

Non-Linear Effect of Modifier Composition on Enantioselectivity in Asymmetric Hydrogenation over Platinum Metals

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Abstract: Prominent non-linear behavior was observed when mixtures of cinchona alkaloids were applied as chiral modifiers in enantioselective hydrogenations over Pt/Al₂O₃ and Pd/TiO₂. The phenomenon is traced to differences in the strength and geometry of alkaloid adsorption on the metal surface. In ethyl pyruvate hydrogenation under close to ambient conditions the weaker adsorbing quinidine (QD) outperformed the generally preferred modifier cinchonidine (CD) and afforded the highest ee (96–98%) at 1–5 bar. In the partial hydrogenation of 4-

methoxy-6-methyl-2-pyrone to the dihydro derivative **4** CD gave 73% ee to (*S*)-**4** and QD provided 72% ee to (*R*)-**4**, and still the alkaloid mixture containing less than 5 mol % CD afforded 15% ee to (*S*)-**4**. This non-linear behavior may be advantageous in asymmetric synthesis as low purity chiral compounds can be applied as efficient modifiers for Pt or Pd.

Keywords: asymmetric hydrogenation; cinchona alkaloids; ethyl pyruvate; 4-methoxy-6-methyl-2-pyrone; palladium; platinum

Introduction

From a synthetic point of view, a promising strategy in heterogeneous asymmetric hydrogenation is the use of a conventional metal hydrogenation catalyst together with a strongly adsorbed chiral compound (“modifier”) as the source of chirality.^[1–11] Cinchona alkaloids, and in particular cinchonidine (CD), are versatile chiral modifiers of Pt and Pd: they provide the highest ee in the hydrogenation of various α -functionalized (activated) ketones,^[12–20] α,β -unsaturated carboxylic acids^[21,22] and various functionalized 2-pyrones.^[23] The two groups of important cinchona alkaloids, which afford the opposite

enantiomers in excess over Pt and Pd, are shown in Figure 1.

An interesting and yet overlooked point is that the purity of commercial CD is rather low: it contains a considerable amount of QD (in our sample 7%) and also some QN (1%). As CD and QD afford the opposite enantiomer in excess compared to that formed with QN, it is at first sight astonishing that the CD-QN-QD mixture can afford 97–98% ee on Pt^[13,14,24] and 94% ee on Pd.^[23] It is even more startling when considering the inevitable racemic reaction, i.e., hydrogenation of the substrate without involvement of the chiral modifier. Analysis of this phenomenon revealed an interesting non-linear behavior of cinchona alkaloid mixtures, which is in some aspects analogous to the well-known non-linear effect (NLE) in homogeneous catalysis,^[25–27] although the physicochemical background is remarkably different.

Results and Discussion

At first we investigated the hydrogenation of ethyl pyruvate (**1**, Scheme 1), a commonly used test reaction for the Pt-cinchona system. Under ambient conditions in AcOH, QD was more effective than (commercial) CD: it afforded 3% higher ee when it was used alone. Still, CD controlled the enantioselection when mixtures of the two alkaloids were used as modifiers (Figure 2a). Even with a QD-CD molar ratio of 20, (*R*)-**2** formed as the major enantiomer at 11% ee. An explanation based

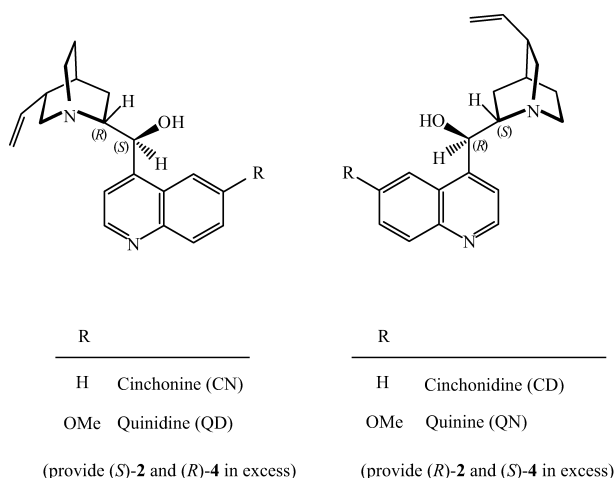


Figure 1. Some cinchona alkaloids and their abbreviations.

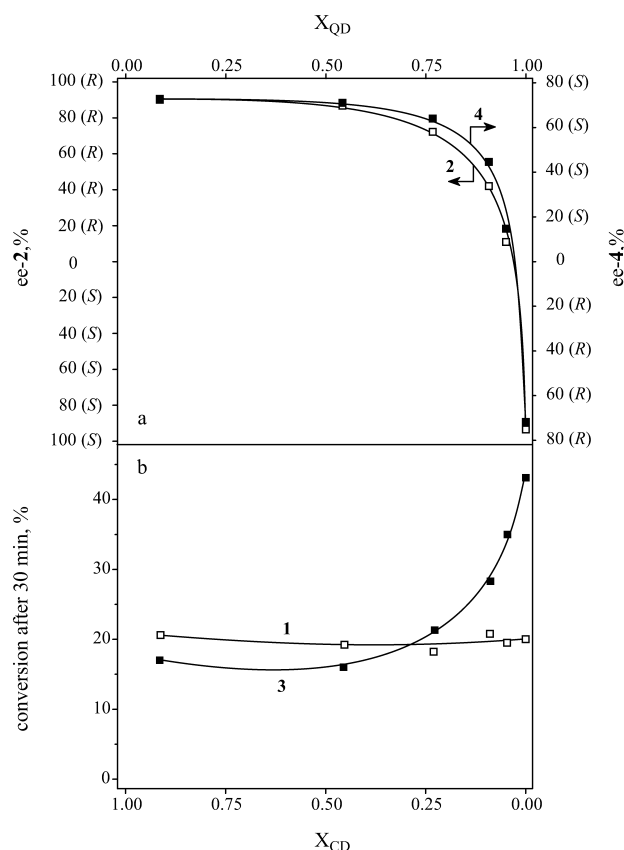
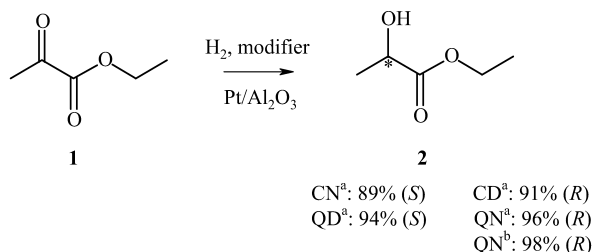


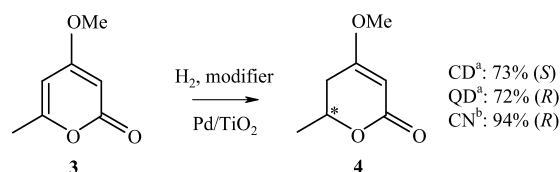
Figure 2. Influence of change in composition of a binary modifier mixture (CD-QD) on the hydrogenation of **1** to **2** over $\text{Pt}/\text{Al}_2\text{O}_3$ (Scheme 1, method C), and **3** to **4** over Pd/TiO_2 (Scheme 2, method D). (a) Enantioselectivities to **2** and **4**; (b) conversion of **1** and **3** after 30 min reaction time.



Scheme 1. Hydrogenation of ethyl pyruvate (**1**) to ethyl lactate (**2**) over cinchona-modified 5 wt % $\text{Pt}/\text{Al}_2\text{O}_3$. a: method A (1 bar); b: method B (5 bar).

on different reaction rates can be ruled out, as the conversion was almost independent of the alkaloid composition (Figure 2b).

The non-linear behavior was slightly more pronounced in the hydrogenation of **3** to the corresponding dihydropyrone **4** over 5 wt % Pd/TiO_2 (Scheme 2 and Figure 2a). Again, CD controlled the enantiodifferentiation in the presence of CD-QD mixtures though the two alkaloids alone afforded very similar ees to the opposite enantiomers. The observed non-linear behav-



Scheme 2. Partial hydrogenation of a 4-methoxy-6-methyl-2-pyrone (**3**) over cinchona-modified 5 wt % Pd/TiO_2 . a: method D; b: optimized value.^[23]

ior is even more impressive when the reaction rates are also considered: in the presence of QD alone the rate was 2.5 times faster than the rate of hydrogenation with CD as the sole modifier of Pd (Figure 2b). Clearly, the dominance of CD in enantioselection cannot be assigned to kinetic effects.

Let us assume an ideal case where (i) the two modifiers adsorb on the metal surface with the same adsorption free energy, (ii) they do not interact with each other in solution or on the metal surface, and (iii) both modifiers catalyze the enantioselective hydrogenation of the reactant with the same rate and ee that are characteristic for each modifier when they are used alone. For this ideal case an expected ee can be calculated based on the linear combination of specific rates and ees determined independently. When the measured ee deviates considerably from the calculated value, this is an indication that the above assumptions are not valid for that case. This situation is termed here as “non-linear behavior”.

Wells and coworkers^[28] have already observed small deviations from the expected linear correlation in the hydrogenation of **1** using mixtures of the diastereomers CD and CN, or QN and QD. They attributed the deviations between the observed and calculated ees to differences in the adsorption strength of the alkaloids. Tungler et al.^[29] compared the efficiency of vinca and cinchona alkaloid mixtures in the Pt-catalyzed hydrogenation of **1** and the Pd-catalyzed hydrogenation of isophorone. The strong non-linear behavior in the second reaction is particularly interesting as either the vinca or the cinchona alkaloid controlled the stereochemical outcome of the reaction, depending on the catalyst applied (Pd or Pd/C). This is a clear indication for the crucial importance of adsorption on the metal surface. Note that when modifying Pd by a vinca or a cinchona alkaloid, not only the adsorption strength and thus their surface concentration may differ, but also the nature of reactant-modifier interaction may be different,^[30] which is not the case for mixtures of cinchona alkaloids.^[31] Recently, we have found a considerable non-linearity in the hydrogenation of **1** using mixtures of CN and a synthetic modifier (R)-NPE (1-[1-naphthyl]-2-[pyrrolidin-1-yl]ethanol).^[32] Deviation from the expected linear correlation was rationalized by rapid saturation of the naphthyl rings of NPE in the early

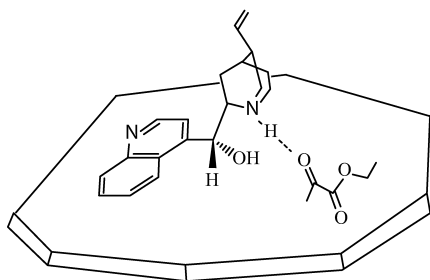


Figure 3. Schematic representation of CD-1 interaction over an ideally flat Pt surface in the enantiodifferentiating step.^[31] The π -bonded quinoline rings of CD and the two carbonyl groups of **1** lie approximately parallel to Pt; the quinuclidine part is above the surface.

stage of the reaction, resulting in a weak adsorption and replacement of saturated NPE by the more stable and strongly adsorbing cinchona alkaloid.

An explanation for the non-linear behavior shown in Figure 2, which would be based on the different resistance of the alkaloids against hydrogenation, can be excluded. In a control experiment we repeated the hydrogenation on Pt/ Al_2O_3 in the absence of **1** and in the presence of CD or QD alone (method A with half amount of alkaloid). A complete conversion of the quinoline moiety was observed by UV-Vis and NMR analysis after about 45 min for both alkaloids. Saturation of the vinyl groups was much faster but this transformation barely influences the enantioselectivity.^[33,34]

Preliminary studies of the adsorption of CD and QD on Pt/ Al_2O_3 by UV-Vis analysis indicated that CD adsorbs stronger on Pt by a factor of approximately 2–2.5, though this value is distorted by the slow hydrogenation of the alkaloids during the *in situ* adsorption study. At first sight, the relatively small difference in adsorption strength cannot account for the striking non-linearity shown in Figure 2. To find a feasible explanation we have to consider the possible adsorption modes of substrate and modifier on the metal surface and their interaction during hydrogen uptake. According to the mechanistic models, developed for the hydrogenation of **1** over Pt by Wells et al.^[35] and our group,^[31,36] the cinchona alkaloid adsorbs *via* the quinoline rings lying parallel to the Pt surface (π -bonded “anchoring moiety”). The substrate **1** adsorbs also flat *via* the C=O bonds parallel to the Pt surface (Figure 3). In this position the quinuclidine N-atom interacts with the carbonyl O-atom of **1** *via* an H-bond. In AcOH this interaction corresponds to the **1**-protonated CD interaction,^[37] in apolar medium the complex resembles the half-hydrogenated state of **1**.^[35]

At least three differently adsorbed species could be identified by *in situ* ATR-studies of CD adsorption on platinum:

- (i) a π -bonded species adsorbed via the aromatic rings nearly parallel to the metal surface (schematically shown in Figure 3),
- (ii) an N-lone pair-bonded species in which the aromatic rings are tilted relative to the Pt surface, and
- (iii) a species where the aromatic rings are tilted relative to the surface and the hydrogen atom in α -position to the quinoline N has been abstracted (α -quinolyl-like).^[38,39]

The strongly adsorbed π -bonded species (Figure 3) was inferred to be the crucial species for catalysis, in agreement with the previous model suggestions. The two tilted species adsorb more weakly and are considered as spectator species since they are not involved in the enantiodifferentiating step. We assume that upon applying CD-QD mixtures CD will dominantly adopt the adsorption mode with the quinoline rings lying nearly parallel to Pt, while the weaker adsorbing QD will prevalently adsorb as a tilted species. This arrangement minimizes the overall adsorption free energy and allows the control of enantiodifferentiation by the stronger adsorbing alkaloid, CD.

Compared to adsorption on Pt, CD is more weakly bound on Pd under hydrogenation conditions, as evidenced very recently by a comparative ATR-IR study of CD adsorption on both metals.^[40] Also, the relative stability of the π - and N-lone pair-bonded species is different for the two metals, with the π -bonded species being relatively more stable on Pt. The weaker adsorption of CD in the π -bonded mode on Pd than on Pt may explain why typically a higher modifier to reactant ratio is needed in Pd-catalyzed enantioselective hydrogenations to minimize the faster non-modified reaction.^[21–23,41] As concerns the mechanism of the hydrogenation of **3** (Scheme 2), we assume that in the enantiodifferentiating step the cinchona alkaloid and **3** adsorb *via* π -bonding of the aromatic rings approximately parallel to the Pd surface, but the real nature of substrate-modifier interaction(s) is not clarified yet.^[23,42]

Beside the different adsorption strength of cinchona alkaloids, a further point to be addressed is the various electronic and steric effects among the adsorbed species. An illustration to the importance of these interactions is shown in Figure 4. Hydrogenation of **3** over Pd/ TiO_2 was carried out with CD-CN mixtures. Only small deviations related to the calculated ee were observed and, interestingly, in this reaction CN dominated in the mixture. The “expected” ee was calculated assuming that the molar ratios of alkaloids in solution and on the Pd surface are identical, and the reaction rates and ees are linear combinations of those measured with CD or CN alone. In fact, a minimum in rate was observed in the reactions where alkaloid mixtures were applied. A plausible explanation may be that mixtures of CD and CN occupy more surface Pd sites than any of them alone and this effect reduces the overall reaction rate. Besides,

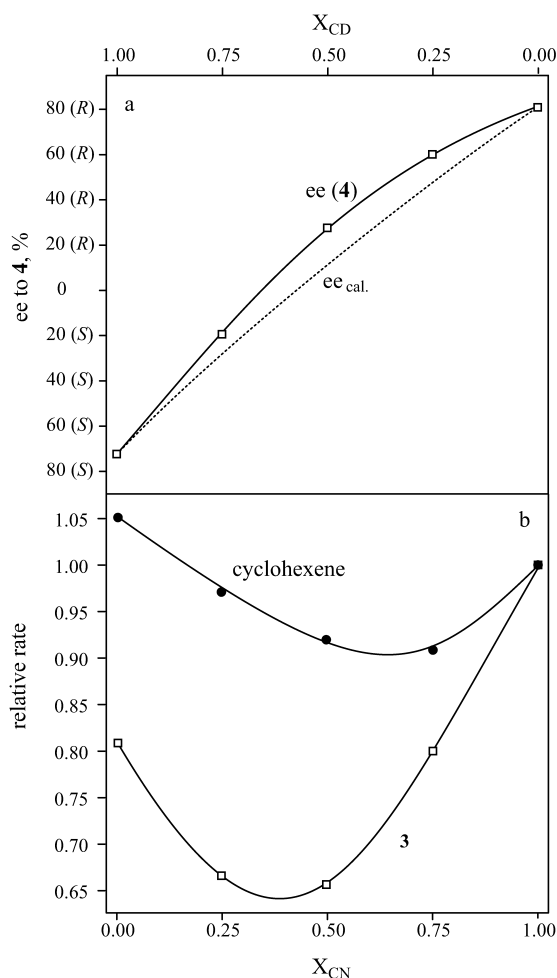


Figure 4. Hydrogenation of 4-methoxy-6-methyl-2-pyrone (**3**) and cyclohexene (**5**) over Pd/TiO₂ in the presence of CD-CN mixtures. (a): calculated (based on linear combination) and measured enantioselectivity in the hydrogenation of **3**; (b): relative rate of substrate conversion in the hydrogenation of **3** (method D) and **5** (method E), related to the rate with CN alone.

the modifier-modifier interactions may also affect the substrate-modifier interaction and thus the ee. To support this hypothesis we repeated the reactions and replaced **3** by cyclohexene (**5**, Figure 4b). In contrast to the enantioselective hydrogenation of **3**, no special alkaloid-substrate interaction is expected in the hydrogenation of **5**. The effect of using alkaloid mixtures on the relative rate was smaller but a clear minimum was observed at intermediate alkaloid concentrations. This is a confirmation for the assumption that mixtures of the two diastereomers CD and CN adsorb differently on Pd than the diastereomers alone.

A practically useful consequence of the present study is that the different adsorption strength of cinchona alkaloids has to be taken into account when selecting the appropriate conditions for the reaction. For example, in the hydrogenation of **1** under high pressure conditions

(70–100 bar) CD afforded the highest ee of 97.5%.^[13,14] The likely explanation is that among the cinchona alkaloids CD adsorbs strongest and can best compete with hydrogen for the surface Pt sites. Repeating the hydrogenation at different pressures with all four alkaloids (Scheme 1) we found that by lowering the hydrogen pressure the efficiency of CD decreased, whereas that of QD and QN increased. At 5 bar QN afforded 98% ee to (*R*)-**2** and at 1 bar 96% (Scheme 1). At atmospheric pressure even QD is more effective than CD (94% vs. 91% ee) – an interesting fact that has been overlooked as yet.

Another consequence of the observed non-linearity is that due care is necessary when applying cinchona derivatives as chiral modifiers. If traces of the unreacted alkaloid are still present and they adsorb stronger than the derivative, this impurity may distort the ee and lead to incorrect mechanistic conclusions. For the same reason, interpretation of high-throughput catalyst screening experiments may be flawed when several modifiers are applied simultaneously, as the adsorption strength on the metal may differ considerably.

Finally, we have to emphasize the differences between the classical non-linear effect (NLE) thoroughly investigated by Kagan and others^[25–27] in homogeneous asymmetric catalysis and the non-linearity discussed here. The asymmetric amplification or depletion in homogeneous catalysis is attributed to molecular interactions (associations) between two enantiomers of the auxiliary or ligand. In contrast, we assume that in heterogeneous catalysis the non-linear behavior of modifier mixtures (i.e., diastereomers or even chemically different compounds) is mainly due to differences in the strength and geometry of their adsorption on Pt or Pd.

Conclusions

Different adsorption strength and adsorption mode (geometry) of chiral modifiers may lead to strong non-linear behavior in heterogeneous asymmetric hydrogenations that are relevant from both synthetic and mechanistic points of view. CD is considered as the most effective chiral modifier for Pt, and also for Pd in several reactions. However, our study revealed that QN and QD might outperform CD when their weaker adsorption on the metal surface is taken into account by an appropriate selection of reaction conditions.

Experimental Section

Materials

The commercially available cinchona alkaloids contained high amounts of impurities: CD (Fluka, 92%; impurities: 1% QN,

7% QD, determined by HPLC at Fluka), CN (Fluka, 85%; impurity: 15% 10,11-dihydro-CN, determined by HPLC at Fluka), QD (Fluka, >90%; impurity: <10% 10,11-dihydro-QD, determined by HPLC at Fluka), and QN (Fluka, >95%; impurity: <5% 10,11-dihydro-QN, determined by HPLC at Fluka). Ethyl pyruvate (Fluka) was distilled before use. 4-Methoxy-6-methyl-2-pyrone **3** was synthesized as described earlier^[43] and purified by sublimation in vacuum (410 K, 0.1 mbar), followed by double recrystallization from hexane.

The 5 wt % Pt/Al₂O₃ catalyst (Engelhardt 4759) was treated with flowing H₂ for 60 min at 400 °C and cooled to room temperature in H₂ for 30 min. After flushing with Ar, the catalyst was transferred to the reactor within 10 min. A 5 wt % Pd/TiO₂ was prepared by precipitation of Pd hydroxide onto suspended TiO₂.^[44] Small portions of the dry catalyst were reduced in an H₂ flow at room temperature for 30 min and stored in air until use.

Catalytic Hydrogenations

The reactions were carried out in a magnetically stirred 100 mL glass reactor. A magnetically stirred stainless steel autoclave equipped with a 100 mL glass liner and a PTFE cap was used for the high-pressure experiments. In a standard procedure, the catalyst was prereduced in the solvent in flowing H₂ for 5 min, at 1 bar and room temperature. Then the modifiers were added in 1 mL solvent. After 5 min preadsorption the reaction was started by introducing the reactant.

Method A: 0.5 mL (4.1 mmol) **1**, 20 mg 5 wt % Pt/Al₂O₃, 3.4 μmol alkaloid or alkaloid mixture, 10 mL AcOH, 1 bar, 25 °C.

Method B: As method A but at 5 bar and 15 °C.

Method C: As method A but with 2 mL (16.5 mmol) **1**.

Method D: 50 mg (0.35 mmol) **3**, 20 mg 5 wt % Pd/TiO₂, 10 mL 2-propanol, 3.4 μmol alkaloid or alkaloid mixture, 25 °C, 1 bar.

Method E: As method D but with 1.2 mmol cyclohexene (**5**). Conversion and enantioselectivity were determined by an HP 6890 gas chromatograph using a Chirasil-DEX CB column (Chrompack). An HP-5 column was applied for the analysis of cyclohexene/cyclohexane mixtures.

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References

- [1] Y. Orito, S. Imai, S. Niwa, *J. Chem. Soc. Jpn.* **1979**, 1118–1120.
- [2] Y. Izumi, *Adv. Catal.* **1983**, 32, 215–271.
- [3] A. Tai, T. Harada, in *Tailored Metal Catalysts*, (Ed.: Y. Iwasawa), D. Reidel, Dordrecht, **1986**.
- [4] A. Baiker, *J. Mol. Catal. A: Chem.* **1997**, 115, 473–493.
- [5] H.-U. Blaser, H. P. Jalett, M. Müller, M. Studer, *Catal. Today* **1997**, 37, 441–463.
- [6] A. Pfaltz, T. Heinz, *Top. Catal.* **1997**, 4, 229–239.
- [7] P. B. Wells, A. G. Wilkinson, *Top. Catal.* **1998**, 5, 39–50.
- [8] T. Sugimura, *T. Catal. Surv. Jpn.* **1999**, 3, 37–42.
- [9] T. Osawa, T. Harada, O. Takayasu, *Top. Catal.* **2000**, 13, 155–168.
- [10] A. Tungler, G. Fogassy, *J. Mol. Catal. A* **2001**, 173, 231–247.
- [11] M. von Arx, T. Mallat, A. Baiker, *Topics Catal.* **2002**, 19, 75–87.
- [12] G.-Z. Wang, T. Mallat, A. Baiker, *Tetrahedron: Asymmetry* **1997**, 8, 2133–2140.
- [13] X. Zuo, H. Liu, M. Liu, M. *Tetrahedron Lett.* **1998**, 39, 1941–1944.
- [14] B. Török, K. Felföldi, G. Szakonyi, K. Balázsik, M. Bartók, *Catal. Lett.* **1998**, 52, 81–84.
- [15] M. Schürch, N. Künzle, T. Mallat, A. Baiker, *J. Catal.* **1998**, 176, 569–571.
- [16] N. Künzle, A. Szabo, M. Schürch, G. Z. Wang, T. Mallat, A. Baiker, *Chem. Commun.* **1998**, 1377–1378.
- [17] M. Studer, S. Burkhardt, H.-U. Blaser, *Chem. Commun.* **1999**, 1727–1728.
- [18] B. Török, K. Felföldi, K. Balázsik, M. Bartók, *Chem. Commun.* **1999**, 1725–1726.
- [19] M. von Arx, T. Mallat, A. Baiker, *Tetrahedron: Asymmetry* **2001**, 12, 3089–3094.
- [20] M. von Arx, T. Mallat, A. Baiker, *Catalysis Lett.* **2002**, 78, 267–271.
- [21] Y. Nitta, K. Kobiro, K. *Chem. Lett.* **1996**, 897–898.
- [22] K. Borszeczy, T. Mallat, A. Baiker, *Tetrahedron: Asymmetry* **1997**, 8, 3745–3753.
- [23] W. R. Huck, T. Mallat, A. Baiker, *New J. Chem.* **2002**, 26, 6–8.
- [24] M. Sutyinszki, K. Szöri, K. Felföldi, M. Bartók, M. *Catal. Commun.* **2002**, 3, 125–127.
- [25] D. Guillaneux, S. H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, 116, 9430–9439.
- [26] M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez, J. C. Palacios, *Tetrahedron: Asymmetry* **1997**, 8, 2997–3017.
- [27] C. Girard, H. B. Kagan, *Angew. Chem.-Int. Edit.* **1998**, 37, 2923–2959.
- [28] K. E. Simons, P. A. Meheux, A. Ibbotson, P. B. Wells, *Stud. Surf. Sci. Catal.* **1993**, 75, 2317–2320.
- [29] A. Tungler, K. Fodor, T. Máthé, R. A. Sheldon, *Stud. Surf. Sci. Catal.* **1997**, 108, 157–165.
- [30] A. Tungler, Y. Nitta, K. Fodor, G. Farkas, T. Máthé, *J. Mol. Catal. A* **1999**, 149, 135–140.
- [31] A. Baiker, *J. Mol. Catal. A* **2000**, 163, 205–220.
- [32] M. Schürch, T. Heinz, R. Aeschimann, T. Mallat, A. Pfaltz, A. Baiker, *J. Catal.* **1998**, 173, 187–195.
- [33] H.-U. Blaser, H. P. Jalett, D. M. Monti, A. Baiker, J. T. Wehrli, *Stud. Surf. Sci. Catal.* **1991**, 67, 147–155.
- [34] M. Bartók, G. Szöllösi, K. Balázsik, T. Bartók, *J. Mol. Catal. A* **2002**, 177, 299–305.
- [35] K. E. Simons, P. A. Meheux, S. P. Griffiths, I. M. Sutherland, P. Johnston, P. B. Wells, A. F. Carley, M. K. Rajumon, M. W. Roberts, A. Ibbotson, *Recl. Trav. Chim. Pays-Bas* **1994**, 113, 465–474.
- [36] O. Schwalm, J. Weber, J. Margitfalvi, A. Baiker, *J. Mol. Structr.* **1993**, 297, 285–293.

- [37] O. Schwalm, B. Minder, J. Weber, A. Baiker, *Catal. Lett.* **1994**, 23, 271–279.
- [38] D. Ferri, T. Bürgi, A. Baiker, *Chem. Commun.* **2001**, 1172–1173.
- [39] D. Ferri, T. Bürgi, *J. Am. Chem. Soc.* **2001**, 123, 12074–12084.
- [40] D. Ferri, T. Bürgi, A. Baiker, *J. Catal.* **2002**, 210, 160–170.
- [41] T. Tarnai, A. Tungler, T. Mathe, J. Petro, R. A. Sheldon, G. Toth, *G. J. Mol. Catal. A.* **1995**, 102, 41–47.
- [42] W.-R. Huck, T. Mallat, A. Baiker, *A. Catal. Lett.* **2002**, 87–92.
- [43] P. De March, M. Morena-Mañas, R. Pi, I. Ripoll, F. Sánchez-Ferrando, *J. Heterocyclic. Chem.* **1985**, 22, 1537–1542.
- [44] W. R. Huck, T. Bürgi, T. Mallat, A. Baiker, *J. Catal.* **2001**, 200, 171–180.
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