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New Chiral 1,1'-Bis(Phospholano)ferrocene Ligands for Asymmetric Catalysis

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Abstract: The synthesis of two new 1,1'-bis(phospholano)ferrocene ligands are described. Preliminary catalytic studies showed that enantioselectivities as high as 83% ee could be achieved in the hydrogenation of several model olefin, ketone, and hydrazone substrates.

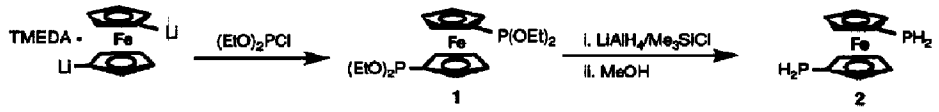
The conformational properties of ligands are well known to influence the reactivity and selectivity of transition metal catalysts.[1] This is particularly evident in asymmetric catalysis where development and use of conformationally restricted chiral bidentate ligands has resulted in the attainment of very high enantiomeric excesses in numerous processes.[2] We recently have designed a series of 1,2-bis(phospholane) ligands possessing various backbone structures.[3,4] In particular, we have found that 1,2-bis(phospholano)benzene (DuPHOS) ligands possessing the conformationally restricted 1,2-phenylene backbone were superior in terms of enantioselectivity in rhodium-catalyzed hydrogenation of C=C and C=N double bonds.[4,5]

While conformationally restricted chiral diphosphines have proven beneficial in terms of enantioselectivity, flexible backbone structures often are required for achieving high catalytic rates. For example, we recently have found that the cationic DuPHOS-Rh catalysts, so useful for C=C and C=N reductions, were relatively ineffective for ketone reductions at low hydrogen pressures (≤ 100 psi). Our studies,[3c] as well as those of Tani,[6] have suggested that electron-rich diphosphines possessing a conformationally flexible ligand backbone may be necessary for high rates in ketone hydrogenations. Consistent with this hypothesis, we recently have found that the ligand 1,1'-bis(diisopropylphosphino)ferrocene (DiPFc) satisfies both the electronic and conformational requirements. Cationic rhodium catalysts bearing the DiPFc ligand allowed efficient hydrogenation of a variety of ketones and aldehydes under very mild reaction conditions.[7]

Given the need for a highly enantioselective ketone hydrogenation catalyst that operates efficiently under mild conditions (25 °C, ≤60 psi H_2), we sought to design asymmetric versions of the DiPFc ligand. Toward that goal, herein we outline the synthesis of two new 1,1'-bis(phospholano)ferrocene ligands and describe preliminary catalytic results.

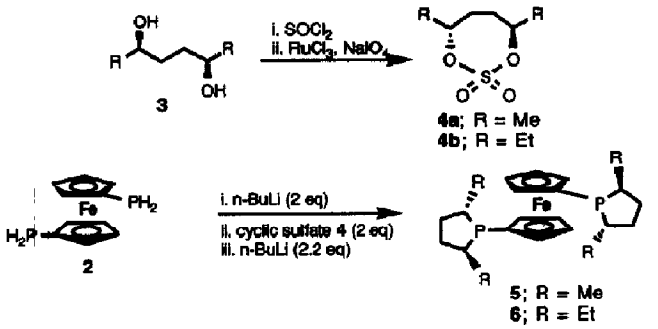
We have developed a route to the 1,1'-bis(2,5-dialkylphospholano)ferrocene ligands **5** and **6** via the novel intermediate 1,1'-diphosphinoferrocene **2** (Scheme 1). Reaction of the known

dilithioferrocene (TMEDA adduct)[8] with chlorodiethylphosphite (4 equivalents) afforded the bis-diethylphosphonite derivative **1**. Attempted reduction of **1** under standard conditions with $LiAlH_4$ led to a mixture containing little of the desired diphosphine. Smooth reduction of the bis-phosphonite was accomplished, however, with the reducing agent $LiAlH_4/Me_3SiCl$ (1/1), previously introduced by Kyba et al. for the reduction of phosphonate esters.[9] Under these conditions, but using an anhydrous methanol rather than aqueous workup procedure, 1,1'-diphosphinoferrocene (**2**) was obtained in very high yield (98%).[10]



Scheme 1. Preparation of 1,1'-diphosphinoferrocene

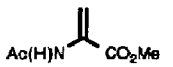
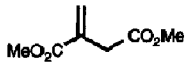
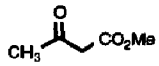
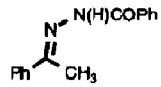
We recently introduced a versatile method for the preparation of *trans*-2,5-dialkylphospholane ligands through successive treatment of primary phosphines with n-BuLi (2 equiv), followed by chiral 1,4-diol cyclic sulfates (2 equiv), and then another 2.2 equiv. n-BuLi.[4] Following this standard protocol, 1,1'-diphosphinoferrocene (**2**) was reacted with (*R,R*)-2,5-hexanediol cyclic sulfate **4a** in THF to afford the product 1,1'-bis((2*S*,5*S*)-2,5-dimethylphospholano)ferrocene **5** as an orange crystalline solid in good isolated yield (86%). Similarly, the analogous 1,1'-bis((2*R*,5*R*)-2,5-diethylphospholano)ferrocene **6** was obtained upon reaction of **2** with (*S,S*)-3,6-octanediol cyclic sulfate **4b** (Scheme 2).[11]



Scheme 2. Preparation of 1,1'-bis(dialkylphospholano)ferrocenes via cyclic sulfates 4

In order to gain information concerning the potential effectiveness of ligands **5** and **6** in asymmetric catalytic applications, we have examined the rhodium-catalyzed hydrogenation of several model substrates. Cationic rhodium catalyst precursors $[COD)Rh(P_2)]^+OTf^-$ (P_2 = **5** or **6**) were prepared as previously described.[4,5] The results of these studies are shown in Table 1.

Table 1. Enantioselectivities in asymmetric hydrogenation reactions[a]

Substrate		Ligand	% ee
	7	5	64
		6	83
	8	5	72
		6	83
	9	5	33
		6	58
	10	6	31

[a] Reaction conditions: 0.05-0.10 M substrate, methanol solvent, 60 psi H_2, 25°C, catalyst precursor [(COD)Rh(P_2)]$^+$OTf$^-$ (0.2 mol %, P_2 = **5** or **6**). Reactions were stirred for 6-24 h, and in all cases, 100 % conversion was observed. Enantiomeric excesses were determined by chiral capillary GC using Astec's Chiraldex G-PN column for reactions involving **8** and **9** , or Chrompack's ChiralsII-L-Val column for reactions involving **7** and **10**.

In all cases, the ethyl-substituted phospholane ligand **6** outperformed the methyl-substituted ligand **5**. As can be seen, respectable enantioselectivities were achieved in hydrogenation of the olefinic substrates N-α-acetamidoacrylate (**7**) and dimethyl itaconate (**8**), where the cationic catalyst derived from **6** provided the products in 83% ee. Smooth hydrogenation of the β-keto ester methyl acetoacetate (**9**) also was achieved, although the enantioselectivity was somewhat lower at 58% ee. Importantly, while the enantioselectivity of this reaction was only moderate, high catalytic activity was observed under mild conditions (25°C, 60 psi H_2). This stands in contrast to the best current systems typified by Ru-BINAP, which reportedly require hydrogen pressures as high as 100 atm for reasonable rates in β-keto ester reductions.[12] Moreover, the enantioselectivity observed using the ligand **6** was significantly higher than that achieved in the hydrogenation of **9** with the similarly flexible 1,3-bis(diethylphospholano)propane (22% ee).[3c] Hydrogenation of the C=N double bond of acetophenone N-benzoylhydrazone (**10**) afforded the product in 31% ee.

Overall, we have described a convenient route to new chiral bis(phospholane) ligands possessing a ferrocenyl backbone. The promising results described above suggest that suitable modifications of the phospholane substituents, or the ferrocenyl backbone, of ligands such as **5** and **6** may lead to effective new catalysts for the enantioselective hydrogenation of ketones under mild conditions.

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10. Preparation of 1,1'-diphosphinoferrocene **2**: To a solution of chlorodiethylphosphite (8.0 g, 0.051 mol) in THF (25 mL) was added dropwise a solution of 1,1'-dilithioferrocene TMEDA adduct[8] (4.0 g, 0.013 mol) in THF. After 2h at 25°C, the reaction was concentrated, the residue extracted with pentane (75 mL), filtered, and the filtrate concentrated to provide the bis-phosphonite **1** as a dark orange oil (5.13 g, 95%). ^{1}H NMR (C_6D_6): δ 1.05 (t, 12 H, CH_3), 3.75 (m, 8 H, CH_2), 4.25 (s, 4H, Cp-H), 4.45 (s, 4H, Cp-H); ^{31}P NMR (C_6D_6) δ 156.5. The crude product was sufficiently pure to use in the next step. The reducing agent was prepared by mixing a THF slurry of $LiAlH_4$ (1.07 g, 0.028 mol) with Me_3SiCl (3.06 g, 0.028 mol) in THF at -30°C and allowing to stir for 1.5 h at 25°C.[9] To the resulting reducing agent mixture was added bis-phosphonite **1** (2.0 g, 4.7 mmol) in THF (10 mL) at 25°C. After 6 h, MeOH (6.0 mL) was added dropwise. After an additional 45 min., the reaction was filtered and concentrated. The residue was extracted with pentane, filtered through celite, and concentrated to provide the desired diphosphine **2** as a dark orange oil (1.15 g, 98%). ^{1}H NMR (C_6D_6): δ 3.69 (ddd, 4 H, J_{PH} = 3.3 Hz, 202 Hz, PH_2), 3.92 (d, 4H, J_{HH} = 1.7 Hz, Cp-H), 3.96 (d, 4H, J_{HH} = 1.5 Hz, Cp-H); ^{13}C NMR (C_6D_6) δ 72.1, 76.9, 77.0 (d, J_{PC} = 15.2 Hz); ^{31}P NMR (C_6D_6) δ -145.5 (t, J_{PH} = 202 Hz).
11. 1,1'-bis((2*R*,5*R*)-2,5-diethylphospholano)ferrocene **6**: ^{1}H NMR (C_6D_6) δ 0.88 (m, 6H, CH_3), 0.9-1.20 (m, 4H, CH_2), 1.11 (t, J_{HH} = 7.3 Hz, 6H, CH_3), 1.20-1.40 (m, 4H, CH_2), 1.45-1.70 (m, 4H, CH_2), 1.70-1.90 (m, 4H, CH), 2.10 (m (br), 2H, CH_2), 2.40 (m, 2H, CH), 3.90 (m, 1H, CpH), 4.25 (m, 2H, CpH), 4.35 (m, 1H, CpH); ^{31}P NMR (C_6D_6) δ -9.4; ^{13}C NMR (C_6D_6) δ 14.27 (d, J_{PC} = 16.1 Hz), 14.82 (d, J_{PC} = 7.9 Hz), 23.76, 30.07, 30.49, 34.03, 34.34 (d, J_{PC} = 4.4 Hz), 42.42 (d, J_{CP} = 9.9 Hz), 44.44 (d, J_{CP} = 11.9 Hz), 70.88 (d, J_{CP} = 6.2 Hz), 71.24, 71.96 (d, J_{CP} = 7.7 Hz), 77.33 (d, J_{CP} = 32.8 Hz); HRMS (EI, direct insert): *m/z* 470.1976 (M^+, exact mass calcd for $C_{26}H_{40}P_2Fe$: 470.1955).
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