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Planar−Chiral Ferrocenes in Asymmetric Catalysis: The Impact of Stereochemically Inhomogeneous Ligands

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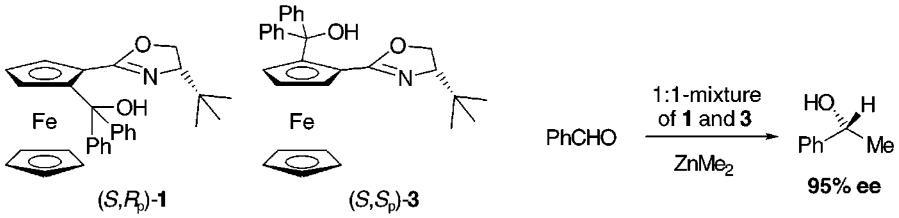
ABSTRACT

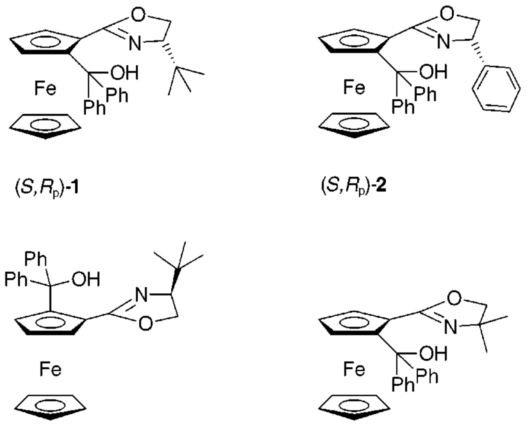


(S,R_p)-**1** (S,S_p)-**3**

The catalytic properties of stereochemically inhomogeneous mixtures of chiral ferrocenes in dimethylzinc additions to benzaldehyde have been investigated. With planar chiral ferrocene (R_p)-4 a linear correlation between the enantiomeric excess of the ferrocene and that of the product was found. In contrast, a significant departure from linearity was revealed when mixtures of diastereomeric ferrocenes (S,R_p)-1 and (S,S_p)-3 were employed. Thus, even in the reaction with a catalyst obtained from a 1:1 ratio of diastereomers 1 and 3, formation of a product with an enantioselectivity of 95% ee was achieved.

The stereoselective synthesis of planar−chiral ferrocenes and their use in asymmetric catalysis has been well-established over the past years.[1] In 1995, Sammakia, Richards, and Uemura independently reported the preparation of enantiopure 2-ferrocenyloxazolines and their diastereoselective *ortho* functionalization.[2−5] Subsequently, the resulting ferrocenes were used as chiral ligands in a series of metal-catalyzed processes.[6−11] Within this context, we have recently reported the synthesis of ferrocenyl hydroxyloxazolines **1**−**4** (Figure 1).[12−14]

Studies on the application of these ferrocenes led to a comprehensive investigation[13] of the role of planar chirality in diethylzinc additions to aldehydes.[15] Furthermore, in the addition to benzaldehyde (**5**), we found no deviation from



(S,R_p)-**1** (S,R_p)-**2**

(S,S_p)-**3** (R_p)-**4**

Figure 1. Planar chiral ferrocenes.

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(3) (a) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, 74. (b) Richards, C. J.; Mulvaney, A. W. *Tetrahedron: Asymmetry* **1996**, *7*, 1419.

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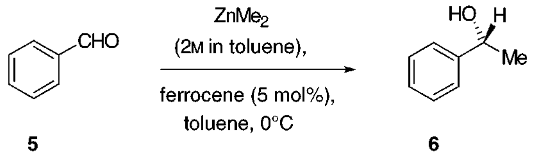
Scheme 1



linearity (nonlinear effect, NLE[16]) between the enantiomeric excesses of the ferrocene and the product alcohol[13] by using mixtures of enantiomers of **2**, which is a ferrocene with both a stereogenic center and a plane of chirality. The same linear relationship was now revealed in catalyzed additions of dimethylzinc to benzaldehyde in the presence of ferrocene (R_p)-**4** which displays planar chirality only (Scheme 1, Figure 2).

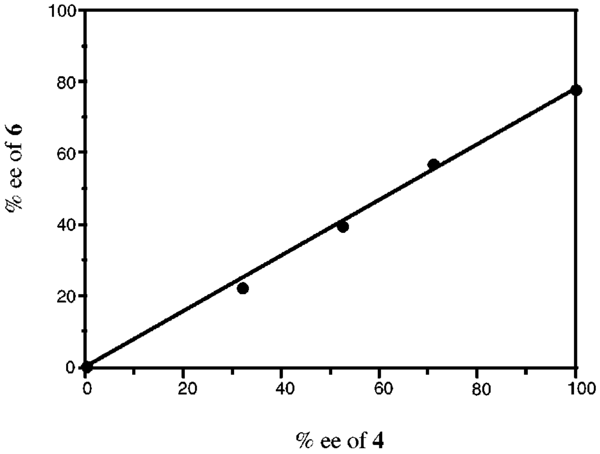


Figure 2.

In both of these amplification studies, nonequal mixtures of *enantiomeric* ferrocenes were employed, and we now wondered about the catalytic properties of mixtures of *diastereomeric* ferrocenes. These results are of particular interest in cases where the initial *ortho* functionalization, which is used in the synthesis of ferrocene ligands such as **1**, does not occur in a highly stereoselective manner. A mixture of diastereomers is then obtained, and a separation is required to isolate each diastereomeric product in stereochemically homogeneous form. However, if these mixtures of diastereomers themselves could efficiently be used in the catalysis, this additional separation step would become unnecessary and the overall process would be simplified.

Table 1. Data for the Asymmetric Methylation of Benzaldehyde (**5**) To Give **6** in the Presence of 5 mol % of Mixtures of **1** and **3**

entry	ratio **1**:**3**[a]	reaction time (h)	yield of **6** (%)[b]	ee of **6** (%)[c]
1	100:0	6	99	97
2	88:12	12	99	96
3	67:33	12	97	95
4	50:50	12	98	94
5	43:57	14	89	91
6	35:65	11	69	90
7	26:74	13	74	88
8	13:87	15	71	79
9	6:94	12	36	20
10	2:98	12	22	−32
11	0:100	14	17	−50

[a] Determined by ^{1}H NMR. [b] After column chromatography. [c] Determined by HPLC using a Chiralcel OD column.

We therefore decided to study the intentional application of non-diastereomerically pure planar−chiral ligands in asymmetric catalysis using nonequal mixtures of diastereomeric ferrocenes **1** and **3** in enantioselective dimethylzinc additions to benzaldehyde (**5**) as model system. The results for catalyses with 5 mol % of ferrocenes are given in Table 1 and are depicted as graphical representation in Figure 3.

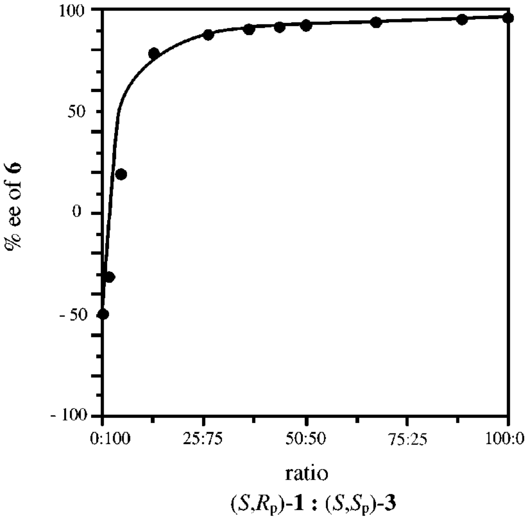


Figure 3.

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(4) (a) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79. (b) Nishibayashi, Y.; Segawa, K.; Arikawa, Y.; Ohe, K.; Hidai, M.; Uemura, S. *J. Organomet. Chem.* **1997**, *545−546*, 381.

(5) See also: Ahn, K. H.; Cho, C.-W.; Baek, H.-H.; Park, J.; Lee, S. *J. Org. Chem.* **1996**, *61*, 4937.

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(7) Transfer hydrogenation: (a) Sammakia, T.; Stangeland, E. L. *J. Org. Chem.* **1997**, *62*, 6104. (b) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1998**, *17*, 3420. (c) Arikawa, Y.; Ueoka, M.; Matoba, K.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Organomet. Chem.* **1999**, *572*, 163.

(8) Allylic substitution: (a) Ahn, K. H.; Cho, C.-W.; Park, J.; Lee, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1179. (b) Ahn, K. H.; Cho, C.-W.; Park, J.; Lee, S. *Bull. Korean Chem. Soc.* **1997**, *18*, 789. (c) For the importance of planar chirality in this reaction, see: You, S.-L.; Zhou, Y.-G.; Dai, L.-X. *Chem. Commun.* **1998**, 2765.

(9) Michael addition: Stangeland, E. L.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16503.

(10) Grignard cross-coupling: Richards, C. J.; Hibbs, D. E.; Hursthouse, M. B. *Tetrahedron Lett.* **1995**, *36*, 3745.

(11) Asymmetric rearrangement of allylic imidates: Donde, Y.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933.

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A very pronounced nonlinear relationship between the ee of product **6** and the de of the ferrocene—adjusted by mixing of appropriate amounts of (S,R_p)-**1** and (S,S_p)-**3**—was observed. The highest enantiomeric excess for **6** was obtained in a catalysis with diastereomerically pure (S,R_p)-**1** (Table 1, entry 1). Interestingly however, decreasing the de of the ferrocene had only a minor impact on the ee of the product. Thus, even with a 1:1 mixture of diastereomeric ferrocenes (S,R_p)-**1** and (S,S_p)-**3** (entry 4), the enantiomeric excess of **6** was still 94%. Moreover, with an increased catalyst loading of 10 mol %, complete conversion of **5** was observed and product **6** had 96% ee!

Since we found no indication for the formation of higher aggregates in catalyses with ferrocenes **2** and **4** and since the rate of the methyl transfer was almost independent of the composition of the ligand mixture (entries 1−8), we conclude that the present nonlinear effect (NLE) is *not* a consequence of the formation of catalytically inactive aggregates.[17,18] Instead, we understand that it is a result of drastically different rates[19] of the two diastereomeric catalysts derived from **1** and **3**.

This assumption is also substantiated by the observation that reactions with ferrocene mixtures in which **3** is the major component give product **6** of *R* configuration (entries 5−9). In contrast, *S*-configurated **6** is obtained with diastereomerically pure ferrocene **3** (entry 11).

It is noteworthy that in a related investigation, Noyori observed significantly different selectivity profiles when diastereomeric isoborneol-based amino alcohols such as DAIB were used in the asymmetric addition of diethylzinc to benzaldehyde.[20] In this case, due to the high reactivity of each diastereomeric catalyst and the existence of heterochiral aggregates the nonlinear behavior was completely dominated by the stereoisomer in excess. In addition, use of equimolar mixtures of diastereomeric DAIBs with opposite chirality led to a significant decrease in reaction rate.

To the best of our knowledge, there is only one other example of a NLE based on the use of catalysts with two kinetically competing nonenantiomeric ligands. In 1995, Kagan described osmium-catalyzed AD reactions in the presence of cinchona alkaloid mixtures.[21] A strong nonlinear relationship between the ee of the product and the (formal) de of the ligand was revealed. In this case, however, the ligands did not have a diastereomeric relationship, but instead they were distinctly different in structure.[22]

In summary, we have shown that asymmetric catalysis does not necessarily require the use of diastereomerically pure ligands for achieving high enantioselectivities. If the diastereomeric catalysts operate on significantly different rates, even a ligand with a small de can give a product with high ee. This principle could be of general preparative importance in those cases where no complete stereoselectivity in a ligand functionalization process is feasible.[4b,6,23] In the present context, it is important to realize that the diastereomeric mixture of **1** and **3** formally represents the product of an *unselective ortho* functionalization of a chiral 2-ferrocenyloxazoline. Thus, even if this functionalization process was not stereoselective, the resulting diastereomeric mixture as such could also be highly useful in enantioselective catalysis.

Acknowledgment. We are grateful to the Deutsche Forschungsgemeinschaft (DFG) within the Collaborative Research Center (SFB) 380 “Asymmetric Synthesis by Chemical and Biological Methods” and the Fonds der Chemischen Industrie for financial support. We thank Dr. K. Günther at DEGUSSA-HÜLS AG, Hanau/Germany, for preparative HPLC separation of ferrocene **4** and J. Rudolph for assistance with the preparation of the graphical figures.

Supporting Information Available: General procedures for dimethylzinc addition to benzaldehyde, results of catalyses as detailed in Figure 2, HPLC separation conditions for ferrocene **4**, and spectral reproduction of a mixture of diastereomeric ferrocenes **1** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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