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A Versatile Modular Approach to New Chiral C_2-Symmetrical Ferrocenyl Ligands: Highly Enantioselective Rh-Catalyzed Hydrogenation of α-Acetamidoacrylic Acid Derivatives[1]

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Abstract

An easy, efficient, flexible modular synthesis of a new family of chiral C_2-symmetrical ferrocenyl diphosphines (FERRIPHOS) is described. These new ligands gave high enantioselectivities (up to 99.4 % *ee*) in the rhodium-catalyzed hydrogenation of different enamide derivatives.
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The increasing importance of transition metal-catalyzed enantioselective reactions has run parallel to the development of new ligands. Diphosphine ligands have been widely used for this purpose. Since the first catalytic asymmetric hydrogenation using a Wilkinson-type complex[1] by Horner[2] and Knowles[3], various chiral bidentate diphosphine ligands, some of them with C_2-symmetry (DIOP[4], DIPAMP[5], CHIRAPHOS[6], BINAP[7], DUPHOS[8], [2.2]PHANEPHOS[9]), others with only C_1-symmetry (BPPFA[10], BPPM[11], JOSIPHOS[12]), have been applied with success to several asymmetric metal-catalyzed reactions. The search for new chiral ligands readily obtained by a modular approach is still an important goal in asymmetric catalysis.

C_2-Symmetrical diphosphine ligands are a specially interesting class of ligands because the limited number of possible transition states in the asymmetric catalytic reactions. Among the various backbones that can be used, those with a ferrocene unit are very versatile because they can be easily modelled to fulfill a better interaction with the substrates[13]. There are few examples of C_2-symmetrical ferrocenes with only planar chirality[14] or with planar and central chirality[15] due to the difficulty of their synthesis. Recently we have developed an easy, flexible preparation of a wide spectrum of C_2-symmetrical ferrocenyl derivatives[16].

[1] Presented as part of a lecture at the PPG-SIPSY 2nd Symposium on "New Frontiers in Asymmetric Synthesis": Nice, June 22th, 1998. A patent for the use in asymmetric hydrogenation of the FERRIPHOS ligands has already been filled together with Degussa AG.

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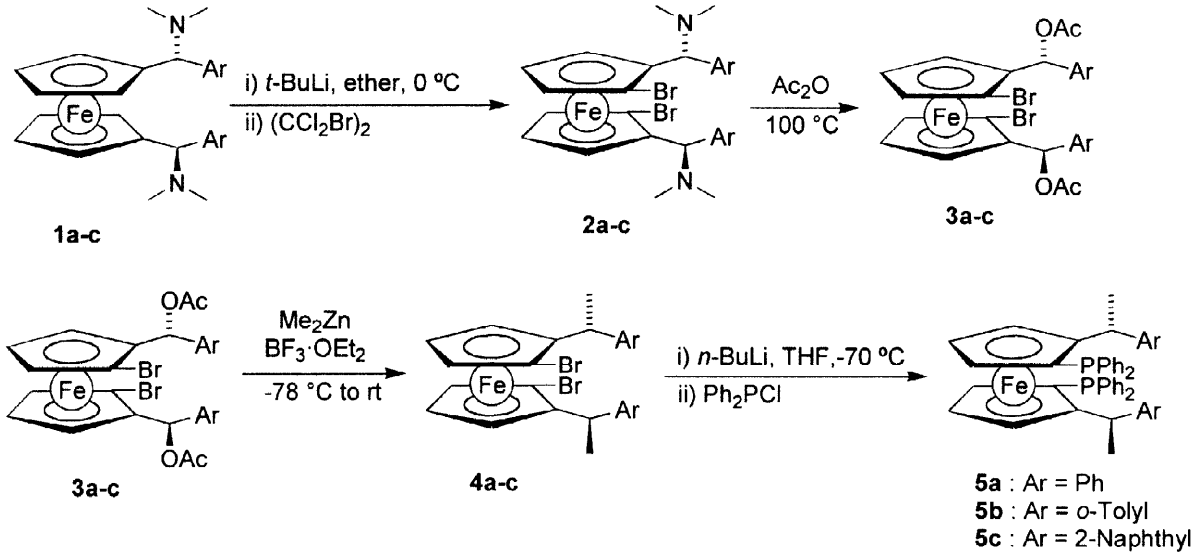
Prompted by the publication of related work[14b], we describe here the application of our previous findings to the synthesis of new C_2-symmetrical ferrocenyl diphosphines.

Dilithiation of ferrocenyl diamines **1a-c**[16c][2] with *t*-BuLi in diethyl ether (0 °C, 0.5 h) and quenching with $(CCl_2Br)_2$ furnished the corresponding C_2-symmetrical diaminodibromo ferrocenes **2a-c**[3] as single diastereoisomers (no other diastereoisomer was detected by NMR analysis)[17] in 80, 52 and 43 % yield respectively. After treatment of compounds **2a-c** with Ac_2O (100 °C, 2 h)[18], diacetates **3a-c**[4] were isolated in quantitative yield. Reaction of diacetates **3a-c** with 3 equivalents of Me_2Zn in the presence of $BF_3{\cdot}OEt_2$ (THF, -78 °C to rt, 1.5 h)[16b] yielded the desired dibromoferrocenes **4a-c**[5] in 94, 100 and 92 % yield as single diastereoisomers (> 99 % *ee*)[6]. Final bromine-lithium exchange (*n*-BuLi, THF, -78 °C, 0.25 h) followed by slow addition of Ph_2PCl afforded the corresponding C_2-symmetrical diphosphines **5a-c**[7] {named (*R*)-(*S*)-Arylethyl-FERRIPHOS[19]} in 68, 64 and 46 % yield, respectively (Scheme 1). These phosphines are all crystalline, air stable solids (no oxidation products were observed after 3 months of air exposure).

Scheme 1



To evaluate the efficiency of this new family of ligands, rhodium-catalyzed hydrogenation of α-acetamido cinnamic acid and its methyl ester were performed. The hydrogenation reaction proceeded under very mild conditions (0.1 MPa H_2; rt) in the presence of 1 mol% of the catalyst prepared *in situ* [1 mol% of $Rh(COD)_2BF_4$; 1 mol% ligand]. In all cases, the half-times were less than 2 minutes. The results obtained are summarized in Table 1.

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[2] **1b** : $[\alpha]_D^{23}$ =+120.1 (*c* 1.29, $CHCl_3$); mp 104-106°C.

[3] **2a** : $[\alpha]_D^{23}$ =+154.5 (*c* 0.88, $CHCl_3$). **2b** : $[\alpha]_D^{23}$ =+224.2 (*c* 0.78, $CHCl_3$); mp 169-171°C. **2c** : $[\alpha]_D^{23}$ =-49.6 (*c* 0.74, $CHCl_3$); mp 147-148°C.

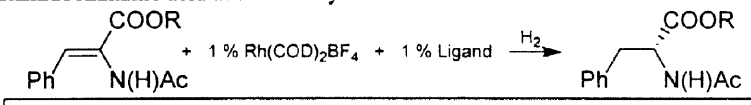
[4] **3a** : $[\alpha]_D^{23}$ =+83.2 (*c* 0.90, $CHCl_3$); mp 145-147°C. **3b** : $[\alpha]_D^{23}$ =+71.5 (*c* 0.92, $CHCl_3$); mp 143-144°C. **3c** : $[\alpha]_D^{23}$ =+55.6 (*c* 1.11, $CHCl_3$); mp 90-93°C.

[5] **4a** : $[\alpha]_D^{23}$ =+171.4 (*c* 1.10, $CHCl_3$). **4b** : $[\alpha]_D^{23}$ =+118.9 (*c* 0.73, $CHCl_3$); mp 76-78°C. **4c** : $[\alpha]_D^{23}$ =+86.5 (*c* 1.04, $CHCl_3$); mp 58-60°C.

[6] Determined by HPLC. A Chiralcel OD column (Daicel Chemical Industries) was used at 20 °C with *n*-heptane / 2-propanol 99.7 : 0.3 as mobile phase; flow 0.6 mL / min; detection by diode array UV-VIS detector at 254 nm.

[7] **5a** : $[\alpha]_D^{23}$ =-245.2 (*c* 0.40, $CHCl_3$); mp 181-182°C; ^{31}P NMR (162 MHz, $CDCl_3$, H_3PO_4 as external reference): -22.88. Anal. calcd. for $C_{50}H_{44}FeP_2$: C, 78.74; H, 5.81. Found: C, 78.47; H, 5.86. **5b** : $[\alpha]_D^{23}$ = -402.4 (*c* 0.67, $CHCl_3$); mp 164-166°C; ^{31}P NMR (162 MHz, $CDCl_3$, H_3PO_4 as external reference): -22.89. Anal. calcd. for $C_{52}H_{48}FeP_2$: C, 78.98; H, 6.12. Found: C, 78.74; H, 5.92. **5c** : $[\alpha]_D^{23}$ = -256.3 (*c* 0.54, $CHCl_3$); mp 208-210°C; ^{31}P NMR (162 MHz, $CDCl_3$, H_3PO_4 as external reference): -22.68. Anal. calcd. for $C_{58}H_{48}FeP_2$: C, 80.74; H, 5.61. Found: C, 80.33; H, 5.72.

Table 1
Hydrogenation of (*Z*)-α-acetamidocinnamic acid and its methyl ester.[a]



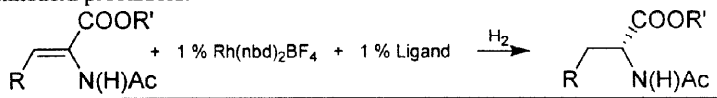
Entry	Ligand	R	ee (%)
1	**5a**	Me	98.6
2	**5a**	H	97.3
3	**5b**	Me	98.1
4	**5b**	H	97.6
5	**5c**	Me	98.6
6	**5c**	H	97.3

[a]Reaction conditions: 0.1 MPa H_2; 0.07 M solutions of substrates in MeOH. The half-times were in all cases less than 2 minutes. The enantiomeric excesses were determined by GC on chiral phases; 10 m x 0.2 mm fused silica; XE-60L-valin-*tert*-butylamine; oven temperature 150 °C. The hydrogenation product of (*Z*)-α-acetamidocinnamic acid was esterified with trimethylsilyldiazomethane before the GC measurements. The absolute stereochemistry was stablished by comparison with the literature reported values of the methyl esters and in all cases the *R* enantiomer was obtained.

Concerning the hydrogenation of the free acid, these results are better than other reported ee values for the same substrates {BINAP[7], 96 %; [2.2]PHANEPHOS[9], 98 %; BPPFA[10], 93 %; JOSIPHOS[12], 84 %}. The same remark can be made concerning the hydrogenation of the methyl ester {[2.2]PHANEPHOS[9], 83 % *ee*; BPPFA[10], 23 % *ee*; JOSIPHOS[12], 96 % *ee*}.

Good enantioselectivities are also obtained in the hydrogenation of other dehydroaminoacid derivatives under the same reaction conditions (Table 2).

Table 2
Hydrogenation of different aminoacid precursors.[a]



Entry	Ligand	R	R'	ee (%)
1[b]	**5a**	H	Me	97.9
2[b]	**5a**	H	H	98.0
3[c]	**5a**	Ph	Me	98.0
4[d]	**5a**	2-Naphthyl	Me	98.3
5[d]	**5a**	2-Naphthyl	H	98.2
6[b]	**5b**	H	Me	97.7
7[b]	**5b**	H	H	98.7
8[b]	**5c**	H	Me	98.4
9[b]	**5c**	H	H	98.3

[a]See footnote of Table 1 for general conditions. All the acids were esterified prior to the ee measures. [b]Enantiomeric excesses were determined by GC on chiral phases; 25 m x 0.2 mm fused silica WCOT; Chirasil-L-Val (0.12 μm); oven temperature 80 °C. [c]Reaction performed in the presence of 0.5 mol% of the in situ prepared catalyst. [d]Enantiomeric excesses were determined by HPLC. A Chiralcel OD column (Daicel Chemical Industries) was used at 30 °C with *n*-heptane / 2-propanol 9 : 1 as mobile phase; flow 0.6 mL / min; detection by diode array UV-VIS detector at 254 nm.

It is noteworthy to notice that due to the short reaction times (less than 5 minutes in all cases) the hydrogenation reactions can be performed at lower temperatures with a better enantiomeric excess. For example, reaction of entry 4, table 2 was performed at -14 °C in 5 minutes and the ester was isolated with 99.4 % ee.

In summary, we have applied our previous findings on the ferrocene chemistry to the synthesis of a wide family of C_2-symmetrical diphosphine ligands (the FERRIPHOS family) which are good ligands in the rhodium-catalyzed hydrogenation of both dehydroaminoacids

and dehydroaminoesters. Due to the high air-stability and to the fact that they can tolerate non degassed solvents (< 0.1 % H_2O) an industrial application is being planned by Degussa AG. Further extension to other transition-metal catalyzed reactions are in progress in our laboratory.

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[19] (*R*)-(*S*)-FERRIPHOS relates to a C_2-symmetrical diphenylphosphino ferrocene unit with planar chirality (*S*) and central chirality (*R*) at the 2,2'-carbon where the groups that precede to the word FERRIPHOS are attached.