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Unsymmetrical Hybrid Ferrocene-Based Phosphine-Phosphoramidites: A New Class of Practical Ligands for Rh-Catalyzed Asymmetric Hydrogenation

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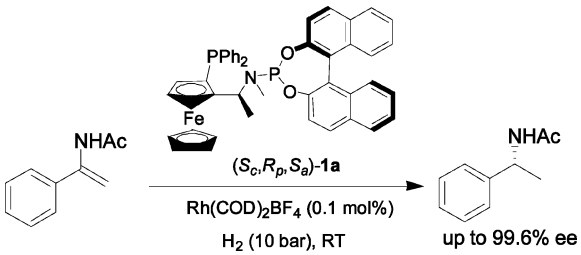
ABSTRACT



The synthesis and application of a new family of air-stable, highly unsymmetrical ferrocene-based phosphine-phosphoramidites is described. The new ligands exhibit excellent enantioselectivities (over 99% ee) in the Rh-catalyzed asymmetric hydrogenation of enamides, dimethyl itaconate, and methyl (*Z*)-acetamidocinnamate even with high catalyst turnovers (S/C = 10 000). The binaphthyl moiety is crucial for reactivity and enantioselectivity, and its absolute configuration plays a dominant role in determining the chirality of the hydrogenation products.

Asymmetric catalytic hydrogenations by a metal catalyst complexed with chiral ligands are some of the most powerful tools for obtaining a wide range of enantiomerically pure or enriched compounds.[1] In addition to some monodentate phosphorus-containing ligands,[2] most of the ligands that have been used successfully in this reaction are bidentate *P*-chelate ligands,[3] and most have a C_2-symmetrical structure or at least two closely related binding sites. Examples include BINAP,[4] DuPhos,[5] DIPAMP,[6] DIOP,[7] TangPhos,[8] and many ferrocene-based ligands.[9] In contrast, there have been few reports on unsymmetrical *P*-chelate ligands. Compared to the widely used C_2-symmetrical bidentate ligands with two equivalent

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P atoms, ligands with two different coordinating functionalities are commonly believed to be capable of generating a large number of diastereomeric transition states, which makes the stereocontrol of the process more difficult.[10] However, because the two coordinating groups influence the reactivity and selectivity of the metal catalyst in different manners, their structures can be optimized individually to achieve the desired catalytic outcome.[11] Therefore, the greater complexity introduced by unsymmetrical ligands may be advantageous in catalyst design for achieving chiral environments inaccessible with C_2-symmetrical ligands.[12] The successful application of some unsymmetrical bidentate ligands in industrial processes, e.g., Josiphos,[13] has clearly demonstrated the value of unsymmetrical ligand design for obtaining more selective and efficient catalysts. We surmised that the combination of a phosphine and a phosphoramidite moiety would result in a highly unsymmetrical ligand, which could be expected to exhibit good activity in catalytic hydrogenation. To the best of our knowledge, however, with the exception of the good results achieved with QUINAPHOS in Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate (Figure 1),[14] no

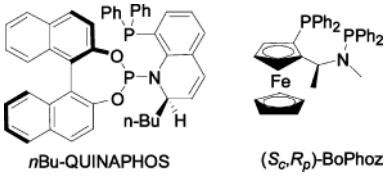


Figure 1. *n*Bu-QUINAPHOS and (S_c,R_p)-BoPhoz.

phosphine-phosphoramidites have been reported to show high enantioselectivity in asymmetric catalytic hydrogenation. Among the wide structural diversity of chiral frameworks commonly used in asymmetric catalysis, the planar chirality of 1,2-disubstituted ferrocene derivatives has received considerable attention.[15] Within this context, in this report we introduce a new family of highly unsymmetrical phosphine-phosphoramidite ligands **1** (Figure 2), which contain a planar-chiral ferrocenyl backbone and an axial-chiral binaphthyl moiety, as highly efficient chiral bidentate ligands for the Rh(I)-catalyzed asymmetric hydrogenation of a variety of functionalized C═C bonds. In all three of the stereogenic elements, axial chirality plays a crucial role in terms of reactivity and enantioselectivity, and the highest enantio-

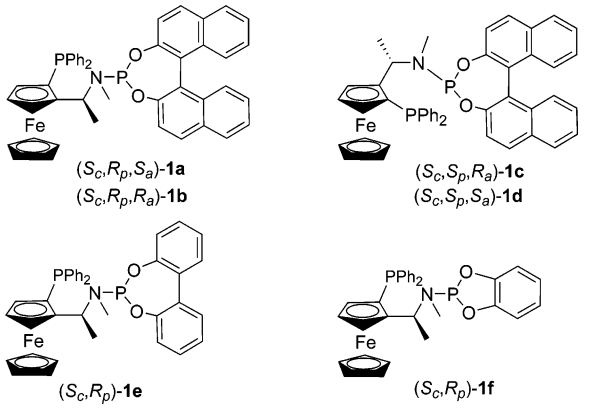
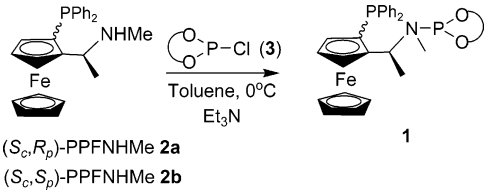


Figure 2. Highly unsymmetrical bidentate ferrocene-based phosphine-phosphoramidite ligands **1**.

selectivity was achieved using ligand **1a** with (S_c)-central, (R_p)-planar, and (S_a)-axial absolute configurations.

One major advantage of these ferrocene-based phosphine-phosphoramidite ligands is that their synthesis, despite their complex appearance, is straightforward, and purification is very convenient. Although these newly developed ligands have three stereogenic elements, all four of their diastereoisomers can be easily prepared in nearly quantitative yields by the reaction of (S_c,R_p)-PPFNHMe **2a** or (S_c,S_p)-PPFNHMe **2b** with chlorophosphites **3** in toluene at 0 °C, as outlined in Scheme 1. The synthetic protocol described here enables

Scheme 1. Synthesis of Ferrocenylphosphine-Phosphoramidite Ligands **1**



the preparation of a series of ligands that differ with regard to the nature of the phosphoramidite fragment, as well as the stereogenic elements, and thus can cover a wide structural diversity for ligand optimization. The purification of these ligands was very easy. By adding *n*-hexane to the reaction mixture, the targeted phosphine-phosphoramidites were precipitated in sufficient purity for direct use. The key intermediate (S_c,R_p)-**2a** was easily prepared as described in the literature;[16] however, the synthesis of its diastereoisomer (S_c,S_p)-**2b** was somewhat problematic. This problem was successfully addressed by using an easily removable blocking

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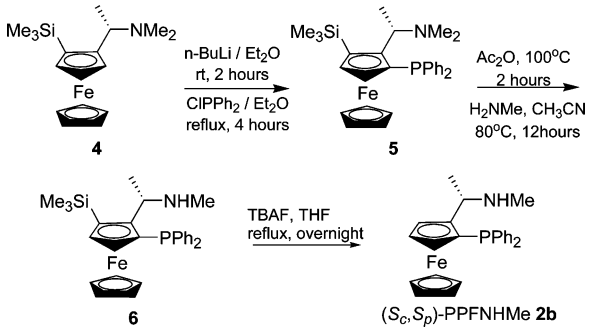
(17) Standard conditions are 0.5 mmol of substrate and 1 mol % of catalyst (L/Rh = 1.1/1) in 3 mL of solvent at room temperature and a H_2 pressure of 10 bar.

group (TMS) prior to introduction of the phosphine moiety, and (S_c,S_p)-**2b** was synthesized in satisfactory yield and high enantiomeric purity (Scheme 2).

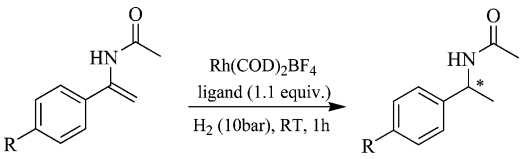
Scheme 2. Synthesis of (S_c,S_p)-PPFNHMe **2b**



In the first set of experiments, we used the Rh-catalyzed asymmetric hydrogenation of enamides **7** to benchmark the potential of these phosphine-phosphoramidite ligands for asymmetric catalysis. Hydrogenation was conducted at room temperature under a H_2 pressure of 10 bar in the presence of 1 mol % of catalysts prepared in situ from $Rh(COD)_2BF_4$ and 1.1 equiv of chiral ligand, and the results are summarized in Table 1. When a rhodium catalyst containing (S_c,R_p,S_a)-**1a** with a (S_a)-binaphthyl moiety was used in the hydrogenation of substrate **7a**, a significant increase in the ee value of the product to 99.6% was obtained in comparison with the result using Bophoz, which has the same (S_c,R_p)-ferrocenyl backbone.[16] In sharp contrast, however, ligand (S_c,R_p,R_a)-**1b** with a (R_a)-binaphthyl fragment gave only 10.6% ee and favored a hydrogenation product with a configuration opposite that obtained with (S_c,R_p,S_a)-**1a** (entry 3). This result suggested that the introduction of a chiral binaphthyl moiety into the planar ferrocenyl backbone strongly influenced the catalytic activity and enantioselectivity. Using (S_c,S_p,R_a)-**1c**, a hydrogenation product was obtained with 99.6% ee but with a chirality opposite that obtained with (S_c,R_p,S_a)-**1a** (entry 4). In contrast, (S_c,S_p,S_a)-**1d** only gave a hydrogenation product with 82.6% ee in the same configuration as that obtained with (S_c,R_p,S_a)-**1a** (entry 5). When ligands with an achiral phosphoramidite moiety were used in the model reaction, only moderate enantioselectivity was obtained (entries 6 and 7). These results indicate that the binaphthyl moiety plays a crucial role in the enantioselectivity and controls the chirality of the hydrogenation products. The matched stereogenic elements are S_c,R_p,S_a or S_c,S_p,R_a. When the catalyst loadings were decreased to as low as 0.02 mol %, a similar enantioselectivity was obtained (entries 8 and 9). The hydrogenation of other enamides also gave very high ee values (entries 10−13).

Remarkable enantioselectivity and catalytic activity were also observed in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate **9** (Table 2). The most efficient catalyst was prepared in situ from $Rh(COD)_2BF_4$ and (S_c,R_p,S_a)-**1a**, which provided the hydrogenation products in 99.9% ee under standard hydrogenation conditions (entry 2). The reaction was not solvent-dependent and proceeded smoothly in all of the solvents tested to give the product with >99% ee (entries 2−5). The rhodium complex of this preferred ligand (S_c,R_p,S_a)-**1a** was particularly effective for the hydro-

Table 1. Rh-Catalyzed Asymmetric Hydrogenation of Enamides **7**[a]



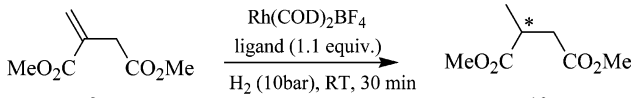
7a: R = H; **7b**: R = F; **7c**: R = Cl;
7d: R = Br; **7e**: R =CF_3

8

entry	ligand	substrate	Rh (mol %)	ee (config)[b]
1	BoPhoz	**7a**	1	61.8 (*R*)
2	(S_c,R_p,S_a)-**1a**	**7a**	1	99.6 (*R*)
3	(S_c,R_p,R_a)-**1b**	**7a**	1	10.6 (*S*)
4	(S_c,S_p,R_a)-**1c**	**7a**	1	99.6 (*S*)
5	(S_c,S_p,S_a)-**1d**	**7a**	1	82.6 (*R*)
6	(S_c,R_p)-**1e**	**7a**	1	81.5 (*S*)
7	(S_c,R_p)-**1f**	**7a**	1	78.1 (*R*)
8	(S_c,R_p,S_a)-**1a**	**7a**	0.1	99.6 (*R*)
9	(S_c,R_p,S_a)-**1a**	**7a**	0.02	99.3 (*R*)
10	(S_c,R_p,S_a)-**1a**	**7b**	0.1	98.7 (*R*)
11	(S_c,R_p,S_a)-**1a**	**7c**	0.1	98.8 (*R*)
12	(S_c,R_p,S_a)-**1a**	**7d**	0.1	99.0 (*R*)
13	(S_c,R_p,S_a)-**1a**	**7e**	0.1	99.2 (*R*)

[a] Reactions were performed under standard conditions using CH_2Cl_2 as a solvent.[17] Full conversions were achieved in all reactions. [b] Enantiomeric excesses were determined by GC using a Chiral Select 1000 capillary (0.25 mm × 30 m) column. The absolute configuration was determined by comparing the GC retention times with GC data in the literature.

Table 2. Rh-Catalyzed Hydrogenation of Dimethyl Itaconate **9**[a]



9 **10**

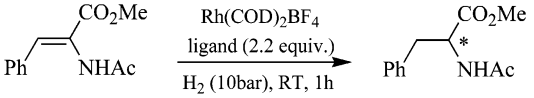
entry	ligand	solvent	[Rh] mol %	ee (config)[b]
1	BoPhoz	CH_2Cl_2	1	94.0[c]
2	(S_c,R_p,S_a)-**1a**	CH_2Cl_2	1	99.9 (*S*)
3	(S_c,R_p,S_a)-**1a**	CH_3OH	1	99.9 (*S*)
4	(S_c,R_p,S_a)-**1a**	THF	1	99.9 (*S*)
5	(S_c,R_p,S_a)-**1a**	toluene	1	99.6 (*S*)
6	(S_c,R_p,S_a)-**1a**	CH_2Cl_2	0.1	99.9 (*S*)
7	(S_c,R_p,S_a)-**1a**	CH_2Cl_2	0.01	99.1 (S)

[a] Reactions were performed under standard conditions.[17] Full conversions were achieved in all reactions. [b] Enantiomeric excesses were determined by GC using a γ-DEX-225 capillary (0.25 mm × 30 m) column. The absolute configuration was determined by comparing the GC retention times with GC data in the literature. [c] The data were reported by Boaz under 300 psi hydrogen in MeOH for 6 h using $Rh(COD)_2OTf$ as a precatalyst.

genation of dimethyl itaconate **9**. An ee value of 99.1% was obtained even at low catalyst loadings (S/C = 10 000:1) (entry 7).

In contrast to the hydrogenation of enamides and dimethyl itaconate, 2.2 equiv of (S_c,R_p,S_a)-**1a** to rhodium were required to achieve the highest enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of methyl (*Z*)-acetamidocinnamate **11**, which is consistent with the results using QUINAPHOS in the hydrogenation of methyl 2-acetamidoacrylate (Table 3).[14] Interestingly, the presence of a small quantity of air or moisture seems to enhance the enantioselectivity. When the reaction was carried out in unprotected conditions (undried and undegassed solvent, autoclave not purged by inert gas before use), an ee value of 99. 9% was achieved (entry 3). The reaction performed in toluene also gave high enantioselectivity (entry 4). The rhodium complex of (S_c,R_p,S_a)-**1a** was also highly efficient for the hydrogenation of methyl (*Z*)-acetamidocinnamate **11**: an ee value of 99.0% was obtained even at low catalyst loadings (S/C = 10 000:1) (entries 5 and 6).

Table 3. Rh-Catalyzed Hydrogenation of Methyl (*Z*)-Acetamidocinnamate **11**[a]



11 **12**

entry	solvent	[Rh/L] mol %	ee (config)[b]
1	CH_2Cl_2	1/1.1	97.6 (*R*)[c]
2	CH_2Cl_2	1/2.2	99.0 (*R*)[c]
3	CH_2Cl_2	1/2.2	99.9 (*R*)
4	toluene	1/2.2	99.9 (*R*)
5	CH_2Cl_2	0.1/0.22	99.9 (*R*)
6	CH_2Cl_2	0.01/0.022	99.0 (*R*)

[a] Reactions were performed under standard conditions except that 2.2 equiv of ligand was used under unprotected conditions.[17] Full conversions were achieved in all reactions. [b] Enantiomeric excesses were determined by GC using a CP-Chiralsil-L-Val capillary (0.25 mm × 30 m) column. The absolute configuration was determined by comparing the GC retention times with GC data in the literature. [c] Reactions were performed under protected conditions in a glovebox.

Another salient and practical feature of these phosphine-phosphoramidite ligands is their excellent air- and moisture-stability. Even after being held at ambient temperature in open air for more than 6 months, ligand (S_c,R_p,S_a)-**1a** did not show any change in its ^{1}H or ^{31}P NMR spectra and exhibited the same activity and enantioselectivity in catalytic hydrogenation. Remarkably, preparation of the active Rh-catalyst complexed ligand (S_c,R_p,S_a)-**1a**, as well as asymmetric hydrogenation with it in an unprotected atmosphere using common solvents without degassing and drying, did not cause an observable decrease in catalytic reactivity or enantioselectivity. Moreover, a marked increase in enantioselectivity was observed in the hydrogenation of methyl (*Z*)-acetamidocinnamate **11** when the reaction was conducted under air and using solvents straight from the bottle.

In conclusion, we have developed a new family of highly unsymmetrical bidentate chiral phosphine-phosphoramidite ligands by combining a ferrocenyl backbone and a binaphthyl fragment. We observed excellent levels of enantioselectivity in the Rh-catalyzed hydrogenation of enamides, dimethyl itaconate, and methyl (*Z*)-acetamidocinnamate even at low catalyst loadings, and these are the highest levels reached so far for bidentate phosphine-phosphoramidite ligands. Their ease of preparation, extraordinary stability toward air and moisture, and tolerance of various hydrogenation conditions make this family of catalysts highly practical for general laboratory preparations, as well as scale-up operations. Further investigations of other catalytic asymmetric reactions with these phosphine-phosphoramidite ligands are underway.

Supporting Information Available: Experimental details, spectroscopic data for **1**, **2** and **6**, and analytical data for **8**, **10**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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