl

Scheme 5



Scheme 6

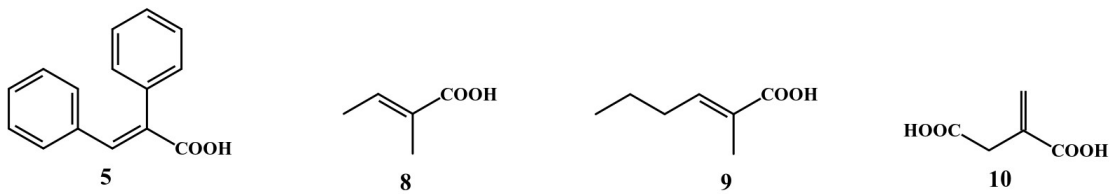
The addition of BA proved to have a beneficial effect on ee in the hydrogenation of the latter compound, but decrease of the reaction temperature resulted in a decrease in ee, in contrast with the other acids studied to date in this catalyst system. The results obtained were interpreted in terms of the probable effects of the heteroaromatic rings on the strength and mode of adsorption of these acids and by the modifications in the interaction strengths with the adsorbed CD.

IV. Enantioselective hydrogenations of α,β-unsaturated carboxylic acids in a continuous-flow system

We examined the enantioselective hydrogenations of the α,β-unsaturated carboxylic acids (*E*)-2,3-diphenylpropenoic acid (**5**), (*E*)-2-methyl-2-butenoic acid (**8**), (*E*)-2-methyl-2-hexenoic acid (**9**) and itaconic acid (**10**) over a CD-modified Pd/Al_2O_3 catalyst in the H-Cube continuous-flow system, using a fixed-bed reactor (Scheme 7).

The hydrogenations of the aliphatic substrates resulted in products with slightly lower ee-s relative to those obtained in batch reactors under similar reaction conditions. The optical purity of the product formed in the hydrogenation of (*E*)-2,3-diphenylpropenoic acid was over 70%, exceeding the value obtained in the same solvent in a slurry reactor. The ee-increasing effect of BA was also observed in the fixed-bed reactor.

The results obtained by changing the modifier concentration in the feed lead us to suggest that the interactions of the substrates with CD may occur in the liquid phase and the complexes formed are adsorbed on the Pd surface. Thus, relatively high concentrations of such complexes and consequently modifier amounts are necessary to obtain good ee-s in the hydrogenations of α,β-unsaturated carboxylic acids.



Scheme 7

E. PUBLICATION

I. **Beáta Hermán**, György Szőllősi, Ferenc Fülöp, Mihály Bartók
Enantioselective hydrogenation of α,β-unsaturated carboxylic acids in fixed-bed reactor
Applied Catalysis A: General **2007**, *331*, 39. IF = 3.166

II. György Szőllősi, **Beáta Hermán**, Károly Felföldi, Ferenc Fülöp, Mihály Bartók
Effect of the substituent position on the enantioselective hydrogenation of methoxy-substituted 2,3-diphenylpropenoic acids over palladium catalyst
Journal of Molecular Catalysis A: Chemical **2008**, *290*, 54. IF = 2.814

III. György Szőllősi, **Beáta Hermán**, Károly Felföldi, Ferenc Fülöp, Mihály Bartók
Up to 96 % enantioselectivities in the hydrogenation of fluorine substituted (*E*)-2,3-diphenylpropenoic acids over cinchonidine-modified palladium catalyst
Advanced Synthesis and Catalysis **2008**, *350*, 2804. IF = 5.619

IV. **Beáta Hermán**, György Szőllősi, Károly Felföldi, Ferenc Fülöp, Mihály Bartók
Enantioselective hydrogenation of propenoic acids bearing heteroatomic substituent over cinchonidine modified Pd/alumina
Catalysis Communications **2009**, *10*, 1107. IF = 2.791

Sum of impact factors of the published papers: 14.39

F. OTHER PUBLICATIONS

V. György Szőllősi, **Beáta Hermán**, Ferenc Fülöp, Mihály Bartók
Continuous enantioselective hydrogenation of activated ketones on a Pt-CD chiral catalyst: use of H-Cube reactor system
Reaction Kinetics and Catalysis Letters **2006**, *88*, 391. IF = 0.514

VI. György Szőllősi, **Beáta Hermán**, Erika Szabados, Ferenc Fülöp, Mihály Bartók
On the scope of the cinchonidine-modified Pd catalyst in enantioselective hydrogenation; adsorption mode of (*E*)-2,3-diphenylpropenoic acids evidenced by chlorine substituted derivatives
Journal of Molecular Catalysis A: Chemical **2010**, *333*, 28. IF = 3.135

VII. György Szőllősi, **Beáta Hermán**, Ferenc Fülöp, Mihály Bartók
Cinchona methyl ethers as modifiers in the enantioselective hydrogenation of (*E*)-2,3-diphenylpropenoic acids over Pd catalyst
Journal of Catalysis **2010**, *276*, 259. IF = 5.288

G. CONFERENCE LECTURES

VIII. **Hermán Beáta**, Szőllősi György
Enantioszelektív hidrogénezések királisan módosított heterogén katalizátorokon folyamatos rendszerben
XXIX. Kémiai Előadói Napok
Szeged, 2006. október 30-31. Abstr.: 60.

IX. **Hermán Beáta**, Szőllősi György, Felföldi Károly, Fülöp Ferenc, Bartók Mihály
Szubsztituált α,β-diaril akrilsav származékok enantioszelektív hidrogénezése
Magyar Kémikusok Egyesülete, Centenáriumi Vegyészkonferencia
Sopron, 2007. május 29 - június 1. Abstr.: SZ-P-22

X. György Szőllősi, Kornél Szőri, **Beáta Hermán**, Szabolcs Cserényi, Károly Felföldi, Ferenc Fülöp, Mihály Bartók
Scope of the cinchona alkaloids-modified palladium catalysts in enantioselective hydrogenation of unsaturated carboxylic acids
EuropaCat VIII
Turku, Finland, August 26-31, 2007, Abstr.: 5-13.

XI. **Hermán Beáta**, Szőllősi György
Metoxi-szubsztituált α-fenilfahéjsav származékok enantioszelektív hidrogénezése királisan módosított heterogén katalizátorokon
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Szeged, 2007. október 29-31. Abstr.: 73.

XII. **Hermán Beáta**, Szőllősi György, Felföldi Károly, Fülöp Ferenc, Bartók Mihály
Metoxi- és fluor-szubsztituált α-fenilfahéjsav származékok enantioszelektív hidrogénezése királisan módosított heterogén katalizátoron
Magyar Kémikusok Egyesülete, Vegyészkonferencia
Hajdúszoboszló, 2008. június 19-21. Abstr.: P-29

XIII. György Szőllősi, **Beáta Hermán**, Károly Felföldi, Ferenc Fülöp, Mihály Bartók
Heterogeneous enantioselective hydrogenations of heteroatomic analogs of (*E*)-α-phenylcinnamic acid
Tenth International Symposium on Heterogeneous Catalysis
Varna, Bulgaria, August 23-27, 2008, Abstr.: P-35

XIV. **Hermán Beáta**, Szőllősi György

Metoxi- és fluor-szubsztituált α-fenilfahéjsav származékok enantioszelektív hidrogénezése

XXXI. Kémiai Előadói Napok

Szeged, 2008. október 27-29. Abstr.: 85.

XV. György Szőllősi, **Beáta Hermán**, Ferenc Fülöp, Mihály Bartók

Effect of modifier structure on the enantioselective hydrogenation of substituted (*E*)-2,3-diphenylpropenoic acids over palladium catalyst

EuropaCat IX Catalysis for a Sustainable World

Salamanca, Spain, 30th August - 4th September 2009. Abstr.: P2-73