Catal Lett (2008) 124:46–51
DOI 10.1007/s10562-008-9498-1

New Data of Nonlinear Phenomenon in the Heterogeneous Enantioselective Hydrogenation of Activated Ketones

Katalin Balázsik · György Szöllősi · Mihály Bartók

Received: 11 March 2008 / Accepted: 16 April 2008 / Published online: 1 May 2008

Abstract Results on nonlinear phenomenon (NLP) in the liquid phase hydrogenation of methyl benzoylformate (MBF) and pyruvaldehyde dimethyl acetal (PA) on chiral Pt-cinchona catalyst are reported for the first time (enantiomeric excess 90–95%). The new data support the conclusions of the NLP studies on ethyl pyruvate (EP) and ketopantolactone (KPL). Namely, the order of the adsorption strengths of the parent cinchona alkaloids are: CD > CN > QN ~ QD and the results of the NLP measurements indirectly verify the so-called 1:1 model of enantioselection. The new data, however, call attention to a new, substrate and modifier dependent phenomenon, which necessitates further experiments for a better understanding of the mechanism of the Orito reaction.

Keywords Asymmetric hydrogenation · Platinum · Cinchona alkaloids · Ketones · Nonlinear phenomenon

1 Introduction

The enantioselective hydrogenation of prochiral ketones and C=C containing compounds on tartaric acid modified Ni [1] and on Pt and Pd catalysts modified by cinchona alkaloids (Orito reaction, Scheme [2]) are important methods among various selective catalytic organic reactions (e.g. [3]). The significance of the Orito reaction is underlined not only by its industrial application [4] and the high enantioselectivities observed [5–7], but also by numerous reviews (since 2005: [8]) discussing and evaluating the steady flow of novel results in the enantioselective hydrogenation of activated ketones. The preferred model compound for this research has been ethyl pyruvate (EP) that can be hydrogenated in ee over 90%. Only a few papers have reported on the hydrogenation of MBF and PA, two compounds with structures different from that of EP but also hydrogenated in high ee [7]. Detailed studies on the mechanism of the enantioselective hydrogenation of these compounds may yield further important information for the interpretation of the origin of chiral induction.

The present report gives account of new results in a narrow segment of reaction mechanism research, the so-called nonlinear phenomenon (NLP). This phenomenon, termed "nonlinear effect" may arise in the interaction of a substrate with two enantiomers of opposite configurations and was first recognized in 1986, in a study on homogeneous asymmetric catalysis [9]. Nonlinearity in the Orito reaction was first observed by Wells et al. in the hydrogenation of methyl pyruvate (MP) [10]. Baiker et al. and later many other authors have widely utilized NLP in their studies on the heterogeneous enantioselective hydrogenation of activated ketones. The results of studies carried out to date (using modifier mixtures, transient method, continuous flow measurements) can be summarized as follows. Studies on NLP have mainly been performed in enantioselective hydrogenations on Pt [10–21] and Pd [22–25] catalysts. A study using Rh catalyst has also been published [26]. The substrates hydrogenated over Pt catalysts were MP [10], but most of all EP [11, 14, 16–18, 21, 24, 27] and KPL [12, 13, 15, 19, 26, 27]; hydrogenations over Pd were performed on 4-methoxy-6-methyl-2-pyrone [25], α-phenylcinnamic acid [23] and isoforon [22], and those over Rh

---

K. Balázsik · G. Szöllősi · M. Bartók
Stereochemistry Research Group of the Hungarian Academy of Sciences, Dóm tér 8, 6720 Szeged, Hungary

M. Bartók (✉)
Department of Organic Chemistry, University of Szeged, Dóm tér 8, 6720 Szeged, Hungary
e-mail: bartok@chem.u-szeged.hu

on KPL [26] as substrate. One component of the chiral modifiers used was a parent cinchona alkaloid (CD, CN, QN, QD), whereas the other component was the opposite enantiomer of CD, CN, QN, QD or their C9-O-R derivatives [12, 13, 16, 18, 19, 24, 26–28]. In addition to cinchona alkaloids and their derivatives, other chiral modifiers including synthetic chiral compounds and achiral modifiers were also investigated [11, 15, 20, 22].

Experimental results on NLP have yielded, on one hand, information on the adsorption strength and the way of adsorption of chiral modifiers. On the other hand, studies on NLP have also contributed with new experimental evidence to the elucidation of the mechanism of the Orito reaction, namely they have verified that, in the hydrogenation of EP and KPL, the intermediate complex responsible for chiral induction is the 1:1 complex of the chiral modifier and the substrate formed on the catalyst surface.

The present publication has a dual aim: on the one hand, to study NLP for compounds not tested before; on the other hand, to determine whether or not the conclusions drawn from NLP studies on EP and KPL can be generalized to the enantioselective hydrogenation of activated ketone types not studied before. MBF and PA were selected as model compounds (Scheme 1).

2 Experimental

2.1 Materials

MBF, PA, CD, CN, QN, QD and solvents were from Aldrich or Fluka, and used as received. MBF (b.p. 391–393 K at 5 Hg mm) and PA (b.p. 325–327 K at 25 Hg mm) were distilled in vacuum using Vigreaux-column. H_2 (99.999%) was purchased from Linde. The pretreated Engelhard E4759 Pt-alumina catalyst was used as in Ref. [27]. Using ultrasound treatment also improve the catalyst performance [29].

2.2 Spectroscopy

NMR spectra were recorded on Bruker Avance 200 and 400 MHz spectrometers, using $CDCl_3$ as solvent. The ESI-MSD-ion-trap (AGILENT 1100 LC-MSD TRAP SL ion-trap MS) was operated under positive ion and auto MS-MS mode as described earlier [30].

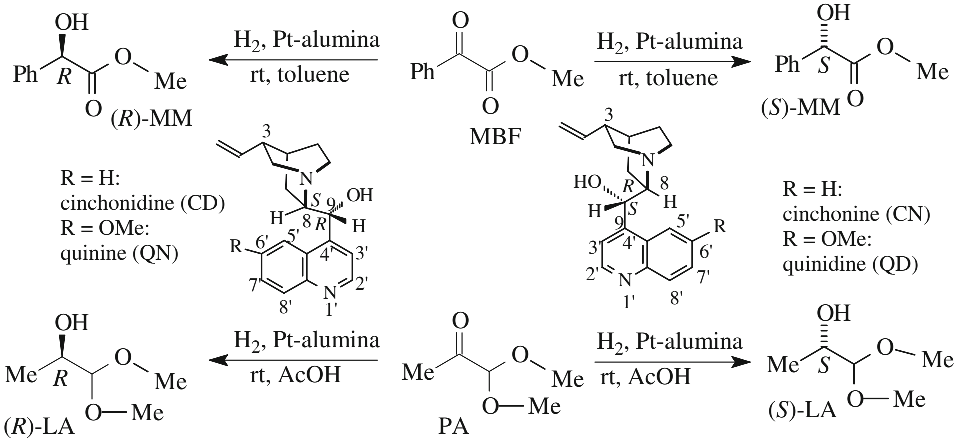
2.3 Hydrogenation

Hydrogenations were performed as in Ref. [27]. Standard conditions were: 12.5 mg E4759, 2.5 mL solvent (AcOH or T), 1 bar hydrogen pressure, 294–297 K, 1 mM of modifier concentration, 900–1,000 rpm, 0.5 mmol of substrate. The product identification and the enantiomeric excess [$ee\% = ([R] - [S]) \times 100/([R] + [S])$] were monitored by gas chromatography (HP 6890 N GC-FID, 30 m long Cyclodex-B capillary column. Retention times (min): MBF 383 K, 25 psi He: 21.7 of MBF, 29.9 of (*R*)-methyl mandalate (*R*)-MM), 30.9 of (*S*)-methyl mandalate (*S*)-MM); PA 338 K, 21.65 psi He: 5.2 of PA, 8.6 of (*R*)-lactaldehyde dimethyl acetal (*R*)-LA), 9.1 of (*S*)-lactaldehyde dimethyl acetal (*S*)-LA); reproductibility was ±2% (for abbreviation see Scheme 1).

2.4 Measurements Using Mixtures of Modifiers

Hydrogenation with mixtures of modifiers (1 mM) and transient behavior measurements (0.5 mM for both modifier) was carried out in T and AcOH as described above for a single modifier with the exception that in the transient method the hydrogenation was continued after the addition of the second modifier to the reaction mixture containing the first modifier (standard conditions were: 25 mg E4759, 5 mL solvent, 1 bar H_2, 294–297 K, 1 mmol substrate). The procedure was as follows: hydrogenation was performed until 10% conversion was achieved; at this point stirring was stopped and after 1 min a sample was taken.

Scheme 1



The second modifier was added next and hydrogenation and sampling were continued. Ee was measured as described above.

3 Results and Discussion

3.1 Enantioselective Hydrogenation of MBF and PA (Figs. 1, 2)

Considering that studies on NLP necessitate the use of chiral modifiers of opposite configurations, and that this type of research has not been included in studies on the hydrogenation of MBF and PA, the parent cinchonas were selected for these investigations (Scheme 1). The experimental results of enantioselective hydrogenation are shown in Figs. 1 and 2. Of the solvents that had been found optimal in previous hydrogenation studies, T was selected for hydrogenation of MBF and AcOH for that of PA.

Comparison of the data in Figs. 1 and 2 with the data of the extensively studied EP hydrogenation and comparison of the data of MBF hydrogenation with those of PA leads to the following main conclusions: (i) hydrogenation of EP is faster than that of MBF and considerably faster than that of PA; (ii) the rate of MBF hydrogenation runs an identical course with that of EP, depending on the chiral modifier, i.e. CD > CN > QN ~ QD and the ee values follow the same order; (iii) after optimization, ~95% ee can be attained for both compounds (MBF and EP), for EP in AcOH and for MBF in T; (iv) the most remarkable phenomenon among the hydrogenation results presented is the very slow hydrogenation of PA, associated with an unusually high ee (over 90%) independently of the 4 parent cinchonas; (v) this phenomenon, so far unprecedented in the history of the hydrogenation of activated ketones [4], i.e. low rate + high enantioselectivity can be attributed to the effect of the structure of PA, which is different from that of other activated ketones (α-ketoester—α-ketoacetal, Scheme 1), on the mechanism of enantioselective hydrogenation. Similar phenomenon to the best of our knowledge during the hydrogenation of β-ketoesters over tartaric acid modified Ni was not observed [1e].

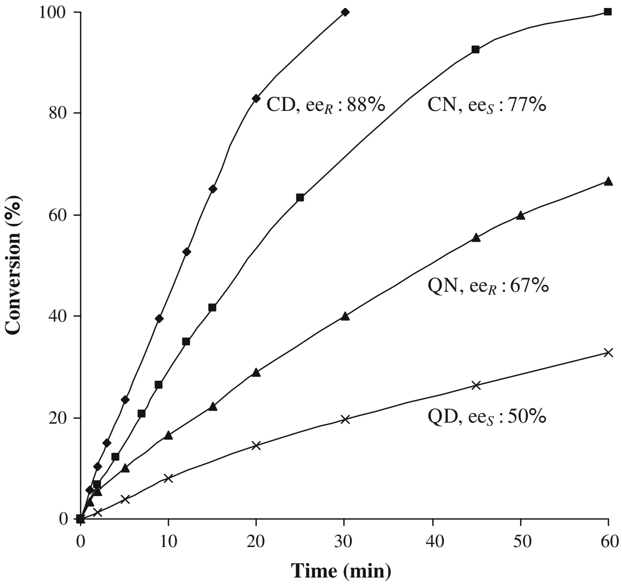


Fig. 1 Enantioselective hydrogenation of MBF in toluene: the effect of chiral modifiers on conversion and ee (standard conditions)

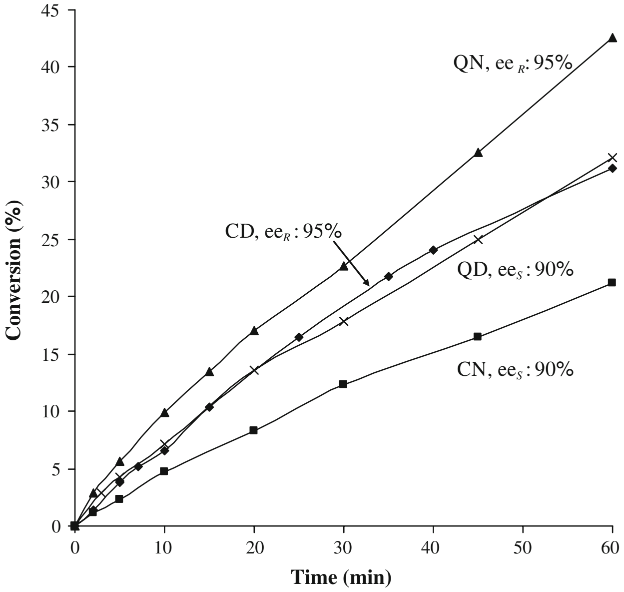


Fig. 2 Enantioselective hydrogenation of PA in AcOH: the effect of chiral modifiers on conversion and ee (standard conditions)

3.2 NLP Results Using Modifier Mixtures and Transient Method

To our best knowledge, no data on the nonlinear behavior of modifiers in the MBF and PA hydrogenation have been published in the pertinent literature. The experimental data on MBF and PA hydrogenation are summarized in Figs. 3–6, respectively. The shape of the individual ee-time-conversion curves reveals that they are somewhat different from those observed for EP and KPL. These differences may be related to differences in hydrogenation rate due to different substrate adsorption.

3.2.1 Results of NLP in MBF Hydrogenation (Figs. 3, 4)

When MBF was hydrogenated over Pt-alumina catalyst modified by mixtures of CD + CN of various compositions in either solvent, nonlinearity was observed (Fig. 3), just like in the case of EP and KPL [27]. The adsorption

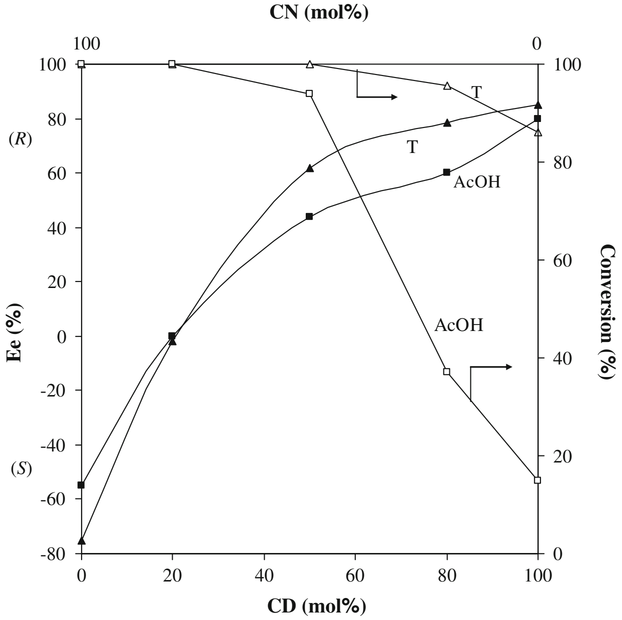


Fig. 3 Hydrogenation of MBF over Pt-alumina modified by CD + CN mixtures (standard conditions: [CD + CN] = 1 mM, T = toluene, hydrogenation time 60 min in AcOH and 30 min in T)

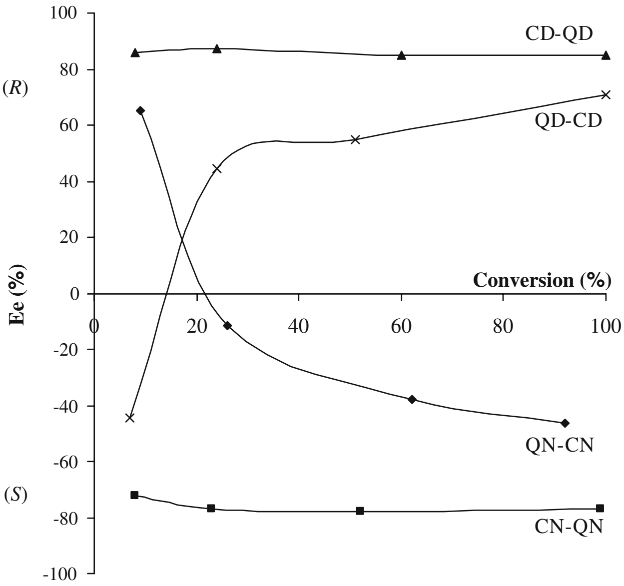


Fig. 4 Transient behavior in the enantioselective hydrogenation of MBF in toluene: effect of modifier mixtures (standard conditions, [modifiers] = 1 mM, first abbreviation—modifier used first, second abbreviation—modifier added afterwards, hydrogenation time 25–60 min)

strength of CD is higher than that of CN, therefore mostly (*R*)-methyl mandalate is formed and any considerable excess of (*S*)-methyl mandalate is only formed when the CN content of the modifying mixture exceeds 80%. From the data in Fig. 3 and from transient measurements in toluene (Fig. 4), the order of the adsorption strengths of the four modifiers can be derived. The most probable order is CD > CN > QN ~ QD, because, in the case of identical cinchona concentrations, QD does not affect the formation of (*R*)-methyl mandalate on Pt-CD chiral catalyst, just like QN does not affect the direction of enantioselective hydrogenation on Pt-CN chiral catalyst. The higher adsorption strength of CD as compared to QD and of CN as compared to QN is verified by the observation that CD replaces QD on the Pt-QD chiral catalyst and CN replaces QN on the Pt-QN chiral catalyst.

3.2.2 Results of NLP in PA Hydrogenation (Figs. 5, 6)

Since no experimental data have been published on NLP in the case of PA, it was expedient to carry out these studies in the presence of the CD + CN mixtures in toluene and in AcOH. When PA was hydrogenated in the presence of mixtures of CD + CN, the process produced surprisingly low conversion in both solvents, in spite of the 2-h hydrogenation time (Fig. 5). The result of transient measurements was the same (Fig. 6); interpretation of these results necessitates further experiments. The order of adsorption strengths in AcOH was CD > CN > QN ~ QD, because CD can replace CN more readily than vice versa, CD can replace QD more readily than CN replaces QN.

In the case of the CD–QD pair, in addition to the already well-known large difference between adsorption strengths, the higher conversion relative to the other modifier pairs is also noteworthy. Independently of all these differences, it

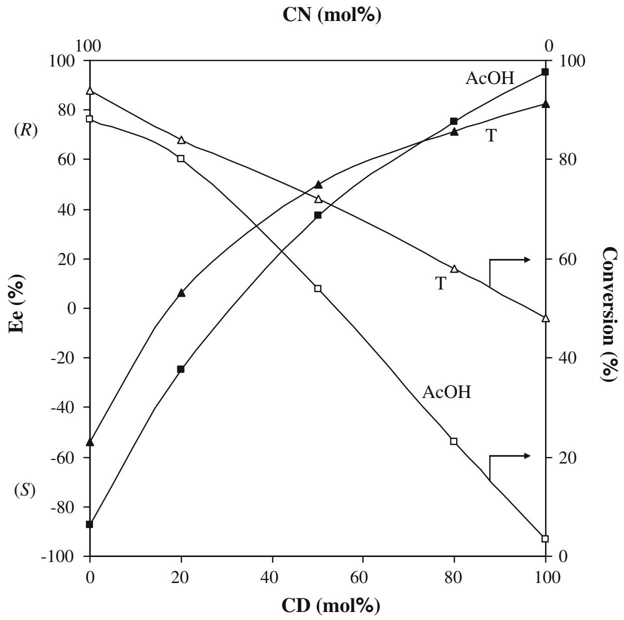


Fig. 5 Hydrogenation of PA over Pt-alumina modified by CD + CN mixtures (standard conditions: [CD + CN] = 1 mM, hydrogenation time 120 min)

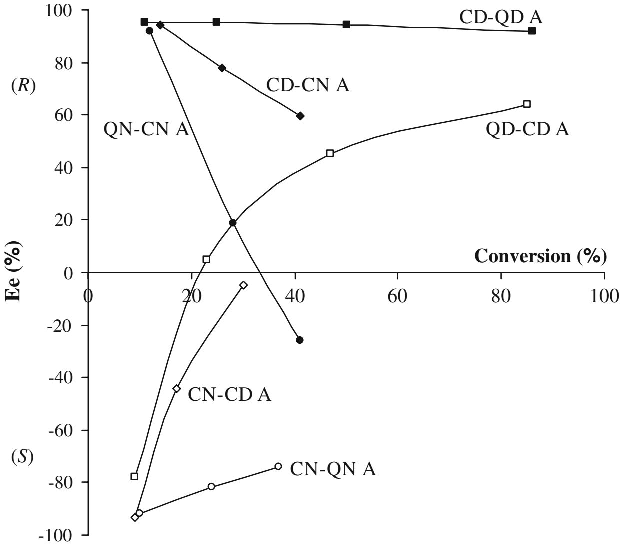


Fig. 6 Transient behavior in the enantioselective hydrogenation of PA in AcOH: effect of modifier mixtures (standard conditions, [modifiers] = 1 mM, first abbreviation—modifier used first, second abbreviation—modifier added afterwards, hydrogenation time 90–120 min)

should be emphasized that an ee exceeding 90% is achievable with all four parent alkaloids and this observation also calls for further research. The recent in situ RAIRS results [20] based on the earlier studies by Zaera and coworkers [31] revealed a different adsorption order of the cinchona alkaloids, thus, the interpretation of the phenomenon (K_{ads} solvent dependence, adsorption mode of the alkaloids) calls the attention on the importance of further studies.

4 Conclusion

The research carried out to realize the dual objective outlined in the Introduction suggest that the new results of NLP studies on substrates not studied before (MBF, PA) are mostly in agreement with the conclusions of research on EP and KPL. Namely, in T and AcOH the order of the adsorption strengths of the chiral modifiers studied is CD > CN > QN ~ QD. The relative different adsorption strength and the different adsorption modes of the modifiers are the primary reason of the NLP on the metal surface. These new results are in agreement with the proposed mechanistic models for the interpretation of the origin of chiral induction in the Orito reaction assuming 1:1 type modifier-substrate intermediate complexes. There is no consensus so far, however, on the structure if intermediate complexes [10, 32] and [33]. The remarkable phenomenon that has not yet received sufficient attention in the Orito reaction and the speciality of the enantioselective hydrogenation of PA, presented in the manuscript, is the extremely high ee at low reaction rates. The same unusual phenomenon is indicated by the NLP results obtained with PA. The data shown in Figs. 5, 6 raise novel problems that urge further experimentation. Answering these newly raised questions may open new possibilities to get a better understanding of the mechanism of a complex heterogeneous catalytic reaction occasionally producing outstandingly high ee values, and may thereby bring us closer to the interpretation of the origin of chiral induction.

The high enantioselectivities achieved during hydrogenation of MBF and PA make necessary the investigation of the following parameters and factors regarding the mechanism of the Orito reaction: adsorption of the individual substrates, nucleophilicity of the C=O group to be hydrogenated, interaction of substrates and cinchona alkaloids in solution, adsorption and stability of the resulting intermediate complex.

The role of the above parameters has been extensively studied in the case of EP and KPL, however, similar studies have not been performed on activated ketones of the either type. At the present time only questions and assumptions may be formulated which can only be answered and verified when experimental evidence becomes available. These studies naturally necessitate the application of various methods and their results may contribute to the elucidation of the origins of chiral induction and its further practical utilization.

Acknowledgments Financial support by the Hungarian National Science Foundation (OTKA Grant T 048764, K 72065) is highly appreciated. Gy. Sz. thanks the Hungarian Academy of Sciences for the award of Bolyai János scholarship.

References

1. Izumi Y (1971) Angew Chem Int Ed Engl 10:871; Izumi Y (1983) Adv Catal 32:215; Bartók M, Wittmann Gy, Göndös Gy, Smith GV (1987) J Org Chem 52:1139; Wittmann Gy, Bartók GB, Bartók M, Smith GV (1990) J Mol Catal 60:1; Osawa T, Harada T, Takayasu O (2006) Curr Org Chem 10:1513
2. Orito Y, Imai S, Niwa S (1979) J Chem Soc Jpn 8:1118; Orito Y, Imai S, Niwa S, Hung NG (1979) J Synth Org Chem 37:173
3. Fine Chemicals Through Heterogeneous Catalysis (2001) Sheldon RA, van Bekkum H (eds) Wiley, Weinheim; Bartók M, Notheisz F, Zsigmond ÁG (1980) J Catal 63:364; Notheisz F, Bartók M, Ostgard D, Smith GV (1986) J Catal 101:212; Molnár Á, Smith GV, Bartók M (1986) J Catal 101:67; Molnár Á, Bucsi I, Bartók M, Resofszki G, Gáti Gy (1991) J Catal 129:303; Molnár Á, Katona T, Bartók M, Varga K (1991) J Mol Catal 64:41
4. Blaser HU, Schmidt E (eds) (2004) In: Asymmetric catalysis on industrial scale. Challenges, approaches and solutions, Wiley-VCH, Weinheim, p 480; Studer M, Blaser H-U, Exner C (2003) Adv Synth Catal 345:45

5. von Arx M, Bürgi T, Mallat T, Baiker A (2002) Chem Eur J 8:1430; Künzle N, Szabo A, Schürch M, Wang G, Mallat T, Baiker A (1998) Chem Commun 1377; von Arx M, Mallat T, Baiker A (2001) Tetrahedron: Asym 12:3089
6. Török B, Balázsik K, Szöllösi Gy, Felföldi K, Bartók M (1999) Chirality 11:470; Balázsik K, Szöri K, Felföldi K, Török B, Bartók M (2000) Chem Commun 555; Sutyinszki M, Szöri K, Felföldi K, Bartók M (2002) Catal Commun 3:125
7. Studer M, Burkhardt S, Blaser HU (1999) Chem Commun 1727; Török B, Felföldi K, Balázsik K, Bartók M (1999) Chem Commun 1725; Exner C, Pfaltz A, Studer M, Blaser HU (2003) Adv Synth Catal 345:1253
8. Baiker A (2005) Catal Today 100:159; Murzin DY, Maki-Arvela P, Toukoniitty E, Salmi T (2005) Catal Rev Sci Eng 47:175; Hutchings GJ (2005) Ann Rev Mat Res 35:143; Bartók M (2006) Curr Org Chem 10:1533; Klabunovskii E, Smith GV, Zsigmond Á (2006) Heterogeneous enantioselective hydrogenation. Springer, Dordrecht; Mallat T, Orglmeister E, Baiker A (2007) Chem Rev107:4863
9. Puchot C, Samuel O, Dunach E, Zhao S, Agami C, Kagan HB (1986) J Am Chem Soc 108:2353; Avalos M, Babiano R, Cintas P, Jimenez JL, Palacios JC (1997) Tetrahedron: Asym 8:2997; Girard C, Kagan HB (1998) Angew Chem Int Ed 37:2923
10. Simons KE, Meheux PA, Griffiths SP, Sutherland IM, Johnston P, Wells PB, Carley AF, Rajumon MK, Roberts MW, Ibbotson A (1994) Recl Trav Chim Pays-Bas 113:465
11. Schürch M, Heinz T, Aeschimann R, Mallat T, Pfaltz A, Baiker A (1998) J Catal 31:173
12. Diezi S, Szabó A, Mallat T, Baiker A (2003) Tetrahedron: Asymmetry 14:2573
13. Diezi S, Mallat T, Szabo A, Baiker A (2004) J Catal 228:162
14. Bartók M, Sutyinszki M, Balázsik K, Szöllősi Gy (2005) Catal Lett 100:161
15. Balazs L, Mallat T, Baiker A (2005) J Catal 233:327
16. Bartók M, Sutyinszki M, Bucsi I, Felföldi K, Szöllősi Gy, Bartha F, Bartók T (2005) J Catal 231:33
17. Meier DM, Mallat T, Ferri D, Baiker A (2006) J Catal 244:260
18. Cserényi Sz, Felföldi K, Balázsik K, Szöllősi Gy, Bucsi I, Bartók M (2006) J Mol Catal A Chem 247:108
19. Bartók M, Balázsik K, Bucsi I, Szöllősi Gy (2006) J Catal 239:74
20. Ma Z, Zaera F (2006) J Am Chem Soc 128:16414; Ma Z, Lee I, Zaera F (2007) J Am Chem Soc 129:16083
21. Meier DM, Ferri D, Mallat T, Baiker A (2007) J Catal 248:68
22. Tungler A, Fodor K, Máthé T, Sheldon RA (1997) Stud Surf Sci Catal 108:157
23. Nitta Y, Shibata A (1998) Chem Lett 161
24. Huck WR, Bürgi T, Mallat T, Baiker A (2003) J Catal 216:276; Huck WR, Mallat T, Baiker A (2003) Catal Lett 87:241
25. Huck WR, Mallat T, Baiker A (2003) Adv Synth Catal 345:255
26. Maris M, Mallat T, Baiker A (2005) J Mol Catal A Chem 242:151
27. Balázsik K, Bucsi I, Cserényi Sz, Szöllősi Gy, Bartók M (2008) J Mol Catal A Chem 280:87
28. Wahl M, von Arx M, Jung TA, Baiker A (2006) J Phys Chem B 110:21777
29. Szöllösi Gy, Török B, Szakonyi G, Kun I, Bartók M (1998) Appl Catal A Gen 172: 225; Balázsik K, Török B, Felföldi K, Bartók M (1999) Ultrason Sonochem 5:149; Török B, Felföldi K, Szakonyi G, Bartók M (1997) Ultrason Sonochem 4:301
30. Bartók M, Bartók T, Szöllösi Gy, Felföldi K (1999) Catal Lett 61:57; Bartók M, Szabó PT, Bartók T, Szöllösi Gy (2000) Rapid Commun Mass Spectrom 14:509
31. Kubota J, Zaera F, (2001) J Am Chem Soc 123:11115; Ma Z, Kubota J, Zaera F (2003) J Catal 219:404; Ma Z, Lee I, Kubota J, Zaera F (2004) J Mol Catal A Chem 216:199; Ma Z, Zaera F (2005) J Phys Chem B 109:406; Zaera F (2005) J Mol Catal A Chem 228:21
32. Bonalumi N, Bürgi T, Baiker A (2003) J Am Chem Soc 125:13342; Vargas A, Ferri D, Baiker A (2005) J Catal 236:1; Taskinen A, Nieminen V, Hotokka M, Murzin DY (2007) J Phys Chem C 111:5128
33. Augustine RL, Tanielyan SK (1996) J Mol Catal A Chem 112:93; Margitfalvi JL, Hegedűs M (1996) J Mol Catal A Chem 107:281; Bartók M, Sutyinszki M, Felföldi K, Szöllősi Gy (2002) Chem Commun 1130; Vayner G, Houk KN, Sun YK (2004) J Am Chem Soc 126:199; Lavoie S, Laliberte MA, Temprano I, McBreen PH (2006) J Am Chem Soc 128:7588; Martinek TA, Varga T, Fülöp F, Bartók M (2007) J Catal 246:266; Carneiro JWD, de Oliveira CDB, Passos FB, Aranda DAG, de Souza PRN, Antunes OAC (2005) J Mol Catal A Chem 226:221