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Asymmetric Synthesis of A New Cylindrically Chiral and Air-Stable Ferrocenyldiphosphine and Its Application to Rhodium-Catalyzed Asymmetric Hydrogenation

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Abstract

A novel, cylindrically chiral air-stable ferrocenyldiphosphine ligand has been synthesized and its rhodium complexes have been applied to asymmetric hydrogenation. High reactivity and selectivity have been realized in hydrogenation of various dehydroamino acid derivatives. © 1998 Elsevier Science Ltd. All rights reserved.

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Catalytic asymmetric synthesis is one of the most powerful and economically promising methods for the synthesis of enantiomerically enriched compounds.[1] Optically active diphosphines of various ingeniously designed topography[2] play a significant role as the chiral ligands in various transition metal-catalyzed asymmetric reactions and numerous chiral C_2-symmetric diphosphines have been designed and synthesized over the past three decades since the cornerstone preparation of DIOP by Kagan in 1971.[3] However, even though these alkyl-substituted phosphines are prone to be oxidized by air, relatively less attention has been paid to optically active air-stable triaryl-substituted diphosphines except for the cases of BINAP,[4a] BIPHEP[4b] and others,[1,2] which enjoyed a great deal of popularity as asymmetric ligands in asymmetric synthesis.

Even with such limitation, perhaps more compelling and intellectually fascinating to chemists are the shape and electronic aspects of the ligands. The air-stable ligands mentioned above are cleverly designed so that the axially chiral backbones of the arylene systems are used as scaffolds for the arrangement of the diphenylphosphinyl groups. While exceedingly high selectivity was obtained in many reactions employing the axially-chiral ligands,[1] there are a variety of reactions where these ligands are not very efficient in their activity and selectivity. Certainly, fine tuning is sometimes necessary for a given reaction, but we feel that introduction of higher symmetry by utilizing cylindrical chirality[5] may help selectivity if additional steps required for more elaboration are not unbearably troublesome.

We have designed a new cylindrically chiral, air-stable ferrocenylbis(phosphine), ($_p$S,$_p$S)-1,1'-bis(diphenylphosphino)-2,2'-di-3-pentylferrocene **1** (abbreviated as (S,S)-FerroPHOS, hereafter) which is expected to be an effective chiral ligand for several types of transition metal-catalyzed asymmetric reactions. Herein, we wish to report a practical preparation of our new chiral ligand and its application to rhodium(I)-catalyzed enantioselective hydrogenation of

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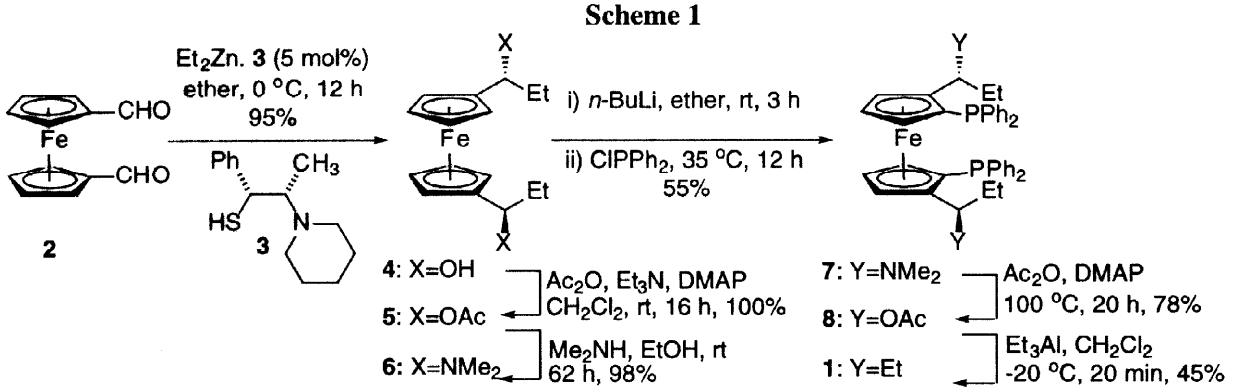
some dehydroamino acid derivatives.[6]

Slow addition of diethylzinc solution in toluene (2.0 equiv) to 1,1'-ferrocenedicarboxaldehyde **2**[7] in the presence of 5 mol% thiazazincolidine catalyst[8] derived from **3** provided the desired diol (R,R)-**4** in high yield and over 99.9% ee[9] with contamination of a small amount of the *meso*-diol (R,S)-**4** (1-2%) (**Scheme 1**) (*cf.* other possible routes[10]). The resulting diol (R,R)-**4** was subsequently transformed into the diamino diphosphine **7** in 3 high-yielding steps following the standard procedures[11]: The chiral diol **4** was acetylated (Ac_2O, Et_3N, DMAP) to the diacetate **5**, which, without isolation, was aminated with 50% aq dimethylamine in EtOH to furnish the desired bis(dimethylamino)ferrocene **6** in quantitative yield and also without loss of the original configurations.[11,12] Subsequent two-fold diastereoselective lithiation[12] of **6** with *n*-BuLi (2.5 equiv, 23 °C, 3 h) followed by slow addition of chlorodiphenylphosphine in THF afforded the bis(phosphine) compound **7** in 55% isolated yield, which was treated with acetic anhydride (20 equiv) and a catalytic amount of DMAP under oxygen-free condition to give the diacetate **8** in 78% yield.[11] This was followed by treatment with triethylaluminum (5 equiv)[13] to give the new cylindrically chiral and air-stable triaryl ferrocenyl ligand,[14] (S,S)-FerroPHOS (**1**), in 45% yield after recrystallization from hot EtOH.[15]

Scheme 1



The outstanding structural feature of our new ligand is the introduction of bulky alkyl groups (3-pentyl group) as a face-blocker on the planar chiral platform with bis(phosphine) moieties, which may be represented by a quadrant diagram devised by Knowles (Figure 1).[6b,16] Additionally, it should be noted that the triaryl-substituted bis(phosphine) **1** neither changed, nor did lose its reactivity and selectivity in hydrogenation even after long exposure to atmospheric condition: In a ^{31}P-NMR study, no detectable air-oxidation of **1** was observed even after a long exposure (3 weeks) to atmospheric environment.

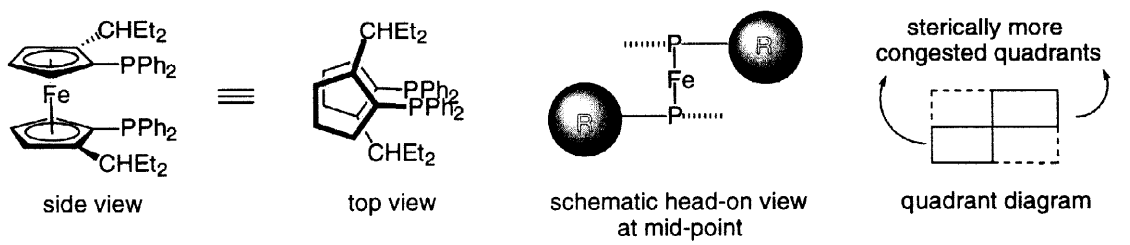


Figure 1. (S,S)-FerroPHOS (**1**)

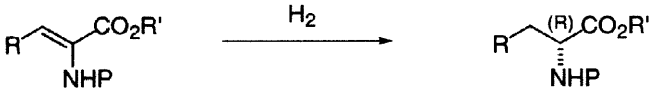
Rhodium(I)-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids and esters to produce the corresponding amino acid derivatives has been studied extensively due to its

application in commercial processes, a fact which is good for comparison for effectiveness of a new chiral ligand system. To this end, the catalytic efficiency and selectivity of our new ligand **1** was examined in enantioselective hydrogenation reaction of the dehydroamino acid derivatives.

In the first, asymmetric hydrogenation of α-acetamidocinnamic acid was employed in the presence of the catalyst prepared *in situ* from $[Rh(COD)_2]BF_4$ (1.0 mol%) and **1** (1.1 mol%) (**Table 1**). The hydrogenation reaction proceeded completely under mild condition (2 atm, 20-23 °C). The more active catalyst precursor $[(1)Rh(COD)]^+BF_4^-$ was prepared by treatment of **1** with $[Rh(COD)_2]BF_4$ to form an orange colored complex, it gave a slightly increased selectivity. At constant initial pressure (2 atm), reaction temperature (20-23 °C) and concentration (0.3 M), the choice of solvents varied the enantiomeric selectivities. The best selectivity (98.9% ee) was obtained, when EtOH was used as a solvent. But similar results were observed in other solvents such as THF and MeOH (97.5 and 97.7% ee, respectively).

These results with α-acetamidocinnamic acid compare favorably with the reported ee values of the asymmetric hydrogenation of α-acetamidocinnamic acid with other air-stable triaryl-substituted ligand: BINAP, 84%[4a]; [2.2]PHANEPHOS, 98%.[6d]

Table 1. $[Rh(1)]^+$-Catalyzed Asymmetric Hydrogenation of α-(Acylamino)acrylic Acids and Esters[a]



Entry	R	R'	P	Solvent	% Ee[b]	Config[c]
1[d]	Ph	H	Ac	EtOH	98.7 (99.8)[e]	R
2	Ph	H	Ac	EtOH	98.9	R
3	Ph	Me	Ac	EtOH	97.6	R
4	Ph	Me	Cbz	MeOH	85.3	R
5	H	H	Ac	MeOH	98.2	R
6	H	Me	Ac	MeOH	97.5	R
7	2-Np	H	Ac	MeOH	95.7	R

[a]Reaction at 20-23 °C until complete consumption of substrate (3-12 h) with initial H_2 pressure of 2 atm employing 1 mol% of $[(1)Rh(COD)]BF_4$ as a catalyst (substrate concentration: 0.3 M). [b]Determined by chiral capillary GC using a 25 m Chrompack Chiralsil-L-Val column on the corresponding methyl ester. [c]Confirmed by comparison of sign of optical rotation and chiral GC elution order. [d]*In situ* catalyst, $[Rh(COD)_2]BF_4$ (1.0 mol%) and **1** (1.1 mol%), was stirred for 30 min prior to introduction of H_2. [e]After recrystallization from 5% E.A./*n*-hexane.

Similar high selectivity was also obtained in hydrogenation of other dehydroamino acid derivatives under optimized conditions. Slightly decreased (less than 1%) selectivity was obtained in reduction of the corresponding methyl ester of dehydroamino acid derivatives. For example, while the asymmetric hydrogenation of 2-acetamidoacrylic acid gave the corresponding *N*-acetylalanine in 98.2% ee, reduction of the corresponding methyl ester resulted in 97.5% ee under similar condition. The asymmetric hydrogenation of amino acid precursor bearing easily removable protecting group, *N*-Cbz, was also examined (entry 4). Unfortunately, relatively low value of 85.3% ee was obtained under higher initial pressure of H_2 (3 atm).

In summary, we have prepared a new *cylindrically* chiral, air-stable ferrocenylbis(phosphine) ligand, ($_p$S,$_p$S)-1,1'-bis(diphenylphosphino)-2,2'-di-3-pentylferrocene **1** ((S,S)-FerroPHOS)) employing a highly enantioselective (>99.9% ee) catalytic method avoiding the tedious and rather unpredictable resolution operations. The cylindrically chiral ligand **1** gave high enantioselectivity in the rhodium-catalyzed asymmetric hydrogenation of various dehydroamino acid derivatives. Due to high stability of our new ligand towards air, it can be used in commercial processes. Further extension of this chirality, hydrogenation reaction and other transition metal-catalyzed asymmetric reactions are in active progress in our laboratories.

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[9] Ee was determined by chiral HPLC of **4** using a Daicel Chiralcel OD column. (2% *i*-PrOH/*n*-hexane, 0.5 mL/min, R_t = 19.95 ((S, S)-**4**), 24.78 ((R,S)-**4**), 35.58 ((R, R)-**4**); >99.9% ee. The (S,S)-isomer was not detected); (R, R)-**4** : (R,S)-**4** = 98.33 : 1.67)

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[15] Data for compound **1**: $[\alpha]_D^{25}$ -578 (*c* 1.0, $CHCl_3$); mp 182.5-183.2 °C; Anal. Calcd for $C_{44}H_{48}FeP_2$: C, 76.08; H, 6.96. Found: C, 75.95; H, 6.75; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.468 (t, J_{HH} = 7.5 Hz, 6 H, CH_3), 0.961 (t, J_{HH} = 7.5 Hz, 6 H, CH_3), 1.10-1.17 (m, 2 H, CH_2), 1.50-1.55 (m, 2 H, CH_2), 1.56-1.63 (m, 2 H, CH_2), 1.89-1.94 (m, 2 H, CH_2), 2.60 (br s, 2 H, CH), 2.92 (s, 2 H, Cp), 4.19 (s, 2 H, Cp), 4.38 (s, 2 H, Cp), 7.03-7.06 (m, 4 H, C_6H_5), 7.16-7.18 (t, 10 H, C_6H_5), 7.23-7.30 (m, 6 H, C_6H_5); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 8.494, 12.48, 25.03, 26.12 (d, J_{PC} = 4.7 Hz), 38.91(d, J_{PC} = 8.4 Hz), 70.82 (d, J_{PC} = 3.0 Hz), 71.00 (d, J_{PC} = 5.3 Hz), 73.36 (d, J_{PC} = 9.2 Hz), 73.59 (d, J_{PC} = 5.3 Hz), 101.7 (d, J_{PC} = 26.0 Hz), 127.5, 127.7 (d, J_{PC} = 6.2 Hz), 128.0 (d, J_{PC} = 8.3 Hz), 128.8, 132.1 (d, J_{PC} = 18.3 Hz), 135.0 (d, J_{PC} = 22.1 Hz), 137.4 (d, J_{PC} = 7.7 Hz), 140.7 (d, J_{PC} = 8.3 Hz); ^{31}P NMR ($CDCl_3$, 202.4 MHz) δ -24.27.

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