Ph.D. Thesis

Isocichona alkaloids in heterogen catalytic enantioselective hydrogenation

Mária Sutyinszki

Supervisor:

Dr. Mihály Bartók

Organic Catalysis Research Group of Hungarian Academy of Sciences, University of Szeged

Department of Organic Chemistry, University of Szeged

Szeged

2004

I. Introduction

The preparation of optically pure chiral molecules has prime importance in the area of pharmaceuticals, agrochemicals, flavors and fragrances. The reason is the fact that the two enantiomers of a chiral compound interact differently with living organisms. An innocent example is the limonene molecule, its (*R*)-enantiomer has lemon aroma, while the (*S*)-enantiomer has orange. However, in the 1960's it was found that the wrong enantiomer of the medicine called Contergan® had teratogen effect.

Especially this scandal helped in placing the preparation of enantiomerically pure materials in the focus of research. Basically, there are two different approaches in achieving this goal. One is the preparation of racemic mixtures, then resolution, using chiral resolution agents and the other is asymmetric synthesis. Resolution does not seem to be economic, since half of the product is wasted, nevertheless, sometimes it still can be economic on the industrial scale. The requirement of asymmetric synthesis is the presence of chiral environment. Under homogenous catalytic conditions it can be met with chiral ligands in the complex functioning as the catalyst. Nevertheless, there are problems with these reactions, e.g., the instability of the complex, difficult work-up procedure and expensive reagents.

Heterogeneous catalytic asymmetric synthesis may offer the advantage of using solid substance and catalysis. Here, enantioselectivity can be achieved by using chiral auxiliaries. At present, two catalyst-modifier systems are known to give higher then 95% optical yields. They are the tartaric acid modified Raney nickel catalyst, successful in the hydrogenation of β-ketoesters and β-diketones, and the cinchona alkaloid modified platinum catalyst system, performing superbly in the hydrogenation of α-ketoesters.

The Organic Catalysis Research Group of the Hungarian Academy of Sciences at the Department of Organic Chemistry at the University of Szeged started to study the asymmetric hydrogenation of ethyl pyruvate in 1997. This molecule is the model compound in the research of the cinchona alkaloid modified platinum catalyst system.

We aimed to gain deeper insight into this catalyst system through using new cinchona alkaloids as chiral modifiers. In the light of new experimental results we hoped to collect significant novel information concerning the mechanism of the reaction.

II. Experimental

The catalyst used in the hydrogenations was Engelhard 4759, a 5% Pt/Al_2O_3 catalyst. Hydrogenation was performed in an atmospheric batch reactor and in a 30 ml stainless steel autoclave.

Product identification was based on mass spectra (HP 5890 GC-HP 5970 MS, 50 m long HP-1 column), while quantitative analysis including enantiomeric separation was performed with an HP 5890 GC-FID gas chromatograph (30 m long Cyclodex-B and Lipodex-A columns).

After the hydrogenation reactions the reaction mixtures were analyzed with HPLC, HPLC-MS, MS, ESI-MS, ESI-MS/MS, NMR and UV.

III. Results and Discussion

1. We have synthesized in one step the mixture of α-isocinchonine (α-ICN) and β-isocinchonine (β-ICN) and the two alkaloids were separated by repeated column chromatography. The molecules thus prepared were used to modify the Pt/Al_2O_3 (E4759) catalyst in the liquid phase, in the enantioselective hydrogenation of ethyl pyruvate (EtPy).
2. The effects of the modifier concentration, the temperature, and the hydrogen pressure have been examined in the presence of these novel catalysts. It has been found that experimental conditions strongly affected the reaction rates as well as the optical yields. Both reaction rates and enantioselectivities (enantiomeric excess – ee) significantly depended on the solvent (acetic acid or toluene) used.
3. In acetic acid the reaction rate decreased in the order of β-ICN > 11,12-dihydrocinchonine (DHCN) > α-ICN. Under mild experimental conditions (273 K, 1 bar H_2 pressure) the expected (*S*)-ethyl lactate ((*S*)-EtLt) formed in excess in the presence of both modifiers. The ee values were 82% and 62 % with α-ICN and β-ICN, respectively.
4. In toluene with α-ICN as modifier (*S*)-EtLt was formed in excess, with 27% as the highest ee. In the presence of β-ICN, however, the direction of optical rotation has unexpectedly changed and (*R*)-EtLt has been formed with 50% ee. The inversion strongly suggests that the reaction mechanism has changed in this solvent.

5. ESI-MS and ESI-MS/MS measurements revealed that under the mild experimental conditions (273 K, 1 bar H_2 pressure) there were no DHCN or its hydrogenated derivatives in solution in detectable amounts. Thus, it may be safely stated that the α-ICN and β-ICN are responsible for the chiral induction. This conclusion was further supported by HPLC-MS-MS and NMR observations.
6. Measurements with modifier mixtures indicate that β-ICN adsorbs more strongly than α-ICN, meaning that the adsorption through the quinoline ring is different.
7. The observed inversion of optical rotation in the hydrogenation of EtPy over the β-ICN modified E4759 catalyst prompted us to investigate the changes in ee in acetic acid-toluene mixtures too. A linear relationship was found between the direction of chiral induction and the composition of the solvent mixture, indicating changes in the mechanism.
8. Knowing the structures and, moreover, the conformers of the two modifiers and using the widely accepted adsorption model, we are confident that the structures of the intermediates responsible for the direction of enantioselection are not the same in acetic acid and toluene. Furthermore, these interactions are different from those envisaged until now.

IV. List of publications

Papers related to the subject of the Thesis:

1. M. Bartók, **M. Sutyinszki**, K. Felföldi, G. Szöllösi:
   Unexpected change of the sense of the enantioselective hydrogenation of ethyl pyruvate catalyzed by a Pt-alumina-cinchona alkaloid system,
   Chem. Commun., **2002**, 1130. IF = 3.902
2. K. Szőri, **M. Sutyinszki**, K. Felföldi, M. Bartók:
   Heterogeneous asymmetric reactions 28. Efficient and practical method for the preparation of (*R*)- and (*S*)-α-hydroxy esters by the enantioselective heterogeneous catalytic hydrogenation of α-ketoesters,
   Applied Catal. A: General **237** (2002) 275. IF = 2.258
3. M. Bartók, **M. Sutyinszki,** K. Felföldi:
   Enantio selective hydrogenation of ethyl pyruvate catalyzed by α- and β-isocinchonine-modified Pt/Al_2O_3 in acetic acid,
   J. Catal. **220** (2003) 207. IF = 3.293
4. M. Bartók, Z. Kele, **M. Sutyinszki**, I. Bucsi, K. Felföldi:
   Investigation of chiral reactions: the structural detection of new hydrogenated isocinchona alkaloids from mixtures without isolation using electronspray ionization tandem mass spectrometry,
   Rapid Commun. Mass Spectrom. **18** (2004) 1352. IF = 2.478
5. M. Bartók, **M. Sutyinszki** , K. Felföldi, I. Bucsi, Gy. Szöllősi, T. Bartók:

Enantioselective hydrogenation of ethyl pyruvate catalyzed by α- and β-isocinchonine, modified Pt/Al_2O_3 in toluene: inversion of enantioselectivity,

J. Catal. (submitted).

Other publications:

1. **M. Sutyinszki,** K. Szöri, K. Felföldi, M. Bartók:
   Heterogeneous asymmetric reactions 29. Enantioselective hydrogenation of ethyl benzoylformate over dihydrocinchonidine-modified platinum-alumina catalyst in acetic acid,
   Catal. Lett., **81** (2002) 281. IF = 1.852
2. **M. Sutyinszki**, K. Szõri, K. Felföldi, M. Bartók:
   98% Enantioselectivity in the asymmetric synthesis of a useful chiral building block by heterogeneous method: enantioselective hydrogenation of ethyl benzoylformate over cichona modified Pt/Al_2O_3 catalysts in the acetic acid,
   Catal. Commun., **3** (2002) 125. IF = ?
3. K. Felföldi, **M. Sutyinszki**, N. Nagy, I. Pálinkó:
   Synthesis of *E*- and *Z*-methoxy-substituted 2,3-diphenylpropenoic acids and its methyl esters,
   Synth. Comm., **30** (2000) 1543. IF = 0.912

Lectures and posters

1. **Sutyinszki M.**, Felföldi K.**,** Bartók M.:
   Enatioselective hydrogenation of ethylpyruvate on Pt/Al_2O_3 catalyst int he presence of α-isocinchonine as chiral modifier,
   Conference of Hungarian Chemists Association 2001.
   Abstracts p. 113. (P-79)

2. **Sutyinszki M.**, Felföldi K.**,** Bartók M.:
Enantioselective hydrogenation of ethyl-pyruvate in the presence of α- and β-isocinchonine modifiers over Pt/Al_2O_3,
Conference of Hungarian Chemists Association 2003.
Abstracts p. 143. (P-95).

3. **Sutyinszki M.**:
Highly enantioselective asymmetric synthesis. Synthesis of α - and β-isocinchonine and use in the presence of Pt/Al_2O_3 catalyst,
Endowment for Supporting Young Organic Chemists of Szeged, 3rd Scientific Meeting 2003., first prize.

4. **M. Sutyinszki,** K. Felföldi, M. Bartók**:**
Chiral induction by isocinchona alkaloids in enantioselective hydrogenation of ethyl pyruvate,
EUROPACAT VI, 2003. Innsbruck, Poster program A3.032.

5. **M. Sutyinszki:**
Catalytic enantioselective hydrogenation of α-ketoesters over Pt/Al_2O_3 modified by α- and β-isocichonine,
Catalysis Committee of the Hungarian Academy of Sciences
October, 2003. Szeged.