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A Novel Chiral Ferrocenyl Phosphine Ligand from Sugar: Applications in Rh-Catalyzed Asymmetric Hydrogenation Reactions

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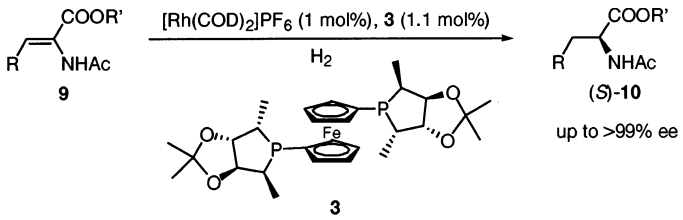
ABSTRACT



A new chiral ferrocenyl diphosphine ligand 3 was synthesized from readily available D-mannitol. Rh-complex with this ligand showed high enantioselectivity and reactivity in the asymmetric hydrogenation of dehydroamino acid derivatives and itaconic acid derivatives. Up to over 99% ee and 10 000 TON were achieved with this catalytic system.

An increasing number of chiral compounds and enantiomerically pure drugs are prepared through transition metal-catalyzed asymmetric reactions.[1] Since the reactivity and stereoselectivity of an asymmetric transformation are highly dependent on the structure of the chiral ligand coordinated to the transition metal, the design and synthesis of efficient chiral ligands are important in this area and have attracted a great deal of attention from both academia and industry.[2] For many years, the ferrocene moiety has been extensively explored as a backbone of chiral phosphine ligands due to its easy modifiability and highly electron donating property. In addition, the ferrocene-derived ligands generally crystallize readily and are relatively air stable compared to their nonferrocenyl analogues. These features are beneficial for purification and usage of the ligands. Excellent results have been achieved with ferrocene-based ligands in asymmetric hydrogenation. JosiPhos,[3] TRAP[4]and FERRIPHOS[5] are some examples of these ligands. Recently, we also reported a C_2-symmetric ferrocene-linked seven-membered phosphane ligand (f-Binaphane) and illustrated its high enantioselectivity for the hydrogenation of imine substrates.[6] DuPHOS and BPE type ligands have proven to be versatile in asymmetric hydrogenation reactions and these ligands have the five-membered *trans*-2,5-disubstituted phospholane motif. Some other polysubstituted phospholanes were also reported to be efficient ligands for asymmetric catalysis.[7] However, few good ligands have been reported with both the ferrocene backbone and the five-membered phospholane moiety. Ligand **1** (Figure 1) has the combination of a ferrocene linker

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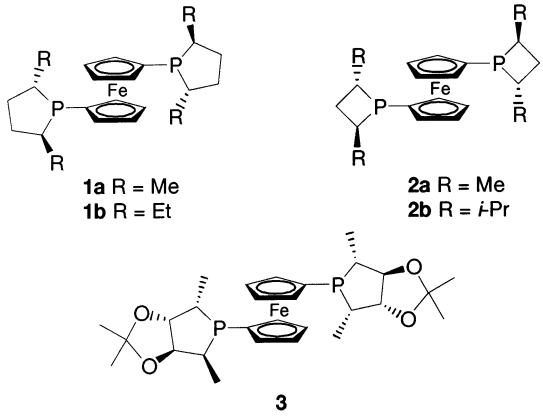


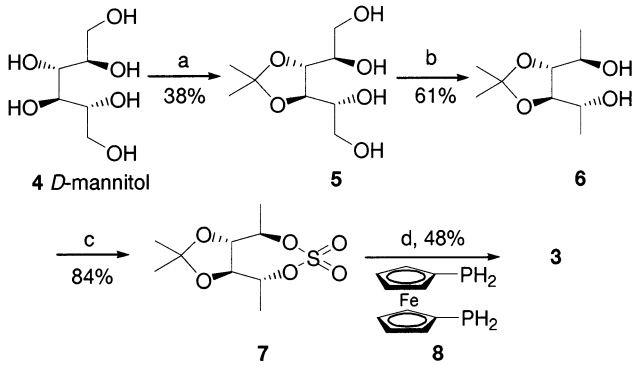
Figure 1.

and *trans*-2,5-disubstituted phospholanes and shows significantly lower enantioselectivities in hydrogenation reactions compared to its DuPHOS and BPE analogues.[8] Herein, we wish to report the synthesis of a new chiral ferrocenyl polysubstituted phospholane ligand, (3a*S*,3′a*S*,4*S*,4′*S*,6*S*,6′*S*,-6a*S*,6′a*S*)-5,5′-[1,1′-ferrocenyl]bis[tetrahydro-2,2,4,6-tetramethyl-4*H*-phospholo[3,4-*d*]-1,3-dioxole] (**3**) and its excellent applications in asymmetric hydrogenation reactions.

Burk and co-workers synthesized the ferrocenyl analogue of DuPHOS (ligand **1**) by using a flexible and more electron-donating 1,1′-ferrocenyl bridge as a linker between two phosphorus atoms.[8] These catalysts exhibited excellent catalytic activity for the hydrogenation of various olefins and carbonyl groups, but a decrease in the enantioselectivity was observed. Recently, both Marinetti[9] and Burk[10] prepared new ferrocenyl bisphosphetane ligands **2** (FerroTANE), which had shown superior utility in the asymmetric hydrogenation of itaconate derivatives. Compared to ligands **1**, higher enantioselectivities were achieved in the asymmetric hydrogenation of dehydroamino acids with this new class of ligands.[9] It is noteworthy that changing the steric bulk on the 2,4-disubstituents (from methyl in **2a** to isopropyl in **2b**) resulted in a marked increase in enantioselectivity in the Rh-**2** catalyzed hydrogenation of α-(*N*-acetamido)acrylate (69% ee (*S*) and 94% ee (*R*), respectively). A similar trend was also observed in the Rh-**1** catalytic system for hydrogenation of the same substrate.[8] We reasoned that an appropriate bulky chiral phosphorus heterocycle might have a better asymmetric induction than a less bulky heterocycle. On the basis of this assumption, we envisioned that the ferrocene-bridged polysubstituted phospholane ligand (**3**) might be an excellent ligand. It was thought that the increased steric hindrance and rigidity of this ketal phospholane may result in high enantioselectivity.[11]

The synthetic route to ligand **3** is shown in Scheme 1. The key intermediate 1,4-diol cyclic sulfate **7** was prepared according to the reported method from the commercially available and inexpensive D-mannitol.[7e] The 1,1′-bis(phosphino)ferrocene **8** was prepared from ferrocene through a two-step procedure.[8] Nucleophilic attack of **7** with **8** in the

Scheme 1[a]

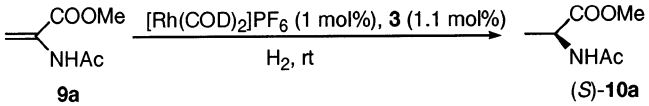


[a] Reagents and conditions: (a) (i) acetone, H_2SO_4 (cat.), rt 2 d, (ii) HOAc (70%, aq), 2 h; (b) (i). TsCl, pyridine, CH_2Cl_2, 0 °C 4 h, (ii) LAH, THF, rt 1 h, then reflux for 2 h; (c) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C 1 h, (ii) $NaIO_4$, $RuCl_3 \cdot H_2O$, MeCN, CCl_4, H_2O, 0 °C 1 h; (d) *n*-BuLi, THF, −78 °C to reflux.

presence of *n*-BuLi afforded ligand **3**. This new ligand can be easily isolated by running it through a short silica gel plug followed by recrystallization to afford orange crystals, which are air-stable in the solid state.

The Rh(I)-catalyzed hydrogenation of dehydroamino acids and their ester derivatives was investigated with ligand **3**. The catalyst was prepared in situ by mixing $[Rh(COD)_2]PF_6$ and **3** in a solvent. The commercially available α-(*N*-acetamido)acrylate **9a** was initially chosen to screen the reaction conditions. The results are shown in Table 1.

Table 1. Rh(I)-**3** Catalyzed Asymmetric Hydrogenation of α-(*N*-Acetamido)acrylate[a]



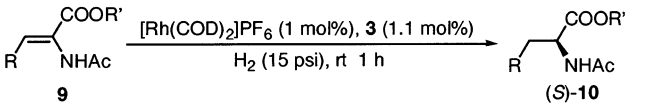
entry	ligand	solvent	pressure of H_2 [psi]	time [h]	ee [%][b]
1[c]	**1a**	MeOH	60	6	64
2[c]	**1b**	MeOH	60	6	83
3[d]	**2a**	MeOH	60	18	69
4[d]	**2b**	MeOH	60	18	94
5	**3**	MeOH	45	0.5	99.4
6	**3**	CH_2Cl_2	45	0.5	99.2
7	**3**	THF	45	0.5	99.4
8	**3**	toulene	45	0.5	98.8
9	**3**	THF	15	0.5	99.9
10	**3**	toulene	15	0.5	99.6

[a] See Experimetal Section for details. [b] The *S* absolute configuration was assigned by comparison of optical rotation with reported data. Enantiomeric excesses were determined by chiral GC (Chirasil-VAL III FSOT). [c] These results are from ref 8; [Rh(**1**)(COD)]OTf was used as catalyst precursor. [d] These results are from ref 9; catalyst was formed in situ from $[Rh(COD)_2]$OTf and ligand **2**.

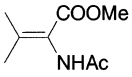
Excellent enantioselectivities (up to 99.9% ee) were observed for this reaction under all tested conditions. This result is superior to those obtained with the analogous ligands **1**

(entries 1 and 2)[8] and **2** (entries 3 and 4).[9] To optimize the reaction conditions, another compound methyl (*Z*)-α-acetamidocinnamate **9b** was selected as the substrate (Table 2, entries 1−6). A small solvent effect was seen and THF gave the best results. Toluene was not a favorable choice because it did not provide sufficient solubility for the majority of the substrates tested. Low hydrogen pressure was favorable for achieving higher enantioselectivity (Table 2, entries 2−4). The reaction was complete at ambient H_2 pressure within 30 min, which suggests that this catalytic system is highly efficient.

Table 2. Rh(I)-**3** Catalyzed Asymmetric Hydrogenation of α-Dehydroamino Acid Derivatives[a]



9 (*S*)-**10**

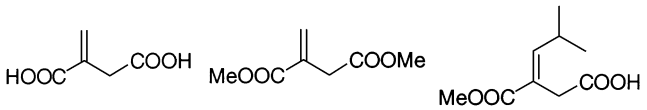
entry	substrate	solvent	conversion [%]	ee [%][b]
1	**9b** R = Ph, R' = Me	MeOH	100	97.4
2		THF	100	99.0
3		THF[c]	100	99.5
4		THF[d]	100	95.9
5		CH_2Cl_2	100	98.6
6		Toluene	100	99.5
7	**9c** R = H, R' = H	THF	100	99.4
8	**9d** R = *i*-Pr, R' = H	THF	100	>99.9
9	**9e** R = 2-Naphthyl, R' = Me	THF	100	99.0
10	**9f** R = 2-Naphthyl, R' = H	THF	100	>99.9
11	**9g** R = *o*-Cl-Ph, R' = Me	THF	100	98.0
12	**9h** R = *o*-Cl-Ph, R' = H	THF	100	99.3
13	**9i** R = *m*-Br-Ph, R' = Me	THF	100	99.3
14	**9j** R = *m*-Br-Ph, R' = H	THF	100	98.8
15	**9k** R = *p*-F-Ph, R' = Me	THF	100	98.4
16	**9l** R = *p*-F-Ph, R' = H	THF	100	98.7
17	**9m** R = *p*-MeO-Ph, R' = Me	THF	100	97.8[e]
18	**9n** 	THF	100	87.3[f]

[a] See Experimetal Section for details. [b] The *S* absolute configuration was assigned by comparison of optical rotation with reported data. Enantiomeric excesses were determined by chiral GC (Chrialsil-VAL III FSOT). The ee values of the acids were determined on the corresponding methyl ester. [c] 45 psi of H_2 pressure was used. [d] 150 psi of H_2 pressure was used. [e] The ee value was determined by Chiral HPLC (Chiralcel OJ). [f] Reaction time was 3 h.

Table 2 summarizes the results of Rh(I)-**3** catalyzed hydrogenation of various trisubstituted α-dehydroamino acid derivatives **9d**−**m**. All the reactions went to completion in 1 h at ambient H_2 with excellent ee values observed (up to over 99.9%). A tetrasubstituted dehydroamino acid **9n** was also explored, while the ee value (87.3%) was a little lower than those for the trisubstituted substrates (Table 2, entry 19). The overall enantioselectivities for the Rh(I)-**3** catalyzed hydrogenation of dehydroamino acid derivatives were excellent and these results compare favorably to other C_2-symmetric ferrocenyl bisphosphine ligands reported to date.[8,9,12]

To further investigate the catalytic efficiency of the Rh(I)-**3** system, the pure catalyst precursor [Rh(COD)**3**]PF_6 (**11**) was isolated. α-(*N*-Acetamido)acrylate (**9a**) was subject to 3 atm of H_2 in the presence of 0.01 mol % of [Rh(COD)**3**]-PF_6 in THF. (*S*)-**10a** was obtained in 100% yield within 12 h as a single enantiomer detected by GC (>99.9% ee). Thus, a high turnover number of 10 000 can be achieved in this system.

Hydrogenation of itaconic acid derivatives was also explored with the Rh(I)-**3** catalytic system.[13] Good to excellent results (up to >99% ee) were achieved for itaconic acid (**12a**) and its derivatives **12b** and **12c** (Figure 2).



12a 99.5% ee *R* **12b** 89.9% ee *R* **12c** 95.9% ee *R*

Figure 2. Rh(I)-**3** catalyzed asymmetric hydrogention of itaconic acid and its derivatives.

In conclusion, a new chiral polysubstituted bisphospholane ligand possessing a ferrocenyl backbone was prepared. The bulky ketal substituent on both of the phospholane rings results in a significant improvement on the enantioselectivity of Rh-catalyzed hydrogenation of dehydroamino acid derivatives compared to its disubstituted phospholane and phosphetane analogues. Hydrogenation of selected itaconic acid derivatives also gave high ee values. More detailed studies on this type of substrate as well as other utilities of this ligand in asymmetric catalysis are in process.

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(13) The reactions were carried in methanol at room temperature under 80 psi of H_2 pressure for 12 h following a similar procedure described in the experimental section. The reactions went with 100% conversion. The *R* absolute configuration was assigned by comparison of optical rotation with reported data. Enantiomeric excesses were determined on the corresponding dimethyl esters by chiral GC using a γ-225 column.

Supporting Information Available: Experimental procedures and spectroscopic data for **3** and **11**, and general procedure for asymmetric hydrogenation of dehydroamino acid derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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